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The clinical impact of continued smoking in patients with breast and other hormone-dependent cancer: A systematic literature review

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ABSTRACT

We conducted a systematic review of studies that investigated whether quitting smoking at or around diagnosis improves survival of patients with hormone-dependent cancers (HDC). Nine studies published in 2013–2022 were included. Studies were very diverse in terms of design, definition of quitters and continued smokers, and prevalence of prognostic factors other than smoking cessation (e.g. patients' demographics, tumour characteristic, and treatments). For breast, ovarian, and endometrial cancer, all included studies found that quitters had better overall, disease specific, and disease-free survival than continued smokers. For prostate cancer, there was no evidence of an association of smoking cessation with improved survival. This literature review provided suggestive evidence that female smokers diagnosed with cancer of the breast, ovary, or endometrium may improve their chances of surviving by stopping smoking. Smoking cessation counselling should become part of standard oncological care for these patients and integrated into breast cancer screening programs.

1. Introduction

Hormone-dependent cancers (HDC) encompass cancers at several body sites (breast, ovary, endometrium, and thyroid among women, and prostate and testis among men) that depend on hormones for growth and progression and may share common mechanisms of carcinogenesis. HDC account for approximately 25–30% of newly diagnosed cancers, with breast cancer (11.7%) and prostate cancer (7.3%) that rank among the most common non-cutaneous cancers respectively in women and men in terms of incidence rate and prevalence (Sung et al., 2021). HDC vary also in terms of survival and treatment possibilities (i.e. which and how many therapeutic approaches exist that are effective in extending survival), and many clinical as well psychological patient's characteristics may affect the chance of recovery over time (Marzorati et al., 2019; Gorini et al., 2018). Considering the high mortality rates and low improvement in therapy for some of these cancers in recent times (e.g. ovarian cancer), any effort aimed to improve their survival is worth pursuing.

Smoking is known to play a role in the aetiology of most HDC (Jones et al., 2017; Huncharek et al., 2010; Jordan et al., 2006), although the exact mechanisms of action underlying this association are still poorly understood. Concerning breast cancer, there is evidence that components of cigarette smoke can reach the breast tissues, and many known carcinogens found in cigarettes (e.g. benzo[*a*]pyrene and isoprene) are suspected to own the potential to initiate breast carcinogenesis (Kispert and McHowat, 2017). The formation of DNA adducts is another

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potential mechanism of breast carcinogenesis linked to cigarette smoke. Concerning prostate cancer, hypothesized mechanisms encompass the alteration of the hormonal milieu leading to increased androgenic exposure of prostate cells, and the direct exposure to the many carcinogenic substances found in cigarette smoke (Plaskon et al., 2003). Hormones are important also for tumour progression, thus it could be hypothesized that smoking may affect survival as well. To this regard, there is some evidence that the prognosis of these cancers does indeed differ by smoking status as determined at cancer diagnosis (Bérubé et al., 2014; Foerster et al., 2018; Praestegaard et al., 2017), but it is currently unclear whether smoking cessation after diagnosis (the only actionable item by clinicians, either during diagnostic workout or after diagnosis e.g. during treatment and follow-up) can favourably affect survival. Evidence supporting a positive impact of smoking cessation on survival would likely lead to a practice change. We recently showed that stopping smoking at or around diagnosis is associated with substantial survival improvement (20–30% longer survival compared to continued smokers) among patients with lung cancer (Caini et al., 2022a) and head and neck cancer (Caini et al., 2022b) (tumours for which a direct carcinogenic role for smoking is well established), but no systematic literature review and meta-analysis has been attempted so far for HDC to the best of our knowledge.

To fill this knowledge gap, we reviewed and summarized the studies that focused on whether smokers who stop smoking at or around the diagnosis of HDC have a prognostic advantage over those who do not stop smoking.

2. Methods

2.1. Protocol and search strategy

The protocol of this study was registered prior to the start of the investigation in the International prospective register of systematic reviews database (PROSPERO) with the following registration number: CRD42021245560 (National Institute for Health Research, 2022). This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021).

