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Food experience in cancer patients undergoing antineoplastic therapies

Affective responses to food and inputs for new tailor-made food solutions

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Abstract

Although the advances in cancer management, particularly with the advent of immunotherapy, chemotherapy remains the most widely used treatment approach. However, its limited selectivity leads to cytotoxic effects also on rapidly renewing cells, including taste and olfactory receptors. Chemosensory alterations represent therefore a frequent side effect, affecting up to 93% of patients undergoing chemotherapy. Despite this high rate these alterations are considered “orphan symptoms”, as they are generally unaddressed in clinical practice. Yet chemosensory alterations, may impact the patient's daily eating experience by altering the palatability of foods, leading to aversion for certain dishes and changes in food preferences and behaviors. Furthermore, the loss of the ability to enjoy favorite foods can exacerbate emotional responses and trigger concern and anxiety in patients, making participation in social gatherings more challenging, worsening the quality of life.

The unexpected occurrence of chemosensory alterations can lead to significantly different, and sometimes opposing, outcomes: on the one hand, loss of appetite, reduced food intake, failure to meet nutritional needs, and consequent weight loss; on the other, satisfaction of specific food cravings, increased caloric intake, and consequent weight gain. Both scenarios place patients at high risk of malnutrition. Nutritional support is not used as routinely as an adjunct to antineoplastic therapies as chemosensory alterations are often considered as unavoidable side effects of treatment. In addition, the accessibility to a variety and attractive food products is limited for oncological patients. Although a variety of oral nutritional supplements are currently available on the market, there is a notable lack of food products specifically designed for cancer patients experiencing chemosensory alterations. Furthermore, the dietary advice currently offered in oncology is often

generic and non-personalized, failing to adequately address the individual sensory and nutritional challenges patients face during treatment.

Given the complexity and multidimensional nature of chemosensory alterations in cancer patients and considering their significant impact on both nutritional status and emotional well-being, a deeper understanding of this phenomenon is essential. Such understanding is necessary to develop personalized nutritional interventions that effectively meet patients' specific needs, improve their quality of life, and help restore the pleasure of eating. The overall goal of this thesis is therefore to explore the phenomenon of chemosensory alterations as a side effect of anticancer treatment and to understand the impact of these disturbances on the daily eating experience and quality of life, focusing on food preferences, emotional responses to foods, eating habits, and nutritional status. This impact also varies according to individual differences (e.g., food neophobia, disgust sensitivity, PROP responsiveness). This will allow us to develop personalized recommendations and input for new products and recipes tailored to the needs of cancer patients, improving their eating experience, nutritional status, and quality of life.

The data of the thesis were collected as part of the larger ongoing ALTERTASTE project on a total of 71 patients with a mean age of 50.5 ± 12.6 years, treated with platinum-based or taxane-based chemotherapy for breast, bladder, prostate or testicle cancer. Patients were followed longitudinally across multiple session: before the treatment (T0), 58 patients after the 1st cycle (T1), 66 patients after the 2nd cycle (T2), 57 patients after the 4th cycle (T4), 42 patients at (T6), 33 patients at (T8), 56 patients at (TF). Chemosensory perception was measured using suprathreshold aqueous solutions at lower/higher concentration presented for basic tastes (sweet, salty, sour, bitter) and a pungent sensation. Self-reported chemosensory alterations are collected using an adapted version of the Italian

Chemotherapy Induced Taste Alteration Scale. Self-reported taste/smell ability and chemestetic perception during treatment were collected using an adapted version of a questionnaire set up to measure chemosensory changes due to COVID-19, together with a questionnaire developed for the study assessing changes in hedonic responses to basic tastes and changes in eating habits (use/liking of condiments) during treatment. Food Preference and Emotion Questionnaire (FP&EQ) was a new tool developed specifically for the study, in order to track any changes in preferences and emotions elicited by foods differing in key sensory properties during the whole treatment period. Food involvement of patients was assessed using the subscale "Preparation and eating" of the Food Involvement Scale. Body composition (weight, fat mass, lean mass) was determined through a bioelectrical impedance analysis device (TANITA, model BC-613). To understand the impact on quality of life the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ 30) was used. PROP responsiveness, food neophobia and sensitivity to disgust were measured to investigate their role in the development of chemosensory alteration during therapy and in food preferences and emotional responses.
Finally, qualitative semi-structured interviews allowed for further insight into chemosensory alterations and their impact on the eating experience.

The study shows that chemotherapy induced a variety of chemosensory alterations, detected through both sensory tests and self-reported questionnaire. Although the ability to correctly identify basic tastes and pungent in aqueous solutions remained generally preserved, a significant reduction in the perception of intensity was observed, especially for sweet and salty, even in the early stages of treatment, at both the lower and higher concentrations.

From a self-report perspective, the alterations emerged very early. Already after the first cycle, 39.7% of patients reported general alterations/parageusia/increased perception and 44.8% reported phantogeusia. The decline in basic taste perception was particularly reported after the second cycle, affecting half of the sample. These alterations tended to increase during treatment, with subsequent recovery three months after the end of chemotherapy.

PROP responsiveness remained stable throughout treatment and reflected individual differences in taste and trigeminal sensitivity. Patients High PROP responders reported more severe taste alterations, particularly phantogeusia, at certain stages of therapy, although there was no consistent association over time, suggesting that increased taste sensitivity may enhance the perception of sensory changes.

Regarding food experience, patients showed highly heterogeneous responses to chemosensory alterations. Although no immediate changes in food preferences emerged after the first cycle of therapy, emotions associated with habitually liked foods began to worsen early on, especially in the Sweet vs. Bitter dimension of FP&EQ, both basic tastes influenced by changes in liking.

As treatment progressed, changes in food preferences were observed, especially in patients with general taste alterations/parageusia/increase in taste perception. The preference changes regarded particularly Texture and Flavor dimensions. Some patients preferred more flavorful foods or additional seasonings to compensate for a reduced or altered taste perception, while others showed the opposite tendency, turning to milder foods to avoid unpleasant or distorted sensations. This variability reflects the adoption of personal and non-unique coping strategies aimed at rediscovering the food pleasure and preventing weight loss.

At the same time, patients with chemosensory alterations reported worse quality of life across several domains, including physical condition, fatigue, social and emotional functioning, and experienced more pronounced treatment-related symptoms, such as nausea, vomiting, and loss of appetite. These findings indicate that taste perception disorders have consequences that extend well beyond the experience of eating, affecting general well-being, while not affecting body composition.

The "ideal snack" analysis indicated that chemosensory changes did not result in distinct sensory preference profiles across the different types of changes. Overall, salty snacks were consistently preferred throughout treatment, with crunchy and tasty identified as the most desirable attributes. Conversely, pasty, liquid, or excessively soft textures were generally avoided, likely reflecting the high prevalence of oral discomfort, already reported by 47.9% of patients before treatment and increasing to 81% after the first cycle and 87.9% after the second.

These findings highlight the importance of prioritizing flavor intensity and texture in dietary interventions for patients undergoing chemotherapy, supporting the development of personalized sensory and nutritional strategies.

Based on data collected through questionnaires and interviews, it was possible to identify different profiles of chemosensory alterations. However, these profiles did not translate into homogeneous patterns, as the response to these alterations was often highly individual, with patients adopting personal strategies, sometimes compensatory or, conversely, avoidance, to maintain the pleasure of food during treatment. From the analysis of these alterations and their impact on the eating experience, personalized sensory and nutritional recommendations were developed, based on taste-odor integration, with the aim of improving palatability without impacting health through increased salt or sugar intake. The recommendations were translated into practical advice and recipes adapted to

individual profiles, providing a basis for the development of tailor-made dietary solutions aimed at preserving the pleasure of food and supporting nutritional status during therapy.

1. Introduction

The World Health Organization reported approximately 20 million new cancer cases and 9.7 million cancer deaths worldwide in 2024. Although therapeutic advances have significantly improved survival perspectives for many patients, there is a growing focus on quality of life during cancer treatments, recognizing the importance of addressing not only the clinical dimension of the disease, but also the psychological, social and nutritional aspects (Lewandowska et al., 2020; Dehkordi et al., 2009; de Vries, Boesveldt, et al., 2018; Ponticelli et al., 2017; Prieto-Callejero et al., 2020).

However, despite some recent contributions, some dimensions of patients' eating experience remain unexplored, particularly those related to the emotional sphere, the pleasure of food and satisfaction and the resulting eating behaviors. These aspects are often overlooked in both clinical practice and research, despite their influence on the general well-being of patients.

Among the main challenges for cancer patients undergoing treatment is to prevent, mitigate, or treat malnutrition, which is highly prevalent during the disease and varies depending on cancer site and stage (Stratton et al., 2003; Beirer, 2021). However, even in the absence of clinical malnutrition, many patients experience an altered relationship with food, in terms of reduced food intake due to treatment-related side effects, or development of patterns of overeating, emotional eating, or selective food avoidance (McQuestion et al., 2011; De Vries et al., 2016; Bernhardson et al., 2007). This is often the result of alterations in sensory perception of food but also of multiple side effects, including nausea, vomiting, mucositis, loss of appetite, and dysphagia. These symptoms collectively diminish the enjoyment of eating and lead to reduced quality of life (De Vries, Boesveldt, et al., 2018; Gamper et al., 2012; Turcott et al., 2016).

This thesis is the result of a longitudinal study aimed at exploring the food experience of cancer patients undergoing chemotherapy who develop chemosensory alterations and other related side effects with a particular focus on food preferences, emotions elicited by food, eating habits, nutritional status and quality of life. The aim is to contribute to a deeper understanding of the eating experience during the oncological journey, offering useful insights to develop more effective, personalized and truly person-centered support strategies.

1.1 Chemosensory perception

The sensory experience of eating is a major determinant of food intake control, often attributed to the positive hedonic response associated with certain sensory stimuli (McCrickerd & Forde, 2016). Eating is not simply a biological act of nutrient intake, but a complex experience shaped by multiple interacting factors. Among these, chemosensory perception is central to how people evaluate, appreciate, and choose foods. These sensory modalities work together to guide food selection, enhance pleasure, and support physiological regulation, making them essential for both survival and quality of life. Taste and smell are crucial for evaluating the nutritional content of foods, support oral intake, and prevent ingestion of potentially toxic substances (Brisbois et al., 2011).

Taste is mediated by specialized epithelial cells located across several regions of the upper aerodigestive tract including the oral cavity, oropharynx, larynx, and upper third of the esophagus (Epstein & Barasch, 2010). Interestingly, taste receptors have also been identified in the gastrointestinal tract, where they are thought to contribute to the detection of nutrients and the regulation of digestive functions (Depoortere 2014; Pennaneach et al., 2025). For taste signals to be effectively detected, saliva plays a crucial role by dissolving food compounds and enabling their interaction with the taste receptor cells. Once activated, these

receptors release neurotransmitters that stimulate afferent nerve fibers, which then transmit the sensory information to the central nervous system. Greater taste sensitivity is present near the tip and posterior side of the tongue; however, no segregation of taste qualities has been mapped, and the taste receptors appear to be pluripotent (Scott, 2004; Chandrashekar et al., 2006). Taste receptor cells are continuously renewed, with an average lifespan of approximately 10 days (Sugita, 2006).

It is generally assumed that the sense of taste can differentiate five primary sensory qualities: sweet, sour, salty, bitter, and umami. Each taste quality is thought to represent different nutritional or physiological needs or indicate a potential dietary risk (Chaudhari & Roper, 2010). Sweet, salty, and umami are associated with beneficial nutrients (such as carbohydrates, electrolytes, and amino acids) and are perceived as pleasant in moderate concentrations but may become aversive when overly intense (Reed et al., 2006). In contrast, bitter and sour are associated with compounds that are potentially harmful and are generally regarded as innate aversions. A sour taste allows acid detection and is therefore important to avoid ingesting acids in excess and overloading the mechanisms that maintain the pH body. Sour is also used to maintain electrolytic balance in humans. Bitter taste is thought to guard against consuming poisons, noxious substances, or toxins, many of which taste bitter to humans (Chaudhari & Roper, 2010).

Olfactory perception, like taste, is triggered by chemical stimuli. Odorant molecules interact with specific receptors located on the cilia of olfactory sensory neurons within the nasal epithelium. Once activated, these receptors initiate a neural signal that is transmitted to the olfactory bulb, the brain's first processing center for smell. From there, the signal is relayed to higher brain regions, including the primary olfactory cortex and the caudal part of the orbitofrontal cortex. Smell receptors are renewed every 30 days (Hadley et al., 2004).

Chemesthesis also contributes to chemosensory perception. Hotness, pungency, and coolness are chemically induced sensations involving receptors that can be activated both by temperature and by specific irritant substances contained in some foods (Green, 2016).

As mentioned, the eating experience is influenced by multiple sensory modalities, among which flavor and texture play a central role.

Flavor, often confused and used synonymously with taste (Spence et al., 2015), is the "complex combination of olfactory, gustatory, and trigeminal sensations perceived during tasting" as defined by International Standard Organization. In the orbitofrontal cortex the information from both smell and taste converges, allowing for the construction of the complex sensory experience of flavor (Hadley et al., 2004). Perceived flavor is then integrated with texture and temperature to give the overall sensory perception of food (Rolls, 2006).

Texture perception is a multifaceted and dynamic process, influenced by multiple physical parameters and involving the activation of different sensory receptors and tissues (Szczesniak, 2002). Some aspects of texture, such as shape, consistency, or surface characteristics, are perceived when food enters the mouth, while most are detected during chewing, when food is deformed and fractured under the action of mechanical forces (Guinard et al., 1996; Chen, 2009; Morell et al., 2013). Unlike taste or smell, there is no specific texture receptor; instead, a network of mechanoreceptors, thermoreceptors, proprioceptors, and auditory signals (e.g., crunching sounds) contribute to the perception (Jessop et al., 2006). Texture is perceived by the tongue, teeth, oral mucosa, and jaw muscles. The brain integrates signals from various sources to form a unified perception of food texture, a process often described in terms of Gestalt, where the whole sensory experience is greater than the sum of its parts (Guinard, 1996; Gorden, 1991).

1.2 Chemosensory disorders during cancer treatment

1.2.1 Effects of chemotherapy on chemosensory perception

Food perception is a complex sensation which involves a cross-modal interplay between taste, smell, and somatosensations. In addition to taste molecules, various receptors in the oral cavity also detect somatosensory stimuli consisting of tactile, thermal, and nociceptive stimulations (Riantiningtyas, Carrouel, et al., 2023). Overall, the integration of taste, smell, chemesthesis, and texture contribute to the multisensory experience of eating, which not only promotes proper nutritional intake but also influences pleasure, satisfaction, and eating behaviors. Alterations in one of these components, such as those caused by chemotherapy or oral mucositis, can disrupt the balance of sensory inputs and compromise the pleasure of food, profoundly affecting the eating experience, food intake, and quality of life, even in the absence of a specific taste or olfactory alteration.

Despite the advances in cancer management, particularly with the advent of immunotherapy, chemotherapy remains the most widely used treatment approach, either alone or in combination with other types of treatment, as target therapy. However, one of the major limitations of chemotherapy is the lack of selectivity: it acts upon both cancer cells and cells with a rapid turnover (Chaveli-López, 2014). Since taste and olfactory receptors proliferate rapidly, they too may be sensitive to the cytotoxic effects of chemotherapy (Bartoshuck, 1990). Little is known about targeted therapy impact on perception (Van Oort et al., 2018). It has been observed (Belqaid et al., 2016; Di Meglio et al., 2022) that this treatment, alone, or in combination with chemotherapy, causes taste alterations and related side effects. Van der Werf et al., (2017) reviewed possible mechanisms such as oral toxicity and altered taste or smell perception, but further research is necessary.

Overall, in cancer patients undergoing chemotherapy or radiation therapy, the rapid turnover of taste bud cells makes them vulnerable to treatment-related damage or cell death. In addition, damage to salivary glands alter saliva composition, which can prevent taste from being transported to receptors, while local infections or inflammation can promote cell loss by apoptosis and interrupt taste signal transmission (Rathee & Jain, 2023). This is due to the injury to taste receptor cell innervations, epithelial changes (mouth sores) or changes in saliva composition.

Several chemotherapeutic agents have been associated with taste and smell disorders, with varying degrees of severity and prevalence (Buttiron Webber et al. 2023; Van Oort et al., 2018). Among them, taxane-based therapies, commonly used in the treatment of breast or prostate cancer, are most frequently linked to occurrence of these alterations (Boltong et al., 2014; de Vries, Boesveldt et al., 2018), reporting metallic taste, bad taste, weird taste, lack of taste, loss of interest in eating and preparation of meal, and loss of appetite (Speck et al., 2013). Particularly, docetaxel has been linked to more severe and persistent disturbances compared to other taxanes as paclitaxel or nab-paclitaxel (Kaizu et al., 2021). Other commonly implicated agents include anthracyclines, platinum-based therapies (e.g. cisplatin or carboplatin alone or in combination as in PEB (cisplatin, etoposide, bleomycin) or VIP (etoposide, isofosfamide, cisplatin), epirubicin, cyclophosphamide, and capecitabine, used in different types of cancer including breast and testicular cancers (Amézaga et al., 2018; de Vries et al., 2018, 2019; Turcott et al., 2016; Walliczek-Dworschak et al., 2017; Campagna et al., 2018). For instance, cisplatin, known for its ototoxic and nephrotoxic effects (Karasawa & Steyger, 2015), may impacts sensory nerves and epithelial integrity, contributing to chemosensory disorders. However, clinical observations suggest that platinum-based regimens, particularly when combined with gemcitabine (e.g., for bladder

cancer), tend to be associated with comparatively lower rates of alterations (Campagna et al., 2018; Gamper et al., 2012), possibly due to the specific dosing, cancer type, or mitigating effects of the combination therapy. Instead, cyclophosphamide appears particularly damaging to the fungiform papillae located on the anterior part of the tongue (Mukherjee et al., 2013; 2017).

Additionally, 5-fluorouracil and its oral analogues are associated with a high prevalence of chemosensory alterations (Imai et al., 2013). These agents interfere with DNA synthesis in rapidly dividing cells and are known to induce significant oral mucositis, contributing to an altered perception (Vanlancker et al., 2016). Other chemotherapeutic agents, as alkylating agents, anthracyclines, antimetabolites, antitumor agents, taxane-based, and vinca alkaloids can cause oral mucositis and xerostomia that may influence the perception (Naidu et al., 2004) by interfering with saliva production and oral mucosa integrity, both of which are crucial for dissolving tastants and maintaining taste bud function (Murtaza et al., 2017; Spotten et al., 2017). Wang et al. (2015) suggest that oral mucositis may occur when oral bacteria are unable to offer protection with the disruption of the ecological balance during chemotherapy.

As common side effects of numerous chemotherapeutic agents, nausea and vomiting have been linked to the presence of chemosensory disturbances (Silva et al., 2024). Data from Bernhardson et al. (2008) show that patients who reported taste and smell disturbances more frequently also experienced nausea, vomiting, oral discomfort, loss of appetite, and depressed mood. These findings suggest a potential bidirectional relationship, in which nausea and reduced food intake may exacerbate chemosensory dysfunction, which in turn may further diminish appetite and contribute to ongoing gastrointestinal discomfort.

Given the wide variety of chemotherapeutic agents involved, chemosensory alterations cannot be considered isolated events but represent a frequent side

effect in different oncological therapeutic protocols. Indeed, up to 93% of patients undergoing chemotherapy report some form of alteration of taste or smell (Larsen et al., 2021). Despite this high rate these alterations are considered “orphan symptoms” (Santini et al., 2020), as they are generally unaddressed in clinical practice (Sevryugin et al., 2021). This is partly because they are often perceived as unavoidable side effects of treatment, not immediately life-threatening (Comeau et al., 2001; Hong et al., 2009; Rehwaldt et al., 2009; Zabernigg et al., 2010), and sometimes even dismissed as imaginary or psychological in nature (Bernhardson et al., 2007). Furthermore, these symptoms are rarely reported spontaneously by patients (Battle et al., 2020), probably due to the difficulty in describing and distinguishing them, as well as the tendency to normalize them as an expected part of treatment, or even to interpret them as a sign of therapeutic efficacy (Prieto-Callejero et al., 2020).

Not all patients describe and suffer taste and smell alterations in the same way or with the same intensity (Drareni et al., 2021). Moreover, assessment methodologies vary widely, ranging from questionnaire to standardized psychophysical tests, resulting in discrepancies in results and their interpretation. A further element of confusion is the lack of a clear distinction between the different types of chemosensory disorders (Kano & Kanda 2013). In sensory research, several tools are used to assess chemosensory perception, but their application in oncology is limited (Nolden, Hwang et al., 2019).

The occurrence and progression of chemosensory alterations during chemotherapy show a considerable interindividual variability, not only in terms of type of alteration. Some patients report alterations in perception already during or immediately after the first chemotherapy cycle (Bernhardson et al., 2008; Denda et al., 2020; Ijpma et al., 2017; Kaizu et al., 2021; Obayashi et al., 2023), while others develop them after the second or third cycle (Boltong et al., 2014; Wickham et al.,

1999). This indicates that these alterations are present from the early stages of treatment. Moreover, they may be persistent or fluctuant, often showing a cyclical pattern of disorder and partial recovery during the treatment (Bernhardson et al., 2008; Spotten et al., 2017).

Although these disturbances are usually temporary, with recovery of sensory function typically occurring within 2–6 months of the end of treatment, a complete return to normal may take up to a year in some cases (Boltong et al., 2012, 2014; Steinbach et al., 2009; Ijpma et al., 2017; de Vries, Boesveldt, et al., 2018, de Vries, Winkels, et al., 2018; Pedersini et al., 2022). This time frame reflects the regenerative capacity of the taste epithelium, which is highly sensitive to cytotoxic agents due to its rapid turnover, but capable of repairing itself after treatment (Nelson, 1998).

However, despite this trend, current knowledge remains uncompleted due to the limited number of longitudinal studies that monitor patients throughout the course of cancer therapy. Most data come from cross-sectional snapshots or short-term observations, which may not capture the evolutionary nature of these symptoms or fail to capture the occurrence and late recovery phases.

1.2.2 Classification of taste and smell disorders

Disorders of taste and smell can be classified into different types, including change of sensitivity, distorted perception and hallucinations (Leopold et al., 2002, 2009). Among the taste abnormalities (Hong et al., 2009; McLaughlin & Mahon 2012) there are **quantitative disorders** related to perceived intensity of basic tastes (sweet, salty, sour, bitter, umami):

- **Ageusia:** a condition characterized by a complete loss of taste function of the tongue; it occurs when a patient cannot recognize one or more tastes, even at high intensity (Mirza et al., 2008; Ruo Redda & Allis 2006).

- **Hypogeusia:** a decreased sensitivity to taste perception (Hong et al., 2009).
- **Hypergeusia:** an increased sensitivity to taste perception (Özkan et al., 2022; Risso et al., 2020).

As highlighted by several literature reviews (Spotten et al., 2017; Hannon et al., 2023; Togni et al., 2021; Hovan et al., 2010), many studies on the subject do not clearly distinguish between the different types of taste alterations. Often, in fact, they limit themselves to reporting an overall percentage of alteration or reduction of taste perception (Wickham et al., 1999; Leyrer et al., 2014; Davies et al., 2021; Tebidze et al., 2019), sometimes without specifying whether it is, for example, ageusia, hypogeusia, or hypergeusia, or whether the alteration affects specific basic tastes. However, other studies have more precisely identified which taste is affected, offering a more detailed understanding of the chemosensory changes experienced by patients. For instance, the studies by O'Donoghue et al. (2023) and McGettigan et al. (2019) reported that patients may experience an increase, decrease, or misidentification of sweet, salty, sour, and bitter tastes, although with different prevalence. Sandow et al. (2006) observed increased detection thresholds for all basic tastes, indicating a general reduction in taste sensitivity. However, from the review of Spotten et al. (2017) emerged that few studies have investigated the individual basic tastes with hypergeusia and hypogeusia observed for salt and sweet tastes occurring most frequently (Bernhardson et al., 2007; 2008), although changes in bitter and sour sensation have also been reported (Steinbach et al., 2009; 2012; Nishijima et al., 2013).

Among **qualitative disorders** there is dysgeusia (Jafari et al., 2021), which, although often improperly known as a general term for any alteration of taste (Risso et al., 2020), it is a qualitative distortion of taste perception (Carvalho et al., 2019), which can occur as:

- **Parageusia/cacogeusia:** distorted/unpleasant perception of taste in presence of a taste stimulus (Campagna et al., 2016; Kano & Kanda, 2013; Özkan et al., 2022)
- **Phantogeusia:** perception of a phantom taste in absence of a taste stimulus
- **Gustatory agnosia**: defined as a partial or complete inability to recognize sensory stimuli, which cannot be explained by a defect in elementary sensation or by a reduced level of alertness (Doty et al., 1984; Small et al., 2005).

Dysgeusia may be clinical expressions of regional neuropathy (Femiano et al., 2002; Granot & Nagler, 2005; Strasser et al., 2008), where injury to peripheral nerves leads to phantom sensations in the affected extremity. In the oral cavity or in food tasting, this can translate in a “new taste sensation” described as “not recognizable” and comparing it with “paper”, “sawdust”, “musty”, “chemical”, “drug”, “blood” but very often as unpleasant, unexplained, and persistent “metallic” (Rhodes et al., 1994; Wickham et al., 1999; Bernhardson et al., 2007, 2008; Boltong et al., 2012; Amézaga et al., 2018). Metallic taste has been also characterized as "a peculiar palatal sensation, similar to that observed when an iron nail or metal foil is placed in the mouth" (Clark et al., 2009). Mechanisms that could explain the perception of this metallic taste include the release of iron ions (Fe^{2+}/Fe^{3+}) from hemoglobin during cell damage, which can react through Fenton-type reactions generating volatile compounds perceived as metallic through both taste and smell pathways (Ijpma et al., 2015). Amézaga et al., 2018 hypothesize that metallic taste is likely due to the secretion of chemotherapy drugs in saliva and direct interaction with taste receptors. Metallic sensations have also been reported as a consequence of ingestion of specific foods (Hurrell, 2002), artificial sweeteners (Zygler et al., 2009), or by electrical stimulation of the tongue or chorda tympani nerve (Stillman et al., 2003; Eliasson & Gisselsson, 1954), burning mouth syndrome (López-Jornet

et al., 2010), during pregnancy (Nordin et al., 2004, 2005), and as a result of stapedectomy or anesthesia damage to the chorda tympani nerve (Bull, 1965; Yanagisawa et al., 1998). Furthermore, sensations evoked by metallic salts, such as iron, copper, and zinc, have been described as metallic (Lawless, 2004; Yang & Lawless, 2005).

Additionally, dysgeusia could be caused by alterations in oral and gut microbiota, or by xerostomia and alterations of oral pH. When saliva becomes thick or excessively concentrated in salts, or when its pH shifts toward acid levels (below 7), the solubilization and transport of taste molecules to the receptor cells are affected, altering the overall quality of taste (Ramya et al., 2015; Baliga et al., 2013; Granot & Nagler, 2005).

Patients with a bad taste in the mouth often also complain of a burning sensation in the mouth (Femiano et al., 2002). Burning in the mouth can be a reaction of the trigeminal nerve to taste stimuli received by the taste receptors, or a somatosensory reaction to stimuli transmitted by the glossopharyngeal nerve. Therefore, patients with dysgeusia often complain of increased pain during eating and prefer soft and bland foods.

Among the smell abnormalities (Hong et al., 2009) there are **quantitative disorders** as:

- **Anosmia**: a complete loss of the sense of smell. From the olfactory bulb, the signal is further processed by several other structures of the brain, including the piriform cortex, entorhinal cortex, amygdala, and hippocampus. Any damage, degeneration or destruction of the pathway along which smell is transferred and processed may result in anosmia (Li & Lui, 2023).

- **Hyposmia**: a partial reduction in olfactory sensitivity. It may result from less severe damage to the olfactory epithelium, partial obstruction of nasal airflow, or a decline in the function of olfactory receptor neurons.
- **Hyperosmia**: an increased sensitivity to odor perception. Hernandez et al. (2023) do not consider hyperosmia as a dysfunction but rather an amplified normal function of the olfactory system. They have proposed a distinction between hyperosmia, which is an objectively measurable increase in olfactory ability, and olfactory intolerance, which refers to a subjective hypersensitivity to odors that may not be supported by clinical tests. The clarification aims to avoid confusion between a measurable improvement and a perceived, often distressing, hypersensitivity to odors, which does not necessarily reflect a real increased olfactory performance.

With decrease or absence of smell, the patient usually has a normal perception of salty, sweet, sour, and bitter substances, but cannot discriminate between flavors since this greatly depends on normal olfaction (Moini & Piran, 2020).

Among the **qualitative disorders** there is **dysosmia**, a distorted ability to identify odors, which can occur as:

- **Parosmia/Cacosmia**: altered/unpleasant odor perception in the presence of another odor (Hawkes, 2003).
- **Phantosmia**: an odor hallucination in the absence of an odor in the environment. The patient may report smelling something that no one else can smell. When this belief is persistent and interpreted as having a personal meaning despite evidence to the contrary, it is considered a delusion, sometimes called olfactory reference syndrome. Olfactory hallucinations can result from dysfunction anywhere in the olfactory pathway, from the nasal cavity to the primary olfactory cortex in the medial temporal lobe. Patients may describe a wide range of odors, most commonly unpleasant or

nauseating. In some cases, they believe the odor comes from themselves (intrinsic hallucination) and may attribute it to a nasal problem. In others, the odor is perceived as coming from an outside source (extrinsic hallucination) (Hawkes, 2003).

- **Olfactory agnosia**: an inability to associate odors with their source even though one can smell them. It has been associated with right inferior temporal lesions (Hawkes, 2003).

Smell alterations seem to be less frequent overall compared to taste alterations (Ruiz Ceamanos et al., 2022). In the literature review of Spotten et al. (2017) few studies about smell alterations are reported. First of all, it is possible to observe that alterations in the perception of odors are generally less reported by patients if compared to alterations in taste. This is because taste and smell are often confused by patients (de Vries, Winkels et al., 2018). Some studies (Cohen et al., 2014; Riga et al., 2015; Steinbach et al., 2012; Yakirevitch et al., 2005) reported a general decrease in smell perception, while Bernhardson et al. (2008) reported smell changes of cleaning products, cooking odors, exhaust fumes, hospital smells, body smell, perfume.

1.2.3 Non-pharmacological causes of chemosensory disorders

Although treatments such as chemotherapy and radiation therapy are commonly recognized as significant contributors to taste and smell disorders in cancer patients, it is essential to recognize that several nonpharmacological factors can also influence chemosensory function. A review by Risso et al. (2020) highlighted how factors such as genetics, external influences (e.g., surgeries, smoking, alcohol consumption), nutritional deficiencies, biological variables, and viral illnesses may independently or synergistically contribute to the occurrence of chemosensory alterations.

Genetic factors can significantly influence taste perception across various taste modalities. In more severe instances, hereditary conditions like familial dysautonomia may lead to a reduction or complete absence of taste papillae, resulting in diminished or lost ability to detect taste stimuli (Smith et al. 1965). Although genetics plays a role in taste alterations, most such alterations arise due to environmental factors. Many chemicals (including exposure to toxic chemicals and to industrial agents, as well as liver and kidney failure, uremia, and diabetes) have been shown to affect perception by interfering with the chemical composition or quantity of saliva, changing the oral mucus membranes, reducing the number, activation, or the regenerative ability of taste receptor cells and efficacy of signal transduction, and directly affecting taste nerves (Genter & Doty, 2019).

Physical trauma is another recognized cause of taste disorders. Injuries to the tongue, cranial nerves, or brain (such as contusions or hemorrhages) can lead to taste loss either immediately or after a delayed period (Schofield & Doty, 2019). Similarly, surgical procedures may result in postoperative ageusia or dysgeusia, generally caused by partial or complete nerve transection, traction, or stretching, have also been described (Elterman et al., 2014; McLaughlin, 2014).

Oral health has also been implicated in chemosensory alterations. Dental prostheses, fillings, or conditions such as dry mouth, lichen planus, and burning mouth syndrome have all been associated with taste changes. These issues are often linked to reduced salivary flow and potential damage to peripheral or central gustatory pathways (Bromley, 2000; Klasser et al., 2008).

The multifactorial nature of chemosensory disturbances is further compounded by lifestyle habits. Smoking, for example, can reduce the density and blood flow to the fungiform papillae and increase the risk of respiratory and dental infections that negatively affect the perception of taste. (Schneller et al., 2018). Even alcohol has been shown to alter the sensitivity of taste receptors and interfere with the

absorption of key micronutrients, leading to both functional changes in saliva and structural modifications in taste buds, which further impair taste perception (Silva et al., 2015).

Nutritional factors, especially deficiencies in trace elements such as zinc, are also relevant. Inadequate zinc levels have been associated with dysgeusia or other forms of long-lasting taste alterations and appetite changes, particularly in individuals with malnutrition and altered dietary intake (Yagi et al., 2013).

Taste perception problems increase with aging, particularly after the age of 65 years there is a greater likelihood of experiencing phantogeusia and hypogeusia (Cowart et al., 1997). This is likely due to a reduction in taste bud and taste bud density and reduced neural reactivity to tastes with age (Toffanello et al., 2013).

As highlighted by Jiang and Chiang (2023), both age and gender influence taste function. While aging is associated with a general decline, females appear to retain better taste function than males. Overall, as stated by Gudziol and Hummel (2007), female taste function is more sensitive than that observed in men. These differences have been partly attributed to genetic variations related to PROP (6-n-propylthiouracil) status. Females are more acute tasters than males (Blakeslee and Salmon, 1931) Indeed as reported by Dinnella et al. (2022), confirming results of Monteleone et al. (2017) females rate PROP bitterness significantly higher than males. Moreover, PROP Tasters reported heightened responsiveness to basic tastes compared to Non-Tasters (Prescott et al., 2001; Hayes et al., 2008; Fischer et al., 2014; Dinnella et al., 2018; Nolden et al., 2020; Piochi et al., 2021; Robino et al., 2022). This disparity may reflect differences in the taste system. Evidence from behavioral and neurophysiological studies indicates that sex hormones, particularly estrogen, play a modulatory role in taste processing. Estrogen receptors have been identified in several brain regions, and levels of these

hormones may influence taste-induced activity in the periphery and brainstem, particularly in the limbic pathway (Martin & Sollars 2016).

Viral upper respiratory tract infection represents a significant non-pharmacological cause of chemosensory disturbances. These conditions often lead to temporary loss or alteration of taste and smell due to nasal congestion, mucosal inflammation, and excessive mucus production, which can obstruct the olfactory pathways and modify the local chemical environment (Akerlund et al., 1995; Damm et al., 2002). While these symptoms generally resolve once the infection subsides, some patients may experience more persistent chemosensory dysfunction, characterized by reduced sensitivity or complete inability to perceive and identify taste and smell stimuli (Henkin et al., 1975; 2013). Recently, these symptoms have received renewed clinical attention in the context of the COVID-19 pandemic, as smell and taste disorders have emerged as frequent complications of SARS-CoV-2 infection. Approximately 60% of individuals with COVID-19 have reported olfactory and gustatory alterations (Rosati et al., 2024), with early studies indicating prevalence rates of up to 80% for conditions such as dysgeusia, ageusia, hyposmia, and anosmia (Cooper et al., 2020).

1.3 Assessment of chemosensory perception, its disorders, and related side effects in oncology field

Assessing chemosensory perception and recognizing its disorders early is crucial to ensure timely intervention and maintain a good quality of life in cancer patients. However, to correctly interpret the data collected in this area, the robustness of the study design is essential (Drareni et al., 2019). In particular, the duration and structure of the study strongly influence the ability to identify and understand sensory changes related to cancer treatments, as their severity, character and

intensity could vary among and within patients on a daily basis (Belqaid et al., 2016). Cross-sectional studies, which involve data collection at a single point during or after treatment (Wickham et al., 1999; Hutton et al., 2007; Bernhardson et al., 2008; Sánchez-Lara et al., 2010; Brisbois et al., 2011; Ponticelli et al., 2017), offer a view of a specific time window of treatment, but do not allow us to establish whether the alterations found are actually consequent to the treatment or pre-existing, perhaps linked to other factors such as age, lifestyle habits (smoking, alcohol), comorbidities or individual traits (Nolden, 2021). On the other hand, longitudinal studies, which follow patients over time by collecting data at multiple points (before, during and after treatment), allow monitoring the evolution of taste and smell function during treatment (Zabernigg et al., 2010; Boltong et al., 2014; Belqaid et al., 2016; Spinelli, Mini et al., 2021). This approach allows us to trace the trajectory of sensory changes and to better understand their impact on patients' daily life and well-being.

1.3.1 Clinical assessment of chemosensory alterations

Today, in the oncology field, particularly in outpatient settings, chemosensory abnormalities are commonly identified (Atkinson et al., 2016) using a rapid clinical tool called the Common Terminology Criteria for Adverse Events (CTCAE), developed by the United States National Cancer Institute. Since 1999, this system has allowed physicians to record the severity of adverse events, such as dysgeusia, directly in the patient's medical record. Through this tool, dysgeusia can be classified on a scale from grade 0 to grade 2, based on the degree of interference with oral intake and nutritional status (Table 1).

Table 1 Example of "Dysgeusia" on Common Terminology Criteria for Adverse Events (AIOM – Associazione Italiana di Oncologia Medica)

	Grade 0 (no event)	Grade1 (mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	Grade 2 (moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)	Grade 3 (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)	Grade 4 (life-threatening consequences; urgent intervention indicated)	Grade 5 (death related to adverse event)
Dysgeusia	No alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	–	–	–

Although the CTCAE is a valuable and widely used tool for the clinical assessment of taste alterations, it is superficial, as it primarily captures the nutritional impact rather than the sensory characteristics themselves. Therefore, several studies have adopted alternative or complementary methods, such as self-administered questionnaires and sensory tests, to obtain a more precise characterization of chemosensory alterations.

1.3.2 Self-reported assessment of chemosensory alterations

Enriquez-Fernández et al. (2020) found seventeen questionnaires to assess chemosensory perception. Each tool varies in structure, length, and scope, with some focusing exclusively on taste and others integrating olfaction and related domains such as appetite or nausea. Among the most widely used is the Taste and Smell Survey (16 items), employed in multiple studies (Álvarez-Camacho et al., 2016; Belqaid et al., 2014, 2016; Brisbois et al., 2011; McGreevy et al., 2014). The Chemotherapy-induced Taste Alteration Scale, in its original 18-item form (Kano & Kanda, 2013) and translated or extended version (Corremans et al., 2021; Campagna et al., 2016; Sozeri & Kutluturkan, 2018; IJpma et al., 2017), has also been adopted to assess specific dimensions of taste changes related to chemotherapy. Other commonly used questionnaires include the Taste and Smell Subjective Changes questionnaire (Steinbach et al., 2009), and the Questionnaire for the Assessment of Subjective Chemosensory Complaints (Amezaga et al., 2018). Tools that assess broader aspects such as appetite and sensory perception include the Appetite, Hunger and Sensory Perception Questionnaire (de Vries, Boesveldt et al., 2018; IJpma, Renken, Gietema et al., 2016, 2017). Moreover, additional instruments were designed to capture taste-specific (Harris & Griffin, 2003; Ponticelli et al., 2017; Sánchez-Lara et al., 2010; Turcott et al., 2016).

1.3.3 Qualitative assessment of chemosensory alterations

Although structured questionnaires are valuable for detecting the presence and type of self-reported chemosensory changes in larger samples, especially in the clinical routine, they are inherently limited to predefined items and categories. Therefore, they can only measure what is already hypothesized or known to the researcher. Compared to written questionnaires, qualitative interviews have the

advantage of being interactive and allowing for the emergence of unexpected topics, which can be addressed by the researcher (Busetto et al., 2020). This flexibility has made semi-structured interviews a preferred method in many qualitative studies in oncology (Bernhardson et al., 2007; de Vries et al., 2016; van den Brink et al., 2022; Carlucci Palazzo et al., 2019; Boltong et al., 2012; Speck et al., 2013). Indeed, overall interviews are among the most familiar and common strategies for collecting qualitative data (Dicicco-Bloom & Crabtree, 2006; Taylor, 2005; Kallio et al., 2016). Among these, the semi-structured format is the most frequently used interview technique in qualitative research, particularly in health research (Gill et al., 2008), as it combines a defined structure with the flexibility needed to explore emerging themes in greater depth. Structured interviews, on the other hand, tend to generate quantitative rather than qualitative data (DiCicco-Bloom & Crabtree, 2006). The semi-structured format offers the flexibility to adapt and deepen participants' responses through improvised follow-up questions (Hardon et al., 2004; Rubin & Rubin, 2005; Polit & Beck, 2010), while also offering participants the opportunity to express their thoughts in their own words. However, to conduct semi-structured interviews effectively it is necessary to have a solid knowledge of the research topic (Wengraf, 2001; Kelly, 2010), as the development of the interview guide is based on prior knowledge and familiarity with relevant literature.

1.3.4 Sensory assessment of chemosensory alterations

On the other hand, in the research field, chemosensory perception and its alteration can be evaluated through quantitative methods that aim to provide reproducible measurements. These psychophysical taste assessments can be designed to measure either detection thresholds (lowest concentration at which a taste is perceived) or suprathreshold (perceived intensity or identification of taste

stimuli at concentrations above thresholds) (Lawless & Heymann, 1998). Both measures are used in cancer research, and they can be divided into those that assess taste perception throughout the mouth (whole mouth) and those that focus on spatial (or regional) perception. Whole mouth taste test refers to the assessment of the taste perception involving the whole oral cavity. Among the most used methods in this category are liquid tastants, such as aqueous solutions, drops and sprays of varying concentrations (threshold and suprathreshold) (Mulder et al., 1983; Sánchez-Lara et al., 2010; Boltong et al., 2014; Turcott et al., 2016; Schalk et al., 2018; Riantiningtyas, Valenti et al., 2023). To accurately measure taste responsiveness, suprathreshold measurements are needed (Keast & Roper 2007), because they are faster, less demanding, and more discriminatory than threshold measurements (Bartoshuk et al., 1994; Tepper, 2008; Tepper et al., 2017). Moreover, suprathreshold measurements reflect the perception of intensity in the "real world" (Bartoshuk, 2000). However, few studies applied this approach in the oncology field (Trant et al., 1982; Mulder et al., 1983; Riantiningtyas, Valenti et al., 2023). Less commonly used are also food models (Trant et al., 1982; Bossola et al., 2007; de Vries, Winkles, et al., 2018). This method consists of a food matrix (e.g. a juice, a legume cream) designed to assess variations in intensity perception and hedonic responses by modulating specific sensations. Food models offer higher ecological validity by considering more complex interaction of factors (Lippi et al., 2024).

Instead, spatial (regional) taste perception focuses on evaluating taste sensitivity in specific areas of the tongue or oral mucosa. This is typically done (Steinbach et al., 2009; Steinbach et al., 2012; Ijpma, Renken, Gietema et al., 2016; Ijpma et al., 2017; de Vries, Winkles, et al., 2018; de Vries et al., 2019; Postma et al., 2020; Kaizu et al., 2021) using filter paper strips or disks impregnated with taste solutions of varying concentrations, applied directly to different regions of the

tongue. These tools are convenient, portable, and easier to use in a clinical setting. However, their effectiveness can be affected by poor oral conditions, such as reduced salivary flow and oral mucositis (Pugnaloni et al., 2020), common conditions in cancer patients, and regional variability in taste sensitivity depending on the area of application (Feeney & Hayes, 2014).

Lastly, electrogustometry consists of application of a weak electric oral stimulus in a specific area of the tongue that produces a taste (Ellegard et al., 2007; Ikeda et al., 2005) in order to assess its detection (Mahmoud et al., 2011). However, electrical stimuli rarely produce the classic taste sensations of sweet, sour, bitter, and salty. Instead, they are more frequently described as nonspecific sensations, such as sparkling, metallic, or buzzing (Murphy et al., 1995).

In the assessment of olfactory function, the most used measurements are based on detection and recognition thresholds, respectively the lowest concentration of an odorant that a person can perceive and the minimum concentration at which the specific odor can be correctly identified (Epstein & Barasch, 2010). The most widely used tool in oncology field is the Sniffin'Sticks test (Steinbach et al., 2012; Ijpma et al., 2017; de Vries, Winkles, et al., 2018; de Vries et al., 2019) that allow the evaluation of threshold, discrimination and identification (Kobal et al., 1996; Hummel et al., 1997). A more simplified approach is represented by the "scratch and sniff" tests, which consist of cards impregnated with specific odors. Upon scratching, the odor is released, and participants are asked to identify it. Although this method does not assess detection thresholds, it provides a practical and rapid way to assess odor recognition and has been used in both clinical and research settings (Doty et al., 1984; Hoffman et al., 2009; Manesse et al., 2021).

Quantitative results of these methods facilitate comparison of perception capabilities among populations, but they do not reflect the "real world" eating experience (Boltong & Keast, 2012) as they do not capture dimensions of taste

important to patients such as food enjoyment (McGowan, 2008), or hedonic changes (Boltong et al, 2012). These aspects, which may represent early signs of chemosensory changes perceived by patients, are best explored through qualitative or mixed-method approaches. Psychophysical methods are considered more effective for accurately assessing changes in chemosensory acuity, such as ageusia, hypogeusia, and hypergeusia (Epstein & Barasch, 2010; Kano & Kanda, 2013). In contrast, self-reported measures are more suitable for capturing qualitative disturbances like phantogeusia, parageusia, or cacogeusia (Kano & Kanda, 2013), as well as other phantosmia, parosmia, and other aspects of the chemosensory experience that are meaningful to patients (Bernhardson et al., 2008; McGowan, 2008). These types of disturbances are typically diagnosed based on patients' own verbal reports and cannot be reliably assessed through quantitative testing (Payne et al., 2023). Consequently, the use of self-reported questionnaires and qualitative methods are recommended to capture the subjective experience (Bernhardson et al., 2008; Brisbois et al., 2011; Wismer, 2008).

1.4 Impact of chemotherapy and chemosensory alterations on food experience of cancer patients

Anticancer treatment and particularly chemosensory alterations can strongly affect the daily eating experience, affecting appetite, food preferences, food intake and leading food avoidance or not appropriate coping strategies which, over time, can contribute to nutritional imbalances and malnutrition, whether by deficiency (undernutrition) or excess (overnutrition) (Holmes, 1993; Hong et al., 2009; Sherry et al., 2002; Drareni et al., 2019; Nolden, Hwang, et al., 2019; Spotten et al., 2017; Speck et al., 2013).

In addition to nutritional challenges, chemosensory changes can also affect broader aspects of daily life. For example, they can interfere with practical routines related to shopping, cooking, or meal planning, and impact social functioning by disrupting food-related rituals, such as eating with family and friends (Bernhardson et al., 2007, 2009; Rehwaldt et al., 2009). These experiences can contribute to emotional distress and social isolation, further reducing quality of life.

1.4.1 Impact on food preferences

Food preferences can be defined as affective evaluations of foods based primarily on sensory properties, reflecting the degree of liking and disliking of specific foods. However, preference does not necessarily mean liking. Usually it refers to selection/comparison of one item over another and can reflect contextual influences on food choice independent of liking (Understanding Consumers - Prescott, 2023). Accordingly, food preferences should be considered within the broader process of food choice, which represents the outcome of interactions between sensory evaluations and a range of non-sensory factors including expectations and attitude (Rozin, 1996), health-related information and claims (Vickers, 1993), price (Vickers, 1993), ethical concerns (Sparks et al., 1995), and mood (Rogers, 1996).

In the oncology context, this interaction between sensory and non-sensory factors in food choice is further complicated by treatment-related chemosensory changes and concomitant physical and psychological symptoms. It has long been known that taste and smell are important drivers for individuals' food preferences (Drewnowski, 1997). Therefore, an alteration of these senses during an anticancer treatment might reduce food palatability, limiting food choices and reducing the variety of the diet (Kim et al., 2020; Kourouniotis et al. 2016). However, it is still unclear when this condition occurs and how long it persists.

Previous research on food preferences among cancer patients has produced conflicting results, partly due to differences in treatment phases and the heterogeneity of the populations studied (de Vries et al., 2019; Postma et al., 2020). Further complicating the picture are the different cancer types, treatment modalities, and methodologies employed across studies (Enriquez-Fernández et al., 2019). While some studies have observed significant changes in preferences over the course of treatment, individual variability prevents the identification of consistent patterns (IJpma et al., 2017).

Despite these inconsistencies, several studies converge on the idea that cancer treatment influences not only the sensory experience of food, but also the types of foods consumed. These changes are often influenced by factors such as fatigue, decreased appetite, and nausea, which lead to selective preferences or aversions and significant dietary changes (Coa et al., 2015). However, as highlighted in a recent scoping review (Nolden, Hwang et al., 2019) mixed results are often obtained, due to the lack of association between sensory tests and assessment of food preferences.

In the oncology field, one of the most used tools (de Vries, Winkels et al., 2018; Postma et al., 2020;) for assessing food preferences is the Macronutrient and Taste Preference Ranking Task (de Bruijn et al., 2017). This method consists of images of products from four macronutrient categories (high-carbohydrate, high-fat, high-protein, and low-energy) including both sweet and salty products. Participants are asked to rank four products according to their desire to consume them. These rankings are used to assess relative preferences for the four macronutrient categories and for the two tastes, sweet and salty. Another method used by Ijpma, Renken, Gietema et al. (2016; 2017) is a similar method to the previously described tool. In particular, the preference is expressed for pictures of snack products varying in taste (sweet/savory) and in nutritional content

(fat/protein). The relative food preference is measured as the frequency of choice for each food category. Even Kim et al. (2020) used a ranking method in which 57 dishes grouped in 6 were ranked according to preference.

Food acceptance is frequently assessed through measures of hedonic liking, which primarily capture sensory pleasure that has been widely used to predict food choices and intake. Products that receive higher liking scores are typically selected more frequently than those with lower scores, and products disliked are not consumed (De Graaf et al., 2005; Keller et al., 2022). Many studies on cancer patients measured the hedonic liking through 9-point hedonic scale from “like extremely” (9) to “dislike extremely” (1) (Peryam & Pilgrim, 1957; Boltong et al., 2014), or through a 10-point hedonic scale from “like extremely” (10) to “dislike extremely” (1) (Bossola et al., 2007).

However, quantitative tools such as preference ratings and hedonic scales, while useful for capturing structured responses, may not fully reflect the complex, personal, and dynamic experience of food during cancer treatment. Several studies (Bernhardson et al., 2007; Adamczyk et al., 2024; Carlucci Palazzo et al., 2019; de Vries et al., 2016; Álvarez-Camacho et al., 2016; Boltong et al., 2012; Speck et al., 2013; van den Brink et al, 2022) have therefore adopted qualitative methodologies, such as semi-structured interviews, repertory grid interviews, or focus groups, to gain a deeper understanding of how patients perceive and relate to food in their daily lives. These approaches allow researchers to explore individual narratives, including patients' emotions, memories, beliefs, and contextual challenges related to food and eating. Through interviews, patients often report specific aversions or cravings, describe how their food preferences evolve during treatment, or explain how symptoms such as nausea, fatigue, dry mouth, or taste distortions influence their eating behaviors and food preferences. Furthermore, qualitative data often

capture psychosocial dimensions, such as frustration, sadness, or social isolation, associated with the inability to enjoy meals as before.

Taste changes and the emergence of food aversions can be a confusing and distressing experience for cancer patients, particularly when previously enjoyed foods are suddenly rejected. This sense of disorientation may arise from the unpredictability of chemosensory changes, which disrupts established eating habits and familiar routines. As a result, patients often find themselves experiencing shifts in food preferences, developing new aversions to previously preferred foods or cravings, diminished ability to enjoy meals and experimenting with different flavors and textures in an attempt to adapt. Food preferences during cancer treatment tend to vary, and no clear or systematic patterns have been identified. This is largely because most studies do not correlate objective assessments of chemosensory function with affective measures such as food liking, preferences, or eating behaviors. Furthermore, patients often experience a multitude of co-occurring symptoms such as nausea, fatigue, dry mouth, mucositis, making it difficult to identify a single trigger. This complexity contributes to the heterogeneity and variability of results reported in the literature (Nolden, Hwang et al., 2019). Furthermore, research has focused primarily on the nutritional content of sweet and salty foods, failing to consider other sensory properties such as texture, odor, flavor, acidity, bitterness, or the presence of spices, which play an important role in food preference and intake (McCrickerd & Forde, 2016).

In their scoping review, Nolden, Hwang et al. (2019) examined studies that measured both chemosensory function and behaviors including preference and food intake. They found that, where a reduction in sweet taste sensitivity was observed, this was often associated with a decreased intake of macronutrients and appetite.

Further results of studies on food preferences in cancer patients undergoing antineoplastic therapy showed that in the presence of reduced taste function, there was a lower preference for high-protein foods and a higher preference for lower energy foods (Postma et al., 2020; De Vries, Winkels et al., 2018). Indeed, it is known that cancer patients have difficulties maintaining an adequate protein intake (Del Fabbro et al., 2017) and that high-protein foods like meat are often reported to be aversive during chemotherapy (Boltong & Keast, 2012; Mattes et al., 1987), because meat is considered too bitter or metallic (Dewys & Walters, 1975; Ijpma et al., 2015).

Moreover, patients undergoing chemotherapy were found to prefer mild and soft dishes over fried/oily/flavorful/spicy dishes (Kim et al., 2020; de Vries et al., 2016). In fact, a study by de Vries, Winkels et al. (2018) showed that during and immediately after therapy the liking for high-fat products was reduced. The most preferred foods in these studies were porridge, soft bread, boiled eggs, vegetable juices, blanched vegetables, soft fruits, mild soup, yogurt, while the least favorite were cereals, fried eggs, soy milk, fried potato, and spicy foods. However, other patients instead showed a countertrend, reporting a need for more stronger flavors, which was reflected by addition of condiments like sugar, seasonings and salt or by choosing products with distinctive flavor as umami flavors foods (e.g. soups, tastier cheese, sausage) or salty foods (e.g. chips, peanuts, crackers) (de Vries et al., 2016; Sørensen et al., 2012). Thus, sometimes patients experienced periodic cravings or dislike for these foods (Sørensen et al., 2012).

Sometimes patients described cravings for specific tastes. In a study of Sørensen et al. (2012) patients describe a desire for sour tastes (e.g. certain fruits, pickled vegetables, cola, yogurt, citrus flavored drinks, sour side dishes). On the other hand, sour tastes could be very unpleasant for patients suffering from xerostomia or oral infections (Müller et al., 2023).

Patients with swallowing problems or dysphagia due to the type of cancer (head and neck, esophagogastric) or due to treatment (head and neck radiation therapy), or patients with dry mouth or mucositis, report an increased preference for liquid/easy-to-eat foods, such as soups or juices with an avoidance for bread and meat, because they could not easily pass the esophagus (de Vries et al., 2016). However, in contrast to this trend, Sørensen et al., (2012) reported that some patients deliberately choose more challenging foods, such as open sandwiches instead of soup, as a way to reestablish a sense of normalcy and reconnect with their usual eating habits. For many, solid foods were perceived as more "normal" or "healthy," and despite chewing or swallowing difficulties, the sensory experience of textures (e.g., crunchy or crispy elements) was highly valued. Patients who consumed predominantly soft or liquid diets often expressed a sense of loss associated with the absence of varied textures and the physical act of chewing. In addition, as reported from the same study, patients suffering from nausea and vomiting typically choose foods that they perceive as stomach settling, as drier foods such as crackers (Sørensen et al., 2012). Chemotherapy, especially those platinum-based, induced an enhanced sensitivity to cold, which resulted in a preference for warm foods or an urge to put all foods in the microwave before consumption (de Vries et al., 2016).

Even sweet foods appear less preferred during therapy in many studies on several cancer populations (de Vries, Winkels et al., 2018, Kim et al., 2020; van den Brink et al., 2022; Postma et al., 2022); however, studies on breast cancer patients (Speck et al., 2013; Carlucci Palazzo et al.,2019) found that these patients tend to prefer and desire sweet foods, such as candy, cookies or sweetened beverages, constituting a greater percentage of the daily caloric intake (Trant et al., 1982).

Besides preference for more or less flavorful/sweet/soft/hot foods, patients sometimes need to choose or avoid specific food, for instance bitter and/or

metallic taste foods as chocolate, tea, wine and coffee (Boakes et al., 1993; Boltong & Keast, 2012; Holmes, 1993; Steinbach et al., 2009), or sour foods as juices and citrus or sweet-sour fruits (Boltong & Keast, 2012; Kim et al., 2020).

1.4.2 Impact on emotions elicited by foods

As mentioned, food acceptance is often assessed in terms of hedonic liking. However, food choice is influenced by more than just liking; a variety of factors contribute to why a product is selected. Emotions elicited by food, for instance, can strongly influence the decision-making process (Jiang et al., 2014), playing a key role in food liking and choices (Cardello et al., 2012; Jaeger et al., 2022; Ng et al., 2013, Spinelli, 2021), suggesting that both sensory and emotional factors need to be considered to fully understand food preferences in cancer patients (Meiselman 2021). This is because food is more than just a source of nutrients (Prinyawiwatkul, 2023). Indeed, King (2016) claimed that food "*nourishes the body and soul*". Therefore, while food delivers nutrients to the body, there are other elements, such as enjoyment and pleasure, associated with food. Macht (2008) uncovered a relationship between eating and emotions, suggesting, as an example, that emotions regulate eating, and eating regulates emotions. Currently, there is no universally accepted definition of emotions (Frijda, 2008.; Scherer, 2005). However, there is widespread consensus that emotions are multifaceted and consist of various components, including physiological arousal, motivation, expressive motor behavior, action tendencies, and subjective experience (Scherer, 2005). Emotions can be described as appraisal-driven processes, in which the triggering event and its consequences must be relevant to the organism's primary concerns. Emotions are generally considered complex personal experiences that involve simultaneous changes in cognition, behavior, expression, and physiological function. The cognitive appraisal of a stimulus allows individuals to evaluate it as positive or

negative in valence. This is accompanied by physiological arousal through the activation of the central and autonomic nervous systems and hormonal responses, which prepare the body to respond to the perceived event. These traits distinguish emotions from other affective phenomena, such as moods, attitudes, preferences, affective dispositions, and interpersonal positions (Scherer, 2005).

Furthermore, emotions, especially when combined with psychological traits or individual differences, have been shown to significantly influence food consumption (Canetti et al., 2002). For instance, negative emotions, such as disgust, are commonly associated with food avoidance, while positive emotions tend to promote food acceptance and increased intake (Randler et al., 2017).

In recent years, there has been growing interest in understanding how emotions influence food-related experiences, particularly in the fields of sensory and consumer science (Prescott, 2017). Consequently, a wide variety of methodologies have been developed to assess emotional responses to food, ranging from verbal measures with questionnaires to psychophysiological measures and applied neuroscience techniques (Spinelli & Monteleone, 2018).

Verbal methods, such as self-report questionnaires, remain the most commonly used tools and the only one available to measure subjective feelings (Barrett et al., 2004). These often include emotional terms, either as single words or complete sentences, to help participants describe their emotional reactions to a given food stimulus. For example, the EmoSemio protocol (Spinelli et al., 2014) uses complete sentences adapted to specific cultural and linguistic contexts to reduce ambiguity and improve response accuracy.

To analyze and interpret data collected through these approaches, researchers often use factor analysis or principal components analysis, which consistently reveal two fundamental dimensions underlying emotional responses: valence (pleasantness) and arousal (level of activation) (Russell, 1980; Posner et al., 2005 Watson & Tellegen, 1985). One of the most influential models based on these dimensions is the Circumplex Model of Affect developed by Russell (1980) (Figure 1), in which emotions are positioned along a circular plane based on their levels of valence, which ranges from pleasant to unpleasant, and arousal, which reflects the degree of physiological and psychological activation (Russell & Barret 1999). High-arousal emotions can be either positive, such as excitement or joy, or negative, such as anger or disgust. Conversely, low-arousal emotions include positive emotions such as relaxation and negative ones such as boredom or sadness.

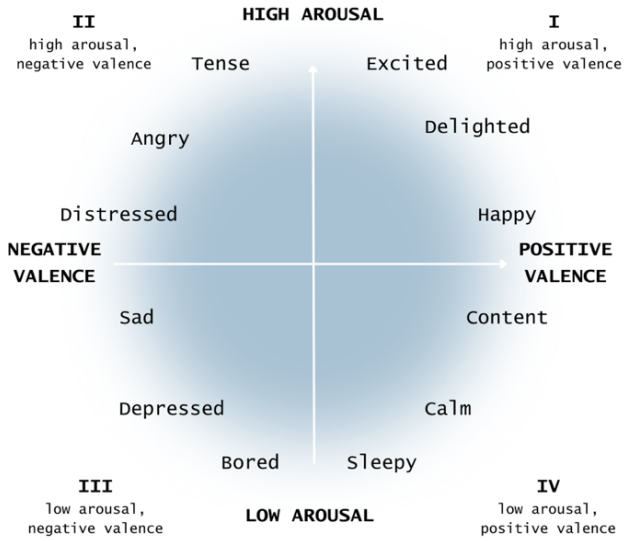


Figure 1 Circumplex model of affect.

Although previous studies (Boltong et al., 2012; de Vries, Boesveldt, et al., 2018; de Vries, Winkels, et al., 2018; Kim et al., 2020; Ponticelli et al., 2017; Postma et al., 2020; Speck et al., 2013) have explored the potential causes of chemosensory alterations and their impact on preferences, nutritional status, and quality of life in

cancer patients, the emotions elicited by food remain largely unexplored. While emotions associated with food have been studied in vulnerable people such as children, (Aguiar-Bloemer & Diez-Garcia, 2018; Gallo et al., 2017; Sick et al., 2020) they have yet to be investigated in cancer patients. This gap leaves a critical area of understanding unaddressed, especially considering that cancer patients face psychological and physical challenges during treatment (Metz et al., 2005; Tang et al., 2023).

1.4.3 Impact on attitude towards foods

While emotional responses represent transient reactions that can significantly influence immediate food-related decisions, more stable cognitive-affective constructs, such as attitudes, also play a crucial role in shaping food preferences and long-term dietary behaviors. Despite their recognized importance, the precise definition and conceptual boundaries of attitudes have long been debated in the field of social psychology (Eagly & Chaiken, 1993; Zanna & Rempel, 1988). Attitudes can be defined as a psychological inclination that is expressed by evaluating a specific entity with a certain degree of favor and disfavor (Eagly & Chaiken, 1993). They are generally conceived as multidimensional constructs (Hsu, 2020) comprising affective (emotional), behavioral (action-oriented), and cognitive (belief-based) components, each of which may contribute differently depending on the context (Fazio & Olson, 2003).

In the context of eating behavior, attitudes have been shown to significantly influence food choices, often serving as predictors of both food preferences and consumption patterns.

Various methods have been developed to assess food-related attitudes, ranging from structured questionnaires to in-depth interviews. Among the used tools is the Food Choice Questionnaire (FCQ), developed by Steptoe et al. (1995), which

assesses the importance of various motivational dimensions, such as health, convenience, sensory appeal, natural content, and price, in determining food choices. This instrument has been widely applied to several populations to explore attitudinal factors underlying eating behaviors. Furthermore, the Health and Taste Attitude Scales (HTAS) (Roininen et al., 1999) measure the importance of health and taste aspects of foods in the food choice process. In particular, this tool includes subdimensions such as Pleasure and Using of food as a reward, which capture the hedonic and motivational aspects of eating behavior. Instead, the Dutch Eating Behavior Questionnaire (DEBQ), for instance, has been used to identify emotional, restrained, and external eating tendencies (Van Strien et al., 1986), highlighting how attitudes may manifest in observable dietary patterns. Finally, the Food Involvement Scale (FIS) by Bell and Marshall (2003) was developed to assess an individual's level of involvement with food. This scale considers both cognitive and behavioral dimensions, such as interest in food preparation, awareness of ingredients, and attention to food decisions. Food involvement can be an important mediator of a wide range of eating behaviors. Because of this potential mediation effect, it is recommended that food involvement, and reward-related attitudes, as captured by the HTAS, are considered when conducting food sensory testing and eating behavior research (Bell & Marshall, 2003).

Eating behavior is strongly influenced by reward-related mechanisms. Food reward refers to the motivational and hedonic value attributed to foods, encompassing both the pleasure derived from eating and the motivation to obtain food (Berridge & Kringelbach, 2008). These reward processes interact closely with attitudes and emotions, guiding food choices beyond nutritional or health considerations. Foods, especially those which are highly palatable (sweet, salty, and fat), can enhance mood through activation of brain reward pathways in a manner similar to other addictive substances (Geliebter & Aversa, 2003; Meguid et al., 2000; Saper et al.,

2002; Shimura et al., 2002). In other words, food can be used for 'self-medicating' purposes that sometimes exceed basic energy requirements (Davis et al., 2004). In cancer patients, treatment-induced chemosensory alterations and emotional distress can modulate the reward value of foods, contributing to changes in appetite, cravings, and overall eating behavior (Speck et al., 2013; Boltong & Keast, 2012; de Vries, Winkels et al., 2018).

In cancer patients undergoing treatment, studies report a shift toward healthier nutritional attitudes, with an increasing interest in consuming healthier foods (Metz et al., 2005; Tang et al., 2022; Pedersini et al., 2021) given the belief that diet and nutrition influence their cancer's response to conventional therapy. On the other hand, some patients need more support and counselling to adopt a healthy lifestyle and dietary trends with the aim of improving rehabilitation and general health during the years following cancer diagnosis and treatment. It has been shown that adjuvant treatment in breast cancer is associated with weight gain and hormonal changes increasing the risk of other conditions, such as cardiovascular disease, diabetes and osteoporosis (Rock & Demark-Wahnefried, 2002). Many women with breast cancer report ambivalent attitudes toward food, in which the desire to eat healthily coexists with episodes of emotional eating or food cravings, especially during chemotherapy. In this context, food cravings, especially for sweet and high-energy foods, are frequently reported. A qualitative study revealed that women who gained weight during chemotherapy often described a loss of control overeating, increased appetite, and a greater tendency to seek out foods that provide emotional comfort.

These observations highlight that nutritional attitudes in this population can be complex, conflicting, and strongly influenced by psychological factors. These conflicting attitudes, combined with emotional responses to food and sensory alterations experienced during cancer treatment, ultimately influence not only what

patients prefer, but also what they actually eat. Therefore, it is essential to examine how these factors translate into observable eating habits during and after treatment.

1.4.4 Impact on eating habits

Eating habits represent the behavioral outcome of repeated food choices, which are influenced by underlying food preferences but also shaped by situational, social, and health-related constraints. Eating habits are defined as "conscious, collective and repetitive behaviors, which lead people to select, consume and use certain foods or diets, in response to social and cultural influences" (FEN Eating Habits, 2019). These behaviors include not only what individuals eat, but also how, when, where, and with whom it is consumed. Eating habits include both routine patterns, such as meals' times and frequency, as well as more behaviors related to food preparation, preferences, and social context. In the oncology setting, eating habits can undergo significant changes due to both physiological changes and psychosocial challenges associated with the disease and its treatment (Pedersini et al., 2021). To evaluate changes in eating habits during cancer treatment, researchers have employed a variety of both quantitative and qualitative methods. Among the most commonly used tools in oncology (Pedersini et al., 2021; Ijpma, Renken, Gietema et al., 2016; Lambert et al., 2019; Sánchez-Lara et al., 2010) is the Food Frequency Questionnaire (Willett et al., 1985), which consists of a list of foods and beverages with response categories to indicate usual frequency over the period queried. Another applied instrument is the 24-hour dietary recall, in which patients report all foods and beverages consumed in the previous day. This method provides detailed data on intake. Complementing this, food diaries (Ovesen et al., 1991; Hutton et al, 2007), in which individuals record their food intake over several

days, offer insights into meal frequency, portion sizes, and contextual eating patterns.

In pediatric oncology, specific tools such as the Eating Behavior Questionnaire have been used (Fistikçi and Bilsin Kocamaz, 2024) to assess not only food intake but also eating-related behaviors and difficulties.

In addition to structured questionnaires, qualitative methods, including semi-structured interviews, are increasingly used (Boltong et al., 2012; de Vries et al., 2016) to explore the subjective experiences behind eating behavior.

Together, these tools provide a multidimensional understanding of how eating habits are altered during cancer care, capturing not only nutrient intake but also behavioral, emotional, and contextual components of food consumption.

Evidence suggests there is a link between cancer and certain types of altered eating behaviors, such as orthorexia, food cravings, and food addiction (Aslan et al., 2020; Martinkova et al. 2011; Bobonis Babilonia et al., 2020; Shams-White et al., 2016; Cohen et al. 2018), but even loss of appetite, eating less, reduction in desire for food and anorexia (Turcott et al., 2016; Zabernigg et al., 2010; Boltong et al., 2012; 2014; McGreevy et al., 2014). In particular, the presence of chemosensory alterations, although not considered life-threatening, has been identified to have a profound impact on eating habits (Risso et al., 2020). Moreover, Pedersini et al. (2021) found that cancer patients nowadays are highly motivated and inclined to change their eating habits towards a healthier direction in order to prevent weight increase and potentially improve treatment efficacy. Pedersini et al. (2021) found also a significant reduction of intake of pasta or rice, bread, red meat, fat salami, snack, added sugar, milk, soft drinks, alcoholic beverages, and added condiments (butter and oil) was found. However, a persistent condition with chemosensory alteration and other related side effects could lead to serious complications in terms of health consequences, generated from shifts towards unhealthy eating

habits (Risso et al., 2020). Indeed, it is known that stress states favor craving episodes involving sweetened foods and drinks (Speck et al., 2013) although sometimes patients try to reconcile the desire for sweets with a healthy diet (Carlucci Palazzo et al., 2019). However, the evidence in the literature remains somewhat controversial. While some patients actually adopt healthier behaviors, others, especially those with persistent chemosensory changes and related side effects, may develop compensatory eating patterns characterized by a preference for stronger or more intense flavors, achieved through the addition of condiments, like sugar, seasonings and salt (de Vries et al., 2016; Adamczyk et al., 2024).

Another frequently reported change concerns meal preparation: many patients avoid cooking due to a heightened sensitivity to specific food odors, which are often perceived as aversive (de Vries et al., 2016; Speck et al., 2013; Bernhardson et al., 2009). This can lead to increased reliance on prepackaged or cold foods, such as sushi or sandwich (Sørensen et al., 2012), and reduced participation in the social and pleasurable aspects of cooking. In addition to reduced food intake, some patients report intentionally avoiding meals or social gatherings due to discomfort, embarrassment, or a decreased appetite. These behaviors can reinforce isolation and disrupt previously established habits not only in terms of eating (Bernhardson et al., 2009; de Vries et al., 2016) but even in terms of household roles (e.g. partners that take over grocery shopping and cooking) and social interactions (e.g. not eating out or inviting friends for dinner) (Bernhardson et al., 2007; Gamper et al., 2012).

1.4.5 Impact on nutritional status

The impact of cancer and its treatments on chemosensory perception, food preferences, emotional responses to food, and eating habits inevitably extends to nutritional status.

It has been demonstrated that cancer patients with chemosensory changes are more vulnerable to nutritional unbalance, including weight loss or gain, or severe malnutrition.

Malnutrition, when detected by different screening or other tools of varying complexity, is frequent and has been reported to be present in 20–87% of cancer patients, depending on tumor entity, stage of disease and clinical settings (Dewys et al., 1980; Hosseini et al., 2025). These prevalence estimates vary markedly by cancer site: higher rates of malnutrition have been reported in patients with pancreatic (80–85%), gastric (65–85%), head and neck (65–75%), and lung cancers (45–60%), while lower but still substantial rates are observed in other solid cancers such as colorectal cancers (30–60%) (Ghias et al., 2023; Hosseini et al., 2025). Among genitourinary cancers, an increased nutritional risk has been reported in 28.6–44.8% of patients with urological cancers (Planas et al., 2016). On the other hand, the highest percentage (>70%) of normal nutrition status is related to breast cancers (Hosseini et al., 2025).

When interpreting nutritional alterations in cancer patients, it is important to consider the diversity of cancer treatments. Chemotherapy is often administered in combination with other therapies, including targeted therapies and immunotherapy. These new treatments are associated with distinct toxicity profiles, such as endocrine and metabolic alterations, which are known to impact nutritional status and health-related quality of life (Michot et al., 2016; Ramos-Casals et al., 2020). However, the specific contribution of chemotherapy-combined treatments, such as immunotherapy, to sensory and nutritional alterations is not clearly distinguished from that of chemotherapy in the current literature. This lack of differentiation may partly explain the heterogeneity of nutritional outcomes reported across studies.

Loss of appetite, reduced caloric intake, aversion to certain foods, and reduced dietary variety can lead to an imbalance between metabolic needs and actual nutrient availability. The state of chronic nutritional deficiency can progress to cancer cachexia, defined as a disorder characterized by weight loss with specific losses of skeletal muscle and adipose tissue. Cachexia is caused by a variable combination of reduced dietary intake and metabolic alterations, including high energy expenditure, excessive catabolism, and inflammation (Baracos et al., 2018). Conversely, weight gain during chemotherapy for breast cancer has been reported (Demark-Wahnefried et al., 1993) due to hormonal imbalances, a sedentary lifestyle, stress, emotional instability, or episodes of emotional eating (da Silva & dos Santos, 2010; Carlucci Palazzo et al., 2019). Changes in dietary habits, such as increasing salt intake to enhance flavor, consuming sweets, or conversely abstaining from food, can negatively impact nutritional status and potentially increase the risk of metabolic and cardiovascular diseases (Sergi et al., 2017; Xue et al., 2020). These nutritional imbalances are associated with a wide range of morbidities, and they can exacerbate the toxicity of cancer treatments and increase the risk of clinical complications, ultimately compromising therapeutic efficacy and clinical outcomes for patients.

In the oncological setting nutritional screening is necessary even when malnutrition is not clearly present, as the impact of early and adequate nutritional intervention on the quality of life of cancer patients and on short-term outcomes by reducing the complications has been demonstrated (Marín Caro et al., 2007). Nutritional screening must be efficient, brief, and inexpensive, with high sensitivity and good specificity (Arends et al., 2017; Sealy et al., 2016). The tools used for this purpose include data obtained from medical history, dietary intake, biochemical markers, and, above all, anthropometric data (Koom et al., 2012).

Among the most widely used tools in research on cancer patients with chemosensory alterations is the Body Mass Index (BMI). Although BMI is a widely used indicator due to its simplicity, it has significant limitations in oncology, as it does not distinguish between muscle mass and fat mass (Strulov Shachar & Williams, 2017) and may not reflect recent changes in nutritional status or body composition, especially in the presence of conditions such as cachexia or sarcopenia (loss of muscle mass and function), which can occur even in patients with a normal or high BMI. This condition, often referred to as the obesity paradox (Lee et al., 2022), is particularly common among cancer patients and has been associated with lower treatment tolerance, greater toxicity, reduced physical function, and a worse overall prognosis.

To address this issue, body composition measurement tools such as bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), or magnetic resonance imaging (MRI) are tools that allow for detailed quantification of fat mass, lean mass, and fluid status, providing a clearer picture of a patient's nutritional status. This is particularly relevant in cancer patients with chemosensory changes, in whom a reduced intake of protein- or fat-rich foods, can lead to muscle loss despite a stable body weight. Identifying this "hidden malnutrition" through body composition analysis is crucial for implementing timely nutritional interventions and preventing further deterioration in quality of life.

Additionally, specific and validated nutritional screening tools have been developed, recommended by international guidelines, including those of the European Society for Clinical Nutrition and Metabolism (ESPEN), the Academy of Nutrition and Dietetics, and the American Society for Parenteral and Enteral Nutrition (ASPEN). These tools are intended not only for initial assessment at diagnosis, but also for periodic reassessment during and after treatment. Among

the tools used is the Nutritional Risk Screening (NRS-2002) (Kondrup et al., 2003), developed for use in hospitalized patients, which rapidly assesses recent weight loss, reduced dietary intake, and disease severity. The Malnutrition Screening Tool (MST) (Ferguson et al., 1999), on the other hand, is based on self-reported unintentional weight loss and appetite loss. The Patient-Generated Subjective Global Assessment (PG-SGA) (Ferguson, 2003) is considered the gold standard for nutritional assessment in oncology. This tool includes both patient- and physician-reported components, including anthropometric data, dietary intake, symptoms, functional status, and the impact of disease and treatment. It not only identifies nutritional risk but also helps guide and monitor nutritional interventions over time. The Mini Nutritional Assessment (MNA) (Vellas et al., 1999) is a tool developed in older populations, and it includes 18 items grouped into four assessment categories (anthropometry, general, diet and subjective assessment) useful to identify the malnutrition risk. Finally, the Malnutrition Universal Screening Tool (MUST) used by Al-Amouri & Badrasawi (2024) is a five-step screening tool that considers BMI, unintentional weight loss, and the presence of an acute illness affecting food intake. Although less detailed than the PG-SGA, it is easy to administer and useful for regular monitoring, especially when a rapid assessment is needed.

However, body composition assessment is considered a more accurate and clinically relevant method for assessing nutritional status in cancer patients (Brown et al., 2018; Strulov Shachar & Williams, 2017), particularly those undergoing treatments that affect metabolism and muscle mass.

1.4.6 Impact on quality of life

Quality of life (QoL) is a multidimensional construct that includes physical, psychological, emotional, and social well-being and is crucial during cancer

treatment. Indeed, side effects of cancer treatment such as fatigue, pain, nausea, and sensory alterations often lead to a significant deterioration in quality of life.

In recent decades, despite significant advances in early diagnosis and cancer treatment that have led to increased patient survival and improved treatment response, side effects persist as a major source of discomfort for cancer patients during and after treatment. Among these, chemosensory alterations, while not directly life-threatening, profoundly impact the patient's psychological, social, and physical well-being. Taste and smell, in fact, are closely linked not only to the pleasure of food, but also to social rituals, daily habits, and emotions, and their impairment can significantly reduce the quality of the eating experience and, consequently, the overall quality of life (Lewandowska et al., 2020; Dehkordi et al., 2009; Ponticelli et al., 2017; Prieto-Callejero et al., 2020). This is because, as discussed in previous sections, patients often begin to avoid social situations (Bernhardson et al., 2007; Gamper et al., 2012) involving food, such as meals shared with family or friends, due to embarrassment, loss of appetite, discomfort caused by altered taste and smell perceptions, or the loss of pleasure from food. In some cases, the inability to enjoy food as before can trigger frustration, sadness, or anxiety, particularly when eating is reduced to a purely functional act, sustained only by psychological resilience rather than pleasure or appetite (Ejder et al., 2023; Sørensen et al., 2012; Bernhardson et al., 2007; Wickham et al., 1999).

Given the multifaceted nature of quality of life and its central role in cancer care, several validated tools have been developed to assess it. The widely used is the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30), a cancer-specific tool that evaluates physical functioning, role functioning, emotional well-being, and symptom burden, including appetite loss and nausea (Aaronson et al., 1993). This questionnaire was adapted in several versions based on different pathologies (Greimel et al., 2006;

Sprangers et al., 1996; Taphoorn et al., 2010), different types of treatment's side effects, and symptoms with a negative effect on patients' food behavior and nutritional status. However, because general QoL instruments may not fully capture the specific impact of eating disorders and sensory changes, the Food-Related Quality of Life (FR-QoL) questionnaire (Mercier et al., 2021; Drareni et al., 2025) was developed to assess the influence of food and eating difficulties on patients' emotional and social well-being. The FR-QoL explores 9 factors in the food-related quality of life, as cooking enjoyment, attention to nutrition, attention to meal quality and variety, adaptive dietary practice, hedonic appreciation, sensory alteration, meal experience, altered digestion, dining and commensality.

Several studies have examined the association between chemosensory alterations and quality of life in cancer patients, highlighting the multidimensional impact of these changes. While Kaizu et al., 2021 report no association between chemosensory alterations and quality of life, some studies (Ponticelli et al., 2017; Brisbois et al., 2011; Hutton et al., 2007) showed that patients who reported alterations in taste and smell perception reported a worse quality of life, and social, emotional, role functioning, nausea-vomiting episodes, and lower appetite during, shortly after and 6 months after the treatment.

These findings emphasize the need for early identification and management of sensory alterations during cancer therapy, allowing clinicians to offer timely interventions, such as combined nutritional strategies and psychological support, which can alleviate symptoms, prevent malnutrition and promote pleasure of eating emphasizing a better quality of life (Tueros & Uriarte, 2018). Therefore, a more holistic and patient-centered approach to cancer therapy must consider the sensory and psychosocial dimensions of nutrition, in addition to clinical outcomes.

1.5 Individual differences in food experience

Despite the widespread impact of cancer therapies on eating behavior and quality of life, not all patients are affected equally. When studying the eating experience of cancer patients, it is therefore necessary to consider interindividual variability (Köster, 2009; Monteleone et al. 2017). This variability can be attributed to a combination of biological and psychological factors that are known to affect taste and smell sensitivity and food preferences and thus may have an impact on altered perception and preferences during chemotherapy (Spinelli, Mini et al., 2021). Among these factors, there is the different response of individuals to bitterness of 6-n-propylthiouracil (PROP), which reflects the oral responsiveness and is considered as an index of oral acuity (Tepper et al., 2014; Dinnella et al, 2018). Beyond perceptive factors, psychological traits have been found to affect food behaviors and taste responsiveness. The following paragraphs will explore in greater detail the role of personality traits and chemosensory perception in food experience.

1.5.1 Personality traits and their impact on perception, food preferences and behaviors

As reported by APA Dictionary of Psychology (2018), a psychological trait represents a relatively stable, consistent, and enduring internal characteristic that is deduced from a pattern of an individual's behaviors, attitudes, feelings, and habits. The study of personality traits can be useful for summarizing, predicting, and explaining an individual's behavior. These characteristics have been increasingly recognized as determinants of eating behavior, linked to different eating styles, such as eating in response to negative emotions, stress, or environmental stimuli (Jaeger et al., 2017; Keller & Siegrist, 2015; Knaapila et al.,

2011; Spinelli et al., 2018), sometimes posing a threat to healthy behaviors (Morris et al., 2016; Tapper et al., 2015)

Food neophobia, defined as the reluctance to eat unfamiliar foods (Pliner & Hobden, 1992), is a psychological trait deeply rooted in evolutionary mechanisms designed to protect the body from potentially harmful substances (Rozin, 1979). Although adaptive in ancestral environments, in modern contexts it is considered a maladaptive behavior, as it may lead to decreased dietary variety and poor diet quality (Kral, 2018; Birch, 1999), as it can lead to reduced dietary variety and negatively impact nutritional quality. Individuals with high levels of food neophobia tend to have a reduced diet variety and lower preference for vegetables and other foods (Kral, 2018, Jaeger et al. 2017).

Sensitivity to disgust, is a negative emotion, consisting of disgust in response to food, animals, and from the body itself and its products. It drives people to defend themselves from harmful circumstances (Spinelli, Cunningham et al., 2021). Applied to the food domain, high disgust sensitivity is associated with the avoidance of certain tastes, such as bitter, perceived as unpleasant or dangerous (Schienle et al., 2015; Oaten et al., 2009; Calder et al., 2007).

