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ORIGINAL ARTICLE

MelaNostrum: a consensus questionnaire of standardized epidemiologic and clinical variables for melanoma risk assessment by the melanostrum consortium

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Abstract

Background Many melanoma observational studies have been carried out across different countries and geographic areas using heterogeneous assessments of epidemiologic risk factors and clinical variables.

Aim To develop a consensus questionnaire to standardize epidemiologic and clinical data collection for melanoma risk assessment.

Methods We used a stepwise strategy that included: compilation of variables from case–control datasets collected at various centres of the MelaNostrum Consortium; integration of variables from published case–control studies; consensus discussion of the collected items by MelaNostrum members; revision by independent experts; addition of online tools and image-based charts; questionnaire testing across centres and generation of a final draft.

Results We developed a core consensus questionnaire (MelanoQ) that includes four separate sections: A. general and demographic data; B. phenotypic and ultraviolet radiation exposure risk factors and lifestyle habits; C. clinical examination, medical and family history; and D. diagnostic data on melanoma (cases only). Accompanying online tools, informative tables, and image-based charts aid standardization. Different subsections of the questionnaire are designed for self-administration, patient interviews performed by a physician or study nurse, and data collection from medical records.

Conclusions The MelanoQ questionnaire is a useful tool for the collection and standardization of epidemiologic and clinical data across different studies, centres, cultures and languages. This will expedite ongoing efforts to compile high-quality data for pooled analyses or meta-analyses and offer a solid base for the design of clinical, epidemiologic and translational studies on melanoma.

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Conflict of interest

None declared.

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Introduction

The incidence of cutaneous melanoma (CM) has steadily and significantly increased in populations of European descent in recent years,[1] including the Mediterranean populations.[2–4] CM is responsible for the largest proportion (60–80%) of skin cancer-related deaths.[5] In 2012, more than 232 000 people worldwide were diagnosed with CM and more than 55 400 succumbed to the disease.[5,6] Data from population-based European registries have shown an increased incidence of *in situ* and invasive melanoma but a stable mortality rate in Italy and Spain between 1995 and 2012.[7] Melanoma risk factors include ultraviolet (UV) radiation exposure, positive family history for melanoma, phenotypic traits with a strong genetic component such as red or blonde hair, light-coloured eyes, and fair skin complexion, and an increased number of common and atypical melanocytic nevi. Even though the advent of targeted therapies and immune checkpoint inhibitors has improved melanoma prognosis in a subgroup of patients, the mortality risk and the socio-economic burden associated with advanced disease emphasize the importance of prevention strategies in high-risk individuals and of screening programs for early detection.

Numerous case–control studies have been carried out focusing on the environmental and phenotypical risk factors of CM.[8–16] The variables assessed were often heterogeneous, and this has limited the possibility of pooled analyses. Tools for standardized data recording are therefore needed to design prospective studies and to guide retrieval of previously collected data across various centres. Earlier questionnaires or surveys in melanoma studies focused only on few variables or lacked high test–retest reliability.[17–21] We sought to generate a comprehensive tool that would allow us to pool data from studies on CM carried out by the MelaNostrum Consortium as well as by other centres.

MelaNostrum is an international Consortium of researchers and clinicians involved in melanoma research in Mediterranean (i.e. Southern European) populations, which have been, so far, under-represented in studies of CM. Formally established in 2017, MelaNostrum comprises experts in various disciplines, including epidemiologists, dermatologists, medical oncologists, pathologists, molecular biologists, geneticists and statisticians. The primary goals of MelaNostrum were as follows: (i) to identify genetic, environmental and phenotypic features associated with melanoma risk; (ii) to investigate disease development and clinical outcomes using molecular classification of melanoma and of melanoma precursors and (iii) to study the role of genetics and immunity in melanoma progression and response to treatment. Currently, MelaNostrum collects and analyzes data and biological samples from 12 centres across Greece, Italy and Spain. A complete list of current MelaNostrum centres and members is provided as Table S1.