The objectives of this systematic review were defined according to the following PECO criteria: Population: subjects who were active smokers, or who had quit less than 12 months, at the time they were diagnosed with a HDC (breast, ovary, endometrium, thyroid, testis, and prostate); Exposure: smoking cessation at or around diagnosis (i.e. HDC patients were considered as "exposed" if they had stopped smoking up to 12 months before diagnosis, or stopped after it, e.g. shortly after diagnosis or during treatment); Comparison: HDC patients who continued to smoke upon diagnosis; and Outcome: patients' survival (overall, cancer-specific, progression-free, or recurrence-free). PubMed and EMBASE databases were searched from inception to 30th April 2022 for original articles investigating whether quitting smoking at or around diagnosis confers a survival advantage to patients who are active smokers at the time of HDC diagnosis. The following search string was used: (smok*) AND (cease OR cessation OR quit* OR stop*) AND (cancer OR carcinoma OR tumo(u)r OR malignanc*) AND (survival OR prognos* OR outcome OR mortality). No language, time or geographical restrictions were applied as long as an English abstract was available to decide on eligibility.

2.2. Study selection and data extraction

After removing duplicates, titles and abstracts were screened by three independent researchers (SC, MDR and VV). The articles not discarded at this stage were considered potentially eligible for inclusion, retrieved in full copy, and independently read by two authors (MDR and VV): in case of disagreement, a consensus choice was taken with a third author (SC). We finally included all original full papers that evaluated the effect of smoking cessation at or around diagnosis on any of HDC patients' overall survival (OS), cancer-specific survival, progression-free survival (PFS), or recurrence-free survival (RFS). "Quitters" were defined as HDC patients that stopped smoking at diagnosis, early before it (up to 12 months before), or at some point afterwards (i.e. during treatment). To be eligible for inclusion, a study had to provide a hazard ratio (HR) and 95% confidence intervals (95% CI) or another measure of statistical uncertainty (e.g. standard errors or exact p-values). Studies in which the specific timing of smoking cessation was not made explicit were ineligible for inclusion, as well as studies that did not present any original findings (e.g. editorials, viewpoints, or letters without data). The reference list of the eligible papers and previously published reviews and meta-analyses were checked by means of backward citation chaining for further relevant references.

Data extraction was organised using an internally piloted spreadsheet. Two independent researchers (MDR and VV) entered the following information, previously extracted from each eligible study: country/region and year(s) in which the study was conducted; study design; total number of HDC patients included in the study that were active smokers at diagnosis (or in the year before diagnosis), and their breakdown into quitters and continued smokers; exact definition of quitters and continued smokers; age distribution of HDC patients; cancer site, stage at diagnosis, and any treatments that the patients underwent; duration of the follow-up period (median/mean and minimum/maximum, depending on availability); details on statistical analysis methods; and variables used for adjustment, if any.

2.3. Statistical analysis and quality assessment

Due to the limited number of included studies, it was not possible to conduct a meta-analysis (the initial plan was to merge study-specific HRs into summary HRs (van Houwelingen et al., 2002), assess the heterogeneity of HRs across studies by using the I^2 statistics, and run meta-regression and subgroup analysis to identify potential sources of variability of HRs across studies (Higgins and Thompson, 2002); Cochrane Handbook for Systematic Reviews of Interventions, 2022). Moreover, the outcomes of interest were reported in different ways in the included studies: some authors compared quitters and continued smokers directly, while other authors used another group of patients (never smokers, or all those who were not active smokers at diagnosis) as a reference group to whom quitters and continued smokers were separately compared. Despite being eligible for inclusion in the review, the latter group of studies could not be used for meta-analysis purposes (as it is not possible to estimate a measure of statistical uncertainty for the HR comparing the survival of quitters and continued smokers). Because of the paucity of studies and of the aforementioned limitations in reporting, study-specific results were shown in dedicated tables and commented upon in the results section of the manuscript, but we made no attempt to calculate summary measures of association.

Finally, the study quality and susceptibility to bias of all studies included in the review was evaluated by using the Quality in Prognosis Studies (QUIPS) tool (Hayden et al., 2013).

3. Results

3.1. Literature search and articles selection

The literature search in PubMed and EMBASE produced a total of 12,048 non-duplicate entries, and additional 296 articles were found by backward citation chaining (Fig. 1). A total of 11,462 articles were discarded based on their title and abstract, and 586 articles were read in full text. Of these, 577 were removed for not matching the inclusion criteria; the main reasons for exclusion were smoking cessation at or around diagnosis not considered as exposure of interest (n = 258), and the focus on outcomes other than survival endpoints (n = 138). The study by Karlsson et al. was not included as the post-diagnosis smoking