Individuals characterized by high levels of food neophobia and disgust sensitivity often exhibit overlapping eating behaviors (Al-Shawaf et al., 2015). Existing studies have shown that these individuals have lower preference for foods characterized by bitter, astringent, sour, or pungent tastes (Laureati et al., 2018; Spinelli et al., 2018; De Toffoli et al., 2019), probably because such individuals, particularly those with high levels of food neophobia, have been shown to have a higher responsiveness to bitterness and astringency (Laureati et al., (2018), and to spiciness (Spinelli et al., 2018). However, it has been suggested that differences in perception between individuals with high/low food neophobia or high/low disgust sensitivity may not be due to differences in taste perception, but rather to the

subjective meaning attributed to food stimuli (Laureati et al., 2018; Spinelli et al., 2018). Both traits have been associated with heightened levels of anxiety (Pliner & Hobden, 1992; Raudenbush & Capiola, 2012; Viar-Paxton & Olatunji, 2016), which may facilitate the detection of subtle sensory alterations (Pliner & Melo, 1997). Consequently, when these individuals perceive warning sensations, such as bitter or spicy, their anxiety may amplify the sensory experience, leading to more intense or aversive perceptions. This increased reactivity may not reflect intrinsic sensory hypersensitivity, but rather an amplification of perception triggered by hypervigilance to potential risk (Laureati et al., 2018; Spinelli, Cunningham et al., 2018; Jaeger et al., 2021). It could therefore be hypothesized that cancer patients with higher levels of food neophobia or disgust sensitivity may experience more chemosensory alterations during chemotherapy. This is because their predisposition to hypervigilance and anxiety may heighten their awareness of chemosensory changes, making them more likely to report such alterations. However, despite these hypotheses, there is a lack of studies in the literature directly exploring the relationship between these psychological traits and chemosensory changes in cancer patients.

1.5.2 Taste responsiveness and its impact on food preferences and behaviors

Individual differences in taste responsiveness may influence liking, food preferences and behaviors (Ullrich et al., 2004; Dinnella et al., 2018; Puputti et al., 2019). Taste responsiveness can be defined as the ability to perceive a taste, such as sweet, sour, salty, and bitter (Lanfer et al., 2013). It can be measured with several methods such as tests with aqueous solutions, and responsiveness to 6-n-propylthiouracil (PROP) bitterness intensity. Particularly the ability to perceive the bitterness of PROP (PROP status) varies among individuals and therefore is considered as an oral acuity index (Tepper, 1998; Tepper, 2008; Tepper et al.,

2014) and it is primarily determined by genetic differences in the TAS2R38 bitter taste receptor gene. Based on their oral responsiveness to PROP, individuals can be classified into three phenotypic groups: Non-Tasters (NT) who perceive PROP as weak or not bitter (with intensity ratings <17 on the general Labeled Magnitude Scale, gLMS); Medium-Tasters (MT), who perceive moderate bitterness (scores ≥17 and <53); and Super-Tasters (ST), who report very high PROP bitterness (scores ≥53 on gLMS) (Hayes et al., 2010; Fischer et al., 2013; Monteleone et al., 2017). PROP status has been associated with different chemosensory experiences (Keller et al, 2002; Tepper & Nurse., 1998), for example PROP tasters have a lowered acceptance of some bitter foods or a heightened responses to basic tastes, oral irritation, and tactile stimuli (Ervina et al., 2020; Prescott et al., 2001; Bajec & Pickering, 2008; Hayes et al., 2008; Fischer et al., 2014; Dinnella et al., 2018; Piochi et al., 2021; Robino et al., 2022; Yackinous & Guinard, 2001, Hayes & Duffy, 2007). In oncology field, variations in individual taste sensitivity have been proposed as a possible explanation for why some cancer patients experience greater taste alterations, as highlighted in several previous studies (Comeau et al., 2001; Drareni et al., 2019; Nolden, Hwang et al., 2019; Nolden, 2021; Ruiz-Ceamanos et al., 2022).

1.6 Coping strategies, clinical management, nutritional advice and food innovations tailor-made to patients' needs

The public image of cancer patients is often influenced by stereotypical media portrayals: they are typically depicted as thin, nauseous, bald, and with a limited life expectancy (Bahrami et al., 2017). Chemosensory disorders are rarely mentioned among these characteristics despite the multidimensional impact they have on cancer patients' daily life. Therefore, it is essential to identify and develop

effective coping strategies and innovative interventions tailored to the real needs and experiences of patients to prevent and tackle malnutrition and improve patients' eating experience and food-related pleasure. Nutrition support is not routinely used as an adjunct to antineoplastic therapies (Tueros & Uriarte, 2018; O'Donoghue et al., 2023) as chemosensory alterations are often considered as unavoidable side effect of treatment (Zaberingg et al., 2010) leading physicians to devote limited attention to these issues. Consequently, some patients report feeling unsupported and express a desire for more guidance and practical advice from their clinical team (Kwok et al., 2015). In addition, the accessibility to a variety and attractive food products tailor-made for oncological patients is limited. Despite the wide availability of oral nutritional supplements designed to prevent or treat malnutrition, most products remain poorly tailored to individual clinical and sensory needs, which may limit their acceptance and adherence among patients (IJpma, Renken, Ter Horst et al., 2016b; Darmon et al., 2008; de Haan et al., 2021). In particular, sensory characteristics play a crucial role, as many patients report that oral supplements have unpleasant or monotonous flavors and textures, resulting in "taste fatigue" and poor adherence. A systematic review by Enriquez-Fernández et al. (2019) found that cancer patients' liking for oral supplements differs significantly from that of healthy individuals, with milk-based supplements generally preferred over synthetic or juice-based ones. The authors emphasized that taste inadequacy remains a key obstacle to consumption, underscoring the urgent need for personalized, sensory-adapted nutritional solutions for this population. These findings highlight a critical gap in the current market: the lack of food products specifically designed for the sensory and emotional needs of cancer patients with chemosensory disorders (Tueros & Uriarte, 2018). Beyond nutritional adequacy, future developments should focus on sensory food design, integrating aspects such as taste, smell, flavor, texture, and appearance to

counteract sensory fatigue and increase food enjoyment. Furthermore, approaches such as co-creation with patients and diet education could offer new opportunities to restore the pleasure of eating and support nutritional rehabilitation (Lippi et al., 2025). In addition, the dietary advice currently offered in oncology is often generic and non-personalized, failing to adequately address the individual sensory and nutritional challenges patients face during treatment. Therefore, many patients sometimes report an absence of such guidance, and they are often left to manage their chemosensory changes on their own, implementing a variety of coping strategies and dietary choices that are not always effective or appropriate. This can lead to significantly different, and sometimes opposing, outcomes: on the one hand, loss of appetite, reduced food intake, failure to meet nutritional needs, and consequent weight loss; on the other, satisfaction of specific food cravings (eating sweet foods, fruit, candies), increased calorie intake, and consequent weight gain. Both scenarios place patients at high risk of malnutrition (Nielsen et al., 1980; Tueros & Uriarte, 2018; Bernhardson et al., 2009; Speck et al., 2013; Bernhardson et al., 2007; Boltong & Keast, 2012).

In the oncology outpatient setting, several practical strategies are proposed to help patients manage chemosensory disturbances and food aversions. However, most of these recommendations lack a solid scientific basis and are largely derived from anecdotal patient reports. In clinical practice, such advice is often disseminated through educational materials and patient support resources, including websites, brochures, and leaflets, produced by hospitals, oncology departments, or associations such as the Italian Association for Cancer Research (AIRC), AIMaC, the Umberto Veronesi Foundation, and the Italian League for the Fight Against Cancer (LILT). While these guidelines can provide psychological reassurance and practical support, they are not consistently supported by controlled studies evaluating their actual effectiveness on chemosensory function or nutritional outcomes.

Furthermore, the heterogeneity of recommendations reflects the lack of standardized, evidence-based protocols for managing taste and smell alterations in cancer care. This gap highlights the need for interdisciplinary research that combines clinical nutrition, sensory science, and patient-reported outcomes to develop validated and personalized strategies. Generic recommendations such as "eat what you want or what you can," "try to maintain your weight," or "choose bland foods to reduce nausea" are well-intentioned, but often ineffective, as they fail to take into account the complexity of sensory disturbances or the emotional relationship many patients have with food. To supplement these basic recommendations, cooking and flavoring techniques are sometimes proposed to mask unpleasant tastes, such as marinating meat with condiments such as soy sauce, wine, or fruit juice (Grant & Kravits, 2000). Other suggestions include using lemon drops or chewing gum before meals to stimulate salivation and improve taste sensitivity. However, it is important to note that citrus flavors may be poorly tolerated by some patients, particularly those with mucosal irritation or taste hypersensitivity (Huldij et al., 1986; Holmes, 1993). In addition to dietary advice, healthcare workers and patient support resources (websites, flyers, brochures) also suggest several non-food strategies such as using plastic utensils, drinking from a straw, brushing the teeth and tongue before meals, and using baking soda (Speck et al., 2013; Ijpma et al., 2015).

For bitter or metallic tastes, patients may be advised to limit their consumption of foods such as red meat, coffee, tea, acidic fruit juices, and tomatoes, opting instead for milder-tasting, high-protein alternatives such as poultry, dairy products, fish, or eggs (Buss, 1987). The use of plastic utensils instead of metallic silverware is also recommended (Hong et al., 2009; Holmes, 1993; Sherry, 2002). This practice is likely related to the interaction between metal utensils and saliva or foods, which can release metal ions and intensify metallic sensations (Lawless et al., 2004;

Carvalho & Spence, 2021). However, this explanation remains theoretical, as no studies have directly evaluated this effect in cancer patients undergoing chemotherapy.

For xerostomia, sugar-free candy or chewing-gum are recommended to increase salivary flow and to avoid increasing the risk of dental caries (Wickham et al., 1999). Grant and Kravits (2000) also emphasize the importance of avoiding favorite foods during treatment sessions to prevent the development of strong conditioned taste aversions (CTA). CTA (Garcia & Koelling, 1966) is a form of associative learning in which a specific taste becomes associated with an unpleasant physiological experience, such as nausea or vomiting. As a result of this learned association, the taste becomes aversive: when re-experienced, individuals often exhibit disgust reactions, may re-experience nausea, and subsequently avoid further exposure to that food. Subsequent studies confirmed these findings in both pediatric and adult cancer populations, emphasizing the clinical relevance of CTA and its contribution to reduced food intake and increased risk malnutrition (Bernstein, 1978; Mattes et al., 1987). Mattes et al. (1987) further observed that although any type of food may become aversive, frequently consumed and highly preferred items are often particularly affected, with potential implications for patients' quality of life. This finding suggests that avoiding favorite foods close to treatment sessions may help reduce the risk of developing strong aversions. To minimize such associations, patients may instead consume foods devoid of significant emotional or cultural significance at these times. Furthermore, the strategy of consuming small, frequent meals is widely encouraged, as it is often better tolerated and helps maintain nutritional intake.

However, each patient presents a unique combination of nutritional needs, food preferences, and treatment-related side effects, underscoring the need for a

personalized and case-specific approach to nutritional and sensory support (Tueros & Uriarte, 2018; O'Donoghue et al., 2023; Holmes, 1993).

The perception of food or drink flavors reflects information from multiple sensory inputs, including gustatory, olfactory, and somatosensory fibers (Small & Prescott, 2005). Evidence from sensory science shows that congruent odors can increase the perceived intensity of a corresponding taste: for example, the aroma of vanilla or strawberry can increase the perception of sweetness (Frank & Byram 1988; Frank et al. 1989, 1993; Bingham et al. 1990; Cliff & Noble 1990; Clark & Lawless 1994; Prescott 1999b; Stevenson et al. 1999), while flavors such as soy sauce or cheese can increase saltiness (Pionnier et al. 2004; Djordjevic et al. 2004). Conversely, incongruent odors can suppress or distort the perception of a specific taste (Frank and Byram 1988), such as peanut butter for sweetness. Based on this evidence, sensory integration mechanisms can serve as a starting point for the development of nutritional strategies aimed at mitigating chemosensory disturbances in cancer patients. By exploiting odor-taste congruence, it is possible to increase the perceived intensity of diminished flavors or suppress unpleasant sensations such as bitterness or metallic. Such strategies, if integrated into nutritional guidelines or food formulations, could improve palatability, increasing food enjoyment and helping maintain adequate nutritional intake during chemotherapy. Therefore, the recommendations developed during this project were inspired by these sensory principles, translating experimental evidence into practical dietary advice, adapted to different types of chemosensory disturbances.

2. Aims of the thesis

Given the complexity and multidimensional nature of chemosensory alterations in cancer patients and considering their significant impact on both nutritional status and emotional well-being, a deeper understanding of this phenomenon is essential to develop personalized nutritional interventions that effectively meet patients' specific needs, improve their quality of life, and help restore the pleasure of eating. The overall goal of this thesis is therefore to explore the phenomenon of chemosensory alterations as a side effect of anticancer treatment in breast and urological cancer patients and to understand the impact of these disturbances on the daily eating experience and quality of life, focusing on food preferences, emotional responses to foods, eating habits, and nutritional status, adopting a longitudinal approach (from before the therapy to after three months since the last treatment). This temporal framework allows us to capture the onset, progression, and recovery of sensory and behavioral changes. Moreover, individual differences will be investigated, considering factors that affect food experience (such as taste responsiveness and personality traits). Secondly, on this basis, this thesis is aimed at developing personalized recommendations and inputs for new products and recipes tailored to the needs of cancer patients, improving their eating experience, nutritional status, and quality of life.

Based on the overall aim, several research questions (RQ), objectives (O) and their connected hypothesis can be identified.

RQ1 - *What types of chemosensory alterations occur in breast and urological cancer patients receiving chemotherapy and how frequently?*

O1: To follow patients throughout the course of chemotherapy treatment to determine which chemosensory changes occur, when they occur, and how long they persist. The hypothesis is that a significant proportion of patients will

experience chemosensory changes early in chemotherapy, while others may develop symptoms later due to cumulative treatment effects or individual variations in sensitivity. However, some patients may not experience noticeable changes or may only report transient symptoms that do not persist over time. Of those affected, the majority are expected to fully recover chemosensory perception within three months of completing treatment. By integrating sensory testing, self-report measures, and semi-structured qualitative interviews, this study will provide a more comprehensive understanding of the frequency, nature, and progression of chemosensory disturbances in breast and urological cancer patients undergoing chemotherapy with similar cytotoxic agents.

RQ2 – *Which is the impact of chemosensory alterations on food preferences, emotions and eating habits?*

O2: To understand the impact of chemosensory alterations on food preferences and emotions considering the sensory characteristics of the foods at different stages of treatment. The hypothesis is that beyond the diversity of sensory alterations and their associated side effects, there is significant variability in how patients adapt to these changes. For instance, patients with hypogeusia are expected to prefer more flavored and spicy foods, increasing the use of salt or other strong seasonings while patients with parageusia are expected to prefer more unflavored or sweet products due to the altered, bitter or bad perception in foods, avoiding naturally bitter foods such as dark chocolate, coffee, and certain green vegetables like kale and radish. Moreover, the presence of discomfort with side effects like mucositis and nausea can make it difficult to eat some seasoned and flavored foods, but also foods with a specific texture. Similarly, patients with altered olfactory perception (either an increased sensitivity to odors or nausea triggered by odor perceived as too strong or different) may avoid foods with intense

aromas, such as cooked fish, aged cheese, and cruciferous vegetables (like broccoli and cauliflower) which release sulfurous compound when heated. Additionally, hot foods, which tend to have stronger odors, may be less tolerated by patients, leading to eating room-temperature or cold meals. Conversely, patients with phantogeusia are not expected to immediately change their food preferences, as the alteration is not specifically related to food intake but occurs independently of food consumption. However, because the unpleasant taste is persistent, these patients may gradually modify their diet or eating habits to find relief.

RQ3 – *Which is the impact of chemosensory alterations on nutritional status of cancer patients?*

O3: To study the effect over time of chemosensory alterations on nutritional status in terms of weight, BMI, fat mass and lean mass to establish which alteration profiles expose patients to a higher risk of malnutrition. The hypothesis is that the presence of chemosensory alterations may lead to changes in eating behaviors that are not always consistent with healthy dietary patterns. Consequently, patients may experience changes in body composition, including fluctuations in weight, BMI, fat mass, and lean mass. For example, the presence of hypogeusia may lead some individuals to experiment with a wide range of foods in an attempt to perceive their flavor, potentially resulting in increased energy intake and a nutritional imbalance that promotes weight or fat mass gain. This variability highlights the need to explore how different sensory alteration profiles relate to nutritional outcomes during treatment.

RQ4 – *Which is the impact of chemosensory alterations on quality of life?*

O4: To understand the impact of chemosensory alterations on dimensions of quality of life, with the connected hypothesis that, also in this case, the different

profiles of alteration could influence the quality of life in different ways. However, accordingly with other studies (Brisbois et al., 2011; Hutton et al., 2007; Prieto-Callejero et al., 2020) it is expected that, in general, patients who experience chemosensory alterations of any kinds have a worse quality of life than patients who did not.

RQ5 - *Are individual differences in psychological traits (e.g., food neophobia, disgust sensitivity) and oral responsiveness (PROP status) associated with a greater likelihood of experiencing chemosensory alterations in cancer patients, and how do they influence food preferences and emotional responses to food in cancer patients?*

O5: To investigate whether food neophobia, disgust sensitivity, and PROP status are (1) associated with a greater propensity to develop and report chemosensory alterations and (2) related to differences in food preferences and emotional responses to food, independently of the presence of such alterations. The related hypothesis is that patients with higher levels of food neophobia, disgust sensitivity, and PROP status are more likely to report chemosensory alterations, which in turn may cause a change in preferences. Furthermore, these traits are expected to be associated with more negative food-elicited emotional responses as therapy progresses, potentially impacting the overall eating experience and dietary flexibility during treatment.

RQ6 - *Which sensory characteristics should food products have to improve the eating experience of cancer patients?*

O6: To develop personalized recommendations and recipes to cope with chemosensory alterations and to collect inputs for the development of a snack tailor-made to the needs and tastes of patients undergoing chemotherapy.

Overall, these objectives aim to develop a comprehensive understanding of how chemosensory alterations influence the eating experience of cancer patients and to translate this knowledge into practical, personalized tools to support their nutritional and emotional well-being during treatment.

3. Materials and methods

3.1 Organization and management of the study

The present data were collected as part of the larger ongoing ALTERTASTE project (Spinelli, Mini et al., 2021, Clinical trial CEAVC n. 20839), a longitudinal prospective study started in 2022 and currently in progress (April 2025) at Careggi University Hospital (Florence, Italy) and IRCCS Humanitas Research Hospital (Rozzano, Milan, Italy). Study procedures were approved by the Ethics Committee for Clinical Trials in Tuscany Region – Large Central Area section (Rif. CEAVC n. 20839, CEAVC Em. 2022-418 ID 20839), and by the Independent Ethics Committee of the Humanitas Clinical Institute (3531/ID. 20839) and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants enrolled in the study in line with the GDPR (General Data Protection Regulation) 2016/679.

3.2 General project methods: ALTERTASTE protocol

3.2.1 Patients: recruitment and inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study: a histologically confirmed breast cancer (BC), prostate cancer (PC), testicular cancer (TC), or bladder cancer (BLC); an Eastern Cooperative Oncology Group performance status ≤ 1; a treatment plan with taxane-based or platinum-based chemotherapy; an adequate hematological, hepatic, renal and cardiac function; an age ≥ 18 years; a written informed consent dated and signed by both patient and investigators. The exclusion criteria were a major surgery within 2 weeks of study enrollment; brain metastases or leptomeningeal disease; severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, such as severe malnutrition.

Based on the inclusion criteria, a total of 71 patients with a mean age of 50.5 ± 12.6 were recruited (79.4% in Florence and 29.6% in Milan). The data were collected on 71 patients before the treatment (T0), 58 patients after the 1st cycle (T1), 66 patients after the 2nd cycle (T2), 57 patients after the 4th cycle (T4), 42 patients after the 6th cycle (T6), 33 patients after the 8th cycle (T8), 56 patients three months after the last therapy (TF). The variability in sample size at different time points reflects data collection based on treatment plan, patient availability and clinical condition. As often occurs in longitudinal studies involving oncology patients, dropout (n=7; 9.9%) may occur due to several reasons, such as reduced motivation (n=4), lack of time (n=1), clinical worsening (n=1), or death (n=1). Furthermore, as the study is currently ongoing, some patients (n=11) had yet to complete the therapy at the time this thesis was written. Additionally, 4 patients who had only recently started chemotherapy were not yet eligible for inclusion in the thesis analyses.

Treatment delivery

1) Adjuvant or neoadjuvant chemotherapy adopted for BC includes alternatively:
    - four cycles every 2 weeks (dose dense) or 3 weeks of epirubicin (90 mg/m^2) or doxorubicin (60 mg/m^2) in combination with cyclophosphamide (600 mg/m^2) followed by 12 cycles of weekly paclitaxel (175 mg/ m^2) with or without 4 cycles of carboplatin (5-6 AUC) every three weeks. The treatment can also be administered in reverse mode.
    - four cycles every 3 weeks of docetaxel (75 mg/m^2) administered with cyclophosphamide (600 mg/m^2).

- our cycles every 2 weeks (dose dense) or 3 weeks of epirubicin (90 mg/m^2) or doxorubicin (60 mg/m^2) in combination with cyclophosphamide (600 mg/m^2) followed by 4 cycles of docetaxel (75 mg/m^2).
- Adjuvant or neoadjuvant chemotherapy adopted for BC includes 12 cycles of weekly paclitaxel (80 mg/ m^2) with or without 4 cycles of carboplatin (5-6 AUC).

2) Chemotherapy regimen adopted for PC includes six cycles every 3 weeks of docetaxel (75 mg/m^2) or cabazitaxel (mg/ m^2).
3) Chemotherapy regimen *PEB* adopted for TC includes from one to three cycles (it depends on type of treatment) of cisplatin (P) (20 mg/m^2) on days 1-5, etoposide (E) (100 mg/m^2) on days 1-5, and bleomycin (B) (30 IU) on days 1,8 and 15.
4) Chemotherapy regimen adopted for BLC includes four cycles every 3 weeks of cisplatin (70 mg/m^2) or carboplatin (mg/ m^2) in combination with gemcitabine (1000 mg/m^2).

For the breast, in relation to the stage of the disease (metastatic or adjuvant) and biological parameters, chemotherapy treatment was associated with targeted therapy (trastuzumab) or with immunotherapy (pembrolizumab).

To make the experimental design more understandable, for weekly paclitaxel the "chemotherapy cycle" was considered as a group of 3 weekly treatments for a total of 3 weeks.

The observation time points varied based on type of therapeutic plan as shown in Table 2.

Table 2 Planning of observation times for each site of cancer and related treatment regimen

Type of cancer and treatment plan	**T0 n=71**	**T1 n=58**	**T2 n=66**	T3 n=22	**T4 n=57**	**T6 n=42**	**T8 n=33**	**TF n=56**
Bladder – a total of 4 cycles of 21days (carboplatin + gemcitabine) (cisplatin + gemcitabine)	Before treatment N=5	After the 1st cycle *(3 weeks)*	After the 2nd cycle *(6 weeks)*	After the 3rd cycle *(9 weeks)*	After the end of the treatment (after the 4th cycle) *(12 weeks)*			3 months after the end of the treatment
Testicle – a total of 1-3 cycles of 21 days (cisplatin + etoposide + bleomycin)	Before treatment N=5	After the 1st cycle *(3 weeks)* (the test was conducted also after *7 days**)	After the 2nd cycle *(6 weeks)*	After the treatment (after the 3rd cycle) *(9 weeks)*				3 months after the end of the treatment
Prostate – a total of 6 cycles of 21 days (docetaxel) (cabazitaxel)	Before treatment N=4	After the 1st cycle *(3 weeks)*	After the 2nd cycle *(6 weeks)*	After the 3rd cycle *(9 weeks)*	After the 4th cycle *(12 weeks)*	After the treatment (after the 6th cycle) *(18 weeks)*		3 months after the end of the treatment
a) Breast** – a total of 8 cycles (4 cycles of 21 days of epirubicine and cyclophosphamide + 4 cycles of 21 days of docetaxel (or 12 weekly paclitaxel***) and carboplatin)	Before treatment N=22	After the 1st cycle *(3 weeks)*	After the 2nd cycle *(6 weeks)*		After the 4th cycle *(12 weeks)*	After the 6th cycle *(18 weeks)*	After the treatment (after the 8th cycle) *(24 weeks)*	3 months after the end of the treatment
b) Breast** – a total of 8 cycles (dose dense 4 cycles of 4 days of epirubicine and cyclophosphamide + 4 cycles of 21 days of docetaxel)	Before treatment N=11	After the 1st cycle *(2 weeks)*	After the 2nd cycle *(4 weeks)*		After the 4th cycle *(8 weeks)*	After the 6th cycle *(14 weeks)*	After the treatment (after the 8th cycle) *(20 weeks)*	3 months after the end of the treatment
c) Breast** –a total of 4 cycles (4 cycles of 21 days of docetaxel and cyclophosphamide) or (12 weekly cycles*** of paclitaxel,)	Before treatment N=7	After the 1st cycle *(3 weeks)*	After the 2nd cycle *(6 weeks)*	After the 3rd cycle *(9 weeks)*	After the end of the treatment (after the 4th cycle) *(12 weeks)*			3 months after the end of the treatment

** To explore the platinum influence (IJpma et al., 2017). ** For the breast cancer, in relation to the stage of the disease (metastatic or adjuvant) and biological parameters, chemotherapy treatment was associated with targeted therapy with trastuzumab or immunotherapy with pembrolizumab. ***For weekly treatment, 1 cycle was considered as a group of three (total of 21 days). Observations* ***emboldened*** *were considered in this thesis.*

Patients were recruited during the oncological visit in which general information about the study was given. They were invited to attend a maximum of 7 sessions depending on the treatment: before therapy, after 1st week (for TC), after 1 cycle, after 2 cycles, after 3 cycles, after 4 cycles, after 6 cycles, after 8 cycles and 3 months after the conclusion of the chemotherapy. The data collection happened always right before the next cycle, e.g. "after 2 cycles" refers to a data collection right before the 3rd cycle, i.e. considering a cycle of three weeks this corresponds to 21 days after the infusion. Observation times varied based on the type of therapeutic plan as shown in Table 2.

At T0, before the beginning of treatment, patients were introduced to the general organization of the session (Figure 2). At the same time oncologists provided demographics, clinical and health data. After the welcome, only at T0, patients were asked to fill out the Italian Child Food Neophobia Scale (Laureati et al., 2015; Pliner & Hobden, 1992) and the 8-item short form Sensitivity to Disgust Scale (Haidt et al., 1994.; Inbar et al., 2009; Spinelli et al., 2018). Instead, the following procedures were carried out at each session. Weight, height, and body composition were collected. Quality of life was assessed using European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ 30) (Aaronson et al., 1993) version 3.0 (Bjordal et al., 2000); self-reported taste/smell/chemestetic sensation responses were collected using an adapted version of a questionnaire set up to measure chemosensory changes due to COVID-19 (Global Consortium of Chemosensory Research questionnaire- GCCR questionnaire) (Parma et al., 2020) together with a questionnaire developed for the study assessing changes in hedonic responses to basic tastes and changes in eating habits (use of condiments) during treatment; self-reported taste responses were also collected using and adapted version of the Italian Chemotherapy Induced Taste Alteration Scale (CiTAS) (Campagna et al., 2016; Kano & Kanda, 2013).

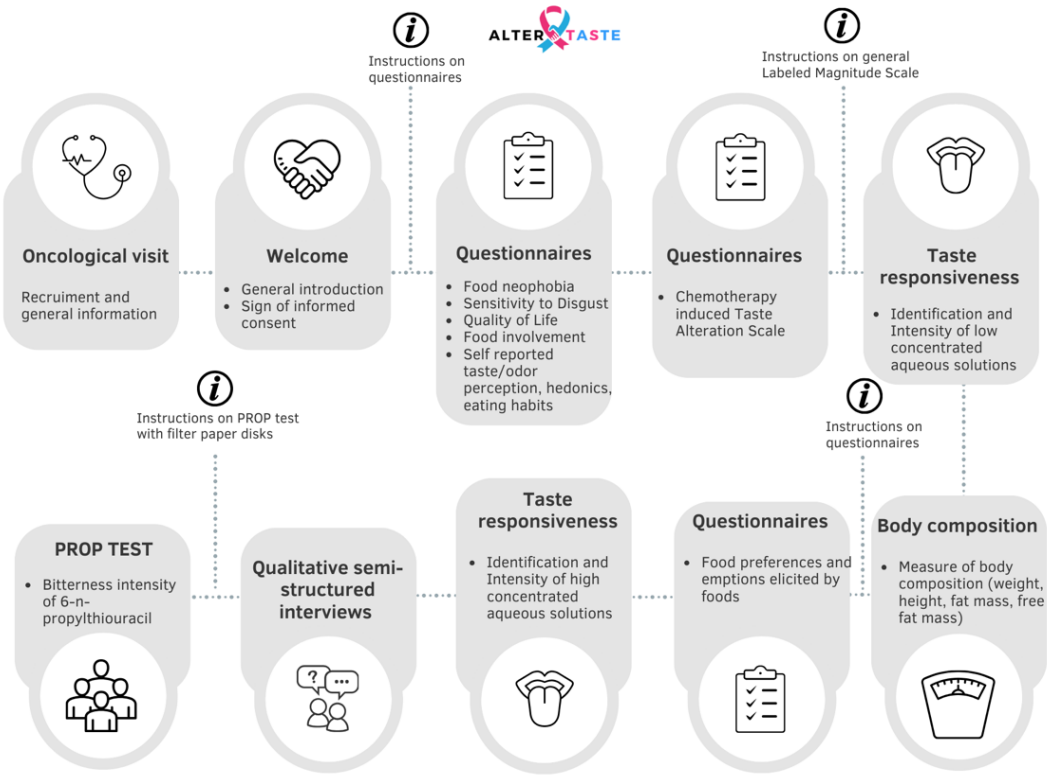


Figure 2 Overview of data collection.

Then, patients were asked to identify and rate the intensity of a series of five samples of water solutions at low/moderate concentration ("lower concentration") following a standardized procedure (Monteleone et al., 2017). Then, they had a break and were asked to fill out the Food Preferences and Emotions elicited by foods Questionnaire developed specifically for this study and the short form of Food Involvement Scale (Bell & Marshall, 2003). After the break patients had to identify and rate the intensity of other five samples of aqueous solutions at moderate/high concentration ("higher concentration". During another break qualitative semi-structured interviews were conducted. Finally, the oral acuity index was measured through a PROP test with filter paper disks (Rorandelli et al., 2023; Zhao et al., 2003). Each session lasted approximately 1 hour. All the evaluation sessions were in-person: patients were guided throughout the whole testing procedures by researchers, with timers and on-screen instructions. Only in some limited cases when the patient was unable to reach the hospital, tests were

administered online and sensory tests were not conducted (n=42 test sessions out of a total of 383, 10.9%).

3.3 Procedures

Data were collected through the software Compusense v. 23.0.46 (Compusense Inc. Guelph, Ontario, Canada).

3.3.1 Socio-demographic, clinical and health data

Collected socio-demographics data, clinical and health status are shown in Q1 (Appendix- Questionnaires). The questionnaire used to collect this information includes forced-choice questions and open-ended questions.

3.3.2 Saliva collection

Although salivary microbiota analysis was not included among the objectives of this doctoral thesis, at each time points saliva samples were collected from participants to enable future investigations into the relationship between oral microbiota composition and chemosensory alterations.

Sample collection followed a standardized protocol to minimize variability. Participants were asked to abstain from eating foods or chewing gum, drinking coffee or other beverages (except water), smoking, for 30 minutes prior to collection. To facilitate salivation, they were advised to drink water approximately 15 minutes before the procedure.

Each participant provided a saliva sample in a sterile container. To stimulate salivation, patients were asked to gently massage their cheeks with their tongue, press the tip of their tongue against their teeth, yawn, or perform chewing

movements. Samples were stored at room temperature during collection but were transferred to the laboratory as soon as possible and stored at +4°C for up to 48 hours. Subsequently, aliquots of 200µL each were prepared in sterile cryotubes and stored at -80 °C until analysis.

3.3.3 Body composition

During the first observation (T0) the barefoot standing height (H) was measured by using a wall-mounted stadiometer (Gima 27335; Gima Italy).

Bioelectrical impedance from foot to foot was measured using the Tanita BC-613 body-fat analyzer (Tanita Corp., Tokyo, Japan). Weight (W), fat mass (FM) and free fat mass (FFM) were collected.

Patients had to stand on the metal sole plates of the machine without shoes, socks and heavy objects in their pockets. To minimize potential errors from acute shifts in fluid distribution, all measurements were made after a period of at least 10 minutes standing.

Body mass index (BMI) was calculated by taking patients' weight, in kilograms, divided by their height, in meters squared meters.

3.3.4 Sensory tests

Chemosensory responsiveness was measured using:

1) responses in terms of perceived intensity to tastants in water solutions presented at two different concentrations (lower and higher) for basic tastes (sweet, bitter, salt, and sour) and for pungent sensation following a standardized procedure (Monteleone et al., 2017);

2) response to bitterness of the 6-n propylthiouracil (PROP) using paper disks, generally considered as an oral acuity index and a general marker of individual variability in oral sensitivity (Rorandelli et al., 2023; Zhao et al., 2003).

3.3.4.1 Test with aqueous solutions

Before test with aqueous solutions, patients were trained to the use of general Labeled Magnitude Scale (gLMS) (0: no sensation – 100: the strongest imaginable sensation of any kind) consistent with published standard procedure (Bartoshuk, 2000; Green et al., 1993, 1996). The gLMS consists of a 100-unit vertical line with labels placed at “no sensation” (0); “barely detectable” (1.4); “weak” (6); “moderate” (17); “strong” (34.7); “very strong” (52.5); and “strongest imaginable sensation of any kind” (100). Numerical labels are not reported on the scale. Patients were instructed to treat the “strongest imaginable sensation” as the most intense sensation they can imagine that involves remembered/imagined sensations in any sensory modality. This includes the deafening noise of a plane that is flying low, and the strong pain felt when shutting a finger in a door (Rorandelli, 2025).

Then, patients were presented with a first series of five water solutions at lower concentration (Table 3) corresponding to the weak/moderate labels of gLMS. The aqueous solutions corresponded to four basic tastes (sweet with 67 g/L of sucrose Sigma Aldrich, Milan, Italy; sour with 1.3 g/L of citric acid Sigma Aldrich, Milan, Italy; salty with 5 g/L of sodium chloride Sigma Aldrich, Milan, Italy; bitter with 0.75 g/L of caffeine Sigma Aldrich, Milan, Italy) and one chemesthetic sensation (pungent with 0.00055 g/L of capsaicin Sigma Aldrich, Milan, Italy). After a break of 5 minutes patients were presented with the second series of five water solutions at higher concentration (sweet with 200 g/L of sucrose Sigma Aldrich, Milan, Italy;

sour with 4 g/L of citric acid Sigma Aldrich, Milan, Italy; salty with 15 g/L of sodium chloride Sigma Aldrich, Milan, Italy; bitter with 3 g/L of caffeine Sigma Aldrich, Milan, Italy; and pungent with 0.0015 g/L of capsaicin Sigma Aldrich, Milan, Italy).

Table 3 Concentrations of stimuli in aqueous solutions

Stimulus	Lower concentration	Higher concentration
Sweet – sucrose	67 g/L	200 g/L
Sour – Citric acid (HCl)	1.3 g/L	4 g/L
Salty – Sodium cloride (NaCl)	5 g/L	15 g/L
Bitter – Caffeine	0.75 g/L	3 g/L
Pungent – Capsaicin	0.00055 g/L	0.0015 g/L

The procedure was the same as just described. Both lower and higher concentrations were selected to cover a range of intensity ratings from weak/moderate to moderate/strong on the gLMS based on preliminary studies and on the literature (Yeomans et al., 2007; Hayes et al., 2010; Feeney & Hayes, 2014; Masi et al., 2015; Webb et al., 2015; Monteleone et al., 2017; Nolden & Hayes, 2017; Pierguidi et al., 2023; Spinelli et al., 2023; Rorandelli, 2025).

Each sample (10 mL) was presented at room temperature in an 80cc plastic cup, identified by a three-digit code (Figure 3).

The presentation order of samples was randomized for the basic tastes while the pungent solution was always evaluated as the last sample to avoid perceptual interference between samples due to the carry-over of capsaicin. Patients had to hold the sample in their mouth for a total of 3 seconds, then spit, wait 3 seconds (or 5 seconds for bitter and pungent solutions) and identify one or more perceived sensations (sweet, sour, salty, bitter, astringent, pungent, tasteless, other (open-ended) with a Check-All-That-Apply (CATA) format. Then were asked to evaluate the overall intensity of the sensation on the gLMS. Between the samples, there was a break of 60 seconds in which patients had to rinse their mouth with still water, had a cracker (optional) and rinsed again before the following solution.

Figure 3 Aqueous solution samples.

3.3.4.2 Oral acuity index: PROP status

For the assessment of PROP responsiveness 1.5 cm diameter 6-n-propylthiouracil impregnated filter paper disks were used (Whatman, Sigma Aldrich, Milan, IT) following a standardized procedure (Rorandelli et al., 2023; Zhao et al., 2003). Throughout the testing procedure participants received guidance from researchers, who provided precise timing and on-screen instructions. Each patient was presented with a single PROP disk placed on a Petri dish labeled with a three-digit code. To conduct the PROP evaluation, subjects were instructed to put the disk on the tip of the tongue (Figure 4) close the mouth and wait until moistened with saliva

(25 s), then remove it, and after a further 20 s during which they had to move the tongue, rate the bitterness intensity on the gLMS. After the evaluation, a standardized mouth-rinsing protocol was implemented, consisting of water, plain crackers containing 1.25% NaCl, and a final rinse with water (Monteleone et al. 2004).

Figure 4 PROP test: position of PROP disk on the tongue.

3.3.5 Scales and questionnaires

3.3.5.1 Psychological traits

Italian-validated questionnaires were administered to assess patients based on selected personality traits known to influence taste perception: food neophobia and sensitivity to core-visceral disgust. The first one was assessed using Italian Child Food Neophobia Scale (Laureati et al., 2015) and the second one using the 8-item short form Sensitivity to Disgust Scale (Spinelli et al., 2018).

3.3.5.1.1 Food Neophobia Scale

Food neophobia is the reluctance to try novel foods, and it was assessed using the 8-item Italian Child Food Neophobia Scale developed by Laureati et al. (2015)

based on Pliner & Hobden (1992). This scale was selected as it includes a simple and easy to understand vocabulary, making it suitable for use even with older patients that are included in the study and could have problems with Food Neophobia Scale for adults as it includes items related to ethnic restaurants that may be unfamiliar to them. Individual Food Neophobia scores were computed as the sum of ratings given to the eight items using a 5-point Likert scale from 1 (very false for me) to 5 (very true for me) as shown in Q2 (Appendix - Questionnaires). Some items (1, 4, 5, and 8) were reversed before the calculation of the total score. Individual scores thus ranged from 8 to 40, with higher scores corresponding to higher food neophobia levels.

3.3.5.1.2 Sensitivity to Disgust Scale

Core disgust is a negative emotion, consisting of disgust in response to food, animals, and to body products. The sensitivity to core-disgust was assessed using the 8-item short form of the Disgust Sensitivity Scale (Olatunji et al., 2007) (validated in Italian: Spinelli et al., 2018). The scale (Q3; Questionnaires - Appendix) includes two subscales, each presented with a specific scale: subscale 1 ranges from 1 (strongly disagree/very untrue about me), to 5 (strongly agree/very true about me), while subscale 2 ranges from 1 (not at all disgusting), to 5 (extremely disgusting). Individual scores were computed as the sum of ratings. Items 1 and 3 of the subscale 1 were reversed before the calculation of the score. Individual scores thus ranged from 8 to 40, with higher scores corresponding to higher sensitivity to disgust.

3.3.5.2 Attitudes towards food – Food Involvement Scale

Food Involvement, defined as the level of importance of food in a person's life, was measured though the Italian version (Cliceri et al., 2018) of the subscale "Preparation and Eating" of the Food Involvement Scale by Bell & Marshall (2003) (Q4; Appendix – Questionnaires). Specifically for this study, the item "Among the decisions I have to make, deciding what to eat is very important to me" was slightly reworded while maintaining its original meaning to make them easier to understand. In particular, the item was worded positively, unlike the original questionnaire, which used negative wording (e.g., "Compared to other daily decisions, my food choices are not very important").

The subscale was designed to assess various aspects of food involvement, including the acquisition, preparation, cooking, and consumption of food. Individual food involvement scores were calculated by adding the ratings assigned to the nine items in the subscale, using a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). Responses to items 1, 2, 7, and 8 were reversed before calculating the individual score. As a result, the final score ranged from 9 to 63, with higher scores indicating a greater level of food involvement.

3.3.5.3 Self-reported responses on chemosensory perception and alterations

Self-reported responses were collected using two methods that were adapted specifically for the study: the Chemotherapy-induced Taste Alteration Scale (CiTAS) and the Global Consortium of Chemosensory Research questionnaire (GCCR).

3.3.5.3.1 Chemotherapy-induced Taste Alteration Scale

The CiTAS used in the study (Q5) was adapted from the original Italian scale (Campagna et al., 2016), which was translated from the Japanese version (Kano & Kanda 2013). Originally the CiTAS is a 18-item questionnaire which evaluates the 4 dimensions of some conditions related to taste and smell perception using a Likert scale 1-5: decline in basic tastes (quantitative disturbances in the perception of sweet, bitter, sour, salty, umami tastes), discomfort (reduced appetite, difficulty in eating certain types of food, nausea), phantogeusia and parageusia (qualitative disturbances in the perception of tastes), and general taste alterations. In the original questionnaire, the first six items were graded as follows: 1="no difficulties in taste perception", 2="slight taste impairment", 3="intermediate taste impairment", 4="very difficult taste perception", 5="inability in tasting". The other items were graded as follows: 1="no", 2="slightly", 3="medium", 4="quiet", 5="very".

Specifically for the study, the questionnaire was adapted by adding five items: "I sometimes feel a metallic taste in my mouth" and "I sometimes feel a sour taste in mouth", "I perceive some tastes as more intense than usual", "dry mouth" and "I suffer from mucositis/inflammation/pain/ulcerations in mouth". These additions were based on the literature (Corremans et al., 2021.; IJpma et al., 2015; Mahmoud et al., 2011; McGettigan et al., 2019; O'Donoghue et al., 2023; Silva et al., 2021), and on preliminary interviews with cancer patients. The items "have difficulty tasting food", "unable to perceive the smell or flavor of food" and "have difficulty eating meat" were removed. The first because it was considered too generic. The second because it combines distinct sensory experiences such as smell and flavor, which can lead to ambiguity and reduce the clarity of data collected. Although smell contributes significantly to the perception of flavor, it may not always be the cause of its alteration. Additionally, the term "flavor" does not exist in the Italian

language, and it can be particularly confusing for some patients (Belqaid et al., 2016; Spence et al., 2015), especially older individuals, as they may struggle to fully understand its meaning, further complicating their responses. The item “have difficulty eating meat” was removed because it can have multiple meanings, not necessarily related to sensory discomfort. For example, the difficulty could arise from psychological factors, such as sarcophobia (fear or aversion to meat), or from a common inclination to change eating habits towards a healthier direction in order to prevent weight intake and potentially improve treatment efficacy (Pedersini et al., 2021; Salminen et al., 2004). Furthermore, the item “I have difficulty perceiving umami tastes” was modified by replacing the word “umami” with “savory”, as the concept of umami might be difficult for patients to understand due to its unfamiliarity in Europe. Thus, the adapted version used for the study was composed of 20 items grouped in 4 dimensions: decline in basic tastes (5), general taste alterations, parageusia, and increase in taste perception (3), phantogeusia (5), discomfort (7). The labels of the 5-point Likert scale were uniformed across the different subscales as follows: 1=”not at all”, 2=”slightly”, 3=”quiet”, 4=”very”, 5=”very much”. A score was calculated for each domain and in total as a mean of the scores for each individual.

Psychometric analysis of CiTAS

The adapted version of the Italian CiTAS showed excellent internal consistency, with a Cronbach’s alpha coefficient of 0.912. The data were suitable for factor analysis, as indicated by a Kaiser-Meyer-Olkin (KMO) value of 0.903 and a significant Bartlett’s test of sphericity ($p<.0001$). In line with previous studies (Kano & Kanda, 2013; Campagna et al., 2016), a four-factor structure was tested using Promax rotation with Kaiser normalization, explaining 46.86% of the total variance.

Details on factor loadings, explained variance, and internal consistency of each dimension are reported in Table 4. As can be seen, the questionnaire assesses the impact of chemotherapy-related taste disturbances on four key factors: general taste alterations, parageusia, and increase in taste perception (F1), decline in basic tastes (F2), discomfort (F3), and phantogeusia (F4).

Table 4 Factor analysis with Promax Rotation of Chemotherapy-induced Taste Alteration Scale

	Cronbach's alpha	D1	D2	D3	D4
Italian Chemotherapy induced Taste Alteration Scale - new version	**.912**				
Factor 2: Decline in basic tastes	**.837**				
1. I have difficulty perceiving sweet tastes		-.062	**.756**	-.003	.113
2. I have difficulty perceiving salty tastes		.152	**.676**	.093	-.261
3. I have difficulty perceiving sour tastes		-.196	**.822**	.031	.236
4. I have difficulty perceiving bitter tastes		-.100	**.832**	-.045	.069
5. I have difficulty perceiving savory tastes (stock cube; parmesan cheese…)		.232	**.787**	-.122	-.077
Factor 1: General taste alteration, parageusia, and increase in taste perception	**.880**				
6. When I eat, everything tastes bitter		**.703**	.024	-.111	.255
7. When I eat, everything tastes bad		**.852**	.020	-.090	.147
8. It seems to me that the flavors of the foods I usually eat are no longer the same		**.495**	.184	.345	-.092
20.I perceive some tastes more intense than usual		**.337**	.099	**.358**	.170
Factor 4: Phantogeusia	**.831**				
9. I sometimes feel a bad taste in my mouth		.225	.056	.298	**.336**
10. I sometimes feel a bitter taste in my mouth		.270	.015	.078	**.531**
11. I sometimes feel a metallic taste in my mouth		.155	-.029	.287	**.378**
12. I sometimes feel a sour taste in my mouth		.245	.038	-.014	**.577**
Factor 3: Discomfort	**.803**				
13.I feel nausea or disgust for food		.011	-.039	**.627**	.045
14.I am brothered by the smell of food		-.149	-.053	**.760**	.161
15. I have difficulty or discomfort eating hot foods		.002	-.041	**.692**	-.094
16. I have difficulty or discomfort eating oily foods		-.099	-.032	**.602**	.210
17. I have a reduced appetite		.138	.032	**.548**	-.058
18. I suffer from mucositis (inflammation in the mouth e.g. redness, burning, pain, ulcerations)		.077	-.012	**.538**	-.049
19. I feel dry mouth		.005	.102	**.491**	-.073

3.3.5.3.2 Modified version of the Global Consortium of Chemosensory Research questionnaire

The questionnaire used in the study (Q6; Questionnaires - Appendix) was an adapted version of the questionnaire originally developed by the Global Consortium for Chemosensory Research (GCCR) (Parma et al., 2020) to investigate self-reported smell and taste dysfunction during the SARS-CoV-2 pandemic. In the original version, participants were asked to rate their ability to perceive odors, tastes (in general and specific tastes), and chemesthetic sensations (such as burning, coolness, or tingling) before and during the illness using 100-point visual analog scales (0="no sense/not sensitive at all" - 100="excellent sense/very sensitive"). The questionnaire also included questions regarding any qualitative changes, such as olfactory distortions or hallucinations, and an open-ended section for free description of perceived alterations. Other sections covered the presence of respiratory symptoms, nasal obstruction, and general information about the participant's health and lifestyle. Furthermore, in the original version, participants were asked to think of a food or drink they consumed regularly, such as their morning coffee, tea, or a favorite fruit, and to indicate whether the overall taste, smell, or flavor of that food had changed as a result of their illness, describing the nature of the change. The original questionnaire was adapted to the oncology setting with the aim of making it more targeted and easily understandable for patients undergoing chemotherapy. Some elements of the original questionnaire have been retained, such as the questions on the overall perception of taste, smell, and chemesthetic sensations, the open-ended section for free description of alterations, and the usual food or drink to assess any changes in overall taste, smell, or flavor. Instead, some changes have been made. The 100-point linear analog scales were replaced with 9-point numerical scales, deemed more intuitive and less cognitively demanding, especially in patients who are

fatigued or have difficulty concentrating. The adaptation also included the option of researcher-assisted completion, useful in cases where the patient is unable to complete the questionnaire independently, while acknowledging the risk of potential variability in interpretation by the interviewer.

Chemesthetic function (perception of burning, coolness, and tingling) was assessed only during and at the end of chemotherapy, rather than before treatment initiation, to allow for a subjective comparison with the patient's usual perception. Responses were then divided into three categories: "as before," "more intense," or "less intense".

3.3.5.4 Hedonic responses to basic tastes and use/liking of condiments

A questionnaire (Q7; Questionnaires - Appendix) was developed to assess the hedonic responses to basic tastes. Specifically, patients were asked to evaluate their liking of each basic taste (salty, sweet, sour, and bitter) by indicating whether they like it more, less, or the same as before when compared to their pre-treatment period. As in the case of the adapted version of the CiTAS questionnaire, the "umami" taste was not included because of the hypothesized difficulty in understanding the word for a cultural reason (§3.3.5.3.1 See *Chemotherapy-induced Taste Alteration Scale*).

Additionally, an evaluation of condiments (Q8; Questionnaires - Appendix) in terms of liking or use was incorporated into the questionnaire. Patients were asked to rate on a 9-points scale, ranging from "not at all" to "very much" the use of sugar, Parmesan cheese, black pepper or liking of salt, chili pepper, spices, lemon and vinegar.

3.3.5.5 Food Preference and Emotion Questionnaire

The Food Preferences & Emotions Questionnaire (FP&EQ) was originally developed in order to track any changes in preferences and emotions elicited by foods differing in key sensory properties during the whole treatment period. The questionnaire (Q9; Questionnaires - Appendix) is composed by 6 different dimensions:

- Flavor (more/less intense)
- Texture (soft, liquid, creamy/hard, crunchy)
- Odor (more/less intense)
- With/without Herbs and spices
- Sweet vs Bitter
- Sweet vs Sour

Each dimension contains 5 food/drink/odor pairs (for a total of 30 pairs of items), designed and tested to recall the different levels of target sensations. In the questionnaire, patients were presented with food pairs and were asked to express their preferences, selecting one option (forced choice) in each pair based on their daily experiences or expectations in a specific eating context (e.g. "Between 'dark chocolate' and 'milk chocolate', indicate which one you would prefer to eat as a snack. If you like both or neither of them, choose the one you are more inclined to eat"): main meals (either lunch or dinner, 18 pairs), snacks (9 pairs), all-day consumption (3 pairs). For food pairs relevant to odor dimension, participants specified which option they would rather avoid in each given context (e.g. You are in a room where someone has just finished eating/cooking and you can smell food. Indicate the option you would least like to smell between 'boiled rice' and 'cooked tomato').

The presentation order of the items within each pair, and of the pairs within the questionnaire, was randomized across patients. After each choice between options,

patients were asked: “How does it make you feel?” (Spinelli et al., 2014) and they should indicate at least one (or more) emotions elicited by each item (both the chosen and the unchosen one) using a Check-All-That-Apply (CATA) format.

The emotions were selected based on previous studies on food products (Spinelli, 2021; Spinelli et al., 2014; Spinelli & Jaeger, 2019) and on the *circumplex model of affect* (Russell et al., 1980), that describe emotions based on valence (positive/pleasure *vs.* negative/displeasure) and arousal (high/activation *vs.* low/deactivation). Five negative emotions and four positive emotions were chosen for the questionnaire (Table 5).

Table 5 List of emotions of Food Preference and Emotion Questionnaire

Emotions	Valence	Arousal
Joy	Positive	High
Curiosity	Positive	High
Happiness	Positive	Low
Relax	Positive	Low
Annoyance	Negative	High
Disgust	Negative	High
Boredom	Negative	Low
Indifference	Negative	Low
Sadness	Negative	Low

Validation of Food Preference and Emotion Questionnaire

Each dimension consists of 5 food/drink/odor pairs (for a total of 30 pairs of items), designed and tested to recall the different levels of target sensations (e.g. higher/lower in flavor intensity). Some of the items were selected from the IT-Food Choice Questionnaire (Monteleone et al., 2017), with sensory differences between pairs validated in previous studies (De Toffoli et al. 2019, Pagliarini et al. 2021).

The remaining items were developed exclusively for the study based on scientific literature on sensory differences between products. The new items were subjected to a preliminary validation involving 36 to 117 consumers recruited to perform a pairwise comparison test. Participants were asked to indicate in each pair which product was more “intense in flavor/creamier/sweeter/intense in odor” (all products and questions are reported in Table 6). The results were analyzed through a unilateral test based on which it was possible to conclude whether there was a perceptible difference between the two products through a minimum number of correct answers.

The results indicate that only one pair was not validated (vegetable soup vs bean soup) and thus it was excluded from the following analyses.

Table 6 Validation of pairs of Food Preference and Emotion Questionnaire products – Results of the unilateral test

Number of respondents	Question	Product 1 (number of answers)	Product 2 (number of answer)	**Minimum number of correct answers α=0.05**	Result
117	Which of the two products has the more intense flavor?	Smashed potato (13)	**Baked potato (104)**	68	**Valid**
81	Which of the two products has the more intense flavor?	Fresh pecorino (7)	**Aged pecorino (74)**	48	**Valid**
81	Which of the two products has the more intense flavor?	Cow mozzarella (4)	**Buffalo mozzarella (77)**	48	**Valid**
81	Which of the two products has the more intense flavor?	Cooked ham (5)	**Dry cured ham (76)**	48	**Valid**
81	Which of the two products has the more intense flavor?	Lettuce and valerian salad (1)	**Radicchio and rocket salad (80)**	48	**Valid**
81	Which of the two products is creamier?	**Semolina (76)**	Couscous (4)	48	**Valid**
36	Which of the two products is sweeter?	Raspberry jam (8)	**Apricot jam (28)**	24	**Valid**
36	Which of the two products is sweeter?	**Strawberry sorbet (35)**	Lemon sorbet (1)	24	**Valid**
117	Which of the two odor is more intense?	Vegetable soup (54)	Bean soup (63	68	Invalid
117	Which of the two odor is more intense?	Tomato sauce (8)	**Bolognese sauce (109)**	68	**Valid**
117	Which of the two odor is more intense?	Grilled meat (37)	**Fried cutlet (80)**	68	**Valid**
117	Which of the two odor is more intense?	Boiled rice (22)	**Cooked tomato (95)**	68	**Valid**
117	Which of the two odor is more intense?	Vegetable broth (13)	**Meath broth (104)**	68	**Valid**

Favorite and most disliked foods

At each time point, in addition to the FP&EQ, participants were asked to provide open-ended responses, identifying both their favorite and most disliked foods during that specific period (Q9a; Questionnaires – Appendix). This question aimed to capture potential temporal fluctuations in food preferences and aversions related to treatment experience and chemosensory alterations.

Ideal snack

To further explore patients' sensory expectations and needs, patients were asked at each time point to describe the sensory characteristics of their ideal snack during that period (Q9b; Questionnaire – Appendix). First, they were asked to choose between a sweet or salty snack using a forced-response preference question (If you were feeling peckish in the morning, would you prefer a 'sweet' or 'salty? snack? Choose one). Next, they were asked to identify must have and must not have from a predefined list of sensory characteristics (soft, crunchy, hard, liquid, tasty, creamy, pasty, dense, juicy) using a CATA. An open-ended option was included at the end of the CATA list to allow participants to indicate any additional sensory attributes they deemed important but were not listed (What should it be? – Choose one or more attributes from this list. If the attribute you are looking for is not present, enter it in "other" – What should it NOT be? – Choose one or more attributes from this list. If the attribute you are looking for is not present, enter it in "other").

3.3.5.6 Assessment of Quality of Life - European Organization for Research and Treatment of Cancer Quality of Life questionnaire

The quality of life (QoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), version 3.0 (Aaronson et al., 1993; Bjordal et al., 2000) (Q10; Appendix - Questionnaires). This 30-item questionnaire is designed to capture the multidimensional nature of QoL through various multi-item scales and single-item measures (Ware et al., 1980; Schipper et al., 1990). It includes five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), and a global health status/QoL scale. Additionally, several single-item measures assess common cancer-related symptoms such as dyspnea, appetite loss, insomnia, constipation, and diarrhea, along with the financial impact of the disease and treatment (Aaronson et al., 1993).

Responses for functional and symptom-related items were recorded using a 4-point Likert scale (1="no" to 4="very much"), while global health status/QoL items were rated on a 7-point scale (1="very poor" to 7="excellent"). To facilitate interpretation, all scores were linearly changed to a 0-100 scale, following the questionnaire's guidelines (Fayers et al., 2001). Higher scores on functional and global health status/QoL scales indicate better functioning or higher quality of life, whereas higher scores on symptom scales reflect greater symptom severity or distress (Fayers et al., 2001).

3.3.6 Qualitative semi-structured interviews

To gain deeper insights into the patients' daily eating experience, qualitative semi-structured interviews (Q11; Appendix- Questionnaires) were conducted at each

time point after the start of the treatment. The interview guide was developed based on key themes from literature as well as the clinical expertise and practical experience of the research team and further adapted during the study.

The interviews, lasting between 10 and 20 minutes, explored changes in taste and smell perception, the timing and duration of such changes, and their emotional and social impact on everyday life. Participants were also asked to describe how these sensory alterations influenced their food preferences and eating behaviors. In addition, the interviews investigated both the personal strategies patients had adopted to cope with these changes, as well as hypothetical strategies they believed could have helped them improve or maintain a more satisfying eating experience.

To structure and deepen the exploration of patients' food-related experiences, the means-end chain (MEC) technique (Gutman, 1982; Reynolds & Gutman,1988) was applied during the interviews. The MEC is a value-based, cognitive model that facilitates the better understanding of decision-making and consumer behavior. It connects the tangible attributes of a product (the means) to highly abstract and intangible personal and emotional values (the ends) (Olson and Reynolds, 2001).

Through a series of laddering questions, inviting participants to progressively explain the “why” behind their statements, it has been possible to construct conceptual chains that connect attributes (such as concrete or abstract characteristics of the experience, e.g., metallic taste), to consequences (such as immediate outcomes of those attributes e.g., reduced attributes), to values (such as higher personal goals or aspirations that are affected, e.g. quality of life). This method therefore allows for the systematic emergence of connections between practical aspects and deeper motivations, contributing to a more understanding of the daily eating experience of the cancer patients with sensory alterations.

3.3.7 Data analysis

Statistical analyses were performed using XLSTAT Statistical and Data Analysis Solution 2025.1.1429 (Lumivero 2023, Paris, France). Data were expressed as mean ± standard deviation (SD) or percentage, as appropriate.
A p-value of 0.05 was considered as threshold for statistical significance in all analyses.

Psychometric analyses of the scales

To evaluate the factor structure and validity of the Italian versions of the Child Food Neophobia Scale, the 8-item Short Form of the Sensitivity to Disgust Scale, the adapted version of the CiTAs, the "Preparation and Eating" of Food Involvement Scale, and the EORTC QLQ C30 (Physical functioning, Emotional functioning, Social functioning, Fatigue, Nausea and Vomiting, Appetite loss, Global Health status/QoL status), Exploratory Factor Analyses (EFAs) were conducted.
For the Child Food Neophobia Scale and the Sensitivity to Disgust Scale, EFA was performed on baseline data (n=71), as these questionnaires were only administered at that time point. The CiTAS analysis was conducted on data collected from T1 to TF (N=312). The QLQ C30 analysis on data collected from T0 to TF (N=383). The "Preparation and Eating" FIS analysis was conducted on data collected from T0 to TF (N=299).
The adequacy of the data for factor analyses was verified using the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity (Tabachnick & Fidell, 2001). All Exploratory Factor Analyses were based on Spearman correlation matrices, using Principal Factor Analysis as the extraction method. Depending on the theoretical assumptions and factor correlations, both Varimax and Promax rotations were applied to facilitate the interpretation of the

factor structure. Items with factor loadings greater than 0.30 were retained (Tabachnick & Fidell, 2001).

Classification of patients based on psychological traits

Patients were classified into groups representing Low and High levels of expression of each personality trait (FN and DS) and based on the median value of the total score of each trait for the total sample. Patients with ratings equal to the median were excluded from the analysis.

Changes in PROP responsiveness during and after the therapy and classification according to PROP status

In order to evaluate whether the oral acuity index, represented by the perceived intensity of the bitterness of PROP, could be influenced by the treatment, the stability of this measure over time was analyzed. At first, the perceived intensity ratings of bitterness were assessed for normality with the Shapiro-Wilk test and examining the Q-Q plots. As the data deviated from a normal distribution ($p<.0001$), non-parametric methods were employed. Specifically, Kruskal-Wallis was performed to provide a general overview of perceived intensity of bitterness over time. When significant effect was found, Dunn's post hoc tests with Bonferroni correction were applied to identify which time points differed significantly.

Since the perception of bitterness of PROP did not change during treatment, the classification of patients was carried out considering the scores at baseline (T0). Therefore, based on responsiveness to the PROP, patients were classified into two groups, Low PROP and High PROP responders, splitting their individual ratings by

the median value of the total sample at baseline. Patients with ratings equal to the median were excluded from the analysis.

Changes in aqueous solutions perception during/after the treatment

The same analyses were conducted on low and high concentration solutions as follows*:*

Taste identification. First, descriptive statistics were calculated on CATA responses to assess the percentage of correct identification of each stimulus (sweet, salty, sour, bitter, pungent) at each time point. A response was considered correct if the target sensation was selected from the list (e.g., “salty” for the salty solution), even when chosen in combination with another sensation (e.g., “salty” and “sour” for the salty sample). In cases where the correct target was not selected, further descriptive analyses were conducted to determine which alternative sensations participants had selected, expressed as a percentage for each time point. This allowed for a better understanding of the most common misclassifications.

McNemar's test was then applied to assess differences between the percentages of patients who correctly identified individual tastes, in the subgroups of patients who completed the assessment both at baseline (T0) and at least one of the subsequent time points.

Chemosensory responsiveness. To examine potential changes in chemosensory perception during the chemotherapy, perceived intensity ratings were first assessed for normality with the Shapiro-Wilk test and examining the Q-Q plots. As the data deviated from a normal distribution ($p<.0001$), non-parametric methods were employed. Specifically, Kruskal–Wallis tests were conducted separately for lower and higher concentration solutions.

A first analysis was performed considering all five chemosensory stimuli together (sweet, salty, sour, bitter, pungent), to provide a general overview of intensity variation over time (T0, T1, T2, T4, T6, T8, TF). Subsequently, a second set of analyses was conducted for each stimulus individually, separating lower and higher concentrations, to detect specific trends for each taste or sensation.

For all analyses, the Kruskal–Wallis test was used to assess differences across the time points. When significant effects were found, Dunn's post hoc tests with Bonferroni correction were applied to identify which time points differed significantly.

Given that previous research has consistently identified sweet as the taste most frequently and severely affected during chemotherapy, a Principal Component Analysis was conducted on lower concentration sweet solution perception to identify potential patient clusters with different perceptual trajectories during treatment. The matrix used for PCA was structured with time points (T0, T2, T4, TF) in rows and patients in columns, and the values represented the intensity ratings assigned to the lower concentration sweet solution. Principal component analysis (PCA) was applied to group patients based on their temporal variation patterns. Cluster boundaries were determined through visual inspection of the PCA score plot, allowing for the identification of distinct groups with similar perceptual trajectories. Once patients were assigned to a specific cluster, a three-way repeated measures ANOVA with mixed models using Satterthwaite's approximation method was run with patients as the random factor, time as the repeated factor (4 levels: T0, T2, T4, TF), and cluster as the fixed factor, to verify and compare the temporal trends of the identified clusters.

To gain a more targeted understanding of a breast cancer patient group, a principal component analysis (PCA) was performed to track individual trajectories of

chemosensory perception over time at T0, T2, T4, and TF. The data matrix was organized so that each row represented a specific subject-time point combination, and each column corresponded to the aqueous solutions (sweet, sour, salty, bitter, pungent). Cell values represented the perceived intensity ratings for each taste at each time point for each subject. This organization allowed for the visualization of individual perceptual trajectories within PCA space by linking sequential measurements for the same subject, enabling the identification of sensory profiles during treatment.

Self-reported responses on chemosensory ability over time – GCCR questionnaire

To show a general overview of self-reported ability to perceive taste through GCCR questionnaire during treatment, the mean scores of the items "Evaluate your ability to perceive tastes/odors" were first assessed for normality with the Shapiro-Wilk test. As the data deviated from a normal distribution ($p<.0001$), non-parametric methods were employed. Specifically, Kruskal–Wallis test was conducted to assess differences across the time points. When significant effects were found, Dunn's post hoc tests with Bonferroni correction were applied to identify which time points differed significantly.

In assessing chemesthetic function, a descriptive analysis was performed at each time point for the three sensations considered (burning, coolness, and sparkling). For each sensation, the percentage of patients reporting an intensity equal to, greater than, or less than the period before treatment was calculated. This analysis allowed us to observe the variations of chemesthetic function during treatment.

To analyze self-reported changes in olfactory perception, a descriptive analysis was conducted. Response percentages were calculated for each of the selectable options, considering that participants could indicate more than one response.

Self-reported responses on chemosensory alterations over time and classification of patients based on type of alteration – CiTAS

To provide an overall view of self-reported chemosensory changes during the whole period of chemotherapy, the mean scores for each CiTAS dimension were analyzed. The Shapiro-Wilk test was used to assess normality, and since the data significantly deviated from a normal distribution ($p < .0001$), non-parametric tests were computed.

Specifically, Kruskal-Wallis tests were conducted for each dimension to identify differences across the time points. In cases of significant results, Dunn's post hoc test with Bonferroni correction was used to determine specific pairwise differences. For each time point patients were classified with self-reported alterations through the CiTAS first by calculating the average score for each dimension per patient, then by identifying as "patients with alterations" those for whom the score was different from 1 (="not at all") for each dimension.

Impact of psychological traits and PROP status on chemosensory perception and alterations

At each time point, Spearman's correlations were computed between food neophobia, disgust sensitivity, and PROP scores, and the intensity ratings of lower and higher concentration aqueous solutions and CiTAS scores.

To deepen the effect of PROP status on self-reported chemosensory alteration, CiTAS scores were compared between the low and high PROP groups using the nonparametric Mann-Whitney U test, as the data deviated significantly from a normal distribution ($p<.0001$). This approach allowed us to further investigate group differences in self-reported changes at specific time points.

Hedonic responses to basic tastes and impact of chemosensory alterations

To assess potential changes in hedonic responses to basic tastes during treatment, a general descriptive analysis was conducted to summarize the distribution of responses ("as usual," "less," "more") for each basic taste (sweet, salty, sour, bitter) across all post-treatment baseline time points (T1-TF).

At each time point, the percentage of "less than usual" and "more than usual" responses for each basic taste was calculated, dividing patients based on the presence or absence of self-reported chemosensory alterations (CiTAS). Then, differences in proportions between altered and non-altered patients were tested using two-proportion z-tests.

Impact of chemosensory alterations, psychological traits and PROP status on food preferences

Preferences expressed for each food/beverage/odor pair within every dimension of the FP&EQ (Flavor, texture, odor, herbs and spices, sweet vs bitter, and sweet vs sour), and for each time point were indicated using binary data based on whether the patient selected the less intense/creamy/sweet (0) or the more intense/grainy/hard/sour/bitter option (1). For odors, however, the choice data reflect aversion rather than preference, with 0 indicating an aversion to less intense odors and 1 indicating an aversion to more intense odors.

For each patient, a "strong score" was calculated for every dimension by summing the binary scores across the corresponding pairs. This resulted in a score ranging from 0 to 5 for the dimensions Flavor, Texture, Herbs and Spices, Sweet/Bitter, and Sweet/Sour; and from 0 to 4 for Odor dimension. Higher scores indicated a greater preference for more intense sensory stimuli in that specific food domain, while higher scores in the Odor dimension indicate a greater aversion for more intense odor.

Spearman's rank correlation analyses were conducted separately for each time point to examine associations between self-reported chemosensory alterations through the CiTAS and FP&EQ dimension scores.

To examine whether the sweet taste perception clusters identified through PCA differentially influenced preferences for sweet foods over time, the temporal trends of preference scores for the Sweet vs. Bitter and Sweet vs. Sour dimensions were analyzed using the Kruskal-Wallis test within each cluster (Enhancer, Non-Altered, and Decliners). In addition to assessing temporal variations within each sweetness perception cluster, additional Kruskal-Wallis tests were conducted at each time point (T0, T2, T4, TF) to examine potential differences in preference scores of Sweet vs. Bitter and Sweet vs. Sour dimensions between clusters (Decliners, Enhancers, Non-Altered). This allowed us to test whether membership in a specific cluster was associated with distinct food preference patterns at different stages of treatment.

The significance of the changes in preference for treatments T1, T2, T4, T6, and T8 compared to T0 for each dimension of the questionnaire between subjects with and without self-reported alteration or high and low neophobia or disgust was

tested through a Chi square analysis (a=0.05). For this purpose, for the T0vsT1, T0vsT2, T0vsT4, T0vsT6, T0vsT8 comparisons, a 2x2 contingency table was prepared with the presence of alterations or high/low trait on the rows (Yes; No) and the preference changes in the columns (Yes Change; No Change). Fisher exact test was run to test the significance by cell with significance level set at a=0.05. In order to understand if based on the specific self-reported alteration or psychological trait there was a specific direction of changes in preferences, a Mann-Whitney U test was computed considering the preferences scores at T0 and the preferences scores at subsequent observation characterized by preference changes.

To assess whether preference changes remained associated with a specific type of chemosensory alteration over time, a follow-up analysis was performed. For each FP&EQ dimension and time point at which a significant association had previously been observed between the presence of an alteration (as classified by CiTAS at that time) and the occurrence of a preference change (e.g., between T0 and T2), patients were grouped according to their alteration status at that specific time point. The same classification was then applied to the T0-TF comparison with Chi-Square analysis to assess whether the previously observed association persisted at the end of treatment or whether preferences returned to baseline values. This procedure was repeated for each time point and only for the dimensions where a preference change had been detected.

Favorite and most disliked foods

A qualitative content analysis was conducted on patients' open-ended responses regarding their favorite and disliked foods. The analysis focused on the time point that showed the greatest number of changes in food preferences associated with

specific chemosensory changes. At that time point, only participants who reported the specific alteration through the CiTAS were included. Their open-ended responses were extracted and analyzed.

The textual data was preprocessed by merging synonymous or closely related items into broader food categories, while preserving the original meaning. Finally, separate word clouds were generated for favorite and most disliked foods, with word size proportional to the frequency of mention among participants. These visualizations were used to qualitatively explore the most frequently mentioned items and identify emerging patterns in food preferences and aversions.

Ideal snack

Descriptive analyses were conducted on the entire study population to examine preferences for sweet versus salty snacks and to identify the sensory attributes most frequently selected as "must have" and "must not have" at each time point. Selection percentages for each attribute were calculated to describe temporal trends during the treatment period.

Since T2 represented the time point with the largest number of participants, it was selected for a more detailed CATA data analysis. This choice was also motivated by its location at the beginning of the treatment cycle, a phase considered critical for the implementation of timely interventions aimed at minimizing the impact of sensory changes on eating behavior and nutritional status. For this reason, CATA data at T2 were analyzed by comparing patients classified through the CiTAS with and without chemosensory alterations. Separate descriptive summaries of the attributes were produced for each alteration type (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, and phantogeusia) as well as for non-altered patients. In addition, spider plots were generated to

visualize the evolution of attribute selections between T0 and T2 for altered group and between the altered and non-altered groups for each time.

Impact of chemosensory alterations, discomfort, and individual differences on emotional responses

In order to understand if based on the specific alteration, discomfort, psychological trait, or PROP responsiveness, there was a change in valence of emotions elicited by the chosen options of the preferences questionnaire, a McNemar test was computed. The McNemar test was used to analyze changes within the same group of patients over time and therefore to study differences in dichotomous data before and after a certain treatment. A 2x2 contingency table was prepared for each comparison (T0 with T1; T0 with T2; T0 with T4; T0 with T6; T0 with T8) which has in the rows the valence (positive/negative) at T0 and in the columns the valence (positive/negative) at the subsequent observation individually (T1, T2, T4, T6, or T8), as reported in Table 7.

Table 7 Example of a 2x2 contingency table for Mc Nemar test – Analysis of changes in emotional valence of chosen options

		T1, T2, T4, T6, or T8	
		Positive	Negative
T0	Positive	n (positive valence for chosen options in both observation)	n (positive valence of emotions for chosen options before treatment, which are replaced by the negative valence)
	Negative	n (negative valence of emotions for chosen options before treatment, which are replaced by the positive valence)	n (negative valence for chosen options in both observation)

Impact of chemosensory alterations on eating behavior

Food involvement scores were analyzed using the Kruskal–Wallis test to assess changes over time across all treatment phases. When the overall effect of time was significant, post hoc pairwise comparisons were performed using the Dunn test with Bonferroni correction. To explore the effect of chemosensory alterations on food involvement, Mann–Whitney U tests were used to compare patients with and without each type of alteration at each time point.

To explore associations between self-reported chemosensory alterations and use/liking of condiments at each time point a Spearman's correlation was calculated between CiTAS scores and the scores for each condiment.

Impact of chemosensory alterations on body composition

To investigate potential changes in body composition parameters over the course of treatment in relation to chemosensory alterations, comparisons were conducted between each time point and baseline (T0). Because the composition of the subgroups (patients with and without self-reported chemosensory alterations according to the CiTAS) varied across time points, independent comparisons were performed at each time point (T0–T1; T0–T2; T0–T4; T0–T6; T0–T8; T0–TF). Specifically, Mann–Whitney U tests were used to assess whether significant increases or decreases in weight, BMI, fat mass, and lean mass occurred compared to baseline values.

Impact of chemosensory alterations on quality of life

To assess quality of life, only selected subscales of the EORTC QLQ-C30 were analyzed: Physical Functioning, Emotional Functioning, Social Functioning, Fatigue, Nausea and Vomiting, Loss of Appetite, and Global Health/Quality of Life.

First, changes over time for each subscale in the study population were assessed using the Kruskal-Wallis test with Dunn's post hoc and Bonferroni correction to identify significant pairwise differences between time points.

To investigate the potential impact of chemosensory alterations on these quality-of-life dimensions, at each time point, Mann-Whitney U tests were used to compare subscale scores between patients with and without the specific CiTAS alteration at each time point.

Qualitative analysis

Qualitative data were analyzed using template analysis (King, 1998), a thematic analysis for identifying, analyzing and reporting themes (Braun & Clarke 2006; Clarke & Braun 2013). The researcher identifies codes or themes that summarize key ideas, concept actions or experiences extracted from the interviews by reading and re-reading the text. Themes were derived from the data in an inductive way. When patients did not experience any changes in chemosensory function, interviews were not or only partly included, although all interviews were reviewed for the final template.

Thematic analysis identified two main themes namely 1) chemosensory changes and related side effects and 2) altered eating experience. In discussing chemosensory changes, interview data could be grouped into two sub-groups: nature (quality), timing (occurrence and duration). Data regarding altered eating

experience was grouped into the sub-groups: food preferences, coping strategies and eating behavior, emotions.

Development of nutritional-sensory recommendations

The nutritional-sensory recommendations were developed during the study. The process was guided by the progressive integration of multiple sources of information, including sensory measures; self-reported chemosensory alterations assessed using the CiTAS; data on food preferences and characteristics of ideal snacks; and qualitative interviews describing coping strategies and daily eating behaviors.

The development of the recommendations was conducted through regular interdisciplinary discussions within the research team, combining the clinical, nutritional, and sensory expertise of the team members. This process resulted in the formulation of illustrative, personalized nutritional-sensory profiles and examples, aimed at exploring how heterogeneous sensory responses could be translated into practical dietary advice.

These part of the study is exploratory in nature as recommendations were not formally tested for effectiveness here.

4. Results

4.1 Description of study population

4.1.1 Demographic, clinical and nutritional data

The description of the study population is reported in Table 8. The analyses were performed on a total of 71 patients at T0, 58 patients at T1, 66 patients at T2, 57 patients at T4, 42 patients at T6, 33 patients at T8, and 56 patients at TF. Of the total patients (mean age 50.5 ± 12.6), 77.5% were female (mean age 48.9 ± 9.9) and 22.5% were male (mean age 57.3 ± 18.2).

Table 8 Description of study population

Study population n=71	
Age 23-82 (mean ± SD)	50.5 ± 12.6
Sex (%)	F (77.5); M (22.5)
Smoking habits (%)	Never tried (46.5); Not smoking (38.0); Yes habitually (11.3); Yes, occasionally (4.2)
Educational level (%)	Post degree (0.0); Degree (40.9); Upper secondary (38.0); Lower secondary (19.7); Primary (1.4); None (0.0)
Number of people in the household (%)	Alone (12.7); One (32.4); Two or more (54.9)
Site of cancer (%)	Breast (77.5); Bladder (8.5); Testicle (7.0); Prostate (7.0)
Stage of cancer (%)	I (18.3); II (36.6); III (19.7); IV (15.9); undefined (12.7)
Type of treatment (%)	Chemotherapy (69.0); Chemotherapy+Target therapy (16.9); Chemotherapy+Immunotherapy (14.1)
BMI at baseline (%)	Underweight <18.5 kg/m^2 (0)
	Normal weight 18.5 - 24.9 kg/m^2 (50.7)
	Overweight 25.0-29.9 kg/m^2 (33.8)
	Obesity >30 kg/m^2 (15.5)

4.1.2 Psychological traits

4.1.2.1 Food neophobia

Psychometric analysis of Italian Child Food Neophobia Scale

The Italian Child Food Neophobia Scale showed a good internal consistency with a Cronbach's alpha coefficient of 0.88. A Kaiser-Meyer-Olkin (KMO) of 0.86 and a significant Bartlett's sphericity test ($p < .0001$) indicated that the data was adequate for Factor Analysis. Exploratory Factor Analysis (EFA) on Spearman correlation matrix was conducted using principal factor analysis for factor extraction. The Scree plot suggested a one-factor structure which explained 48.89% of the total variance. All the 8 items demonstrated salient factor loadings on Factor 1 (≥ 0.60) (Table 9).

Table 9 Factor analysis of the Italian Child Food Neophobia Scale

Items	Factor loadings (F1)
I often eat new and unusual foods (R)	**0.696**
I don't trust new foods	**0.604**
If a food is new, I don't try it	**0.749**
I like to try weird tastes and foods, which are unusual and coming from different countries (R)	**0.807**
When I'm at a party, I like to eat new foods (R)	**0.798**
I'm afraid to eat food i have never tried before	**0.683**
I'm very fussy when it's a matter of food	**0.580**
I really eat everything! (R)	**0.638**

Patients' classification based on food neophobia scores

The score distribution is shown in Figure 5. Based on the median value (17) of the total score of all samples, patients were divided into sub-groups representing Low (n=33) (LN) and High (n=31) (HN) levels of food neophobia. Patients with scores equal to the median were removed and not included in the analyses. The median-based approach was adopted because it allows for a balanced distribution of participants across subgroups, given the sample size. Further subdivision based on quartiles would have resulted in subgroups too small to ensure statistical reliability. Furthermore, higher median scores have been reported in developmental samples such as children (median=22 in Sick, 2022; median=21 in Piochi, Fino, & Torri, 2025; median=20 in Kokkorou et al., 2025), reflecting the typically greater food neophobia observed at younger ages and supporting the plausibility of the median value obtained in the current adult oncology sample.

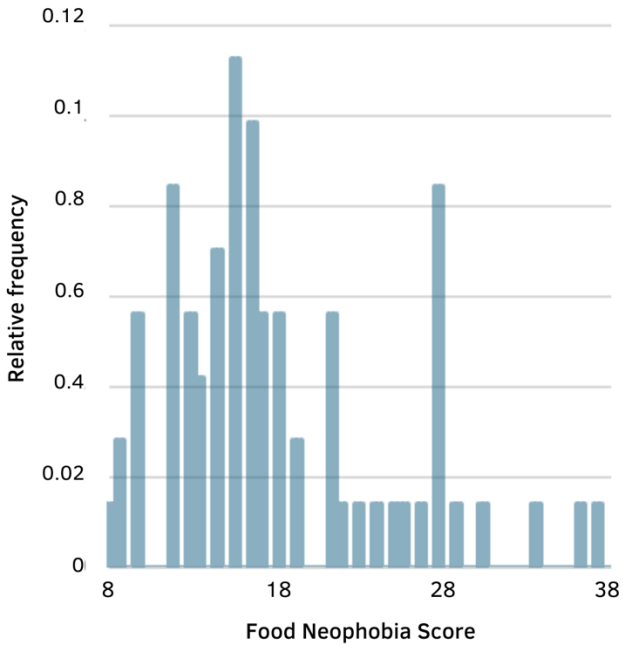


Figure 5 Food Neophobia score distribution of study population.

4.1.2.2 Sensitivity to Disgust

Psychometric analysis of Disgust Sensitivity Scale (short form)

The Disgust Sensitivity Scale (short form) showed an acceptable internal consistency with a Cronbach's alpha coefficient of 0.66. A Kaiser-Meyer-Olkin (KMO) of 0.68 and a significant Bartlett's sphericity test (p=.0001) indicated that the data was adequate for Factor Analysis. Exploratory Factor Analysis (EFA) on Spearman correlation matrix was conducted using principal factor analysis for factor extraction. The Scree plot suggested that no more than two factors should be extracted, which explained respectively 26.38% and 11.90% of the total variance before rotation. The 8 items demonstrated factor loadings on Factor 1, with six of them exceeding the conventional threshold of 0.30 supporting a primarily unidimensional structure. The remaining two items showed lower loadings (< 0.3) but still contributed to the internal consistency of the factor. Moreover, the Cronbach's alpha for Factor 2 was very low (0.34), further confirming that a single-factor solution was more appropriate (Table 10).

Table 10 Factor analysis of Italian Sensitivity to Disgust Scale

Items	Factor loadings (F1)
I might be willing to try eating monkey meat under some circumstances. (R)	**0.397**
If i see someone vomit it makes me sick to my stomach.	0.254
Seeing a cockroach in someone else's house does not bother me. (R)	**0.483**
Even if Ii was hungry, Ii would not drink a bowl of my favorite soup if it had been stirred by a used but thoroughly washed fly swatter.	0.184
To see maggots on a piece of meat in an outdoor garbage pail.	**0.653**

To smell urine while you are walking through a tunnel under a railroad track.	**0.901**
A friend offers you a piece of chocolate shaped like dog-doo.	**0.459**
To see a bowel movement left unflushed in a public toilet.	**0.589**

Patients' classification based on sensitivity to disgust scores

The score distribution is shown in Figure 6. Based on the median value (28) of the total score of all samples, patients were divided into sub-groups representing Low (n=35) (LD) and High (n=34) (HD) levels of sensitivity to disgust. Patients with scores equal to the median were removed and not included in the analyses. The median-based approach was adopted because it allows for a balanced distribution of participants across subgroups, given the sample size. Further subdivision based on quartiles would have resulted in subgroups too small to ensure statistical reliability. Furthermore, the median value observed in the present sample is consistent with value (29) reported in previous study of Spinelli et al. (2018).

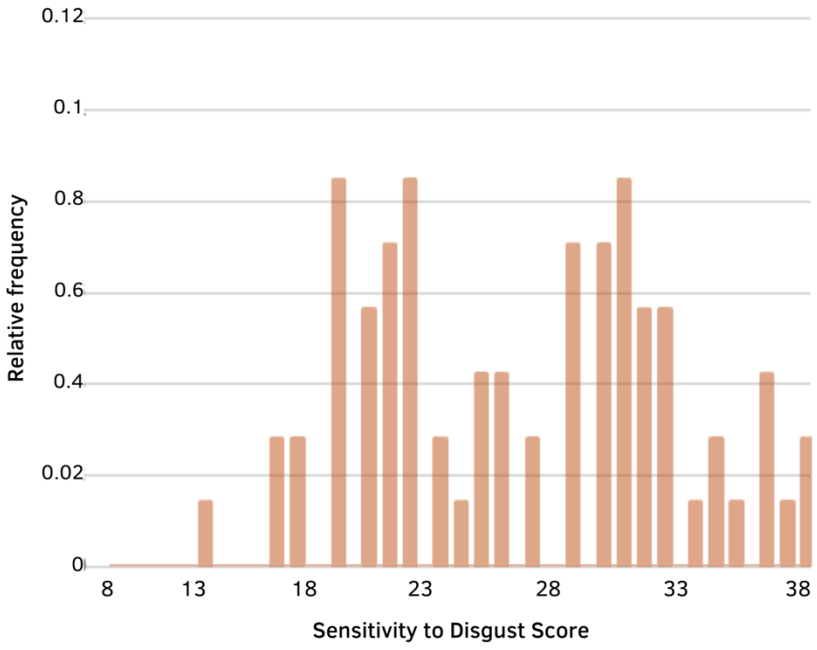


Figure 6 Sensitivity to disgust score distribution of study population.