Given the heterogeneous recording of variables across melanoma studies, the MelaNostrum investigators were confronted with the difficult task of harmonizing epidemiologic and clinical information from each centre to perform association studies. The present work reports on the stepwise strategy employed to

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A complete list of members of the MelaNostrum Consortium is provided in the Table S1.

develop a data collection tool (hereafter named as MelanoQ) that could be used as a full or itemized template for the standardization of retrospective data from case–control and other epidemiology studies or in prospective studies aimed at the investigation of genetic, lifestyle, epidemiologic and clinical factors associated with melanoma.

Material and methods

Development of the questionnaire

The questionnaire was developed in 7 steps as outlined in Fig. 1.

Step 1: compilation of variables from case–control datasets collected by the MelaNostrum centres. Step 2: distribution of the variable list to MelaNostrum members, initial evaluation of differences and similarities across centres and categorization of the items in sections. This step also included enrichment of the variables based on published case–control studies. Step 3: two face-to-face meetings of the MelaNostrum clinical core of investigators, during which each variable in the list was discussed. The first meeting also involved physical examination of patients to achieve consensus on criteria for nevus count and (other) pigmented skin lesion diagnosis. As a result, a draft of the MelanoQ was generated (Barcelona, Spain) and subsequently improved (Athens, Greece). Step 4: review of the draft questionnaire by an independent expert panel (MT, DW, VB) and implementation of the suggested modifications. Step 5: addition of (i) online tools to ease recording of residency and occupations, (ii) tables with lists of ethnicities, outdoor occupations and recreational activities, and (iii) image-based charts for data standardization pertaining to eye and hair colour, tanning ability, freckles and nevi number. Step 6: questionnaire testing across centres, using different languages and recording the time required for completion. Step 7: establishment of the final draft after consensus discussion through email exchange by the MelaNostrum team.

Results

MelanoQ is organized in 4 main sections (A-D) and includes a total number of 64 items related to: general and demographic information (section A); phenotypic, UV exposure risk factors and lifestyle habits (section B); clinical examination, medical history and family history (section C); tumour characteristics, including histology, staging and molecular profile (section D). Only sections A, B and C are included in the MelanoQ for controls. In each section, the items are formulated as closed-ended questions with only few exceptions. Different subsections are designed for self-administration, patient/control interviews performed by a physician or study nurse, and data collection from medical records. The questionnaire is briefly outlined in Table 1, while it is provided in full as Table S2.

Section A should be filled in by the physician or study nurse (subsection I) and by the study participant (subsection II). In subsection I, the date of questionnaire administration and