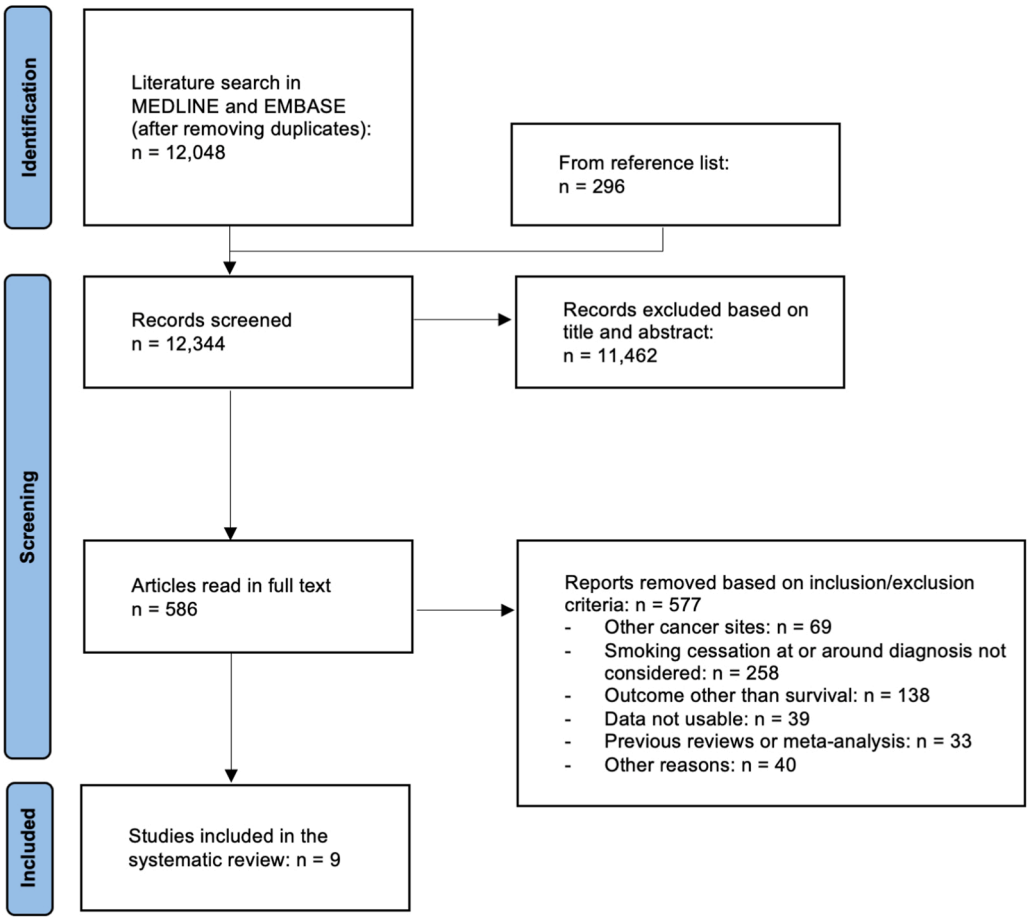

Fig. 1. Flow-chart of the literature search and articles selection for the systematic review on the effect of quitting smoking at or around diagnosis on the survival of hormone-dependent cancer patients.

status was imputed via machine learning algorithms, instead of being ascertained through biological measures (e.g. exhaled CO) or self-reported by the patients (Karlsson et al., 2021). Finally, a total of nine independent studies were included in the systematic review (Singareeka Raghavendra et al., 2022; Mizota et al., 2020; Parada et al., 2017; Passarelli et al., 2016; Warren et al., 2013; Gansler et al., 2018; Tao et al., 2013; Hansen et al., 2020; Wang et al., 2020).

The nine articles that were included in this systematic review were published between 2013 and 2022 and included breast cancer patients (n = 5, encompassing a total of 9042 patients, ranging from a minimum of 580 to a maximum of 4652); ovarian cancer patients (n = 3, for a total of 1936 patients); endometrial cancer patients (only one study based on 326 patients); and prostate cancer (PC) patients (n = 3, with 9756 patients overall) (Table 1). We found no article that examined the association between at/around diagnosis smoking cessation and the prognosis of testis or thyroid cancer. In most of the studies, the category of quitters included exclusively those who had stopped smoking at diagnosis or shortly (up to 1 year) thereafter. Only one study verified cessation or monitored abstinence by measuring exhaled carbon monoxide (CO) or cotinine concentration in urine or saliva, while all the others relied on self-reporting (Table 2). This was one of the main issues that affected the quality of the studies and their susceptibility to bias (Supplementary File 1).