Result summary 4.1

- The study population was heterogeneous in terms of cancer characteristics, treatments and baseline nutritional status.
- Psychological traits were assessed using validated scales, allowing patients to be classified into subgroups based on median values for subsequent analyses.

4.2 Overview of chemosensory perception before, during and after chemotherapy

4.2.1 Oral acuity index – PROP responsiveness

PROP responsiveness over time

As shown in Figure 7, the Kruskal-Wallis analysis revealed no significant changes over time in the perceived intensity of PROP bitterness ($\chi^2(6)=2.36$; $p=.884$), indicating that the treatment did not affect oral acuity as measured through PROP.

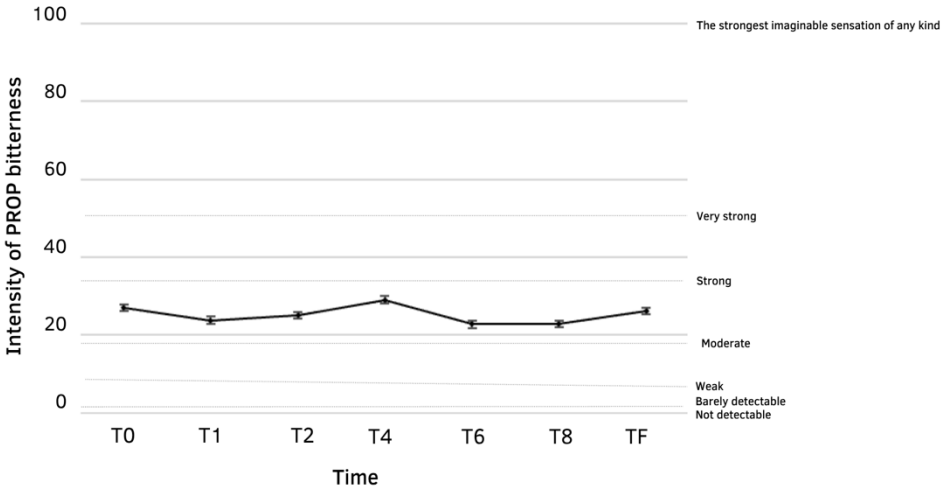


Figure 7 Mean intensity ratings of PROP bitterness across treatment period. Total observations N=342; T0=71; T1=48; T2=56; T4=47; T6=36; T8=30; TF=54.

Classification of Patients According to PROP responsiveness

Because bitterness PROP scores remained stable over time, patients were divided into subgroups based on their responses before the treatment. Given the limited sample size, participants were classified into two groups (Table 11): low PROP responders and high PROP responders, using the median PROP score of the total sample (24.89) as a cutoff. This approach was adopted instead of the conventional three-level classification (non-tasters, medium tasters, and super tasters) described by Bartoshuk et al. (1994), because the sample size would have resulted in subgroups too small to ensure adequate statistical power. Patients with scores equal to the median were not considered in the analyses.

Table 11 PROP responsiveness: range, mean, standard deviation (SD), median, and number of patients (n) for each group (Low/High)

Variable	Range	Mean	SD	Median	n Low	n High
PROP responsiveness	0-89.33	26.95	24.16	24.89	35	35

4.2.2 Measuring chemosensory perception - identification and perceived intensity of aqueous solutions

Lower concentration solutions

The percentages of identification for the five stimuli at lower concentration are shown in Table 12. Recognition of sweetness and pungency remained consistently high throughout the observation period, with accuracy levels approaching 90-100%. In contrast, identification of sourness fluctuated slightly, averaging around

85%, but showed a decline, even if non-significant, after the 2nd, 4th, and 8th cycles, during which identification rates dropped to approximately 80% or below. When not correctly identified as sour, participants most frequently misclassified the solution as astringent (14.3% at T2, 12.3% at T4, and 16.7 at T8) or salty (8.2%) at T2.

The salty solution was correctly identified at baseline (87.32%), but its recognition decreased during and after treatment. The lowest identification rates were observed after the 2nd and, significantly, after the 6th ($p=.039$) and 8th ($p=.016$) cycles, indicating a statistically significant reduction in perceptual accuracy over time. At T2 when not correctly identified as salty, participants most frequently misclassified the solution as sour (8.3%). At T6 when not correctly identified as salty, participants most frequently misclassified the solution as tasteless (27.20%), astringent (18.20%), sour (18.20%), sweet (18.20%), bitter (9.10%), pungent (9.10%). At T8 when not correctly identified as salty, participants most frequently misclassified the solution as sour (37.50%), sweet (25.0%), bitter (25.0%), tasteless (12.50%).

The lower concentration bitter solution was the least accurately identified of all the stimuli even at baseline. However, its recognition showed fluctuating improvement over the treatment period, with identification rates increasing intermittently rather than following a steady trend. When not correctly identified as bitter, patients most frequently misclassified the solution as tasteless (23.9%) or astringent (12.7%) at T0, as tasteless (16.7) or sour (10.4%) at T1, sour (14.3%), astringent (14.4%), or tasteless (10.7%) at T2, as astringent (16.7%) at T4, as sour (16.2), tasteless (13.5%) or astringent (10.8%) at T6, as tasteless (16.7%) or sour (10%) at T8, as sour (13%) and astringent (11.2) at TF.

Table 12 Percentage of identification of lower concentration samples at baseline (T0), the first (T1), the second (T2), the fourth (T4), the sixth (T6), the eighth (T8) cycles of chemotherapy, and at follow up (TF). p-values in parentheses refer to McNemar's test.

Lower concentration aqueous solutions	T0 Correct identification %	T1 Correct identification % (McNemar test p-value difference T0-T1)	T2 Correct identification % (McNemar test p-value difference T0-T2)	T4 Correct identification % (McNemar test p-value difference T0-T4)	T6 Correct identification % (McNemar test p-value difference T0-T6)	T8 Correct identification % (McNemar test p-value difference T0-T8)	TF Correct identification % (McNemar test p-value difference T0-TF)
Sweet (sucrose 67 g/l)	100	97.92	100	100	97.30	93.33	100
Sour (citric acid 1.3 g/l)	87.32	87.50	76.78	79.60	91.89	80	85.18
Salty (NaCl 5 g/l)	87.32	81.25	78.57	81.63	75.67 (**.039**)	76.67 (**.016**)	79.63
Bitter (caffeine 0.75 g/l)	56.34	58.33	60.71	60.42	56.76	63.33	59.26
Pungent (capsaicin 0.00055 g/l)	91.55	85.42	92.86	87.75	91.90	86.67	94.44

Kruskal-Wallis analysis of perceived intensity for all lower concentration aqueous solutions showed an overall decline during treatment ($\chi^2(6)=17.12$, $p=.009$), with a significant decrease observed after the fourth ($p=.001$) and sixth ($p=.002$) cycles of therapy (Figure 8). A partial recovery was observed both at the end of treatment, and three months after treatment.

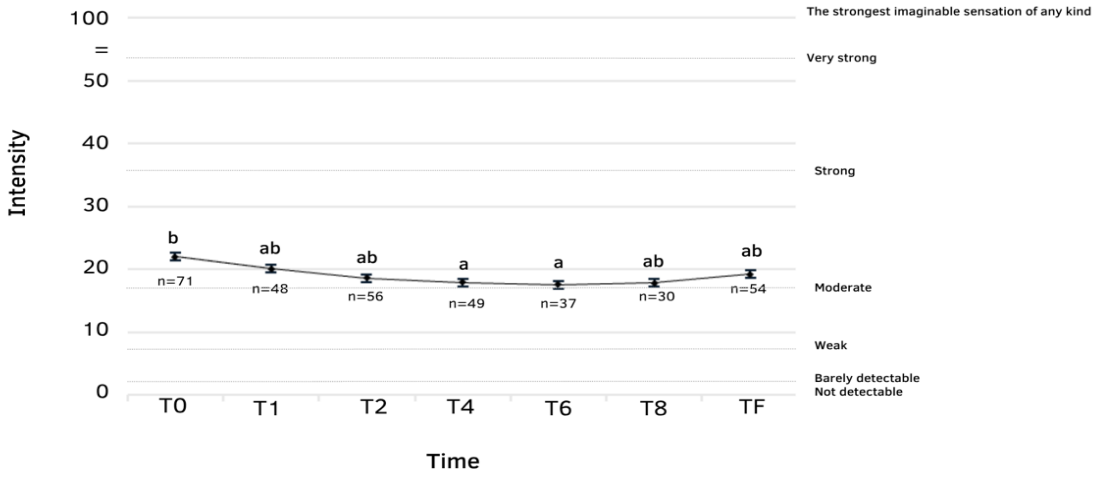


Figure 8 Mean intensity ratings of lower concentration aqueous solutions. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction.

No statistically significant changes over time were observed for the sour ($\chi^2(3)=4.84$, $p=.564$), bitter ($\chi^2(3)=5.258$, $p=.511$) and pungent ($\chi^2(3)=4.225$, $p=.646$) solutions at lower concentration. Instead, the perceived intensity of saltiness (Figure 9) decreased during treatment ($\chi^2(3)=19.87$, $p=.003$), with a

significant reduction observed after the fourth (p=.002) and the sixth (p=.001) cycles. A recovery was observed three months after the end of therapy.

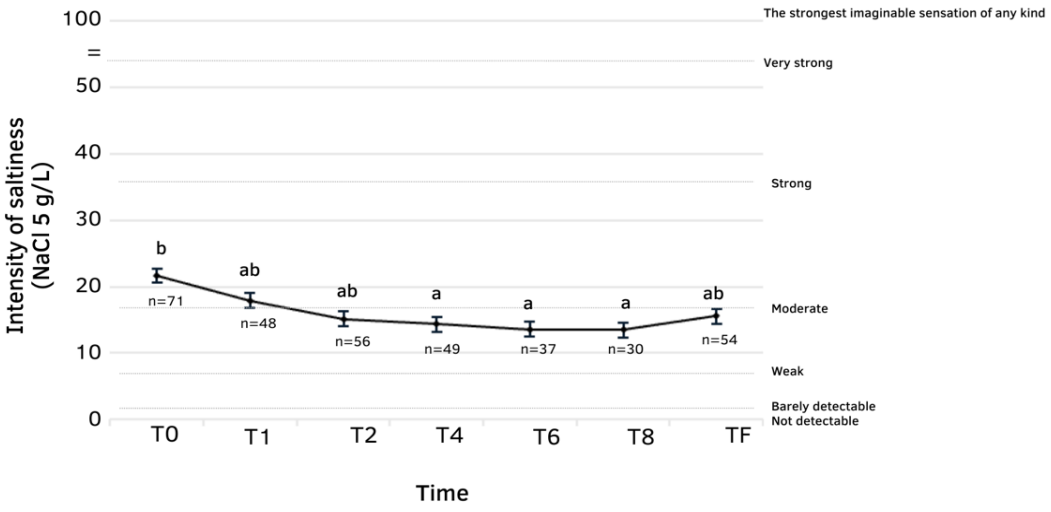


Figure 9 Mean intensity ratings of lower concentration salty solution. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction.

Patients reported a significant decline in the perceived intensity of the sweet solution at lower concentration ($\chi^2(3)=19.57$, p=.003), with a marked reduction already evident after the 2nd cycle of treatment (p=.001). This decrease persisted through the 4th cycle (p=.0001), but a partial recovery was observed at the 6th and

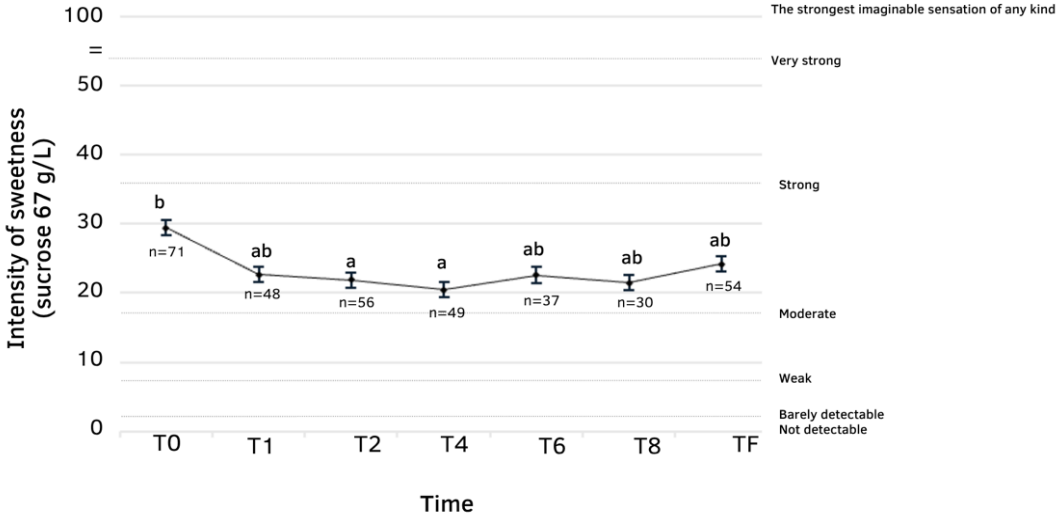


Figure 10 Mean intensity ratings of lower concentration sweet solution. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction.

8th cycles, as well as three months post-treatment (Figure 10), although mean intensity ratings, which were above moderate at baseline (T0), remained below the moderate level at follow-up (TF).

Insights on sweet taste

To explore individual differences in the decline for sweet taste, a principal component analysis (PCA) was performed on a subgroup of patients (n=36 for which the time-points T0, T2, T4, and TF were all available) based on the perceived intensity of the lower concentration sweet solution at baseline (T0), T2, T4, and follow-up (TF). The first two principal components explained 80.27% of the total variance (F1: 43.03%, F2: 37.24%).

The analysis identified three distinct patient clusters (Figure 11) based on the change in perceived sweet intensity at the selected time points:

- Sweet Decliners (red cluster): patients characterized by a reduction in perceived intensity over time compared to baseline.

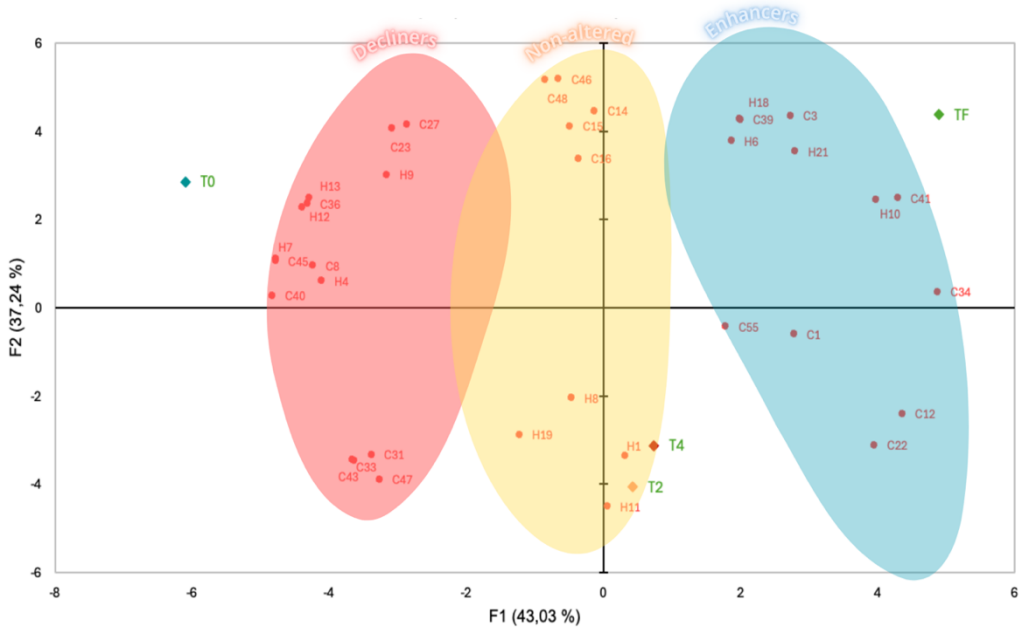


Figure 11 Clusters identified by Principal Component Analysis (PCA) based on the perceived intensity of the lower-concentration sweet solution at baseline (T0), after the second (T2) and fourth (T4) chemotherapy cycles, and at follow-up (TF) in a subgroup of patients.

- Non-altered (yellow cluster): patients characterized by a stable perception or a change in perception followed by a return to baseline levels.
- Sweet Enhancers (blue cluster): patients characterized by an overall increase in perceived intensity compared to baseline.

The characteristics of each cluster are shown in Table 13. The results indicate that the Sweet Enhancer cluster was older than the other two clusters, particularly the one that reported decline.

Table 13 Demographic and clinical characteristics of patient clusters (Enhancers, Decliners, and Non-altered) identified from PCA of sweet taste perception

Cluster (n, %)	Mean age	Sex (n, %)	Therapeutic plan (n, %)	Site (n, %)	Stage (n, %)
Enhancers (12, 33.3)	61.4 ± 10.7	F (8, 75.0) M (3, 25.0)	Chemotherapy (8, 61.6) Chemotherapy + target therapy (3, 25.0) Chemotherapy + immunotherapy (1, 8.3)	Breast (9, 75.0) Bladder (2, 16.7) Prostate (1, 8.3)	1 (2, 16.7) 2a (2, 16.7) 2b (2, 16.7) 3a (3, 25.0) 4 (3, 25.0)
Decliners (15, 41.7)	48.4 ± 10.3	F (14, 93.3) M (1, 6.7)	Chemotherapy (8, 53.3) Chemotherapy + immunotherapy (4, 26.7) Chemotherapy + target therapy (3, 20.0)	Breast (14, 93.3) Bladder (1, 6.7) Prostate (1, 8.3)	0 (1, 6.7) 1a (4, 26.7) 1b (1, 6.7) 2a (3, 20.0) 2b (4, 26.7) 3a (1, 6.7) 3c (1, 6.7)
Non-altered (9, 25.0)	53.7 ± 12.6	F (6, 66.7) M (3, 33.3)	Chemotherapy (6, 66.7) Chemotherapy + immunotherapy (2, 22.2) Chemotherapy + target therapy (1, 11.1)	Breast (6, 66.7) Prostate (2, 22.2) Bladder (1, 11.1)	1a (1, 11.1) 1b (1, 11.1) 2a (2, 22.2) 2b (1, 11.1) 3a (1, 11.1) 4 (3, 33.3)

The repeated measure ANOVA with mixed model confirmed a significant interaction between time and cluster on the perception of lower concentration sweetness

($F_{(6,90.9)}$=7.389, p<.0001). Tukey's post hoc tests clarified the nature of these differences (Figure 12).

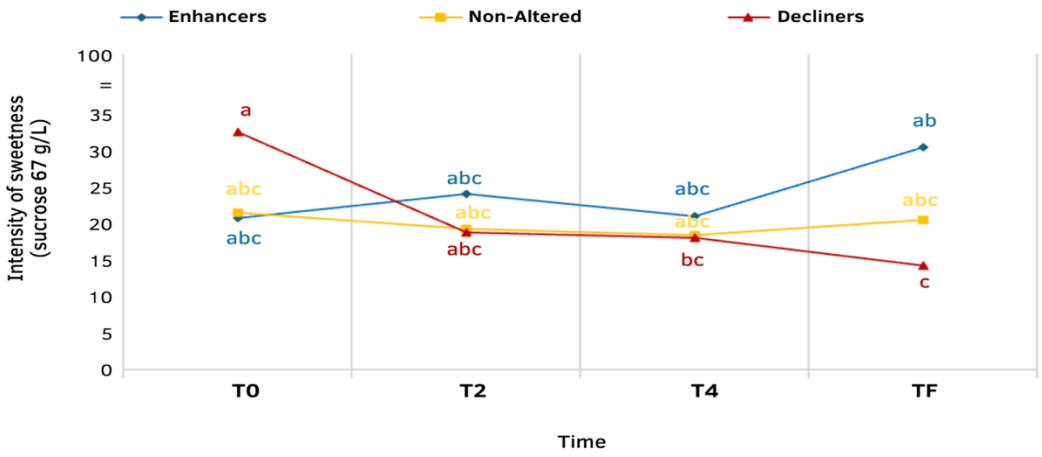


Figure 12 Effect of time (T0, T2, T4, TF) and cluster (Enhancers, Non-altered, Decliners) on the perceived intensity ratings of the lower concentration sweet solution (Least Square means). Different letters indicate significant differences according to Tukey's post hoc test (p<0.05).

At baseline (T0), Decliners (red line) reported the highest sweetness intensity, higher than both Enhancers and Non-altered. However, their perception progressively decreased during treatment, reaching its lowest level at TF, where scores were significantly lower than at T0 and the other clusters.

Non-altered (yellow line) showed non-significant alteration in perceived intensity of sweet during treatment period. The Enhancers (blue line) showed an opposite trend to the Decliners, starting with the lowest scores at T0, but progressively increasing during treatment, reaching a peak at TF. The difference between T0 and TF, however, was not significant.

Higher concentration

The percentages of identification for the five stimuli at higher concentration are shown in Table 14. Recognition of sweetness and pungency remained consistently

high throughout the observation period, with accuracy levels approaching 90–100%. Conversely, sourness identification showed non-significant decline after the sixth treatment cycle, with correct identification dropping to 72.22%. When not correctly identified as sour, participants most frequently misclassified the solution as astringent (19.5%).

The bitter solution showed identification rates stabilized at around 80–85% even before the start of treatment. A significant decline was observed after the sixth cycle, with correct identification dropping to 66.67%. When incorrectly identified as bitter, participants misclassified the solution most frequently as sour (30.5%).

Saltiness was correctly identified before treatment (95.77%) and remained relatively stable after the first cycle (91.67%). However, a significant decline in identification was observed after the second cycle. At this time point, when not correctly recognized as salty, participants most frequently misclassified the stimulus as astringent (46.2%), sour (38.5%), bitter (7.7%), or sweet (7.7%). Identification rates subsequently recovered, although they remained slightly below baseline, stabilizing around 85–90% in the following time points.

Table 14 Percentage of identification of higher concentration samples at baseline (T0), the first (T1), the second (T2), the fourth (T4), the sixth (T6), the eighth (T8) cycles of chemotherapy, and at follow up (TF). p-values in parentheses refer to McNemar's test

Higher concentration aqueous solutions	T0 Correct identification %	T1 Correct identification % (McNemar test p-value difference T0-T1)	T2 Correct identification % (McNemar test p-value difference T0-T2)	T4 Correct identification % (McNemar test p-value difference T0-T4)	T6 Correct identification % (McNemar test p-value difference T0-T6)	T8 Correct identification % (McNemar test p-value difference T0-T8)	TF Correct identification % (McNemar test p-value difference T0-TF)
Sweet (sucrose 200 g/l)	100	100	100	100	97.22	100	100
Sour (citric acid 4 g/l)	91.55	95.83	89.29	89.36	72.22	90	81.50
Salty (NaCl 15 g/l)	95.77	91.67	80.36 (**.004**)	89.58	86.49	86.67	88.89
Bitter (caffeine 3 g/l)	88.73	85.42	85.71	85.42	66.67 (**.012**)	80	87.04
Pungent (capsaicin 0.0015 g/l)	100	93.95	94.43	89.60	91.67	97.70	98.15

Kruskal-Wallis analysis of perceived intensity for all higher concentration aqueous solutions showed a significant overall decline during treatment ($\chi^2(6)=35.61$, $p<.0001$). As shown in Figure 13, the trend was fluctuating, with significant decrease observed after the 1st, 4th, and 8th cycles of therapy.

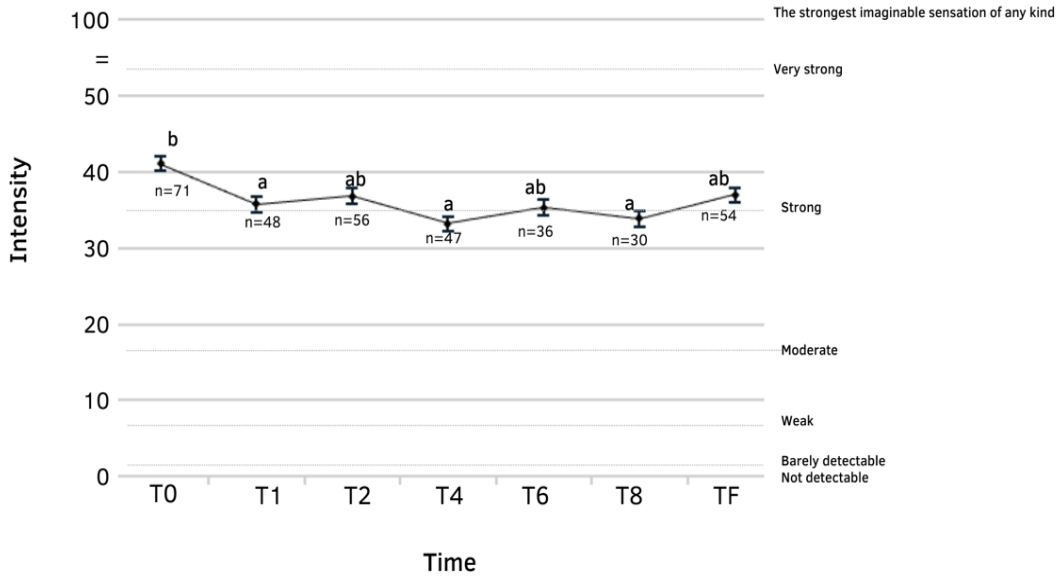


Figure 13 Mean intensity ratings of higher concentration aqueous solutions. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction.

For the higher concentration sweet solution, perceived intensity showed a trend of decrease close to significance ($\chi^2(6)=12.17$, $p=.058$), as shown in Figure 14. Overall, the perception of sweetness remained in the "strong" intensity range but decreased throughout treatment, with a nadir at the fourth cycle.

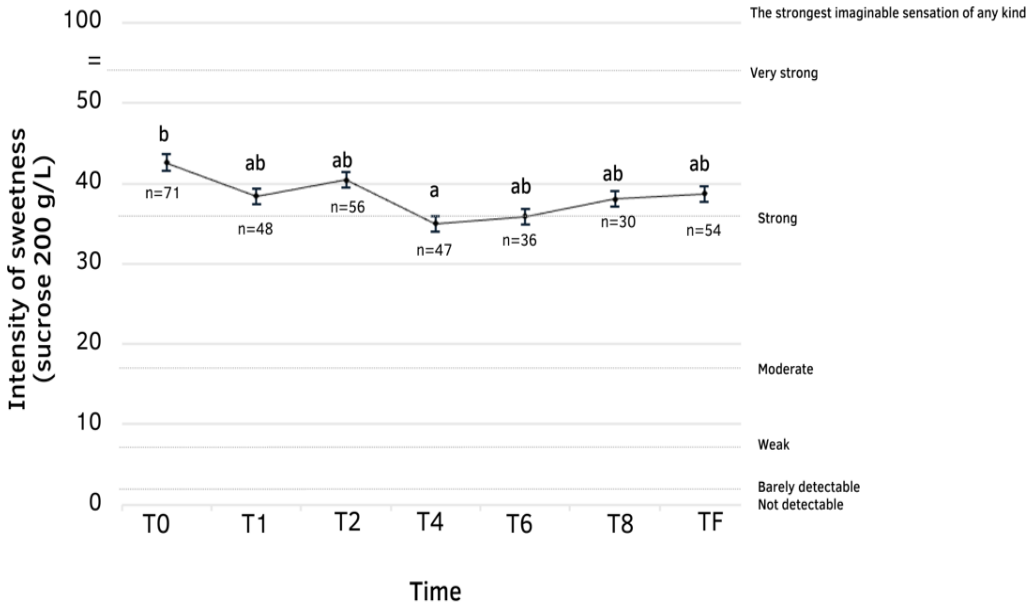


Figure 14 Mean intensity ratings of higher concentration sweet solution. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction.

For the higher concentration salty solution, a significant overall effect of time on perceived intensity was observed ($\chi^2(6)=12.17$; $p=.001$). As shown in Figure 15, intensity values progressively decreased during treatment, with significant reductions at T4, T6, and T8.

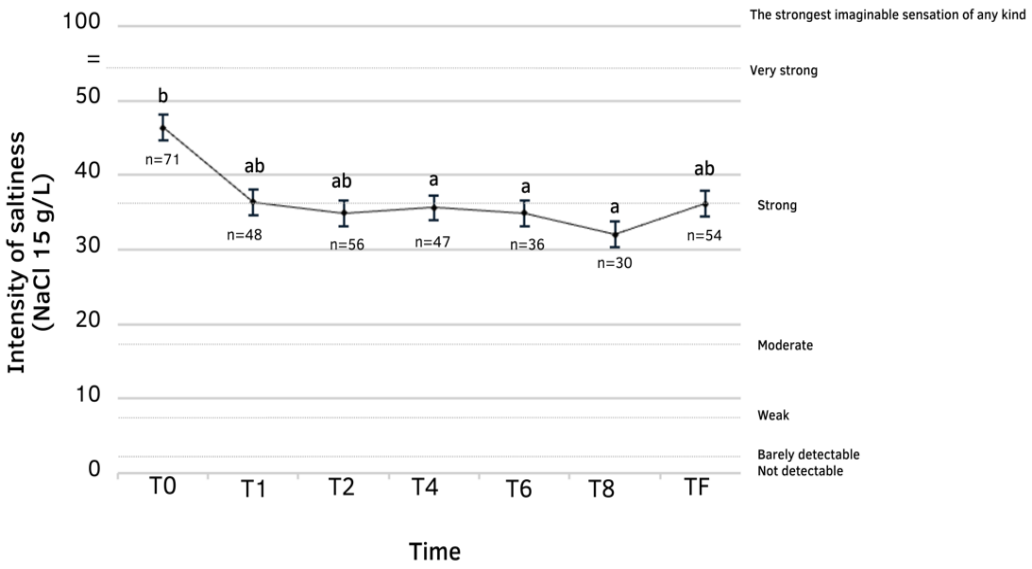


Figure 15 Mean intensity ratings of higher concentration salty solution. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction.

Although a slight increase in perceived intensity was observed at the final time point (TF, three months after treatment), suggesting a recovery, the mean intensity ratings did not return to baseline (T0) values, staying around the "strong" label.

Insights on a specific group: Interindividual variability in sensory trajectories of breast cancer patients

PCA analysis from a subgroup of breast patients conducted on the intensity ratings of the stimuli (sweet, salty, sour, bitter, pungent) at lower and higher concentration explained 56.73% of the total variance between the first two components (F1=40.88%, F2=15.85%).

As shown in the biplot (Figure 16), all stimuli were projected on the right side of the graph, correlated with the first component. This axis can therefore be interpreted as a gradient of perceived intensity, ranging from a weak perception on the left to a strong perception on the right side of the graph.

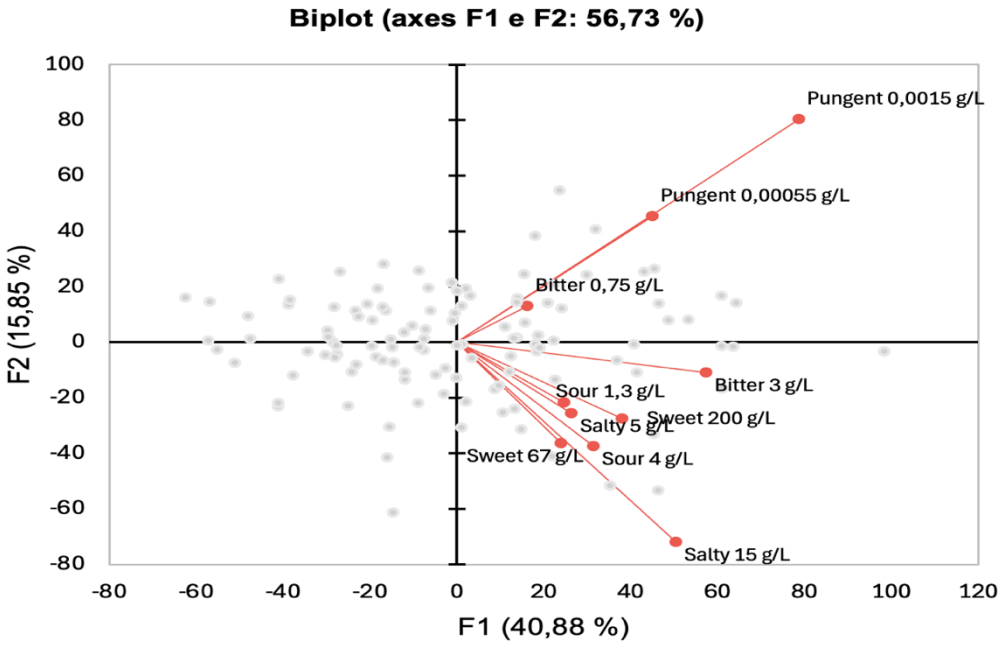


Figure 16 Bi plot of PCA conducted on intensity ratings of higher and lower concentration aqueous solutions in a subgroup of breast cancer patients. Vectors represent the perception of stimuli positively related along the first component.

By connecting the sequential time points for each subject (T0->T2->T4->TF), it was possible to identify four types of trajectories of chemosensory change:

- **decliners** (red lines) (Figure 17): subjects showing a progressive shift from right to left, corresponding to a decrease in intensity perception during treatment without recovery.
- **recovering decliners** (orange lines) (Figure 18): subjects who initially shifted to the left (loss of intensity) but then returned to the right, indicating a partial or complete recovery of perception in subsequent phases.
- **enhancers** (green lines) (Figure 19): participants showing a left-to-right trajectory, suggesting an increase in perceived intensity over time.
- **recovering enhancers** (blue lines) (Figure 20): individuals whose trajectories shifted to the right (increase) and then back to the left.

This visualization highlights the heterogeneity of the dynamic of individual responses, showing that while some patients experience a persistent decline in chemosensory function, others show an increase, or fluctuating patterns over the course of chemotherapy.

Figure 17 Trajectories of decliners (red lines) across treatment time points. Each line connects the sequential time points for the same subject (T0 → T2 → T4 → TF). This pattern reflects a progressive reduction in chemosensory perception throughout treatment, with no recovery observed at follow-up.

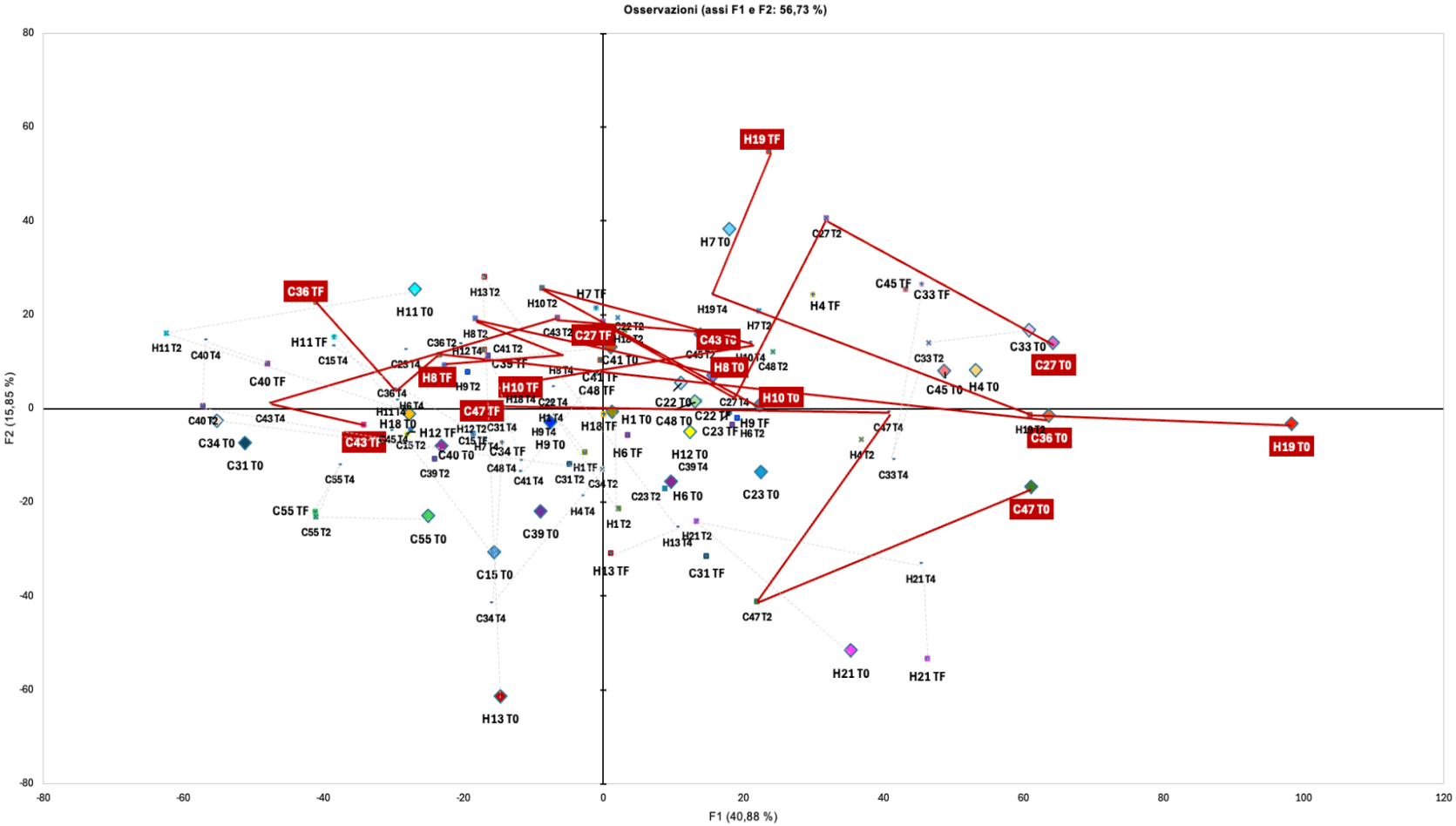


Figure 18 Trajectories of recovering decliners (yellow lines) across treatment time points. Each line connects the sequential time points for the same subject (T0 → T2 → T4 → TF). This pattern reflects a progressive reduction in chemosensory perception throughout treatment, with recovery at follow up.

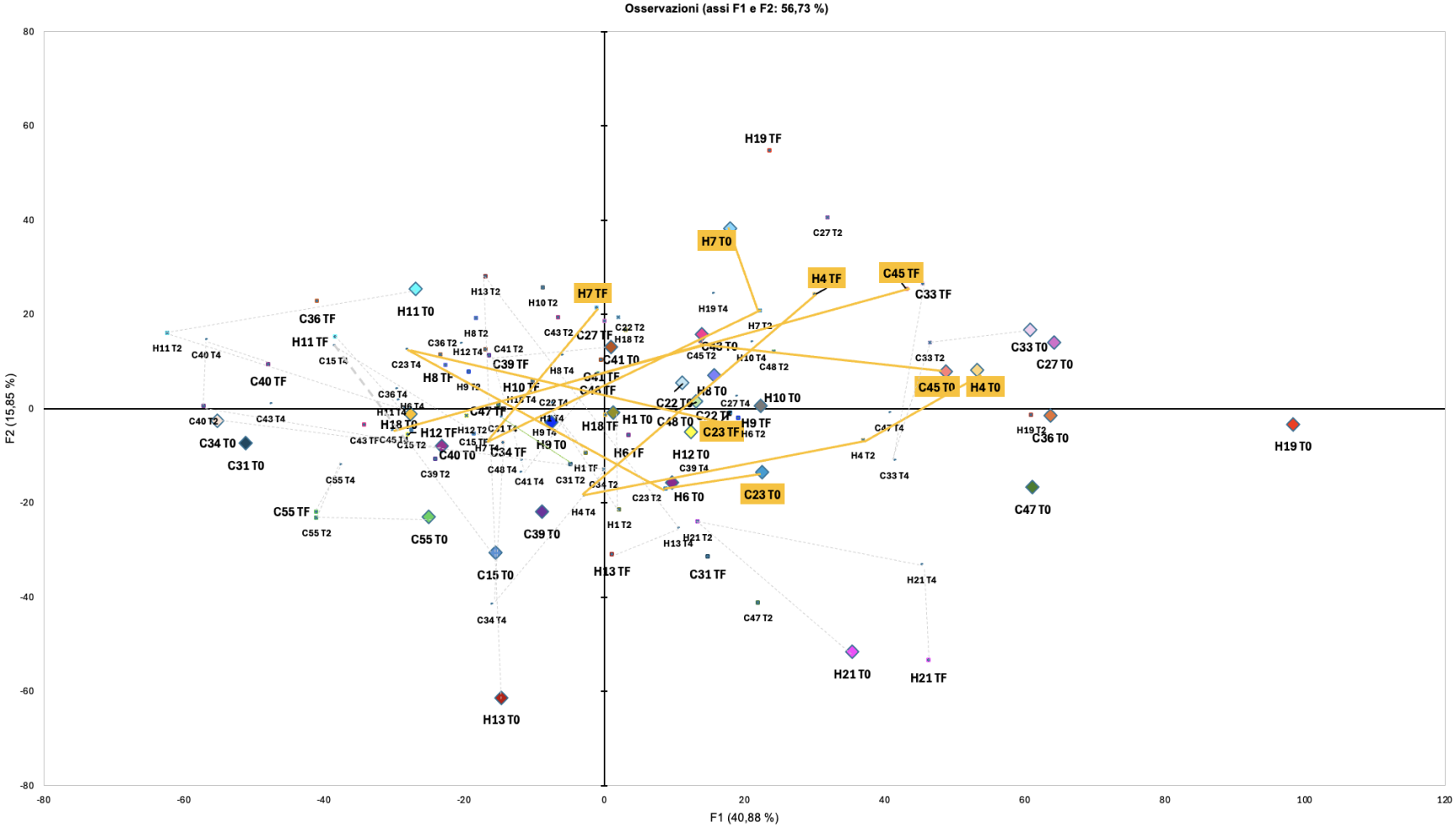


Figure 19 Trajectories of enhancers (green lines) across treatment time points. Each line connects the sequential time points for the same subject (T0 → T2 → T4 → TF). This pattern reflects an increase in chemosensory perception throughout treatment, with no recovery observed at follow up.

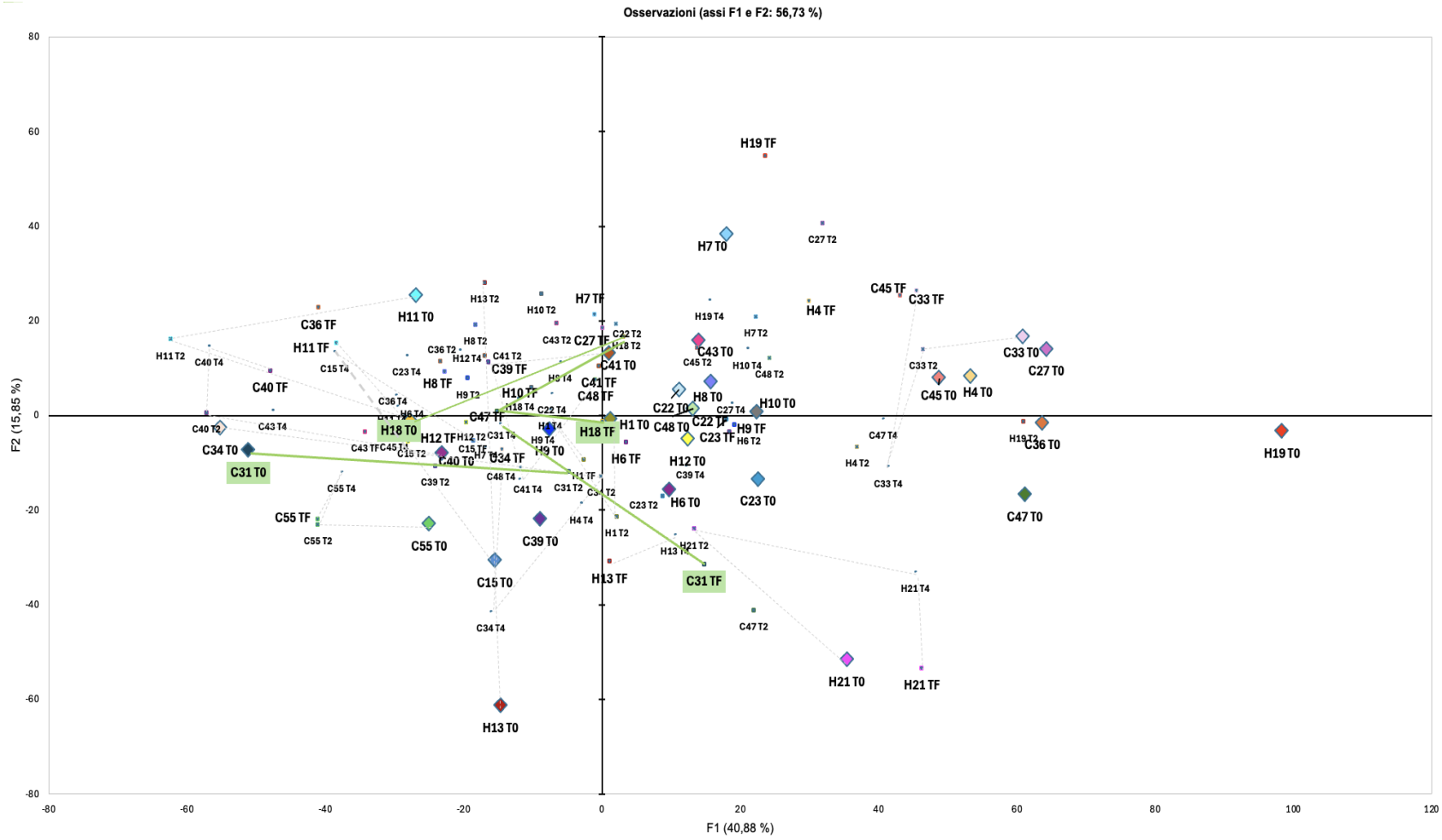
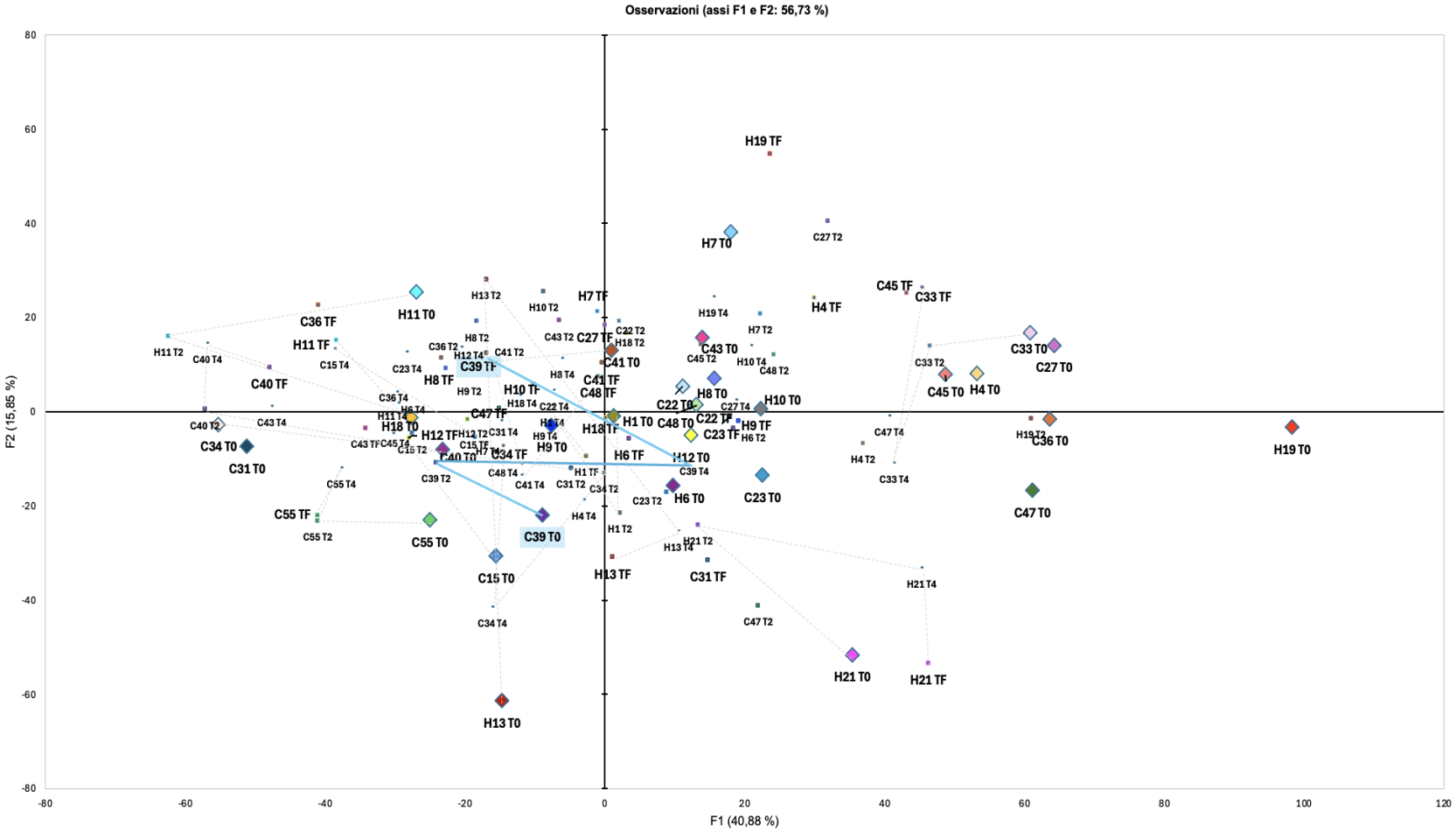


Figure 20 Trajectories of recovering enhancers (blue lines) across treatment time points. Each line connects the sequential time points for the same subject (T0 → T2 → T4 → TF). This pattern reflects an increase in chemosensory perception throughout treatment, with recovery at follow up



4.2.3 Self-reported chemosensory perception and alterations

4.2.3.1 Self-reported ability to perceive taste and alterations of chemestetic sensations

As illustrated in Figure 21, self-reported ability to perceive tastes changed significantly over time (χ^2 (6)=112.99, p<.0001). At baseline (T0) and after the first cycle (T1), patients reported high scores (means above 7), indicating generally good taste perception. However, a marked decline was observed starting from the second cycle (T2), with scores decreasing significantly (approximately 5.5) until T8. Self-assessments showed significant recovery at follow-up (TF), with values returning to statistically comparable levels at baseline (T0 and T1).

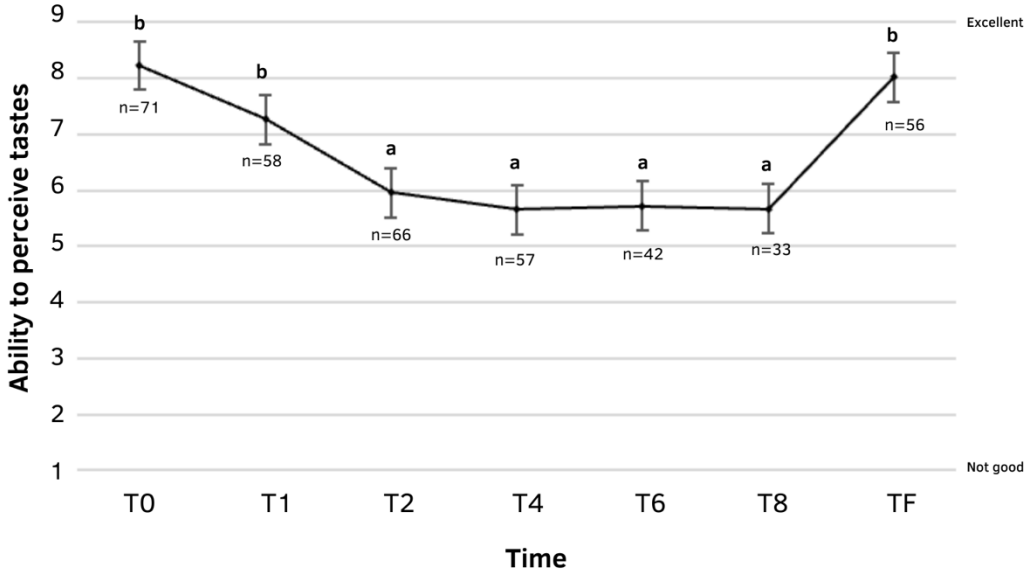


Figure 21 Mean intensity ratings of self-reported ability to perceive tastes across treatment time points. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction (p=0.0024).

Figures 22, 23, and 24 show patients' responses to the question assessing chemesthesic sensations, such as pungency, coolness, and tingling, typically elicited by compounds like capsaicin, menthol, or sparkling water. The question specifically asked whether patients noticed changes in these oral sensations after

chemotherapy cycles or at the end of treatment comparing them with the period before the start of treatment.

The data show that the self-reported perception of spiciness (Figure 22) remains relatively stable after the first cycle (T1), with the majority of patients (84.5%) reporting no change. However, from T2, the percentage of patients perceiving these sensations as altered progressively increases. Specifically, at T8, only 48.5% of respondents still reported a usual spiciness perception, while 21.2% perceived a reduction and 30.3% an intensification of these sensations.

At follow-up (TF), a clear trend towards recovery is observed. The percentage of patients reporting normal spiciness perception increases to 80.3%, while altered perceptions decrease significantly.

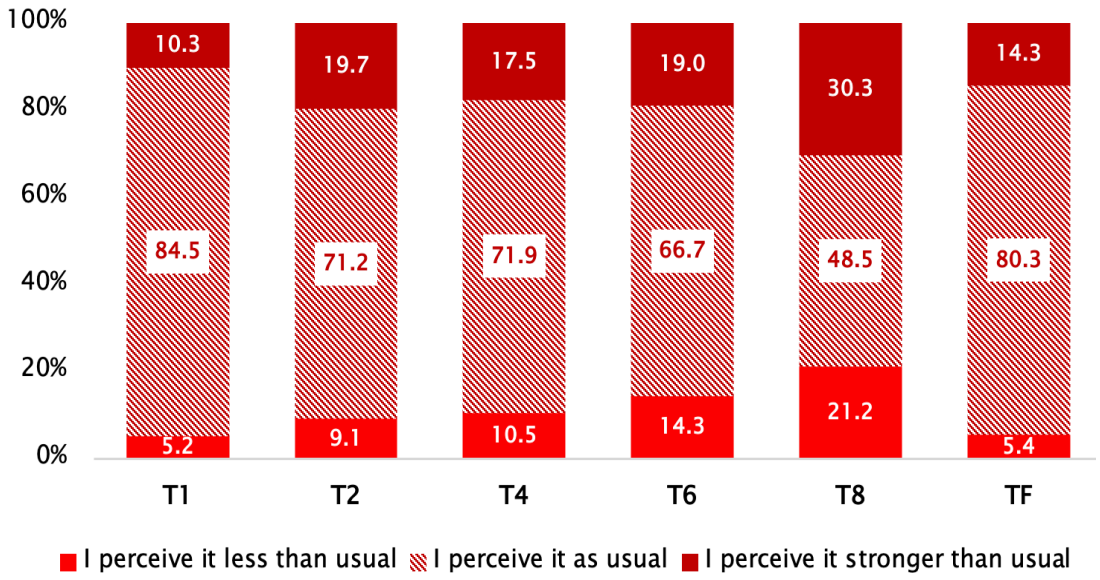


Figure 22 Self-reported spiciness perception after the start of the treatment. Pink indicates "I perceive it less than usual", red lines indicate "I perceive it as usual", red indicates "I perceive it stronger than usual".

The perception of coolness (Figure 23) shows a variable trend during chemotherapy treatment. After the first cycle (T1), most patients (82.8%) reported an unchanged perception, but after the second cycle (T2) only 60.6% perceived coolness as usual, while 13.6% perceived it as less intense and 25.8% as more intense. After the fourth

cycle (T4), an increase in patients reporting hypersensitivity to coolness was observed (33.3%). After the sixth cycle (T6), perception began to progressively normalize. At T8, 69.7% of patients perceived coolness as usual, with a reduction in alterations. Three months after the end of therapy (TF), an almost complete recovery of perception is observed: 87.5% of patients report normal perception, while increased or decreased perceptions are drastically reduced (7.1% and 5.4%, respectively).

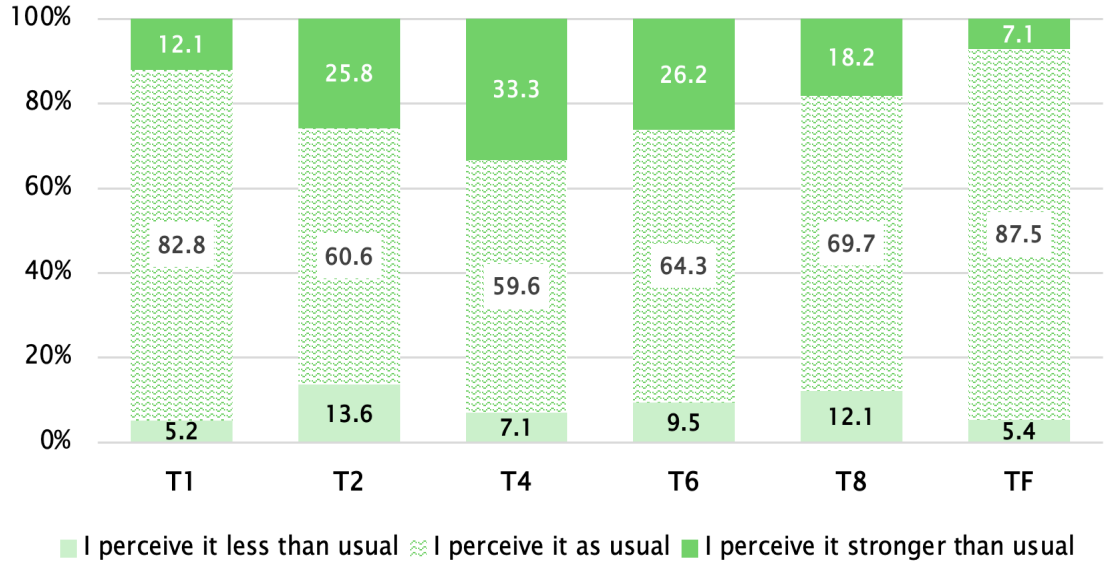


Figure 23 Self-reported coolness perception after the start of the treatment. Light green indicates "I perceive it less than usual", green lines indicate "I perceive it as usual", dark green indicates "I perceive it stronger than usual".

The perception of tingling (Figure 24) shows a variable trend during chemotherapy treatment. After the first (T1) and second (T2) cycles, most patients (respectively 87.90% and 84.80%) reported an unchanged perception, but after the fourth cycle (T4) 77.20% perceived tingling as usual, while 17.50% perceived it as stronger. Similarly, at T6 and T8 14.30% and 24.20% of patients reported the tingling perception stronger as usual. Three months after the end of the treatment an almost complete recovery of perception can be observed.

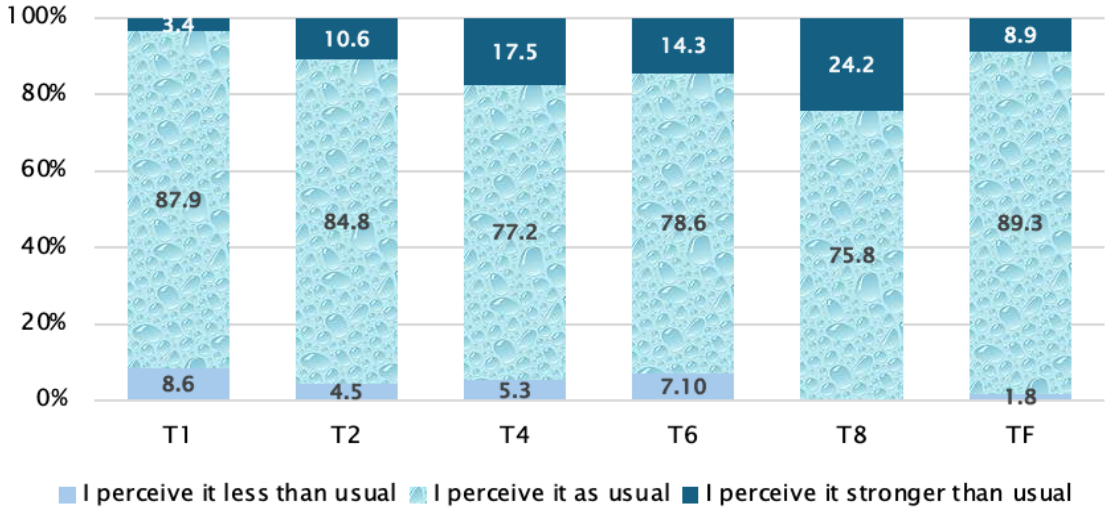


Figure 24 Self-reported tingling perception after the start of the treatment. Light blue indicates "I perceive it less than usual", blue bubbles indicate "I perceive it as usual", dark blue indicates "I perceive it stronger than usual".

4.2.3.2 Self-reported ability to perceive smell and its alterations

As illustrated in Figure 25, self-reported ability to perceive smell remained consistently high throughout the observation period, with mean scores never falling below 7, which could be considered a good level on the scale. Although the

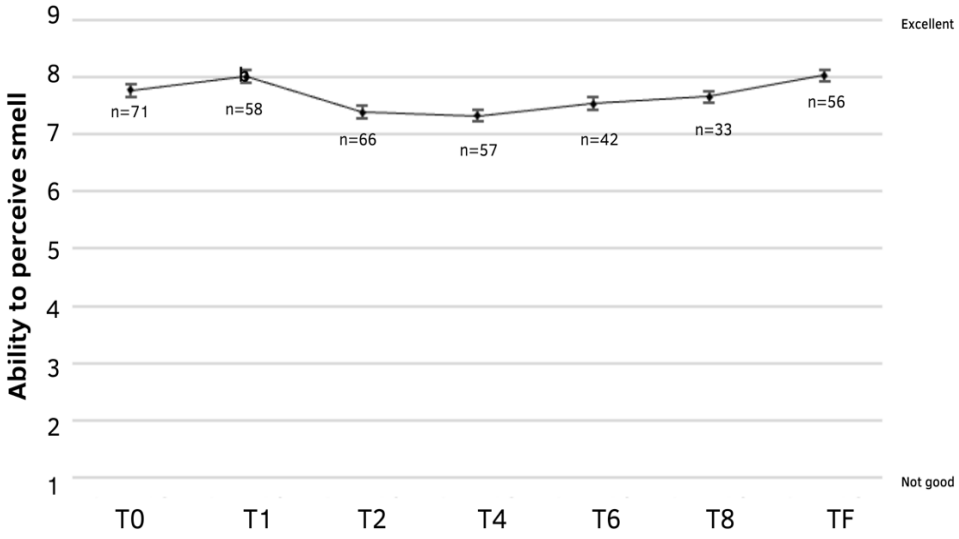


Figure 25 Mean intensity ratings of self-reported ability to perceive smells across treatment time points.

Kruskal-Wallis test indicated a statistically significant effect of time ($\chi^2(6)=14.27$,

p=.027), Dunn's post hoc comparisons with Bonferroni correction revealed no significant differences between specific time points.

Figure 26 shows the results of the descriptive analysis of the "Check-All-That-Apply" (CATA) assessment of changes in odor perception during and after chemotherapy (T1-TF). Because the question explicitly addressed changes, it was administered only after treatment began, and participants could select multiple options simultaneously.

Overall, descriptive analysis shows that across all time points, a substantial percentage of patients reported no noticeable changes in odor perception, as shown also in the previous graph regarding odor perception ability, with the highest frequency observed at TF (80.3%) and the lowest at T2 (54.5%). This general trend suggests that, for many patients, olfactory function is perceived as largely preserved. However, alterations were reported by some patients, especially between T2 and T8. The most frequently selected changes included: increased odor intensity, peaking at T8 (30.3%), odors perceived as unpleasant (e.g., previously pleasant odors now bothersome) were consistently reported over time (12–24%), peaking at T8 (24.2%). Specific bothersome odors often included cooked and fried foods, coffee, smoke, detergents, and perfumes.

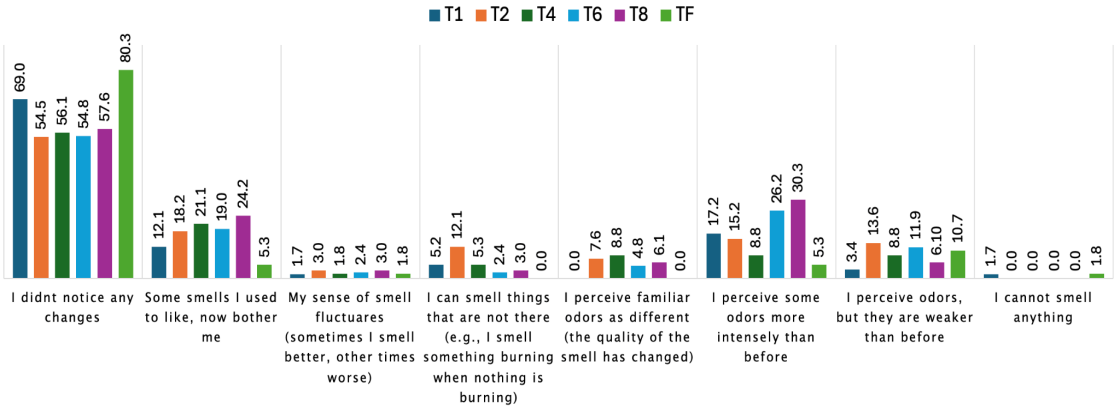


Figure 26 Descriptive analysis of changes in odor perception during and after chemotherapy.

4.2.3.3 Self-reported chemosensory alterations

Responses over time of Chemotherapy induced Taste Alteration Scale

To explore the evolution of self-reported chemosensory alteration over time, CiTAS scores were analyzed using the Kruskal-Wallis test, assessing differences across time points.

Self-reported scores on the "Decline in Basic Tastes" (Figure 27) dimension of the CiTAS showed a significant increase ($\chi^2(6)=101.76$, $p<.0001$) in mean scores starting from T2, indicating a reduction in the ability to perceive basic tastes (sweet, salty, sour, bitter, and umami). However, at TF, the post hoc Dunn's test following the Kruskal-Wallis analysis showed no significant differences from baseline, suggesting a recovery in the perception of basic tastes as reported by patients.

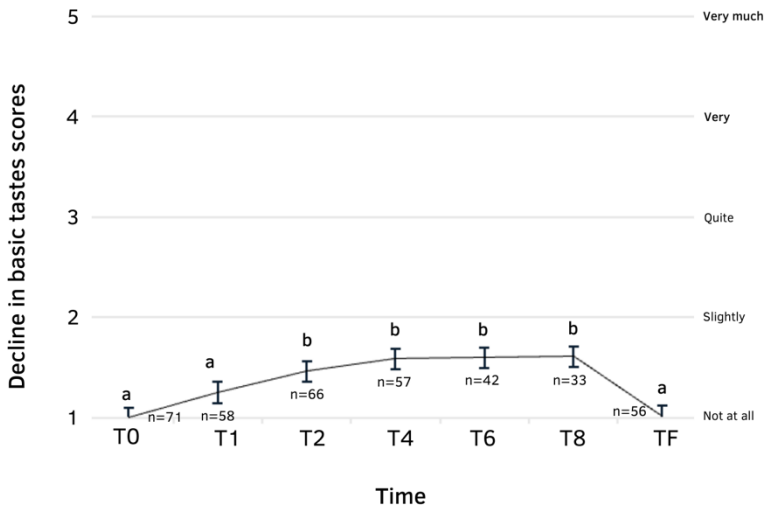


Figure 27 Mean scores of "Decline in basic tastes" dimension across treatment period. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction (p=0.0024).

Self-reported scores on the CiTAS "General Taste Alteration/Parageusia/Increase in Taste Perception" (Figure 28) dimension showed a significant increase

($\chi^2(6)=113.39$, $p<.0001$) in mean scores starting from T1, indicating an early occurrence of these types of alterations. Dunn's post hoc test with Bonferroni correction showed a peak in reported alterations at T4, followed by a gradual return to baseline levels. At TF, scores suggested a complete recovery.

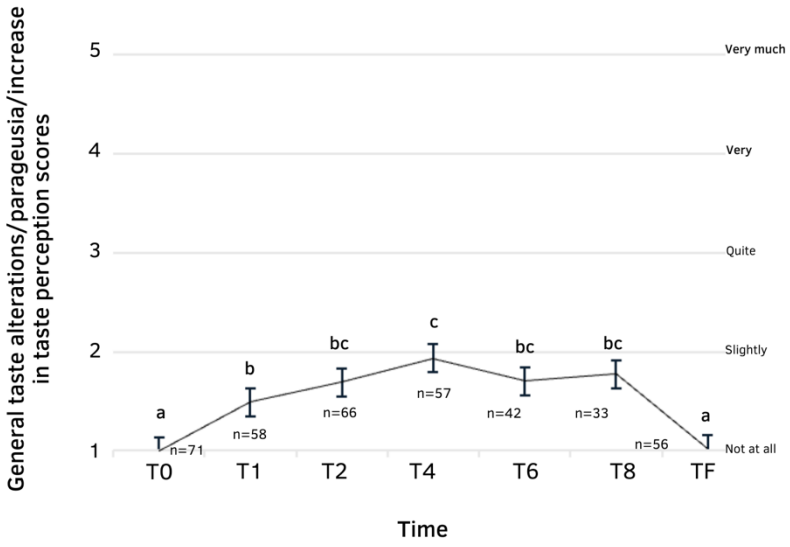


Figure 28 Mean scores of "General taste alterations/parageusia/increase in taste perception" dimension across treatment period. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction (p=0.0024).

Phantogeusia (Figure 29) was significantly reported starting from T1 ($\chi^2(6)=91.88$; $p<.0001$), with persistently elevated values up to T8 and a decrease at TF.

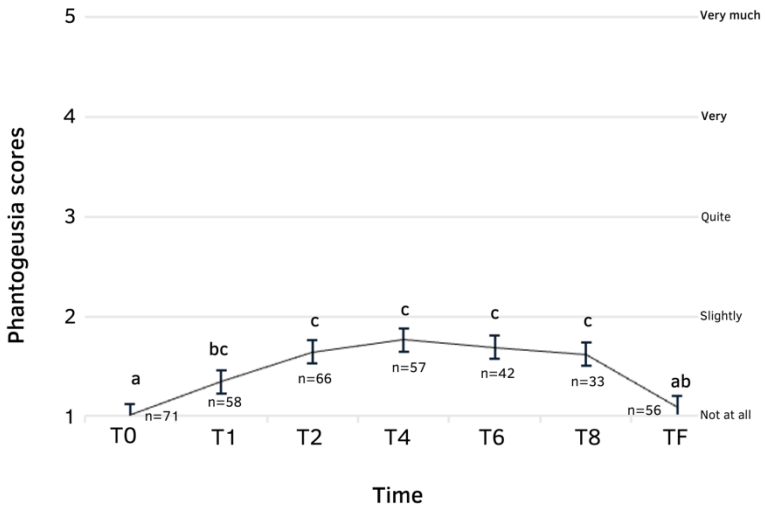


Figure 29 Mean scores of "Phantogeusia" dimension across treatment period. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction (p=0.0024).

Discomfort (Figure 30), reported by some patients already before the start of therapy, increased significantly after the first cycle, returning to values similar to T0 at follow-up($\chi^2(6)=98.24$; $p<.0001$).

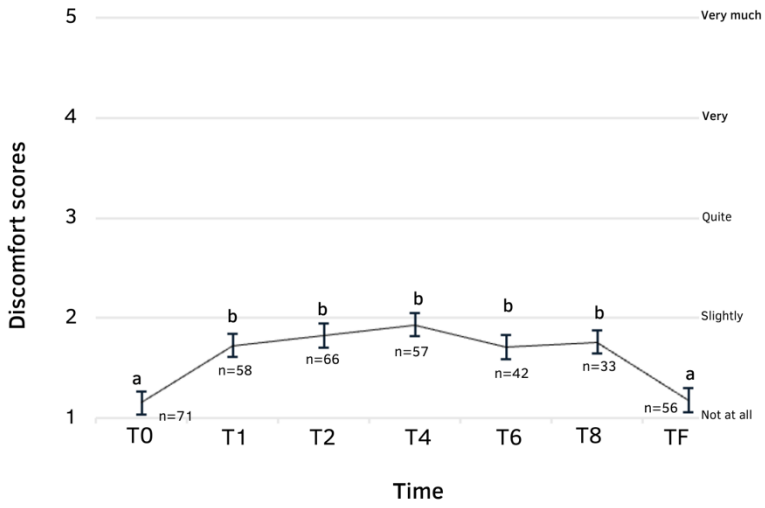


Figure 30 Mean scores of "Discomfort" dimension across treatment period. Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction (p=0.0024).

Patients' classification based on CiTAS scores

Patients were classified with self-reported alterations or related conditions through the CiTAS first by calculating the average score for each dimension per patient, then by identifying as "patients with alterations/with discomfort" those for whom the score was different from 1 (="not at all") for each dimension. Table 15 shows the percentage of patients who self-reported the different types of conditions (mean scores >1) represented by the CiTAS dimensions before the start, during the treatment, and at follow-up.

Table 15 Percentage of patients who self-reported the different types of conditions represented by the CiTAS dimensions during the baseline (T0), the first (T1), the second (T2), the fourth (T4), the sixth (T6), the eighth cycles of chemotherapy, and the follow-up (TF).

	% of patients self-reporting alteration						
CiTAS dimension	T0	T1	T2	T4	T6	T8	TF
Decline in basic tastes	0.0	20.7	50.0	57.9	54.8	66.7	8.9
General taste alterations /parageusia/ increase in taste perception	0.0	39.7	57.6	64.9	59.5	57.6	7.1
Phantogeusia	2.8	44.8	59.1	61.4	57.1	66.7	17.0
Discomfort	47.9	81.0	87.9	85.9	85.7	93.9	28.6

4.2.3.4 Qualitative insights into the nature of chemosensory alterations

In addition to the structured questionnaires, interviews provided further information on the nature of chemosensory alterations as they are experienced by patients in everyday life. Patients were asked to recall the sensations and perceptions they experienced in the days following the last treatment, when the interviews took place (immediately before the next infusion).

During treatment the most frequently mentioned disorder was the **occurrence of a phantom metallic/chemical/bad/bitter/blood taste in the mouth**, but even “acid” and “sweet” or “licorice” were mentioned. The metallic taste was the most mentioned, and sometimes it was perceived with the food itself:

“I always have a very strong metallic taste in my mouth when I'm resting. When I eat, it also mixes with the bitter and sour tastes. Food no longer tastes the way it should and the way I remember it."

“I have a metallic taste in my mouth, like the taste of blood”

“I have a metallic taste in my mouth, my teeth also feel metallic, and I also taste metallic in “food.”

Some patients reported **phantom odors that were occasionally linked to taste**, with some patients perceiving them as metallic or medicinal:

"I seem to smell a metallic odor at times, and I can even feel it in my mouth"

Several patients experienced **changes in the quality of taste of foods**, reporting altered tastes **(parageusia)**:

"Fruit purees taste sour and bitter even though they're not,"

"Tea with two tablespoons of honey tasted bitter"

"Parmesan cheese tasted sour/rancid"

"Chocolate tastes totally different, rancid, sour."

"Bread tastes like mud, it's disgusting!"

“Meat tastes a bit metallic”

Some patients reported that the **bad taste (in mouth or in food)** was triggered or intensified by drinking water or wine:

"Water triggers a metallic taste"

“The food was bitter. It all started with a glass of wine at a restaurant, and from there it continued for all foods. So, I had a severe loss of appetite”

Patients often described a **loss of taste, particularly for salty, sweet, and sour (hypogeusia)**

"Everything seems saltless"

"Grandma's lasagna tasted like nothing"

"It feels like eating cardboard",

"Nutella and jam seemed less sweet",

"I could no longer tell the difference between coffee with sugar and coffee without sugar!"

"I also tasted less sour in lemon"

"I also tried eating lemon, which usually gives me the shivers just thinking about it because it bothers me so much, I didn't feel anything".

Conversely, some reported a **heightened perception or an aversion for certain tastes** or foods:

"The ham was super salty. I can't eat it!"

"The coffee was more bitter and I don't drink it for my usual breakfast".

"I've noticed the tastes are much stronger. Everything is stronger, and this is accentuated by the salt and seasonings."

Discomfort was often associated with these changes, with patients reporting **burning sensations, mouth ulcers, or general oral irritation**:

"My tongue feels like fire"

"My mouth feels cooked, burned"

"My mouth feels sore"

"My mouth feels numb"

"I have a metallic taste, but I think it's because my mouth is corroded and it peels easily. So, it could be the taste of blood"

Some patients linked these sensations to **nausea, loss of appetite, or disgust**, while others attributed the changes to **dry mouth**.

“My mouth always feels sour, and the day I started treatment, the acid bothered me; it felt stronger… Then my mouth started to become dry and I could taste the bitterness from the day after treatment.”

“I had a lot of nausea so the tastes bothered me.”

“I have constant nausea and I don't know if that's interfering with my appetite and making me less appreciative of food. My appetite has decreased.”

About olfactory changes, patients described a wide variety of disorders during chemotherapy, ranging from reduced sensitivity to odors to increased perception, to the appearance of phantom odors. Many reported a general amplification of odors:

"Smells bothered me. I smelled them too strong... even the smell of flowers, cut grass, and cigarette smoke (and I'm a smoker!) bothered me; they were very strong and made me nauseous"

This hypersensitivity was often linked to **nausea**, especially when **triggered by cooking odors** or specific foods such as coffee, meat, or fried foods:

"The smell of coffee really bothers me"

"I can't stand the smell of coffee and ragù”

"Once my son made fried cutlets, and I couldn't stay home. The smell was too strong"

In many cases, **hypersensitivity** was reported to perfumes and detergents.

"I smell stronger, more intense scents, for example, that of bathroom freshener"

"The perfume my children wear bothers me"

Others described distorted perceptions or the presence of unpleasant odors that weren't actually there, reflecting **experiences of phantosmia**:

"Sometimes I smell odors that aren't there: in particular, I could smell and taste like scorpionfish soup, even though no fish or tomatoes were cooking in the house"

"Sometimes I smell unpleasant odors that aren't actually there. For example... I smell something like mold, and I also smell an odor of public restrooms"

"I smell odors that aren't there, both good and bad, but they're not actually there. I've even smelled the scent of flowers coming up from the sink drain"

Conversely, a smaller group of patients reported a diminished sense of smell:

"The smell is gone. I couldn't even smell strong odors like garlic"

Moreover, many women noted that the perceived intensification of odors was related to previous experiences, such as pregnancy.

"I smell stronger odors, just like during pregnancy"

Several patients mentioned a **change in their body odor**:

"I feel like my skin odor has changed; I feel like I stink. I can't explain what it smells like. I don't sweat, and it doesn't smell like sweat; it's just a strange odor"

"After a shower, I smell a metallic odor coming from my body".

Others reported increased sensitivity to specific environmental odors, including those associated with medical settings, due to **phenomena of conditioned odor/taste aversions**:

"The smell of the hospital makes me nauseous every time I go in"

"I used to like soups and broths, but even now I can't eat them because the smell reminds me of the hospital. I'm bothered by smells that remind me of the hospital canteen, like soups and broths... It's not a question of perception, but of association with the hospital. The other day I passed by the hospital, and even though there wasn't actually any smell of food, it was as if I imagined it".

At **follow-up (TF)**, patients described a general improvement in their chemosensory perception, often referring to a progressive return to normal. Many reported a complete recovery:

"Everything is back to normal"

"I think everything is back to how it was before the therapy"

Some even described a renewed enjoyment of food:

"I finally enjoy eating again"

"I think I've even gained weight because I appreciate food more now"

However, recovery was not universal. Several patients continued to experience specific **changes in taste intensity or discomfort** with certain sensations:

"Sometimes I still get a strange aftertaste in my mouth"

"The spicy and sparkling sensations seem more intense than before"

"I still can't eat spicy food; it burns"

"Salty foods don't taste the same. I still don't taste much salt, I notice this because I always have to add a lot of it"

Regarding olfactory perception, most participants reported an improvement, although **recovery was sometimes partial.** Some noted a reduction in their sense of smell compared to the pre-treatment period:

"I seem to perceive fewer odors than before"

Others reported **increased sensitivity**, especially to odors they associated with treatment:

"I still smell everything more strongly; perhaps it's a psychological issue"

"There are odors that remind me of chemotherapy and make me feel unwell, like the smell of disinfectant of the hospital"

4.2.3.5 Timing and duration of chemosensory alterations: insights from qualitative Interviews

Qualitative interviews provided a detailed account of the evolution of chemosensory alterations over time, allowing for a precise reconstruction not only of the nature of the chemosensory alterations, but also of their occurrence and

duration. Because the tests were conducted a few days before the next chemotherapy administration, patients were able to recall and describe with relative precision the sensations they experienced at home, in everyday life, and in the moments immediately following treatment.

Interviews revealed that the onset of sensory alterations often occurs within 24 hours of chemotherapy administration, sometimes even during the same day. Indeed, several patients reported noticing changes *"as early as the day"* of treatment, or *"from the evening"* of the infusion, or *“the day after”.*

The changes often peaked in the first few days and gradually subsided over the course of the week. One patient clearly described this progression:

"For me, it starts the day of chemotherapy and lasts about five days. Then I slowly start to taste things again"

Others indicated similar timescales, sometimes referring to specific patterns that repeated themselves with each cycle:

"It was like clockwork: the day after chemotherapy, everything had a metallic taste. Then around the fourth day, it started to subside"

"After the 'red' therapies, everything tasted bitter. But by the fifth or sixth day, I felt a little better"

However, some patients experienced more persistent or fluctuating changes. Some reported that taste disturbances could last more than a week or appear and disappear unpredictably:

"Sometimes they would last until the next chemotherapy session, sometimes they would disappear and recur without warning"

“It's getting better now (about 3 weeks), but it's not completely back to normal yet because I still can't taste the salt”

“It still hasn't gone away after 3 weeks”

“After 10 days it starts to get better”.

4.2.4 Impact of individual differences on chemosensory perception and alterations during treatment

Impact of food neophobia on perceived intensity of aqueous solutions

To explore the relationship between food neophobia and chemosensory perception of aqueous solutions during treatment, at each time point, correlations were computed between food neophobia scores and the perceived intensity of each aqueous solution using Spearman's rank correlation coefficient (ρ), given the non-normal distribution of the data. The correlation coefficients (Spearman's ρ) and their corresponding significance levels (p-values) for each time point and taste modality are summarized in Table 16.

Table 16 Spearman's rank correlation coefficients (ρ) between food neophobia scores and the perceived intensity of basic tastes and pungent aqueous solutions at each treatment time points. p-values (in parentheses) are reported only for significant correlations (p<.05).

	T0	T1	T2	T4	T6	T8	TF
				Food neophobia score			
Sweet intensity (67 g/L)	0.078	0.212	0.079	-0.164	0.270	0.197	0.142
Sour intensity (1.3 g/L)	0.104	0.301 (**.038**)	0.058	0.093	-0.032	0.049	0.341 (**.012**)
Salty intensity (5 g/L)	0.015	0.174	0.185	-0.040	-0.081	-0.037	0.067
Bitter intensity (0.75 g/L)	-0.011	-0.138	-0.017	-0.373 (**.009**)	0.072	0.058	0.138
Pungent intensity (0.00055 g/L)	-0.002	0.138	-0.074	-0.281	-0.115	0.215	0.016
Sweet intensity (200 g/L)	0.103	-0.005	-0.087	-0.042	0.026	0.154	0.203
Sour intensity (4 g/L)	0.154	0.059	-0.005	0.156	-0.137	0.236	0.131
Salty intensity (15 g/L)	-0.049	0.164	0.069	0.084	-0.154	-0.381 (**.039**)	-0.121

Bitter intensity (3 g/L)	0.143	0,147	-0.194	-0.079	0.345 (**.040**)	0.102	-0.193
Pungent intensity (0.0015 g/L)	-0.058	0.028	-0.097	-0.084	-0.190	-0.190	-0.011

Most correlation coefficients were weak and not statistically significant, indicating that food neophobia did not substantially influence the perceived intensity of aqueous solutions overall. However, few moderate associations emerged at isolated assessments: higher food neophobia was associated with lower ratings for bitter at lower concentration at T4 ($\rho = -0.373$) and for salty at higher concentration at T8 ($\rho = -0.381$), whereas it was associated with higher ratings for sour at lower concentration at T1 ($\rho = 0.301$) and TF ($\rho = 0.341$) and for bitter at higher concentration at T6 ($\rho = 0.345$). No consistent longitudinal pattern was observed across stimuli or concentrations.

Impact of food neophobia on self-reported chemosensory alteration

Correlations between food neophobia scores and CiTAS dimension scores were calculated at each time point using Spearman's rank correlation coefficient (ρ) to examine whether individual differences in neophobia were associated with self-reported chemosensory alterations during chemotherapy (Table 17).

Significant associations emerged only at specific time points: at T8, food neophobia was negatively correlated with both the decline in basic tastes ($\rho = -0.394$, $p = .024$) and with general taste alterations/parageusia/increase in taste perception ($\rho = -0.378$, $p = .031$), suggesting that more neophobic patients reported fewer chemosensory changes toward the end of chemotherapy.

Table 17 Spearman's rank correlation coefficients (ρ) between food neophobia scores and CiTAS scores of each dimension (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, phantogeusia, discomfort) at each treatment time points. p-values (in parentheses) are reported only for significant correlations (p<.05).

	T0	T1	T2	T4	T6	T8	TF
				Food neophobia score			
Decline in basic tastes	-	-0.048	-0.045	-0.084	-0.177	-0.394 (**.024**)	-0.115
General taste alterations, parageusia, increase in taste perception	-	-0.084	-0.116	-0.175	-0.049	-0.378 (**.031**)	0.177
Phantogeusia	0.006	-0.061	-0.243 (**.049**)	-0.240	-0.258	-0.402 (**.021**)	-0.022
Discomfort	0.017	0.094	-0.070	-0.067	-0.064	-0.331	-0.049

Furthermore, a negative correlation was found for phantogeusia at T2 (ρ=-0.243, p=.049) and T8 (ρ=-0.402, p=.021), indicating that higher neophobia was associated with a lower incidence of phantom tastes.

No significant relationships were observed for the dimension of discomfort at any time point.

These findings suggest that food neophobia is not a consistent predictor of self-reported chemosensory alterations and that the few significant correlations likely reflect transient or context-specific variations rather than systematic effects.

Impact of sensitivity to disgust on perceived intensity of aqueous solutions

To explore the relationship between sensitivity to disgust and chemosensory perception of aqueous solutions during treatment, at each time point, correlations were computed between sensitivity to disgust scores and the perceived intensity of each aqueous solution using Spearman's rank correlation coefficient (ρ), given the non-normal distribution of the data (Table 18).

Table 18 Spearman's rank correlation coefficients (ρ) between sensitivity to disgust scores and the perceived intensity of basic tastes and pungent aqueous solutions at each treatment time points. p-values (in parentheses) are reported only for significant correlations (p<.05).

	T0	T1	T2	T4	T6	T8	TF
				Sensitivity to disgust score			
Sweet intensity (67 g/L)	0.111	0.255	0.241	−0.049	0.159	0.027	−0.231
Sour intensity (1.3 g/L)	0.181	0.248	0.273 (**.042**)	−0.053	−0.078	0.006	0.061
Salty intensity (5 g/L)	0.285 (**.016**)	0.249	0.227	0.085	0.028	0.087	0.0003
Bitter intensity (0.75 g/L)	0.322 (**.006**)	0.160	0.236	−0.138	0.207	0.003	0.154
Pungent intensity (0.00055 g/L)	0.310 (**.009**)	0.188	0.180	0.075	−0.004	0.313	0.200
Sweet intensity (200 g/L)	0.287 (**.016**)	0.161	0.084	0.237	0.099	0.175	−0.110
Sour intensity (4 g/L)	0,198	0.051	0.096	−0.058	−0.025	0.072	0.110
Salty intensity (15 g/L)	0.283 (**.017**)	0.299 (**.039**)	0.463 (**.0004**)	0.142	0.005	−0.148	0.014
Bitter intensity (3 g/L)	0.343 (**.004**)	0.237	0.162	0.021	0.358 (**.033**)	0.340	0.074
Pungent intensity (0.0015 g/L)	0.111	0.267	0.235	0.304 (**.038**)	0.260	0.058	0.248

Overall, several significant positive correlations were observed, particularly at baseline (T0) and during the early stages of treatment, indicating that greater disgust sensitivity was associated with greater perceived intensity of taste stimuli. At T0, disgust sensitivity was positively correlated with salty at lower concentration (ρ=0.285, p=.016), bitter at lower concentration (ρ=0.322, p=.006), pungent at lower concentration (ρ=0.310, p=.009), sweet at higher concentration (ρ=0.287, p=.016), and salty at higher concentration (ρ=0.283, p=.017).

Further positive correlations emerged at T1 for salty at higher concentration (ρ=0.299, p=.039) and at T2 for sour at lower concentration (ρ=0.273, p=.042) and salty at higher concentration (ρ=0.463, p<.0001).

Over the course of treatment, correlations were fewer and weaker, with significant associations isolated at T6 for bitter at higher concentration (ρ=0.358, p=.033) and at T4 for pungent at higher concentration (ρ=0.304, p=.038).

No consistent associations were observed at T8 or at the post-treatment follow-up (TF).

Overall, these findings suggest that individuals with higher disgust sensitivity perceive taste and chemesthetic stimuli as more intense before and in the early stages of chemotherapy, while this relationship weakens as treatment progresses, pointing a potential decline in individuals more sensitive to disgust.

Impact of sensitivity to disgust on self-reported chemosensory alteration

Correlations between sensitivity to disgust scores and CiTAS dimension scores were calculated at each time point using Spearman's rank correlation coefficient (ρ) to examine whether individual differences in disgust were associated with self-reported chemosensory alterations during chemotherapy (Table 19).

Table 19 Spearman's rank correlation coefficients (ρ) between sensitivity to disgust scores and CiTAS scores of each dimension (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, phantogeusia, discomfort) at each treatment time points. p-values (in parentheses) are reported only for significant correlations (p<.05).

	T0	T1	T2	T4	T6	T8	TF
				Sensitivity to disgust score			
Decline in basic tastes	-	-0.002	-0.004	-0.069	-0.026	-0.101	-0.011
General taste alterations, parageusia, increase in taste perception	-	0.206	0.028	0.114	0.323 (**.037**)	0.089	0.039
Phantogeusia	-0.253 (**.033**)	0.301 (**.022**)	0.143	0.096	0.167	0.145	0.219
Discomfort	0.083	0.368 (**.005**)	0.236	0.153	0.311 (**.045**)	0.166	0.069

Overall, several positive associations emerged at specific time points, suggesting that greater disgust sensitivity was related to more intense self-reported chemosensory disturbances during chemotherapy.

Specifically, disgust sensitivity was positively correlated with general taste alterations/parageusia/increase in taste perception at T6 (ρ=0.323, p=.037) with discomfort at T1 (ρ=0.368, p=.005) and T6 (ρ=0.311, p=.04). Interestingly, sensitivity to disgust was negatively associated with phantogeusia at T0 (ρ=-0.253, p=.033) and positively at T1 (ρ=0.301, p=.022), indicating that after the first cycle individuals with higher sensitivity to disgust report more phantogeusia.

Impact of PROP status on perceived intensity of aqueous solutions

To explore the relationship between PROP responsiveness and chemosensory perception of aqueous solutions during treatment, at each time point, correlations were computed between sensitivity to disgust scores and the perceived intensity of each aqueous solution using Spearman's rank correlation coefficient (ρ), given the non-normal distribution of the data (Table 20).

Overall, positive and significant correlations were found primarily for pungent and salty stimuli, indicating that individuals with greater PROP responsiveness tended to perceive these sensations as more intense.

Specifically, PROP responsiveness was positively correlated with salty stimuli at lower concentration (ρ=0.312, p=.008), bitter stimuli at higher concentration (ρ=0.287, p=.016), and pungent stimuli at higher concentration (ρ=0.440, p<.0001) at baseline (T0).

Across treatment, this pattern persisted, with significant correlations for salty at higher concentration (ρ=0.327, p=.024) and pungent at higher concentration (ρ=0.409, p=.004) at T1, at T2 (ρ=0.436, p=.001), and at T4 (ρ=0.386, p=.008).

Table 20 Spearman's rank correlation coefficients (ρ) between PROP responsiveness and the perceived intensity of basic tastes and pungent aqueous solutions at each treatment time points. p-values (in parentheses) are reported only for significant correlations (p<.05).

	T0	T1	T2	T4	T6	T8	TF
				PROP responsiveness at T0			
Sweet intensity (67 g/L)	0.127	0.079	0.054	0.003	-0.245	0.264	-0.246
Sour intensity (1.3 g/L)	-0.051	-0.022	-0.009	-0.145	-0.345 (**.037**)	0.160	-0.211
Salty intensity (5 g/L)	0,312 (**.008**)	0.063	0.019	0.088	0.095	0.348	-0.225
Bitter intensity (0.75 g/L)	0.169	0.280	0.043	-0.057	-0.149	-0.031	-0.202
Pungent intensity (0.00055 g/L)	0.388 (**.001**)	0.225	0.151	0.179	0.118	0.525 (**.003**)	0.242
Sweet intensity (200 g/L)	0.228	0.153	0.179	0.218	-0.056	0.539 (**.002**)	-0.074
Sour intensity (4 g/L)	0.188	0.018	0.004	0.033	-0.164	0.239	0.050
Salty intensity (15 g/L)	0.171	0.327 (**.024**)	0.129	0.212	0.089	0.422 (**.021**)	0.244
Bitter intensity (3 g/L)	0.287 (**.016**)	0.178	0.190	0,069	-0.282	0.258	0.203
Pungent intensity (0.0015 g/L)	0.440 (**.0001**)	0.409 (**.004**)	0.436 (**.001**)	0.386 (**.008**)	0.196	0.421 (**.021**)	0.463 (**.0005**)

Additional positive associations emerged at T8 for sweet at higher concentration (ρ=0.539, p=.002), salty at higher concentration (ρ=0.422, p=.021), and pungent at higher concentration (ρ=0.525, p=.003).

These consistent positive correlations across multiple sessions suggest that PROP tasters generally experience more intense oral sensations, particularly for pungent and salty stimuli, but that this sensory responsiveness remains stable throughout

treatment only for pungency. In the other cases (salty and bitter), the correlation is not anymore significant after the baseline, indicating a potential decline in PROP tasters.

Impact of PROP status on self-reported chemosensory alteration

Correlations between PROP responsiveness scores and CiTAS dimension scores were calculated at each time point using Spearman's rank correlation coefficient (ρ) to examine whether individual differences in PROP responsiveness were associated with self-reported chemosensory alterations during chemotherapy (Table 21).

Table 21 Spearman's rank correlation coefficients (ρ) between PROP responsiveness and CiTAS scores of each dimension (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, phantogeusia, discomfort) at each treatment time points. p-values (in parentheses) are reported only for significant correlations (p<.05).

	T0	T1	T2	T4	T6	T8	TF
				PROP responsiveness			
Decline in basic tastes	-	0.025	0.073	0.047	0.011	0.161	-0.045
General taste alterations, parageusia, increase in taste perception	-	0.147	0.102	0.274 (**.040**)	0.074	0.286	0.053
Phantogeusia	0.015	0.092	0.277 (**.025**)	0.190	0.205	0.344 (.051)	0.157
Discomfort	0.175	0.254	0.227	0.112	0.237	0.372 (**.034**)	0.025

Overall, most correlations were positive but weak, suggesting that greater PROP responsiveness was generally associated with slightly greater self-reported chemosensory disturbances.

Significant associations emerged in isolated assessments: PROP reactivity was positively correlated with phantogeusia at T2 (ρ=0.277, p=.025) and at T8

(ρ=0.277, p=.051), with general taste alterations/parageusia/increase in taste perception at T4 (ρ=0.274, p=.040), and with discomfort at T8 (ρ=0.372, p=.034).

Insights of impact of PROP status on self-reported chemosensory alteration

Differences between the high and low PROP groups were examined with the Mann-Whitney test on the CiTAS dimensions to determine whether PROP status influenced the subjective experience of chemosensory alterations during chemotherapy.

Significant differences were observed across several CiTAS dimensions at specific time points. On the general taste alteration/parageusia/increase in taste perception dimension, patients classified as high PROP responders reported significantly higher alteration scores at T4 (U=567; p=.002) and T8 (U=179.50; p=.017), compared to the low PROP responders. Similarly, on the phantogeusia dimension, high PROP respondents reported higher score of phantom tastes at T2

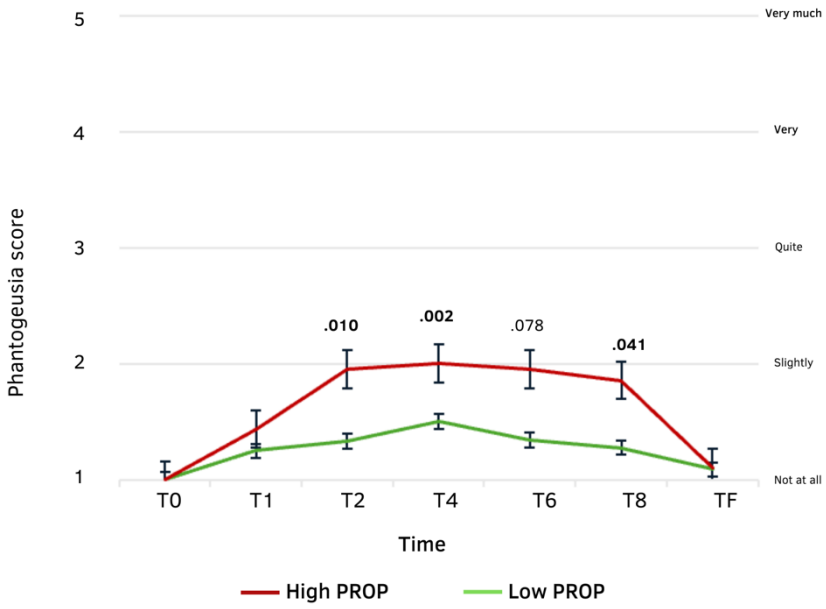


Figure 31 Differences in Phantogeusia scores between High PROP responders and Low PROP responders at each time point. Significant differences between groups at each time point were determined using the Mann-Whitney test (p<.05) and indicated by emboldened values.

(U=717.50; p=.010), T4 (U=567; p=.002), close to significance at T6 (U=264; p=.078), and T8 (U=171.50; p=.0041) compared to low PROP group (Figure 31).

Regarding the discomfort dimension, significant differences were observed in the early phases of treatment, at T1 (U=530; p=.041) and close to significance at T2 (U=673.50; p=.056), with the high PROP group again reporting greater discomfort, potentially due to increased oral sensitivity or increased susceptibility to treatment-related side effects, such as nausea, mucositis, or oral pain.
These results suggest that PROP sensitivity may play a role in modulating the experience of chemosensory disturbances during chemotherapy.

Result summary 4.2

- PROP responsiveness remained stable throughout the treatment period;
- Stimulus identification in aqueous solutions remained generally high throughout treatment; salty taste identification decreased at specific cycles (already after T1 for lower concentration and at T2 for higher concentration) and partially recovered at follow-up, while bitter taste at low concentration was the most difficult to identify.
- Perceived taste intensity showed an overall decline during chemotherapy, with recovery at follow-up; sweet and salty tastes showed the most pronounced decreases over time.
- PCA of perceived sweet taste intensity at low concentrations identified distinct clusters (Decliner, Unaltered, Enhancer) with a significant time × cluster interaction.
- In a subgroup of breast cancer patients, PCA of the intensity of all aqueous solutions suggested multiple trajectory profiles (decliner, recovering

decliner, enhancer, recovering enhancer), further supporting heterogeneous sensory dynamics during treatment.

- Self-reported taste ability decreased early during treatment and recovered at follow-up.
- Self-reported chemesthesis (sensations of pungency, cooling, tingling) increased during treatment, with recovery after therapy.
- Self-reported olfactory ability remained generally preserved, although qualitative changes (e.g., phantom or intensified odors) were reported during chemotherapy cycles.
- Self-assessed chemosensory changes by the CiTAS increased early, already after the first cycle of therapy, and returned to baseline levels at follow-up; discomfort was already present in some patients before the start of treatment.
- Qualitative interviews highlighted metallic and phantom tastes, parageusia/hypogeusia, oral discomfort, and odor hypersensitivity or phantosmia, often associated with nausea and food aversion. Onset was typically rapid after infusion (within 24–48 hours), and recovery was common but not universal.
- Patients High PROP responders reported more severe taste alterations, particularly phantogeusia, at certain stages of therapy, suggesting that increased taste sensitivity may enhance the perception of sensory changes.

4.3 Impact of chemosensory disorders on hedonic responses to basic tastes, food preferences, and eating habits during chemotherapy

4.3.1 Changes in the hedonic responses to basic tastes

Descriptive analysis of hedonic responses to sweet taste (Figure 32) during chemotherapy revealed that most patients reported liking sweet taste as usual,

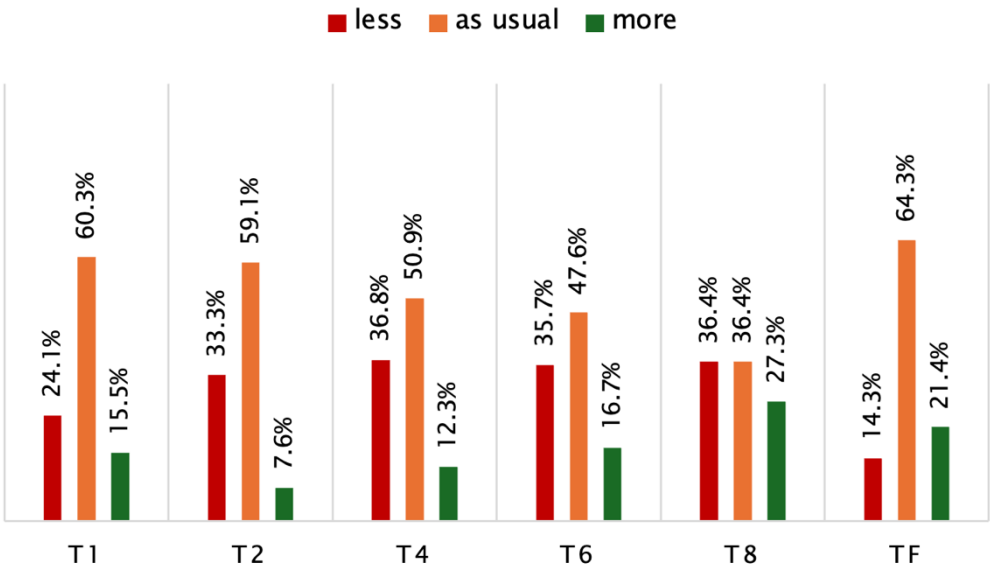


Figure 32 Descriptive analysis of hedonic responses ("I like it as usual", "I like it less than usual", "I like it more than usual") to sweet taste after the start of the treatment.

particularly at the beginning (T1: 60.3%) and at the end of treatment (TF: 64.3%). However, a shift occurred during the intermediate phases of treatment. At T2, the percentage of patients reporting a reduced liking for sweet taste increased to 33.3%, suggesting an early impact of chemotherapy on sweet taste liking. This trend peaked at T4 (36.8%) and T6 (35.7%), indicating that the intermediate phases of treatment may represent a period of greater change in sweet taste hedonic responses.

Interestingly, at T8 a decrease in "as usual" responses (36.4%) and a relative increase in both “less” (36.4%) and “more” (27.3%) responses were observed.

Finally, based on the TF, the pattern returned to baseline levels, with the highest percentage of "as usual" responses (64.3%) and the lowest of “less” responses (14.3%), suggesting a potential recovery of sweet taste liking after treatment.

Descriptive analysis of hedonic responses to salty taste (Figure 33) showed that

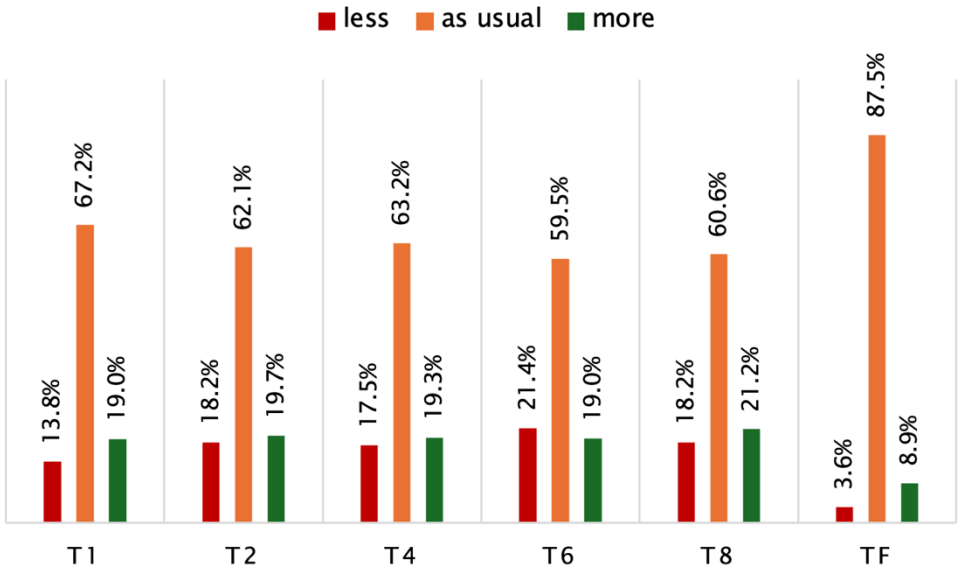


Figure 33 Descriptive analysis of hedonic responses (“I like it as usual”, “I like it less than usual”, “I like it more than usual”) to salty taste after the start of the treatment.

most patients reported liking salty taste "as usual" across all time points. However, some variations were observed during treatment.

At T6, the percentage of "as usual" responses dropped to its lowest point (59.2%), while the percentage of patients reporting a change ("less" or "more") increased slightly. Notably, at T2 and T4, responses were more distributed across the three responses than at other time points. Specifically, at T2, 18.2% of patients reported liking salty taste "less" and 19.7% "more," suggesting transient variability in hedonic response early in treatment.

Despite these fluctuations, the overall trend returned to baseline at TF, with the highest rate of “as usual” responses (87.5%) and the lowest rate of “less” (3.6%) and “more” (8.9%) responses.

Hedonic responses to sour taste (Figure 34) indicate that, in most cases, patients report liking it as usual. However, between T2 and T8, a slight decrease in the "as usual" response is observed, with a parallel increase in the percentage of patients reporting less liking for sour taste, particularly at T2 (24.2%), T4 (22.8%), and T8 (24.2%). "More" responses, however, remain low, with a slight increase at T6 (11.9%) and T8 (15.2%).

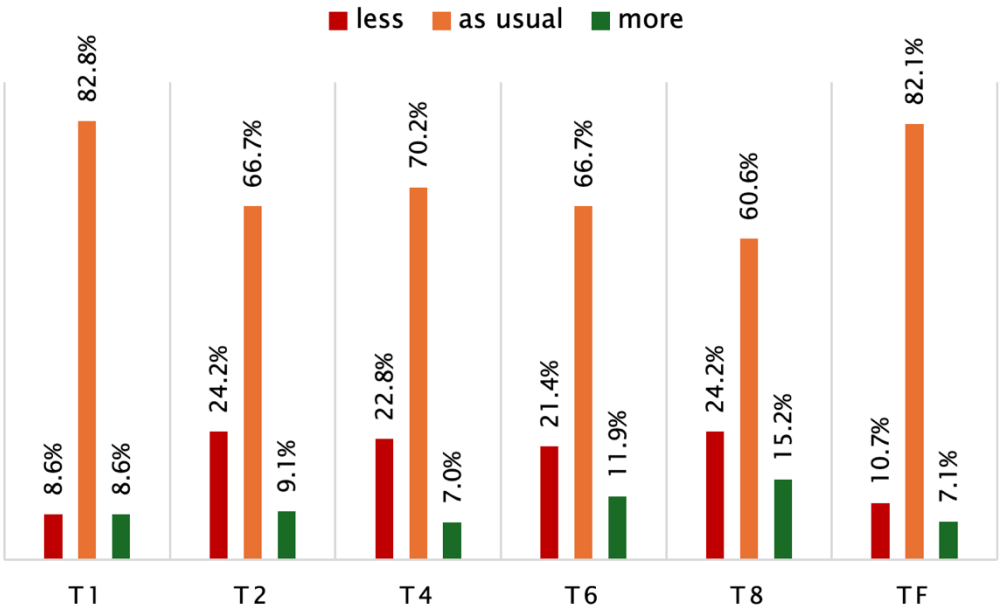


Figure 34 Descriptive analysis of hedonic responses ("I like it as usual", "I like it less than usual", "I like it more than usual") to sour taste after the start of the treatment.

Overall, these data suggest that during the central phase of chemotherapy, some patients tend to report a decrease in sour taste liking, with a recovery at the end of treatment.

Descriptive analysis of hedonic responses to bitter taste (Figure 35) revealed that most patients reported liking bitter taste "as usual" throughout the chemotherapy period. However, from T1 to T8, a progressive increase in the percentage of "less" responses was observed. Interestingly, the "more" response option was rarely

reported, with very low percentages. These results suggest that bitter taste may be particularly vulnerable to hedonic worsening during treatment.

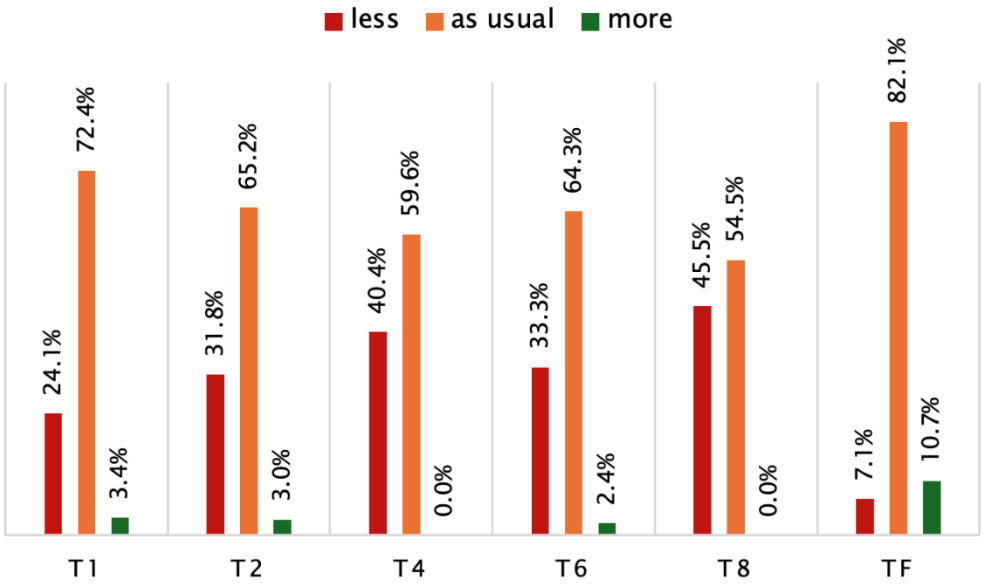


Figure 35 Descriptive analysis of hedonic responses ("I like it as usual", "I like it less than usual", "I like it more than usual") to bitter taste after the start of the treatment.

To further explore chemosensory changes, the descriptive analysis was deepened by focusing on the self-reported alterations (CiTAS) comparing hedonic responses between patients who reported a specific alteration (decline in basic tastes, general taste alterations/parageusia/increase in taste perception) and those who did not. In particular, the analysis focused on the hedonic responses "I like it less than usual" and "I like it more than usual".

Focusing on the self-reported decline in basic tastes, Table 22 presents the distribution of responses to the question "I like it less/more than usual" across the different basic tastes, comparing patients who reported this alteration with those who did not.

Table 22 Descriptive analysis of hedonic responses ("I like it less than usual" and "I like it more than usual") to basic tastes at each treatment time point (T1-TF), comparing patients who self-reported decline in basic tastes (Yes) with those who did not (No), measured with CiTAS. Reported p-values refer to two-proportion tests assessing differences between groups. ***Emboldened*** *p-value<.05 indicates a significant difference at 95%. ^ sign on p-value indicates a value close to significance.*

I like it less than usual	**Yes/No decline in basic tastes**	T1 (Yes, 12 – No, 46)	T2 (Yes, 33 – No, 33)	T4 (Yes, 33 – No, 24)	T6 (Yes, 25 – No, 19)	T8 (Yes, 22 – No, 11)	TF (Yes, 5 – No, 51)
Sweet	Yes, % (n)	42.9 (6)	54.5 (12)	61.9 (13)	73.2 (11)	75.0 (9)	25.0 (2)
	No, % (n)	57.1 (8)	45.5 (10)	38.1 (8)	26.7 (4)	25.0 (3)	75.0 (6)
	p-value	.077	.794	.848	.179	.689	.440
Salty	Yes, % (n)	37.5 (3)	75.0 (9)	80.0 (8)	77.8 (7)	66.7 (4)	50.0 (1)
	No, % (n)	62.5 (5)	25.0 (3)	20.0 (2)	22.2 (2)	33.3 (2)	50.0 (1)
	p-value	.505	.101	.188	.260	1.000	.695
Sour	Yes, % (n)	20.0 (1)	68.8 (11)	84.6 (11)	77.8 (7)	50.0 (4)	16.7 (1)
	No, % (n)	80.0 (4)	31.2 (5)	15.4 (2)	22.2 (2)	50.0 (4)	83.3 (5)
	p-value	1.000	.142	**.032**	.260	.496	1.000
Bitter	Yes, % (n)	35.7 (5)	61.9 (13)	82.6 (19)	78.6 (11)	60.0 (9)	0.0 (0)
	No, % (n)	64.3 (9)	38.1 (8)	17.4 (4)	21.4 (3)	40.0 (6)	100.0 (4)
	p-value	.274	.284	**.001**	^.069	.710	1.000
I like it more than usual							
Sweet	Yes, % (n)	11.1 (1)	60.0 (3)	57.1 (4)	66.7 (5)	75.0 (6)	25.0 (3)
	No, % (n)	88.9 (8)	40.0 (2)	28.6 (3)	33.3 (2)	25.0 (3)	75.0 (9)
	p-value	.696	1.00	1.00	.650	1.00	.164
Salty	Yes, % (n)	63.6 (7)	38.5 (5)	63.6 (7)	50.0 (4)	71.4 (5)	0.0 (0)
	No, % (n)	36.4 (4)	61.5 (8)	36.4 (4)	50.0 (4)	28.6 (2)	100.0 (5)
	p-value	**.003**	.533	.928	.972	1.00	1.00
Sour	Yes, % (n)	60.0 (3)	50.0 (3)	50.0 (2)	100.0 (5)	100.0 (5)	25.0 (1)
	No, % (n)	40.0 (2)	50.0 (3)	50.0 (“)	0.0 (0)	0.0 (0)	75.0 (3)
	p-value	.231	1.000	1.000	^0.055	.075	.863
Bitter	Yes, % (n)	50.0 (1)	50.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
	No, % (n)	50.0 (1)	50.0 (1)	0.0 (0)	100.0 (1)	0.0 (0)	100.0 (6)
	p-value	.913	1.000	-	.902	-	.862

Among those who selected the "I like it less than usual" responses, a general trend emerged indicating that patients who reported a decline in basic tastes tended to

show a lower liking for basic tastes during treatment. Significant differences were found at T4 for the tastes sour (p=.032) and bitter (p=.001), where more patients with decline in basic tastes reported a decrease in liking compared to those without decline. In contrast, responses to the "I like it more than usual" showed no clear or systematic differences between the groups. The only significant result emerged at T1 (p=.003), where patients with decline in basic taste reported an increase in liking for salty taste.

Overall, these results indicate that the decline in basic tastes is associated not only with a general reduction in liking for basic tastes, particularly sour and bitter, but also with an increased liking for salty foods. This heterogeneity reflects individual adaptation or compensatory strategies in the presence of impaired chemosensory function.

Focusing on the self-reported general taste alterations/parageusia/increase in taste perception, Table 23 presents the percentages of responses “I like it less than usual” and “I like it more than usual” to the different basic tastes, comparing patients who reported these alterations with those who did not.

Table 23 Descriptive analysis of hedonic responses (“I like it less than usual” and “I like it more than usual”) to basic tastes at each treatment time point (T1-TF), comparing patients who self-reported general taste alterations/parageusia/increase in taste perception (Yes) with those who did not (No) measured with CiTAS. Reported p-values refer to two-proportion tests assessing differences between groups. ***Emboldened*** *p-value<.05 indicates a significant difference at 95%. ^ sign on p-value indicates a value close to significance.*

I like it less than usual	**Yes (n)/No (n) General taste alterations/parageusia/increase**	T1 (Yes, 23 – No, 35)	T2 (Yes, 38 – No, 28)	T4 (Yes, 37 – No, 20)	T6 (Yes, 25 – No, 17)	T8 (Yes, 19 – No, 14)	TF (Yes, 4 – No, 52)
Sweet	Yes, % (n)	78.6 (11)	68.2 (15)	90.5 (19)	80.0 (12)	75.0 (9)	25.0 (2)
	No, % (n)	21.4 (3)	31.8 (7)	9.5 (2)	20.0 (3)	25.0 (3)	75.0 (6)
	p-value	**.002**	.318	**.0004**	^.062	.213	.325

Salty	Yes, % (n)	75.0 (6)	91.7 (11)	100.0 (10)	88.9 (8)	100.0 (6)	0.0 (0)
	No, % (n)	25.0 (2)	8.3 (1)	0.0 (0)	11.1 (1)	0.0 (0)	100.0 (2)
	p-value	.092	**.006**	**.002**	^.053	**.017**	1.000
Sour	Yes, % (n)	100.0 (5)	87.5 (14)	92.3 (12)	88.9 (8)	75.0 (6)	33.3 (2)
	No, % (n)	0.0 (0)	12.5 (2)	7.7 (1)	11.1 (1)	25.0 (2)	66.7 (4)
	p-value	**.035**	**.004**	**.010**	^.053	.434	.254
Bitter	Yes, % (n)	92.9 (13)	81.0 (17)	100.0 (23)	78.6 (11)	66.7 (10)	75.0 (3)
	No, % (n)	7.1 (1)	19.0 (4)	0.0 (0)	21.4 (3)	33.3 (5)	25.0 (1)
	p-value	**<.0001**	**.009**	**<.0001**	.114	.533	**.006**
I like it more than usual							
Sweet	Yes, % (n)	44.4 (4)	60.0 (3)	51.7 (4)	51.7 (4)	55.6 (5)	0.0 (0
	No, % (n)	55.6 (5)	40.0 (2)	42.9 (3)	42.9 (3)	44.4 (4)	100.0
	p-value	1.000	1.000	.972	1.000	1.000	(12)
							.100
Salty	Yes, % (n)	63.6 (7)	46.2 (6)	81.8 (9)	50.0 (4)	42.9 (3)	20.0 (1)
	No, % (n)	36.4 (4)	53.8 (7)	18.2 (2)	50.0 (4)	57.1 (4)	80.0 (4)
	p-value	.161	.545	.282	.838	.654	.861
Sour	Yes, % (n)	40.0 (2)	66.7 (4)	100.0 (4)	100.0 (5)	60.0 (3)	100.0 (4)
	No, % (n)	60.0 (3)	33.3 (2)	0.0 (0)	0.0 (0)	40.0 (2)	0.0 (0)
	p-value	1.000	.968	.173	^.060	1.000	**<.0001**
Bitter	Yes, % (n)	50.0 (1)	100.0 (2)	0.0 (0)	100.0 (1)	0.0 (0)	33.3 (2)
	No, % (n)	50.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	66.7 (4)
	p-value	1.000	.551	-	1.000	-	.254

For the response "I like less than usual," patients with general taste alterations more frequently reported a reduction in basic tastes liking. The effect was statistically significant for sweet (T1: p=.002; T4: p=.0004), salty (T2: p=.006; T4: p=.002; T8: p=.017), sour (T1: p=.035; T2: p=.004; T4: p=.010), and bitter (T1: p<.0001; T2: p=.009; T4: p<.0001; TF: p=.006) tastes. Even when not statistically significant, the percentage of patients with alterations who reported liking basic tastes less than usual was higher than those without alterations.

In contrast, for the question "I like it more than usual," a greater percentage of patients with alterations reported an increase in liking for sour taste at the final

time point (TF: p<.0001) and there is a trend at some intermediate time points (T4: p=.060), likely reflecting adaptive or compensatory changes in liking for sour tastes. For other tastes, including sweet, salty, and bitter, the differences between groups were not significant, with the proportion of patients reporting increased liking varying between those with and without alterations across time points. Overall, these findings suggest that general taste alterations and parageusia are primarily associated with decrease in hedonic liking for basic tastes, while isolated increases in liking may represent individual adaptive responses to altered chemosensory input rather than a consistent trend across patients.

Focusing on the self-reported phantogeusia, Table 24 presents the distribution of responses to the question "I like it less/more than usual" across the different basic tastes, comparing patients who reported this alteration with those who did not.

Table 24 Descriptive analysis of hedonic responses ("I like it less than usual" and "I like it more than usual") to basic tastes at each treatment time point (T1-TF), comparing patients who self-reported phantogeusia (Yes) with those who did not (No) measured with CiTAS. Reported p-values refer to two-proportion tests assessing differences between groups. ***Emboldened*** *p-value<.05 indicates a significant difference at 95%. ^ sign on p-value indicates a value close to significance.*

I like it less than usual	**Phantogeusia**	T1 (Yes, 26 – No, 32)	T2 (Yes, 39 – No, 27)	T4 (Yes, 35 – No, 22)	T6 (Yes, 24 – No, 18)	T8 (Yes, 22 – No, 11)	TF (Yes, 9 – No, 47)
Sweet	Yes, % (n)	78.6 (11)	72.7 (16)	90.5 (19)	80.0 (12)	91.7 (11)	25.0 (2)
	No, % (n)	21.4 (3)	27.3 (6)	9.5 (2)	20.0 (3)	8.3 (1)	75.0 (6)
	p-value	**.007**	.163	**<.0001**	**.034**	**.013**	.847
Salty	Yes, % (n)	75.0 (6)	83.3 (10)	80.0 (8)	66.7 (6)	83.3 (5)	0.0 (0)
	No, % (n)	25.0 (2)	16.7 (2)	20.0 (2)	33.3 (3)	16.7 (1)	100.0 (2)
	p-value	.152	.080	.283	.781	.584	1.000
Sour	Yes, % (n)	83.3 (5)	100.0 (16)	92.3 (12)	88.9 (8)	75.0 (6)	33.3 (2)
	No, % (n)	16.7 (1)	0.0 (0)	7.7 (1)	11.1 (1)	25.0 (2)	66.7 (4)
	p-value	.129	**<.0001**	**.005**	**.038**	.880	.623
Bitter	Yes, % (n)	71.4 (10)	85.7 (18)	91.3 (21)	92.9 (13)	80.0 (12)	50.0 (2)
	No, % (n)	28.6 (4)	14.3 (3)	8.7 (2)	7.1 (1)	20.0 (3)	50.0 (2)
	p-value	**.045**	**.001**	**<.0001**	**.0001**	.232	.423

I like it more than usual							
Sweet	Yes, % (n)	44.4 (4)	60.0 (3)	87.7 (6)	71.4 (5)	66.7 (6)	41.7 (5)
	No, % (n)	55.6 (5)	40.0 (2)	14.3 (1)	28.6 (2)	33.3 (3)	58.3 (7)
	p-value	1.000	1.000	.252	.662	1.000	**.050**
Salty	Yes, % (n)	72.7 (8)	58.3 (7)	72.7 (8)	87.5 (7)	85.7 (6)	80.0 (4)
	No, % (n)	27.3 (3)	41.7 (5)	27.3 (3)	12.5 (1)	14.3 (1)	20.0 (1)
	p-value	.086	1.000	.558	.081	.377	**.033**
Sour	Yes, % (n)	60.0 (3)	50.0 (3)	100.0 (4)	100.0 (5)	100.0 (5)	50.0 (2)
	No, % (n)	40.0 (2)	50.0 (3)	0.0 (0)	0.0 (0)	0.0 (0)	50.0 (2)
	p-value	.812	.969	.151	^.054	.075	.424
Bitter	Yes, % (n)	100.0 (2)	100.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)	16.7 (1)
	No, % (n)	0.0 (0)	0.0 (0)	0.0 (0)	100.0 (1)	0.0 (0)	83.3 (5)
	p-value	.421	.572	-	.898	-	1.000

When analyzing the "I like it less than usual" responses, a clear pattern emerged indicating that patients with phantogeusia reported reduced liking for most basic tastes. The difference was statistically significant for sweet (T1: p=.007; T4: p<.0001; T6: p=.034; T8: p=.013), sour (T2: p<.0001; T4: p=.005; T6: p=.038), and bitter (T1: p=.045; T2: p=.001; T4: p<.0001; T6: p=.0001), demonstrating that the presence of phantogeusia was strongly associated with a reduced hedonic response to these tastes. Overall, even when the results were non-significant, patients with phantogeusia almost always represented the majority of those reporting a decrease in liking.

In contrast, for the responses "I like it more than usual," the results were more variable and generally non-significant. Toward the later time points, a greater percentage of patients with phantogeusia reported an increase in liking for salty taste (T8: p=.033) and for sweet taste (TF: p=.050). Overall, these results indicate that phantogeusia is predominantly associated with a reduction in the liking of basic tastes, particularly sweet, sour, and bitter, reflecting the unpleasant or intrusive nature of phantom sensations.

4.3.2 Food preferences during chemotherapy

Kruskal–Wallis tests performed on the general population to assess temporal changes in preference scores across the six dimensions (Flavor $\chi^2(6)=3.156$, $p=.789$, Texture $\chi^2(6)=1.910$, $p=.928$, Odor $\chi^2(6)=11.271$, $p=.080$, Herbs and Spices $\chi^2(6)=4.223$, $p=.647$, Sweet vs. Bitter $\chi^2(6)=2.568$, $p=.861$, and Sweet vs. Sour $\chi^2(6)=1.487$, $p=.960$) showed no significant differences across time points, suggesting that, at the population level, there was no directional shift in preferences (e.g., toward more or less intense stimuli) over the course of treatment. As shown in Figure 36, the percentage distribution of food preferences across the different FP&EQ dimensions remained relatively stable during chemotherapy.

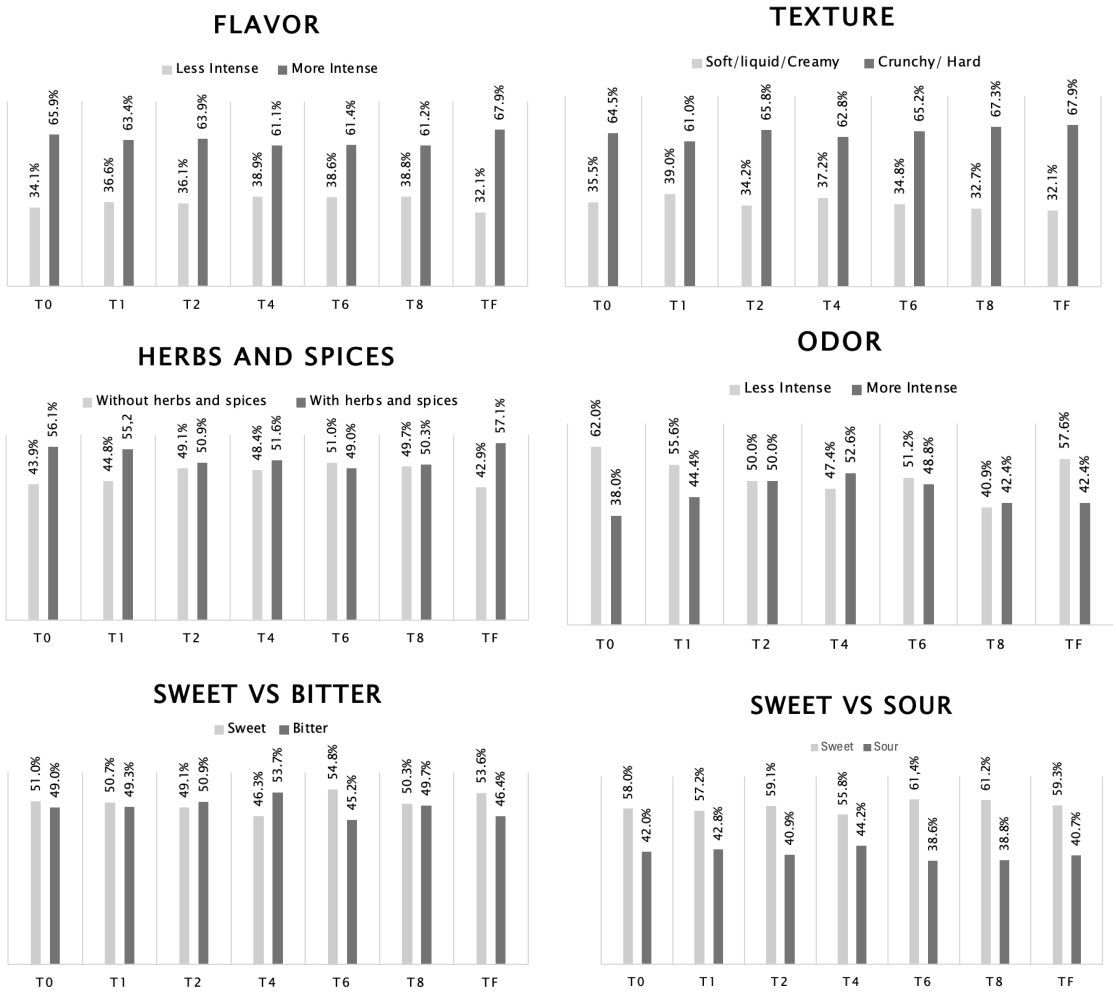


Figure 36 Percentage distribution of food preferences across the different dimension of Food Preference and Emotion Questionnaire at different time points.

Regarding flavor and texture, most patients consistently preferred more intense and crunchier/harder options. Similarly, preferences for herbs and spices were evenly distributed among those who preferred foods with or without seasoning, showing no directional trend over time.

A different pattern emerged for odor, where odor aversions appeared more balanced in the initial phases, suggesting a modest shift in aversion toward more intense odors as treatment progressed, although this change was not statistically significant ($p > 0.05$).

In the sweet-bitter and sweet-sour contrasts, the proportions remained balanced at all time points.

This overall stability in preference scores highlights the potential relevance of interindividual variability and the impact of chemosensory alterations. To further explore this issue, subsequent analyses examined the influence of self-reported chemosensory alterations (as measured by the CiTAS) and individual differences (food neophobia, disgust sensitivity, PROP responsiveness) on food preferences.

4.3.2.1 Impact of self-reported chemosensory alterations on food preferences

The impact of self-reported chemosensory changes and discomfort using the CiTAS on food preference scores was assessed using a Spearman correlation for each time point and for each dimension of the FP&EQ. The results of the analyses are summarized in Table 25.

Table 25 Spearman's rank correlation coefficients (ρ) between CiTAS scores of each dimension (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, phantogeusia, discomfort) and preference scores of Food Preference and Emotion Questionnaire dimensions (Flavor, Texture, Odor, Herbs & Spices, Sweet vs Bitter, Sweet vs Sour) at each treatment time points. Significant correlations (p <.05) are indicated in parentheses. ^sign on p-value indicates a value close to significance.

	T0	T1	T2	T4	T6	T8	TF
				Flavor			
Decline in basic tastes	-	-0.117	-.046	-0.294 (**.027**)	-0.110	0.003	0.027
General taste alterations, parageusia, increase in taste perception	-	-0.467 (**.0002**)	-0.406 (**.001**)	-0.568 (**<.0001**)	-0.320 (**.039**)	-0.256	-0.085
Phantogeusia	0.185	-0.180	-0.373 (**.0002**)	-0.526 (**<.0001**)	-0.159	-0.367 (**.037**)	-0.187
Discomfort	0.029	-0.393 (**.002**)	-0.248 (**.045**)	-0.471 (**.0003**)	-0.414	-0.377 (**.031**)	-0.162
	T0	T1	T2	T4	T6	T8	TF
				Texture			
Decline in basic tastes	-	-0.106	-0.149	-0.167	-0.202	-0.038	0.137
General taste alterations, parageusia, increase in taste perception	-	-0.092	-0.276 (**.025**)	-0.404 (**.002**)	-0.156	-0.301	-0.168
Phantogeusia	-0.040	0.042	-0.306 (**.013**)	-0.385 (**.003**)	-0.383 (**.013**)	-0.331	-0.007
Discomfort	-0.146	0.033	-0.092	-0.235	-0.160	-0.249	-0.066
	T0	T1	T2	T4	T6	T8	TF
				Odor			
Decline in basic tastes	-	-0.221	-0.41	-0.006	0.147	-0.019	-0.306 (**.022**)
General taste alterations, parageusia, increase in taste perception	-	0.041	0.092	0.183	0.185	0.094	0.091
Phantogeusia	0.001	-0.066	0.277	0.093	0.245	0.010	0.116
Discomfort	-0.140	0.077	0.179	0.213	0.450 (**.003**)	-0.003	0.044

	T0	T1	T2	T4	T6	T8	TF
				Herbs and Spices			
Decline in basic tastes	-	-0.020	0.145	-0.103	0.203	0.325 (^.066)	0.034
General taste alterations, parageusia, increase in taste perception	-	-0.062	0.150	-0.213	-0.138	0.029	-0.122
Phantogeusia	-0.053	-0.170	0.035	-0.139	-0.021	-0.118	-0.157
Discomfort	0.092	-0.260 (**.049**)	-0.079	-0.141	-0.216	-0.205	-0.137
	T0	T1	T2	T4	T6	T8	TF
				Sweet vs Bitter			
Decline in basic tastes	-	-0.209	0.067	-0.126	0.201	0.383	-0.057
General taste alterations, parageusia, increase in taste perception	-	-0.099	-0.058	-0.177	0.904	0.031	0.156
Phantogeusia	0.057	-0.129	-0.091	-0.214	0.001	0.010	-0.259
Discomfort	0.064	-0.146	-0.072	-0.027	-0.035	-0.256	-0.169
	T0	T1	T2	T4	T6	T8	TF
				Sweet vs Sour			
Decline in basic tastes	-	0.062	-0.099	-0.029	0.132	0.018	0.049
General taste alterations, parageusia, increase in taste perception	-	-0.050	-0.128	-0.161	-0.089	0.011	0.014
Phantogeusia	0.004	-0.005	0.035	-0.228	-0.107	0.0003	-0.247 (^.061)
Discomfort	0.028	-0.130	-0.064	0.014	-0.205	0.0008	-0.158

Significant negative correlations were found between the Flavor dimension and three CiTAS dimensions: general taste alterations/parageusia/increase in taste perception (ρ=-.467, p=.0002 at T1; ρ=-.406, p=.001 at T2; ρ=-.568, p<.0001 at T4; ρ=-.320, p=.039 at T6), phantogeusia (ρ=-0.373, p=.0002 at T2; ρ=-0.526, p<.0001 at T4; and ρ=-0.367, p=.037 at T8), and discomfort (ρ=-0.393,

p=.002 at T1; ρ=-0.248, p=.045 at T2; ρ=-0.471, p=.0003 at T4; and ρ=-0.377, p=.031 at T8).

These negative associations indicate that higher scores for these alterations are related to a preference for less intense flavors (lower scores) during treatment. No significant association was found for the decline in basic tastes, except for a negative correlation at T4 (ρ=-0.294, p=.027).

Similarly, negative correlations were observed between Texture scores and general taste alterations/parageusia/increase in taste perception and phantogeusia. Significant differences were found at T2 (ρ=-0.276, p=.025) and T4 (ρ=-0.404, p=.002) for general alterations, and at T2, T4, and T6 for phantogeusia (ρ=-0.306, p=.013; ρ=-0.385, p=.003; ρ=-383, p=.013). This suggests that greater alterations corresponded to a preference for softer/liquid/creamier foods.

Correlations with Odor preference scores were generally weak. Only discomfort at T6 was significantly and positively correlated (ρ=.450, p=.003), suggesting that greater discomfort corresponded to greater aversion to more intense odors.

No systematic correlations were found between preference scores on the Herbs and Spices dimension and self-reported alterations. Only a negative correlation was found between discomfort and this dimension at T1 (ρ=-0.260, p=.049), suggesting that greater discomfort correlates with lower scores and therefore a preference for foods without herbs and spices.

No significant correlations were found between alterations and preference scores of the Sweet vs. Bitter and Sweet vs. Sour dimensions. Only a negative correlation tending towards significance was found at TF between the Sweet vs. Sour dimension and phantogeusia (ρ=-.247, p=.061), suggesting that higher levels of phantogeusia corresponded to a lower preference for sour over sweet foods.

Insights on sweet clusters

Patients were divided into three clusters based on their perception of sweet taste (see § 4.2.2): enhancers, non-altered, and decliners. For each group, the temporal trend of preference scores for the Sweet vs. Bitter and Sweet vs. Sour dimensions was assessed using a Kruskal Wallis test. For the Sweet vs. Bitter dimension, no significant differences were observed between time points for Decliners ($\chi^2(3)=0.412$, $p=.938$), Enhancers ($\chi^2(3)=1.615$, $p=.656$), or Non-Altered ($\chi^2(3)=0.581$, $p=.901$). For the Sweet vs. Sour dimension, no significant differences were observed between time points for Decliners ($\chi^2(3)=1.411$, $p=.703$), Enhancers ($\chi^2(3)=1.150$, $p=.765$), or Non-Altered ($\chi^2(3)=2.026$, $p=.567$).

To further examine the effect of cluster on food preferences, Kruskal-Wallis tests were also performed comparing the Decliners, Enhancers, and Non-Altered groups at each time point (T0, T2, T4, TF). No significant differences emerged between clusters for the Sweet vs. Bitter dimension (T0: $\chi^2(2)=0.955$, $p=.620$; T2: $\chi^2(2)=2.572$, $p=.276$; T4: $\chi^2(2)=0.350$, $p=.839$; TF: $\chi^2(2)=2.027$, $p=.363$). However, for the Sweet vs. Sour dimension, significant differences emerged before the start of the treatment ($\chi^2(2)=8.877$, $p=.012$) and at the end of therapy ($\chi^2(2)=7.252$, $p=.027$), with trends toward significance at T2 ($\chi^2(2)=5.330$, $p=.070$) and T4 ($\chi^2(2)=5.473$, $p=.065$). Dunn's post hoc test showed that Enhancers consistently espressed a greater preference for sweeter products than Decliners, suggesting a stable divergence in sweet-sour preference associated with differences in sweetness perception profiles.

4.3.2.2 Association between self-reported chemosensory alterations and changes in food preferences during chemotherapy

Beyond differences in preference scores, additional analyses were conducted to explore whether patients with specific chemosensory alterations were more likely to report changes in food preferences after each cycle of treatment compared to the baseline.

Table 26 summarizes the associations between self-reported chemosensory alterations and changes in food preference dimensions at each time point compared to baseline (T0). For each CiTAS dimension, the table reports the p-values from Chi-Square tests and Fisher's exact tests indicating the association between self-reported chemosensory alterations and changes in food preference at each time point compared to baseline (T0).

Table 26 *Association between self-reported chemosensory alterations with changes in food/odor preferences during treatment. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).* ***Emboldened*** *p-value<.05 indicates a significance. ^ sign on p-value indicates a value close to significance.*

		Changes in preferences				
CiTAS alteration	FP&EQ dimensions	T0-T1	T0-T2	T0-T4	T0-T6	T0-T8
Decline in basic tastes	All the dimensions	.548	.590	> **.031**	> **.030**	.626
	Flavor	.253	.159	> **.054**	.236	.330
	Texture	.677	.123	.942	.974	.797
	Odor	.544	.674	.402	.409	> **.028**
	Herbs and Spices	.178	.349	.102	.299	.138
	Sweet vs Bitter	.861	.386	.272	.636	1.000
	Sweet vs Sour	.156	.590	.891	.051	.134
	All the dimensions	.857	>	>	>	>

			.001	**<.0001**	**.0003**	**.013**
	Flavor	.193	> ^ .077	.093	.125	.530
General taste alterations /parageusia/ increase in taste perception	Texture	.109	.346	> **.003**	.948	.991
	Odor	.692	.135	.383	> **.001**	> **. 022**
	Herbs and Spices	.980	.440	> **.031**	> **.030**	.148
	Sweet vs Bitter	.205	> **.004**	.470	.337	.265
	Sweet vs Sour	.612	.638	.127	.373	.579
Phantogeusia	All the dimensions	. 310	.091	> **.0001**	> **.001**	> **.001**
	Flavor	.869	.921	> **.024**	.083	.126
	Texture	.878	.639	> **.026**	.769	.369
	Odor	.717	.228	.861	> **.034**	.287
	Herbs and Spices	.288	.948	.215	.510	> ^ .067
	Sweet vs Bitter	.377	> **.015**	.362	.874	> **.034**
	Sweet vs Sour	.308	.164	> **.008**	> **.004**	.341

(after the first cycle of chemotherapy: T0-T1)

After the first cycle of therapy, no type of alteration recorded with the CiTAS had an impact on the patients' food preferences.

(after the second cycle of chemotherapy: T0-T2)

After the second cycle of treatment patients who self-reported general taste alteration/parageusia/increase in taste perception (YES - red in Figure 37) showed greater changes in general food preferences (p=.001, χ^2=11.51, significance by cell p=.001), and particularly in Sweet vs. Bitter dimension (p=.003, χ^2=8.75, significance by cell p=.004), compared to patients without this alteration (NO - grey). A trend was observed for Flavor (p=.068, χ^2=3.33, significance by cell p=.077),

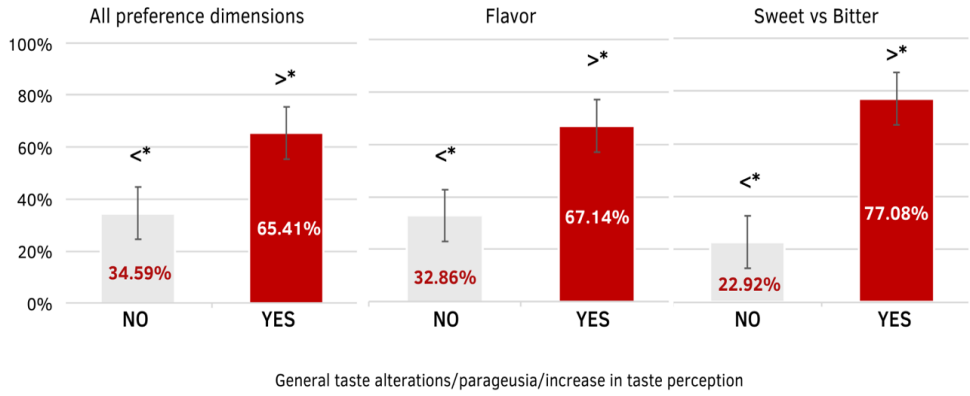


Figure 37 Association between the presence of general taste alterations/parageusia/increase in taste perception (red) and changes in food preferences (all the dimensions, Flavor, and Sweet vs. Bitter) after the 2nd cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

At the same time point patients who self-reported phantogeusia (YES - red in Figure 38) showed significant and greater changes in Sweet vs. Bitter dimension (p=.015 χ^2=5.88, significance by cell p=.015), compared to patients without phantogeusia (NO - grey).

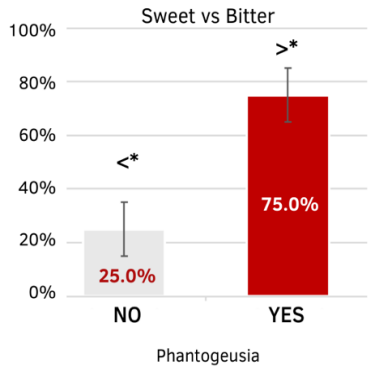


Figure 38 Association between the presence of phantogeusia (red) and changes in food preferences of the dimension Sweet vs. Bitter after the 2nd cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

Mann-Whitney U tests did not reveal a consistent direction of changes (i.e., increase or decrease in preference scores) associated with these alterations.

(after the fourth cycle of chemotherapy: T0-T4)

After the fourth cycle decline in basic tastes (YES - red in Figure 39) was associated with greater changes in general food preferences (p=.031, χ^2=4.65, significance by cell p=.034), but particularly in Flavor dimension (p=.043, χ^2=4.11, significance by cell p=.054).

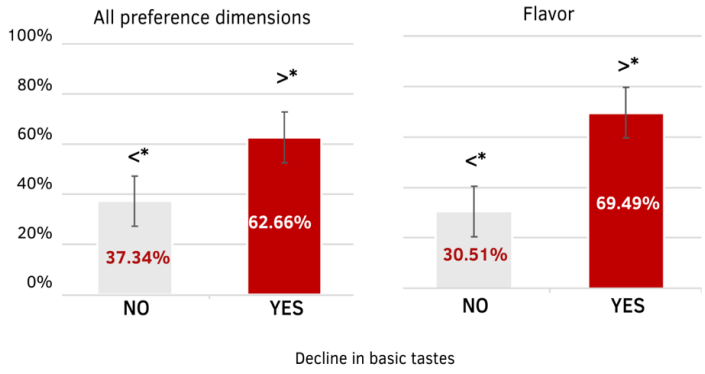


Figure 39 Association between the presence of decline in basic tastes (red) and changes in food preferences (all the dimension and Flavor) after the 4th cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

Patients with general taste alterations/parageusia/increase in taste perception (YES - red in Figure 40) showed greater changes in general food preferences ($p<.0001$, $\chi^2=17.64$, significance by cell $p<.0001$) and, in particular, in Texture ($p=.003$,

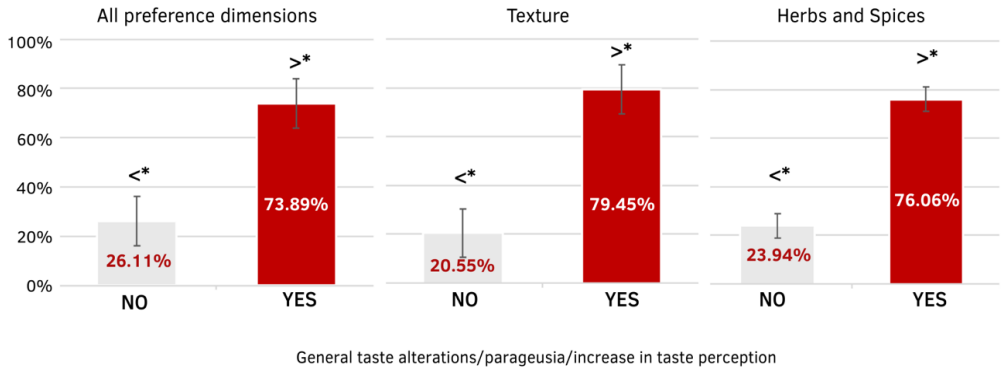


Figure 40 Association between the presence of general taste alterations/parageusia/increase in taste perception (red) and changes in food preferences (all the dimension, Texture, and Herbs & Spices) after the 4th cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

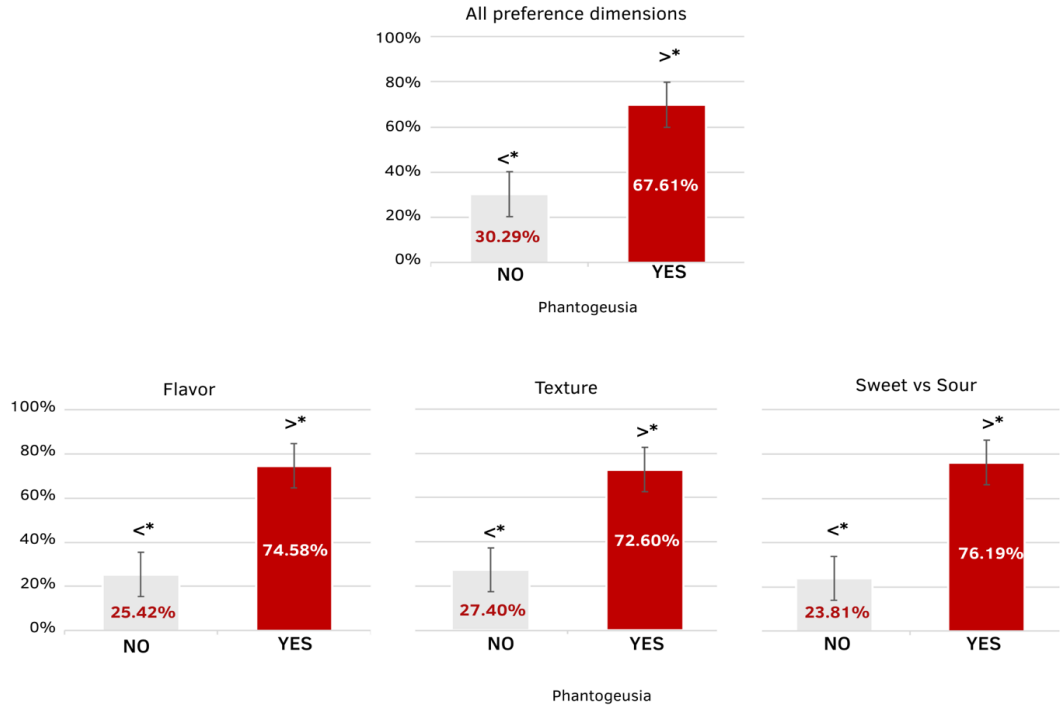


Figure 41 Association between the presence of phantogeusia (red) and changes in food preferences (all the dimension, Flavor, Texture, and Sweet vs. Sour) after the 4th cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

χ^2=9.11, significance by cell p=.003) and Herbs and Spices (p=.023, χ^2=5.16, significance by cell p=.031) dimensions, compared to patients without this type of alterations (NO - grey).

Phantogeusia (YES - red in Figure 41) was associated with greater changes in general food preferences (p<.0001, χ^2=14.52, significance by cell p<.0001), particularly in Flavor (p=.02. χ^2=5.45, significance by cell p=.024), Texture (p=.023, χ^2=5.19, significance by cell p=.026) and Sweet vs. Sour (p=.006, χ^2=7.46, significance by cell p=.008) dimensions.

Even at this time point, no specific direction was observed for any of the changes presented.

(after the sixth cycle of chemotherapy: T0-T6)

After six cycles of chemotherapy patients with decline in basic tastes (p=.025, χ^2=4.99, significance by cell p=.030), general taste alterations/parageusia/increase in taste perception (p=.0003, χ^2=13.04, significance by cell p=.0003), and phantogeusia (p=.001, χ^2=11.37, significance by cell p=.001) reported greater changes in food preferences.

The presence of general taste alteration/parageusia/increase in taste perception (YES - red in Figure 42) was associated with greater changes in Odor preferences ($p=.001$, $\chi^2=10.7$. significance by cell $p=.001$) and in Herbs and Spices preferences ($p=.023$, $\chi^2=5.16$, significance by cell $p=.030$).

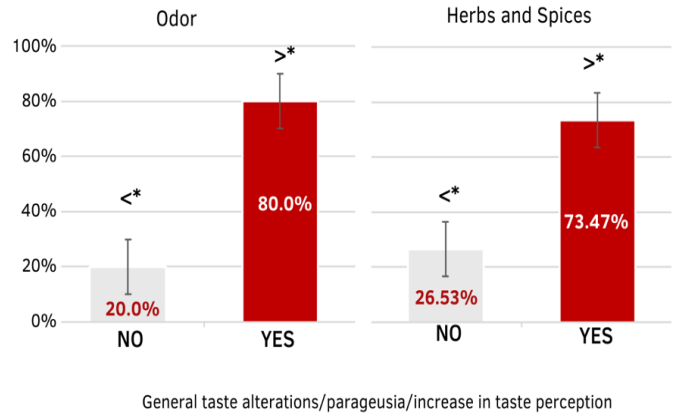


Figure 42 Association between the presence of general taste alterations/parageusia/increase in taste perception (red) and changes in preferences (Odor and Herbs & Spices) after the 6th cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

Patients who self-reported phantogeusia (YES - red in Figure 43) showed greater changes in Odor preferences ($p=.027$, $\chi^2=4.9$. significance by cell $p=.034$) and in

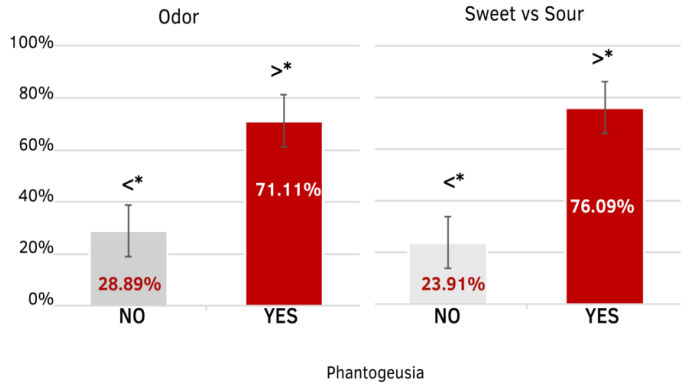


Figure 43 Association between the presence of phantogeusia (red) and changes in preferences (Odor and Sweet vs. Sour) after the 6th cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

food preferences of Sweet vs. Sour dimension (p=.003, χ^2=8.63, significance by cell p=.004), compared to patients without this alteration (YES – grey).

The significance of the direction of preference changes was tested and patients who self-reported general taste alteration/parageusia/increase in taste perception (U=204; p=.030) and phantogeusia (U=158; p=.006), during the sixth cycle of treatment, showed an increase in odor scores, indicating a greater aversion to more intense odors, which were more frequently chosen as less pleasant.

(after the eighth cycle of chemotherapy: T0-T8)

After 8 cycles of the treatment patients who self-reported decline in basic tastes (YES – ed in Figure 44a) (p=.024, χ^2=5.112, significance by cell p=.028) and general taste alterations/parageusia/increase in taste perception (p=.015, χ^2=5.922, significance by cell p=.022) (YES – red in Figure 44b) showed greater changes in Odor preferences, compared to patients without these alterations (NO – grey).

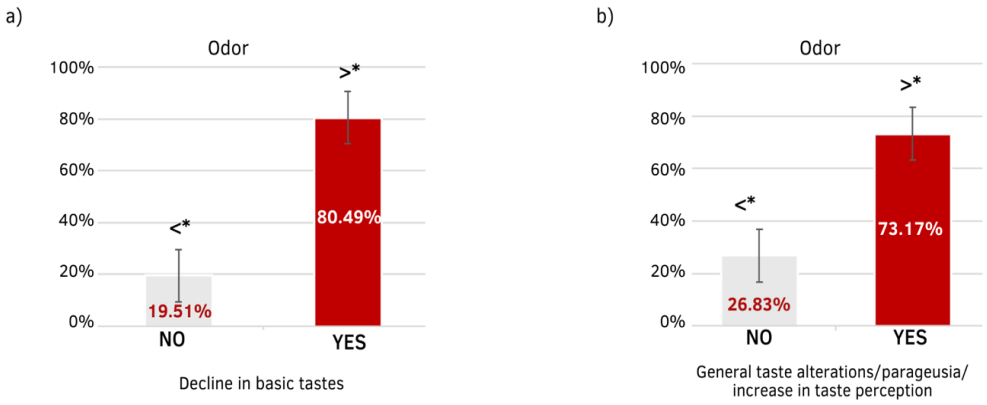


Figure 44 Association between the presence of a) decline in basic tastes (red) b) general taste alterations/parageusia/increase in taste perception and changes in Odor preferences after the 8th cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

During this period of the treatment patients who self-reported decline in basic tastes (U=159; p=.043) and general taste alteration/parageusia/increase in taste perception (U=105; p=.025) treatment showed a statistically significant direction in the dimension of odor preference, as confirmed by Mann-Whitney U tests, with an increase in aversion to intense odors.

Patients who self-reported phantogeusia (YES - red in Figure 45) reported significant changes in food preferences of the Sweet vs. Bitter dimension (p=.032, χ^2=4.583, significance by cell p=.034).

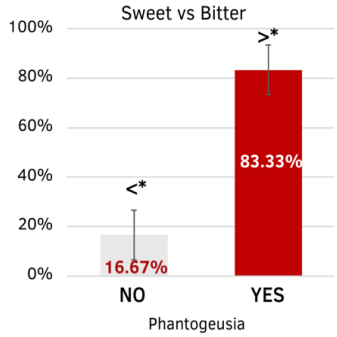


Figure 45 Association between the presence of phantogeusia and changes in food preferences of Sweet vs. Bitter dimension after the 8th cycle of chemotherapy. Grey indicates the percentage of patients without alteration who change preferences. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test).

Insights on food preferences three months after the end of treatment

The results showed that most preference changes observed during treatment had been resolved by TF, as no significant associations between chemosensory alterations and preference changes were found at this time point (p>0.05). The only exception concerned patients who reported phantogeusia at T8, who still showed preference changes in the Sweet vs. Bitter dimension at TF (p=.018, χ^2=5.598, significance by cell p=.019). These changes therefore appeared to be persistent after 3 months of treatment. Table 27 summarizes the results.

Table 27 Follow up analysis of changes in preferences. ***Emboldened*** *p-value<.05 indicates a significant difference at 95%. ^ sign on p-value indicates a value close to significance.*

Type of alteration at T2	Dimension of FP&EQ	Changes T0-T2 p-value	Changes T0-TF p-value
General taste alteration/parageusia/increase in taste perception	Sweet vs. Bitter	***.004**	.343
Phantogeusia	Sweet vs. Bitter	***.015**	.436
Type of alteration at T4		Changes T0-T4 p-value	Changes T0-TF p-value
Decline in basic tastes	Flavor	***.043**	.434
General taste alteration/parageusia/increase in taste perception	Texture	***.003**	.235
	Herbs and Spices	***.031**	.200
Phantogeusia	Flavor	***.024**	.545
	Texture	***.026**	.612
	Sweet vs. Sour	***.008**	.771
Type of alteration at T6		Changes T0-T6 p-value	Changes T0-TF p-value
General taste alteration/parageusia/increase in taste perception	Odor	***.001**	.246
	Herbs and Spices	***.030**	.836
Phantogeusia	Odor	***.034**	.435
	Sweet vs. Sour	***.004**	^.063
Type of alteration at T8		Changes T0-T8 p-value	Changes T0-TF p-value
Decline in basic tastes	Odor	***.024**	.670
General taste alteration/parageusia/increase in taste perception	Odor	***.022**	.406
Phantogeusia	Sweet vs. Bitter	***.004**	***.019**

4.3.2.3 Preferred dishes and most disliked dishes

As summarized in Table 26 (see § 4.3.2.2), the fourth cycle (T4) emerged as the time point with the highest number of preference changes, especially among patients classified as having general taste alterations/parageusia/increase in taste perception. Therefore, as an example of a word cloud (Figure 46), these patients'

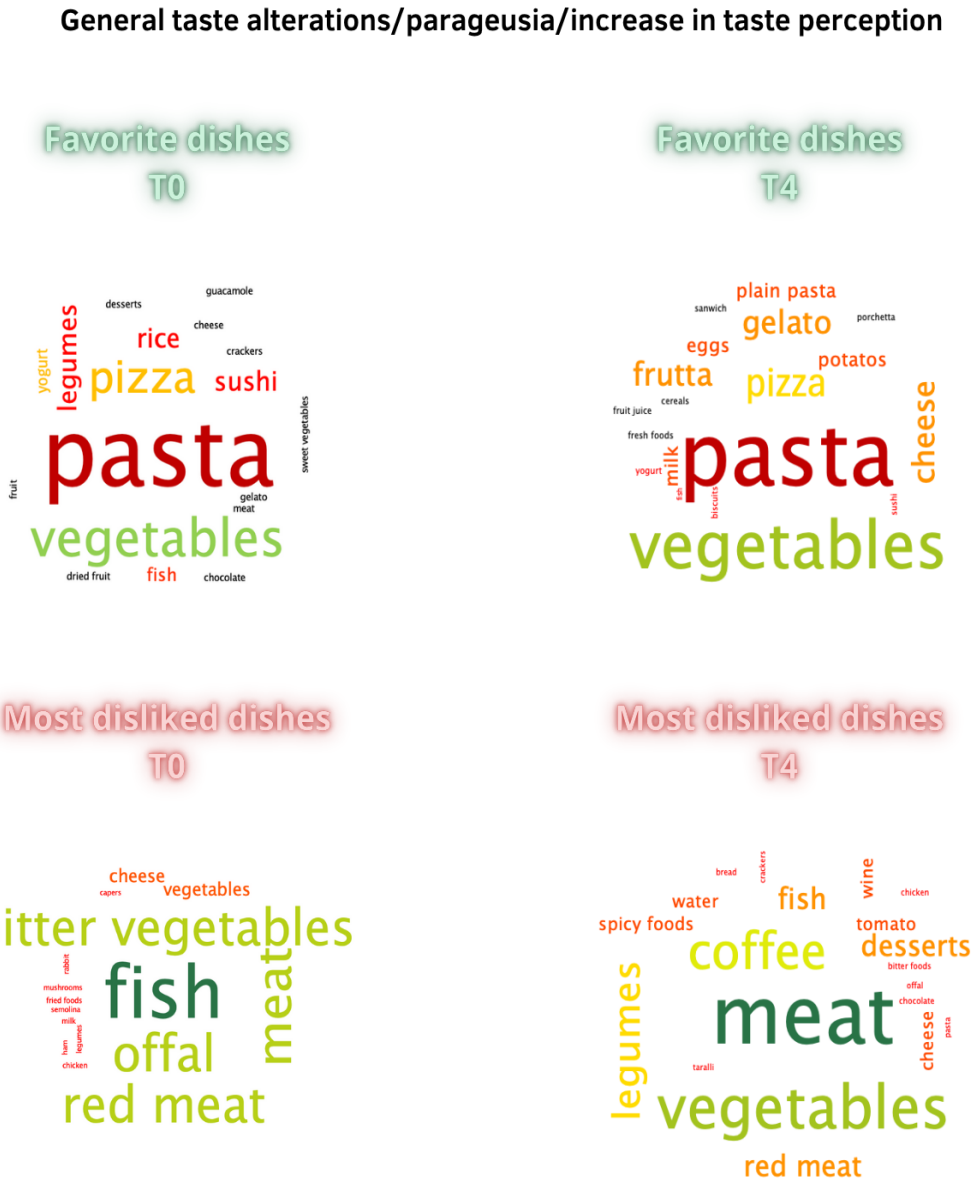


Figure 46 Word clouds – Comparison between T0 and T4 of favorite and most disliked dishes of patients with general taste alterations/parageusia/increase in taste perception.

(n=37) preferred and most disliked foods at T4 were compared with their baseline responses.

Among patients with general taste alterations/parageusia/increase in taste perception, the most frequently reported preferences were pasta, pizza, and vegetables, followed by legumes, rice, and sushi. At T4, preferences for pasta, pizza, and vegetables remained stable, but new foods such as ice cream, fruit, and cheese appeared more frequently, suggesting a shift toward sweeter and softer foods.

Regarding foods reported as most disliked, before treatment, the most frequently mentioned were fish, offal, vegetables, and meat (especially red meat). At T4, disliking for meat increased, but aversions extended to coffee, legumes, as well as sweets, wine, and water. Instead, disliking for fish seems to decrease at T4.

4.3.2.4 Qualitative insights into the food preferences during daily eating experience of patients with chemosensory disorders

Analyzing qualitative interviews during the treatment period, most of the patients interviewed reported changes in food preferences already after the first treatment cycle, although the intensity and nature of the changes varied considerably between subjects. The patients interviewed often described a loss of cravings for foods they consumed before treatment.

Among the most frequently cited was the sweet taste. For some individuals, sweet foods provided a form of comfort, sometimes even helping to mask unpleasant sensory experiences such as a metallic taste in mouth or when the food tastes bitter or bad:

"In the last week, I've noticed that after meals, I really want to eat something sweet, a biscuit or a vin santo, something I never did before."

"I feel like I'm craving more sweet foods, perhaps to tone down the bitterness. I no longer prefer bitter foods; they bother me."

For others, however, the presence of sweetness in foods became a challenge, due to increased sensitivity, nausea, or a general sense of aversion.

"I tend to avoid sweets this week… I didn't like sweet things. The thought of sweets bothered me; it made me a little nauseous (it doesn't bother me in my mouth)."

Conversely, salty, well-seasoned, or spicy foods were often reported as more desirable:

"I prefer foods with a little more flavor; even in the hospital, I would have preferred more seasoning."

"I noticed I craved salty foods more; for example, I really craved salty ham."

Conversely, patients experiencing hypergeusia, altered perception like bad or bitter taste of food, nausea, or mouth inflammation often reported a preference for milder foods, with no added salt and without odor:

"I prefer foods with a blander flavor; I don't feel like adding seasoning or spices. Even during the hospitalization, the canteen food was fine; I wouldn't have preferred it spicier or more intense."

“I feel everything more, so I prefer more unseasoned things.”

Food temperature also emerged as a key factor in reported preferences. A significant number of participants preferred cold foods than hot, often attributing this choice to symptoms such as nausea or oral discomfort (e.g., burning, numbness, mucositis):

"I felt better eating things that were fresh, cold, odorless, and had little flavor."

Texture preferences also changed. Some patients preferred softer foods due to mouth pain, while others preferred dry or crunchy foods:

“I preferred soft foods to hard or crunchy ones, because they bothered me precisely because of the canker sores.”

“I feel the need to blend things, because I prefer creamy consistencies,

“I tended to prefer dry things and because of nausea ate only toast and crackers.”

Furthermore, specific common foods were often avoided. Coffee emerged as the most mentioned product, with many patients developing an aversion to its bitterness or smell already after the first cycle. Meat, particularly red meat and poultry, was also frequently avoided, described as metallic, visually unappealing, or nauseating:

“The coffee I used to like is now the most bitter thing in the world. I want to drink it, but I just can't.”

“I can't stand meat, not even chicken. I don't know why; it makes me nauseous.”

“The meat is a bit metallic, so I prefer other foods.”

Furthermore, some patients have developed strong aversions to specific foods consumed during chemotherapy sessions, particularly when associated with nausea. This suggests a form of learned food aversion, triggered by the moment of eating rather than the taste itself:

"Right after chemotherapy, I ate bresaola, Philadelphia, and honey and felt fine. But then I felt nauseated, and now just thinking about those foods makes me feel sick."

“On the day of treatment, I choose the foods to sacrifice because I know I won't eat them again.”

In addition to taste changes or physical symptoms, several patients described strong food aversions not directly related to the sensory properties of food itself, but rather to contextual or emotional associations, particularly those related to the hospital environment.

Although most patients reported gradually regaining their pre-treatment preferences during follow-up (3 months after completion), these context-based aversions often persisted well beyond the acute phase of chemotherapy:

"I used to like soups and broths, but now I can't eat them because their smell reminds me of the hospital. It's not so much a question of perception, but rather of the association with the hospital canteen. The other day, walking past the hospital, I had the sensation of smelling food, even though there wasn't any, precisely because of this association."

"I can't eat taralli anymore; I brought them with me on the day of my first chemotherapy and since then I can't even look at them or mention them, yet they haven't made me feel nauseous."