3.2. Breast cancer

The median/mean age at breast cancer diagnosis fell in the fifth decade of life in all studies, and no study included men. The proportion of actively smoking patients who quit at or around diagnosis ranged between 4% (Warren et al., 2013) and 37% (Singareeka Raghavendra et al., 2022) (this information, along with other study sample characteristics, was not present in the abstract by Mizota et al., which only reported data on disease-free survival). Studies differed also in terms of treatments that were administered to patients (different combinations of surgery, chemotherapy, hormone therapy, and radiation) and duration of patients' follow-up. Three studies examined the association between post-diagnosis smoking cessation and both OS and breast cancer-specific survival, while two studies only reported either health outcome (Table 3 and Table 4). Quitters were found to have improved OS in the study by Parada et al. (reference category: never smokers; HR 2.30, 95%CI 1.56–3.39 for continued smokers; HR 1.83, 95%CI 1.32–2.52 for quitters), while no association emerged in the studies by Passarelli et al. and Warren et al., although HRs for quitters were found to be lower than for continued smokers. Concerning breast cancer-specific survival, Raghavendra et al. found significant improvements among quitters (HR 0.58, 95%CI 0.36–0.95); also Parada jr. et al. found improved breast cancer-specific survival (reference category: never smokers; HR 1.60, 95%CI 0.79–3.23 for continued smokers; HR 1.01, 95%CI 0.51–1.98 for quitters), as well as Passarelli et al. (HR 0.67, 95% 0.38–0.1.19) and Warren et al. (HR 0.95, 95%CI 0.53–1.19) although not achieving statistical significance. Finally, Mizota et al. reported improved disease-free survival for quitters compared to continued smokers (reference category: never smokers; HR 1.47, 95%CI 0.67–3.34 for quitters; HR 2.13, 95%CI 1.14–3.97 for continued smokers). In summary, all studies that analysed the prognostic impact of smoking cessation at or around the diagnosis of breast cancer found that quitters had better survival than those who continued smoking, even though the magnitude of this association varied across studies and statistical

Table 1
Main characteristics of the studies included in the systematic review on the prognostic effect of quitting smoking at or around diagnosis on the survival of breast, ovarian, endometrial, and prostate cancer patients.

Author, year	Country	Age (years)	No. patients [(a)]	Smoking status			Years of diagnosis	Tumour stage	Follow-up (months)	Treatments
				Non-smokers at diagnosis [(b)]	Continued smokers	Quitters				
Breast Cancer										
Singareeka Raghavendra, 2022	USA	mean 51.1[(c)] and 50.49[(d)]	580	0	367 (63%)	213 (37%)	2006–2017	NA	median 9	surgery, chemotherapy, radiation, hormonal therapy in various combinations
Mizota, 2020[(e)]	Japan	NA	1510	NA	NA	NA	NA	NA	median 61	anastrozole alone or tamoxifen + anastrozole (no details about surgery)
Parada jr, 2017	USA	mean 58.8	1508	674 (45%)	290 (19%)	554 (34%)	1996–1997	invasive (84.4%), in situ (15.6%)	NA	radiation (60.9%), chemotherapy (41.4%), hormone therapy (61.1%)
Passarelli, 2016	USA	mean 59	4562	3776 (83%)	434 (9.5%)	352 (7.5%)	1988–2008	localized (68%), regional (32%)	median 132	NA
Warren, 2013	USA	mean 55.7	882	700 (80%)	143 (16%)	39 (4%)	1982–1998	local (52.3%), regional (39.4%), distant (8.3%)	NA	NA
Ovarian Cancer										
Hansen, 2020	Australia	mean 59.1	512	NA	NA	NA	2012–2015	FIGO stage I (27.5%) II (11.3%) III (53.9%) IV (7.2%)	mean 42	various (primary treatment was either surgery or chemotherapy)
Wang, 2020	USA	mean 65.0 (NHS I) and 52.0 (NHS II)[(g)]	1114	972 (87%)	99 (9%)	43 (4%)	1989–2010	I (23.7%) II (9.0%) III (67.3)	NA	NA
Warren, 2013	USA	mean 55.7	309	256 (83%)	38 (12%)	15 (5%)	1982–1998	local (19.1%), regional (6.2%), distant (74.8%)	NA	NA
Endometrial Cancer										
Warren, 2013	USA	Mean 62.0	326	152 (86%)	35 (11%)	10 (3%)	1982–1998	local (70.9%), regional (16.6%), distant (12.6%)	NA	NA
Prostate Cancer										
Gansler, 2018	USA	NA	9111[(f)]	NA	NA	NA	1992–2003	SEER stage localized (91.1%) regional (8.9%)	NA	first course of treatment was any of prostatectomy, cryosurgery, radiation therapy, hormone therapy only, or watchful waiting
Tao, 2013	China	NA	132	32 (24%)	NA	NA	1986–2010	NA	mean 64	surgery, radiation, chemotherapy in various combinations
Warren, 2013	USA	mean 65.5	513	452 (88%)	48 (9%)	13 (3%)	1982–1998	local (53.0%), regional (34.5%), distant (12.5%)	NA	NA