Result summary 4.3

- Hedonic responses to basic tastes changed during chemotherapy, although unevenly across subjects, with decreased, stable, or occasionally increased liking patterns depending on the taste. Even in the presence of self-reported chemosensory alterations (CiTAS), no uniform hedonic response pattern emerged: some patients showed reduced liking, while others increased liking.
- At the population level, food preference scores (FP&EQ) appeared overall stable over time, suggesting that preference changes are expressed primarily as interindividual variability rather than a uniform directional trend.
- Patients with self-reported alterations (CiTAS) were more likely to report changes in preferences, particularly in terms of flavor and texture (often consistent with adaptations toward less intense flavors and softer/creamier textures) and, at certain points, with increased odor aversion. T4 emerged as the critical time point at which preference changes were most frequently reported.

- Qualitative interviews clarified preference changes, highlighting the role of nausea, disgust, contextual associations, and oral discomfort, in addition to sensory changes.
- Recurring qualitative patterns included preferences for foods that were colder, with less odor, blander, or conversely, more flavorful/salty, as well as frequent avoidance behaviors (e.g., coffee and meat), and learned food aversions related to treatment contexts.
- Recovery at follow-up was common, but some aversions, particularly for foods of the Sweet vs. Bitter dimension, could persist even after treatment.

4.4 Impact of chemosensory disorders on emotional responses to foods

4.4.1 Qualitative interviews on emotional responses to chemosensory changes

Emotional responses to sensory changes during chemotherapy varied greatly from patient to patient. For many, these changes were perceived as temporary and manageable side effects, without significant emotional impact. These patients often described the changes as something to be expected and tolerated, demonstrating a rational and pragmatic approach:

"I know it's temporary, so I don't let it affect me."

However, for many others, the impact was more profound. A recurring theme among interviewees was frustration or sadness due to the loss of the pleasure of eating. Some patients, particularly those with a strong interest in food or cooking, described a profound sense of dissatisfaction:

"I had prepared a delicious ragù, like I always do, but when I tasted it and couldn't taste anything... it was terrible!!"

"It was a disappointment. Losing my sense of taste takes away the joy of eating."

Others reported feeling annoyed, nervous, or emotionally depressed, especially when they couldn't enjoy meals with others due to embarrassment or a lack of desire to participate in food-related events:

"It bothered me a lot and made me sad."

"When I sat at the table, it was a moment of joy. Now, it just seems like a duty."

"At home, I joke about it, but I avoid eating out or going to dinner with people I don't know."

For a smaller group, the emotional burden extended to feelings of anxiety, depression, or isolation. These patients noted that eating had become a source of discomfort:

"I feel down, especially when I go out to eat and can't enjoy anything."

"This addiction to taste has really worn me down mentally. I just wanted it to go away."

"I feel like I've lost a part of myself. I don't even want to eat anymore."

Some participants associated loss of appetite or significant changes in eating behavior with physical health concerns, such as unintentional weight loss:

"I'm worried because I'm losing too much weight. I can see it on my face, in the way my clothes fit."

While some patients adapted over time or found ways to manage their symptoms through psychological support, family encouragement, or the natural course of recovery, others described the period of altered perception as one of the most emotionally challenging phases of treatment:

"Those two months were the worst of my life: the loss of taste for food really got me down."

In conclusion, while some patients responded well and maintained emotional stability, for others, the loss of taste and smell became a significant source of

emotional distress, affecting not only appetite, but also their sense of identity, social life, and psychological well-being.

4.4.2 Chemosensory alterations and emotional responses to foods

To study the influence of the chemosensory alterations or discomfort reported through the CiTAS on emotional responses over time, the McNemar test was applied (Table 28). The analysis showed significant results already at T1. In fact, even in the absence of change in preferences, the emotions elicited by the foods chosen in the FP&EQ were found to be worse compared to the baseline; this result was obtained in patients who self-reported decline in basic tastes in the Herbs and spices dimension (p=.035) in which a significant increase in negative emotions elicited by chosen options from 11.7% at T0 to 22.7% at T1 was observed. Furthermore, patients who self-reported general taste alteration/parageusia/increase in taste perception showed an increase in negative emotions for chosen products in the Texture dimension (p=.003) from 9.6% at T0 to 22.6% at T1 and Sweet vs. Bitter dimension (p=.0002) from 10.4% at T0 to 29.6% at T1. In the same way patients with phantogeusia reported an increase in negative emotions elicited by chosen options of the Texture dimension (p=.004) from 11.5% at T0 to 23.1% at T1, and from 11.5% at T0 to 22.3% at T1 in the Sweet vs. Bitter dimension (p=.016). Lastly, considering the comparison between T0 and T1, patients with discomfort worsen the emotions elicited by favorite options of the Flavor dimension (p=.029) from 10.6% of negative emotions at T0 to 16.6% at T1, of Texture dimension (p=.001), from 11.9% at T0 to 21.3% at T1, of Herbs and Spices dimension (p=.049)), from 16.6% at T0 to 22.5% at T1, and of Sweet vs. Bitter dimension (p=.001), from 10.6% at T0 to 20.4% at T1.

After T2, patients who self-reported general taste alteration/parageusia/increase in taste perception (p=.035), phantogeusia (p=.009), and discomfort (p=.033) showed a worsening in emotional responses to preferred options of the Sweet vs. Bitter dimension. Furthermore, patients with phantogeusia also showed an increase in negative emotions elicited by chosen options of Texture dimension (p=.034).

After 4 cycles, patients who self-reported decline in basic tastes further reported a worsening of the emotions of disliked smells of Odor dimension (p=.037). Instead, patients who self-reported general taste alterations/parageusia/increase in taste perception (p=.004), phantogeusia (p=.003), and discomfort (p=.008) showed a significant increase in negative emotions elicited by chosen options of the Sweet vs. Bitter dimension.

At T6 only the Sweet vs. Bitter dimension was interested by worsening in emotional responses in presence of all types of alterations/condition (decline in basic tastes p=.0003; general taste alterations/parageusia/increase in taste perception p=.019; phantogeusia p=. 0004; discomfort p=.006).

At T8 only in the presence of decline in basic tastes (p=.049) and of discomfort (p=.036) an increase in negative emotions elicited by chosen options of Sweet vs. Bitter dimension was observed.

Table 28 Comparison of percentages of negative emotions elicited by selected options in the FP&EQ between baseline and subsequent time points of chemotherapy in patients with self-reported alterations or discomfort. n= indicates the number of patients with that type of alteration at that specific time point during treatment. ***Emboldened*** *p-value<.05 indicates a significant increase. ^ sign on p-value indicates a value close to significance.*

CiTAS alteration / FP&EQ dimension	T0->T1 % of negative emotions elicited by chosen options (p-value)	T0->T2 % of negative emotions elicited by chosen options (p-value)	T0->T4 % of negative emotions elicited by chosen options (p-value)	T0->T6 % of negative emotions elicited by chosen options (p-value)	T0->T8 % of negative emotions elicited by chosen options (p-value)
Decline in basic tastes	n=12	n=33	n=33	n=23	n=22
Flavor	10.0 → 15.0 (.549)	12.7 → 10.9 (.678)	15.8 → 19.4 (.307)	16.5 → 21.7 (.345)	12.7 → 14.5 (.791)
Texture	11.7 → 21.7 (.146)	13.9 → 15.2 (.860)	17.0 → 17.8 (1.000)	16.5 → 17.4 (1.000)	18.2 → 18.2 (1.000)
Odor	79.2 → 81.3 (1.000)	76.5 → 83.3 (.122)	**78.8 → 87.1 (.037)**	79.3 → 73.9 (.454)	76.1 → 79.5 (.678)
Herbs & spices	**11.7 → 22.7 (.035)**	20.6 → 24.8 (.324)	21.8 → 23.6 (.766)	23.5 → 22.6 (1.000)	23.6 → 21.8 (.856)
Sweet vs. Bitter	10.0 → 20.0 (.210)	11.5 → 12.1 (1.000)	11.5 → 17.0 (.137)	**7.8 → 20.9 (.0003)**	**9.1 → 17.3 (.049)**
Sweet vs. Sour	15.0 → 16.6 (1.000)	19.4 → 17.0 (.572)	18.2 → 21.8 (.391)	22.6 → 23.5 (1.000)	16.4 → 20.0 (.597)
General taste alterations / parageusia / increase in taste perception	n=23	n=38	n=37	n=25	n=19
Flavor	9.6 → 16.5 (.096)	12.1 → 10.0 (.523)	15.1 → 20.5 (.099)	12.0 → 19.2 (.093)	11.6 → 14.7 (.508)
Texture	**9.6 → 22.6 (.003)**	11.6 → 17.9 (^.058)	16.8 → 21.1 (.268)	8.8 → 11.2 (.607)	18.1 → 18.1 (1.000)
Odor	79.3 → 85.9 (.238)	77.0 → 82.2 (.215)	79.1 → 84.5 (.185)	75.0 → 76.0 (1.000)	84.2 → 84.2 (1.000)
Herbs & spices	19.1 → 25.2 (.248)	19.5 → 22.6 (.471)	21.1 → 28.1 (.111)	18.4 → 21.6 (.597)	23.2 → 18.9 (.572)
Sweet vs. Bitter	**10.4 → 29.6 (.0002)**	**10.5 → 17.4 (.035)**	**10.3 → 20.5 (.004)**	**12.0 → 20.8 (.019)**	11.6 → 18.9 (.143)
Sweet vs. Sour	21.7 → 19.1 (.678)	10.0 → 18.9 (.864)	16.8 → 19.5 (.500)	16.0 → 20.0 (p=.424)	16.8 → 18.9 (.845)
Phantogeusia	n=26	n=39	n=35	n=24	n=22
Flavor	12.3 → 16.2 (.405)	12.3 → 11.8 (1.000)	15.4 → 20.6 (.122)	16.8 → 21.8 (.345)	10.9 → 12.7 (.774)
Texture	**11.5 → 23.1 (.004)**	**14.4 → 21.5 (.034)**	15.4 → 21.7 (.099)	17.5 → 19.2 (.832)	13.9 → 11.1 (.607)
Odor	82.7 → 81.7 (1.000)	83.3 → 85.3 (.701)	82.1 → 84.3 (.678)	78.1 → 75.0 (.629)	78.4 → 80.7 (.824)

Herbs & spices	20.0 → 21.5 (.839)	23.1 → 25.1 (.672)	22.9 → 28.6 (.229)	26.7 → 25.0 (.868)	25.5 → 18.2 (.185)
Sweet vs. Bitter	**11.5 → 22.3 (.016)**	**9.7 → 18.5 (.009)**	**9.1 → 20.0 (.003)**	**8.3 → 21.7 (.0004)**	10.0 → 17.3 (.115)
Sweet vs. Sour	23.1 → 16.2 (.093)	20.0 → 17.9 (.652)	20.0 → 21.1 (.864)	21.7 → 25.0 (.585)	17.3 → 16.4 (1.000)
Discomfort	n=47	n=58	n=49	n=36	n=31
Flavor	**10.6 → 16.6 (.029)**	11.0 → 11.7 (.868)	13.1 → 17.1 (.132)	12.8 → 19.0 (.080)	11.6 → 11.8 (.115)
Texture	**11.9 → 21.3 (.001)**	14.5 → 18.3 (.169)	14.7 → 20.4 (^.059)	14.4 → 14.4 (1.000)	15.0 → 15.0 (1.000)
Odor	77.7 → 78.2 (1.000)	80.2 → 81.5 (.761)	79.1 → 85.2 (.073)	77.8 → 77.8 (1.000)	78.2 → 79.8 (.845)
Herbs & spices	**16.6 → 22.5 (.049)**	20.7 → 24.1 (.275)	21.2 → 25.7 (.222)	22.2 → 22.2 (1.000)	22.6 → 19.4 (.522)
Sweet vs. Bitter	**10.6 → 20.4** (.002)	**10.3 → 15.9 (.033)**	**10.2 → 18.0 (.008)**	**10.6 → 18.9 (.006)**	**9.7 → 17.4 (.036)**
Sweet vs. Sour	20.0 → 17.4 (.451)	19.6 → 17.9 (.590)	18.8 → 20.8 (.568)	18.3 → 21.2 (.511)	18.1 → 18.1 (1.000)

Result summary 4.4

- Qualitative interviews showed that loss of pleasure in eating was a central emotional issue, particularly for patients for whom food represented an important source of pleasure, identity, or social interaction. For some patients, chemosensory changes were perceived as temporary and manageable, with limited emotional impact. For others, these changes led to frustration, sadness, annoyance, and loss of motivation to eat, often resulting in avoidance of social eating situations.
- Analyses of emotional responses to foods showed early worsening even in the absence of changes in food preferences. Already after the first cycle (T1), patients who reported any type of chemosensory alteration (decline in basic tastes, general taste alterations/parageusia, phantogeusia, or discomfort) showed a significant increase in negative emotions elicited by foods.
- The Sweet vs. Bitter dimension emerged as the most emotionally sensitive, showing a constant worsening over the course of therapy, even in the final stages, and for all types of chemosensory alterations.
- Overall, the results indicate that emotional responses to food are influenced earlier and more consistently than food preferences, underscoring the importance of addressing emotional and psychological dimensions alongside sensory changes.

4.5 Influence of individual differences on food preferences and emotions

In addition to the impact of treatment-related chemosensory changes, individual differences may also play a central role in shaping food preferences, their evolution over the course of chemotherapy and emotional responses to foods. Characteristics such as food neophobia, disgust sensitivity, food involvement, and PROP taster

status may influence preferences and emotions for certain sensory characteristics of food during treatment.

The following sections present the results of analyses exploring the influence of these individual characteristics on food preferences and emotions elicited by foods.

Impact of individual differences on food preference changes

The changes in food preferences observed in relation to individual differences, specifically, food neophobia, disgust sensitivity, food involvement, and PROP status, are summarized in Table 29.

Regarding food neophobia, no significant associations were found between the high or low food neophobia groups and changes in preferences during the early stages of chemotherapy. However, comparing responses at T6 with those at baseline (T0), patients with low food neophobia (LFN) showed significantly greater changes in food preferences in general ($p=.017$, $\chi^2=5.704$, significance by cell $p=.018$) and particularly in Herbs and Spices ($p=.014$, $\chi^2=6.024$, significance by cell $p=.018$) dimension. Similarly, at T8, greater and close to significance changes in the Smell and Herbs and Spices dimensions were observed in patients with low food neophobia (LFN) ($p=.062$, $\chi^2=3.476$, significance by cell $p=.074$). However, Mann-Whitney U tests did not reveal a specific direction of change (i.e., increase or decrease in preference scores).

High sensitivity to disgust (HD) was instead associated with significant preference changes, particularly in the Flavor dimension, at T1 ($p=.011$, $\chi^2=6.445$, significance by cell $p=.015$) and T6 ($p=.046$, $\chi^2=3.992$, significance by cell $p=.050$). However, as with food neophobia, Mann-Whitney U tests did not reveal a specific direction of change in preference scores.

Regarding PROP status, the results showed a limited association with preference changes over the course of treatment. Specifically, patients classified as high PROP

responders (HP) reported significantly more preference changes in the Herbs and Spices dimension at time T6 (p=.023, χ^2=5.18. significance by cell p=.028) and in the Odor dimension at time T8 (p=.013, χ^2=6.238, significance by cell p=.016), compared to low PROP responders. For the latter dimension, the Mann-Whitney analysis comparing preference scores at time T0 and time T6 revealed a greater aversion to stronger odors (U=219; p=.017). For the other dimension, however, the Mann-Whitney test did not reveal a specific direction in preference scores, making it difficult to determine whether these changes reflect a tendency to prefer more seasoned or non-seasoned foods.

Table 29 Association between individual differences (food neophobia, sensitivity to disgust, PROP responsiveness) with changes in food/odor preferences during treatment. < > indicate that the observed count was significantly greater or less from its expected count (Fisher's exact test). ***Emboldened*** *p-value<.05 indicates significance. ^ sign on p-value indicates a value close to significance*

Trait	FP&EQ dimensions	T0-T1 changes in preferences	T0-T2 changes in preferences	T0-T4 changes in preferences	T0-T6 changes in preferences	T0-T8 changes in preferences
Food Neophobia (LowFN/HighFN)	All the dimensions	.379	.417	.202	**>(LFN) .018**	.119
	Flavor	.463	.203	.185	.769	.556
	Texture	.897	.345	.369	.584	.971
	Odor	.443	.383	.795	.337	**>(LFN) .036**
	Herbs and Spices	.501	.560	.082	**>(LFN) .018**	>(LFN) .074
	Sweet vs Bitter	.826	.246	.634	.498	.690
	Sweet vs Sour	.919	.895	.128	.150	.848
Sensitivity to Disgust (LowD/HighD)	All the dimensions	.083	**>(HD) .017**	.377	**>(HD) .037**	.596
	Flavor	**>(HD) .015**	.135	.458	**>(HD) .050**	.367
	Texture	.297	.259	.783	.837	.489
	Odor	.138	.270	.387	.098	.099
	Herbs and Spices	.920	.093	.890	.869	.444
	Sweet vs Bitter	.914	.411	1.000	.238	.491
	Sweet vs Sour	.371	.198	.886	.668	.640
PROP status (LowP/HighP)	All the dimensions	.251	.463	.504	>(HP) ^.051	.366
	Flavor	.329	.793	.975	.474	.796
	Texture	.742	.481	.456	.890	.812
	Odor	.718	1.000	.979	.312	**>(HP) .016**

Herbs and Spices	.351	.660	.704	**>(HP) .023**	.361
Sweet vs Bitter	.597	.322	.721	.802	.633
Sweet vs Sour	.825	.372	.844	.744	.195

Impact of individual differences on emotion elicited by foods

To verify the influence of the individual differences on emotional responses over time, the McNemar test was applied, and the results of these analyses are summarized in Table 30 (Food Neophobia), Table 31 (Sensitivity to Disgust), and Table 32 (PROP responsiveness).

Table 30 Comparison of percentages of negative emotions elicited by selected options in the FP&EQ between baseline and subsequent time points of chemotherapy in patients with High (H) and Low (L) food neophobia. Emboldened p-value<.05 indicates a significant increase. ^sign on p-value indicates a value close to significance.

Food Neophobia (High/Low)	FP&EQ dimensions	% negative emotions elicited by chosen options at T0	% negative emotions elicited by chosen options at T1	p-value (McNemar test)
T0-T1 High (28) Low (24)	Flavor (H)	13.6	17.1	.359
	Flavor (L)	7.5	13.5	.190
	Texture (H)	14.3	25	**.004**
	Texture (L)	11.7	19.2	.081
	Odor (H)	74.1	74.1	1.000
	Odor (L)	71.4	75.0	1.000
	Herbs & Spices (H)	18.6	27.1	**.029**
	Herbs & Spices (L)	25.7	25.7	.798
	Sweet vs. Bitter (H)	10.7	21.4	**.011**
	Sweet vs. Bitter (L)	8.6	14.3	.683
	Sweet vs. Sour (H)	17.8	16.4	.824
	Sweet vs. Sour (L)	22.8	14.3	.546
T0-T2 High (29) Low (30)	Flavor (H)	11.8	11.1	1.000
	Flavor (L)	10.0	10.0	.803
	Texture (H)	12.4	19.3	^.052

	Texture (L)	16.7	19.3	.571
	Odor (H)	75.9	81.0	.238
	Odor (L)	71.4	89.3	.131
	Herbs & Spices (H)	17.2	25.5	**.036**
	Herbs & Spices (L)	25.7	30.0	.267
	Sweet vs. Bitter (H)	10.3	13.1	.503
	Sweet vs. Bitter (L)	8.6	17.1	.371
	Sweet vs. Sour (H)	16.5	17.2	1.000
	Sweet vs. Sour (L)	22.8	17.1	.724
T0–T4 High (26) Low (25)	Flavor (H)	13.8	18.5	.286
	Flavor (L)	12.0	16.0	.302
	Texture (H)	11.5	23.1	**.006**
	Texture (L)	19.2	20.0	1.000
	Odor (H)	76.9	79.8	.523
	Odor (L)	71.4	85.7	.221
	Herbs & Spices (H)	15.4	24.6	**.029**
	Herbs & Spices (L)	25.7	32.8	.181
	Sweet vs. Bitter (H)	9.2	16.9	**.052**
	Sweet vs. Bitter (L)	8.6	17.1	.371
	Sweet vs. Sour (H)	14.6	18.5	.359
	Sweet vs. Sour (L)	22.8	14.3	.450
T0–T6 High (21) Low (18)	Flavor (H)	13.3	19.0	.263
	Flavor (L)	14.4	18.9	.453
	Texture (H)	8.4	11.4	.581
	Texture (L)	21.1	18.9	.803
	Odor (H)	78.6	73.8	.388
	Odor (L)	71.4	85.7	.289
	Herbs & Spices (H)	14.3	19.0	.332
	Herbs & Spices (L)	25.7	28.6	1.000
	Sweet vs. Bitter (H)	11.4	13.3	.791
	Sweet vs. Bitter (L)	8.6	16.0	.221
	Sweet vs. Sour (H)	13.3	20.9	.077
	Sweet vs. Sour (L)	22.8	20.0	1.000
T0–T8	Flavor (H)	11.3	21.3	^.057

High (16)	Flavor (L)	13.3	13.3	.724
Low (15)	Texture (H)	11.3	17.5	.227
	Texture (L)	21.6	18.9	.789
	Odor (H)	82.8	73.4	.146
	Odor (L)	71.4	78.6	.683
	Herbs & Spices (H)	17.5	17.5	1.000
	Herbs & Spices (L)	25.7	25.7	.773
	Sweet vs. Bitter (H)	11.3	17.5	.302
	Sweet vs. Bitter (L)	8.6	11.4	1.000
	Sweet vs. Sour (H)	15	18.8	.508
	Sweet vs. Sour (L)	22.8	5.7	.077

Table 31 Comparison of percentages of negative emotions elicited by selected options in the FP&EQ between baseline and subsequent time points of chemotherapy in patients with High (H) and Low (L) sensitivity to disgust. Emboldened p-value<.05 indicates a significant increase. ^sign on p-value indicates a value close to significance.

Sensitivity to Disgust (High/Low)	FP&EQ dimensions	% negative emotions elicited by chosen options at T0	% negative emotions elicited by chosen options at T1	p-value (McNemar test)
T0-T1 High (24) Low (32)	Flavor (H)	10.8	21.7	**.015**
	Flavor (L)	12.2	14.3	1.000
	Texture (H)	5.0	18.3	**.0001**
	Texture (L)	24.0	22.0	1.000
	Odor (H)	81.3	77.1	.523
	Odor (L)	77.0	75.0	1.000
	Herbs & Spices (H)	13.3	20.8	.078
	Herbs & Spices (L)	24.0	28.0	.789
	Sweet vs. Bitter (H)	10.0	20.8	**.011**
	Sweet vs. Bitter (L)	12.0	14.0	1.000
	Sweet vs. Sour (H)	16.7	16.7	1.000
	Sweet vs. Sour (L)	18.0	10.0	.289
T0-T2 High (31) Low (33)	Flavor (H)	11.9	15.0	.405
	Flavor (L)	12.2	10.2	1.000
	Texture (H)	11.3	18.8	**.036**
	Texture (L)	24.0	18.0	.505
	Odor (H)	82.0	85.2	.557
	Odor (L)	77.5	85.0	.371

	Herbs & Spices (H)	18.8	25.5	.132
	Herbs & Spices (L)	24	32	.386
	Sweet vs. Bitter (H)	8.8	13.1	.210
	Sweet vs. Bitter (L)	12.0	14.0	1.000
	Sweet vs. Sour (H)	17.5	15.6	.690
	Sweet vs. Sour (L)	18.0	14.0	.783
T0–T4 High (28) Low (28)	Flavor (H)	13.6	21.4	**.035**
	Flavor (L)	12.2	10.2	1.000
	Texture (H)	12.1	23.6	**.004**
	Texture (L)	24.0	18.0	.505
	Odor (H)	80.4	86.6	.248
	Odor (L)	77.5	80.0	1.000
	Herbs & Spices (H)	18.6	26.4	.071
	Herbs & Spices (L)	24	32	.453
	Sweet vs. Bitter (H)	7.9	17.1	**.015**
	Sweet vs. Bitter (L)	12.0	16.0	.752
	Sweet vs. Sour (H)	17.1	20.7	.442
	Sweet vs. Sour (L)	18.0	16.0	1.000
T0–T6 High (24) Low (17)	Flavor (H)	14.2	19.2	.286
	Flavor (L)	12.2	18.3	.546
	Texture (H)	13.3	15.8	.629
	Texture (L)	24.0	18.0	.546
	Odor (H)	81.3	81.3	1.000
	Odor (L)	77.5	70.0	.505
	Herbs & Spices (H)	19.2	25.8	.200
	Herbs & Spices (L)	24.0	20.0	.773
	Sweet vs. Bitter (H)	10.8	16.7	.189
	Sweet vs. Bitter (L)	12.0	18.0	.371
	Sweet vs. Sour (H)	13.3	24.2	.230
	Sweet vs. Sour (L)	18.0	16.0	1.000
T0–T8 High (19) Low (13)	Flavor (H)	11.6	17.9	.146
	Flavor (L)	12.2	16.3	.752
	Texture (H)	13.7	17.9	.388
	Texture (L)	24.0	20.0	.572

Odor (H)	78.9	85.5	.332
Odor (L)	77.5	65	.131
Herbs & Spices (H)	18.9	22.1	.664
Herbs & Spices (L)	24.0	22.0	1.000
Sweet vs. Bitter (H)	10.5	14.7	.424
Sweet vs. Bitter (L)	12.0	21.0	.228
Sweet vs. Sour (H)	18.9	18.9	1.000
Sweet vs. Sour (L)	18.0	16.0	1.000

Table 32 Comparison of percentages of negative emotions elicited by selected options in the FP&EQ between baseline and subsequent time points of chemotherapy in patients with High (H) and Low (L) PROP responsiveness. Emboldened p-value<.05 indicates a significant increase. ^sign on p-value indicates a value close to significance.

PROP responsiveness (High/Low)	FP&EQ dimensions	% negative emotions elicited by chosen options at T0	% negative emotions elicited by chosen options at T1	p-value p-value (McNemar test)
T0-T1 High (26) Low (31)	Flavor (H)	12.3	16.9	.307
	Flavor (L)	9.1	15.9	.371
	Texture (H)	9.2	16.9	^.052
	Texture (L)	20.0	22.0	1.000
	Odor (H)	79.8	78.8	1.000
	Odor (L)	77.8	75	1.000
	Herbs & Spices (H)	18.5	21.5	.608
	Herbs & Spices (L)	20.0	28.9	.221
	Sweet vs. Bitter (H)	13.1	19.2	.169
	Sweet vs. Bitter (L)	4.4	17.6	.114
	Sweet vs. Sour (H)	18.5	15.4	.585
	Sweet vs. Sour (L)	20.0	13.3	.371
T0-T2 High (33) Low (32)	Flavor (H)	13.9	11.5	.503
	Flavor (L)	9.1	15.9	.450
	Texture (H)	14.5	17.0	.597
	Texture (L)	20.0	22.2	1.000
	Odor (H)	80.3	84.8	.286
	Odor (L)	77.8	86.1	.450
	Herbs & Spices (H)	22.4	27.3	.280
	Herbs & Spices (L)	20.0	26.7	.505
	Sweet vs. Bitter (H)	12.7	17.0	.265

	Sweet vs. Bitter (L)	4.4	11.1	.450
	Sweet vs. Sour (H)	18.2	13.9	.281
	Sweet vs. Sour (L)	20.0	24.4	.683
T0–T4 High (31) Low (25)	Flavor (H)	17.4	20.6	.487
	Flavor (L)	9.1	20.4	.071
	Texture (H)	14.8	21.9	.080
	Texture (L)	20.0	24.4	.752
	Odor (H)	79.8	83.9	.405
	Odor (L)	77.8	86.1	.371
	Herbs & Spices (H)	21.3	26.5	.302
	Herbs & Spices (L)	20.0	31.1	.182
	Sweet vs. Bitter (H)	12.3	20.6	**.035**
	Sweet vs. Bitter (L)	4.4	8.9	.683
	Sweet vs. Sour (H)	17.4	20.6	.487
	Sweet vs. Sour (L)	20.0	24.4	.683
T0–T6 High (24) Low (17)	Flavor (H)	16.0	19.2	.572
	Flavor (L)	9.1	20.4	.131
	Texture (H)	15.2	17.6	.678
	Texture (L)	20.0	8.8	.131
	Odor (H)	80.0	77.0	.648
	Odor (L)	77.8	75.0	1.000
	Herbs & Spices (H)	21.6	25.6	.511
	Herbs & Spices (L)	20.0	15.5	.683
	Sweet vs. Bitter (H)	14.4	21.6	.078
	Sweet vs. Bitter (L)	4.4	6.7	1.000
	Sweet vs. Sour (H)	16.8	24.8	.099
	Sweet vs. Sour (L)	20.0	15.5	.617
T0–T8 High (10) Low (12)	Flavor (H)	15.0	14.0	1.000
	Flavor (L)	9.1	27.3	**.013**
	Texture (H)	18.2	18.2	1.000
	Texture (L)	20.0	24.4	.752
	Odor (H)	81.3	80.0	1.000
	Odor (L)	77.8	77.8	.683
	Herbs & Spices (H)	25.0	24.0	1.000

Herbs & Spices (L)	20.0	17.8	1.000
Sweet vs. Bitter (H)	15.0	23.0	.096
Sweet vs. Bitter (L)	4.4	12.5	.182
Sweet vs. Sour (H)	18.0	23.0	.473
Sweet vs. Sour (L)	20.0	15.5	617

Emotional responses to favorite foods during chemotherapy varied depending on individual differences.

Among patients with high levels of food neophobia, several dimensions showed a worsening of the emotional valence associated with favorite foods over the course of treatment. Specifically, in the Texture dimension, compared to T0, negative emotional responses to favorite foods increased after the first cycle (T1, p=.004), after the second cycle T2 (trend, p=.052), and after the fourth cycle (p=.006). A similar trend emerged in the Herbs and Spices dimension, with significant increases in negative emotional responses at T1 (p=.029), T2 (p=.036), and T4 (p=.029). In the Sweet vs. Bitter dimension, emotional valence also worsened, with a significant increase in negative responses at T1 (p=.011) and a trend at T4 (p=.052). A subsequent change was observed in the Flavor dimension, where negative emotions increased by the end of treatment (T8, p=.057). In contrast, patients with low food neophobia showed no significant changes in emotional valence in any of the dimensions examined, suggesting that these patients tend to maintain a more stable emotional relationship with food during chemotherapy.

Among patients with high disgust sensitivity, a significant worsening of the emotional valence associated with favorite foods was observed during treatment. In the Flavor dimension, negative emotional responses increased both immediately after the start of treatment (T1, p=.015) and again at mid-treatment (T4, p=.035). A similar trend was observed in the Texture dimension, where emotional valence significantly worsened at T1 (p<.0001), remained impaired at T2 (p=.036), and persisted at T4 (p=.004). The Sweet vs. Bitter dimension was also affected, with

significant increases in negative emotional responses at T1 (p=.011) and T4 (p=.015). In contrast, patients with low disgust sensitivity showed no significant changes in emotional responses across any sensory dimension, suggesting that these patients have a more stable emotional experience toward food during treatment.

Regarding PROP responsiveness, only limited effects were observed on emotional responses to food. Patients classified as high PROP responders showed worsening of the emotional valence for the chosen foods in specific dimensions of the FP&EQ: in the Texture dimension, negative emotions increased only after the first cycle (T1), while in the Sweet vs. Bitter dimension, a worsening emerged at T4. In contrast, low PROP responders generally maintained stable emotional responses throughout the treatment phases. A single significant change emerged only at the end of therapy (T8) in the Flavor dimension.

This pattern indicates that PROP status is not a strong or stable predictor of emotional changes in food experience, unlike neophobia and disgust sensitivity, which showed more consistent effects.

Result summary 4.5

- Individual traits contributed to the heterogeneity of food-related experiences during chemotherapy, without defining uniform response patterns.
- Food neophobia and disgust sensitivity emerged as primarily influencing emotional responses rather than changes in preferences.
- PROP responsiveness showed weaker and less consistent associations, suggesting a limited role in shaping food-related experiences during treatment.

4.6 Ideal snack

Table 33 shows the percentages of patients' choice for the ideal snack (sweet vs. salty) at different time points.

Overall, a clear and stable preference for salty snacks was observed throughout the study period. At baseline (T0), 66.2% of patients chose a salty snack, and this percentage increased slightly during treatment, peaking at T2 (78.8%). Although slight fluctuations were observed at subsequent time points (T4=71.9%, T6=69.0%, T8=72.7%), the preference for salty options remained consistently higher than that for sweet ones. At the final follow-up (TF), 64.3% of patients still preferred a salty snack, with a distribution similar to the baseline.

Table 33 Percentages of patients' choice for the ideal snack (sweet vs. salty) at different time points.

Ideal snack	T0	T1	T2	T4	T6	T8	TF
Salty, %	66.2	75.9	78.8	71.9	69.0	72.7	64.3
Sweet, %	33.8	24.1	21.2	28.1	31.0	27.3	35.7

Table 34 shows the sensory attributes that patients indicated at different times through the CATA as must have for their ideal snack.

For salty snacks, crunchy and tasty were consistently the most frequently selected attributes throughout treatment. At baseline (T0), patients described their ideal salty snack as crunchy (80.9%) and tasty (72.3%). Although the percentage of respondents indicating crunchiness decreased slightly at T2 (65.4%), this characteristic remained dominant at all time points. Similarly, tasty remained a key attribute (62-75%), highlighting a stable preference for salty and tasty products. Other attributes such as softness (15-24%) and hardness (15-24%) showed moderate appreciation, while creaminess, pastiness, liquidity, and juiciness were rarely selected (<10%).

For sweet snacks, the profile was much more variable over time. The most frequently mentioned attributes were "soft," "creamy," and "crunchy," although their prevalence varied significantly across time points. "Juicy" texture was also mentioned more frequently during the early stages of treatment. At T0, 41.7% of patients preferred a soft texture, but at T2, these proportions increased to 64.3%, suggesting a greater preference for soft texture during the treatment. Instead, preference for crunchiness and creaminess in sweet snacks decreases with treatments.

Table 34 Percentage of selection (CATA) of sensory attributes "must have" for ideal salty and sweet snacks across treatment time points (T0-TF).

Salty snack must have	T0	T1	T2	T4	T6	T8	TF
Soft	14.9%	22.7%	21.2%	21.9%	24.1%	12.5%	16.7%
Crunchy	80.9%	81.8%	65.40%	75.6%	79.3%	79.2%	77.8%
Hard	14.9%	18.2%	23.1%	17.1%	24.1%	20.8%	16.7%
Creamy	14.9%	13.6%	3.8%	4.9%	3.4%	4.2%	5.6%
Liquid	4.3%	2.3%	1.9%	0.0%	0.0%	0.0%	0.0%
Juicy	4.3%	6.8%	1.9%	7.3%	3.4%	0.0%	8.3%
Pasty	6.4%	2.3%	5.8%	2.4%	0.0%	8.3%	2.8%
Dense	10.6%	2.3%	5.8%	4.9%	0.0%	0.0%	8.3%
Tasty	72.3%	75.0%	65.4%	73.2%	65.5%	62.5%	69.4%
Sweet snack must have	**T0**	**T1**	**T2**	**T4**	**T6**	**T8**	**TF**
Soft	41.7%	57.1%	64.3%	37.5%	46.2%	88.9%	30.0%
Crunchy	50.0%	35.7%	50.0%	37.5%	38.5%	22.2%	65.0%
Hard	12.5%	0.0%	14.3%	12.5%	7.7%	0.0%	25.0%
Creamy	66.7%	35.7%	64.3%	43.8%	46.2%	55.6%	30.0%
Liquid	4.2%	7.1%	7.1%	0.0%	0.0%	0.0%	5.0%
Juicy	16.7%	28.6%	35.7%	31.3%	7.7%	22.2%	15.0%
Pasty	20.8%	0.0%	14.3%	18.8%	38.5%	0.0%	10.0%
Dense	4.2%	21.4%	14.3%	0.0%	15.4%	33.3%	5.0%
Tasty	25.0%	28.6%	35.7%	25.0%	7.7%	11.1%	30.0%

Table 35 shows the percentage of patients who indicated, through the CATA, the sensory attributes that should not be present in their ideal salty and sweet snacks at different times. Regarding salty snacks, patients most frequently indicated pasty (31.8–54.3%), liquid (27.3–54.5%), and creamy (14.3–36.2%) textures during treatment as must not have, with percentages that remained consistently high over time. Creamy textures were also commonly reported as undesirable, particularly at T0 (36.2%) and T4 (35.1%), while the selection of soft consistencies as must not have increased slightly towards the end (from 21.3% to 28.6%). In contrast, crunchy and tasty attributes were rarely reported as undesirable (both less than 10% for most time points).

For sweet snacks, the most frequently excluded characteristics were pasty (28.6–55.6%) and liquid (18.8–55.0%) textures, similar to salty snacks. Hard textures were also listed among the must not have. Attributes such as juicy and creamy were rarely mentioned (generally below 15%), and tasty was occasionally selected.

Table 35 Percentage of selection (CATA) of sensory attributes "must not have" for ideal salty and sweet snacks across treatment time points (T0–TF).

Salty snack must not have	T0	T1	T2	T4	T6	T8	TF
Soft	21.3%	18.2%	25.0%	18.9%	17.2%	21.7%	28.6%
Crunchy	4.3%	9.1%	9.1%	5.4%	3.4%	4.3%	2.9%
Hard	12.8%	18.2%	15.9%	13.5%	13.8%	17.4%	20.0%
Creamy	36.2%	29.5%	22.7%	35.1%	24.1%	26.1%	14.3%
Liquid	44.7%	54.5%	27.3%	48.6%	41.4%	43.5%	42.9%
Juicy	19.1%	11.4%	13.6%	13.5%	13.8%	13.0%	5.7%
Pasty	48.9%	36.4%	31.8%	51.4%	41.4%	43.5%	54.3%
Dense	14.9%	9.1%	20.5%	8.1%	10.3%	13.0%	11.4%
Tasty	0.0%	6.8%	4.5%	8.1%	3.4%	8.7%	2.9%
Sweet snack must not have	**T0**	**T1**	**T2**	**T4**	**T6**	**T8**	**TF**
Soft	0.0%	0.0%	0.0%	18.8%	15.4%	22.2%	15.0%
Crunchy	4.2%	21.4%	10.5%	18.8%	23.1%	11.1%	5.0%
Hard	25.0%	50.0%	36.8%	31.3%	23.1%	22.2%	15.0%
Creamy	8.3%	0.0%	10.5%	12.5%	7.7%	0.0%	5.0%

Liquid	37.5%	37.5%	26.3%	18.8%	46.2%	22.2%	55.0%
Juicy	4.2%	7.1%	5.3%	0.0%	15.4%	0.0	5.0%
Pasty	41.7%	28.6%	47.4%	37.5%	53.8%	55.6%	35.0%
Dense	4.2%	14.3%	15.8%	0.0%	0.0%	11.1%	10.0%
Tasty	8.3%	14.3%	5.3%	31.3%	15.4%	0.0%	0.0%

Ideal snack based on CiTAS alterations – Insights on T2

T2, which represented the time point during treatment with the largest number of participants, was therefore selected for an in-depth CATA analysis with the aim of showing ideal snacks for patients with the different types of alterations.

In general, altered patients with any type of alterations in both times compared (T0 and T2) reported preferring a salty snack to a sweet one (decline in basic tastes: T0 salty 60.6%, sweet 39.4; T2 salty 66.7%, sweet 33.3%; general taste alterations/parageusia/increase in taste perception: T0 salty 69.2%, sweet 30.8%; T2 salty 69.2%, sweet 30.8%; phantogeusia: T0 salty 71.3%, sweet 28.2%; T2 salty 76.9%, sweet 23.1%).

Supplementary Table 1 (in Appendix – Supplementary Materials) shows the sensory attributes that patients with and without self-reported alterations through CATA indicated at the different time points (T0 and T2) as must have and must not have in their ideal salty snack (Graphic representation in Appendix – Supplementary Materials 1-2-3). Table 36 summarizes the most frequent sensory attributes (≥20%) reported for salty and sweet snacks classified as "must have" or "must not have" by the overall study population and by subgroups defined based on the main self-reported chemosensory alterations through the CiTAS (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, and phantogeusia).

Table 36 Most frequent sensory attributes (≥20%) selected (CATA) for salty and sweet snacks classified as "must have" or "must not have" by the overall study population and by subgroups defined based on the main self-reported chemosensory alterations via the CiTAS (baseline taste decline, general taste alterations/parageusia/increased taste perception, and phantogeusia).

	Salty snack				Sweet snack			
General population / Alterations	Must have T0	Must have T2	Must not have T0	Must not have T2	Must have T0	Must have T2	Must not have T0	Must not have T2
Whole sample	Crunchy (80.9%) Tasty (72.3%)	Crunchy (65.4%) Tasty (65.4%) Hard (23.1) Soft (21.2%)	Pasty (48.9%) Liquid (44.7%) Creamy (36.2%) Soft (21.3%)	Pasty (31.8%) Liquid (27.3%) Soft (25.0%) Creamy (22.7%) Dense (20.5%)	Creamy (66.7%) Crunchy (50.0%) Soft (41.7%) Tasty (25.0%) Pasty (20.8%)	Soft (64.3%) Creamy (64.3%) Crunchy (50.0%) Juicy (35.7%) Tasty (35.7%)	Pasty (41.7%) Liquid (37.5%) Hard (25.0%)	Pasty (47.4%) Hard (36.8%), Liquid (26.3%)
Decline in basic tastes	Crunchy (90.0%) Tasty (80.0%)	Crunchy (81.8%) Tasty (77.3%) Hard (27.3%)	Pasty (60.0%) Creamy (50.0%) Liquid (40.0%) Soft (30.0%)	Pasty (40.9%) Soft (31.8%) Creamy (36.4%) Liquid (36.4%) Dense (27.3%)	Creamy (76.9%) Crunchy (53.8%) Soft (46.2%)	Soft (45.5%), Crunchy (45.5%) Creamy (27.3%) Juicy (27.3%)	Pasty (46.2%) Liquid (30.8%) Hard (30.8%)	Liquid (27.3%) Pasty (63.6%) Hard (36.4%)
General taste alterations/ parageusia/ increase in taste perception	Crunchy (85.2%) Tasty (66.7%) Creamy (22.2%)	Crunchy (74.1%) Tasty (70.4%) Soft (25.9%) Hard (25.9%)	Pasty (51.9%) Liquid (44.4%) Creamy (37.0%) Soft (25.9%)	Liquid (40.7%) Pasty (33.3%) Creamy (29.6%) Soft (25.9%) Dense (25.9%)	Creamy (83.3%) Soft (41.7%) Crunchy (41.7%) Juicy (25.0%)	Soft (58.3%) Creamy (50.0%) Crunchy (33.3%) Juicy (33.3%)	Liquid (41.6%) Pasty (33.3%) Hard (25.0%)	Pasty (50.0%) Liquid (33.3%) Hard (50.0%) Dense (25.0%)
Phantogeusia	Crunchy (85.7%) Tasty (71.4%)	Crunchy (73.3%) Tasty (70.0%) Hard (30.0%)	Creamy (46.4%) Liquid (42.9%) Pasty (60.7%)	Pasty (40.0%) Liquid (33.3%) Creamy (26.7%) Soft (26.7%) Dense (23.3%) Juicy (20.0%)	Creamy (63.6%) Crunchy (45.5%) Soft (27.3%) Tasty (27.3%)	Soft (44.4%) Creamy (44.4%) Crunchy (33.3%) Juicy (33.3%)	Pasty (45.5%) Liquid (36.4%)	Pasty (55.6%) Hard (44.4%) Liquid (44.4%) Crunchy (22.2%)

Focusing on chemosensory alterations, as shown in Figure 47 and Table 36, the sensory attributes most frequently cited as must have for an ideal salty snack were crunchy and tasty across all alteration types and at both time points (T0 and T2).

For patients who reported a decline in basic tastes, the preference for crunchy salty snacks remained very high (90.0% at T0, 81.8% at T2), together with the tasty attribute (80.0% at T0, 77.3% at T2). At T2 the selection of the hard attribute increased (27.3%).

For patients with general taste alterations/parageusia/and increase in taste perception, the preference for crunchy salty snacks remained high (85.2% at T0, 74.1% at T2), as well as the tasty attribute (66.7% and 70.4%). At T2, soft and hard textures were both reported in 25.9% of cases.

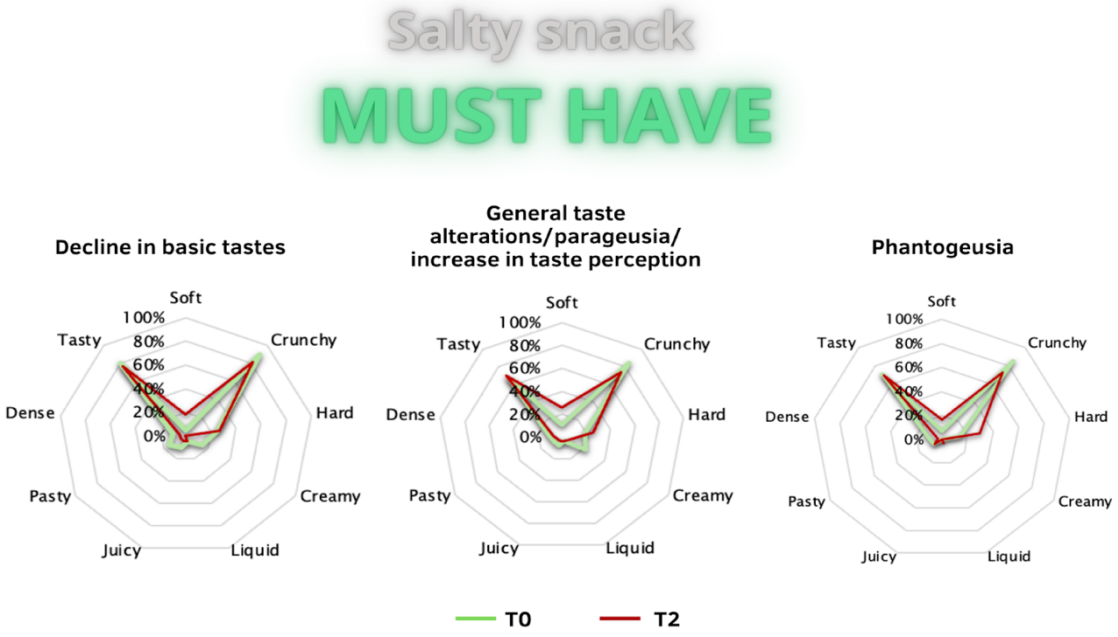


Figure 47 Spider plots of salty snack must have of patients who self-reported chemosensory alterations.

For patients who reported phantogeusia, the preference for crunchy salty snacks was maintained over time (85.7% at T0, 73.3% at T2), together with the tasty attribute (71.4% and 70.0%) and the hard attribute (30.0% at T2).

Conversely, the most frequently selected must not have of the salty snack (Figure 48 and Table 36) for patients with decline in basic tastes were pasty (60.0% at T0 to 40.9% at T2), creamy (50.0% to 36.4%) and liquid (40.0% to 36.4%); soft and dense consistencies were also avoided (approximately 20–30%).

Among patients with general taste alterations, the same attributes were selected as must not have, with pasty decreasing from 51.9% to 33.3%, liquid remaining stable around 40–44%, and creamy and soft textures around 30% at T2, together with dense (25.9%).

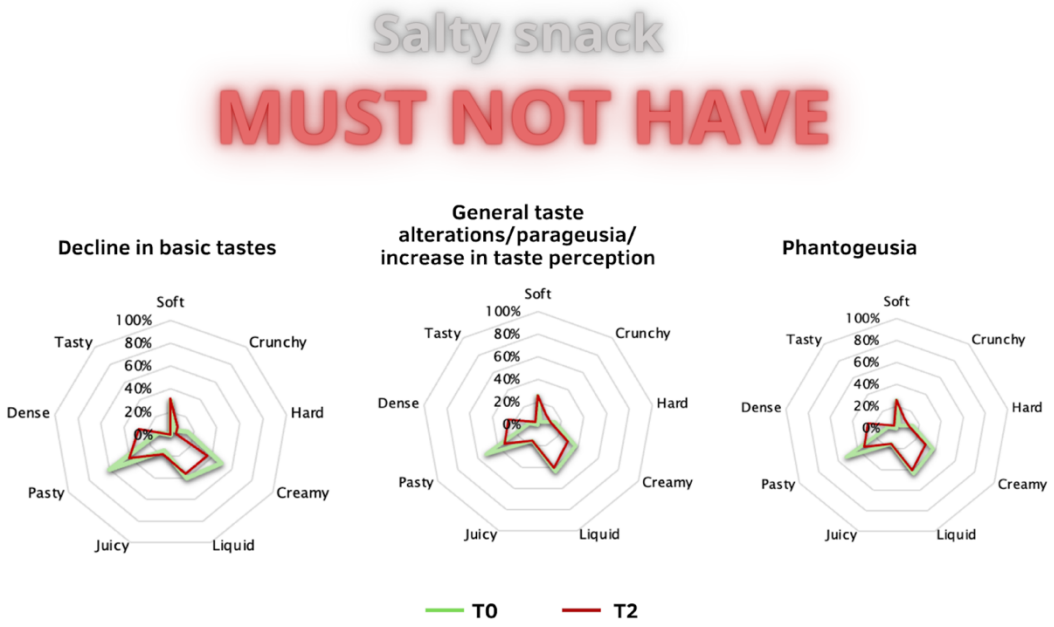


Figure 48 Spider plots of salty snack must not have of patients who self-reported chemosensory alterations.

In phantogeusia, pasty remained the most avoided texture (60.7% at T0, 40.0% at T2), followed by liquid (42.9% and 33.3%) and creamy (46.4% and 26.7%), while at T2 soft (26.7%), dense (23.3%) and juicy (20.0%) were also reported as must not have.

Across all three groups, therefore, the dislike for pasty and liquid textures was consistent, with slightly lower frequencies at T2, suggesting a stable aversion to these textures independent of the specific taste alteration.

Supplementary table 2 (in Appendix - Supplementary Materials) shows the sensory attributes that patients with and without self-reported alterations through CATA indicated at the different time points (T0 and T2) as must have and must not have in their ideal sweet snack (Graphic representation in Appendix - Supplementary Materials 1-2-3). The most frequent sensory attributes (≥20%) reported for salty and sweet snacks classified as must have or must not have by the overall study population and by subgroups defined based on the main self-reported chemosensory alterations through the CiTAS (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, and phantogeusia) are summarized in Table 36.

Focusing on chemosensory alterations, as shown in Figure 49 and Table 36 for sweet snacks the attributes most frequently reported as must have were creamy, soft, and crunchy, with some variations among groups and over time.

In patients who experienced a decline in basic tastes, the most selected attributes at T0 were creamy (76.9%), crunchy (53.8%), and soft (46.2%), while at T2 the preference remained for soft (45.5%) and crunchy (45.5%) textures, with a reduction in creamy (27.3%) and the increased selection of juicy (27.3%).

Among patients with general taste alterations/parageusia/increase in taste perception, the creamy attribute remained predominant (83.3% at T0, 50.0% at T2), together with soft (41.7% and 58.3%), crunchy (41.7% and 33.3%), and juicy (25.0% and 33.3%).

In patients with phantogeusia, the most preferred characteristics for sweet snacks were creamy (63.6% at T0, 44.4% at T2), crunchy (45.5% and 33.3%), and soft (27.3% and 44.4%). The tasty attribute, which was present at T0 (27.3%), decreased below the 20% threshold at T2, while the juicy attribute, with percentages below 20% at baseline, increased to 33.3% at T2.

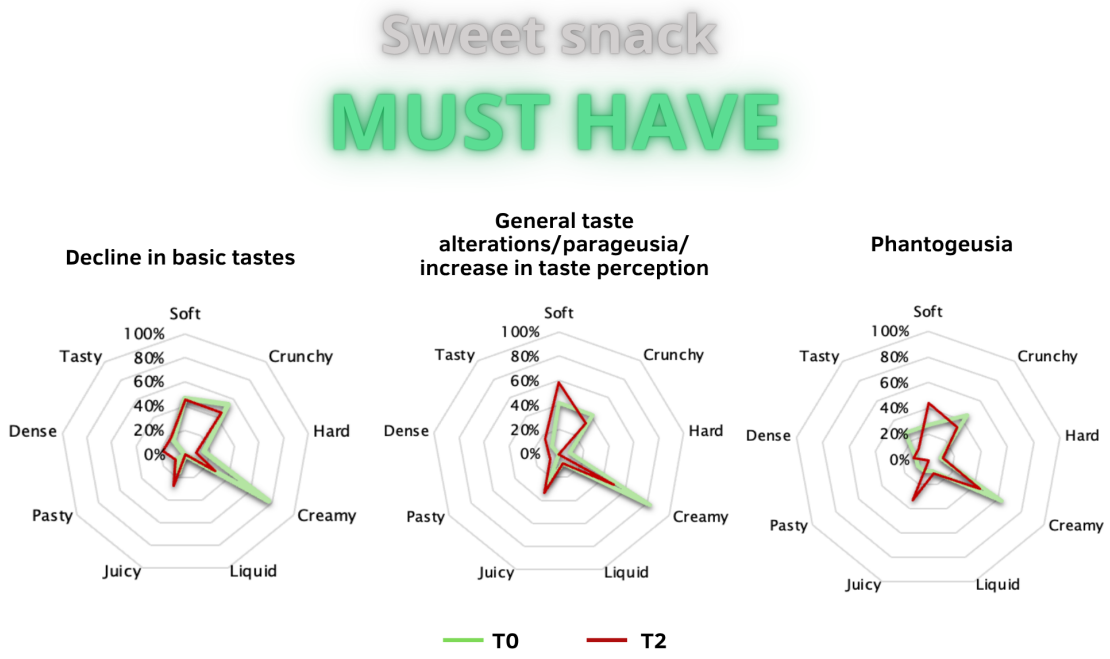


Figure 49 Spider plots of sweet snack must have of patients who self-reported chemosensory alterations.

Finally, the must not have (Figure 50 and Table 36) for the sweet snack for all groups were pasty, hard, and liquid textures, although trends varied slightly by alteration type. In patients with decline in basic tastes, the selection of pasty attribute as must not have increased over time (46.2% at T0, 63.6% at T2), while liquid (30.8% and 27.3%) and hard (30.8% and 36.4%) textures remained consistently undesirable.

Among patients with general taste alterations/parageusia/increase in taste perception, the most selected must not have in both time points were pasty (33.3%–

50.0%), liquid (41.6%–33.3%), and hard (25.0%)–50.0%, and at T2 also dense (25.0%).

Among patients with phantogeusia, the must not have for sweet snacks were pasty and liquid ones (45.5% and 36.4% at T0; 55.6% and 44.4% at T2). At T2, a greater aversion to hard textures (44.4%) and, to a lesser extent, to crunchy ones (22.2%) was also found.

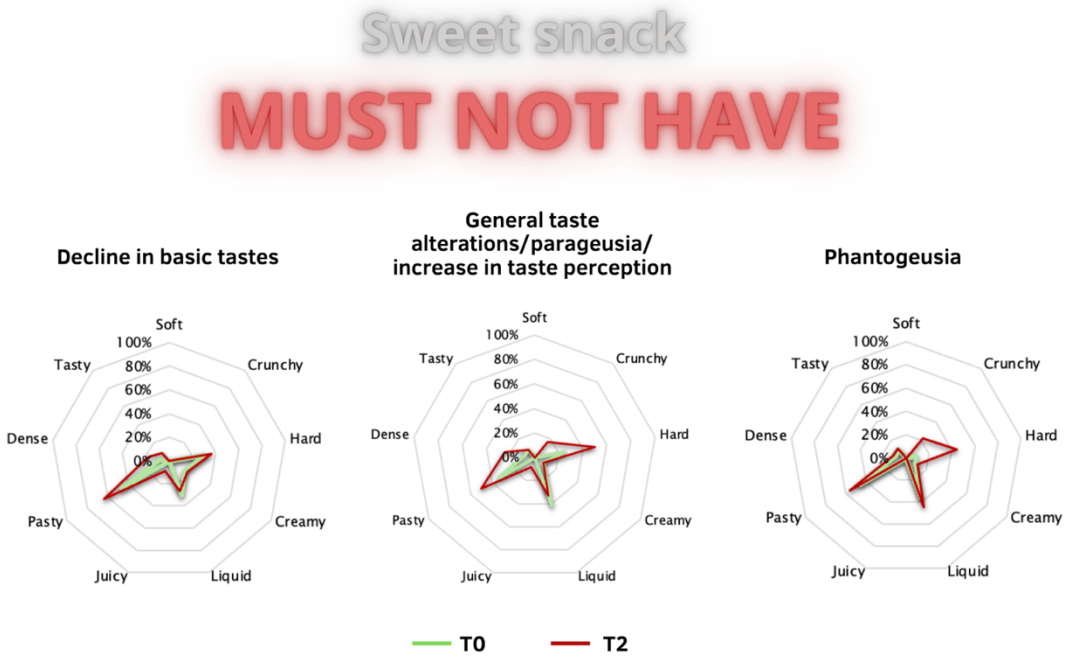


Figure 50 Spider plots of sweet snack must not have of patients who self-reported chemosensory alterations.

Result summary 4.6

- A stable preference for salty snacks over sweet snacks emerged at all time points, including follow-up.
- The ideal profile for salty snacks was characterized by characteristics such as “crunchy” and “tasty”, and an avoidance of “pasty” or “liquid” textures.
- Expectations for sweet snacks were more variable, with a shift toward softer/creamier textures during treatment and greater variability over time.

- Even in the presence of chemosensory alterations, salty snacks remained the preferred option, while sweet snack profiles were more variable based on the type of alteration.

4.7 Impact of chemosensory disorders on eating behaviors

Patients could adopt specific strategies to manage or compensate for these changes in order to preserve their eating experience and avoid emotional distress related to food consumption. In this section we examine the effect of chemosensory alterations on attitudes towards food such as food involvement, use/liking of condiments, coping strategies, and daily eating behaviors.

4.7.1 Attitude towards food

Psychometric analysis of Food Involvement Sub-Scale

The Food Involvement Sub-Scale showed an internal consistency with a Cronbach's alpha coefficient of 0.62. A Kaiser-Meyer-Olkin (KMO) of 0.68 and a significant Bartlett's sphericity test ($p<.0001$) indicated that the data was adequate for Factor Analysis. Exploratory Factor Analysis (EFA) on Spearman correlation matrix was conducted using principal factor analysis for factor extraction. The Scree plot suggested that no more than two factors should be extracted, which explained respectively 24.28% and 12.33% of the total variance. Since all 9 items were intended to be part of the 'Preparation and Eating' subscale, a one-factor structure was expected. However, the 8 items demonstrated not always acceptable factor loadings on Factor 1 ($\geq$ 0.042) (Table 37). Attempts to improve the model by removing items did not lead to greater internal consistency or a clearer factor structure.

Table 37 Factor analysis of Food Involvement Scale – Preparation and eating

Items	Factor loadings (F1)
I don't think much about food during the day (R)	0.083
I don't enjoy cooking or barbequing (R)	**0.912**
Talking about what I ate, or I am going to eat is something I like to do	**0.509**
Compared with other decisions, deciding what to eat is very important to me	**0.370**
When I travel, one of the things I anticipate most is eating local food	0.192
I enjoy cooking for myself and others	**0.833**
When I eat out, I don't think or talk much about the quality of the food (R)	**0.379**
I don't like handling food (e.g. during preparation) (R)	**0.658**
I am usually the one who does the food shopping	0.042

Food Involvement during treatment

A significant overall effect of time was found on Food Involvement, as revealed by the Kruskal–Wallis test ($\chi^2(6)=12.638$, $p=.049$), indicating that patients' food involvement changed across treatment phases. Food Involvement scores showed a decreasing trend throughout treatment, with the lowest point observed around T6, followed by a gradual recovery at subsequent time points (Figure 51). However, post hoc comparisons using the Dunn test with Bonferroni correction revealed not statistically significant pairwise differences between specific time points. Despite the lack of significant pairwise differences, the overall trend suggests a temporary reduction in interest in food during chemotherapy, which appears to normalize at follow-up (TF).

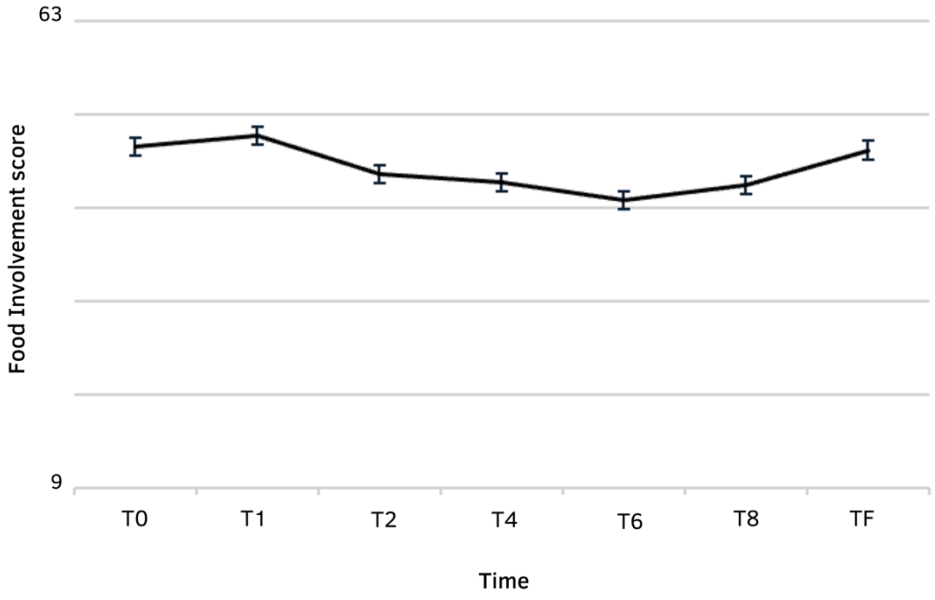


Figure 51 Mean scores of Food Involvement across treatment period. Total observation N=299; T0=71; T1=14; T2=62; T4=41; T6=36; T8=20; TF=55.

Impact of self-reported chemosensory alterations on food involvement

When comparing patients with and without self-reported chemosensory alterations, no significant differences were observed in food involvement levels at any time point ($p<0.05$). The only significant effect was found at the sixth cycle of therapy (T6), where patients reporting general taste alterations/parageusia/increase in taste perception showed significant lower food involvement scores compared to those without such alterations (Figure 52).

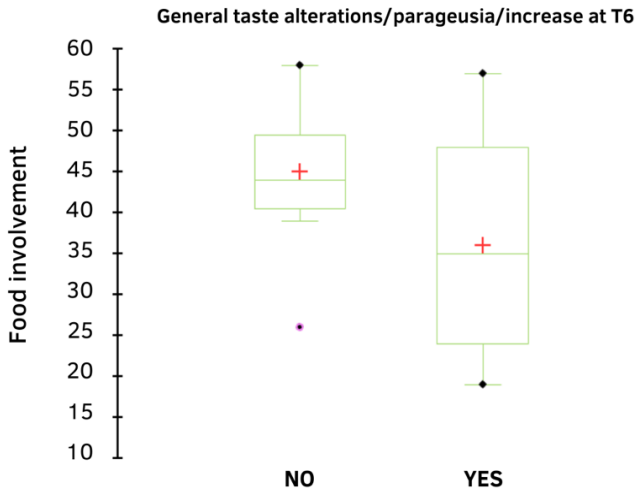


Figure 52 Differences between patients with (YES) and without (NO) general taste alterations/parageusia/increase in taste perception at T6 in food involvement mean scores. Boxplots represent median, interquartile range, and minimum-maximum values; the red cross indicates the mean.

4.7.2 Use and liking of condiments

The impact of self-reported chemosensory changes and discomfort using the CiTAS on use and liking of several condiments of was assessed using a Spearman correlation for each time point and for each condiment (Table 38).

*Table 38 Spearman's rank correlation coefficients (ρ) between liking/use of condiments (9-point scale) and CiTAS scores of each dimension (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, phantogeusia, discomfort) at each treatment time points. Significant correlations (*p *<.05) are indicated in parentheses. ^sign on p-value indicates a value close to significance.*

	T0	T1	T2	T4	T6	T8	TF
				Decline in basic tastes			
Salty liking	-	0.098	-0.077	-0.163	-0.121	-0.089	0.125
Sugar use	-	-0.017	0.192	0.131	0.010	-0.272	-0.043
Parmesan cheese use	-	0.082	0.068	-0.231	-0.138	-0.093	-0.156
Chili pepper liking	-	0.020	0.166	-0.083	-0.113	0.0001	-0.253
Black pepper use	-	-0.246	-0.046	-0.129	-0.052	0.120	0.220
Spices liking	-	0.218	-0.031	-0.072	-0.077	0.048	0.089
Lemon liking	-	0.144	0.003	-0.128	-0.066	0.346 (**.049**)	0.181
Vinegar liking	-	0.048	0.209	0.083	0.148	0.372 (**.033**)	0.180
	T0	**T1**	**T2**	**T4**	**T6**	**T8**	**TF**
				General taste alterations/parageusia/increase in taste perception			
Salty liking	-	-0.118	-0.131	-0.080	-0.230	-0.272	0.131
Sugar use	-	-0.046	0.031	0.120	0.190	0.100	-0.043
Parmesan cheese use	-	-0.228	-0.272 (**.027**)	-0.340 (**.010**)	-0.357 (**.021**)	-0.226	-0.096
Chili pepper liking	-	0.002	-0.109	-0.331 (**.012**)	-0.248	-0.224	-0.178
Black pepper use	-	-0.167	-0.201	-0.216	-0.078	-0.322 (^.068)	-0.090
Spices liking	-	0.069	-0.066	-0.220	-0.296	-0.316	-0.203
Lemon liking	-	-0.073	-0.157	-0.290 (**.029**)	-0.233	-0.223	-0.198
Vinegar liking	-	-0.130	-0.027	-0.023	-0.033	-0.064	-0.070
	T0	**T1**	**T2**	**T4**	**T6**	**T8**	**TF**
				Phantogeusia			
Salty liking	-0.199	-0.112	-0.180	0.173	-0.052	0.021	-0.015

Sugar use	−0.018	0.011	0.054	0.179	0.143	0.024	0.137
Parmesan cheese use	−0.106	−0.175	−0.178	−0.179	−0.199	−0.094	0.113
Chili pepper liking	−0.197	−0.063	−0.265 (**.032**)	−0.296 (**.026**)	−0.223	−0.187	0.010
Black pepper use	0.014	−0.196	−0,236	0.025	−0.151	−0.218	−0.290 (**.031**)
Spices liking	0.138	0.026	−0.243 (**.050**)	−0.229	−0.274	−0.163	−0.160
Lemon liking	−0.015	−0.082	−0.219	−0.303 (**.022**)	−0.232	0.076	−0.231
Vinegar liking	0.010	−0.044	−0.082	−0.072	−0.014	−0.049	−0.049
	T0	**T1**	**T2**	**T4**	**T6**	**T8**	**TF**
				Discomfort			
Salty liking	0.141	−0.054	−0.068	−0.013	−0.089	0.088	−0.080
Sugar use	−0.123	0.016	0.168	0.022	0.243	0.149	0.083
Parmesan cheese use	−0.085	−0.227	−0.162	−0.396 (**.002**)	−0.377 (**.014**)	−0.085	−0.136
Chili pepper liking	−0.252 (**.034**)	−0.246 (^.062)	−0.276 (**.025**)	−0.287 (**.031**)	−0.452 (**.003**)	−0.328 (^.063)	−0.240
Black pepper use	0.040	−0.142	−0.129	0.038	−0.256	−0.239	−0.035
Spices liking	0.052	−0.045	−0.211	−0.059	−0.364 (**.018**)	−0.314 (^.075)	−0.291 (**.030**)
Lemon liking	0.031	−0.060	−0.178	−0.145	−0.218	0.086	−0.099
Vinegar liking	0.113	−0.095	−0.124	−0.044	−0.195	−0.220	−0.018

Patients who experienced a decline in basic tastes showed a positive correlation with liking for sour tastes. Specifically, a significant positive correlation was observed between the decline in basic taste score and liking for lemon at T8 (ρ=0.346, p=.049), as well as with liking for vinegar at T8 (ρ=0.372, p=.033). Other correlations were weak and non-significant among condiments, indicating that the decline in basic tastes was not systematically associated with the liking or use of specific condiments.

Instead, the presence of general taste alterations/parageusia/increase in taste perception correlated negatively with the liking or use of savory and pungent condiments. Specifically, the use of Parmesan cheese was negatively correlated with taste alteration scores at T2 (ρ=-0.272, p=.027), T4 (ρ=0.340, p=.010), and T6 (ρ=-0.357, p=.021), indicating reduced use of this condiment as these symptoms intensified. Similarly, liking for chili pepper decreased significantly with the severity of the disorder at T4 (ρ=-0.331, p=.012), as did liking for lemon at T4 (ρ=-0.290, p=.029).

These results suggest that patients who reported parageusia or a more intense taste perception tended to avoid foods and condiments characterized by strong, pungent, or sour notes, likely due to unpleasant or distorted taste experiences during treatment.

The presence of phantogeusia showed negative correlations with spicy and sour condiments. Liking of chili pepper was inversely correlated with the severity of phantogeusia at T2 (ρ=-0.265, p=.032) and T4 (ρ=-0.296, p=.026), while the use of black pepper also showed a negative correlation at T2 (ρ=-0.290, p=.031). Similarly, liking for spices tended to decrease at T2 (ρ=-0.243, p=.050), and liking for lemon decreased significantly at T4 (ρ=-0.303, p=.022).

Overall, these findings suggest that patients with phantogeusia progressively reduced their preference for spicy and sour tastes, likely as a strategy to minimize the intensity or unpleasantness of the lingering phantom taste.

Negative associations emerged between discomfort and liking or using strong condiments. The use of Parmesan cheese showed a significant negative correlation at T4 (ρ=-0.396, p=.002) and T6 (ρ=-0.377, p=.014), while liking chili pepper was negatively related to discomfort from the early stages of treatment: T0 (ρ=-0.252, p=.034), T1 (ρ=-0.246, p=.062), T2 (ρ=-0.276, p=.025), T4 (ρ=-0.287, p=.031), T6 (ρ=-0.452, p=.003), and T8 (ρ=-0.328, p=.063). Furthermore, liking for spicy

foods was negatively related to discomfort at T6 (ρ=-0.364, p=.018) and TF (ρ=-0.291, p=.030). These consistent associations suggest that patients complaining of discomfort systematically reduced their preference and use of spicy, sour, or umami-tasting foods, likely to avoid irritation or pain in the oral cavity.

Overall, the temporal pattern over which correlations emerge suggests that patients learn to manage sensory disturbances in different ways and at different speeds. For example, those with a decline in basic tastes tend to recognize and adopt compensatory strategies more slowly (such as the use of sour condiments to enhance flavor perception). Conversely, in cases of qualitative alterations such as parageusia, the reduction in liking/use of spices, Parmesan cheese, and strong condiments appears very early, indicating a rapid adaptation aimed at reducing taste discomfort.

4.7.3 Qualitative insights into coping strategies and daily eating behavior

While questionnaire scores offered a useful overview of eating habits at specific times, qualitative interviews provided a deeper understanding of daily eating behaviors. The interviews revealed that, beyond quantifiable scores, chemosensory changes and related coping strategies shaped their eating experience during treatment. In many cases, the strategies adopted to cope with chemosensory alterations inevitably led to actual changes in dietary habits.

Some participants reported no changes in their habits, stating that they could tolerate sensory alterations without difficulty. Others stated that they continued eating as before, even though it was no longer pleasant:

"I still eat even if it's unpleasant."

The usual breakfast, used as a baseline for determining any changes, was often affected. Coffee was the most avoided food due to its bitter taste or smell. In

response, patients reported adding milk or cream to make it more tolerable, or replacing it with tea, fruit juice, or herbal teas.

"I taste coffee stronger, so I add a little milk."

"The first few weeks, I only drank tea for breakfast; I didn't feel like drinking coffee."

"Even coffee, I can't drink it anymore; it makes me nauseous, but mainly because of the smell."

"I changed my breakfast because coffee wouldn't flow; it tasted strange and made me nauseous, and milk tasted a little strange. "

Interestingly, one patient noted that an increased sensitivity to sweetness and a reduction in bitterness allowed her to drink coffee without sugar for the first time.

"Maybe I could taste the sweetness at breakfast more and the bitterness less, so I added less sugar. Before, I would never have been able to drink coffee without sugar, but now I can..."

Some participants reported voluntarily modifying their diet, for health reasons or to follow a prescribed eating plan, increasing their intake of fruits and vegetables, and in many cases eliminating red meat and sweets from their diet.

"I try to eat a little more fruits and vegetables, but for health reasons."

"I eliminated sweets and salty foods. I usually have a sweet tooth, but it's probably influenced by the fact that cancer feeds on sugar."

"I eat less sugar, and more legumes and grains, and more fish (changes due to diet). I eat less meat, especially red meat."

Water emerged as a trigger for the phantom taste in the mouth, while other patients described it as bitter or metallic, which prompted them to drink less, switch to sparkling water, or consume fruit juices and flavored drinks.

"Now I drink only soda drinks, because I can't drink water."

“The first few days after chemo, water was very bitter; I couldn't drink it at all. I heard that other patients had this problem and drank soda drinks. So, I also tried sparkling water, and it worked. I also drank fruit juices, because I didn't like water.”

“Now I drink more water with lemon.”

When water was perceived as sweet, it was generally not considered problematic.

“I always drink water even if it tastes sweet.”

In response to phantom taste in mouth, many patients reported increased food intake or the consumption of beverages other than water as a compensatory strategy. This behavior was often driven by the temporary suppression of the unpleasant taste during the meal:

"I ate more because the bad taste disappeared while I ate."

"Even the persistent flavors didn't help… once I swallowed, the bad taste returned immediately."

Soda and drinks were often consumed to mask both the metallic taste and nausea:

"I drink fruit juices and Coca-Cola, which help mostly with nausea, but also somewhat with the metallic taste."

The use of candy or sweets, especially those with strong flavors, was a common approach:

"I tried strong-flavored candy, but it didn't work; the sour taste remained."

"Mint candies helped briefly, but then the taste returned."

"I chewed gum constantly to mask the bitter taste."

"I ate cookies to mask the metallic sensation."

Specific foods such as ginger, yogurt, or crackers were also mentioned for their coping effects and persistent aftertaste:

"Ginger helps slightly reduce the metallic taste."

"Crackers eliminate the bitterness."

"Even though the metallic taste disappears while I eat, I don't eat more to compensate. I avoid drinking with meals because it triggers the metallic sensation. Yogurt gives me long-lasting relief."

In response to reduced taste perception, some patients reported adding more salt, cheese (such as Parmigiano), pepper or spices to foods to enhance their flavor.

"I tried using the spices I normally use, but it didn't make much of a difference. I'm afraid of adding too much salt, so I ask others to taste the food when I cook."

Nausea and oral inflammation also played a key role in changing eating habits. Several patients reported skipping meals or eating less to avoid discomfort, or tried to manage them:

"The first few days I didn't eat because of nausea."

"For the oily feeling in my mouth, I drank herbal teas. Sparkling water also seemed to work better than still water; I could drink it."

"I tried ginger tea, ginger candies, and Coca-Cola; they helped with the nausea."

"I also tried licorice, strawberry candies, and Coca-Cola. They didn't improve the metallic taste or the nausea. I tried eating popsicles because I couldn't drink, and those helped."

Nausea often led to a preference for dry, crunchy foods, while oral sensitivity or mucositis led to a preference for fresh, soft or creamy textures, especially at breakfast:

"For breakfast, I used to have hot tea with toast and honey; now, I can only eat low-fat yogurt."

"I used to eat dried fruit, but the texture bothered me, so I eliminated it. I ate more yogurt and porridge."

"I used to have muesli and milk for breakfast. Now I can only have milk or rice milk with sugar because I like the cold and sweet liquids, while the crunchiness of muesli bothers me."

In some cases, patients perceived certain foods as too strong or altered, leading them to avoid condiments such as lemon, vinegar, or salt. “

“I've stopped seasoning things, and I've almost completely eliminated salt, because seasoned foods are so strong. I use very little oil, and I've eliminated vinegar and lemon; they make my mouth burn.”

"I prefer to eat foods with a blander flavor; I don't feel like adding seasoning or spices.”

Conversely, others reported that an altered perception of taste (particularly bitterness) led them either to avoid eating, to increase sweet foods or to increase their use of oil, lemon, or salt to make food more palatable.

"Sometimes I add lemon to food and water, which helps, although it gives me heartburn."

"I season everything with lemon."

"I avoided eating foods that had an unpleasant taste."

Some patients eliminated wine from their habit, finding its acidic or strong taste unpleasant during treatment:

“It all started with a wine at the restaurant, it had a terrible taste”

“Wine doesn't taste the same as before, I feel it stronger (that's the only thing) it's like it's burning a little.”

“Usually, in the evening I drank a little wine, but since I had a strong taste that bothered me, I didn't drink it anymore.”

In addition to food, non-dietary strategies have also been employed. Mouthwashes (e.g., baking soda), frequent toothbrushing, and the use of plastic utensils were commonly reported:

"I wash my mouth with baking soda several times a day after treatment and brushed my teeth often; it worked temporarily."

"I used plastic utensils because the metal intensified the metallic taste in food and my mouth."

"Brushing my teeth and using mouthwash gave me relief."

Patients also reported a variety of olfactory disturbances during treatment, commonly described as loss of smell, olfactory distortions (such as phantom odors), or increased sensitivity to odors. These changes prompted the adoption of several coping strategies.

Loss or reduction of olfactory function (hyposmia or anosmia) was addressed by one patient with intentional olfactory stimulation while cooking:

"I tried to smell more consciously while cooking, trying to focus on the smell."

Another reported problem was the perception of phantom odors, for which, however, no coping strategies could be implemented, as they were described as transient.

The most frequently described olfactory problem was increased sensitivity to odors, particularly cooking, perfumes, and environmental odors, which often triggered severe nausea and disgust. These effects often led patients to avoid preparing food, delegate household chores to family members, and asking family members to avoid perfumes:

"I stopped cooking and cleaning the bathroom and asked my husband to do it. When he cooked, I changed rooms."

“I asked my children to avoid wearing perfume.”

Some patients implemented environmental strategies to reduce exposure to odors, such as opening windows or changing rooms:

"I opened the windows to let in fresh air and tried to tolerate it."

"I closed the doors and used vinegar to cover strong odors."

"I avoided the kitchen and ate in a separate room."

Three months after completing chemotherapy, some patients maintained the positive changes implemented during treatment long-term, motivated by the desire to improve overall health and reduce the risk of recurrence.

For others, eating behavior gradually returned to pre-treatment levels, and the recovery of sensory function was experienced as a return to normality and the pleasure of eating.

Interestingly, while many returned to their usual habits, some patients reported continuing to consume more salt due to persistent alterations in taste perception:

"I still tend to add a lot of salt, maybe because I don't feel it as much anymore."

Result summary 4.7

- Food involvement scores showed a temporary decrease during chemotherapy, suggesting a transient reduction in interest in food. Overall, food involvement was only marginally affected by chemosensory alterations.
- Condiment-related behaviors reflected distinct adaptive patterns depending on the type of chemosensory alteration, rather than a uniform response across patients.
- The decline in basic tastes was associated with compensatory strategies that emerged later in the therapy, particularly an increased liking for sour seasonings (e.g., lemon and vinegar).
- Qualitative alterations (e.g. parageusia, phantogeusia) and oral discomfort were associated with early and prolonged avoidance of strong flavors or spicy seasonings, consistent with strategies aimed at reducing unpleasant or persistent sensations reported by patients. Discomfort showed the most consistent and persistent associations with avoidance of spicy, sour, and irritating foods, highlighting oral pain and irritation as key drivers of food restriction.

- Qualitative interviews confirmed that coping strategies were highly individualized and symptom-driven, involving changes in food choices, seasonings, texture, temperature, and food context.

4.8 Impact of chemosensory disorders on body composition

Across all comparisons, no statistically significant differences were observed in any of the evaluated parameters (all $p > .05$), indicating that body composition remained stable throughout chemotherapy regardless of the presence or absence of chemosensory alterations.

Table 39 summarizes the results of Mann-Whitney tests on body composition.

Table 39 Results of the Mann–Whitney tests comparing changes in body composition parameters (weight, BMI, fat mass, lean mass) from baseline (T0) to each treatment time point (T1, T2, T4, T6, T8, TF) between patients with and without self-reported chemosensory alterations (decline in basic tastes; general taste alterations/parageusia/increase in taste perception; phantogeusia). Values represent p-values.

Type of alterations	Body parameters	T0–T1	T0–T2	T0–T4	T0–T6	T0–T8	T0–TF
Decline in basic tastes (YES/NO)	Weight (YES)	.895	.886	.752	.821	.786	.403
	Weight (NO)	.638	.988	.488	.602	.732	.979
	BMI (YES)	.792	.962	.794	.600	.776	1.000
	BMI (NO)	.794	.888	.573	.658	.362	.964
	Fat mass (YES)	.717	.962	.892	.328	.110	.531
	Fat mass (NO)	.834	.841	.833	.716	.425	.697
	Lean mass (YES)	.817	.931	.914	.640	.542	1.000
	Lean mass (NO)	.734	.994	.353	.704	.676	.725
General taste alterations/	Weight (YES)	.581	1.000	.604	.869	.417	.665
parageusia/	Weight (NO)	.762	.763	.289	.372	.328	.869
increase in taste perception (YES/NO)	BMI (YES)	.893	.797	.590	.655	.641	.470
	BMI (NO)	.762	.808	.282	.439	.471	.950
	Fat mass (YES)	.846	.826	.589	.481	.098	.885
	Fat mass (NO)	.559	1.000	.882	.691	.425	.730
	Lean mass (YES)	.581	.714	.994	.972	.918	.885
	Lean mass (NO)	.976	.838	.417	.234	.571	.728
Phantogeusia (YES/NO)	Weight (YES)	.705	.978	.840	.978	.371	.680
	Weight (NO)	.643	.823	.604	.680	.197	.538
	BMI (YES)	.982	.854	.760	.692	.579	.768
	BMI (NO)	.682	1.000	.552	.692	.254	.670
	Fat mass (YES)	.927	.525	.551	.603	.133	.680
	Fat mass (NO)	.569	.686	.831	.961	.323	.977
	Lean mass (YES)	.836	.924	.628	.691	.871	.376
	Lean mass (NO)	.901	.907	.784	.692	.470	.525

Result summary 4.8

- Throughout chemotherapy treatment, body composition parameters (weight, BMI, fat mass, and lean mass) remained stable, with no

significant differences observed between patients with and without self-reported chemosensory alterations.

4.9 Impact of chemosensory disorders on quality of life

Psychometric analysis of EORTC QLQ C30

Psychometric analysis was conducted on responses collected at baseline (T0), after the first (T1), after the second (T2), after the fourth (T4), after the sixth (T6), after the eighth cycle (T8), and three months after the end of therapy (TF) grouped together (N=383), considering the items of the functional scales: physical, emotional, and social functioning (considered in the analyses of this thesis). The selected items showed a good internal consistency with a Cronbach's alpha coefficient of 0.814. A Kaiser-Meyer-Olkin (KMO) of 0.822 and a significant Bartlett's sphericity test ($p<.0001$) indicated that the data was adequate for Factor Analysis. Exploratory Factor Analysis (EFA) on Spearman correlation matrix was conducted using principal factor analysis for factor extraction.

The Scree plot suggested that a two-factor structure might be adequate, however, EFA was rerun using Varimax orthogonal rotation with Kaiser normalization imposing three factors, to align with the factor structure identified for the original questionnaire (Aaronson et al., 1993). The analysis yielded a three-factor structure that explained 36.56% of the total variance. Factor loadings explained variance and Cronbach's alphas for the three-factor structure are reported in Table 40.

A second psychometric analysis was conducted on responses collected at baseline (T0), after the first (T1), after the second (T2), after the fourth (T4), after the sixth (T6), after the eighth cycle (T8), and three months after the end of therapy (TF) grouped together (N=383), considering the items of the symptoms scales, fatigue

and nausea & vomiting, the appetite loss, and the global health status/QoL scale. The selected items showed a not good internal consistency with a Cronbach's alpha coefficient of 0.478. A Kaiser-Meyer-Olkin (KMO) of 0.829 and a significant Bartlett's sphericity test ($p<.0001$) indicated that the data was adequate for Factor Analysis. Exploratory Factor Analysis (EFA) on Spearman correlation matrix was conducted using principal factor analysis for factor extraction. The Scree plot suggested that a one-factor structure might be adequate, however, EFA was rerun using Varimax orthogonal rotation with Kaiser normalization imposing four factors. However, the analysis yielded a three-factor structure that explained 43.69% of the total variance. Factor loadings explained variance and Cronbach's alphas for the three-factor structure are reported in Table 40.

Table 40 Factor analysis of EORTC Quality of Life Questionnaire C30

	Cronbach 's alpha	D1	D2	D3
EORTC QLQ C30 – functional scales	**.814**			
Physical functioning	**.754**			
Do you have difficulty doing strenuous work such as lifting a heavy bag or suitcase?		**0.557**	0.166	0.335
Do you have difficulty going for a long walk?		**0.833**	0.062	0.167
Do you have difficulty going for a short walk outside the house?		**0.695**	0.114	0.094
Do you need to stay in bed or in a chair during the day?		**0.610**	0.157	0.311
Do you need help eating, dressing, bathing or going to the toilet?		**0.245**	0.051	0.034
Emotional functioning	**.755**			
Have you felt tense?		0.001	**0.850**	0.121
Have you worried?		0.066	**0.643**	0.105
Have you felt irritable?		0.202	**0.479**	0.187
Have you felt depressed?		0.319	**0.564**	0.194
Social functioning	**.714**			
Has your physical condition or medical treatment interfered with your family life?		0.161	0.226	**0.729**
Has your physical condition or medical treatment interfered with your social activities?		0.289	0.199	**0.622**
	Cronbach 's alpha	D1	D2	D3
EORTC QLQ C30 – symptoms scales, appetite loss, global health status/QoL scale	**.478**			
Symptoms scales – Fatigue	**.901**			
Have you needed rest?		**0.734**	-0.262	0.281
Have you felt weak?		**0.715**	-0.278	0.327
Have you felt tired?		**0.851**	-0.285	0.296
Symptoms scales – Nausea and vomiting + Appetite loss	**.815**			
Have you felt nauseous?		0.231	-0.146	**0.796**
Have you vomited?		0.127	-0.102	**0.379**
Have you lost your appetite?		0.245	-0.167	**0.570**

Global health status/QoL status	**.649**		
How would you rate your overall health during the last 7 days?	-0.308	**0.726**	-0.201
How would you rate your overall quality of life during the last 7 days?	-0.236	**0.792**	-0.200

Physical functioning

Physical functioning, which indicates the patient's perception of physical ability in daily activities, of the overall study population showed a progressive decrease during chemotherapy, with significantly lower scores at T4, T6, and T8 compared

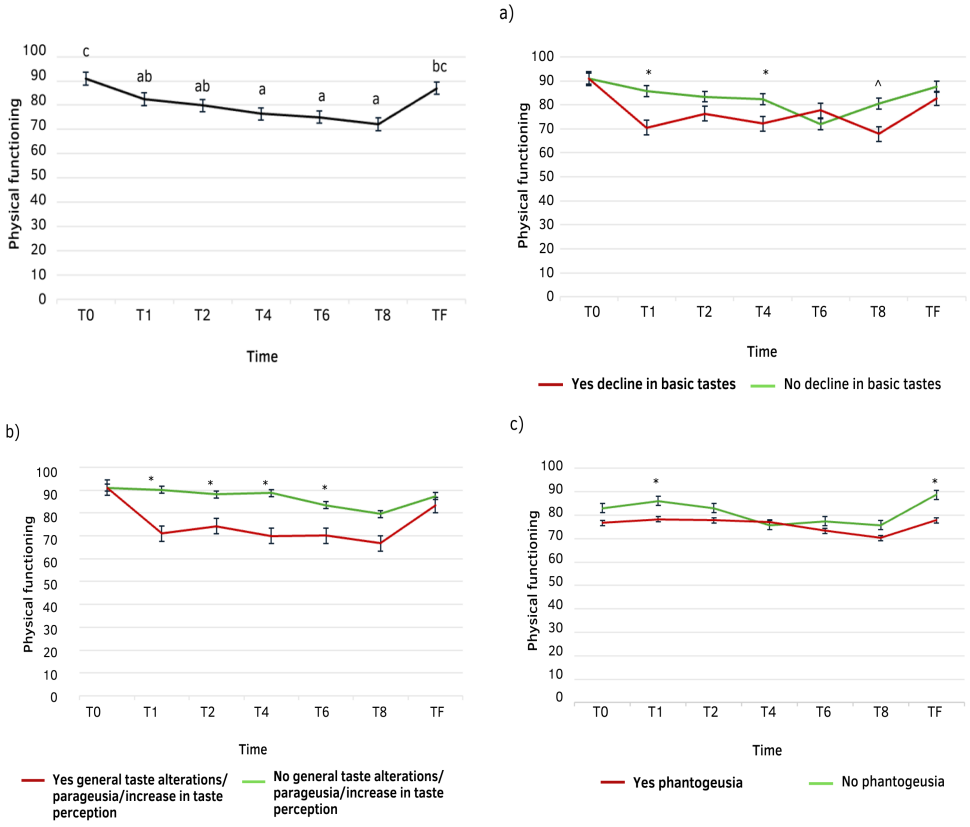


*Figure 53 Mean scores of physical functioning of study population across treatment period. a) Differences in mean scores of physical functioning between patients with and without decline in basic tastes in each time point b) Differences in mean scores of physical functioning between patients with and without general taste alterations in each time point c) Differences mean scores of physical functioning between patients with and without phantogeusia in each time point. * indicates significant results of Mann-Whitney tests ($p<0.05$).*

to baseline, as evidenced by Kruskal-Wallis analysis ($\chi^2(6)=49.36$, $p<.0001$) and Dunn's post hoc test (Figure 53). An increase was observed at TF. Figure 53a shows that patients who reported a decline in basic tastes reported significantly lower physical functioning scores at T1 ($U=390$, $p=.27$) and T4 ($U=543.50$, $p=.016$) compared to those who did not report such alteration. This suggests that the decline in basic tastes already after the first cycle of therapy may contribute to a reduction in perceived physical functioning. A non- trend in the same direction was observed at T8 ($U=169$, $p=.074$).

Similarly, patients classified as having general taste alterations/parageusia/increase in taste perception reported lower physical functioning scores than those without such alterations (Figure 53b). These differences reached statistical significance at multiple time points, more specifically at T1 ($U=675.50$, $p<.0001$), T2 ($U=774.50$, $p=.001$), T4 ($U=616.50$, $p<.0001$), and T6 ($U=291$, $p=.030$). Finally, phantogeusia also showed associations with impaired physical functioning (Figure 53c), as significant differences were observed at T1 ($U=543$, $p=.045$) and again at TF ($U=311$, $p=.024$), where those experiencing phantom tastes reported lower physical functioning scores than those who did not experience them, suggesting both acute (after the first cycle) and late (at follow up) effects of this disorders on daily physical functioning.

Emotional functioning

Emotional functioning, which indicates the emotional and psychological sphere of the cancer patient, i.e. how much the disease and the therapies influence mood, anxiety, tension and sadness in daily life, has a significantly variable trend over time as shown by Kruskal-Wallis test. The results on the overall population (Figure

54) showed a significant increase from baseline (T0) to the early stages of treatment (T1-T2), remaining relatively stable during chemotherapy and increasing again at follow-up (TF) ($\chi^2(6)=19.84$, $p=.003$). Specifically, as shown by Dunn's post hoc test and Bonferroni correction, scores increased significantly at T1 ($p=.002$) and T2 ($p=.001$). Although a slight decrease was observed at T4, T6, and T8, these values did not differ significantly from either the previous time points or from baseline. At TF, emotional functioning scores returned to levels comparable to T1 and T2, and significantly higher than T0 ($p=.0002$).

However, the Mann-Whitney analysis between patients with and without self-reported chemosensory alterations revealed significant differences. Specifically,

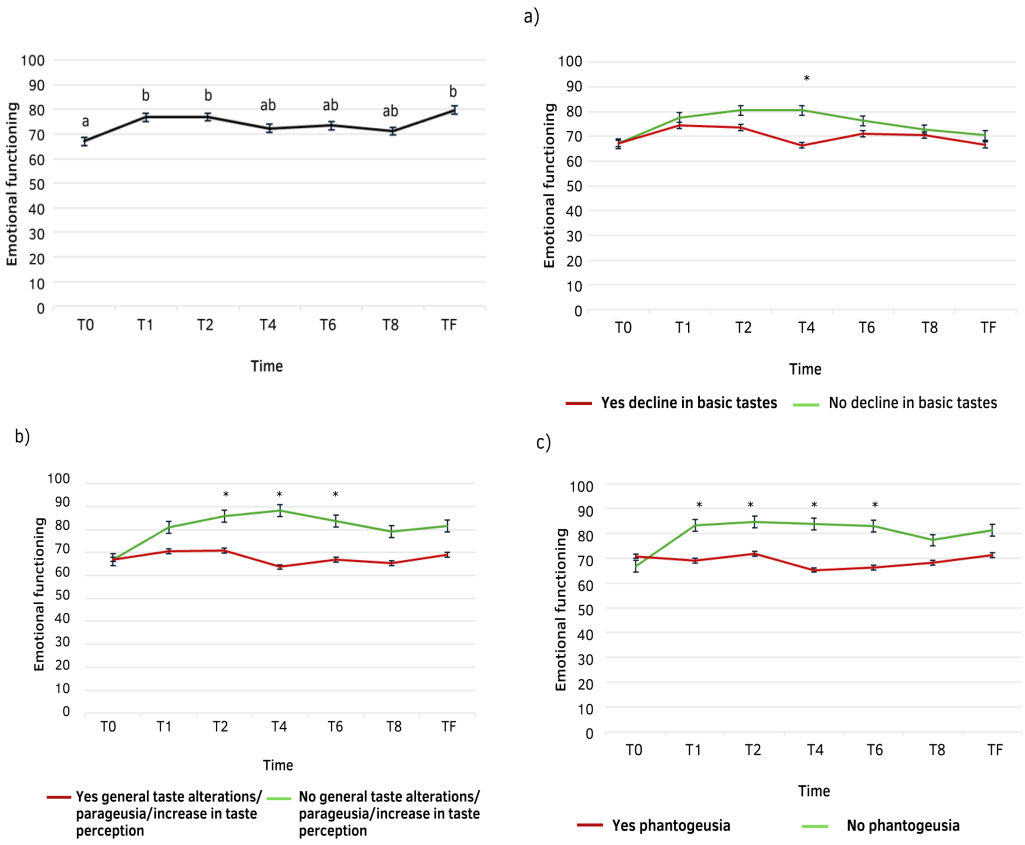


*Figure 54 Mean scores of emotional functioning of study population across treatment period. a) Differences in mean scores of emotional functioning between patients with and without decline in basic tastes in each time point b) Differences in mean scores of emotional functioning between patients with and without general taste alterations in each time point c) Differences mean scores of emotional functioning between patients with and without phantogeusia in each time point. * indicates significant results of Mann-Whitney tests ($p<0.05$).*

patients reporting a decline in basic tastes showed significantly lower scores than those without alterations at T4 (U=538.50, p=.020), indicating greater emotional distress at this specific stage of treatment (Figure 54a).

Significant differences were also observed among patients reporting general taste alterations/parageusia/increase in taste perception: these patients showed significantly lower scores at T2 (U=735.50, p=.006), T4 (U=590, p=.0002), and T6 (U=334, p=.0005), suggesting a persistent impairment of emotional well-being throughout the treatment process (Figure 54b).

Finally, the presence of phantogeusia appears to be associated with a deeper emotional impact. Patients reporting this alteration reported lower scores than patients without phantogeusia at multiple time points during treatment, with statistically significant differences at T1 (U=585, p=.007), T2 (U=746.50, p=.004), T4 (U=580, p=.001) and T6 (U=300.50, p=.030) (Figure 54c).

Social functioning

Regarding the social functioning dimension, which reflects the extent to which the disease and its treatment interfere with patients' family life and social activities, a significantly variable trend over time is observed with Kruskal-Wallis test ($\chi^2(6)=28.23$, $p<.0001$), (Figure 55). In particular, as shown by Dunn's post hoc test, mean scores show a significant decline at T2 and T4, where the minimum value is recorded. Subsequently, a slight improvement is noted at T6, but scores remain lower than baseline and return to being significantly different from the baseline at T8. A more marked recovery is observed at T1, with values returning to comparable values with the baseline ones (T0).

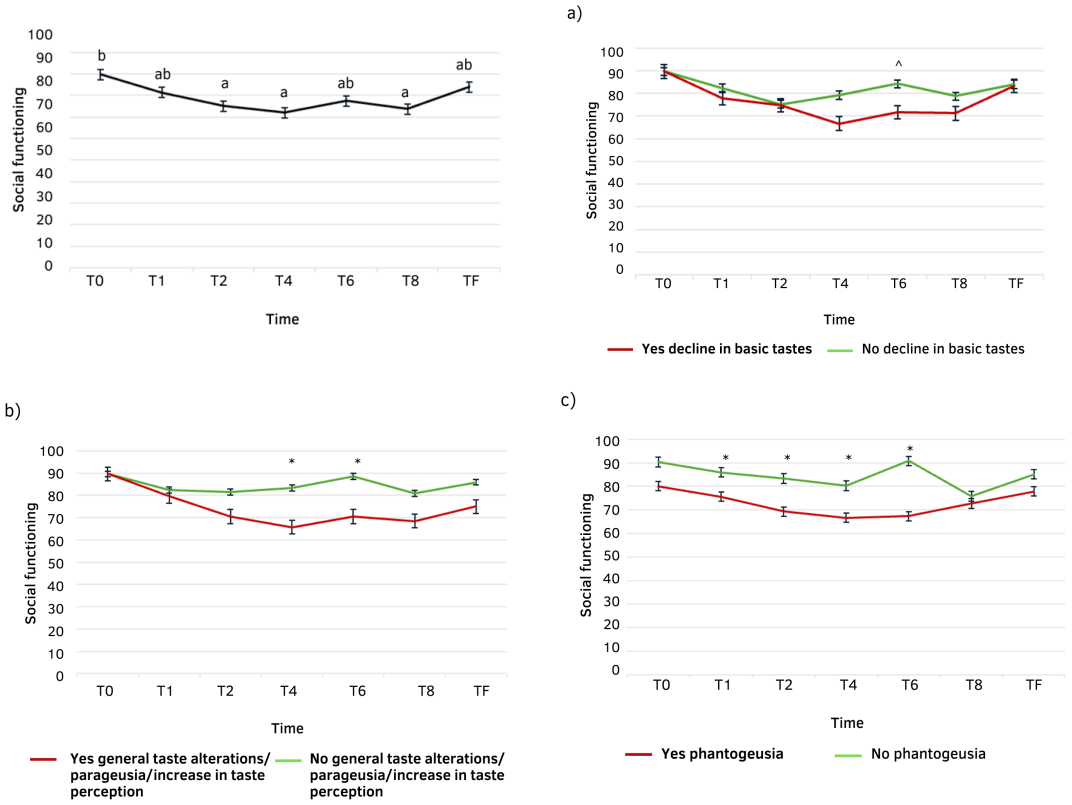


*Figure 55 Mean scores of social functioning of study population across treatment period. a) Differences in mean scores of social functioning between patients with and without decline in basic tastes in each time point b) Differences in mean scores of social functioning between patients with and without general taste alterations in each time point c) Differences mean scores of social functioning between patients with and without phantogeusia in each time point. * indicates significant results of Mann-Whitney tests ($p<0.05$).*

Analyzing the impact of chemosensory alterations on social functioning, some differences emerge. Patients with a decline in basic tastes (Figure 55a) reported lower but non-significantly different mean scores of social functioning than those without this decline. However, the difference between the two groups is close to significance only at time T6 ($U=289.50$, $p=.061$).

In the case of general taste alterations/parageusia/increase in taste perception (Figure 55b), patients reporting these disturbances showed lower scores at multiple time points, with significant differences at T4 ($U=545$, $p=.002$) and T6 ($U=286$, $p=.003$).

Finally, patients reporting phantogeusia (Figure 55c) show significantly lower scores than patients without phantogeusia at T1 ($U=572$, $p=.012$), T2 ($U=669.50$, $p=.052$), T4 ($U=485$, $p=.049$), and T6 ($U=328.50$, $p=.002$). Overall, the presence of taste alterations appears to be associated with worse social functioning during treatment.

Fatigue

During anticancer treatment, fatigue scores (Figure 56) showed a significant increase over time already after the first cycle of therapy, returning to values comparable to T0 three months after the end of therapy ($\chi^2(6)=62.98$, $p<.0001$).

A comparison between patients with and without decline in basic tastes showed greater fatigue in patients who reported decline (Figure 56a), particularly at timepoints T1 ($U=138.50$, $p=.006$), T4 ($U=260$, $p=.026$), and T8 ($U=44.50$, $p=.002$), where the differences between the two groups were statistically significant. These patients reported higher average scores throughout therapy, indicating a condition of greater fatigue.

Similarly, patients with general taste alterations/parageusia/increase in taste perception also showed significantly higher levels of fatigue than patients without these disorders, with significant differences at T1 (U=138.50, p<.0001), T2 (U=261.50, p=.0004), T4 (U=145, p=<.0001), and T6 (U=103, p=.005) (Figure 56b).

Finally, the presence of phantogeusia was also associated with increased fatigue (Figure 56c) because patients reporting this type of alteration showed significantly higher fatigue scores at T1 (U=232, p=.003), T2 (U=373, p=.043), T6 (U=142, p=.057), and TF (U=115, p=.026) compared to those who did not report phantogeusia.

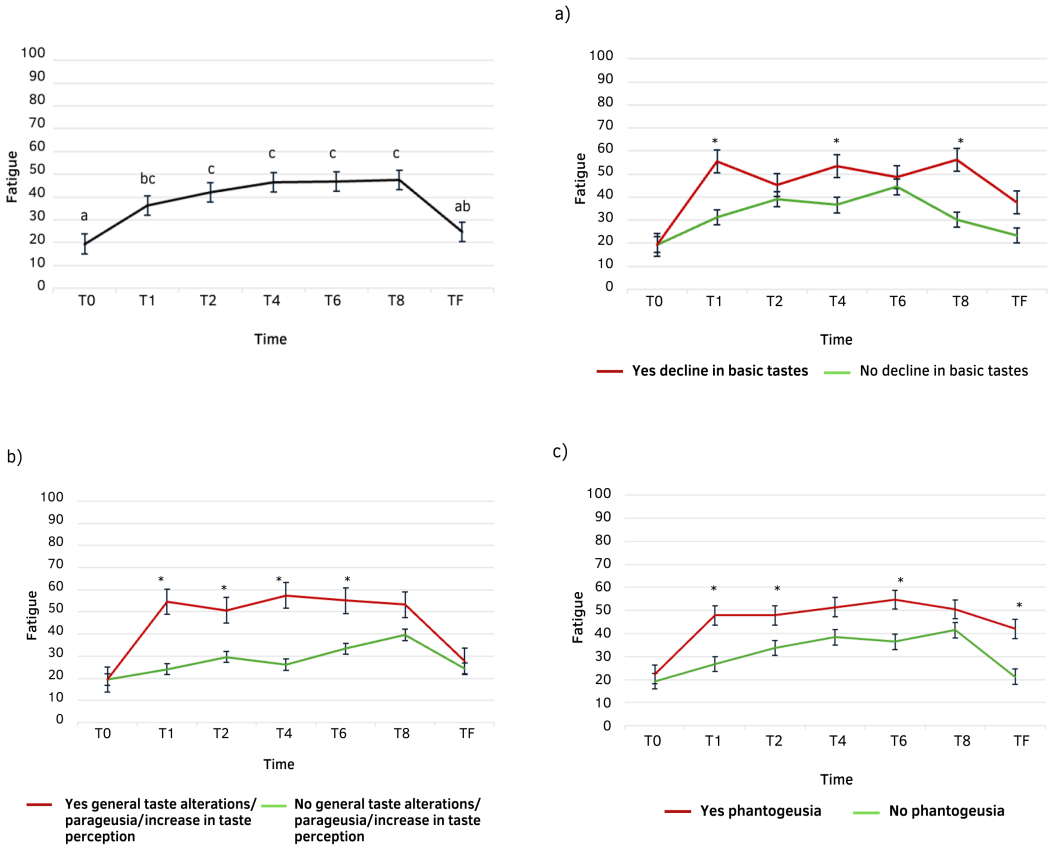


*Figure 56 Mean scores of fatigue of study population across treatment period. a) Differences in mean scores of fatigue between patients with and without decline in basic tastes in each time point b) Differences in mean scores of fatigue between patients with and without general taste alterations in each time point c) Differences mean scores of fatigue between patients with and without phantogeusia in each time point. * indicates significant results of Mann-Whitney tests (p<0.05).*

Nausea and vomiting

Analyzing the overall population, the Kruskal Wallis on "Nausea and Vomiting" dimension (Figure 57) showed a significant increase in scores after the first cycle, with a significant peak observed at T4, followed by a progressive decrease until TF, where scores returned to baseline ($\chi^2(6)=62.98$, $p<.0001$).

When comparing patients with and without a decline in basic tastes (Figure 57a), significant differences were observed at T1 (U=164.50, p=.023) and T4 (U=268, p=.033), with higher nausea and vomiting scores in the group with taste decline, indicating a greater presence of these symptoms in that group.

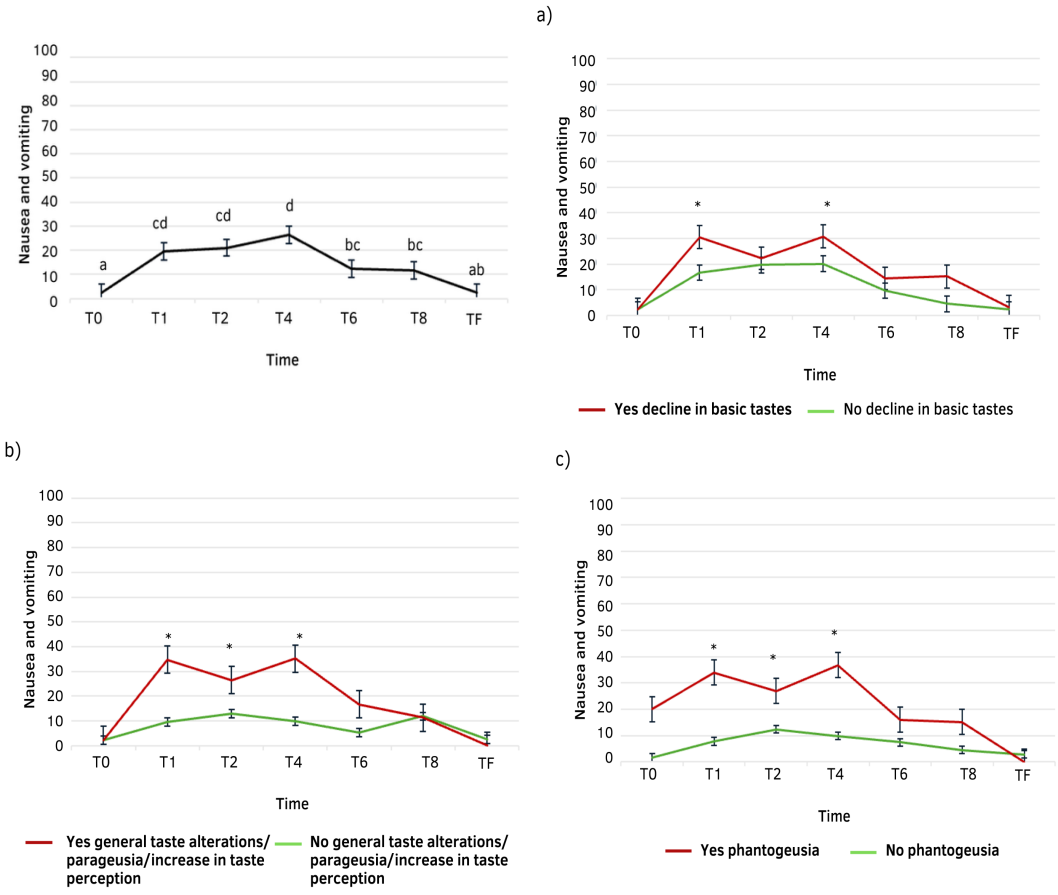


*Figure 57 Mean scores of nausea and vomiting of study population across treatment period. a) Differences in mean scores of nausea and vomiting between patients with and without decline in basic tastes in each time point b) Differences in mean scores of nausea and vomiting between patients with and without general taste alterations in each time point c) Differences mean scores of nausea and vomiting between patients with and without phantogeusia in each time point. * indicates significant results of Mann-Whitney tests (p<0.05).*

Similarly, patients reporting general taste alterations/parageusia/increase in taste perception (Figure 57b) had higher nausea and vomiting scores at T1 (U=137, p<.0001), T2 (U=334, p=.008), and T4 (U=128.50, p<.0001) compared to patients who did not report these alterations, highlighting an association between this alteration and gastrointestinal symptoms, especially in the early phases of treatment.

Finally, the presence of phantogeusia (Figure 57c) was also associated with significantly higher levels of nausea and vomiting at T1 (U=142, p<.0001), T2 (U=314.50, p=.003), and T4 (U=123.50, p<.0001), with improvement in both groups at the end and three months after the end of treatment.

Appetite loss

Over time, appetite loss (Figure 58) showed a significant increase already after the first cycle until T4, followed by a decrease at subsequent timepoints ($\chi^2(6)=39.26$, p<.0001). Regarding the comparisons among groups, patients who reported a decline in basic tastes (Figure 58a) showed consistently higher appetite loss scores than those who did not, with significant differences at T2 (U=353, p=.009) and close to significance at T4 (U=293.50, p=.068).

Similarly, patients who reported general taste alterations/parageusia/increase in taste perception (Figure 58b) had significantly higher scores than those who did not report such alterations at T1 (U=210, p=.0004), T2 (U=334, p=.008), and T4 (U=128.50, p<.0001).

The presence of phantogeusia (Figure 58c) was also associated with greater loss of appetite compared to the absence of phantogeusia, with significant differences at timepoints T1 (U=293, p=.033), T4 (U=270.50, p=.039), and T6 (U=134, p=.019).

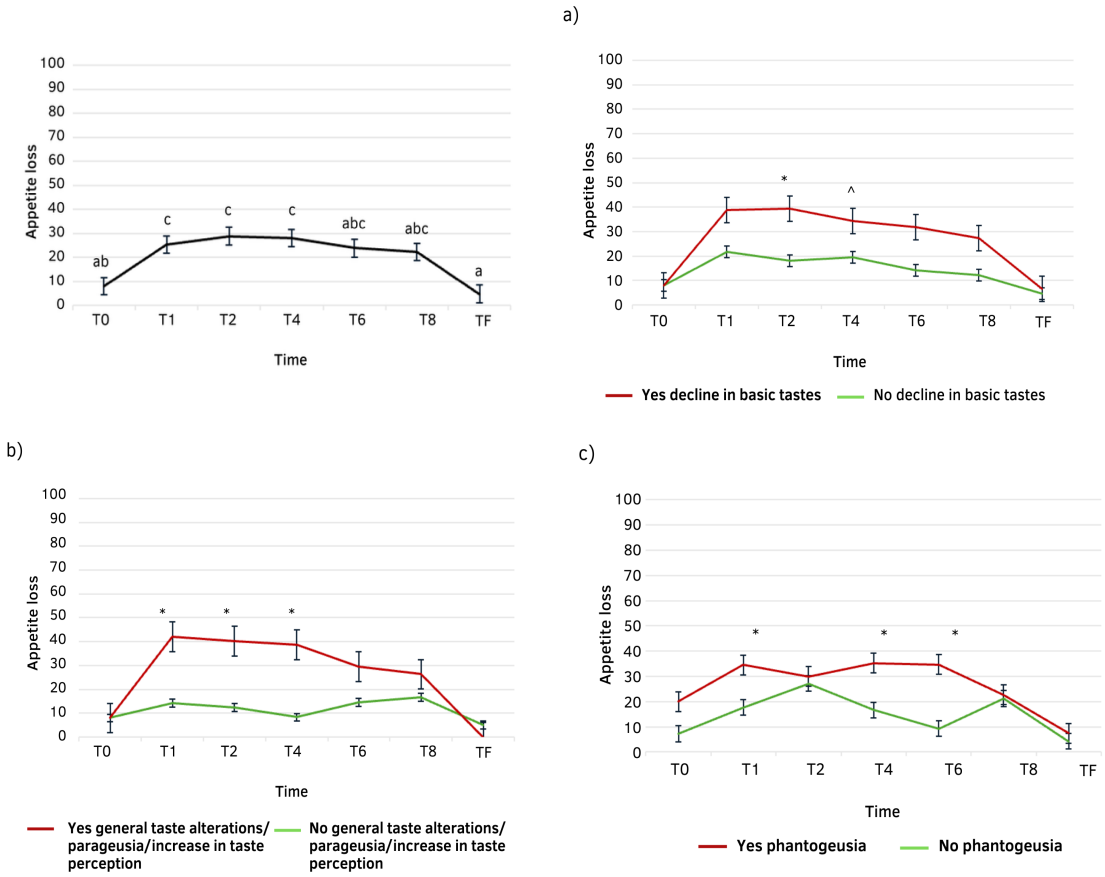


*Figure 58 Mean scores of appetite loss of study population across treatment period. a) Differences in mean scores of appetite loss between patients with and without decline in basic tastes in each time point b) Differences in mean scores of appetite loss between patients with and without general taste alterations in each time point c) Differences mean scores of appetite loss between patients with and without phantogeusia in each time point. * indicates significant results of Mann-Whitney tests ($p<0.05$).*

Global health and quality of life

Quality of life and global health perception (Figure 59) in the study population initially showed a stable trend, with scores not significantly different from T0, but as shown by Dunn's post hoc, at T6 a significant decrease in scores was observed compared to baseline ($\chi^2(6)=27.41$; $p=.0001$).

The analysis of the differences between the CITAS classifications showed that patients reporting decline in basic tastes (Figure 59a) reported significantly lower scores than those who did not experience this disorder, with the significant

difference observed at T8 (U=194, p=.004). The same pattern is observed in patients with general taste alterations/parageusia/increase in taste perception (Figure 59b), who showed worse scores throughout treatment (T1: U=616, p=.001; T2: U=787, p=.001; T4: U=544, p=.003; T6: U=288.50, p=.034; T8: U=202, p=.010). Patients with phantogeusia (Figure 59c) also showed a lower global health/quality of life status than patients without this type of disorder, with a difference close to significance at T8 (U=167.50, p=.075).

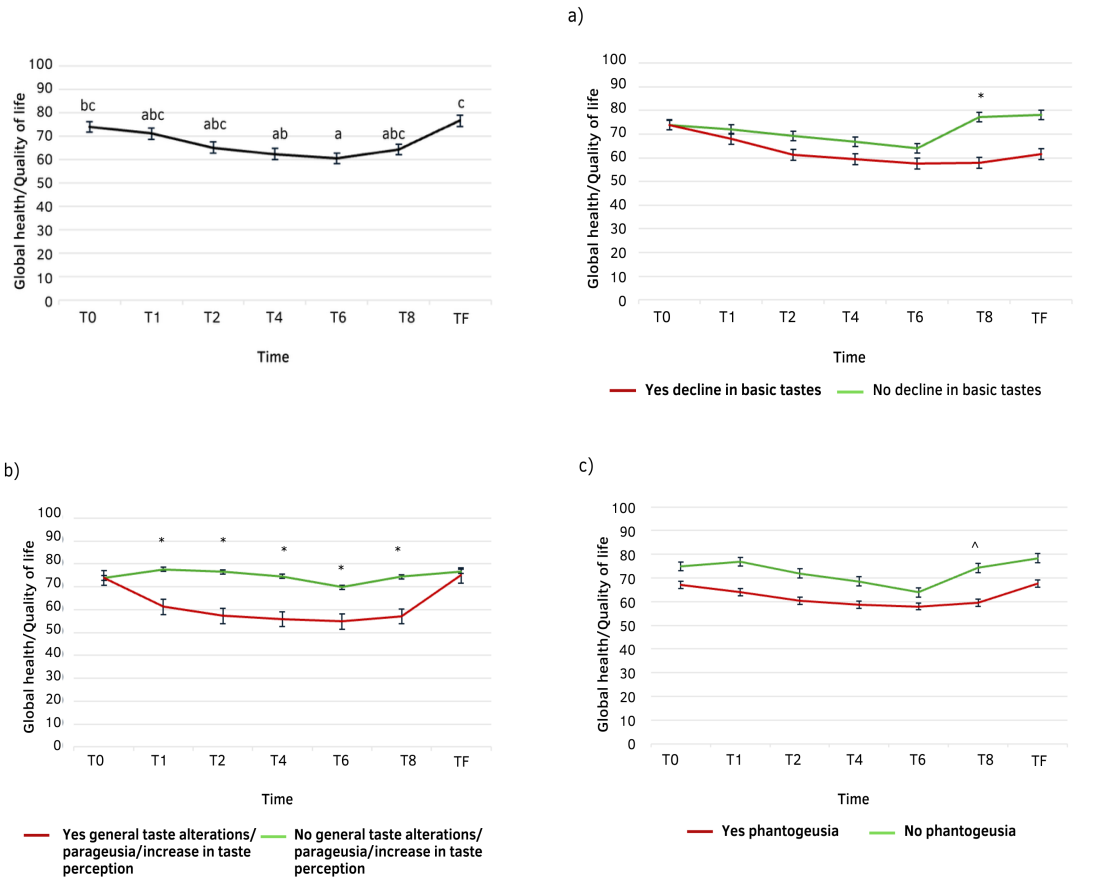


*Figure 59 Mean scores of global health/quality of life of study population across treatment period. a) Differences in mean scores of global health/quality of life between patients with and without decline in basic tastes in each time point b) Differences in mean scores of global health/quality of life between patients with and without general taste alterations in each time point c) Differences mean scores of global health/quality of life between patients with and without phantogeusia in each time point. * indicates significant results of Mann-Whitney tests (p<0.05).*

Results summary 4.9

- Chemotherapy significantly affected all aspects of quality of life, with distinct temporal trajectories for physical, emotional, and social functioning, symptoms, and global health status.
- Physical functioning progressively declined during treatment, reaching its lowest levels later in the therapy, with partial recovery at follow-up. Chemosensory changes, particularly general taste alterations/parageusia/increase in taste perception, were consistently associated with a worsening in physical functioning from the early cycles.
- Emotional functioning improved initially but was significantly worse in patients with chemosensory alterations.
- Social functioning worsened during treatment, particularly in mid-cycles, and was consistently worse in patients with general taste alterations/parageusia/increase in taste perception and phantogeusia.
- Fatigue increased after the start of treatment and was consistently higher in patients who reported chemosensory changes.
- Nausea, vomiting, and loss of appetite worsened early and improved over the follow-up period, but remained higher in patients with chemosensory disturbances, particularly those with qualitative alterations.
- General health and overall quality of life deteriorated during treatment, particularly in patients with general taste alterations.

4.10 Sensory-nutritional advice and input for new tailor-made food solutions

The nutritional-sensory recommendations presented here were developed by integrating evidence from the scientific literature with the results of the present study. Specifically, qualitative interviews provided insights into the coping strategies adopted by patients, while information on food preferences and ideal snack characteristics were used to develop the coping sensory strategies. These recommendations have not been formally tested in an interventional study, but represent a synthesis based on literature, data on observed patient behaviors, preferences, and reported chemosensory alterations.

To establish the nutritional-sensory recommendations, the approach relies on sensory integration mechanisms, such as odor-taste, or on other sensory strategies. For example, congruent aromas can amplify the perceived intensity of a specific taste.

For reduced salt taste, the strategy focuses on enriching foods with salty and congruent flavors, such as anchovies, cured meats, aged cheeses (e.g., Parmesan), broth, soy sauce, mushrooms, or savory herbs and spices (rosemary, oregano, paprika). These ingredients can increase the perception of saltiness, restoring flavor intensity without increasing the amount of added salt, an approach particularly useful for patients on low-sodium diets.

For reduced perception of sweet taste, the use of sweet-congruent flavors such as vanilla, cinnamon, honey, caramel, or fruity flavors (e.g., strawberry) can increase the perception of sweetness while maintaining a moderate sugar intake. This strategy allows patients to rediscover the pleasure of sweet foods without excessive caloric intake.

When patients experience a reduction in their perception of sour taste, small amounts of citrus peel (lemon, lime, orange) can increase acidity without increasing

volume or irritating the oral tissues. However, excessive acidity should be avoided in patients with mucositis or reflux, where sour foods can worsen the discomfort. Conversely, when patients report increased bitterness or a distorted taste perception (parageusia), strategies aim to suppress the bitterness and dull the altered taste perception. This can be achieved by pairing foods with sweet flavors, adding sweetness (e.g., honey-lemon marinades), or balancing the bitterness with sweet sides (e.g., pumpkin or potato puree). The use of sweet-tasting herbs and spices can also help mask unpleasant flavors.

For patients who report a metallic taste in their mouth, refreshing herbs and mild aromatic ingredients such as mint, cucumber, basil, ginger, rosemary, and citrus fruits can help neutralize lingering metallic sensations. Dairy products (e.g., yogurt, milk-based sweets, fresh cheeses) can also reduce unpleasant tastes by binding calcium to iron ions, improving palatability without encouraging overeating. Similarly, when a phantom sour or bitter taste occurs in the mouth, sweet foods (e.g., milk chocolate, potatoes, bananas, pumpkin) and delicate herbal teas can help to tone down the phantom taste, reducing discomfort.

Table 41 summarizes some potential examples of the most common types of chemosensory alterations reported by cancer patients during this study and outlines possible strategies based on sensory integration.

Table 41 Examples of chemosensory alterations, taste-odor integration strategies and opportunities

Type of alteration	Strategies	References	Sensory/nutritional opportunities
Decline of salty taste	Use of congruent salty aromas as enhancers: anchovy, ham, bacon, sardine, peanuts, chicken, cheese (Parmigiano or goat cheese), soy sauce, broth,	Pionnier et al., 2004 Djordjevic et al., 2004 Lawrence et al., 2009 Nasri et al., 2013	Increase of salty/savory perception in foods Decrease of salt use for patients on low-sodium diets

	mushrooms, herbs (rosemary, thyme, oregano, basil) and spices (paprika and black pepper)		
Decline of sweet taste	Addition of congruent aromas as enhancers: strawberry, cinnamon, honey, vanilla, caramel	Frank and Byram, 1988 Frank et al., 1989, 1993 Bingham et al., 1990 Cliff and Noble, 1990 Clark and Lawless, 1994 Prescott, 1999b Stevenson et al., 1999 Small & Prescott, 2005	Increase of sweet perception in foods Limited added sugar and limited glycemic load
Decline of sourness perception	Use of lemon/orange/lime zest or aromas	Veldhuizen et al., 2017	Increase of sour perception in foods Avoiding excess of acidity in case of mucositis or reflux
Increase of bitter perception/altered perception of food tastes (parageusia)	Addition of sweet aromas as suppressor: strawberry, cinnamon, honey, vanilla, caramel Sweet-based marinades for foods with marked bitterness (honey-lemon, orange-maple) Pair bitter foods with sweet side dishes (hummus, yogurt, potato or pumpkin) Addition of herbs (rosemary, thyme, oregano) and spices (paprika and black pepper)	Lawless, 1979 Kroeze et al., 1985	Suppression of dominant bitterness Suppression of bad tastes in foods Limited added sugar and limited glycemic load Decrease of salt use for patients on low-sodium diets

Metallic taste in mouth	Use refreshing herbs, spices, or fruit (mint, cucumber, basil, ginger, citrus, rosemary) Consume strong-flavored herbal teas during the day Incorporate dairy-based options (yogurt, milk candies, fresh cheese)	Ijpma et al., 2015 Rehwaldt et al., 2009	Potential suppression of iron ions responsible for metallic taste through calcium binding (present in dairy-based foods) Low caloric impact Prevention of overeating
Sour/bitter taste in mouth	Use refreshing and sweet herbs, spices, or fruit (mint, cucumber, basil, rosemary, cinnamon) Consume herbal teas during the day Eat foods with persistent sweet taste (honey, milk chocolate, potato, pumpkin, carrots, banana)		Potential suppression of bitter and sour taste by sweet taste Low caloric impact Prevention of overeating

Based on this framework, patient profiles were identified, and sensory principles were translated into practical recommendations and personalized recipes, some of which are presented below. These profiles were based on the convergence of quantitative sensory measures, self-reported chemosensory alterations, and qualitative insights into daily eating experiences. The integration of these data allowed us to characterize individual sensory-nutritional profiles, recognizing the heterogeneity of patient responses to therapy and the need for personalized advice.

PATIENT'S PROFILE #1

- Decrease of perceived intensity of taste (hypogeusia)
- Altered perception of taste of food/drinks (parageusia)

- Aversion to certain odors
- Frequent nausea

GENERAL ADVICE

- Try eating fresh dishes, where cooking isn't necessary.
- Eat your meals in a well-ventilated area.
- Enrich your dishes with herbs and spices.
- During the day, drink herbal teas with ginger and herbs.

SOLUTIONS AND RECIPE IDEAS

FOR YOUR MEALS

- Pasta with pesto (e.g., basil, arugula, zucchini, pistachio)
- Fish/meat with honey-lemon marinade
- Asian soups/condiments (e.g., miso, lemon, lemongrass, soy sauce)
- Crostini with legumes, legume hummus, potato/pumpkin/carrot puree
- Salads with potatoes, celery, and legumes

FOR YOUR SNAKS

SWEET

- Fruit ice cream, or sorbet
- Yogurt with fresh fruit

SALTY

- Rice chips
- Popcorn
- Chickpea chips with rosemary and paprika

PATIENT'S PROFILE #2

- Decrease of perceived intensity of taste (hypogeusia)
- Bad/sour taste in mouth (phantogeusia)

GENERAL ADVICE

- Always practice good oral hygiene
- Add fresh herbs or spices to your dishes
- Drink herbal teas or fruit-infused water frequently throughout the day

SOLUTIONS AND RECIPE IDEAS

FOR YOUR MEALS

- Potato, pumpkin and carrot cream soup
- Legumes cream with rosemary or thyme
- "Mugnaia style" fish/chicken (flour and butter)

FOR YOUR SNAKS

SWEET

- Baked apple with lemon zest (no added juice) with cinnamon and cloves

SALTY

- Pumpkin/carrot chips with rosemary and thyme
- Chickpea chips with rosemary

PATIENT'S PROFILE #3

- Bad/bitter/metallic taste in mouth

GENERAL ADVICE

- Add fresh herbs, spices or fruits to your water
- Try to consume milk sweets (but in moderation)
- Try holding your nose to see if the metallic sensation decrease/disappears
- Avoiding eat/cook with metallic utensils

SOLUTIONS AND RECIPE IDEAS

FOR YOUR MEALS

- Pasta with pesto (e.g. basil, courgettes, pistachio) and a good dose of Parmigiano cheese
- Fresh cheese to be eaten alone accompanied by fresh vegetables or to be consumed as a condiment for first courses (risotto, pasta)
- Coconut milk and curry chicken

FOR YOUR SNAKS

SWEET

- Milk-based ice creams
- Yogurt

SALTY

- Fresh cheeses with herbs

5. Discussion

Given the complexity and multidimensional nature of these disorders, this thesis aimed to longitudinally study the evolution of chemosensory alterations during chemotherapy, considering interindividual differences in psychological and sensory traits. By combining quantitative sensory measures and questionnaires with qualitative interviews, this work aimed not only to study chemosensory alterations in terms of their nature and onset, but also to understand how these changes are experienced, interpreted, and managed by patients in their daily lives. In a context characterized by a large number of methods and questions, this integrative approach was essential to interpret the results which, when considered in isolation, can appear weak, heterogeneous and difficult to summarize. Moreover, this approach allowed for a deeper understanding of cancer patients' eating experiences, including preferences, emotional responses, eating habits, nutritional status, and quality of life, highlighting why group-level effects are sometimes difficult to detect, heterogeneous, or non-directional. The integration of sensory measures, self-reported responses, and qualitative interviews also provided the basis for identifying sensory profiles, providing input for nutritional-sensory recommendations and ideal product characteristics (e.g., snacks) aimed at supporting food intake, enjoyment of eating, and ultimately, quality of life during chemotherapy.

5.1 Chemosensory perception during treatment

Types of chemosensory disorders

Our results showed that although the ability to correctly identify basic tastes and pungency in aqueous solutions remained generally preserved, overall, a significant reduction in the perception of intensity was observed.

Patients were generally able to correctly identify the stimuli in aqueous solutions, particularly at higher concentration. In general, sweetness (induced by sucrose) was the most accurately identified tastants, while bitterness (induced by caffeine) at lower concentration was the least accurately recognized (even at baseline), in line with previous findings (Boltong et al., 2014). Generally, our results on identification suggest that, despite self-reported or measured decreases in perceived intensity, taste recognition remained largely preserved, although salty and sour, as well as bitter, undergo misidentification during treatment, in line with results of Boltong et al. (2014).

Bitter taste at lower concentration was frequently misidentified as tasteless or sour, even at baseline. This finding aligns with previous studies reporting that healthy individuals often confuse bitter and sour stimuli (Meiselman & Dzendolet 1967; Robinson, 1970; Gregson & Baker, 1973; McAuliffe and Meiselman, 1974; O'Mahony et al., 1979, Pangborn, 1961). For sour taste, our analysis shows that participants often confused it with astringent, probably because both evoke similar sensations (Lea & Arnold, 1978). Regarding salty taste, some participants occasionally misidentified it, both at lower and higher concentrations with tasteless (lower concentration), sour or astringent. The literature reports that sour-salty confusion is known. Meiselman & Dzendolet (1967) noted that NaCl was sometimes labeled as "sour" and HCl as "salty," while Robinson (1970) observed a tendency to

call citric acid “salty.” O’Mahony et al. (1979) documented similar misidentification, confirming that this confusion can emerge in healthy populations, especially at low concentrations and in the presence of stimuli of similar intensity.

Our results of sensory measures have shown a general decrease of perceived intensity of lower concentration aqueous solutions during treatment, in agreement with previous studies reporting that the severity of taste alterations gradually increases with increasing drug exposure time (Malta et al., 2022; Martini et al., 2019). At the end of the treatment and three months after the end a recovery was observed. Mean values approached the baseline levels, with differences that were not statistically significant. Our results further expand previous literature that was mainly focused on threshold measurements. The decrease of saltiness perception found both in lower and higher concentration aqueous solutions is consistent with several studies in which such phenomenon was frequently observed through methods using threshold concentrations, qualitative methods, or a combination of both (Boltong et al., 2014; Epstein et al., 2019; Kaizu et al., 2021; Obayashi et al., 2023; Pedersini et al., 2022; Steinbach et al., 2009). Even the perceived intensity of sweet solution at both concentrations significantly decreased during the early stages of chemotherapy, coherently with an increase in the sweet threshold reported in other studies (Dewys & Walters, 1975; Steinbach et al., 2009; Sánchez-Lara et al., 2010; de Vries, Winkels et al. 2018; Schalk et al., 2018). Our results were not consistent with one previous study using suprathreshold concentrations, as Mulder et al. (1983) reported an increase in perceived salty and sweet intensity after each chemotherapy cycle. The reason behind the difference observed can be due to the different types of chemotherapy principles, that were bleomycin, actinomycin D, vindesine and DTIC in Mulder et al, (1983), as well as methodological differences and sample size.

In contrast, intensity ratings of sour, bitter, and pungent stimuli presented at both concentrations showed no significant changes over time, confirming previous studies that did not show effect at a threshold level for sour and bitter (Schalk et al. 2018, de Vries, Winkels et al, 2018, Ijpma, Renken et al. 2017, Kim et al. 2020). This suggests that chemosensory alterations during chemotherapy do not uniformly affect all basic tastes. A possible explanation for the absence of variation in bitter and sour perception lies in their functional role: sour and bitter are considered warning sensations in foods (e.g., the presence of toxic substances, fermentation). Therefore, the perception of bitter and sour could be more resistant to changes induced by chemotherapy, due to attentional and functional mechanisms. Furthermore, patients receiving chemotherapy often experience that foods normally consumed suddenly taste bitter/sour/bad, thus exacerbating the perception of these sensations. Even for the pungent solution at both concentrations no significant changes were observed during the treatment, in contrast with limited evidence that reported a reduction in pungency perception in head-and-neck cancer patients (Riantiningtyas et al., 2023; Epstein et al., 2020). However, in our study, the maximum dose of capsaicin used (0.0015 g/L) may not have been suitable to detect changes in sensitivity. Indeed, when evaluating self-report responses of GCCR questionnaire, it emerged that approximately 20-30% of patients stated to perceive pungency as stronger than usual from the 2nd cycle until the end of therapy. These discrepancies may reflect interindividual variability, as well as the influence of concomitant conditions such as mucositis or xerostomia in the days after treatment, which may increase sensitivity or reduce reactivity due to tissue damage or changes in salivary flow (Thorne et al., 2015). Additionally, medical guidelines often recommend avoiding spicy foods to reduce oral discomfort during treatment (Singh & Singh, 2020), which may result in reduced exposure and induce sensitization (Prescott, 1999a).

Despite the general decline in perceived taste intensity observed at the population level, the PCA analysis of perceived sweet taste intensity at lower concentrations indicated that not all patients experienced a decline, identifying three distinct clusters: Decliners, Non-Altered, and Enhancers. Interestingly, the clusters differed by age, with Enhancer cluster that was older than the other two clusters, particularly the Decliners cluster.

Focusing on the breast cancer subgroup, individual trajectories confirmed marked interindividual variability, with patients showing different patterns of decline and recovery in taste perception over time. These interindividual patterns reflect the heterogeneity of quantitative chemosensory alterations reported in previous research (Kim et al., 2020; O' Donghue et al., 2023), in which both increases and decreases in taste perception have been documented, sometimes within the same population. Recognizing these interindividual differences is essential for both research and clinical practice. From a research perspective, analyses of the entire population can obscure significant variability in sensory changes, potentially masking subgroups of patients experiencing opposing trajectories. From a clinical perspective, identifying patient-specific alteration profiles could guide the development of personalized nutritional and sensory interventions aimed at mitigating the negative impact of chemosensory alterations on food intake and quality of life.

Standard sensory tests with aqueous solutions, while valuable for quantifying changes in detection and recognition thresholds or suprathreshold intensity, are less suitable for detecting qualitative alterations frequently reported by patients, such as phantogeusia, parageusia, and cacogeusia (Kano & Kanda, 2013). Similarly, the use of numerous questionnaires and methods allowed for a broad and detailed assessment of eating experiences and quality of life but inevitably increased the complexity of the results. In this context, the lack of statistically significant results

or the presence of weak and unstable effects does not necessarily reflect poor clinical relevance, but rather the high heterogeneity of individual responses which will benefits from an even larger sample size.

Self-reported data from CiTAS revealed that, starting from the first cycle, patients reported discomfort and different types of chemosensory alterations: decline in basic tastes, general taste alterations/parageusia/increase in taste perception, and phantogeusia. In addition to the variety of sensory changes and their associated adverse effects, there is considerable variability in how patients respond to these changes. Our results suggest that in the presence of these alterations, the relationship with foods of specific categories may worsen, inducing more negative emotions, and that such conditions may, in some cases, lead to a change in food preferences, changes in eating habits, and worsening of quality of life. Moreover, qualitative interviews were instrumental in contextualizing these findings, revealing how chemosensory alterations interacted with other antineoplastic side effects, including nausea, vomiting, dry mouth, sore mouth and throat, excessive thirst, swallowing difficulty, appetite changes, weight loss, dizziness, lack of energy, disturbed sleep, anxiety, and difficulty concentrating, in line with previous studies (Al-Amouri & Badrasawi, 2024; Martini et al., 2019). Some of these conditions are included in the dimension of “Discomfort” where mean CiTAS scores significantly increased after the first chemotherapy cycle. Notably, even before starting therapy, 47.9% of patients in our sample reported discomfort, with mean baseline scores already above the minimum (>1), suggesting that the discomfort is primarily due to the disease itself. It is further aggravated by chemotherapy, as evidenced by the 81% of patients who reported discomfort after just one cycle.

Timing: occurrence, duration, recovery

This study suggests that both sensory and self-reported methods used to assess chemosensory perception and therapy-induced alterations provide useful information.

Based on the perceived intensity data for aqueous solutions, overall, lower concentration solutions showed a significant decrease in perceived intensity only after the fourth chemotherapy cycle, while for the sweet solution, a decline was already evident after the second cycle. In contrast, higher concentration solutions overall showed a significant reduction in perceived intensity after the first treatment cycle. However, when analyzing specific tastes separately, both salty and sweet solutions showed significant decreases only after the fourth cycle.

Some research has shown that taste alterations can peak early in the chemotherapy cycle, in the first 4–6 days after infusion (Boltong et al., 2014; Ijpma, Renken, Gietema, et al., 2016), whereas our study assessed chemosensory function later in the cycle, close to the next infusion, when the effect is presumably lower and recovery has occurred. Furthermore, in the daily food experience, multiple sensory inputs, such as texture and temperature, combine to shape the overall flavor, potentially revealing alterations that are not detected through tests that focus on a single stimulus. Indeed, self-reported CiTAS responses revealed that already after the first cycle of chemotherapy, patients reported significantly higher scores for general taste alterations/parageusia/increase in taste perception and phantogeusia, as well as a marked increase in discomfort, reported by 81% of patients at this early stage. Furthermore, after the second cycle, the decline in basic taste scores also showed a significant increase compared to baseline.

Overall, after the first cycle, 20.7% of patients reported a decline in basic tastes, 39.7% reported general taste alterations/parageusia/increase in taste perception,

and 44.8% experienced phantogeusia, indicating that chemosensory disturbances can emerge very early during chemotherapy and are already noticeable by patients from the beginning of treatment. This discrepancy in respect to sensory tests might be due to the different aspects considered by the two measures. In fact, while the gLMS captures the perceived intensity of isolated chemosensory stimuli under controlled conditions at a specific time (the time of testing), the CiTAS reflects the daily taste experience during food consumption throughout the post-infusion period. Qualitative interviews helped interpret these discrepancies, revealing rapid post-infusion fluctuations, context-dependent triggers, and symptom variability that cannot be captured by quantitative assessments alone at a single point in time. Indeed, qualitative patients' reports offer a valuable within cycle perspective, rarely documented in the existing literature. While previous studies (Boltong et al. 2014, Ijpma, Renken, Gietema, et al. 2016; de Vries, Boesveldt, et al., 2018), have typically focused on variations between chemotherapy cycles or global assessments of taste alterations, our qualitative data capture the precise onset and evolution of these disturbances, offering a more detailed understanding of their onset and progression. Yet, understanding the precise occurrence of chemosensory alterations may be essential to identify a critical time window for targeted nutritional and sensory interventions. Most patients indicated that these disturbances emerged within the first 24 hours following chemotherapy administration, with a peak in intensity between the third and fifth day after infusion, followed by a gradual attenuation.

Findings from the aqueous solution tests, mean self-report scores on the CiTAS and GCCR, and qualitative interview data all indicated that, three months after the end of treatment, chemosensory alterations had resolved for most patients (>80%). This observation is consistent with previous studies (Boltong et al., 2014; Ijpma, Renken, Gietema, et al., 2016) that have shown that taste and smell alterations are

largely transient, although other reports have shown that recovery from chemosensory alterations may take up to six months (de Vries, Boesveldt et al., 2018).

5.2 Impact of chemotherapy and self-reported chemosensory alterations on food experience and quality of life

To better understand the overall impact of chemotherapy on the eating experience, we first analyzed changes in liking, preferences, and emotional responses to food across the entire study population, regardless of specific chemosensory changes. This general overview provides a basis for interpreting subsequent analyses focused on individual changes.

Liking for basic tastes. Descriptive analyses of hedonic responses to basic tastes showed that most patients reported liking them "as usual" during chemotherapy, although some variations emerged during treatment. The liking of sweet taste showed fluctuations, with a temporary reduction in the mid-phase of therapy followed by recovery at the end. Less consistent changes were observed for salty and sour tastes, while bitter taste appeared to become less tolerated over time, suggesting a greater aversive response to this taste during chemotherapy. In the following sections, these general trends are examined in relation to specific self-reported chemosensory alterations to better understand their impact.

Food preferences and emotions. Consistently, no significant associations were observed between chemosensory alterations and preference changes after the first cycle of therapy. However, even though patients did not report changes in preference compared to baseline, their relationship with previously preferred foods appeared to be worse.

The lack of significant changes in preference scores across the FP&EQ dimensions suggests that, at the population level, chemotherapy did not systematically alter the direction of food preferences. Most patients continued to prefer more intense flavors and crunchy or hard textures, indicating that the sensory factors underlying food choice remained relatively stable during treatment.

However, the trend toward greater aversion to intense odors observed over the course of therapy is consistent with previous evidence reporting increased olfactory sensitivity and odor-related discomfort in patients undergoing chemotherapy (Coa et al., 2015; van den Brink et al., 2022). Odor perception is likely affected in most patients (Ishinaga et al., 2018; Nielsen et al., 1980), likely due to the widespread presence of general discomfort.

Quality of life. Our findings, consistent with previous studies (Bjordal et al., 2000; Binotto et al., 2020), indicate that chemotherapy itself significantly impacts quality of life, with marked reductions in physical functioning, social functioning, and global health/quality of life, and increased symptoms, already in the early stages of treatment. Although the literature suggests that the type of chemotherapy regimen may differentially impact quality of life (Zhao et al., 2022), the heterogeneity of regimens in our sample highlights that, overall, chemotherapy exerts a negative effect regardless of the specific protocol. However, interestingly, emotional functioning scores of the study population improved after the first cycle compared to baseline. This finding is somewhat unexpected, as patients frequently report symptoms of anxiety and depression during chemotherapy (Joseph et al., 2021), and several studies have documented a deterioration in emotional functioning over the course of treatment. However, similar to our findings, Bjordal et al. (2000) found no significant impact of treatment on emotional functioning, while Aaronson et al. (1993) even reported a slight increase in scores during treatment compared to before. One possible explanation, as suggested by Ejder &

Sanlier (2023), is that, although many studies highlight the adverse effects of chemotherapy on quality of life, there is also evidence that chemotherapy can improve some aspects of well-being by prolonging life expectancy and offering a sense of active management of the disease. Furthermore, it is plausible that emotional functioning is particularly low before the start of treatment, when patients are faced with uncertainty, fear of the unknown, and the anticipation of side effects, which they often imagine to be worse than they actually experience. In fact, for example, Jacobsen, Bovbjerg, & Redd (1993) reported that anxiety was more widespread and intense before the first infusion.

After outlining the general impact of chemotherapy on food experience and quality of life in the overall sample, the following sections focus on the specific alterations self-reported through the CiTAS and how these influence patients' food experience.

Decline in basic tastes

Table 42 shows the summary of impact of self-reported decline in basic tastes on food experience.

Table 42 – Summary of the impact of self-reported decline in basic tastes (CiTAS) on food experience during treatment. The first row reports the percentage of patients who self-reported a decline in basic taste perception in each time point. In the subsequent rows percentages reported in brackets refer only to the proportion of patients with a decline in basic tastes who experienced a significant change in the corresponding variable. For the section "Changes in liking for basic tastes", symbols (-) and (+) indicate a reported liking "less" or "more" than usual, respectively. For the sections "Food preferences and "Eating habits," symbols (-) and (+) indicate the direction of the statistically significant correlation (negative or positive) between the CiTAS score and the corresponding variable (preference score and use/liking). For the "Changes in emotional responses" percentages and arrows indicate the increase or decrease in negative emotions elicited by chosen options over time compared to baseline.

		T0	T1	T2	T4	T6	T8	TF
Decline in basic tastes	Percentage of study population with decline in basic tastes	0.0%	20.7%	50.0%	57.9%	54.8%	66.7%	8.9%
	Changes in liking for basic tastes (-) less than usual; (+) more than usual (% of patients with decline who reported changes in liking)		(+) salty (63.6%) (+) sour (60.0%)	(-) sweet (54.5%) (-) salty (62.5%) (-) sour (80.0%) (-) bitter (64.3%) (+) sweet (88.9%)	(-) sweet (61.9%) (-) salty (80.0%) (-) sour (84.6%) (-) bitter (82.6%) (+) sweet (57.1%) (+) salty (63.6%)	(-) sweet (73.2%) (-) salty (77.8%) (-) sour (77.8%) (-) bitter (78.6%) (+) sweet (66.7%)	(-) sweet (75.0%) (-) salty (66.7%) (-) bitter (60.0%) (+) sweet (75.0%) (+) salty (71.4%)	
	Food preferences (+/- correlations)				(-) Flavor			(-) Odor
	Changes in food preferences				Flavor		More intente odor aversion	
	Changes in emotional responses - % of negative emotions elicited by chosen options		Herbs and Spices 11.7->22.7%		Odor aversion 78.8->87.1%	Sweet vs Bitter 7.8->20.9%	Sweet vs Bitter 9.1>17.3%	

Eating habits (+/- correlations)		(+) lemon liking (+) vinegar liking

Self-reported data from CiTAS revealed that, starting from the second cycle, patients reported a significant decline in taste perception. This finding is consistent with the findings of Zhang et al. (2025), who stated that patients undergoing more than two chemotherapy cycles were more likely to experience taste alterations. However, after the initial increase in decline in basic tastes scores, they reached a plateau that persisted until the end of treatment, suggesting stabilization rather than progressive worsening of symptoms, despite the progressive increase in patients reporting this disorder over time (20.7% at T1 to 66.7% at T8). Three months after completing therapy, most patients reported that their taste perception had returned to normal, with 8.9% still reporting the presence of this disorder. This trend confirms the data on taste solutions, in which a decrease in perception was recorded, particularly for sweet and salty tastes, a result also confirmed by the qualitative interviews.

Liking for basic tastes. Analysis of changes in liking for basic tastes during treatment revealed that, overall, most patients reported liking all four basic tastes assessed "as usual." However, given that products that receive higher liking scores are typically selected more frequently than those with lower scores, and disliked products are not consumed (De Graaf et al., 2005; Keller et al., 2022), we focused on the percentage of "less as usual" and “more than usual” responses, as these could potentially compromise food intake during chemotherapy.

The results regarding the hedonic perception of basic tastes have been conflicting and unsystematic. Although a decline in the intensity of basic tastes was observed during chemotherapy, the corresponding changes in liking did not follow a linear or consistent trend. After the first cycle of chemotherapy, patients who reported a decline in taste perception did not show a marked reduction in liking for basic

tastes compared to those without decline, likely indicating an early phase of sensory adaptation or limited awareness of the alteration. However, from the second cycle onward, a progressive association emerged between taste decline and reduced liking, particularly for sweet and salty taste. The results that showed a lower liking for sweet taste are consistent with the reduction in liking for sweet described by Boltong et al. (2014), probably due to the reduced ability to perceive this taste. However, some patients with taste decline also reported greater liking for sweet and salty, indicating that the relationship between taste perception and hedonic response is not linear, but rather dynamic throughout chemotherapy. This seemingly paradoxical finding could reflect compensatory mechanisms, such as a greater preference for more intense flavors to compensate for decreased perception (de Vries et al., 2016).

Food preferences and emotions. Focusing on the first cycle, although no changes in food preferences, we observed a trend of worsening of the emotional responses to the preferred food of the "Herbs and Spices" dimension by patients who self-report a decline in basic tastes in the absence of a change in preferences. In the literature, reduced taste perception has been associated with a tendency to select more seasoned foods containing flavor enhancers such as salt, lemon juice, spices, and garlic (Drareni et al., 2023; Speck et al., 2013). The hypothesis is that these foods, already preferred before the start of therapy, fail to provide the expected relief, thus eliciting negative emotions. Second, some foods may be avoided because they are perceived as excessively intense or, conversely, as tasteless. From our findings, no positive correlations were observed between the decline in basic tastes and the use or liking of condiments, despite during interviews they reported adding more salt, Parmesan cheese, or other spices (e.g., pepper, chili pepper) to enhance their perception, in line with previous studies (Rehwaldt et al., 2009; Grant & Kravits, 2000; Adamczyk et al., 2024; de Vries et al., 2016). By the end of therapy

(T8), significant positive correlation between decline in basic tastes and liking for lemon and vinegar was found, supporting the hypothesis that patients with taste decline tend to compensate for reduced taste sensitivity by increasing the use and preference for flavor enhancers. This is in line with Wickham et al. (1999) in which it has been reported that patients identified the most helpful strategies to deal with taste changes were increasing seasonings, fats and sauces.

Significant changes in the Flavor dimension were associated with decline in basic tastes at T4, but without a specific direction. Although both qualitative interview data and existing literature might lead us to expect that a decline in basic tastes would increase the preference for more intense flavors, the lack of a clear directional trend might highlight individual differences in preferences at baseline. Furthermore, the negative correlation between CiTAS scores and preference scores leads us to suppose that people with preference for intensely flavored food at the baseline tend to experiment with new flavors different from those present in their usual diet, sometimes with less intense flavors, as part of a process of evaluating their ability to perceive and appreciate taste, as observed by Rehwaldt et al. (2009). Patients with a decline in basic tastes also showed a further worsening of emotions towards odors they had rated as less preferred at baseline. They also showed a significant change in odor preference, developing aversion toward more intense odors, at the end of treatment. This delayed effect may be explained by the cumulative impact of chemotherapy on chemosensory function, which becomes more evident towards the end of treatment. This could also be due to an increased awareness of odors and a greater emotional reactivity. Ishinaga et al. (2018) reported that cancer patients experiencing food aversion during chemotherapy show increased awareness of odors, which could amplify the perceived unpleasantness of strong odors. Furthermore, prolonged exposure to treatment-

related nausea and discomfort may lead to a conditioned aversion to strong odors, particularly those associated with food or cooking.

In the Sweet vs. Bitter dimension a deterioration of the emotional responses was observed in the last cycles of therapy. This dimension, already compromised in previous cycles and also in presence of other types of alteration, emerged as the most affected dimension of the questionnaire, confirming preliminary findings (Di Meglio et al. 2025).

Three months after the end of chemotherapy, our analyses indicate that changes in preferences were reversed, with patients generally returning to their pretreatment favorite foods.

Quality of life. Decline in basic tastes was associated with limited effects on quality of life indices. In fact, appetite loss, fatigue, nausea and vomiting were higher in altered patients only at specific therapy time points, indicating worse quality of life condition. This finding is consistent with previous studies (Zabernigg et al., 2010; Brisbois et al., 2011; Gamper et al., 2012; de Vries, Boesveldt, et al., 2018; Spotten et al., 2017) demonstrating that impaired taste function is associated with poorer quality of life.

Also emotional and social functioning scales showed only sporadic differences between the groups, suggesting that decline in basic tastes does not have a substantial impact on these aspects.

General taste alterations, parageusia, increase in taste perception

Patients could report an altered ability to perceive taste that does not exclusively reflect changes in intensity perception, but also includes the appearance of a distorted, bitter, or unpleasant perception of food, often linked to changes in odor perception, as both taste and smell work together to create the complete flavor

experience (Amézaga et al., 2018). In our study, we were able to identify the presence of these alterations not only during interviews but also during completion of the modified CiTAS. For instance, the "General taste alterations, parageusia and increase in taste perception" dimension considers the perception of food as bad/bitter/unusual or with an increased taste. Table 43 shows the summary of impact of self-reported general taste alterations/parageusia/increase in taste perception on food experience.

Table 43 - Summary of the impact of self-reported general taste alterations/parageusia/increase in taste perception (CiTAS) on food experience during treatment. The first row reports the percentage of patients who self-reported a general taste alterations/parageusia/increase in taste perception in each time point. In the subsequent rows percentages reported in brackets refer only to the proportion of patients with a general taste alterations/parageusia/increase in taste perception who experienced a significant change in the corresponding variable. For the section "Changes in liking for basic tastes", symbols (-) and (+) indicate a reported liking "less" or "more" than usual, respectively. For the sections "Food preferences and "Eating habits," symbols (-) and (+) indicate the direction of the statistically significant correlation (negative or positive) between the CiTAS score and the corresponding variable (preference score and use/liking). For the "Changes in emotional responses" percentages and arrows indicate the increase or decrease in negative emotions elicited by chosen options over time compared to baseline.

		T0	T1	T2	T4	T6	T8	TF
General taste alterations/ parageusia/ increase in taste perception	Percentage of study population with general taste alterations/ parageusia/increase	0.0%	39.7%	57.6%	64.9%	59.5%	57.6%	7.1%
	Changes in liking for basic tastes (-) less than usual; (+) more than usual (% of patients with alterations who reported changes in liking)		(-) sweet (78.6%) (-) salty (75.0%) (-) sour (100.0%) (-) bitter (92.9%) (+) salty (63.6%)	(-) sweet 68.2%) (-) salty (91.7%) (-) sour (87.5%) (-) bitter (81.0%) (+) sweet (60.0%) (+) sour (66.7%)	(-) sweet (90.5%) (-) salty (100.0%) (-) sour (92.3%) (-) bitter (100.0%) (+) sweet (51.7%) (+) salty (81.8%) (+) sour (100.0%)	(-) sweet (80.0%) (-) salty (88.9%) (-) sour (88.9%) (-) bitter (78.6%) (+) sweet (51.7%) (+) sour (100.0%)	(-) sweet (75.0%) (-) salty (100.0%) (-) sour (75.0%) (-) bitter (66.7%) (+) sweet (55.6%) (+) sour (60.0%)	(-) bitter (75.0%)
	Food preferences (+/- correlations)		(-) Flavor	(-) Flavor (-) Texture	(-) Flavor (-) Texture	(-) Flavor		

Changes in food preferences		Sweet vs Bitter	Texture Herbs & Spices	More intense odor aversion Herbs & Spices	More intente odor aversion
Changes in emotional responses – % of negative emotions elicited by chosen options	Texture 9.6–>22.6% Sweet vs Bitter 10.4–>29.6%	Sweet vs Bitter 10.5–>17.4%	Sweet vs Bitter 10.3–>20.5%	Sweet vs Bitter 12.0–>20.8%	
Eating habits (+/– correlations)		(–) Parmesan cheese use	(–) Parmesan cheese use (–) chili pepper liking (–) lemon liking	(–) Parmesan cheese use	

The percentage of affected patients increased from 39.7% at T1 to 57.6% at T8, with average scores rising significantly already after the first cycle of therapy, with a peak after the fourth cycle of treatment. Our results, both from CiTAS and qualitative interviews, align with previous studies (Amézaga et al., 2018; Bernhardson et al., 2007) in which patients describe the altered taste sensation as a bad taste different from the usual, such as “not recognizable”, “never tasted before”, similar to “paper”, “sawdust”, “metal”, “between sour and salty licorices”. During our qualitative interviews, for example, the taste of coffee is described as unusually burnt or bitter, the taste of water as “metallic”, “sweet” or “bitter”. The meat is perceived as metallic or distasteful. Interestingly, a study by DeWys & Walters (1975) reported that most patients who experienced an aversion to meat also showed increased sensitivity to bitter taste. These results agree with previous qualitative studies reporting that patients often described some foods or beverages in the same way as our patients (Bernhardson et al., 2007; Mahmoud et al., 2011).

Liking for basic tastes. General taste alterations/parageusia/increase in taste perception was associated with a preference for less intense flavors, as indicated by the negative correlation with preference score and by decreased liking for all basic tastes. This trend was also reflected in other eating behaviors: as the intensity

of the alteration increased, patients reported a reduction in the use of Parmesan cheese and a reduced liking for spicy or lemon-containing foods. Overall, these results suggest that patients with more marked chemosensory alterations tend to shift toward milder flavor profiles, likely as an adaptive response to increased perception or altered perception of intensity, as reported in previous studies (De Vries 2016; 2018). However, opposite behaviors have also been reported in the qualitative interview with altered patients reporting the addition seasonings such as lemon to improve the palatability of foods. This ambivalence in behavioral responses to chemosensory alterations is also described in the qualitative study by de Vries et al. (2016).

General taste alterations/parageusia/increase in taste perception was associated with patients that reported a less than usual liking for bitter and sour. This finding may be explained by the nature of these alterations, which often lead patients to perceive foods as distorted, unpleasant, or excessively bitter. Furthermore, sourness and bitterness are commonly innately disliked (Steiner, 1979; Ventura & Mennella, 2011) and may act as warning sensations that negatively influence hedonic responses (Laureati et al., 2018).

Food preferences and emotions. Among the different self-reported chemosensory alterations, general taste alterations/parageusia/increase in taste perception emerged as a condition associated with more pronounced effects on food preferences and emotions. Texture and Sweet vs. Bitter emerged as the dimensions most affected by a worsening in emotional responses in presence of these general alterations at the early stages of the therapy. The worsening of emotions elicited by favorite products in the Texture dimension can be related to the triggering nausea effect reported for specific textures such as pasty, as previously reported by Tan et al. (2020). Qualitative interviews confirmed that some patients tend to prefer dry or crunchy options for nausea relief, while others prefer softer, liquid,

or creamier foods to reduce chewing effort or irritation thus counteracting the oral discomfort.

Despite the change in preference recorded in the Sweet vs. Bitter dimension after the second cycle of therapy, the worsening of the emotions elicited by the chosen foods in this dimension was recorded at all time points during treatment compared to the baseline, suggesting that this dimension is the one most compromised in presence of this type of alteration. These alterations may cause sweet or bitter foods to be perceived as either overly intense or insufficiently rewarding, leading to frustration, dissatisfaction, or emotional disengagement during eating. Preference changes within this dimension, which became evident after the second treatment cycle, did not follow a specific direction. This variability may reflect differences in how alterations influence hedonics; as reported by patients during qualitative interviews, these alterations often resulted in a preference for bitter foods, in presence of an altered perception of sweetness, or alternatively in a preference for sweet foods, as candy, desserts, biscuits, and an avoidance of bitter foods, as coffee, tea, bitter vegetables, in case of a bitter/bad taste of foods. Our results are in line with the systematic review by Boltong and Keast (2012), who reported that the most commonly aversive foods and beverages during chemotherapy are bitter products such as coffee and tea (Grindel et al., 1989; Jacobsen, et al., 1993), as well as sweet/bitter products such as chocolate and cola (Andrykowski and Otis, 1990; Mattes et al., 1987; Steinbach et al., 2009). Therefore, an increased perception of bitterness or the development of an aversion to it, led a substantial percentage of patients to eliminate naturally bitter products, or to add sugar or milk to cope with the bitter taste. At the same time, patients may respond to these sensory challenges in different ways, for example by satisfying specific cravings for sweet foods as a form of emotional compensation

(Nucci et al., 2022) or avoiding them altogether for health reasons, further complicating their emotional relationship with these foods during chemotherapy.

However, the greater preference for bitter foods observed in some patients, although inconsistent with most previous findings, may reflect a compensatory drive toward different taste sensations rather than a true appreciation for bitterness.

Preference changes were observed for Herbs and Spices among patients with general taste alterations/parageusia/increase in taste perception without a specific direction. These variations may reflect coping strategies to manage altered flavor perception, for example, some patients may have increased the use of herbs and spices to enhance taste, while others preferred milder flavors to avoid sensations perceived as unpleasant or distorted. This latter interpretation is supported by our analysis of preference scores, which showed that patients who reported general taste alterations/parageusia/increase in taste perception during therapy (T1-T6) showed a preference for significantly less intense flavors.

General taste alterations/parageusia/increase in taste perception were associated with significant changes in preferences on the Odor dimension in the last stages of treatment. In these cases, more intense odors elicited greater aversion, suggesting a preference for milder odors. Although our analyses did not directly assess whether patients with these alterations actually had an increased perception of odors, self-report data suggested a trend toward increased odor perception in some patients, and this result can be explained by the literature reports on cancer patients and by general trends in self-report data, which indicate increased sensitivity and aversion to specific odors during therapy, particularly cooking odors (Coa et al., 2015; van den Brink et al., 2022). However, these changes in preferences and the development of aversion were not accompanied by a worsening of emotional responses. One possible explanation is that, once aversive

odors are identified and easily avoided, the emotional impact during actual exposure diminishes. Therefore, the change in preference may represent an effective coping mechanism, capable of mitigating the negative emotional response, even if the underlying aversion persists. Moreover, this may reflect both psychological adaptation and relief associated with the approaching conclusion of therapy, which could mitigate the negative emotional impact of ongoing sensory disturbance.

Three months after the end of the treatment the changes in preference observed during therapy had returned to baseline levels. This recovery may reflect the restoration of chemosensory function after cessation of cytotoxic treatment.

The analysis of preferred and most disliked foods of patients with general taste alterations focused on the time at which the greatest preference changes were observed (T4) in comparison with the baseline. For example, at baseline, preferences strongly reflected typical Italian eating habits (e.g., pasta, pizza, vegetables), while after four chemotherapy cycles, other foods such as ice cream, fruit, and cheese also emerged as favorites, most likely due to their soft texture and cool temperature, which are generally preferred by patients as reported in the literature (de Vries et al. 2016; Kim et al. 2020). Conversely, most disliked foods varied over time, from fish frequently mentioned at T0 to meat already mentioned at T0 but mentioned more frequently (and specifically red meat) at T4. Other products such as coffee, legumes, desserts, bitter vegetables, and wine were also mentioned at T4. This qualitative approach therefore provided complementary insights, highlighting the specific most frequently associated by patients with pleasure or discomfort, information that would not have emerged from the FP&EQ. These findings are consistent with previous research showing that patients undergoing chemotherapy often develop a preference for soft and bland dishes (e.g., porridge, soft bread, hard-boiled eggs, vegetable juices, blanched

vegetables, berries, yogurt), avoiding fried, oily, strong-flavored, or spicy foods (Kim et al., 2020; de Vries et al., 2016; de Vries, Winkels et al., 2018). At the same time, a subgroup of patients showed the opposite tendency, reporting a need for stronger flavors, often satisfied through the use of condiments (sugar, spices, salt) or selecting foods with distinctive flavor profiles, such as umami-rich products (soups, aged cheeses, sausages) or salty snacks (crisps, peanuts, crackers) (de Vries et al., 2016; Sørensen et al., 2012).

Psycho-attitudinal traits. Overall, the analysis of food involvement revealed a significant time effect on study population, suggesting that engagement in food-related activities was not entirely stable during chemotherapy. However, post hoc comparisons did not identify statistically significant differences between specific time points, indicating that variations were subtle and not consistently detectable across treatment phases, with the exception of the significant difference found at T6, during which patients with general taste alterations/parageusia/increase in taste perception showed lower food involvement than patients without such alterations. This may be partly explained by the coping strategies actively adopted by patients to preserve their eating experience, despite the presence of chemosensory disturbances. At the same time, the overall trend indicates a possible transient reduction in food involvement during therapy, which is consistent with previous evidence showing that patients who self-reported more intense chemosensory disturbances also reported reduced enjoyment of food (Hutton et al., 2007). Overall, these findings suggest that, although coping strategies can help patients maintain a certain level of engagement, chemosensory alterations can still undermine food-related interest and pleasure, underscoring the importance of monitoring not only sensory perception but also the broader psychological and behavioral dimensions of eating during treatment. Even non-dietary coping strategies, such as using mouthwashes (e.g., baking soda), frequent

toothbrushing, and eating with plastic utensils were reported by patients as effective, but temporary, strategies of alleviating unpleasant oral sensations and taste distortions. These approaches have been previously described in the literature, often as a direct result of clinical counseling in an outpatient setting (Speck et al., 2013; Kinjo et al., 2021), in which patients are advised to adopt simple oral care routines or modify eating utensils (Hong et al., 2009; Sherry 2002) to minimize metallic or bitter sensations.

Quality of life. Comparison between patients with and without general taste alterations/parageusia/increase in taste perception showed that the presence of these alterations was associated with a lower global health/quality of life, which remained consistently worse in patients with these alterations throughout all phases of therapy. Patients with these alterations showed higher scores for loss of appetite, nausea, vomiting, and fatigue, and lower social functioning scores compared to those without alterations. This latter finding is consistent with previous studies reporting that patients experiencing taste alterations during chemotherapy also report limitations in social activities such as going out to eat with friends, sharing meals with family, or shopping (Bernhardson et al., 2007; Wickham et al., 1999). Furthermore, depression and other emotional factors, along with reduced physical functioning, which we found to be significantly worse in these patients, can further compromise participation in these activities, amplifying the overall negative impact on quality of life.

Phantogeusia

Table 44 shows the summary of impact of self-reported phantogeusia on food experience.

Table 44 - Summary of the impact of self-reported phantogeusia (CiTAS) on food experience during treatment. The first row reports the percentage of patients who self-reported phantogeusia in each time point. In the subsequent rows percentages reported in brackets refer only to the proportion of patients with phantogeusia who experienced a significant change in the corresponding variable. For the section "Changes in liking for basic tastes", symbols (-) and (+) indicate a reported liking "less" or "more" than usual, respectively. For the sections "Food preferences and "Eating habits," symbols (-) and (+) indicate the direction of the statistically significant correlation (negative or positive) between the CiTAS score and the corresponding variable (preference score and use/liking). For the "Changes in emotional responses" percentages and arrows indicate the increase or decrease in negative emotions elicited by chosen options over time compared to baseline.

		T0	T1	T2	T4	T6	T8	TF
Phantogeusia	Percentage of study population with phantogeusia	2.8%	44.8%	59.1%	61.4%	57.1%	66.7%	17.0%
	Changes in liking for basic tastes (-) less than usual; (+) more than usual (% of patients with phantogeusia who reported changes in liking)		(-) sweet (78.6%) (-) salty (75.0%) (-) sour (83.3%) (-) bitter (71.4%) (+) salty (72.7%) (+) sour (60.0%)	(-) sweet (72.7%) (-) salty (83.3%) (-) sour (100.0%) (-) bitter (85.7%) (+) sweet (60.0%) (+) salty (58.3%)	(-) sweet (90.5%) (-) salty (80.0%) (-) sour (92.3%) (-) bitter (91.3%) (+) sweet (87.7%) (+) salty (72.7%) (+) sour (100.0%)	(-) sweet (80.0%) (-) salty (66.7%) (-) sour (88.9%) (-) bitter (92.9%) (+) sweet (71.4%) (+) salty (87.5%) (+) sour (100.0%)	(-) sweet (91.7%) (-) salty (83.3%) (-) sour (75.0%) (-) bitter (80.0%) (+) sweet (66.7%) (+) salty (85.7%) (+) sour (100.0%)	(+) salty (80.0%)
	Food preferences (+/- correlations)			(-) Flavor (-) Texture	(-) Flavor (-) Texture	(-) Texture	(-) Flavor	
	Changes in food preferences			Sweet vs Bitter	Flavor Texture Sweet vs Sour	More intense odor aversion Sweet vs Sour	Sweet vs Bitter	
	Changes in emotional responses -		Texture 11.5->23.1% Sweet vs Bitter 11.5->22.3%	Texture 14.4->21.5% Sweet vs	Sweet vs Bitter 9.1->20.0%	Sweet vs Bitter 8.3->21.7%		

% of negative emotions elicited by chosen options		Bitter 9.7–>18.5%		
Eating habits (+/– correlations)		(–) chili pepper liking (–) spices liking	(–) chili pepper liking (–) lemon liking	(–) black pepper use

The percentage of patients reporting phantogeusia through the CiTAS was 44.8% (T1) – 66.7% (T8). The significant increase in mean scores for this dimension after the first cycle suggests that even phantogeusia appears early in treatment and worsen over time affecting more than a half of population. People affected by this alteration also reported this discomfort during qualitative interviews. Similar to our findings, several studies have documented the frequent occurrence of phantom sensations, such as a “metallic taste”, “chemical taste”, “drug taste”, “blood taste”, “bitter taste” in the mouth in absence of an external stimulus (Epstein & Barasch, 2010; Jensen et al., 2008). Among these sensations, metallic taste was one of the most frequently reported complaints by patients altered by phantogeusia according to Ijpma et al. (2015). However, it is still unclear whether it is a true phantom taste or whether external stimuli are involved. In our study, patients often described these sensations as occurring without an identifiable cause, although some linked them to specific triggers such as drinking water or wine. Hurrell (2002), reported that metallic sensations can arise from the interaction of certain foods or beverages with the oral environment, or as a result of inflammation/mucositis. These mechanisms could therefore contribute to sensations that patients perceive as “phantom,” suggesting that, in some cases, such experiences may be partially triggered or amplified by changes in oral physiology rather than occurring entirely in the absence of stimuli.