[(a)] This refers to the patients included in the analyses aimed at estimating the effect of at/around smoking cessation on cancer survival or recurrence (it may be lower than the total number of patients in the study).
[(b)] This category includes never smokers and long former smokers.

[c] Referred to the non-abstinence group
[d] Referred to the abstinence group
[e] Being that of Mizota et al. an abstract, many details on the study were not available.
[f] Non-metastatic prostate cancer patients
[g] The study analysed two different cohorts of patients

Table 2
Definition of quitters and continued smokers in the studies included in the systematic review on the prognostic effect of quitting smoking at or around diagnosis on the survival of HDC patients.

Author, year	Quitters	Continued smokers
Singareeka Raghavendra, 2022	Abstinence assessed at the end of treatment and at 3-, 6-, 9- and 12-month follow-up. Self-reported smoking status was confirmed through carbon monoxide verification.	Continued smoking during follow-up (confirmed through carbon monoxide verification).
Hansen, 2020	Quit smoking after diagnosis (no further details given)	Continued smoking after diagnosis (no further details given)
Mizota, 2020	Quit smoking after diagnosis (no further details given)	Continued smoking after diagnosis (no further details given)
Wang, 2020	Declared having quit smoking at the first post-diagnosis assessment (median 11 months after diagnosis).	Still smoking at the first post-diagnosis assessment.
Gansler, 2018	Quit smoking after diagnosis (no further details given)	Continued smoking after diagnosis (no further details given)
Parada, 2017	Declared not having smoked in the year preceding the five-year follow-up interview.	Still smoking at the five-year follow-up interview.
Passarelli, 2016	Quit smoking after diagnosis (no further details given)	Continued smoking after diagnosis (no further details given)
Warren, 2013	Quit less than one year before diagnosis.	Active smokers at diagnosis.
Tao, 2013	Never smoked cigarettes after diagnosis.	Continued to smoke until death or the latest follow-up interview.

significance was not always achieved.

3.3. Ovarian cancer

The median or mean age at ovarian cancer diagnosis ranged between 55 and 65 years in the three studies that were included. The proportion of quitters was similar in the studies by Wang et al. (4%) and by Warren et al. (5%), while this information was not provided by Hansen and colleagues. The three studies differed in terms of tumour stage at diagnosis, even though most of the included patients were diagnosed with advanced or metastasised ovarian cancers. Data on follow-up (mean: 42 months) and treatment were only provided by Hansen and colleagues. Despite not comparing directly the overall survival of those who quit smoking at or around diagnosis and those who continued smoking (thus preventing meta-analysis from being conducted), the included studies were consistent in reporting a beneficial effect of smoking cessation on ovary cancer survival. In detail, improved OS was reported by Wang and colleagues (reference group: never smokers; HR 1.43, 95%CI 1.11–1.86 for continued smokers; HR 0.91, 0.62–1.35 for quitters) and by Hansen et al. (reference group: never/former smokers; HR 1.90, 95%CI 1.08–3.37 for continued smokers; HR 0.99, 95%CI 0.57–1.72 for quitters). A strong but not significant improvement in the OS was also found by Warren et al. (HR 0.61, 95%CI 0.28–1.30 for quitters vs. continued smokers). Wang et al. and Warren et al. also studied the association between smoking cessation at or around diagnosis and ovarian cancer-specific survival, with quitters appearing to have survival advantages in both studies: Wang found a HR of 0.84 (95%CI 0.54–1.31) compared to never/former smokers (reference category) while continued smokers had a HR of 1.40 (95%CI 1.05–1.87), while Warren and colleagues reported a HR of 0.55 (95%CI 0.24–1.30) for quitters compared to continued smokers. In summary, similarly as for breast cancer, all studies included in this review suggested that quitters had lower HRs (i.e. longer survival) than continued smokers.

Table 3
Hazard ratio (HR), 95% confidence intervals (CI), and details of the statistical analysis, for the association between at/around diagnosis smoking status (cessation/continuation) and overall survival of HDC patients.