Liking for basic tastes. When examining hedonic responses to basic tastes among patients reporting phantogeusia, both "less" and "more than usual" responses to

sweetness were more frequently reported by these patients than by those without this alteration. This dual pattern may reflect the heterogeneous nature of phantom taste experiences: for some patients, sweet taste may provide relief or comfort, serving as a coping strategy to counteract unpleasant or metallic phantom sensations (Ijpma et al., 2015), while for others, sweetness may become aversive when already perceived in the mouth as a phantom taste (Rhodes et al., 1994).

A similar pattern has been observed for salty taste. Saltiness may exacerbate phantogeusia in some patients, while for others, salty or strong flavors may temporarily mask or neutralize unpleasant tastes (Boltong et al., 2012). However, the negative correlation found between phantogeusia and Flavor preference score of FP&EQ, suggest that many patients prefer less intense foods with lower liking for salty taste. Additionally, significant negative correlations were observed between phantogeusia scores and the liking of spicy foods and spices at the early stages of the treatment, as well as with the use of pepper at the final time point (TF).

Sour and bitter tastes showed different patterns. Sour taste elicited both a reduction and, in some cases, an increase in liking among patients with phantogeusia. Our qualitative data indicated that while some patients reported the perception of a sour taste or aftertaste, which may lead to aversive responses, others reported the use of sour condiments (such as lemon) as a coping strategy to counteract unpleasant tastes (Ijpma et al., 2015). However, our analyses showed a negative correlation between phantogeusia and liking of foods seasoned with lemon, suggesting that, although some patients use sour condiments as coping strategies, their actual enjoyment of these foods may decrease as phantogeusia intensifies.

Bitter taste, on the other hand, emerged as particularly problematic for patients with phantogeusia. Across all time points, a significantly higher percentage of

patients with phantogeusia reported reduced liking for bitter taste compared to those without phantogeusia. This finding is consistent with reports that bitter taste often overlaps with or intensifies the unpleasant metallic or chemical components of phantom taste, leading to strong aversive responses and further impairing the hedonic experience of food (Boltong & Keast, 2012; Trant et al., 1982).

Food preferences and emotions. No changes in preference for patients reporting phantogeusia were observed after the first cycle; however, the emotional and hedonic relationship with food was strongly affected across several sensory dimensions.

In the Sweet vs. Bitter dimension, emotions associated with food steadily worsened during treatment, confirming that this is the dimension most affected by qualitative changes. Changes in preferences were also observed, although without a clear direction, reflecting the instability of hedonic responses to these tastes.

The presence of phantom or metallic sensations can cause sweet and bitter foods to be perceived as excessively strong or unpleasant, leading to fluctuating reactions, sometimes resulting in an aversion to bitter products such as coffee and tea consistently with Trant et al. (1982), and other times in a preference for sweeter foods such as desserts or fruit as compensatory strategies (Speck et al., 2013; Drareni et al., 2023). Alterations also affected the Sweet vs. Sour dimension, particularly in the middle stages of therapy. Again, the changes in preference likely reflected coping strategies to manage phantom taste perception, such as adding lemon to water, as reported during qualitative interviews.

Regarding the Texture dimension, emotional deterioration was observed early in treatment, even in the absence of significant changes in preferences. This suggests that phantogeusia may increase sensitivity to oral discomfort, amplifying negative affective reactions to specific textures.

Finally, within the Odor dimension, patients with phantogeusia tended to avoid strong food odors in the later stages of treatment, preferring more milder odors. This finding suggests that olfactory stimuli may interact with the unpleasant phantom sensations experienced by these patients, amplifying their overall sensory discomfort. The resulting change in preferences could therefore be interpreted as an attempt to reduce sensory overload and mitigate the fatigue caused by the constant experience of phantom taste.

Three months after the end of chemotherapy, our analyses indicate that most changes in preferences were reversed, with patients generally returning to their pretreatment favorite foods. The only exception was observed in patients with phantogeusia at T8 and for whom the preference changes that occurred at that time point persisted at follow-up. The persistence of altered preferences may be related to a conditioned taste aversion (Riley and Tuck, 1985). Once the ingestion of a normally acceptable food item is associated with illness the aversion may persist even after the disorder has resolved, leading to long-term avoidance. Furthermore, failure to re-exposure to previously avoided foods may reinforce these altered preferences.

Similarly, the presence of a phantom taste in the mouth leads patients to adopt several unhealthy coping strategies already reported in previous studies (Speck et al., 2013; Risso et al., 2020), including the consumption of energy-dense comfort foods (Vance et al., 2017) such as candy, sweets, chewing gum, crackers, and yogurt, which may lead to an increase in overall food intake and weight gain. Conversely, qualitative interviews also revealed an awareness among some patients of the importance of maintaining health and avoiding unhealthy coping strategies, such as increasing salt intake or eating sugary foods, adopting a healthier lifestyle that could potentially improve treatment effectiveness and prevent relapses (Pedersini et al., 2021; Salminen et al., 2004), particularly by reducing meat

consumption (especially red meat), which is reported as one of the most aversive foods in the study population probably for its metallic taste.

Quality of life. Although phantogeusia was not observed to lead to significantly lower global health/quality of life scores compared to patients without this disorder, it was associated with lower scores in emotional and social functioning. One hypothesis is that the persistent perception of a phantom taste may negatively affect mood, generating frustration or distress, which, in turn, can interfere with social interactions and overall well-being. Furthermore, EORTC QLQ-C30 symptom scores were generally worse in patients with phantogeusia, suggesting that this disorder not only impacts the eating experience but is also closely related to other treatment side effects, thus contributing to a more challenging experience.

Alteration in odor perception

Given the close integration of taste and smell in creating the overall flavor experience, chemosensory assessment in oncology should also consider olfactory function, even though this is particularly under-investigated (Bernhardson et al., 2009). Results on olfactory function indicate that patients did not perceive any alterations in their ability to perceive odors during therapy, as demonstrated by stable mean GCCR scores across all time points. This suggests that, unlike taste function, olfactory perception remained largely preserved. However, from individual responses to the GCCR CATA and qualitative interviews, olfactory disorders of various nature emerged. Through GCCR open-ended responses, several patients reported increased aversion to specific odors, particularly cooking aromas, smoke, perfumes, body odors, and smells related to the hospital environment. These findings indicate that, even in the absence of self-reported impairment in olfactory ability, patients experienced qualitative changes in odor

perception, often describing them as more intense or unpleasant. These experiences are consistent with previous studies describing increased sensitivity and aversion to odors during chemotherapy (Bernhardson et al. 2009; Coa et al. 2015; de Vries et al. 2016). Interestingly, some participants compared this heightened perception to that experienced during pregnancy (Nordin et al., 2004, 2005; Cameron, 2007; 2014). Moreover, some patients during interviews described certain odors, perceived as excessively intense, as interfering with daily activities such as food preparation. Consistent with previous studies (de Vries et al., 2016; Speck et al., 2013; Bernhardson et al., 2009), these aversions led patients not only to avoid cooking, but also to avoid eating in certain contexts, such as closed spaces and kitchens. Consequently, these behaviors resulted in reduced participation in social occasions and a withdrawal from domestic roles (e.g., partners taking on grocery shopping and cooking) as well as social interactions (e.g., not eating out or inviting friends over for dinner), as previously reported in the literature (Bernhardson et al., 2007, 2009; de Vries et al., 2016; Gamper et al., 2012).

However, in line with Epstein et al. 2002, decreased perception of odors is mentioned by a small percentage of patients, although there are several studies reporting that patients during chemotherapy experience a decrease in odor perception (Postma et al., 2020; Yakirevitch et al., 2005) while in Rhodes et al. (1994) many patients describe the changes in smell as unpleasant or increased awareness or sensitivity, with no patients reporting a decrease.

Alteration in chemesthetic sensations

The increased perception of chemesthetic sensations such as pungency, coolness and tingling self-reported by approximately up to 20-30% of patients in the present study, highlights a sensory dimension that remains under-investigated in

oncology populations. While cancer-related chemosensory research has largely focused on taste and smell dysfunctions, emerging evidence suggests that sensory alterations in cancer patients extend to somatosensory perception and are linked to eating difficulties and oral symptoms, underscoring the relevance of chemesthetic sensations for food experience (Riantiningtyas, 2024).

The observed pattern in cycles, with transient hypersensitivity during the intermediate phases of therapy and progressive normalization by T8 and at follow-up, suggests that chemotherapeutic agents may temporarily alter trigeminal sensitivity, leading to variable responses to thermal and tactile stimuli. Interestingly, a similar phenomenon has been reported in other clinical settings. Grayson et al. (2019) demonstrated that oral squamous cell carcinoma can increase trigeminal nerve sensitivity, leading to altered oral sensations.

5.3 The role of individual differences in personality traits and taste responsiveness on alterations, preferences, and emotions during treatment

Psychological traits and taste responsiveness can influence not only chemosensory perception, but also food preferences and emotions during chemotherapy. However, the results revealed that these effects were mostly limited and transient, suggesting that these traits modulate but are not a determining factor in patients' sensory and hedonic experiences during chemotherapy.

Food neophobia. Food neophobia (Table 45) showed only sporadic associations with chemosensory perception during treatment, suggesting a limited role. Patients with lower levels of food neophobia tended to show more frequent changes in food preferences as treatment progressed, particularly for sensory dimensions such as Herbs and spices, and Odors, an expected result, given that these individuals are generally more likely to try new foods. In contrast, individuals with higher levels of

food neophobia maintained more stable preferences but showed an early and persistent worsening of emotional responses to food, especially in Texture, Herbs and spices, and Sweet vs. Bitter dimensions. This suggests that neophobic patients, while avoiding significant changes in preferences, may experience stronger negative emotions towards foods when faced with altered or unfamiliar sensory experiences, reflecting increased vigilance or anxiety regarding sensory alterations.

Table 45 Summary of the effect of food neophobia on perceived intensity of aqueous solutions, self-reported chemosensory alterations, changes in food preferences, and changes in emotional responses to foods. Symbols (-) and (+) indicate the direction of the statistically significant correlation (negative or positive) between the food neophobia score and the corresponding variable (perceived intensity of aqueous solutions and self-reported alterations with CiTAS). For the sections "Changes in food preferences" and "Changes in emotional responses," patients were classified into low or high food neophobia groups based on the median score. For the emotional responses percentages and arrows indicate the increase or decrease in negative emotions elicited by chosen options over time compared to baseline.

		T0	T1	T2	T4	T6	T8
Food Neophobia (FN)	Perceived intensity of aqueous solutions (+/- correlations)		(+) sour low concentration		(-) bitter low concentration	(+) bitter high concentration	(-) salty high concentration
	Self-reported alterations with CiTAS (+/- correlations)			(-) phantogeusia			(-) decline in basic tastes
	Changes in food preferences (classification based on median value)					(Low FN) Herbs & Spices	(Low FN) Odor aversions
	Changes in emotional responses (classification based on median value) - % of negative emotions elicited by chosen options		(High FN) Texture 14.3->25% Herbs & Spices 18.6->27.1%	(High FN) Herbs & Spices 17.2->25.5%	(High FN) Texture 11.5->23.1% Herbs & Spices 15.4->24.6% Sweet vs Bitter 9.2->16.9%		

Sensitivity to disgust. Disgust sensitivity (Table 46) appears to play a more important role in shaping emotional rather than sensory responses. Patients with high disgust sensitivity showed greater reactivity to gustatory and chemesthetic stimuli at baseline and higher decline, phantogeusia and discomfort; furthermore, they reported more changes in food preferences and more frequent and intense negative emotions elicited by food during treatment. Emotional deterioration was evident early on and persisted throughout the treatment period, particularly for dimensions such as Texture, Flavor, and Sweet vs. Bitter. These results indicate that increased disgust sensitivity amplifies negative affective reactions to food, especially when perception is distorted or unpleasant sensations occur. In contrast, patients with lower disgust sensitivity generally maintained more stable emotional experiences.

Overall, the lack of stable positive associations between psychological traits and self-reported chemosensory alterations during treatment only partially supports our original hypothesis (Spinelli, Mini, et al., 2021) that higher levels of neophobia or disgust may be more likely to report alterations, attributable to their greater anxiety and generalized hypervigilance, which may improve their ability to detect even subtle changes in sensory perception and to recognize immediate changes in perception (Spinelli, Cunningham, et al., 2021).

Table 46 Summary of the effect of sensitivity to disgust on perceived intensity of aqueous solutions, self-reported chemosensory alterations, changes in food preferences, and changes in emotional responses to foods. Symbols (-) and (+) indicate the direction of the statistically significant correlation (negative or positive) between the sensitivity to disgust score and the corresponding variable (perceived intensity of aqueous solutions and self-reported alterations with CiTAS). For the sections "Changes in food preferences" and "Changes in emotional responses," patients were classified into low or high sensitivity to disgust groups based on the median score. For the emotional responses percentages and arrows indicate the increase or decrease in negative emotions elicited by chosen options over time compared to baseline.

		T0	T1	T2	T4	T6	T8
Sensitivity to disgust (SD)	Perceived intensity of aqueous solutions (+/- correlations)	(+) salty low/high concentration (+) bitter low/high concentration (+) pungent low concentration (+) sweet high concentration	(+) salty high concentration	(+) sour low concentration (+) salty high concentration	(+) pungent high concentration	(+) bitter high concentration	
	Self-reported alterations (+/- correlations)	(-) phantogeusia	(+) phantogeusia (+) discomfort			(+) general taste alterations/parageusia/increase (+)discomfort	
	Changes in food preferences (classification based on median value)		(High SD) Flavor			(High SD) Flavor	
	Changes in emotional responses (classification based on median value) - % of negative emotions elicited by chosen options		(High SD) Flavor 5.0->18.3% Texture 15.4->24.6% Sweet vs Bitter 10.0->20.8%	(High SD) Texture 11.3->18.8%	(High SD) Flavor 13.3->21.4% Texture 12.1->23.6% Sweet vs Bitter 7.9->17.1%		

PROP responsiveness. In our study, responsiveness of PROP bitterness remained stable throughout treatment, confirming its reliability as an indicator of oral acuity not impacted by alterations. This measure provides a useful framework for

identifying patients with different baseline sensory profiles that may influence their perceptual experience during chemotherapy.

Correlations between PROP responsiveness (Table 47) and perceived intensity of aqueous solutions were significant at some time points before and during treatment. At baseline, perceived PROP intensity was positively correlated with the perceived intensity of salty, bitter, and pungent stimuli, consistent with previous evidence that high PROP responsiveness reflects broader gustatory and trigeminal reactivity (Dinnella et al., 2018; Fischer et al., 2014; Hayes et al., 2008; Nolden et al., 2020; Piochi et al., 2021; Prescott et al., 2001; Robino et al., 2022; Bartoshuk et al., 1993; Spinelli et al., 2018; Karrer & Bartoshuk, 1991; Prescott & Swain-Campbell, 2000).

During treatment, the strength and direction of the correlations with perceived intensity of aqueous solutions varied slightly but remained significant for specific tastes. The relationship between PROP responsiveness and the perception of pungent at higher concentration was the strongest, remaining significant at nearly all time points. This consistent association suggests that trigeminal sensitivity, unlike taste perception, is relatively resistant to the effects of chemotherapy. Positive associations occasionally reappeared for salty and sweet tastes at different stages of treatment, indicating partial recovery phases followed by temporary declines. Overall, these findings suggest that PROP responsiveness continues to reflect individual sensory acuity throughout therapy, while chemotherapy may cause transient and reversible fluctuations in specific taste perceptions.

After the end of chemotherapy, correlations with pungent, sweet, and salty perception reemerged, suggesting that general chemosensory integrity is partially restored once the acute effects of chemotherapy subside.

Moreover, most positive correlations between perceived PROP intensity and self-reported chemosensory changes were positive but weak, suggesting that greater

PROP responsiveness was generally associated with a greater tendency to report taste disturbances, such as phantogeusia and discomfort. Although these associations were not always systematic across time points, they support the initial hypothesis that patients with greater taste sensitivity at baseline may experience chemosensory changes more intensely during treatment. Comparisons between patients classified based on high and low PROP responsiveness confirmed that high PROP responders were more likely to report chemosensory alterations and oral discomfort during treatment suggesting that PROP status may be an index to predict the risk for alterations.

Regarding the food experience, PROP responsiveness appears to occasionally influence the affective dimension of food. Patients with high PROP responsiveness tended to occasionally report negative emotional responses to favorite foods and changes in preference during certain phases of chemotherapy. Their greater acuity, combined with a higher incidence of chemosensory alterations, may have led to frustration or aversion toward previously enjoyed foods. In contrast, patients with low PROP reactivity generally maintained more stable emotions and preferences, suggesting greater tolerance for sensory fluctuations during treatment.

Table 47 Summary of the effect of PROP responsiveness on perceived intensity of aqueous solutions, self-reported chemosensory alterations, changes in food preferences, and changes in emotional responses to foods. Symbols (-) and (+) indicate the direction of the statistically significant correlation (negative or positive) between the perceived intensity of PROP bitterness and the corresponding variable (perceived intensity of aqueous solutions and self-reported alterations with CiTAS). For the sections "Changes in food preferences" and "Changes in emotional responses," patients were classified into low or high PROP based on the median value of perceived intensity of PROP bitterness at baseline. For the emotional responses percentages and arrows indicate the increase or decrease in negative emotions elicited by chosen options over time compared to baseline.

		T0	T1	T2	T4	T6	T8
PROP responsiveness	Perceived intensity of aqueous solutions (+/- correlations)	(+) salty low concentration (+) bitter low concentration (+) pungent low/high concentration	(+) salty high concentration (+) pungent high concentration	(+) pungent high concentration	(+) pungent high concentration	(-) sour low concentration	(+) pungent low/high concentration (+) sweet high concentration (+) salty high concentration
	Self-reported alterations (+/- correlations)			(+) phantogeusia	(+) general taste alterations/parageusia/increase		(+) discomfort
	Changes in food preferences (classification based on median value)					(High PROP) Herbs & Spices	(High PROP) Odor aversion
	Changes in emotional responses (classification based on median value) - % of negative emotions elicited by chosen options		(High PROP) Texture 9.2->16.9%		(High PROP) Sweet vs Bitter 12.3->20.6%		(High PROP) Flavor 9.1->27.3%

5.4 Impact on body composition

Often in the presence of chemosensory alterations patients reported during interviews that they had avoided eating or had eaten more with consequent potential alterations in body composition, as widely documented in the literature

(Turcott et al., 2016; Zabernigg et al., 2010; Boltong et al., 2012; 2014; McGreevy et al., 2014; Vance et al., 2017).

However, in our cohort, both patients who reported chemosensory alterations through CiTAS and those who did not report alterations showed no significant changes in body composition during treatment, neither in terms of weight and BMI nor fat and lean mass, a finding consistent with Pedersini et al. (2022) and Kaizu et al. (2021), who reported no clear association between taste alterations and weight changes. However, other studies have described notably different trajectories. For example, Carlucci Palazzo et al. (2019) observed an increase in weight and BMI during chemotherapy for breast cancer, while Ijpma et al. (2017), focusing on a homogeneous group of patients with testicular cancer, reported a selective deterioration in body composition with an increase in fat mass and a decrease in lean mass. These discrepancies highlight that chemosensory alterations do not inevitably lead to a loss of appetite and therefore weight loss, as generally reported in studies (Halyard, 2009; Ryan et al., 2019; Turcott et al., 2016); rather, their impact appears to depend on multiple factors, including the type of cancer - our sample was mainly composed of breast cancer patients, a population in which the risk of weight loss is generally lower (Vance et al., 2011) , the treatment regimen, and, most importantly, the coping behaviors adopted by patients in response to sensory changes. Indeed, qualitative interviews revealed substantial inter-individual variability, even when similar sensory changes were observed, some patients compensated by increasing their energy intake (e.g., adding more seasonings or experimenting with new foods to enhance flavor perception), while others reduced or completely avoided certain foods, making it difficult to identify a consistent trend. Methodological differences further contribute to the heterogeneity of results reported in the literature, which includes the criteria used to assess sensory alterations, the tools used to measure body

composition (BIA, DEXA, CT vs. simple weight/BMI), and the timing of measurements. In our study, the latter could not be standardized with respect to time of day, as measurements were performed based on patient availability, which may have introduced variability related to hydration status or food intake. This is particularly relevant for hydration-sensitive parameters such as fat mass and lean body mass (Saunders et al., 1998; Algül & Özçelik 2022). However, from a clinical perspective, relying solely on weight or BMI may fail to detect "hidden malnutrition" or sarcopenic obesity, conditions that can occur even in the absence of weight change (Brown et al., 2018; Strulov Shachar & Williams, 2017; Lee et al., 2022). Therefore, regular monitoring of body composition, combined with systematic assessment of eating behaviors and coping strategies, is essential in cancer patients to enable early identification and timely management of unfavorable nutritional status. Although the heterogeneity of our sample may have prevented us from identifying associations that might be more evident in homogeneous populations, the present study nonetheless advances the field by assessing not only weight and BMI, but also body composition, thus providing a more comprehensive basis for patient management and future investigations.

Finally, these findings highlight that the lack of significant changes in body composition does not indicate the absence of nutritional risk. Rather, they underscore the need for personalized sensory and nutritional recommendations that take into account individual coping strategies, emotional responses to food, and daily eating contexts. Personalized guidance can help support adaptive compensations while preventing unhealthy behaviors that could negatively impact nutritional status and long-term quality of life.

5.5 Sensory nutritional interventions and tailor-made strategies

Although no significant changes in body composition were observed in our cohort, these findings should not diminish the importance of developing personalized nutritional and sensory recommendations for patients undergoing chemotherapy. Even in the absence of measurable changes in weight or body composition, chemosensory alterations can substantially impact food intake, enjoyment of food, and overall quality of life, underscoring the need for personalized nutritional support and evidence-based counseling strategies.

Management of chemosensory alterations should not be limited to clinical assessment but should also include practical dietary guidance. Despite their high prevalence and significant impact on patients' quality of life, clear nutritional recommendations for managing these alterations remain scarce and often inconsistent across studies. New innovative food products for cancer patients must be designed, considering nutritional, sensory and emotional needs. The final aims should be to alleviate symptoms, prevent malnutrition, and promote pleasure of eating (Tueros & Uriarte et al., 2018).

The ideal snack analysis did not yield clearly distinct prototypes for each type of alteration defined by the CiTAS; however, differences emerged between groups and across time points. For most patients, the ideal snack both before and after the second cycle of therapy was found to be salty. Tasty and crunchy remained prevalent attributes for this salty snack across all groups of alteration. These findings are partially consistent with those of Coa et al. (2015), who reported that crunchy foods were among the most preferred foods by cancer patients, although they did not rank among the top choices. In contrast, salty foods were identified in that study among the most frequently avoided categories. More recent evidence

from Adamczyk et al. (2024), however, suggests that food products designed for cancer patients suffering from taste and smell alterations should be tastier.

Conversely, for the percentage of patients who preferred something sweet as their ideal snack, soft textures were the most desirable among patients with alterations during treatment (e.g., increased preference for soft textures in cases of general taste alterations and phantogeusia), while they remained the least selected as must have for savory snacks. Furthermore, the juicy texture of sweet snacks emerged as a preferred attribute at T2 in the groups with alterations, despite being below the 20% threshold at baseline. Conversely, hard textures gained prominence in the salty must have at T2 but were conversely selected among the must not have for sweet snacks.

Pasty and liquid textures were selected as must not have both for salty and sweet snacks in all groups of alteration. This preference pattern is likely linked to the presence of discomfort and treatment-related side effects such as nausea and mucositis, reported by over 85% of patients after the second chemotherapy cycle. As noted by Tan et al. (2020), these same textures (pasty, and liquid) were identified as among the most likely to trigger hyperemesis, underscoring the importance of texture optimization in product design for this population.

Overall, our results indicate that, although the ideal snack appears similar across the different types of alteration, patients' sensory preferences are not totally comparable between groups. Although slight, the differences based on the type of alteration highlight that specific texture preferences may vary and should therefore be considered when designing ideal snacks.

Despite efforts to identify common patterns and profiles of alterations, the findings of this thesis demonstrate that each individual presents a unique combination of personality traits, food preferences, food-evoked emotions, eating habits, clinical conditions, and nutritional needs. Furthermore, patients may present with one or

more types of chemosensory alterations and related conditions, which further shape their sensory and nutritional needs. From this perspective, the current findings suggest that patient support could benefit from identifying broader individual profiles, beyond chemosensory alterations alone. As also emerged from qualitative interviews, patients experiencing similar chemosensory alterations may differ substantially in their emotional responses to food, coping strategies, and motivation to eat, resulting in distinct eating challenges and support needs. Integrating emotional and psychological dimensions into patient profiling can therefore help better address individual vulnerabilities and guide more effective and personalized interventions.

In this context, the current findings suggest that certain individual profiles may be associated with distinct vulnerabilities during treatment. For example, patients characterized by high food neophobia may be at greater risk of experiencing emotional worsening in response to chemosensory alterations, despite showing no changes in food preferences. In these patients, eating difficulties appear to be driven less by changes in food choice and more by negative emotional responses to altered or unfamiliar sensory experiences. This profile may therefore benefit from support strategies that prioritize emotional reassurance, gradual exposure to sensory adaptations, interventions aimed at reducing anxiety and avoidance, and sensory-based strategies that focus on emotionally accepting but nutritionally appropriate foods. Conversely, patients with low food neophobia, who demonstrated greater flexibility in modifying their food preferences, may be more receptive to exploratory sensory-nutritional strategies, such as the introduction of new flavors, seasonings, or alternative foods designed to compensate for chemosensory changes. Similarly, patients with high disgust sensitivity may represent a subgroup for whom emotional responses to food are a primary obstacle to adequate intake and enjoyment. In these cases sensory-nutritional support

strategies that take into account emotional responses to specific foods may be particularly important. Finally, individuals with high PROP responsiveness may represent a more vulnerable subgroup due to their heightened perception of certain stimuli and their tendency to exhibit increased negative emotional responses to specific food categories during treatment. This suggests the need for careful modulation of intensity of flavor, texture, and chemosensory stimulation when designing sensory-based recommendations for these patients.

At the same time, the high degree of interindividual variability observed in this thesis highlights the need for a structured starting point to support clinical practice. Sensory and nutritional recommendations represent an evidence-based foundation, as chemosensory alterations are among the most common and widely shared treatment-related symptoms and can be addressed through standardized strategies. It is therefore essential to establish a set of evidence-based recommendations that address the most common alterations and use them as a framework for constructing an individual sensory-nutritional profile. Such a profile would allow for the formulation of highly personalized dietary recommendations and recipes, designed to compensate for specific alterations through targeted sensory interaction strategies, while ensuring nutritional requirements are met. In contrast, emotional responses to food and individual coping strategies are highly personal and context-dependent, making them better targets for subsequent stages of individual customization rather than for developing general recommendations.

The proposed sensory recommendations were based on odor-taste integration mechanisms and strategies aimed at improving palatability in the presence of chemosensory alterations. These strategies were based on consolidated sensory evidence demonstrating that congruent aromas can enhance specific taste qualities, while the use of herbs, spices, and stimuli can reduce unpleasant

sensations such as metallic or bitter taste. In this context, evidence-based sensory-nutritional recommendations can serve as the basis for building an individual sensory-nutritional profile. This profile could then be further refined by integrating emotional, psychological, and behavioral dimensions. However, in the present study, it was not possible to evaluate the effectiveness of the proposed recommendations, as no patient feedback was collected and no snack prototype was developed or tested. Therefore, these results should be considered preliminary and exploratory. Future research should aim to experimentally test the efficacy and acceptability of sensory-based formulations and personalized dietary advice, ideally integrating patient feedback and using co-creation approaches. Such investigations would provide validation of these strategies and could lead to the development of tailored food products for cancer patients with chemosensory alterations and associated side effects.

Beyond this initial phase, the findings of this thesis suggest the need to consider further levels of personalization. Taste responsiveness could represent a stable characteristic that could guide the personalization of sensory strategies. Furthermore, integrating emotional responses evoked by food could allow for a more comprehensive understanding of individual eating-related difficulties. Considering both chemosensory perception and emotional responses could therefore support the development of more targeted and patient-centered interventions that go beyond general recommendations towards truly personalized strategies. Moreover, in the personalized phase, additional support strategies, such as mindful eating approaches can complement interventions, addressing emotional distress, reducing barriers to eating, and supporting patients' enjoyment of eating. Mindful eating has been described as a process of intentionally attending to the experience of eating in a moment-by-moment, nonjudgmental, and nonreactive manner (Kabat-Zinn, 2003). By promoting curiosity and observational skills,

mindful eating encourages individuals to notice subtle sensory changes and internal responses associated with food consumption.

In the context of cancer treatment, mindful eating may be particularly relevant for patients with chemosensory alterations, as it promotes a perception of flavor, going beyond simple taste. Flavor perception emerges from the integration of taste, smell, texture, and temperature, and while taste function may be impaired, other sensory modalities often remain partially preserved (Meyers & Ott, 2008). By guiding patients to consciously pay attention to these aspects, mindful eating could help them rediscover sensory cues that are still accessible, potentially improving the overall eating experience despite sensory deficits.

Practical adaptations can further support food intake and enjoyment in patients experiencing fatigue, nausea, mobility difficulties, or discomfort during meals.

In this context, reducing the physical, sensory and emotional load associated with food can represent an important complementary strategy.

Among these adaptations, finger food, defined as food presented in a form that can be easily picked up by hand and brought to the mouth without the use of cutlery, has been suggested as a low-cost, low-risk strategy in clinical nutrition (Volkert et al., 2019), as well as being considered easier to eat because it reduces the physical and cognitive effort associated with consuming a meal, eliminating the need to manipulate cutlery (Crawley & Hocking, 2011). This may be particularly relevant for patients who experience fatigue, nausea, or reduced motivation to eat, as observed in those in our study who reported increased negative emotions toward food.

Typical finger food options include small sandwiches, pieces of quiche, chopped vegetables, slices of cake, or foods presented in bite-sized portions, usually designed for people who handle foods of normal consistency (IDDSI Committee, 2016). In healthcare and social care settings, the use of finger food has been

recommended to promote independence during meals and to prevent loss of dignity or embarrassment when eating in front of others (Barratt et al., 2001). Evidence from patient populations, including non-oncology patients, suggests that finger foods can encourage meal participation, increase independence, and potentially contribute to improved nutritional intake (Heelan et al., 2020). In the oncology setting, these characteristics may be particularly relevant for patients, suggesting that finger foods could represent a practical, patient-centered strategy for integrating sensory, nutritional, and behavioral interventions into a personalized care framework.

6. Conclusions

This study provides deep insights into the chemosensory alterations experienced by patients undergoing chemotherapy and their impact on food preferences and emotional responses. Our findings highlight the complexity and variability of these changes, underscoring the importance of a multidimensional approach for understanding and addressing the chemosensory side effects of cancer treatment.

RQ1- Occurrence and timing of chemosensory alterations. The study confirmed that most patients experience chemosensory alterations already in the early stages of therapy, in the form of several types (e.g., hypogeusia, parageusia, phantogeusia). Among these, taste function appeared to be the most affected, while olfactory perception was less frequently altered. Chemesthetic sensations were only marginally affected, showing more limited and variable changes across patients. Qualitative data revealed that these disturbances typically emerge within 24 hours of infusion and persist, on average, for approximately five days. Furthermore, post-chemotherapy recovery varies among patients, as even 3 months after the end of chemotherapy some patients experience a partial recovery of perceptual abilities, confirming the heterogeneity of individual profiles and underscoring the importance of longitudinal monitoring.

RQ2 - Impact on food preferences, emotions, and eating habits. The chemosensory alterations significantly influenced the eating experience. Changes in emotional responses to food occurred before actual changes in preferences. In other words, even when preferences appeared stable, patients began to report increasing discomfort, decreased pleasure, or aversion to previously enjoyed foods, indicating that changes in affective responses precede and can determine subsequent changes in food preferences and behaviors. The results showed that chemosensory alterations influence food choices unevenly: some patients reduce or avoid certain

foods (e.g., coffee, red meat, water), while others increase their use of condiments or appeal to compensatory strategies.

Compared to the preliminary results of our exploratory study (Di Meglio et al. 2025), the larger sample size of the present work allowed a more accurate detection of treatment-related effects. In particular, it revealed that after the fourth cycle is actually a critical phase of therapy characterized by in which the greatest number of preference changes, which might have been underestimated in smaller samples.

RQ3 – Nutritional status. Although patients reported alterations in taste and smell, no significant changes in body composition were observed during treatment. This may not only be due to the heterogeneity of the sample, which is predominantly composed of breast cancer patients, but it also suggests that behavioral adjustments, whether increased intake or selective elimination, can compensate for chemosensory alterations, preventing measurable nutritional decline. However, this stability does not rule out the presence of subclinical nutritional risks, underscoring the need for a comprehensive assessment that goes beyond weight or BMI. The observation of early emotional deterioration after the first chemotherapy cycle highlights the importance of timely intervention, not only to maintain adequate nutritional intake but also to preserve the pleasure associated with food. Furthermore, the worsening of sensory perception and the increased number of changes in preferences that emerge by the fourth cycle reinforce the need to anticipate support strategies, intervening in the early stages of treatment.

RQ4 – Quality of life. Confirming our hypotheses, chemosensory alterations have been shown to have a significant impact on quality of life: patients reporting these disturbances showed lower scores in general quality of life, with significant implications for social, emotional, and physical dimensions, as well as greater symptom intensity. In particular, the presence of general taste

alterations/parageusia/increase in taste perception emerged as the most problematic condition, as it was associated not only with changes in food preferences, emotions, food involvement, and eating habits, but also with a worse quality of life.

RQ5 – Role of individual differences. Psychological traits and oral responsiveness showed some associations with chemosensory disturbances. In particular, disgust sensitivity and PROP responsiveness were associated with higher chemosensory alterations and changes in preferences. Psychological traits (high food neophobia and high disgust sensitivity) were associated with a worsening of the emotional experience of food. These findings confirm that individual predispositions can modulate susceptibility to chemosensory disturbances and deserve further exploration in larger sample sizes.

RQ6 – Inputs for tailor-made product innovation and personalized recommendations. Finally, the results of this thesis have provided useful insights for developing personalized nutritional recommendations and more suitable foods and recipes for cancer patients. Currently, nutritional support is not widely integrated into hospital routines and there is a lack of products specifically designed for patients with taste and smell alterations. This study therefore addresses the need to develop foods that meet not only nutritional needs, but also sensory and emotional ones, with the aim of alleviating symptoms, preventing malnutrition, and promoting the enjoyment of food. The “ideal snack” analysis showed a consistent preference for salty, crunchy, and tasty products, while pasty and liquid textures were generally avoided, highlighting the role of texture and flavor intensity in product design. This finding provides useful insights but also highlights the need for further investigation to better understand whether specific chemosensory profiles require distinct product designs or whether common strategies may be sufficient to meet the needs of a broader patient population.

Study limitations

Despite the findings and strengths of this study, namely its longitudinal design with multiple assessments before, during, and after chemotherapy, the integration of sensory tests and self-reported measures of chemosensory alterations, the assessment of food preferences and emotions elicited by foods based on sensory characteristics, the consideration of individual differences as a relevant source of variability, and the focus on quality of life, it is important to acknowledge some limitations that may have influenced the data collection and the results.

One of the main challenges of this work lies in the difficulty of conducting research on cancer patients, especially when data collection spans multiple time points. Chemotherapy is a very demanding treatment, both physically and emotionally, and this inevitably affects patients' availability and willingness to participate in repeated assessments. Furthermore, the clinical severity of the disease can lead to treatment complications, worsening health, or even death, further contributing to drop-out. Consequently, while the longitudinal design represents a major strength, it also introduced practical challenges such as missing data and drop-out, which may have limited the statistical power of some analyses and reduced the generalizability of some findings. Furthermore, while the richness of the dataset allowed for multidimensional approaches, such analyses were only limitedly applied in this study. This choice was primarily driven by the variable sample sizes at different time points. These factors would have limited the robustness and interpretability of multivariate models, potentially leading to unstable results.

Another limitation concerns the heterogeneity of the study population. Although patients were recruited from two cancer groups (breast cancer and urological cancer), differences in clinical history, treatment regimens, and individual

responses may have introduced variability that was difficult to control. Furthermore, the sample was unbalanced in terms of sex distribution, with a predominance of female participants. While this choice allowed us to compare populations undergoing treatment with similar cytotoxic agents, it may have introduced further variability and limited the ability to distinguish sex-related effects from those related to cancer type.

Furthermore, the use of questionnaires to assess food preferences, emotions, and experiences may have been subject to biases, including a potential halo effect. Specifically, patients' global emotional state, nausea, discomfort, and unpleasant sensations could generalize to entire food categories, potentially amplifying negative evaluations even in the absence of clear and specific sensory changes. However, it should be noted that assessing food preferences through choice tasks may have partially limited this effect, as preferences are based on selection rather than ratings of liking. However, these limitations highlight the need for future studies with larger samples followed along the therapy to fully exploit multidimensional analytic approaches.

Future perspectives

This work lays the foundation for a new research perspective on chemosensory alterations in oncology, focusing not only on nutritional aspects but also on the overall food experience, including food preferences, food-evoked emotions, daily eating behaviors, and patients' quality of life. The results demonstrated how the food experience during chemotherapy is the result of a complex interplay between sensory alterations, food preferences, behaviors, and emotions, underscoring the need for a multidimensional approach.

Based on these findings, future research should critically reconsider which variables are essential to prioritize depending on the research objective. Although sensory testing remains relevant for investigating perceptual mechanisms, especially when patients tend to hide or minimize chemosensory alterations as inevitable effects of treatment, our findings suggest that assessing self-reported chemosensory alterations, particularly through qualitative interviews, combined with assessments of food-evoked emotions and eating behaviors, may be sufficient to capture clinically significant changes and identify patients at risk for adverse eating experiences or reduced quality of life.

Future studies should explore these aspects further, expanding sample sizes and including different cancer sites and treatment regimens, to clarify whether the observed patterns are generalizable or specific to some clinical contexts. From this perspective, multidimensional approaches integrating sensory, emotional, behavioral, and psychological variables would represent a key direction for future research. Such approaches would ideally be implemented in larger, more stable samples (with a similar number of patients at each time-point, or focused on selected critical phases of the treatment.

Moreover, although only a small number of dropouts in the current study were related to disease progression or death, it would be interesting to assess whether patients with more advanced or clinically fragile conditions may experience more severe or persistent chemosensory alterations, with a greater impact on their eating experience and food-related quality of life. This aspect is not yet sufficiently explored and requires further investigation. Targeted studies focusing on patients with advanced disease or a higher symptom burden, including those receiving palliative care, could help clarify whether chemosensory alterations intensify with disease progression and overall clinical vulnerability.

From a methodological perspective, focusing assessments on critical phases of treatment, such as the fourth cycle of chemotherapy, appears particularly relevant, as this time point has sometimes been characterized by worsening sensory disturbances and the greatest number of preference changes. Such an approach may improve research efficiency and the comparability of results, while reducing patient burden.

However, the results of this study clearly indicate that the early stages of treatment play a crucial role in the timely identification of chemosensory alterations and deterioration of emotional responses to food, which often emerge already after the first cycle of chemotherapy. Therefore, an optimal methodological strategy should combine early assessment, aimed at prevention and timely intervention, with targeted in-depth evaluation in the later stages of treatment, particularly around the fourth cycle. For clinical and research purposes, emotional assessments may therefore be particularly useful for early diagnosis and timely intervention, while preference assessments are more informative for designing long-term dietary and product-based strategies. Future research should consider integrating both dimensions aimed at prevention and timely intervention.

In terms of clinical implications, although breast and urological cancer patients are generally less likely to experience significant weight loss or measurable changes in body composition during chemotherapy, the current findings suggest the presence of early changes in sensory and overall food experience, such as reduced enjoyment of food, the emergence of avoidance behaviors, or increased reliance on a limited range of foods. Although these changes were not associated with detectable changes in weight, BMI, or body composition in our cohort, they could nevertheless represent early indicators of altered nutritional status that are not captured by conventional anthropometric measures. This underscores the clinical

value of integrating standard nutritional monitoring, particularly in supporting timely and patient-centered interventions.

Furthermore, it will be necessary to expand and integrate nutritional and sensory recommendations, always taking into account individual patient characteristics, with the aim of preserving the pleasure of eating. In this sense, the qualitative analysis conducted in this thesis represents a useful starting point for delineating sensory and nutritional profiles that can guide the creation of innovative recipes and foods for cancer patients.

Finally, it is recommended that oncologists, nutritionists, psychologists, and food technologists work together to transform research findings into concrete tools for patient support: personalized guidelines, patient-specific food products, and educational programs that help effectively manage chemosensory alterations. Only an integrated and multidisciplinary approach will improve patients' quality of life, restoring food not only to its nutritional function, but also to its sensory, social, and emotional functions.

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Appendix

Questionnaires

Q1 – Sociodemographic data, clinical and health status

Questionnaires	Variables	Options
Socio-demographics	Age	Years old at the moment of the test
	Sex at birth	M/F
	Educational level	None/Primary/Lower secondary/Upper secondary/Degree/Post-degree
	Number of people in the household	Open-ended answer
Clinical and health	Smoking habits	1 Never tried/ 2 Not smoking (have tried or quit)/ 3 Yes, occasionally / 4 Yes, habitually If 2: Quit since how long ago?
	Type of cancer	From histological report
	Stage of cancer	From medical records (TNM system)
	Treatment plan	From medical records

Q2 - Italian Child Food Neophobia Scale

Items (8) - English	Italian translation	Very false for me	False for me	So-so	True for me	Very true for me
I often eat new and unusual foods. (R)	Mangio spesso cibi nuovi e diversi dal solito. (R)	1	2	3	4	5
I don't trust new foods.	Non mi fido dei cibi nuovi.	1	2	3	4	5
If a food is new, I don't try it.	Se un cibo è nuovo, non lo assaggio.	1	2	3	4	5
I like to try weird tastes and foods, which are unusual and coming from different countries. (R)	Mi piace provare sapori e cibi strani, diversi dal solito e provenienti da altri paesi. (R)	1	2	3	4	5
When I am at a party, I like to eat new foods. (R)	Quando sono ad una festa mi piace provare cibi nuovi. (R)	1	2	3	4	5
I am afraid to eat food I have never tried before.	Ho paura a mangiare un cibo che non ho mai provato prima.	1	2	3	4	5
I am very fussy when it's a matter of food.	Sono molto schizzinoso/a quando si tratta di mangiare.	1	2	3	4	5
I really eat everything! (R)	Mangio tutto, ma proprio tutto! (R)	1	2	3	4	5

Q3 - Sensitivity to core-disgust scale

Items (8) - English	Italian translation	Very false for me	False for me	So-so	True for me	Very true for me
I might be willing to try eating monkey meat under some circumstances. (R)	In circostanze particolari potrei provare a mangiare carne di scimmia. (R)	1	2	3	4	5
If I see someone vomit it makes me sick to my stomach.	Se vedo qualcuno vomitare mi si rivolta lo stomaco.	1	2	3	4	5
Seeing a cockroach in someone else's house does not bother me. (R)	Vedere uno scarafaggio in casa di qualcun altro non mi infastidirebbe. (R)	1	2	3	4	5
Even if I was hungry, I would not drink a bowl of my favorite soup if it had been stirred by a used but thoroughly washed fly swatter.	Anche se avessi fame, non mangerei mai la mia minestra preferita se fosse stata mescolata da uno schiacciamosche usato anche se accuratamente lavato.	1	2	3	4	5
		Not at all disgusting				Extremely disgusting
To see maggots on a piece of meat in an outdoor garbage pail.	Vedere dei vermi su un pezzo di carne in un cassonetto	1	2	3	4	5
To smell urine while you are walking through a tunnel under a railroad track.	Sentire odore di urina mentre stai attraversando un sottopassaggio della ferrovia.	1	2	3	4	5
A friend offers you a piece of chocolate shaped like dog-doo.	Un amico ti offre un pezzo di cioccolato a forma di escremento di cane.	1	2	3	4	5
To see a bowel movement left unflushed in a public toilet.	Vedere gli escrementi in un bagno pubblico in cui non è stato tirato lo sciacquone.	1	2	3	4	5

Q4- Food Involvement Scale

Items (9) - English	Italian translation	Strongly disagree			Neither agree nor disagree			Strongly agree
I don't think much about food during the day (R)	Durante la giornata non penso molto al cibo (R)	1	2	3	4	5	6	7
I don't enjoy cooking or barbequing (R)	Non mi diverte cucinare o grigliare (R)	1	2	3	4	5	6	7
Talking about what I ate or I am going to eat is something I like to do	Mi piace parlare di quello che ho mangiato o che mangerò	1	2	3	4	5	6	7
Compared with other decisions, deciding what to eat is very important to me	Tra le decisioni che devo prendere decidere cosa mangiare per me è molto importante	1	2	3	4	5	6	7
When I travel, one of the things I anticipate most is eating local food	Quando viaggio una delle cose che mi pregusto di più è mangiare cibo del posto	1	2	3	4	5	6	7
I enjoy cooking for myself and others	Mi diverte cucinare per me e per gli altri	1	2	3	4	5	6	7
When I eat out, I don't think or talk much about the quality of the food (R)	Quando mangio fuori non penso molto o non parlo molto della qualità del cibo (R)	1	2	3	4	5	6	7
I don't like handling food (e.g. during preparation) (R)	Non mi piace maneggiare il cibo (per esempio nella preparazione) (R)	1	2	3	4	5	6	7
I am usually the one who does the food shopping	Sono io a fare la spesa (alimentare) di solito.	1	2	3	4	5	6	7

Q5 – Chemotherapy induced Taste Alteration Scale

Items (20) - English	Italian translation	Not at all	Slightly	Quiet	Very	Very much
Decline in basic tastes						
I have difficulty perceiving sweet tastes	Ho difficoltà nel percepire i sapori dolci	1	2	3	4	5
I have difficulty perceiving salty tastes	Ho difficoltà nel percepire i sapori salati	1	2	3	4	5
I have difficulty perceiving sour tastes	Ho difficoltà nel percepire i sapori acidi	1	2	3	4	5
I have difficulty perceiving bitter tastes	Ho difficoltà nel percepire i sapori amari	1	2	3	4	5
I have difficulty perceiving savory tastes (e.g. stock cube, parmesan cheese)	Ho difficoltà nel percepire i gusti saporiti (es. gusto del dato o del parmigiano	1	2	3	4	5
General taste alterations and parageusia						
When I eat, everything tastes bitter	Quando mangio, tutto ha un sapore amaro	1	2	3	4	5
When I eat, everything tastes bitter	Quanto mangio, tutto ha un sapore cattivo	1	2	3	4	5
It seems to me that the tastes of the foods I usually consume are no longer the same	Mi sembra che i sapori dei cibi che consumo di solito non siano più gli stessi	1	2	3	4	5
Phantogeusia and increase in taste perception						
I sometimes feel a bad taste in my mouth	Mi capita di sentire un gusto cattivo in bocca	1	2	3	4	5
I sometimes feel a bitter taste in my mouth	Mi capita di sentire un gusto cattivo in bocca	1	2	3	4	5
I sometimes feel a metallic taste in my mouth	Mi capita di sentire un gusto metallico in bocca	1	2	3	4	5
I sometimes feel a sour taste in my mouth	Mi capita di sentire un gusto acido in bocca	1	2	3	4	5
I perceive some tastes more intense than usual	Percepisco alcuni sapori più intensi del solito	1	2	3	4	5
Discomfort						
I feel nausea or disgust for food	Sento nausea o disgusto per il cibo	1	2	3	4	5
I'm bothered by the smell of food	Sono infastidito/a dall'odore del cibo	1	2	3	4	5
I have difficulty or discomfort eating hot foods	Ho difficoltà o fastidio a mangiare cibi caldi	1	2	3	4	5
I have difficulty or discomfort eating oily foods	Ho difficoltà o fastidio a mangiare cibi unti	1	2	3	4	5
I have reduced appetite	Ho appetito ridotto	1	2	3	4	5
I suffer from mucositis/inflammation/ pain/ ulcerations in mouth	Soffro di mucosite/ infiammazione/ dolore/ ulcerazioni in bocca	1	2	3	4	5
I feel dry mouth	Sento la bocca secca	1	2	3	4	5

Q6 – Global Consortium of Chemosensory Research questionnaire

These questions relate to your sense of smell (for example, sniffing flowers or soap, or smelling garbage) but not the flavor of food in your mouth.
Italian traslation: Queste domande riguardano l'olfatto (ad esempio, annusare i fiori o il sapone, oppure sentire l'odore della spazzatura), ma non il sapore del cibo in bocca.

Evaluate your ability to smell

Italian translation: Valuta la tua capacità nel percepire gli odori

Not good								Excellent
1	2	3	4	5	6	7	8	9

After the chemotherapy cycle/end of treatment

Items (9) - English	Italian translation
No changes in smell	Nessun cambiamento dell'olfatto
I can't smell anything	Non riesco a sentire gli odori
I can smell the odors, but they are less strong than before	Riesco a sentire gli odori, ma alcuni sono meno forti di prima
I can smell the odors, but some of them are stronger than before	Riesco a sentire gli odori, ma alcuni di loro sono più forti di prima
I perceive odors that I know well as different than usual (the quality of the odor has changed)	Percepisco odori che conosco bene come diversi rispetto a prima (la qualità dell'odore è cambiata)
I can smell things that aren't there (e.g. I smell burning when nothing is burning)	Riesco a sentire l'odore di cose che non ci sono (es. sento odore di bruciato quando niente sta bruciando)
My sense of smell fluctuates	Il mio senso dell'olfatto fluttua
Some smells that I used to like now bother me. Which ones?	Alcuni odori che prima mi piacevano adesso mi danno fastidio. Quali?
Other:	Altro:

The following questions are related to your sense of taste. For example, sweetness, sourness, saltiness, bitterness experienced in the mouth.
Italian translation: Le seguenti domande sono relative al tuo senso del gusto. Ad esempio, dolce, acido, salato, amaro percepiti in bocca.

Evaluate your ability to taste
Italian translation: Valuta la tua capacità di percepire i gusti

Not good								Excellent
1	2	3	4	5	6	7	8	9

Changes in chemesthetic sensations

This question refers to other sensations in the mouth, such as burning, cold, or sparkling. For example, sensations caused by eating chili peppers, chewing gum or mints, or carbonated drinks.
After the chemotherapy cycle/end of treatment have you noticed any changes in these sensations?
Italian translation: Questa domanda si riferisce ad altre sensazioni in bocca, come bruciore/formicolio, freddo o formicolio. Ad esempio, sensazioni causate dal mangiare peperoncini, masticare gomme o mentine o bevande gassate. Dopo il ciclo di chemioterapia/fine del trattamento hai notato cambiamenti in queste sensazioni?

Items (3) - English	Italian transaltion			
Spiciness (e.g. chili pepper)	Piccante (es. peperoncino)	I perceive it less than usual	I perceive it as usual	I perceive it stronger than usual
Coolness (e.g. menthol in toothpaste or mint)	Rinfrescante (es. mentolo del dentifricio o della menta)	I perceive it less than usual	I perceive it as usual	I perceive it stronger than usual
Sparkling (e.g. sparkling water)	Frizzante (es. acqua gassata)	I perceive it less than usual	I perceive it as usual	I perceive it stronger than usual

Changes of usual foods

Think about a food or drink that you consume regularly: for example, your morning coffee or tea, or a piece of fruit that you eat every day. Has the taste, smell, or flavor changed in the last week?
If YES, please describe how they have changed.
Italian translation: Pensa a un alimento o a una bevanda che consumi regolarmente: ad esempio, il tuo caffè o tè mattutino, o un frutto che mangi ogni giorno. Il sapore, l'odore o il sapore sono cambiati nell'ultima settimana?
Se SÌ, descrivi come sono cambiati.

Q7 – Hedonic responses to basic tastes

Compared to how much you normally like them, indicate for each of these tastes if you have noticed any differences after chemotherapy.
For example: I like it more ("I want to eat foods with this taste more than before"); I like it less ("foods with this taste bother me more than before").
Italian translation: Rispetto a quanto ti piacciono normalmente, indica per ciascuno di questi gusti se hai notato delle differenze dopo la chemioterapia.
Ad esempio: Mi piace di più ("Voglio mangiare cibi con questo sapore più di prima"); Mi piace di meno ("I cibi con questo sapore mi danno più fastidio di prima").

Items (4) - English	Italian translation			
SWEET	DOLCE	I like it less	I like it as usual	I like it more
SALTY	SALATO	I like it less	I like it as usual	I like it more
SOUR	ACIDO	I like it less	I like it as usual	I like it more
BITTER	AMARO	I like it less	I like it as usual	I like it more

Q8 – Use/liking of condiments

Usually/After the chemotherapy cycle
Italian translation: Solitamente/dopo il ciclo di terapia

Items (8) - English	Italian translation	Not at all								Very much
How salty do you like to eat?	Quanto salato ti piace mangiare?	1	2	3	4	5	6	7	8	9
How much sugar do you add to your coffee/cappuccino/tea?	Quanto zucchero aggiungi al caffè/cappuccino/tè?	1	2	3	4	5	6	7	8	9
How much Parmesan cheese do you add to pasta?	Quanto Parmigiano aggiungi alla pasta?	1	2	3	4	5	6	7	8	9
How spicy do you like to eat?	Quanto piccante ti piace mangiare?	1	2	3	4	5	6	7	8	9
How much pepper do you add?	Quanto pepe aggiungi?	1	2	3	4	5	6	7	8	9
How much do you like foods with spices?	Quanto speziato ti piace mangiare?	1	2	3	4	5	6	7	8	9
How much do you like dishes with lemon?	Quanto ti piace mangiare pietanze in cui è utilizzato il limone?	1	2	3	4	5	6	7	8	9
How much do you like dishes with vinegar?	Quanto ti piace mangiare pietanze in cui è utilizzato l'aceto?	1	2	3	4	5	6	7	8	9

Q9 – Food Preference and Emotion Questionnaire

For each pair listed below, indicate which food/drink you would prefer to eat during a meal/snack/all day. If you would both or neither, choose the one you are more inclined to eat.	How does it make you feel? (CATA for chosen and unchosen option)
Flavor	
Fresh pecorino/ Aged pecorino	
Cow mozzarella/Buffalo mozzarella	
Cooked ham/Dry cured ham	
Mashed potato/Baked potato	
Valerian and lettuce/Radicchio and rochet	
Texture	
Vegetable soup/Vegetable cream	
Toasted bread/White bread	
Cous cous/Semolina	
Julienned carrots/Cooked carrots	
Chocolate bar/Chocolate pudding	
Herbs and Spices	Joy Happiness Curiosity Relax indifference Disgust Annoyance Sadness Boredom
Vegetables with chili/Vegetables without chili	
Tomato sauce with basil/Tomato sauce	
Herbal tea/Water	
Grilled chicken with thyme/Grilled chicken	
Zucchinis cream with mint/Zucchinis cream	
Sweet vs Bitter	
Panna cotta/Dark chocolate pudding	
Tea with sugar/Tea without sugar	
Milk chocolate/Dark chocolate	
Coffee with sugar/Coffee without sugar	
Pumpkin risotto/Radicchio risotto	
Sweet vs Sour	
Sweetened yogurt/Natural yogurt	
ACE juice/Orange juice	
Strawberry sorbet/Lemon sorbet	
Apricot jam/Raspberry jam	
Apple smoothie/Apple and lemon smoothie	
You are in a room where someone has just finished eating/cooking and you can smell food. Indicate the option you would least like to smell.	
Odor	
Bean soup/Vegetable soup*	
Bolognese sauce/Tomato sauce	
Fried cutlet/Grilled meat	
Meat broth/Vegetable broth	
Cooked tomato/Boiled rice	

Q9a- Favorite and unliked foods

What's your favorite food this period? What's a food you absolutely dislike this period?
Italian translation: Qual è il tuo cibo preferito in questo periodo? Qual è un cibo che proprio non ti piace per niente in questo periodo?

Q9b - Ideal snack

If you were feeling peckish in the morning, would you prefer a SWEET or SALTY snack? Choose one.
What should it be? (Choose one or more attributes from this list. If the attribute you're looking for isn't listed, enter it in "other")
What should it NOT be? (Choose one or more attributes from this list. If the attribute you are looking for is not present, enter it in "other")
Soft
Crunchy
Hard
Liquid
Creamy
Pasty
Tasty
Juicy
Dense
Other:
Italian translation: Se ti venisse un languorino nel corso della mattina preferiresti uno snack DOLCE o SALATO? Scegli una sola opzione.
Come dovrebbe essere? (scegli uno o più attributi da questa lista. Se l'attributo che cerchi non è presente, inseriscilo in "altro")
Come NON dovrebbe essere? (scegli uno o più attributi da questa lista. Se l'attributo che cerchi non è presente, inseriscilo in "altro")
Morbido
Croccante
Duro
Liquido
Cremoso
Pastoso
Saporito
Succoso
Denso
Other:

Q10 – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), version 3.0

Items (30) – English	Italian translation	No			Very much
Do you have difficulty doing strenuous work such as lifting a heavy bag or suitcase?	Hai difficoltà nel fare lavori faticosi come sollevare una borsa della spesa pesante o una valigia?	1	2	3	4
Do you have difficulty going for a long walk?	Hai difficoltà nel fare una lunga passeggiata?	1	2	3	4
Do you have difficulty going for a short walk outside the house?	Hai difficoltà nel fare una breve passeggiata fuori casa?	1	2	3	4
Do you need to stay in bed or in a chair during the day?	Hai bisogno di stare a letto o su una sedia durante il giorno?	1	2	3	4
Do you need help eating, dressing, bathing or going to the toilet?	Hai bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?	1	2	3	4
Have you had any limitations in doing your job or housework?	Hai avuto limitazioni nel fare il tuo lavoro o i lavori di casa?	1	2	3	4
Have you had any limitations in engaging in your hobbies, pastimes or other recreational or leisure activities?	Hai avuto limitazioni nel praticare i tuoi passatempi, hobby o altre attività di divertimento o svago?	1	2	3	4
Have you been short of breath?	Ti è mancato il fiato?	1	2	3	4
Have you had pain?	Hai avuto dolore?	1	2	3	4
Have you needed rest?	Hai avuto bisogno di riposo?	1	2	3	4
Have you had difficulty sleeping?	Hai avuto difficoltà a dormire?	1	2	3	4
Have you felt weak?	Ti sei sentito debole?	1	2	3	4
Have you lost your appetite?	Ti è mancato l'appetito?	1	2	3	4
Have you felt nauseous?	Hai avuto un senso di nausea?	1	2	3	4
Have you vomited?	Hai vomitato?	1	2	3	4
Have you had problems with constipation?	Hai avuto problemi di stitichezza?	1	2	3	4

Have you had problems with diarrhea?	Hai avuto problemi di diarrea?	1	2	3	4
Have you felt tired?	Ti sei sentito stanco/a?	1	2	3	4
Have you felt tense?	Ti sei sentito teso/a?	1	2	3	4
Have you worried?	Ti sei preoccupato/a?	1	2	3	4
Have you felt irritable?	Ti sei sentito/a irritabile?	1	2	3	4
Have you felt depressed?	Ti sei sentito/a depresso/a?	1	2	3	4
Have you had trouble remembering things?	Hai avuto difficoltà a ricordare le cose?	1	2	3	4
Has your physical condition or medical treatment interfered with your family life?	Le tue condizioni fisiche o il trattamento medico hanno interferito con la tua vita familiare?	1	2	3	4
Has your physical condition or medical treatment interfered with your social activities?	Le tue condizioni fisiche o il trattamento medico hanno interferito con le tue attività sociali?	1	2	3	4
Has your physical condition or medical treatment caused you financial difficulties?	Le tue condizioni fisiche o il trattamento medico ti hanno causato difficoltà finanziarie??	1	2	3	4

EN: How would you rate your overall health during the last 7 days?
IT: Come valuteresti in generale la tua salute durante gli ultimi 7 giorni?

1	2	3	4	5	6	7
Very poor						Excellent

EN: How would you rate your overall quality of life during the last 7 days?
IT: Come valuteresti in generale la tua qualità della vita durante gli ultimi 7 giorni?

1	2	3	4	5	6	7
Very poor						Excellent

Supplementary Materials

Supplementary Table 1 – Percentage of selection (CATA) of sensory attributes ("must have" and "must not have") for the ideal salty snack among patients with and without self-reported chemosensory alterations (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, and phantogeusia) at baseline (T0) and after the second chemotherapy cycle (T2).

		Salty snack must have		Salty snack must not have	
CiTAS alteration at T2	Attributes	T0	T2	T0	T2
Decline in basic tastes (YES/ NO)	Soft (YES)	5.0%	18.2%	**30.0%**	**31.8%**
	Soft (NO)	17.4%	**24.0%**	17.4%	**20.0%**
	Crunchy (YES)	**90.0%**	**81.8%**	5.0%	9.1%
	Crunchy (NO)	**69.6%**	**56.0%**	4.3%	8.0%
	Hard (YES)	**25.0%**	**27.3%**	15.0%	4.5%
	Hard (NO)	8.7%	**24.0%**	13.0%	**24.0%**
	Creamy (YES)	15.0%	0.0%	**50.0%**	**36.4%**
	Creamy (NO)	17.4%	8.0%	**30.4%**	**24.0%**
	Liquid (YES)	5.0%	4.5%	**40.0%**	**36.4%**
	Liquid (NO)	4.3%	0.0%	**52.2%**	**32.0%**
	Juicy (YES)	10.0%	4.5%	15.0%	18.2%
	Juicy (NO)	0.0%	0.0%	**30.4%**	12.0%
	Pasty (YES)	15.0%	4.5%	**60.0%**	**40.9%**
	Pasty (NO)	0.0%	8.0%	**47.8%**	**24.0%**
	Dense (YES)	10.0%	4.5%	10.0%	**27.3%**
	Dense (NO)	13.0%	8.0%	**21.7%**	16.0%
	Tasty (YES)	**80.0%**	**77.3%**	0.0%	0.0%
	Tasty (NO)	**62.5%**	**68.0%**	0.0%	4.0%
General taste alterations/parageusia /increase in taste perception (YES/NO)					
	Soft (YES)	11.1%	**25.9%**	**25.9%**	**25.9%**
	Soft (NO)	18.8%	**20.0%**	18.8%	**25.0%**
	Crunchy (YES)	**85.2%**	**74.1%**	3.7%	11.1%

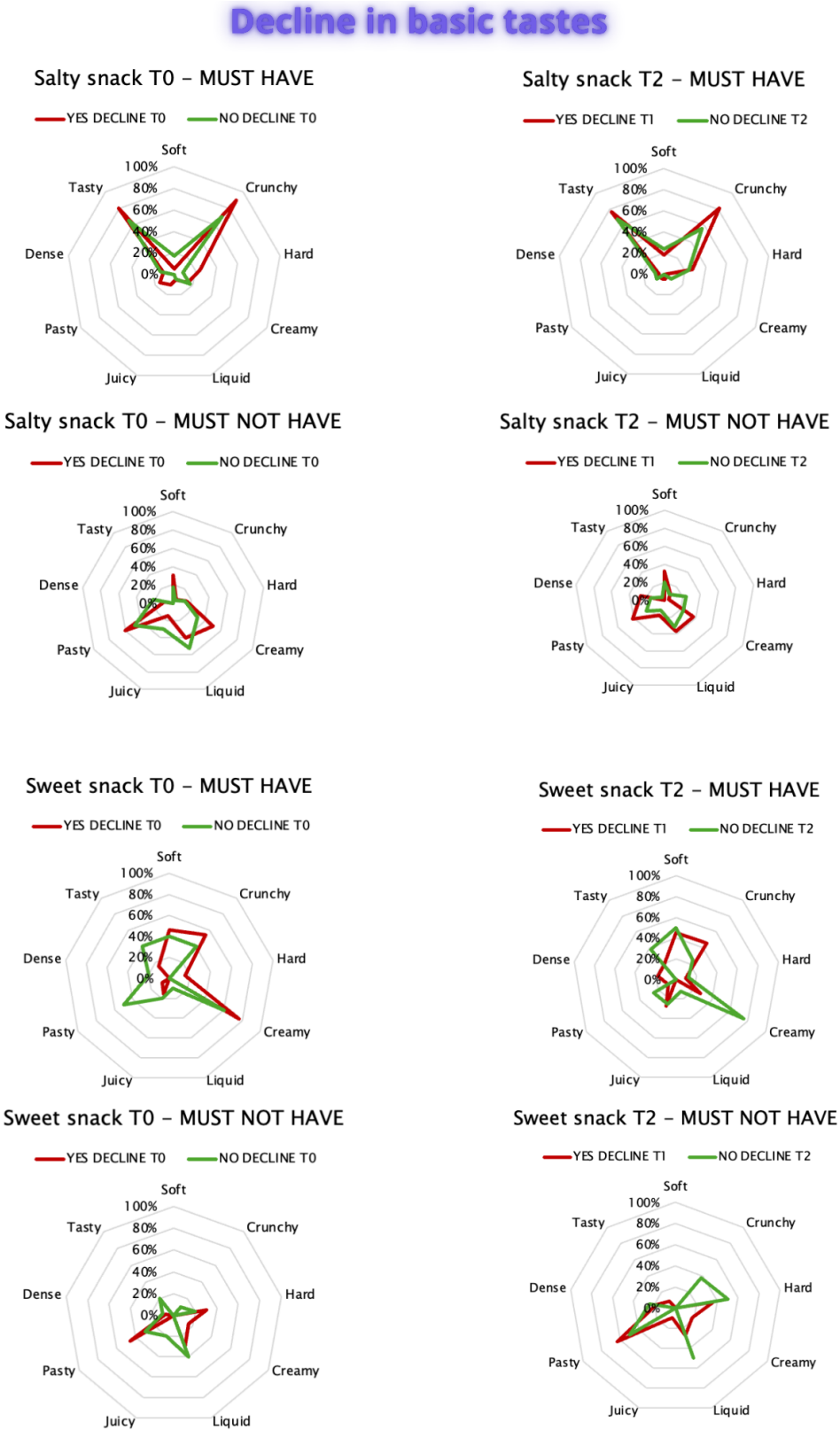
	Crunchy (NO)	**62.5%**	**55.0%**	6.3%	5.0%
	Hard (YES)	18.5%	**25.9%**	14.8%	11.1%
	Hard (NO)	12.5%	**25.0%**	6.3%	10.0%
	Creamy (YES)	**22.2%**	5.3%	**37.0%**	**29.6%**
	Creamy (NO)	18.8%	5.0%	**31.0%**	**30.0%**
	Liquid (YES)	3.7%	3.7%	**44.4%**	**40.7%**
	Liquid (NO)	6.3%	0.0%	**50.0%**	**25.0%**
	Juicy (YES)	7.4%	3.7%	14.8%	14.8%
	Juicy (NO)	0.0%	0.0%	**31.3%**	10.0%
	Pasty (YES)	7.4%	3.7%	**51.9%**	**33.3%**
	Pasty (NO)	6.3%	10.0%	**43.8%**	**30.0%**
	Dense (YES)	11.1%	7.4%	7.4%	**25.9%**
	Dense (NO)	12.5%	5.0%	18.8%	15.0%
	Tasty (YES)	**66.7%**	**70.4%**	0.0%	3.7%
	Tasty (NO)	**81.3%**	**65.0%**	6.0%	0.0%
Phantogeusia					
(YES/NO)	Soft (YES)	7.1%	16.6%	**28.6%**	**26.7%**
	Soft (NO)	**31.6%**	**35.3%**	10.5%	**23.5%**
	Crunchy (YES)	**85.7%**	**73.3%**	3.5%	13.3%
	Crunchy (NO)	**63.2%**	**58.8%**	5.3%	0.0%
	Hard (YES)	14.3%	**30.0%**	3.6%	10.0%
	Hard (NO)	15.8%	17.6%	**26.3%**	17.6%
	Creamy (YES)	0.0%	0.0%	**46.4%**	**26.7%**
	Creamy (NO)	**36.8%**	17.6%	**21.1%**	**35.3%**
	Liquid (YES)	0.0%	3.3%	**42.9%**	**33.3%**
	Liquid (NO)	15.8%	0.0%	**47.4%**	**35.3%**
	Juicy (YES)	0.0%	0.0%	**21.4%**	**20.0%**
	Juicy (NO)	10.5%	5.9%	**21.1%**	11.8%
	Pasty (YES)	7.1%	6.7%	**60.7%**	**40.0%**
	Pasty (NO)	5.3%	5.9%	**36.8%**	**23.5%**
	Dense (YES)	10.7%	3.3%	10.7%	**23.3%**
	Dense (NO)	15.8%	11.8%	**21.1%**	**23.5%**
	Tasty (YES)	**71.4%**	**70.0%**	0.0%	3.3%
	Tasty (NO)	**73.7%**	**82.4%**	0.0%	0.0%

Supplementary Table 2 - Percentage of selection (CATA) of sensory attributes ("must have" and "must not have") for the ideal sweet snack among patients with and without self-reported chemosensory alterations (decline in basic tastes, general taste alterations/parageusia/increase in taste perception, and phantogeusia) at baseline (T0) and after the second chemotherapy cycle (T2).

		Sweet snack must have		Sweet snack must not have	
CiTAS alteration at T2	Attributes	T0	T2	T0	T2
Decline in basic tastes (YES/NO)	Soft (YES)	**46.2%**	**45.5%**	0.0%	0.0%
	Soft (NO)	**40.0%**	**50.0%**	0.0%	0.0%
	Crunchy (YES)	**53.8%**	**45.5%**	0.0%	0.0%
	Crunchy (NO)	**40.0%**	**25.0%**	10.0%	**38.0%**
	Hard (YES)	15.4%	9.1%	**30.8%**	**36.4%**
	Hard (NO)	0.0%	12.5%	**20.0%**	**50.0%**
	Creamy (YES)	**76.9%**	**27.3%**	15.4%	18.2%
	Creamy (NO)	**60.0%**	**75.0%**	0.0%	0.0%
	Liquid (YES)	0.0%	0.0%	**30.8%**	**27.3%**
	Liquid (NO)	10.0%	12.5%	**40.0%**	**50.0%**
	Juicy (YES)	15.4%	**27.3%**	0.0%	9.1%
	Juicy (NO)	**20.0%**	**25.0%**	**20.0%**	0.0%
	Pasty (YES)	7.7%	9.1%	**46.2%**	**63.6%**
	Pasty (NO)	**50.0%**	**25.0%**	**30.0%**	**50.0%**
	Dense (YES)	0.0%	18.2%	7.7%	18.2%
	Dense (NO)	**20.0%**	0.0%	10.0%	**25.0%**
	Tasty (YES)	15.4%	18.2%	0.0%	9.1%
	Tasty (NO)	**40.0%**	**37.5%**	**20.0%**	0.0%
General taste alterations/parageusia/increase in taste perception (YES/NO)					
	Soft (YES)	**41.7%**	**58.3%**	0.0%	0.0%
	Soft (NO)	**45.5%**	**28.6%**	0.0%	0.0%
	Crunchy (YES)	**41.7%**	**33.3%**	0.0%	16.7%
	Crunchy (NO)	**45.5%**	**42.9%**	9.1%	14.3%
	Hard (YES)	8.3%	0.0%	**25.0%**	**50.0%**

	Hard (NO)	9.1%	**28.6%**	**27.3%**	**28.6%**
	Creamy (YES)	**83.3%**	**50.0%**	8.3%	8.3%
	Creamy (NO)	**63.6%**	**57.1%**	9.1%	0.0%
	Liquid (YES)	8.3%	8.3%	**41.6%**	**33.3%**
	Liquid (NO)	0.0%	0.0%	**27.3%**	**42.9%**
	Juicy (YES)	**25.0%**	**33.3%**	0.0%	8.3%
	Juicy (NO)	9.1%	14.3%	18.2%	14.3%
	Pasty (YES)	0.0%	8.3%	**33.3%**	**50.0%**
	Pasty (NO)	**45.5%**	14.3%	**54.4%**	**57.1%**
	Dense (YES)	0.0%	8.3%	8.3%	**25.0%**
	Dense (NO)	18.2%	**28.6%**	0.0%	0.0%
	Tasty (YES)	8.3%	16.7%	8.3%	8.3%
	Tasty (NO)	**54.5%**	**42.9%**	9.1%	0.0%
Phantogeusia (YES/NO)					
	Soft (YES)	**27.3%**	**44.4%**	0.0%	0.0%
	Soft (NO)	**53.8%**	**50.0%**	0.0%	0.0%
	Crunchy (YES)	**45.5%**	**33.3%**	0.0%	**22.2%**
	Crunchy (NO)	**46.2%**	**40.0%**	7.7%	10.0%
	Hard (YES)	9.1%	11.1%	9.1%	**44.4%**
	Hard (NO)	**23.1%**	10.0%	**38.5%**	**40.0%**
	Creamy (YES)	**63.6%**	**44.4%**	9.1%	11.1%
	Creamy (NO)	**69.2%**	**50.0%**	7.7%	10.0%
	Liquid (YES)	9.1%	11.1%	**36.4%**	**44.4%**
	Liquid (NO)	0.0%	0.0%	**30.8%**	**30.0%**
	Juicy (YES)	9.1%	**33.3%**	0.0%	0.0%
	Juicy (NO)	**23.1%**	**20.0%**	15.4%	**20.0%**
	Pasty (YES)	9.1%	0.0%	**45.5%**	**55.6%**
	Pasty (NO)	**30.8%**	**20.0%**	**38.5%**	**60.0%**
	Dense (YES)	9.1%	11.1%	9.1%	11.1%
	Dense (NO)	7.7%	10.0%	0.0%	**30.0%**
	Tasty (YES)	**27.3%**	11.1%	9.1%	11.1%
	Tasty (NO)	**23.1%**	**40.0%**	7.7%	0.0%

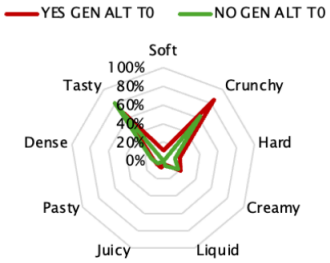
Supplementary Materials 1 – Differences between patients with and without self-reported decline in basic tastes in ideal snack at T0 and T2.



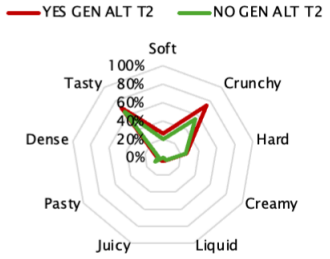
Supplementary Materials 2 - Differences between patients with and without self-reported general taste alterations/parageusia/increase in taste perception in ideal sweet at T0 and T2.

General taste alterations/parageusia/increase

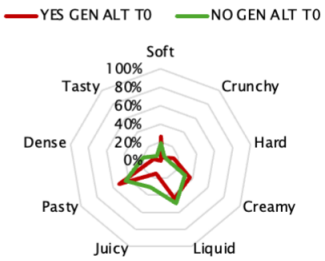
Salty snack T0 – MUST HAVE



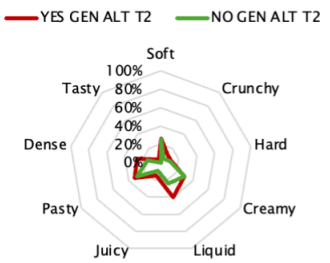
Salty snack T2 – MUST HAVE



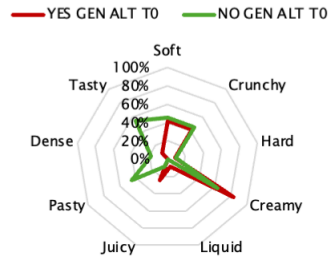
Salty snack T0 – MUST NOT HAVE



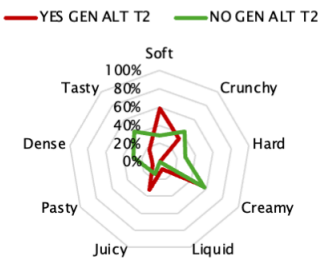
Salty snack T2 – MUST NOT HAVE



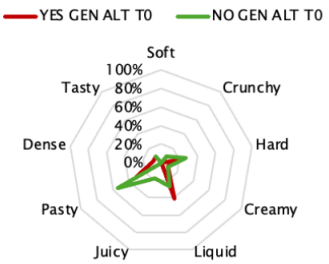
Sweet snack T0 – MUST HAVE



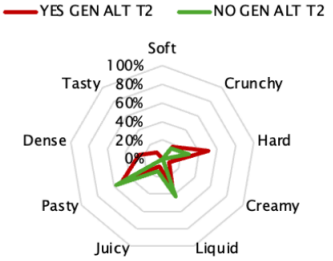
Sweet snack T2 – MUST HAVE



Sweet snack T0 – MUST NOT HAVE



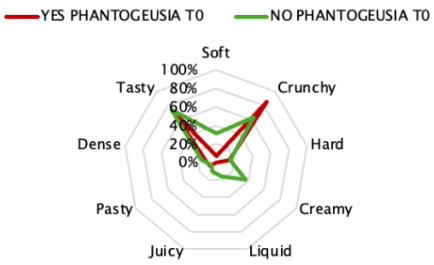
Sweet snack T2 – MUST NOT HAVE



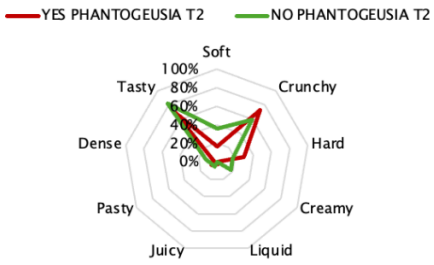
Supplementary Materials 3 - Differences between patients with and without self-reported phantogeusia in ideal snack at T0 and T2

Phantogeusia

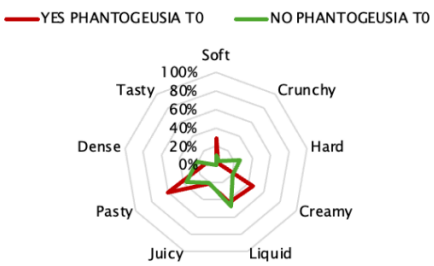
Salty snack T0 – MUST HAVE



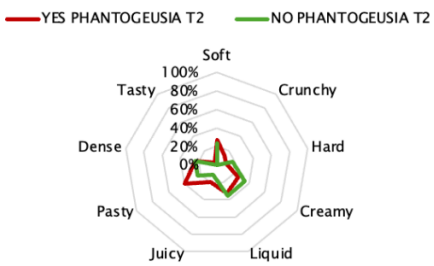
Salty snack T2 – MUST HAVE



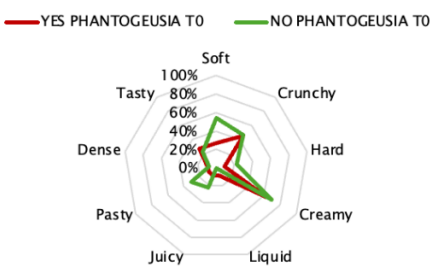
Salty snack T0 – MUST NOT HAVE



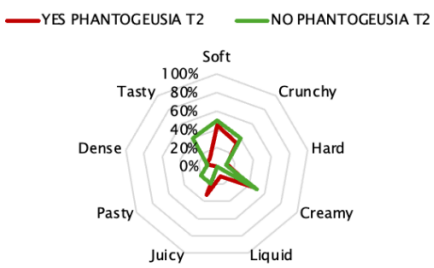
Salty snack T2 – MUST NOT HAVE



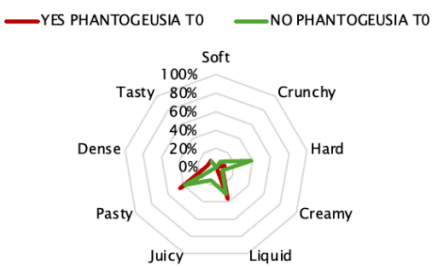
Sweet snack T0 – MUST HAVE



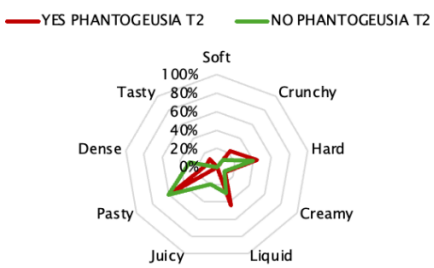
Sweet snack T2 – MUST HAVE



Sweet snack T0 – MUST NOT HAVE



Salty snack T2 – MUST NOT HAVE



Scientific dissemination

List of publications and conference proceedings

Di Meglio, J., Dinu, M., Doni, L., Rossi, G., Giorgione, R., Colombini, B., Antonuzzo, L., & Sofi, F. (2022). Occurrence of Dysgeusia in Patients Being Treated for Cancer. Nutrition and Cancer, 74(8), 2868–2874. https://doi.org/10.1080/01635581.2022.2042569

Di Meglio, J., Rorandelli, C., Dinnella, C., Monteleone, E., Stingo, F. C., Doni, L., Visani, L., Guarino, A., Gambale, E., De Sanctis, R., Gerosa, R., Tiberio, P., Antonuzzo, L., Scotti, V., Meattini, I., Roviello, G., & Spinelli, S. (2025). Changes in chemosensory perception, food preferences and emotional responses to foods in cancer patients during the early stages of chemotherapy: An exploratory study. Food Quality and Preference, 134, 105671. https://doi.org/10.1016/j.foodqual.2025.105671

Di Meglio J., Rorandelli C, Dinnella C et al. Early changes in food preferences and emotional responses to foods in cancer patients with chemosensory alterations. "Pubblicazione Atti del VIII Convegno Nazionale della Società Italiana di Scienze Sensoriali, Alghero 22-24 maggio 2024" *Società Italiana di Scienze Sensoriali*

Rorandelli, C., Di Meglio, J., Dinnella, C., Monteleone, E., Doni, L., Guarino, A., Gambale, E., De Sanctis, R., Gerosa, R., Tiberio, P., Meattini, I., Visani, L., Roviello, G., Spinelli, S. (2024). Taste alterations in cancer patients undergoing chemotherapy: methodological aspects and risk factors for their development, in Pubblicazione Atti del VIII Convegno Nazionale della Società Italiana di Scienze Sensoriali, Alghero (Italia) 22-24 maggio 2024, Società Italiana di Scienze Sensoriali

Rorandelli, C., Spinelli, S., Di Meglio, J., Doni, L., Dinnella, C., de Giorgi, V., Monteleone, E., Zuccaro, B., Gambale, E., Venturi, F., & Roviello, G. (2023, August). *Measuring taste alterations in cancer patients undergoing chemotherapy or target therapy*. In *15th Pangborn Sensory Science Symposium – Meeting New Challenges in a Changing World (PSSS 2023): I01*.