Author, year	Cancer site	Patients group (according to smoking status) [a]	HR	95% CI	Variables used for statistical adjustment
Overall Survival					
Parada jr, 2017	breast cancer	never smokers	1.00 (ref)		age, tumour stage, treatment, other
		continued smokers	2.30	1.56–3.39	
		quitters	1.83	1.32–2.52	
Passarelli, 2016	breast cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	0.91	0.67–1.20	
Warren, 2013[b]	breast cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	0.98	0.61–1.59	
Wang, 2020	ovarian cancer	never smokers	1.00 (ref)		age, tumour stage, other
		continued smokers	1.43	1.11–1.86	
		quitters	0.91	0.62–1.35	
Hansen, 2020	ovarian cancer	never/former smokers	1.00 (ref)		age, tumour stage, residual disease after surgery, other
		continued smokers	1.90	1.08–3.37	
		quitters	0.99	0.57–1.72	
Warren, 2013[b]	ovarian cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	0.61	0.28–1.30	
Warren, 2013[b]	endometrial cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	0.72	0.29–1.85	
Tao, 2013[b]	prostate cancer	continued smokers	1.00 (ref)		age, treatment, other
		quitters	1.08	0.09–12.50	
Warren, 2013[b]	prostate cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	1.20	0.60–2.50	

[a] The reference group were continued smokers for studies in which a HR (and 95%CI) for the direct comparison of continued smokers and quitters was provided, and either never or never + former smokers if the HR (and 95% CI) were only provided for continued smokers and quitters with reference to that category of patients.
[b] The HR and corresponding 95% CI were inverted to present continued smokers as the reference group.

3.4. Endometrial cancer

Only one study was found that investigated the survival impact of quitting smoking at or around endometrial cancer diagnosis (Warren

Table 4
Hazard ratio (HR), 95% confidence intervals (CI), and details of the statistical analysis, for the association between at/around diagnosis smoking status (cessation/continuation) and disease-specific survival (top) or disease-free survival (bottom) of HDC patients.

Author, year	Cancer site	Patients group (according to smoking status) [a]	HR	95% CI	Variables used for statistical adjustment
Disease specific survival					
Singareeka Raghavendra, 2022	breast cancer	continued smokers	1.00 (ref)		Age, tumour stage and grade, treatment, other
		quitters	0.58	0.36–0.95	
Parada jr, 2017	breast cancer	never smokers	1.00 (ref)		age, tumour stage, treatment, other
		continued smokers	1.60	0.79–3.23	
		quitters	1.01	0.51–1.98	
Passarelli, 2016	breast cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	0.67	0.38–1.19	
Warren, 2013[b]	breast cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	0.95	0.53–1.69	
Wang, 2020	ovarian cancer	never smokers	1.00 (ref)		age, tumour stage, other
		continued smokers	1.40	1.05–1.87	
		quitters	0.84	0.54–1.31	
Warren, 2013[b]	ovarian cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	0.55	0.24–1.30	
Warren, 2013[b]	endometrial cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	0.27	0.03–2.44	
Gansler, 2018	prostate cancer (non-metastatic)	never smokers	1.00 (ref)		age, tumour stage, treatment, other
		continued smokers	1.50	0.90–2.49	
		quitters	1.69	0.98–2.90	
Warren, 2013[b]	prostate cancer	continued smokers	1.00 (ref)		age, tumour stage, other
		quitters	1.56	0.62–4.00	
Disease-free survival					
Mizota, 2020	breast cancer	never smokers	1.00 (ref)		age, treatment
		continued smokers	2.13	1.14–3.97	
		quitters	1.47	0.64–3.34	

[a] The reference group were continued smokers for studies in which a HR (and 95%CI) for the direct comparison of continued smokers and quitters was provided, and either never or never + former smokers if the HR (and 95% CI) were only provided for continued smokers and quitters with reference to that category of patients.
[b] The HR and corresponding 95% CI were inverted to present continued smokers as the reference group.

et al., 2013). Specifically, Warren and colleagues reported that smoking cessation improved both OS (HR 0.61, 95%CI 0.28–1.30) and endometrial cancer-specific survival (HR 0.27, 95%CI 0.33–2.44) compared to those who persisted smoking after diagnosis, although statistical significance was not reached.

3.5. Prostate cancer

The only study, out of three that were found eligible for inclusion, that provided information on PC patients' demographics was that by Warren et al. (mean age was 65.5 years at the time of diagnosis). The three studies differed in terms of treatment (combinations of cryosurgery, surgery, radiation, chemotherapy, hormone therapy, or wait and see approach); no information on the duration of the follow-up was available, being the study by Tao et al. the only exception (mean 64 months). Only two studies investigated the association between post-diagnosis smoking cessation and OS, with no significant results (HR 1.08, 95%CI 0.09–12.50 for quitters, compared to continued smokers, in the study by Tao et al.; HR 1.20, 95%CI 0.60–2.50 in the study by Warren et al.). The studies by Gansler et al. investigated post-diagnosis smoking cessation in relation to PC-specific survival, but even in this case no statistically significant association was found (reference group: never smokers; HR 1.50, 95%CI 0.90–2.49 for continued smokers; HR 1.69, 95%CI 0.98–2.90 for quitters). The same emerged in the study by Warren et al. (HR 1.56, 95%CI 0.62–4.00 for quitters compared to continued smokers). In summary, the few available studies did not suggest that smoking cessation at or around diagnosis may be beneficial (in terms of survival) among PC patients who are active smokers at diagnosis.

4. Discussion

We conducted a systematic review and meta-analysis of studies that focused on whether smokers who stop smoking at or around the diagnosis of HDC have a prognostic advantage over those who continue smoking. We included nine papers published between 2013 and 2022 that focused on four different types of hormone-dependent cancer (breast, ovarian, endometrial, and prostate cancer) and encompassed a total of more than 20,000 patients. The studies differed in several aspects, including patient demographics, duration of follow-up, treatments that the patients received, study design, and criteria to define quitters. As already mentioned, the small number of available studies for each cancer site and the large heterogeneity in the presentation of the study findings did not allow us to apply meta-analysis methods to calculate summary measures. However, the results of the studies included in this review suggested that smoking cessation around or post-diagnosis may actually lead to survival benefits for female smokers diagnosed with HDC, while results were not particularly suggestive for prostate cancer patients. In particular, it must be highlighted that, despite the wide diversity in terms of patients' and tumour's characteristics, all the studies included in this systematic review that focused on female cancers reported lower HRs (i.e. improved survival) for

quitters compared to continued smokers, although the magnitude and statistical significance of the association varied considerably across studies.

Smoking is thought to play a role in the growth, progression, and dissemination of many cancers, including HDC. A growing body of evidence is concentrating on the contribution of nicotine to tumour growth and dissemination (and eventually cancer patient's survival), but multiple mechanisms have also been described or hypothesized to explain the possible association of tobacco smoking with the survival of cancer patients, such as the induction of hypoxia that may affect the response to certain treatments as radiotherapy and lead to reduced apoptosis, the enhancement of angiogenesis, the induction of sustained proliferation or the effect on immunity, and others (Chen et al., 2011; Jensen et al., 1991; Wong et al., 2007). Besides, cigarette smoking favours the onset and the aggravation of several comorbidities (such as cardiovascular, pulmonary, and renal illnesses) that in turn represent a negative prognostic factor among cancer patients. With reference to breast cancer, the nicotinic acetylcholine receptors have been found to be expressed on cancer cells: these receptors have a role in regulating cell proliferation, angiogenesis, apoptosis, and metastatic dissemination of the primary tumour by interfering with many different signalling pathways (Singh et al., 2011). Despite the knowledge gaps regarding the mechanisms by which post-diagnosis smoking cessation could improve these patients' survival and prognosis, it should be emphasized that a substantial proportion of HDC patients are likely to be active smokers at diagnosis (although with large geographical variability depending on the prevalence of smoking and other risk factors in the population), thus it is critically important that the advantages brought about by cessation on HDC patients' outcomes are quantified and known by clinicians, and that actions are taken to make the most of the available evidence. To this regard, targeted smoking cessation programmes aimed at promoting smoking cessation among these patients would represent a cost-effective solution potentially able to save many lives, and could be initiated as early as during regular breast cancer screening or during diagnostic workup for patients suspected to have ovary, endometrial, or prostate cancer (for which no structured screening programs exist to date). Overall, in the oncology setting, programs for cessation should be implemented at all levels of the clinical care pathways, from early diagnosis to treatment and follow-up. An integrated approach should be adopted that would also include physical and psychological assessments of the patient, in order to provide more personalized interventions (Masiero et al., 2019). Moreover, along with the implementation of smoking cessation treatments aimed to contrast the craving and urgency for tobacco with pharmacological treatments, cognitive-behavioural protocols should be associated to reinforce patients' motivation and awareness about needs and emotions related to smoking, thus enhancing their chance of successfully quitting (Lucchiari et al., 2016).