Conference contributions

- 11th European Conference on Sensory and Consumer Research (Eurosense 2024) – Dublin, Ireland, 8-11 September 2024 – Flash Presentation and Poster Food Preferences and Emotional Responses to Foods in Cancer Patients with Chemosensory Alterations
- VI Incontro del Gruppo GIOTTO Giovani Uro-Oncologi Toscana – Oncology Conference – Quercianella (LI), November 2024- Speaker in Round Table
- VIII Convegno Nazionale della Società Italiana di Scienze Sensoriali – Alghero, 22-24 May 2024 – Oral presentation "Early changes in food preferences and emotional responses to foods in cancer patients with chemosensory alteration"
- XLIV National conference of Italian Society of Human Nutrition (SINU)– Arezzo, 7-9 June 2023 – Oral presentation "Changes in taste and food preferences in cancer patients undergoing antineoplastic therapies"
- Altered Taste International Symposium – 3rd Edition – Lyon (France), 14-15 September 2023– Poster "Changes in food preferences and taste alterations in cancer patients undergoing antineoplastic treatment"

International experience during the PhD

Visiting PhD student at the Institut Lyfe Research and Innovation Center Lyon, France, three months academic secondment, from the 13th of January to 16th of April 2025.

Awards

2024 Young Researcher SISS Award 2024, 8th Italian Sensory Science Society National Conference, Alghero (IT)

BANDO FAI travel grant, University of Florence

Active member of scientific societies and working group

Member of the Italian Sensory Science Society (SISS) and of the Young Researcher Group SISS
Member of the European Sensory Science Society (E3S) and of the Next Generation Group E3S

Original paper

Di Meglio, J., Rorandelli, C., Dinnella, C., Monteleone, E., Stingo, F. C., Doni, L., Visani, L., Guarino, A., Gambale, E., De Sanctis, R., Gerosa, R., Tiberio, P., Antonuzzo, L., Scotti, V., Meattini, I., Roviello, G., & Spinelli, S. (2025). Changes in chemosensory perception, food preferences and emotional responses to foods in cancer patients during the early stages of chemotherapy: An exploratory study. Food Quality and Preference, 134, 105671. https://doi.org/10.1016/j.foodqual.2025.105671

Food Quality and Preference 134 (2025) 105671

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Changes in chemosensory perception, food preferences and emotional responses to foods in cancer patients during the early stages of chemotherapy: an exploratory study

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ABSTRACT

The prevalence of chemosensory disorders among cancer patients is large and may affect preferences and patients' relationship with foods. The aim of this study is to explore the impact of chemotherapy on chemosensory perception and the impact of self-reported alterations on food experience, specifically on food preferences and emotions elicited by foods in cancer patients during the first cycles of chemotherapy. The data considered here are related to the observations before the start of therapy (T0), after the first (T1), the second (T2) and the fourth (T4) cycle of chemotherapy.

The study shows that chemotherapy induced a variety of chemosensory alterations and disturbances, from self-reported alterations such as phantogeusia and parageusia to decrease of sweet (at lower concentration) and salty (at lower and higher concentration) perception. Self-reported alterations were associated with an increase in negative emotions towards preferred foods after the first cycle of therapy. Self-reported decline in tastes was not associated with changes in preferences, while general taste alterations and parageusia were associated with a change in preference for sweet/bitter foods after the 2nd, and discomfort after the 4th cycle of therapy.

These findings suggest that chemosensory alterations begin early during chemotherapy and progressively worsen, with significant implications for patients' food choices and for their emotional wellbeing. Emotional responses to food may serve as early indicators of sensory-related distress, even before actual changes in preferences occur. This highlights the need for timely personalized supportive interventions to mitigate the impact of these side effects on patients' quality of life.

1. Introduction

The prevalence of taste and smell disorders among cancer patients may exceed 93 % (Larsen et al., 2021) with relevant impact on quality of life by reducing food enjoyment, appetite, and potentially leading to malnutrition (Boltong & Keast, 2012). These symptoms are especially common in patients receiving platinum- or taxane-based chemotherapy (Bernhardson, Tishelman, & Rutqvist, 2008; Gamper et al., 2012; Steinbach et al., 2009), however, they are considered "orphan symptoms" (Santini et al., 2020) because they are often neglected in clinical setting (Sevryugin, Kasvis, Vigano, & Vigano, 2021) and are sometimes not immediately reported by patients (Battle et al., 2020) probably

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because they consider them as part of the treatment, and even as a sign of treatment effectiveness (Prieto-Callejero et al., 2020).

Despite patients receiving chemotherapy often experiencing chemosensory changes, accurately determining the frequency of these problems is difficult due to the variety of assessment methods and different types of alterations. In sensory research, several methodologies are used to assess chemosensory perception, but their application in oncology is limited (Nolden, Hwang, Boltong, & Reed, 2019). This limitation has made it difficult to compare results and has led to variable reports on the frequency and severity of these disorders among cancer patients (Galaniha & Nolden, 2023). Furthermore, methods used in studies which involve the evaluation of taste thresholds using electrical stimulation, filter paper strips or aqueous solutions are effective in the evaluation of disorders as hypogeusia and ageusia, but they typically focus on the lowest detectable concentration of tastants, which does not reflect the intensity level at which taste is normally perceived during real-life food consumption (Bartoshuk, 2000), as instead happens using suprathreshold methods. In addition, these methods fail to assess other symptoms commonly reported by patients, including phantogeusia, parageusia and cacogeusia (Kano & Kanda, 2013).

However, as highlighted by some studies (IJpma et al., 2017; de Vries et al., 2018; de Vries et al., 2019; Postma, Kok, de Graaf, Kampman, & Boesveldt, 2020) self-reported chemosensory changes often do not align with psychophysical assessments of taste and smell functions, as patients may struggle to differentiate between taste and smell, evaluating the overall flavor perception (de Vries, Winkels, et al., 2018). This divergence between methods, rather than representing a limitation, highlights the need to use both approaches in a complementary manner. Using a single method may lead to incomplete information. Therefore, an integrated methodological approach that combines sensory suprathreshold tests with self-reported measures is needed, allowing for a more accurate and broad understanding of chemosensory changes during chemotherapy.

It has long been known that taste and smell are important drivers for individuals' food preferences (Drewnowski, 1997), therefore their alterations during an anticancer treatment might reduce food palatability, limiting food choices and reducing the variety of the diet (Kim et al., 2020; Kourouniotis et al., 2016). However, it is still unclear when this condition occurs and how long it persists. Existing studies use different methods to assess cancer patients' food preferences and affective responses to foods; these include frequency of consumption, qualitative interviews, questionnaires such as the Macronutrient and Taste Preference Ranking Task, and measure of liking using the 9-point hedonic scale (Coa et al., 2015; de Vries, Winkels, et al., 2018; Kim et al., 2020; Nielsen, Theologides, & Vickers, 1980; Pedersini et al., 2021; Postma et al., 2020). The studies indicate a general trend of decreased liking of foods after chemotherapy treatment commencement, and in some cases food aversions have been reported for foods consumed immediately prior to the chemotherapy infusion (Boltong & Keast, 2012). However, as highlighted in a recent scoping review (Nolden et al., 2019) mixed results are often obtained, and a consistent effect was found only for sweetness with a reduced sweet taste function (decreased sensitivity) that was found to be associated with a reduced intake of a variety of different macro and micronutrients, reduced appetite, and overall lower energy intake. Instead, only limited evidence was found to be related to bitter alterations. Indeed, very few studies integrate psychophysical tests and assessment of food enjoyment and eating behaviors which limits the ability to capture the full impact of chemosensory changes on food-related experiences. Furthermore, studies rarely take into account sensory characteristics related to food preferences such as flavor, texture, smell, presence of herbs and spices, sourness, and bitterness, but focus more on their nutritional composition (de Bruijn, de Vries, de Graaf, Boesveldt, & Jager, 2017; Griffioen-Roose, Finlayson, Mars, Blundell, & de Graaf, 2010; Griffioen-Roose, Mars, Finlayson, Blundell, & De Graaf, 2011).

Food acceptance is frequently assessed through measures of hedonic liking, which primarily capture sensory pleasure that has been widely used to predict food choices and intake. Products that receive higher liking scores are typically selected more frequently than those with lower scores, and products disliked are not consumed (De Graaf et al., 2005; Keller, Shehan, Cravener, Schlechter, & Hayes, 2022). However, food choice is influenced by more than just liking; a variety of factors contribute to why a product is selected. Emotions elicited by food, for instance, can strongly influence the decision-making process (Jiang, King, & Prinyawiwatkul, 2014), suggesting that both sensory and emotional factors need to be considered to fully understand food preferences in cancer patients (Meiselman, 2021). This because food is more than just a source of nutrients (Prinyawiwatkul, 2023). Indeed, King (2016) claimed that food "*nourishes the body and soul*". Therefore, while food delivers nutrients to body, there are other elements, such as enjoyment and pleasure, associated with food. Macht (2008) uncovered a relationship between eating and emotions, suggesting, as an example, that emotions regulate eating, and eating regulates emotions. The emotions elicited by foods play a key role in food liking and choices (Cardello et al., 2012; Jaeger, Chheang, Roigard, & Cardello, 2022; Ng, Chaya, & Hort, 2013; Spinelli, 2021). Although previous studies (Boltong, Keast, & Aranda, 2012; de Vries et al., 2018; de Vries, Winkels, et al., 2018; Kim et al., 2020; Ponticelli et al., 2017; Postma et al., 2020; Speck et al., 2013) have explored the potential causes of chemosensory alterations and their impact on preferences, nutritional status, and quality of life in cancer patients, the emotions elicited by food remain largely unexplored. While emotions associated with food have been studied in vulnerable people such as children, (Aguiar-Bloemer & Diez-Garcia, 2018; Gallo, Swaney-Stueve, & Chambers, 2017; Sick, Monteleone, Pierguidi, Ares, & Spinelli, 2020) they have yet to be investigated in cancer patients. This gap leaves a critical area of understanding unaddressed, particularly in how emotional responses to food might influence eating behavior and preferences in cancer patients.

Oncologic treatment effects may differentially affect food preferences as taste changes have been shown to be individual (Brisbois, De Kock, Watanabe, Baracos, & Wismer, 2011). During chemotherapy, while some individuals demonstrated acceptance or even indifference towards their chemosensory disorders, others experienced profound frustration, disappointment, and guilt (Boltong et al., 2012). While some studies (Coa et al., 2015; Crowder et al., 2019; de Vries, Winkels, et al., 2018; Kim et al., 2020; Nielsen et al., 1980; Postma et al., 2020) have attempted to shed light on the impact that such disturbances may have on food preferences, to date, to our knowledge, no study has ever investigated in detail whether certain categories of foods may be associated with greater emotional deterioration. Chemosensory changes are sometimes unpredictable and could lead to emotional consequences which indirectly affect daily life especially in relation to cooking and social rituals of eating (Bernhardson, Tishelman, & Rutqvist, 2007, 2009). This altered relationship with foods and eating in general, which occurs during the treatment, may cause many psychological problems that lead to alienation from social life and significantly affect compliance with the treatment. These situations trigger loneliness and psychological bad feelings in patients over time negatively affecting the quality of life (Ejder & Sanlier, 2023).

The underestimation and consequent non-treatment of the occurrence of chemosensory alterations lead cancer patients to develop coping strategies and make dietary choices that may not always be suitable. As a result, they may face two opposite situations: firstly, they may experience a loss of appetite, have difficulty meeting nutritional requirements (Nielsen et al., 1980) and lose weight (Ryan, Prado, Sullivan, Power, & Daly, 2019; Tueros & Uriarte, 2018); alternatively, they may honor specific food cravings, exhibit irregular eating behaviors with increased caloric intake, leading to subsequent weight gain (Bernhardson et al., 2009; Speck et al., 2013). Both situations increase the risk of malnutrition for patients (Bernhardson et al., 2007; Boltong & Keast, 2012), resulting in reduced compliance in treatment regimen (Doty, Shah, & Bromley, 2008), increased treatment-related

complications, and in severe cases, higher co-morbidity and mortality rates (Ravasco, 2005).

The aim of this study is to investigate the impact of chemotherapy on chemosensory perception using a combined approach that includes both suprathreshold psychophysical tests and validated self-assessment measures. Furthermore, the study aims to explore the consequences of chemosensory alterations on the eating experience, assessing changes in food preferences and emotions elicited by foods differing in key sensory properties (e.g. quality and intensity of taste, texture, …) in cancer patients during the first cycles of chemotherapy.

2. Materials and methods

2.1. Overview and management of the study

The present data were collected as part of the larger ongoing ALTERTASTE project (Spinelli, Mini, Monteleone, Angiolini, & Roviello, 2021, Clinical trial CEAVC n. 20,839), a longitudinal prospective study started in 2022 and currently in progress (March 2025) at Careggi University Hospital (Florence, Italy) and IRCCS Humanitas Research Hospital (Rozzano, Milan, Italy). Study procedures were approved by the Ethics Committee for Clinical Trials in Tuscany Region – Large Central Area section (Rif. CEAVC n. 20839), Careggi University Hospital, Florence (CEAVC Em. 2022–418 ID 20839), and by the Independent Ethics Committee of the Humanitas Clinical Institute (3531/ID. 20839) and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants enrolled in the study in line with the GDPR (General Data Protection Regulation) 2016/679.

This article reports preliminary results from an ongoing prospective study examining the impact of chemotherapy-induced taste alterations on nutritional outcomes in cancer patients. These early findings are shared to underscore emerging patterns that warrant timely discussion, particularly in the context of symptom management in oncology. While data collection is still in progress, the current results provide valuable insights and lay the groundwork for more robust analyses upon study completion.

2.2. Patients: Recruitment, inclusion criteria, and description of study population

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study: a histologically confirmed diagnosis of breast cancer, gastrointestinal cancer, prostate cancer, testicular cancer, or bladder cancer; an Eastern Cooperative Oncology Group performance status ≤ 1; a treatment plan with taxane-based or platinum-based chemotherapy (in the neoadjuvant or adjuvant setting); an adequate hematological, hepatic, renal and cardiac function; an age $\geq$ 18 years; a written informed consent dated and signed by both patient and investigators.

The exclusion criteria were a major surgery within 2 weeks of study enrollment; brain metastases or leptomeningeal disease; severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, such as severe malnutrition.

2.3. Overview of data collection

Patients were recruited during the oncological visit in which general information about the study was given. They were invited to attend a maximum of 7 sessions depending on the treatment: before therapy, after 1 cycle, after 2 cycles, after 4 cycles, after 6 cycles, after 8 cycles and 3 months after the conclusion of the treatment plan. The data considered here are related to the observations before the start of therapy (T0), after the first (T1), after the second (T2) and after the fourth (T4) cycle of chemotherapy.

The data collection happened always right before the next cycle (e.g. "after 2 cycles" refers to a data collection right before the 3rd cycle). Observation times varied based on the type of therapeutic plan as shown in Table 1. At T0, before the beginning of treatment, patients were introduced to the general organization of the session (Fig. 1). After the welcome, only at T0, patients were asked to fill out the 8-item short form Sensitivity to Disgust Scale (Haidt, Mccauley, & Rozin, 1994.; Inbar, Pizarro, & Bloom, 2009; Spinelli et al., 2018) and the Italian Child Food Neophobia Scale (Laureati, Bergamaschi, & Pagliarini, 2015; Pliner & Hobden, 1992). This latter scale was selected because it was simpler to understand, and we expected older patients having more problems in using the Food Neophobia Scale for adults (Pliner & Hobden, 1992) as it includes items related to exotic restaurants that may be unfamiliar to them.

The following procedures were carried out at each session. Weight and height were measured using a stadiometer. BMI was calculated as the weight (kg)/height (m^2). Body composition (fat mass and free fat mass) was determined by a bioelectrical impedance analysis device (TANITA, model BC-613). Quality of life was assessed using European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ 30) (Aaronson et al., 1993); self-reported taste/odor responses, changes in hedonic responses to basic tastes and changes in eating habits, such as use of condiments, during treatment were collected using an adapted version of a questionnaire set up to measure chemosensory changes due to COVID-19 (Global Consortium of Chemosensory Research questionnaire, GCCR questionnaire) (Parma et al., 2020); self-reported taste alterations and related side effects were collected using an adapted version of the Italian Chemotherapy-induced Taste Alteration Scale (CiTAS) (Campagna et al., 2016; Kano & Kanda, 2013). Then, patients were asked to identify and rate the intensity of a series of five samples of aqueous solutions at low/moderate concentration ("lower concentration"). Then, they had a break and were asked to fill out the Food Preferences and Emotions Questionnaire developed specifically for this study and the subscale "Preparation and eating" of the Food Involvement Scale (Bell & Marshall, 2003). After the break patients had to identify and rate the intensity of other five samples of aqueous solutions at moderate/high concentration ("higher concentration"). During another break qualitative semi-structured interviews were conducted. Finally, an index of oral responsiveness was measured through a PROP test with filter paper disks (Rorandelli et al., 2024; Zhao, Kirkmeyer, & Tepper, 2003). Each session lasted approximately 1 h.

2.4. Procedure

2.4.1. Socio-demographics data, clinical and health status

Socio-demographic, clinical and health status data were collected and shown in Table 2. The questionnaire used to collect this information included forced-choice questions and open-ended questions.

The clinical data were obtained through the consultation of medical records.

2.4.2. Measuring taste responsiveness and self-reported alterations

2.4.2.1. Sensory tests with aqueous solutions. Before the test with water solutions, patients were trained to the use of the general Labeled Magnitude Scale (gLMS) (0: no sensation – 100: the strongest imaginable sensation of any kind) consistently with published standard procedure (Bartoshuk, 2000; Green et al., 1996; Green, Shaffer, & Gilmore, 1993). The gLMS consists of a 100-unit vertical line with labels placed at "no sensation" (0); "barely detectable" (1.4); "weak" (6); "moderate" (17); "strong" (34.7); "very strong" (52.5); and "strongest imaginable sensation of any kind" (100). Numerical labels were not reported on the scale. Patients were instructed to treat the "strongest imaginable sensation" as the most intense sensation they can imagine that involves remembered/imagined sensations in any sensory modality. This included the

Table 1
Planning of observation times for each site of cancer and related treatment regimen.

Type of cancer and treatment plan	T0	T1	T2	T3	T4	T6	T8	TF
Bladder – a total of 4 cycles of 21 days (carboplatin + gemcitabine) (cisplatin + gemcitabine)	**Before treatment** ***N* = 5**	**After the 1st cycle** ***(3 weeks)***	**After the 2nd cycle** ***(6 weeks)***	After the 3rd cycle *(9 weeks)*	**After the treatment (after the 4th cycle)** ***(12 weeks)***			3 months after the end of the treatment
Gastrointestinal – a total of 12 cycles of 15 days (5-fluorouracil + oxaliplatin + folinic acid)	**Before treatment** **N = 1**		**After the 2nd cycle** ***(4 weeks)***		**After the 4th cycle** ***(8 weeks)***	After the 6th cycle *(12 weeks)*	After the 8th cycle *(16 weeks)*	3 months after the end of the treatment
Testicle – a total of 1–3 cycles of 21 days (cisplatin + etoposide + bleomycin)	**Before treatment** **N = 5**	**After the 1st cycle** ***(3 weeks)*** (the test was conducted also after *7 days**)	**After the 2nd cycle** ***(6 weeks)***	After the treatment (after the 3rd cycle) *(9 weeks)*				3 months after the end of the treatment
Prostate – a total of 6 cycles of 21 days (docetaxel) (cabazitaxel)	**Before treatment** **N = 4**	**After the 1st cycle** ***(3 weeks)***	**After the 2nd cycle** ***(6 weeks)***	After the 3rd cycle *(9 weeks)*	**After the 4th cycle** ***(12 weeks)***	After the treatment (after the 6th cycle) *(18 weeks)*		3 months after the end of the treatment
a) Breast*** – a total of 8 cycles (4 cycles of 21 days of epirubicine and cyclophosphamide +4 cycles of 21 days of docetaxel (or 12 weekly paclitaxel**) and carboplatin)	**Before treatment** ***N* = 22**	**After the 1st cycle** ***(3 weeks)***	**After the 2nd cycle** ***(6 weeks)***		**After the 4th cycle** ***(12 weeks)***	After the 6th cycle *(18 weeks)*	After the treatment (after the 8th cycle) *(24 weeks)*	3 months after the end of the treatment
b) Breast*** – a total of 8 cycles (dose dense 4 cycles of 4 days of epirubicine and cyclophosphamide +4 cycles of 21 days of docetaxel)	**Before treatment** ***N* = 11**	**After the 1st cycle** ***(2 weeks)***	**After the 2nd cycle** ***(4 weeks)***		**After the 4th cycle** ***(8 weeks)***	After the 6th cycle *(14 weeks)*	After the treatment (after the 8th cycle) *(20 weeks)*	3 months after the end of the treatment
c) Breast*** –a total of 4 cycles (4 cycles of 21 days of docetaxel and cyclophosphamide) or (12 weekly cycles** of paclitaxel,)	**Before treatment** ***N* = 7**	**After the 1st cycle** ***(3 weeks)***	**After the 2nd cycle** ***(6 weeks)***	After the 3rd cycle *(9 weeks)*	**After the treatment (after the 4th cycle)** ***(12 weeks)***			3 months after the end of the treatment

Observations **emboldened** were considered in this paper. *To explore the platinum influence (IJpma et al., 2017). **For weekly treatment, 1 cycle was considered as a group of three (total of 21 days). *** For the breast cancer, in relation to the stage of the disease (metastatic or adjuvant) and biological parameters, chemotherapy treatment was associated with targeted therapy with trastuzumab or immunotherapy with pembrolizumab.

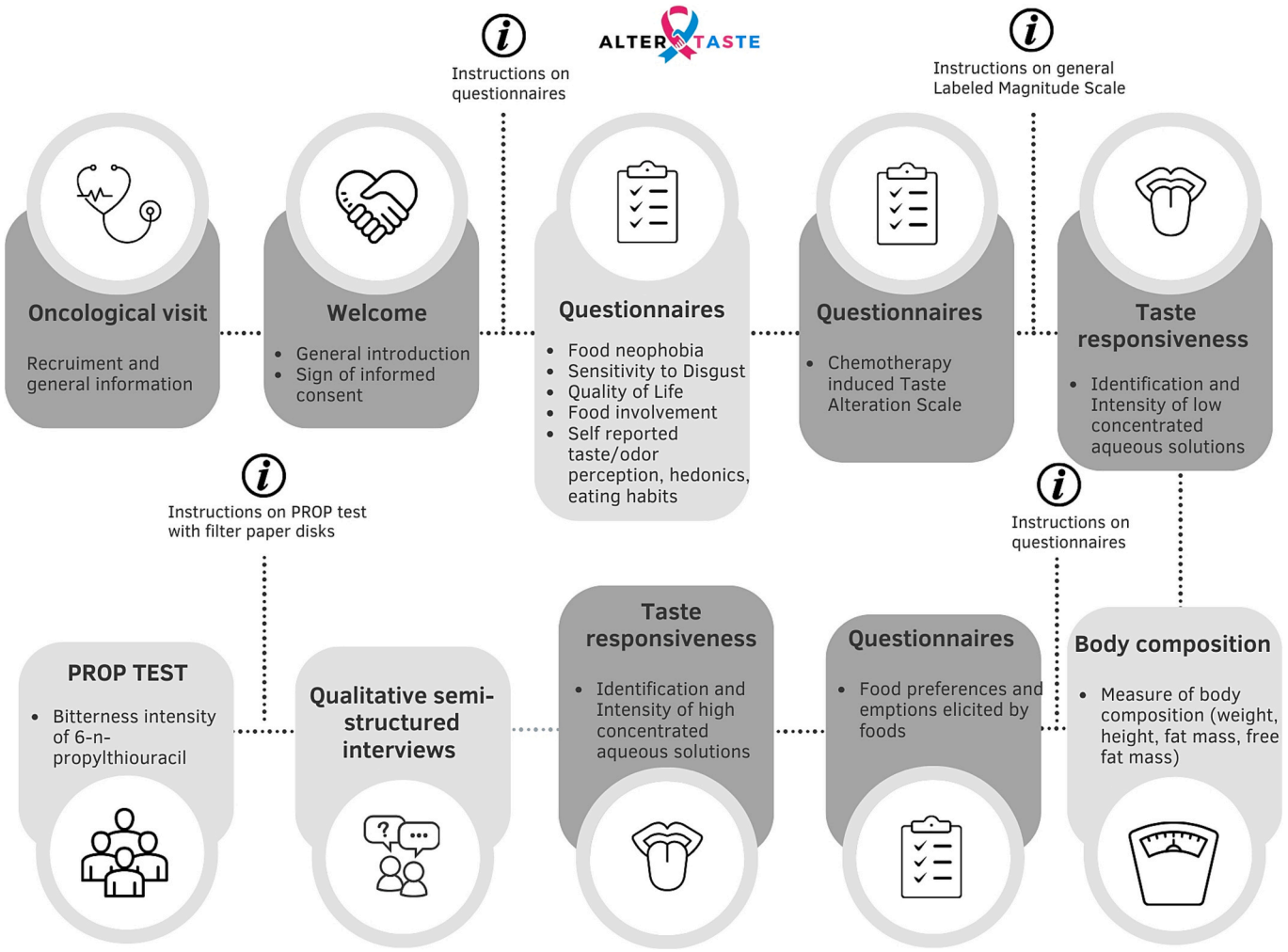

Fig. 1. Overview of data collection (dark grey boxes indicate the variables analyzed in this paper).

Table 2
Demographic, clinical and nutritional data of study population.

Variable	All patients (n = 55)
Age, yr (mean ± SD) min 23; max 82	50.7 ± 13.2
Sex (%)	F (74.5) M (25.5)
Smoking habits (%)	Never tried (45.4) Have tried, quit (38.2) Occasionally (5.5) Regularly (10.9)
Educational level (%)	None (0.0) Primary (1.8) Lower secondary (21.8) Upper secondary (41.8) Degree (34.6) Post degree (0.0)
Site of cancer (%)	Breast (72.7) Bladder (9.1) Testicle (9.1) Prostate (7.3) Colorectal (1.8)
BMI ranges at T0 (%)	Underweight <18.5 kg/m^2 (0) Normal weight 18.5–24.9 kg/m^2 (52.7) Overweight 25.0–29.9 kg/m^2 (38.2) Obesity >30 kg/m^2 (9.1)

deafening noise of a plane that is flying low, and the strong pain felt when shutting a finger in a door.

Then, patients were presented with a first series of five water solutions at lower concentration corresponding to the weak/moderate intensity on the gLMS. The aqueous solutions correspond to four basic tastes (sweet with 67 g/L of sucrose Sigma Aldrich, Milan, Italy; sour with 1.3 g/L of citric acid Sigma Aldrich, Milan, Italy; salty with 5 g/L of sodium chloride Sigma Aldrich, Milan, Italy; bitter with 0.75 g/L of caffeine Sigma Aldrich, Milan, Italy) and one somatosensory sensation (pungent with 0.00055 g/L of capsaicin Sigma Aldrich, Milan, Italy). Each sample (10 mL) was presented in a plastic cup, identified by a three-digit code. The presentation order of samples was randomized for the basic tastes while the pungent solution was always evaluated as the last sample to avoid perceptual interference between samples due to the carry-over effect of capsaicin. Patients had to hold the sample in their mouth for a total of 3 s, then spit and expectorate, wait 3 s (or 5 s for bitter and pungent solutions), identify one or more perceived sensations with a Check-All-That-Apply (CATA) format from a predefined list including sweet, sour, salty, bitter, astringent, pungent, tasteless, other (open-ended), and evaluate the overall intensity of each solution on the gLMS. Between the samples, there was a break of 60 s in which patients had to rinse their mouth with still water, had a cracker (optional) and rinsed again before the following solution.

Afterwards, patients were again presented with a second series of five higher concentration water solutions (sweet with 200 g/L of sucrose Sigma Aldrich, Milan, Italy; sour with 4 g/L of citric acid Sigma Aldrich,

Milan, Italy; salty with 15 g/L of sodium chloride Sigma Aldrich, Milan, Italy; bitter with 3 g/L of caffeine Sigma Aldrich, Milan, Italy; and pungent with 0.0015 g/L of capsaicin Sigma Aldrich, Milan, Italy). The procedure was the same as just described.

Both lower and higher concentrations were selected to cover a range of intensity ratings from weak/moderate to moderate/strong on the gLMS based on preliminary studies and on the literature (Feeney & Hayes, 2014; Hayes, Sullivan, & Duffy, 2010; Masi, Dinnella, Monteleone, & Prescott, 2015; Monteleone et al., 2017; Nolden & Hayes, 2017; Pierguidi et al., 2023; Spinelli et al., 2023; Webb, Bolhuis, Cicerale, Hayes, & Keast, 2015; Yeomans, Tepper, Rietzschel, & Prescott, 2007).

2.4.2.2. Self-reported responses about taste and smell perception. At each session patients completed CiTAS to assess self-responses. The original Italian Version of Chemotherapy-induced Taste Alteration Scale (Campagna et al., 2016) is a 18-item questionnaire which evaluates the 4 dimensions of some conditions related to taste and smell alterations using a Likert scale of 1–5 (where 1 = no difficulty or absence of the disorder and 5 = maximum difficulty or very much discomfort): decline in basic tastes (quantitative disturbances in the perception of sweet, bitter, sour, salty, umami tastes), discomfort (reduced appetite, difficulty in eating certain types of food, nausea), phantogeusia (taste perception in mouth without external stimuli), general taste alterations and parageusia (distorted/bitter/bad taste of food). Specifically for the study, the questionnaire was adapted by adding five items: "metallic taste in mouth" and "sour taste in mouth" and "increase in taste perception" added to the phantogeusia dimension, "dry mouth" and "mucositis/inflammation/pain/ulcerations in the mouth" added to the discomfort dimension. These additions were based on the literature (Corremans, Geurden, Luyten, & Mortelmans, 2021.; IJpma, Renken, ter Horst, & Reyners, 2015; Mahmoud, Aktas, Walsh, & Hullihen, 2011; McGettigan et al., 2019; O'Donoghue et al., 2023; Silva et al., 2021), and on preliminary interviews with cancer patients. The items "have difficulty tasting food", "unable to perceive the smell or flavor of food" and "have difficulty eating meat" were removed. The first because it was considered too generic and difficult to understand by patients. The second because it combines distinct sensory experiences such as smell and flavor, which can lead to ambiguity and reduce the clarity of data collected. Although smell contributes significantly to the perception of flavor, it may not always be the cause of its alteration (Belqaid et al., 2016; Spence, 2015). The item "have difficulty eating meat" was removed because it can have multiple meanings, not necessarily related to sensory discomfort. For example, the difficulty could arise from psychological factors, such as sarcophobia (fear or aversion to meat), or from a common inclination to change eating habits towards a healthier direction in order to potentially improve treatment efficacy (Pedersini et al., 2021; Salminen, Bishop, Poussa, Drummond, & Salminen, 2004). Furthermore, the item "I have difficulty perceiving umami tastes" was modified by replacing the word "umami" with "savory", as we believed that the concept of umami might be difficult for patients to understand due to its unfamiliarity within the European culture. The adapted version of CiTAS used for the study was thus composed by 20 items grouped in 4 dimensions: decline in basic tastes (5), general taste alterations and parageusia (3), phantogeusia and increase in taste perception (5), discomfort (7). The labels of the 5-point Likert scale were uniformed across the different subscales as follows: 1= "not at all", 2 = "slightly", 3 = "quite", 4 = "very", 5 = "very much".

2.4.3. Assessment of food preferences and emotions

The Food Preferences & Emotions Questionnaire (FP&EQ) was developed in order to track any changes in preferences and emotions elicited by foods differing in key sensory properties during the whole treatment period. The questionnaire (Tables 3a) is composed by 6 different dimensions (flavor, texture, herbs and spices, sweet/bitter, sweet/sour, odor) each containing 5 food/drink/odor pairs (for a total of 30 pairs of items), designed and tested to recall the different levels of target sensations. Some of the items were selected from the IT-Food Choice Questionnaire (Monteleone et al., 2017), with sensory differences between pairs validated in previous studies (De Toffoli et al., 2019; Pagliarini et al., 2021). The remaining items were developed exclusively for the study based on scientific literature on sensory differences between products. The new items were subjected to a preliminary validation involving 36 to 117 consumers recruited to perform a pairwise comparison test. Participants were asked to indicate in each pair which product was more "intense in flavor/creamier/sweeter/intense in odor". The results were analyzed through a unilateral test based on which it was possible to conclude whether there was a perceptible difference between the two products through a minimum number of correct answers (*Supplementary materials 1*).

In the questionnaire, patients were presented with pairs of foods, beverages, and odors. They did not taste or smell the products but were

Table 3a
Pairs of products of the Food Preference and Emotion Questionnaire (FP&EQ).

Dimension	Pairs of products
Flavor (less/more intense)	Fresh pecorino/Aged pecorino
	Cow mozzarella/Buffalo mozzarella
	Cooked ham/Dry cured ham
	Smashed potato/Baked potato
	Valerian and lettuce/Radicchio and rocket
Texture (crunchy-consistent/creamy)	Vegetable soup/Vegetable cream
	Toasted bread/White bread
	Couscous/Semolina
	Julienned carrots/Cooked carrots
	Chocolate bar/Chocolate pudding
Herbs and spices (with/without herbs and spices)	Vegetables with chili/Vegetables without chili
	Tomato sauce with basil/Tomato sauce
	Herbal tea/Water
	Grilled chicken with thyme/Grilled chicken
	Zucchinis cream with mint/Zucchinis cream
Sweet vs. bitter	Panna cotta/Dark chocolate pudding
	Tea with sugar/Tea without sugar
	Milk chocolate/Dark chocolate
	Coffee with sugar/Coffee without sugar
	Pumpkin risotto/Radicchio risotto
Sweet vs. sour	Sweetened yogurt/Natural yogurt
	ACE juice/Orange juice
	Strawberry sorbet/Lemon sorbet
	Apricot jam/Raspberry jam
	Apple smoothie/Apple and lemon smoothie
Odor (more/less intense odor)	Bean soup/Vegetable soup*
	Bolognese sauce/Tomato sauce
	Fried cutlet/Grilled meat
	Meat broth/Vegetable broth
	Cooked tomato/Boiled rice

* Note: This pair was excluded based on the validation through the unilateral test (Supplementary Material 1).

Table 3b
List of emotions of the Food Preference and Emotion Questionnaire (FP&EQ).

Emotions	Valence	Arousal
Joy	Positive	High
Curiosity	Positive	High
Happiness	Positive	Low
Relax	Positive	Low
Annoyance	Negative	High
Disgust	Negative	High
Boredom	Negative	Low
Indifference	Negative	Low
Sadness	Negative	Low

asked to express their preferences for each pair based on their daily experiences or expectations in a specific eating context (e.g. "Between 'dark chocolate' and 'milk chocolate', indicate which food/drink you would prefer to eat as a snack. If you like both or neither of them, choose the one you are more inclined to eat"): main meals (either lunch or dinner, 18 pairs), snacks (9 pairs), all-day consumption (3 pairs). For odor pairs, participants specified which option they would rather avoid in each given context (e.g. You are in a room where someone has just finished eating/cooking and you can smell food. Indicate the option you would least like to smell between 'boiled rice' and 'cooked tomato').

The presentation order of the items within each pair, and of the pairs within the questionnaire, was randomized across patients. After the forced choice between products, patients were asked: "How does it make you feel?" (Spinelli, Masi, Dinnella, Zoboli, & Monteleone, 2014) and they should indicate at least one (or more) emotions (Table 3b) elicited by each item (both the chosen and the unchosen one) using a Check-All-That-Apply (CATA) format.

The emotions were selected based on previous studies on food products (Spinelli, 2021; Spinelli et al., 2014; Spinelli & Jaeger, 2019) and on the *circumplex model of affect* (Russell, Clement, Jiwani, Ridgeway, & Schroeder, 1980), that describe emotions based on valence (positive/pleasure vs. negative/displeasure) and arousal (high/activation vs. low/deactivation). Five negative emotions and four positive emotions were chosen for the questionnaire.

2.5. Data analysis of selected variables

First, descriptive statistics were calculated on CATA responses to assess the percentage of correct identification of each stimulus (sweet, salty, sour, bitter, pungent) at each time point (T0, T1, T2, T4). A response was considered correct if the target sensation was selected from the list (e.g., "salty" for the salty solution), even when chosen in combination with another sensation (e.g., "salty" and "sour" for the salty sample). In cases where the correct target was not selected, further descriptive analyses were conducted to determine which alternative sensations participants had selected, expressed as a percentage for each time point. This allowed for a better understanding of the most common misclassifications. A two-sample proportion test was applied to test significant differences between percentages of identification at different time points. To examine potential changes in chemosensory perception during the first four cycles of chemotherapy, perceived intensity ratings were first assessed for normality with the Shapiro-Wilk test and examining the Q-Q plots. As the data deviated from a normal distribution ($p < .0001$), non-parametric methods were employed.

First, a Kruskal-Wallis test was applied to test the differences between time-points (T0, T1, T2, T4) considering all five chemosensory stimuli together (sweet, salty, sour, bitter, pungent) separately for lower and higher concentration solutions, to provide a general overview of intensity variation over time. Subsequently, additional Kruskal-Wallis tests were conducted for each stimulus individually testing the differences between time points, at lower or higher concentrations separately, to detect specific trends over time for each taste or sensation. When significant effects were found, Dunn's post hoc tests with Bonferroni correction were applied to identify which time points differed significantly.

To evaluate the dimensional structure of the adapted version of CiTAS questionnaire, a Factor Analysis was run on responses collected after the first cycle (T1) ($n = 41$), after the second cycle (T2) ($n = 47$) and after the fourth cycle (T4) ($n = 34$) (*Supplementary materials 2*). The internal consistency of the questionnaire was assessed through Cronbach's alpha. The adequacy of the data for Factor Analysis was assessed using the Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity (Tabachnick & Fidell, 2001). Exploratory Factor Analysis (EFA) on Spearman correlation matrix was conducted using Principal Factor Analysis as a criterion for factor extraction. A four-factor structure was examined to align with the factor structure previously identified for the original questionnaires (Campagna et al., 2016; Kano & Kanda, 2013), using Varimax orthogonal rotation with Kaiser normalization. The level for retaining an item was set at a factor loading higher than 0.3 (Tabachnick & Fidell, 2001). To show a general overview of self-reported changes of chemosensory perception measured through the CiTAS during the first four cycles of chemotherapy, the mean scores of each dimension were first assessed for normality with the Shapiro-Wilk test. As the data deviated from a normal distribution ($p < .0001$), non-parametric methods were employed. Specifically, Kruskal–Wallis tests were conducted separately for each dimension of the questionnaire to assess differences across the four time points. When significant effects were found, Dunn's post hoc tests with Bonferroni correction were applied to identify which time points differed significantly.

Patients were classified with self-reported alterations through the CiTAS first by calculating the average score for each dimension per patient, then by identifying as "patients with alterations" those for whom the score was different from 1 (= "not at all") for each dimension.

Preferences expressed for each food/beverage/odor pair within every dimension (flavor, texture, odor, herbs and spices, sweet vs bitter, and sweet vs sour), and for each time point were indicated using binary data based on whether the patient selected the less intense/creamy/sweet/mild (0) or the more intense/grainy/crunchy/sour/bitter/seasoned option (1). The significance of the changes in preference for treatments T1, T2 and T4 compared to T0 for each dimension of the questionnaire between subjects with and without alteration segmented on the basis of self-reported responses of the CiTAS was tested through a Chi square analysis ($a = 0.05$). For this purpose, for the T0vsT1, T0vsT2 and T0vsT4 comparisons, a 2 × 2 contingency table was prepared with the presence of alterations on the rows (Yes; No) and the preference changes in the columns (Yes Change; No Change). Fisher exact test was run to test the significance by cell with significance level set at $a = 0.05$.

In order to understand if based on the specific self-reported alteration there was a specific direction of changes in preferences, a McNemar test

Table 4
Example of a 2 × 2 contingency table for the McNemar test – Analysis of change directions.

		T1 or T2 or T4	
		Sweet	Bitter
T0	Sweet	n (choice of sweet options in both observation)	n (choice of sweet options before treatment, which are replaced by the bitter options)
	Bitter	n (choice of bitter options before treatment, which are replaced by the sweet options)	n (choice of bitter options in both observation)

Table 5
Example of a 2 × 2 contingency table for the McNemar test – Analysis of changes in emotional valence of chosen options.

		T1or T2 or T4	
		Positive	Negative
T0	Positive	n (positive valence for chosen options in both observation)	n (positive valence of emotions for chosen options before treatment, which are replaced by the negative valence)
	Negative	n (negative valence of emotions for chosen options before treatment, which are replaced by the positive valence)	n (negative valence for chosen options in both observation)

Table 6
Percentage of identification of lower concentration samples at baseline (T0), the first (T1), the second (T2), and the fourth (T4) cycles of chemotherapy.

	T0 Correct identification (%)	T1 Correct identification (%)	T2 correct identification (%)	T4 correct identification (%)
Lower concentrated aqueous solutions				
Sweet (sucrose 67 g/l)	100	97.1	100	100
Sour (citric acid 1.3 g/l)	87.3	88.6	79.1	78.6
Salty (NaCl 5 g/l)	87.3	77.1	79.1	78.6
Bitter (caffeine 0.75 g/l)	52.7	60	62.8	67.9
Pungent (capsaicin 0.00055 g/l)	94.5	85.7	95.2	85.7
Higher concentrated aqueous solutions				
Sweet (sucrose 200 g/l)	100	100	100	100
Sour (citric acid 4 g/l)	92.7	97.1	90	88.9
Salty (NaCl 15 g/l)	94.5	91.4	87.5	88.9
Bitter (caffeine 3 g/l)	90.9	82.9	82.5	85.2
Pungent (capsaicin 0.0015 g/l)	100	94.3	95	92.6

was computed. The analysis tests differences in dichotomous data (e.g. bitter/sweet) before and after a certain treatment and it is necessary to set up a 2 × 2 contingency table which considers in the rows the choice at T0 (e.g. sweet/bitter) and in the columns the choice at the subsequent observation (T1; T2; T4) as explained in Table 4.

In order to understand if based on the specific alterations there was a change in valence of emotions elicited by the chosen options of the preferences questionnaire, a McNemar test was computed. The McNemar test was used to analyze changes within the same group of patients over time and therefore to study differences in dichotomous data before and after a certain treatment. A 2 × 2 contingency table was prepared for each comparison (T0 with T1; T0 with T2; T0 with T4) which has in the rows the valence (positive/negative) at T0 and in the columns the valence (positive/negative) at the subsequent observation individually (T1 or T2 or T4), as reported in Table 5.

A *p*-value of 0.05 was considered as threshold for statistical significance in all analyses.

Data were collected through the software Compusense v. 23.0.46 (Compusense Inc. Guelph, Ontario, Canada). Statistical analyses were performed using XLSTAT Statistical and Data Analysis Solution 2023.2.1414 (Lumivero 2023, Paris, France). Data were expressed as mean ± standard deviation (SD) or percentage, as appropriate.

3. Results

3.1. Demographic characteristics

All patients considered in the present paper completed between 1 and 4 cycles of chemotherapy. Demographic and clinical characteristics of the study population are presented in Table 2. Of 55 patients (mean age 50.7 ± 13.2 years) most were females (74.5 %), no-smokers (45.4 % never tried; 38.2 % have tried, quit), and with breast cancer (72.7 %). Before the start of the treatment, according to the body mass index (BMI) classification none of the patients (0 %) were in a condition of underweight, 52.7 % were of normal weight, 38.2 % were overweight, and 9.1 % were obese. The data were collected depending on the availability and conditions of the patients on 55 patients at T0, 41 patients at T1, 47 patients at T2, 34 patients at T4.

3.2. Overview of chemosensory perception: Identification and perceived intensity of aqueous solutions

The percentages of identification for the five stimuli across the four time points are shown in Table 6. Recognition was consistently high for sweetness (around 100 %), sourness, saltiness, and pungency, particularly at higher concentrations, where identification percentages mostly remained above 85 %. The bitter solution at lower concentration was the least accurately identified, although its recognition progressively improved from 52.7 % at T0 to 67.9 % at T4. When not correctly identified as bitter, participants most frequently misclassified the solution as tasteless (T0: 27.3 %; T1: 17.1 %; T2: 14.0 %; T4: 3.6 %), sour (T0: 10.9 %; T1: 5.7 %; T2: 11.6 %; T4: 14.3 %), or astringent (T0: 10.9 %; T1: 5.7 %; T2: 11.6 %; T4: 7.1 %).

While most stimuli were reliably recognized over time, a slight decline in identification rates was observed for some lower concentration solutions, such as salty and sour, particularly from T0 to T4. Despite

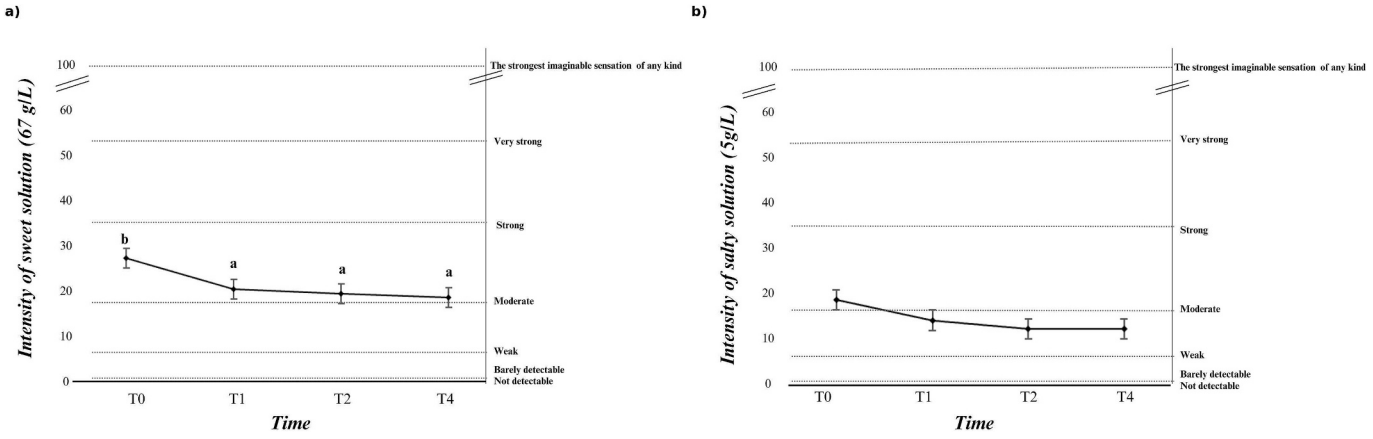

Fig. 2. a. Mean intensity ratings of lower concentration sweet solution at baseline (T0), after the 1st cycle (T1), after the 2nd cycle (T2) and after the 4th cycle (T4). Total observations $N = 158$; T0 $n = 55$; T1 $n = 35$; T2 $n = 40$; T4 $n = 28$.
b. Mean intensity ratings of lower concentration salty solution at baseline (T0), after the 1st cycle (T1), after the 2nd cycle (T2) and after the 4th cycle (T4). Total observations N = 158; T0 n = 55; T1 n = 35; T2 n = 40; T4 n = 28.
Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction.

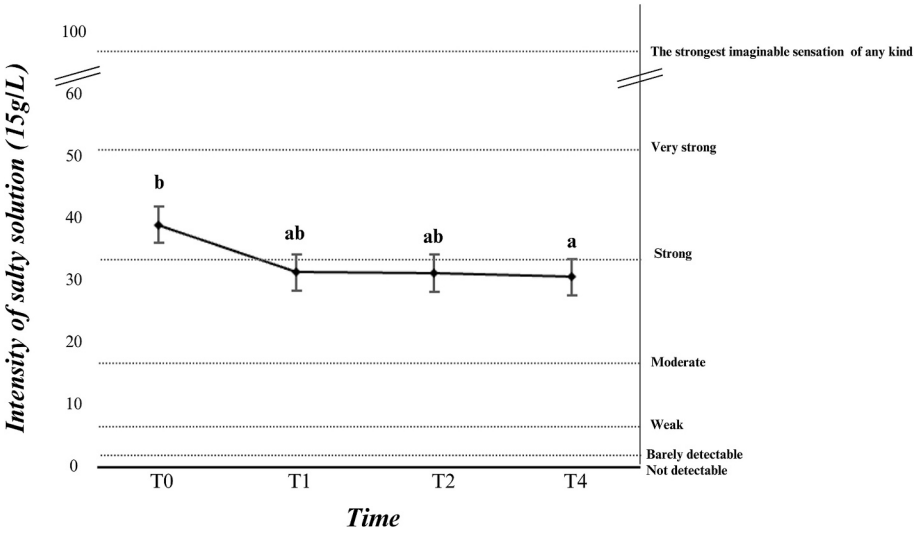

Fig. 3. Mean intensity ratings of higher concentration salty solution at baseline (T0), after the 1st cycle (T1), after the 2nd cycle (T2) and after the 4th cycle (T4). Total observations $N = 157$; T0 n = 55; T1 n = 35; T2 n = 40; T4 $n = 27$.
Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction.

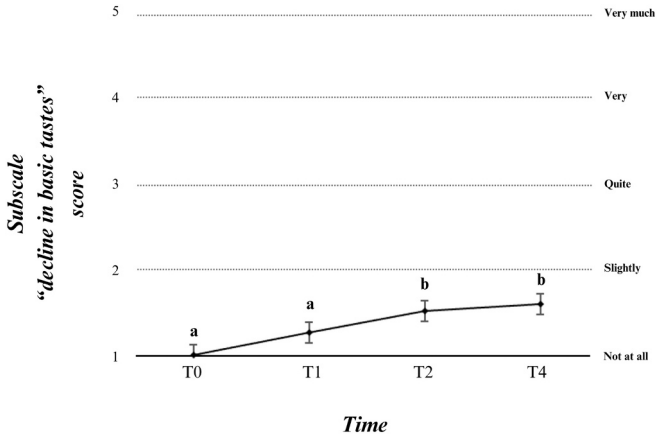

Fig. 4. Mean scores of "Decline in basic tastes" dimension at baseline (T0), after the 1st cycle (T1), after the 2nd cycle (T2) and after the 4th cycle (T4). Total observations $N = 177$; T0 n = 55; T1 $n = 41$; T2 $n = 47$; T4 $n = 34$.
Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction. ($p < .05$).

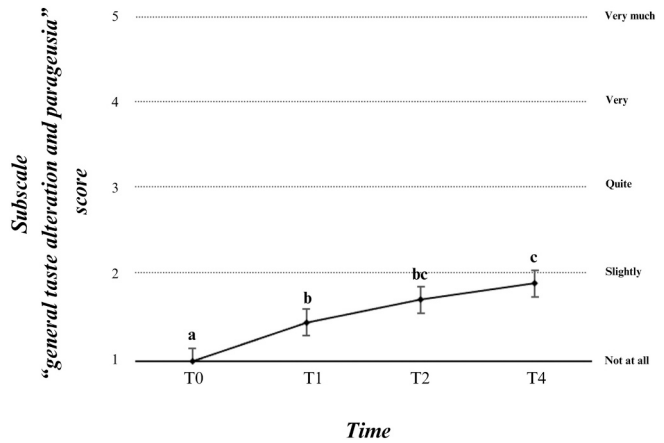

Fig. 5. Mean scores of "General taste alterations and parageusia" dimension at baseline (T0), after the 1st cycle (T1), after the 2nd cycle (T2) and after the 4th cycle (T4). Total observations N = 177; T0 n = 55; T1 n = 41; T2 n = 47; T4 n = 34.
Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction. (p < .05).

this decline, rates remained relatively high, indicating that patients generally maintained the ability to correctly identify target sensations throughout treatment. Additionally, statistical analysis based on two-proportion tests did not reveal significant changes in identification rates across time points, suggesting that, overall, patients maintained a relatively stable ability to recognize basic chemosensory stimuli during chemotherapy.

Patients reported a significant decline in their response to the sweet solution at lower concentration already after the first cycle of treatment ($\chi^2(3) = 13.67$, $p = .003$), with intensity ratings decreasing from moderate/strong (27.55) at T0 to moderate at T1 (20.72) (Fig. 2a). For the salty solution, the Kruskal–Wallis test showed a significant overall difference in perceived intensity across the four time points ($\chi^2(3) = 8.54$, $p = .036$). Although Dunn's post hoc with Bonferroni correction test ($\alpha = 0.0083$) did not identify significant differences between specific time points, a decreasing trend in intensity was observed with a reduction from T0 to T2 close to significance ($p = .009$) (Fig. 2b). No statistically significant changes over time were observed for the sour ($\chi^2(3) = 3.305$, $p = .347$), bitter ($\chi^2(3) = 2.276$, $p = .517$) and pungent ($\chi^2(3) = 4.825$, $p = .185$) solutions at lower concentration (*Supplementary Materials 3a*).

Among the higher concentration solutions, a significant decline in perceived intensity after T4 was found only for the salty solution (Fig. 3; $\chi^2(3) = 9.64$, $p = .022$), decreasing from an intensity rated between 'strong' and 'very strong' (41.66) to an intensity described less than strong (33.45). No significant differences between time points were found in the case of the sweet ($\chi^2(3) = 3.971$, $p = .265$), sour ($\chi^2(3) = 3.698$, $p = .296$), bitter ($\chi^2(3) = 0.866$, $p = .834$) and pungent ($\chi^2(3) = 0.408$, $p = .939$) solutions at higher concentration (*Supplementary Materials 3b*).

3.3. Self-reported responses to Chemotherapy-induced Taste Alteration Scale

The adapted version of the Italian CiTAS showed a good internal consistency with a Cronbach's alpha coefficient of 0.911. A Kaiser-Meyer-Olkin (KMO) of 0.842 and a significant Bartlett's sphericity test ($p < .0001$) indicated that the data was adequate for Factor Analysis. A

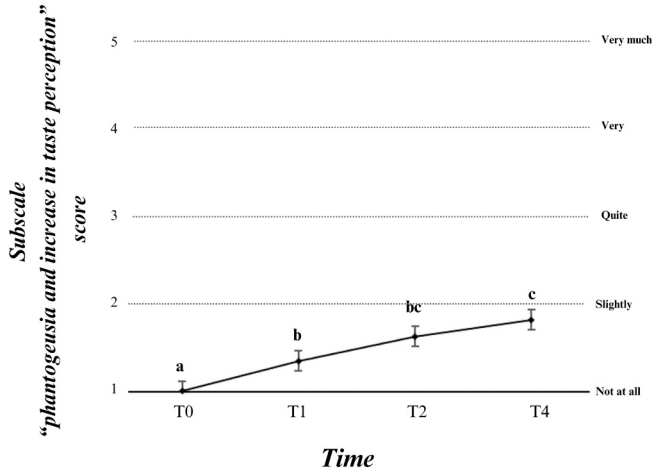

Fig. 6. Mean scores of "Phantogeusia and increase in taste perception" dimension at baseline (T0), after the 1st cycle (T1), after the 2nd cycle (T2) and after the 4th cycle (T4). Total observations N = 177; T0 n = 55; T1 n = 41; T2 n = 47; T4 n = 34.
Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction. ($p < .05$).

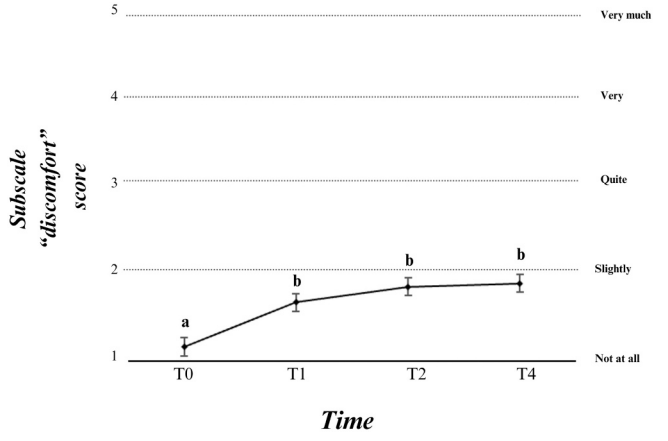

Fig. 7. Mean scores of "Discomfort" dimension at baseline (T0), after the 1st cycle (T1), after the 2nd cycle (T2) and after the 4th cycle (T4). Total observations N = 177; T0 n = 55; T1 n = 41; T2 n = 47; T4 n = 34.
Different letters indicate significantly different ratings according to Dunn's post hoc with Bonferroni correction. ($p < .05$).

Table 7
Percentage of patients who self-reported the different types of conditions represented by the CiTAS dimensions during the baseline (T0), the first (T1), the second (T2), and the fourth (T4) cycle of chemotherapy.

	% of patients who self-reported the condition			
CiTAS dimension	T0	T1	T2	T4
Decline in basic tastes	0.0 %	19.5 %	46.8 %	64.7 %
General taste alterations and parageusia	0.0 %	26.8 %	46.8 %	61.8 %
Phantogeusia and increase in taste perception	3.6 %	41.5 %	63.8 %	76.5 %
Discomfort	45.5 %	78.0 %	89.4 %	85.3 %

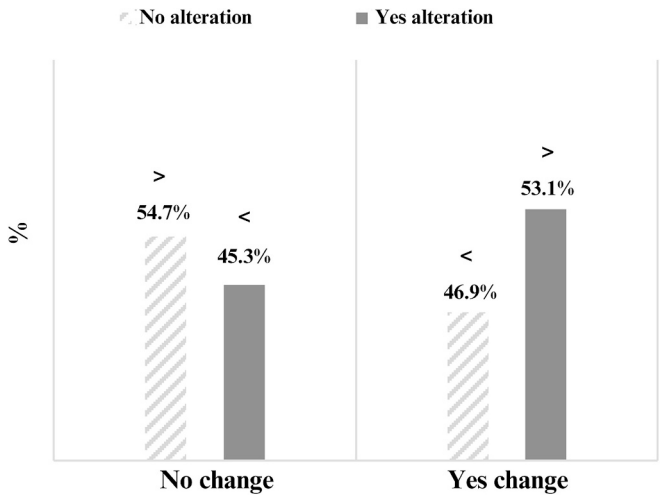

Fig. 8. Chi-Square analysis - Association between General taste alterations and parageusia and food preferences (all the dimensions of questionnaire) after the 2nd cycle of chemotherapy. < > indicate that the observed count was significantly greater or lower than its expected count (Fisher exact test).

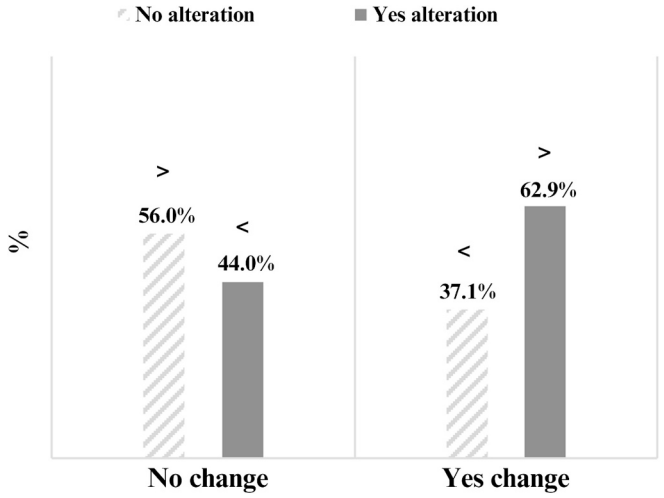

Fig. 9. Chi-Square analysis - Association between General taste alterations and parageusia and food preferences of "Sweet vs Bitter" dimension after the 2nd cycle of chemotherapy. < > indicate that the observed count was significantly greater or lower than its expected count (Fisher exact test).

four-factor structure was examined to align with the factor structure previously identified for the original questionnaire (Kano & Kanda, 2013) and for the Italian version (Campagna et al., 2016), using Varimax orthogonal rotation with Kaiser normalization. Once rotated the four-factor structure explained 55.93 % of the total variance. Factor loadings, explained variance, and Cronbach's alphas for the four-factor structure are reported in Supplementary materials 2.

To get a general overview of self-reported changes of chemosensory perception measured with the CiTAS during the first four cycles of chemotherapy, the scores of each dimension were analyzed through a Kruskal–Wallis test testing the effect of time points.

Starting from the 2nd cycle of chemotherapy the analyses showed a significant increase over time of the mean scores of "Decline in basic tastes" dimension ($\chi^2(3) = 47.43$, $p < .0001$, Fig. 4), and from the 1st cycle in "General taste alterations and parageusia" dimension ($\chi^2(3) = 43.50$, $p < .0001$, Fig. 5), in "Phantogeusia and increase in taste perception" dimension ($\chi^2(3) = 58.12$, $p < .0001$, Fig. 6) and in "Discomfort" dimension ($\chi^2(3) = 41.50$, $p < .0001$, Fig. 7).

Table 8
Comparison of the percentages of negative emotions elicited by selected options in the Food Preference and Emotion Questionnaire (FP&EQ) between baseline and the first cycle of chemotherapy in patients with self-reported alterations.

		% of negative emotions elicited by chosen options		
CiTAS dimension	FP&EQ dimension	T0	T1	p-value
Decline in basic tastes	Flavor	7.5 %	20.0 %	0.125
	Texture	15.0 %	25.0 %	0.344
	Herbs and spices	15.0 %	35.0 %	**0.039**
	Sweet vs bitter	10.0 %	27.5 %	0.092
	Sweet vs sour	17.5 %	20.0 %	1.000
	Odor	87.5 %	81.2 %	0.727
	Flavor	10.9 %	23.6 %	**0.039**
General taste alterations and parageusia	Texture	12.7 %	27.3 %	°0.057
	Herbs and spices	23.6 %	34.5 %	0.238
	Sweet vs bitter	14.5 %	29.1 %	0.096
	Sweet vs sour	23.6 %	18.9 %	0.581
	Odor	79.5 %	84.1 %	0.754
	Flavor	12.9 %	17.6 %	0.388
Phantogeusia and increase in taste perception	Texture	16.5 %	23.5 %	0.210
	Herbs and spices	25.8 %	25.8 %	1.000
	Sweet vs bitter	11.8 %	21.2 %	0.115
	Sweet vs sour	23.5 %	12.9 %	**0.022**
	Odor	82.3 %	76.5 %	0.454
	Flavor	11.9 %	20.6 %	**0.009**
Discomfort	Texture	14.4 %	23.1 %	**0.020**
	Herbs and spices	20.6 %	26.9 %	0.132
	Sweet vs bitter	11.9 %	21.3 %	**0.024**
	Sweet vs sour	20.0 %	17.5 %	0.585
	Odor	78.9 %	72.5 %	0.185

Emboldened p-value<.05 indicates a significant increase. ° sign on p-value indicates a value close to significance.

Table 7 shows the percentage of patients who self-reported the different types of conditions (mean scores >1) represented by the CiTAS dimensions before the start and during the treatment. Based on this classification, the impact of these conditions on food preferences and on emotional responses to foods has been explored and described in the following paragraphs.

3.4. Changes in food preferences in patients with self-reported alterations

After the first cycle of therapy, no type of alteration recorded with the CiTAS had an impact on the patients' food preferences. Instead, after the second cycle, the presence of self-reported "General taste alterations and parageusia" was associated with greater changes in all food preferences ($p = .020$ $\chi^2 = 5.416$, significance by cell $p = .022$) (Fig. 8), suggesting that these alterations have a significant impact on preferences over time.

In particular, the presence of this type of alteration was significantly associated with greater changes in preferences of "Sweet *vs.* Bitter" foods. From the Chi-Square analysis ($p = .039$ $\chi^2 = 4.254$) it emerged that the observed frequencies of patients with "General taste alterations and parageusia" who changed preference were significantly higher than the theoretical frequencies (significance by cell $p = .044$) (Fig. 9).

However, during the second cycle, other conditions such as "Phantogeusia and increase in taste perception", "Decline in basic tastes", and "Discomfort" were not associated with changes in preferences, as indicated by the Chi-Square analysis.

After the 4th cycle of therapy, in patients who self-reported "Discomfort" and therefore a condition that includes symptoms such as nausea, mucositis and discomfort with odors, a significant association with preference changes was observed ($p = .004$ $\chi^2 = 8.188$) and a tendency to change for specific odors was recorded ($p = .063$ $\chi^2 = 3.465$; significance by cell $p = .074$). Conversely, no significant preference changes were observed in the presence of other conditions.

McNemar tests computed to understand whether the observed preference changes had a specific direction were not significant.

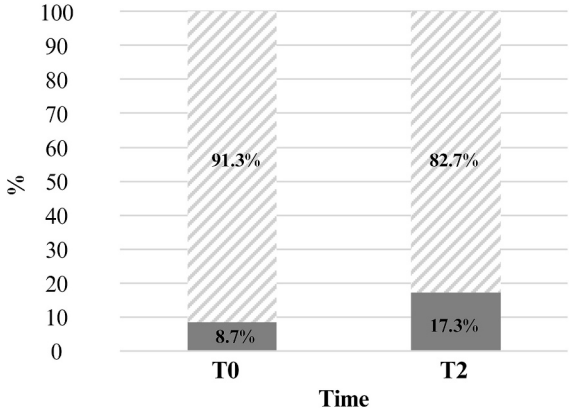

Fig. 10. Increase in percentage of negative emotions (dark grey) elicited by selected options of Sweet bitter dimension, from baseline (T0) to the second cycle of chemotherapy (T2) in patients who self-reported "Phantogeusia and increase in taste perception". Results from McNemar test ($p = .039$).

3.5. Changes in emotional responses to foods in patients with self-reported alterations

After T1 (Table 8) a significant increase in negative emotions elicited by the chosen options of the Food Preference and Emotion Questionnaire was observed in patients who self-reported "Decline in basic tastes" for the products of the "Herbs and Spices" dimension ($p = .039$), in patients who self-reported "General taste alterations and parageusia" for the products of the "Flavor" ($p = .039$) and, close to significance, "Texture" dimension ($p = .057$), and in patients with "Discomfort" for "Flavor" ($p = .009$), "Texture" (p = .020) and "Sweet *vs.* Bitter" ($p = .024$) dimensions. In contrast, patients who self-reported "Phantogeusia and increase in taste perception" showed a significant decrease in negative emotions elicited by the chosen options of the "Sweet *vs.* Sour" dimension ($p = .022$).

After T2, in patients who self-reported "Phantogeusia and increase in taste perception" a significant increase ($p = .024$) in negative emotions elicited by the chosen options was recorded for the "Sweet *vs.* Bitter" dimension from 8.7 % at T0 to 17.3 % at T2 (Fig. 10).

The McNemar test showed that after T4 no changes in emotional responses to the chosen foods were observed in the presence of self-reported conditions.

4. Discussion

The study shows that patients receiving chemotherapy encounter a variety of chemosensory alterations and disturbances, from decline of tastes, with a decrease of sweet (at lower concentration) and salty (at lower and higher concentration) taste perception, to phantogeusia and parageusia. Self-reported alterations were associated in many cases with an increase in negative emotions towards the preferred foods, already after the first cycle of therapy. We observed also that self-reported decline in tastes was not associated with changes in preferences, while general taste alterations and parageusia were associated with a change in preference for sweet/bitter foods after the 2nd cycle of therapy, and discomfort after the 4th cycle of therapy.

Patients were generally able to correctly identify the stimuli in aqueous solutions, particularly at higher concentration. Sweetness (induced by sucrose) was the most accurately identified tastant, while bitterness (induced by caffeine) at lower concentration was the least accurately recognized (even at baseline), in line with previous findings (Boltong et al., 2014). Generally, our results on identification suggest that, despite self-reported or measured decreases in perceived intensity, taste recognition remained largely preserved. Bitter taste at lower concentration was not well identified and was frequently misidentified as tasteless or sour, even at baseline. This finding aligns with previous studies reporting that healthy individuals often confuse bitter and sour stimuli (Gregson & Baker, 1973; McAuliffe & Meiselman, 1974; Meiselman & Dzendolet, 1967; O'Mahony, Goldenberg, Stedmon, & Alford, 1979; Pangborn, 1961; Robinson, 1970).

Our results of sensory measures have shown a significant decrease in perception after one cycle for sweet taste and a general trend of decrease for salty taste presented in aqueous solutions at lower concentration (when the reported intensity is around moderate). Instead, for solutions at higher concentration the decline reported is smaller and was found only for the salty taste after the fourth cycle. Our results further expand previous results that were mainly found on threshold measurements. The decrease of saltiness perception found both in lower (NaCl: 5 g/L) and higher (NaCl: 15 g/L) concentrated aqueous solutions is consistent with several studies in which such phenomenon was frequently observed through quantitative methods using threshold concentrations, qualitative methods, or a combination of both (Boltong et al., 2014; Epstein et al., 2019; Kaizu et al., 2021; Obayashi et al., 2023; Pedersini et al., 2022; Steinbach et al., 2009). Even the perceived intensity of lower concentrated sweet solution (67 g/L) significantly decreased after the first cycle of treatment, coherently with an increase in the sweet threshold reported in other studies (de Vries, Boesveldt, et al., 2018; Dewys & Walters, 1975; Sánchez-Lara et al., 2010; Schalk et al., 2018; Steinbach et al., 2009). However, this increase in threshold may not be sufficient to compromise the perception of the sweet stimulus at higher intensity, as demonstrated by the absence of significant changes in ratings of the most concentrated sweet solution (200 g/L), which remained stable over time. Our results were not consistent with previous study using suprathreshold concentrations, as Mulder et al. (1983) reported an increase in perceived salty and sweet intensity after each chemotherapy cycle. The reason behind the difference observed can be due to the different types of chemotherapy principles (that were bleomycin, actinomycin D, vindesine and DTIC in Mulder et al., 1983) and furthermore the sample size is not reported.

In contrast, as previously anticipated, intensity ratings of sour, bitter, and pungent stimuli presented at both concentrations showed no significant changes over time, confirming previous studies that did not showed effect at a threshold level for sour and bitter (de Vries, Winkels, et al., 2018; IJpma et al., 2017; Kim et al., 2020; Schalk et al., 2018). This suggests that chemosensory alterations during chemotherapy do not uniformly affect all basic tastes. A possible explanation for the absence of variation in bitter and sour perception lies in their functional role: sour and bitter are considered warning sensations in foods (e.g., they indicate the presence of toxic substances, fermentation). Therefore, the perception of bitter and sour could be more resistant to changes induced by chemotherapy, due to attentional and functional mechanisms. Furthermore, patients receiving chemotherapy often experience that foods normally consumed suddenly taste bitter/sour/bad, thus exacerbating the perception of these sensations. However, this remains a hypothesis that requires further targeted investigation.

Even for the pungent solution at both concentrations no significant changes were observed during the treatment, in contrast with limited evidence that reported a reduction in pungency perception in head-and-neck cancer patients (Epstein, Villines, Epstein, & Smutzer, 2020; Riantiningtyas et al., 2023). These discrepancies may reflect interindividual variability, as well as the influence of concomitant conditions such as mucositis or xerostomia, which may increase sensitivity or reduce reactivity due to tissue damage or changes in salivary flow (Thorne, Olson, & Wismer, 2015). Additionally, medical guidelines often recommend avoiding spicy foods to reduce oral discomfort during treatment (Singh & Singh, 2020), which may result in reduced exposure and induce sensitization (Prescott, 1999). Furthermore, in our study, the maximum dose of capsaicin used (0.0015 g/L) may not have been sufficient to detect small changes in sensitivity, particularly in the absence of severe mucosal symptoms.

Alterations may affect not only the perceived intensity, but may occur in the form of a distorted, bitter or bad perception of food often linked to changes in smell perception, as both taste and smell work together to create the full experience of flavor (Amézaga et al., 2018). Patients frequently describe the taste of food as "different than usual" but the information about the timing of the occurrence remains unclear. In our study these alterations were reported by the patients filling out the CiTAS, particularly the "General taste alterations and parageusia" dimension which consider perception of food as bad/bitter/unusual. The percentage of affected patients increased from 26.8 % at T1 to 46.8 % at T2 and 61.8 % at T4, with average scores rising significantly already after the first cycle of therapy. These results align with several studies (Amézaga et al., 2018; Bernhardson et al., 2007) in which patients describe the new taste sensation as "not recognizable" and similar to "paper", "sawdust", "metal", and therefore like a bad taste different from the usual; they also describe the taste of water as "musty", "stale", "sweet" or like "iron", and the taste of coffee as unusually burnt or bitter.

Chemotherapy-treated cancer patients often report sensations, such as a "metallic taste", "chemical taste", "drug taste", "blood taste" and "bitter taste" in the mouth in absence of an external stimulus (Epstein & Barasch, 2010; Jensen et al., 2008). Among these sensations, metallic taste is one of the most frequently reported complaints (Boltong et al., 2012), likely due to chemotherapy drugs being secreted into saliva and directly interacting with taste receptors (Amézaga et al., 2018). In our study the percentage of patients self-reporting phantogeusia and heightened taste perception increased after the first (41.5 %), the second (63.8 %) and the fourth cycle (76.5 %). The significant rise in average scores for this dimension after the first cycle suggests that even these alterations appear early in the treatment and worsen over time.

A variety of antineoplastic side effects are associated with chemosensory alterations, including nausea, vomiting, dry mouth, sore mouth and throat, excessive thirst, swallowing difficulty, appetite changes, weight loss, dizziness, lack of energy, disturbed sleep, anxiety, and difficulty concentrating (Al-Amouri & Badrasawi, 2024; Martini et al., 2019). Some of these conditions are included in the dimension of "Discomfort" where mean CiTAS scores significantly increased after the first chemotherapy cycle. Notably, baseline scores were already above the minimum (>1), suggesting that discomfort is primarily derived from the disease itself. It is further exacerbated by chemotherapy, as evidenced by 78 % of patients reporting discomfort after already one cycle.

Preliminary results on CiTAS responses show that the percentage of patients reporting qualitative alterations, as general taste alterations and parageusia or phantogeusia, or discomfort, increases as the treatment progresses, suggesting a cumulative drug effect of the treatment. However, this trend of cumulative effect was not consistently reflected

in ratings of perceived intensity of aqueous solutions. This discrepancy may be due to the specific nature of the alterations. In fact, also when measured with the CiTAS the cumulative effect is limited to some types of alterations; in the case of "taste decline" once the decline happens, it seems to remain stable. Instead, other types of alterations such as parageusia, phantageusia, or discomfort report an ongoing increase up to the 4th cycle, supporting the hypothesis of a cumulative effect of the chemotherapy. Furthermore, this discrepancy may reflect differences in the assessment methods and timing of measurements between solutions and self-report measures. Recent research has shown that taste alterations may peak early in the chemotherapy cycle, in the first 4–6 days after the infusion (Boltong et al., 2014; IJpma et al., 2016), whereas our study assessed chemosensory function later in the cycle, close to the next infusion, when supposedly the effect is lower and intracycle recovery has happened. While the gLMS captures the perceived intensity of isolated chemosensory stimuli under controlled conditions at a specific time point (the time when the test was run), the CiTAS reflects the everyday taste experience during food consumption in the last period. In daily eating experience, multiple sensory inputs, such as texture, and temperature, combine to shape the overall flavor, potentially revealing alterations that are not detected through tests that focus on a single stimulus.

In addition to the variety of sensory changes and their associated adverse effects, there is considerable variability in how patients respond to these changes. Our results suggest that in the presence of specific conditions, the relationship with foods belonging to specific categories may worsen, inducing more negative emotions, and that such conditions may, in some cases, lead to a change in food preferences. After the first cycle of therapy, the presence of chemosensory alterations does not seem to have an effect such as to cause the modification of food preferences, but even though patients did not change preference compared to baseline, the relationship with the preferred foods appears to change. The "Sweet *vs.* Bitter" dimension showed the largest number of significant changes in emotional responses to foods during the first cycle of chemotherapy in relation to different types of alterations. Patients classified by different self-reported chemosensory alterations, decline in basic tastes, phantogeusia and increased taste perception, and discomfort, experienced a worsening of their emotional relationship with foods in this category, despite no significant changes in food preferences. We may hypothesize that the presence of chemosensory alterations may cause sweet or bitter foods to be perceived as excessively strong or insufficiently satisfying, leading to frustration, dissatisfaction, and indifference. Our data indicate a reduced sweet perception, while no change in bitterness perception is detected. This suggests that previously preferred bitter foods (e.g. coffee or tea) may now be perceived as less satisfying, and/or too bitter due to the reduced effect of suppression of sweetness, even if still preferred compared to an alternative option.

The presence of a phantom taste in the mouth and the increase in the perception of tastes in our patients were not associated with changes in preferences but nevertheless led to an altered emotional relationship with foods in the "Sweet *vs.* Bitter" dimension after the second cycle of therapy. The hypothesis, consistent with Trant, Serin, and Douglass (1982), is that the presence of a bitter or metallic taste in the mouth leads to a rejection of bitter foods and therefore to a worse relationship with them. In fact, symptoms such as phantogeusia may cause some patients to perceive sweet or bitter foods as excessively intense or unpleasant, even if the intensities of the sweetness and bitterness have not actually increased. This can turn the consumption of these foods into a monotonous and/or unpleasant experience. Boltong et al. (2014) reported a lower liking for sweet foods during treatment and therefore we can hypothesize that this decline may also worse positive emotions for normally preferred sweet foods.

Preference changes were observed after the second cycle of therapy in patients who report general taste alteration and parageusia, particularly in the dimension "Sweet *vs*. Bitter". This is consistent with a systematic review of Boltong and Keast (2012) which reports that the most commonly aversive foods and beverages during chemotherapy are bitter items as coffee and tea (Grindel, Cahill, & Walker, 1989; Jacobsen et al., 1993) and sweet/bitter items as chocolate and cola (Andrykowski & Otis, 1990; Mattes, Arnold, & Boraas, 1987; Steinbach et al., 2009). At the same time, patients may respond to these challenges in different ways, such as satisfying specific cravings (Nucci et al., 2022) for sweet foods as a form of emotional compensation or avoiding them altogether for health reasons, further complicating their emotional relationship with these foods during chemotherapy.

Furthermore, a trend of worsening of the emotions elicited by the foods chosen in the "Flavor" dimension of the FP&EQ was observed in patients with general taste alteration and parageusia. These types of disorder could lead to an altered relationship with foods with a more or less intense flavor. Our hypothesis is that an altered taste in food (parageusia) could be worsened by more intense flavors and cause emotions of annoyance and disgust. Discomfort as well is associated to an increase of negative emotions in the "Flavor", "Texture" and "Sweet *vs*. Bitter" dimensions. This maybe because the presence of nausea, inflammation in the mouth, reduction of appetite, and disturbance in smelling food could cause annoyance, frustration and increase in such disturbances in consuming those usual foods that have a specific flavor. Moreover, when nausea follows ingestion of a food, people tend to develop a dislike for the taste of that food (Pelchat & Rozin, 1982). Furthermore, food texture may influence satiety through differences in appetite sensations, gastrointestinal peptide release and food intake (Stribiţcaia, Evans, Gibbons, Blundell, & Sarkar, 2020) and specific types of food textures, such as pasty, are more likely to cause nausea (Tan et al., 2020).

Still focusing on the first cycle, we observed a trend of worsening of the emotional responses to food of the "Herbs and Spices" dimension by patients who self-report a decline in basic tastes in the absence of a change in preferences. In general, literature has reported that a reduced perception leads to choosing seasoned foods with enhancing agents such as salt, lemon juice, spices and garlic (Drareni et al., 2023; Speck et al., 2013), however our hypotheses are multiple. First, it is possible that these foods, being already preferred before the start of therapy, may still not bring the hoped-for relief, thus arousing negative emotions. The second hypothesis is that there is a tendency to avoid specific foods because they are perceived as too flavorful or, on the contrary, as tasteless. Interestingly the domain of odor has not been impacted, suggesting that probably this is a dimension affected for all patients independently from taste alterations (Ishinaga et al., 2018; Nielsen et al., 1980).

These results taken together suggest that provoking different taste and chemosensory alterations, chemotherapy is associated with an altered affective relationship with foods, with a general worsening of the experience. Even preferred foods become more associated with negative emotions. We may hypothesize that this impact that we observe on emotional responses does not affect preference in the short run. In fact, patients do not change their preferences even when they experience a worsening of the emotional experience of these foods. Probably this is due to the fact that the alternative option is not perceived as better, as already not appreciated (it was not preferred at baseline), or also to the fact that for changing preferences more time is needed. These results further expand findings of studies on liking that showed that emotions may discriminate beyond liking, suggesting that they can discriminate also beyond preference (Spinelli, 2021). For patients, it may take time to readjust the habits and develop strategies to cope with the new altered perception that they are experiencing. In fact, we observed changes in preferences but only after the 2nd cycle in people with general taste alterations and parageusia (particularly for the "Sweet *vs.* Bitter" dimension) and after the 4th cycle for people with discomfort. Furthermore, the fact that the results of the tests to identify the direction of the change of preference are not significant may be indicative of inter-individual differences in preferences at baseline. A larger sample is needed to observe these associations considering individual differences.

These results have implications for the supportive care of patients

undergoing chemotherapy as they suggest that the experience of foods should be more considered as it contributes to a worsening of patients' quality of life. Tailor-made recommendations should be developed to suggest to patients what they can do to improve their relationship with food based on the specific alterations that they are experiencing, avoiding the increase of negative emotions.

While the study is the first to show an impact of alterations on emotional responses to foods in cancer patients receiving chemotherapy, it is not without limitations. First of all, the sample size is relatively small and heterogeneous, which limits the generalizability of the results. This is partly due to the fact that the data were collected in a hospital setting, where recruitment depended on patient availability and willingness to participate, as well as the availability of places to conduct the test and of the oncologist to mediate the recruitment. Confounding variables such as age, gender and individual differences in preference may have influenced the results, such as the variety in the cancer type and treatment. However the vast majority of the sample is affected by breast cancer, with similar treatment plans. In addition, as the study is still ongoing the current lack of longitudinal data beyond the chemotherapy treatment period leaves unanswered questions about recovery and long-term impacts.

5. Conclusions

This study provides valuable insights into the chemosensory alterations experienced by patients receiving chemotherapy and their impact on food preferences and emotional responses. Our findings highlight the complexity and variability of these changes, emphasizing the importance of a multidimensional approach to understand and address the chemosensory side effects of anticancer treatment.

The integration of both measurements, such as aqueous solution tests, and self-reported responses using CiTAS provided a better understanding of chemosensory alterations. Furthermore, the investigation of emotional responses to food allowed the identification of changes in the relationship with food, highlighting how these sensory changes can influence the daily eating experience and quality of life even when preferences remain stable. In particular, the early detection of significant changes in chemosensory perception and emotional responses already after the first cycle of therapy underscores the importance of timely interventions. Based on these exploratory results, future research should focus on developing tailored interventions that could help mitigate the impact of the changes on patients' daily lives. It is also needed to complete the study to investigate the persistence or recovery of chemosensory changes and their effects on eating habits and quality of life after treatment.

Ethical statement

The study obtained the approval from the Ethics Committee for Clinical Trials in Tuscany Region – Large Central Area section (Rif. CEAVC n. 20839), Careggi University Hospital, Florence (CEAVC Em. 2022–418 ID 20839), and the Independent Ethics Committee of the Humanitas Clinical Institute (3531/ID. 20839).

CRediT authorship contribution statement

J. Di Meglio: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **C. Rorandelli:** Writing – review & editing, Methodology, Investigation. **C. Dinnella:** Writing – review & editing, Supervision, Methodology, Conceptualization. **E. Monteleone:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **F.C. Stingo:** Writing – review & editing, Formal analysis. **L. Doni:** Writing – review & editing, Investigation. **L. Visani:** Writing – review & editing, Investigation. **A. Guarino:** Writing – review & editing, Investigation. **E. Gambale:** Writing – review & editing, Investigation. **R. De Sanctis:** Writing – review & editing, Investigation. **R. Gerosa:** Writing – review & editing, Investigation. **P. Tiberio:** Writing – review & editing, Investigation. **L. Antonuzzo:** Writing – review & editing, Investigation. **V. Scotti:** Writing – review & editing, Investigation. **I. Meattini:** Writing – review & editing, Supervision, Investigation. **G. Roviello:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation. **S. Spinelli:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodqual.2025.105671.

Data availability

Data will be made available on request.

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