This is the first attempt to systematically review the evidence on the impact of smoking cessation on the survival of patients with HDC. In the Surgeon's General 2020 Report (United States Public Health Service Office of the Surgeon General, 2020), the evidence in favour of "*a causal relationship between smoking cessation and improved all-cause mortality in cancer patients who are current smokers at the time of a cancer diagnosis*" was judged as no more than "*suggestive*". The Surgeon's General 2020 Report reviewed only two studies focusing on HDC: here, we extended the literature review from 2016 to 2022, and the slightly increased number of existing studies provide further evidence suggesting that the aforementioned causal relationship may indeed be true for female HDC. However, the available evidence can not be considered as conclusive yet: besides being still limited in number, the studies included in our review suffer from potential sources of bias and other limitations that is important to acknowledge. For instance, because of the impossibility to randomize patients (for obvious ethical reasons), there might be systematic differences between quitters and continued smokers that could affect the survival, and there is no certainty that these were sufficiently adjusted for in the analysis (e.g. quitters might differ in terms of demographic, stage or treatment characteristics). The definition of the prognostic factor under study (smoking cessation) was vague and not very well detailed in most studies, and relied on self-reporting (instead of being determined with more reliable methods) in all but one study. Moreover, the unsuitability of the studies for a proper meta-analytic approach hampered the possibility of formally identifying (and quantifying) a significant favourable prognostic effect of smoking cessation for HDC patients.

With reference to the above, we would like to appeal to cancer researchers to conduct more studies in this field (not limited to HDC, but in general to cancer at all sites, in particular those known to be strongly associated with tobacco smoke), and try to outline some of the most important quality requirements that such studies should meet. Critically, the patient's smoking history and current status should be defined in a standard way (i.e. using validated questionnaires) at the time of diagnosis, and then monitored using objective methods (e.g. exhaled carbon monoxide and/or urinary/salivary cotinine) during treatment and at regular intervals thereafter (e.g. every three or six months at least). Moreover, precautions should be taken to minimize or remove confounding; information should be gathered about any patient- and cancer-related prognostic factor as well as any administered treatment; appropriate statistical methods should be applied that accommodate quickly time-varying exposures; and reporting should be complete and include stratification according to important prognostic factors.

In conclusion, we believe that an important merit of the present review is to call attention to a topic that has been largely neglected so far, despite early reports (those reviewed here) showed promising results. The findings of this systematic review, albeit suggestive, require confirmation in well-designed and adequately sized prospective investigations and in future meta-analyses, and the magnitude of the clinical impact of smoking cessation, as well as the effectiveness of smoking cessation programs in the clinical setting, will need better determination. Yet, the currently available data suggest that smoking cessation at or around diagnosis may have the potential to bring large survival benefits to HDC patients, and smoking cessation programmes should therefore be integrated as part of standard multidisciplinary oncological care for these patients.

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CRediT authorship contribution statement

Marco Del Riccio: Conceptualization; Data curation; Methodology; Validation; Writing – original draft, **Virginia Vettori**: Conceptualization; Data curation; Validation; Writing - review & editing, **Sara Raimondi**: Data curation; Formal analysis; Visualization; Writing - review & editing, **Chiara Lorini**: Investigation; Methodology; Writing – original draft, **Giovanna Masala**: Investigation; Project administration; Supervision; Writing – review & editing, **Maria Sofia Cattaruzza**: Conceptualization; Methodology; Project administration; Writing – review & editing, **Luca Mazzarella**: Investigation; Methodology; Writing – review & editing, **Guglielmo Bonaccorsi**: Investigation; Methodology; Project administration; Writing – review & editing, **Marianna Masiero**: Investigation; Methodology; Writing – review & editing, **Benedetta Bendinelli**: Investigation; Validation; Writing – original draft, **Giuseppe Curigliano**: Investigation; Methodology; Writing – review & editing, **Gabriella Pravettoni**: Investigation; Methodology; Project administration; Writing – review & editing, **Elisa Pastore**: Investigation; Methodology; Writing – review & editing, **Sara Gandini**: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology;

Project administration; Resources; Software; Visualization; Writing – review & editing, **Saverio Caini**: Conceptualization; Data curation; Investigation; Methodology; Supervision; Writing – original draft.

Conflict of interest statement

All authors have no conflicts of interest to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.103951.

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