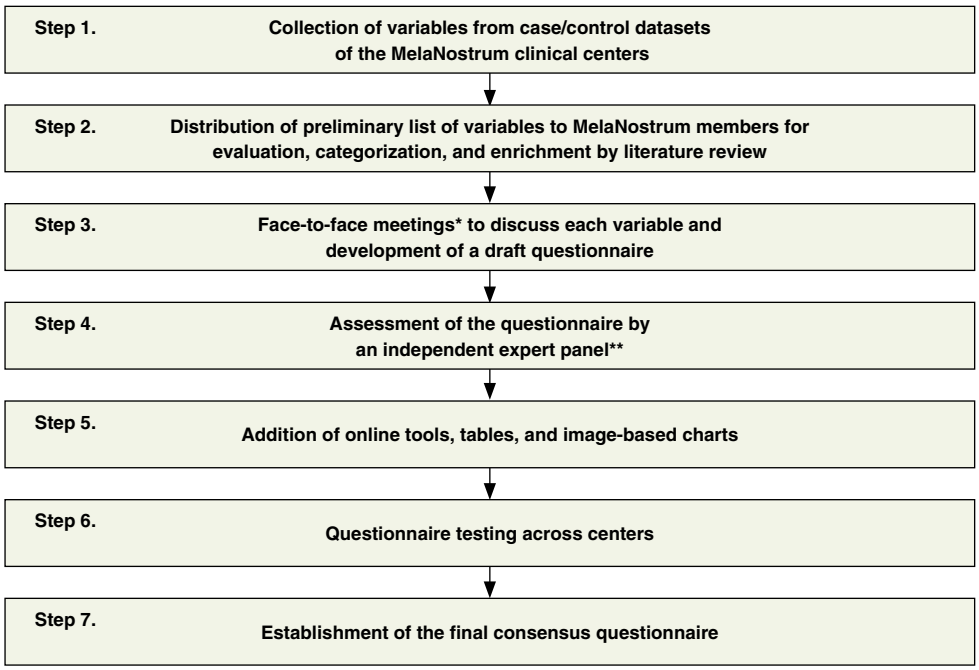

Figure 1 Stepwise strategy used to develop the MelanoQ. *one meeting including patient examination to define criteria for pigmented lesion assessment and nevus count. **The expert panel consisted of M. Tucker (USA), V. Bataille (UK) and D. Whiteman (Australia).

Table 1 Design and variables of MelanoQ.

Section	Completed by	Variables	Items
SECTION A (case/control)			
General	Physician/study nurse	Subject ID, date and update of questionnaire, sporadic/familial case	1–5
Demographic	Self-administered	Sex, age, weight, height, ethnicity, residency, education, and occupation	6–13
SECTION B (case/control)			
Phenotype	Self-administered	Skin type, eye/hair colour, freckles, nevi in childhood	1–5
History of sun and UVR exposure	Self-administered	Sun exposure and related habits, sunburns, lamps	6–14
Lifestyle habits	Self-administered	Vitamins, smoking	15–18
Section B Completion evaluation questions	*Self-administered*	*Questionnaire evaluation*	*19–20*
SECTION C (case/control)			
Clinical examination	Physician/study nurse	SOLAR lentigines, nevi, actinic keratosis	1–8
Medical history/medications	Physician/study nurse	Non-cancer diagnoses, treatments, pregnancies, other cancers	9–13
Family history	Physician/study nurse	Melanoma and other cancers among relatives, genetic test	14–16
Section C Completion evaluation questions	*Physician/study nurse*	*Questionnaire evaluation*	*17–18*
SECTION D (case)			
Melanoma characteristics (for each melanoma diagnosis)	Physician/study nurse	Clinical presentation, number of melanomas, date of diagnosis, site, histological type and features, SLN*, AJCC stage, mutation status	1–13

*Sentinel Lymph Node Biopsy.

phenotyping is annotated and the date(s) of the updated phenotyping can also be recorded if additional patient interviewing or clinical evaluation is performed during follow-up. Subsection II includes questions about age, sex, weight and height, ethnicity, residency, education and occupation. The question about the place of residence is open-ended to capture all possible changes (and duration thereof). To facilitate categorization, geocoding is advisable. The question regarding history of occupation is also designed as open-ended and could also be supported by online tools or flash cards. The question about education has been harmonized to take into account country-specific differences. For this purpose, age categories defining educational levels have been set broadly to enable collection of the relevant data across different cohorts.

Section B is completed by the study subject. Its subsection I pertains to epidemiologic and clinical risk factors including skin type, eye colour, hair colour, freckling and nevi in childhood/adolescence. To facilitate consistency in data reporting, the questions regarding the skin type are formulated to combine the subject's skin response to sun exposure with his/her ability to tan (Figure S1). The term 'skin colour' is not included in MelanoQ to avoid subjective assessment. Information on eye and hair colour has been merged into fewer categories (light: blue/green/grey, medium: light brown/hazel and dark: dark brown/black, for eye colour; and red, blond, light brown, dark brown and black, for hair colour) to facilitate statistical analyses. Definition of freckles and solar lentigines is included to ensure proper identification of these lesions. Charts with images of eye and hair colour (Figures S2 and S3, respectively), as well as freckle and nevi density (Figures S4 and S5, respectively) have been included to standardize categorization and recording. *Section B* also includes questions on occupational and recreational sun exposure, use of artificial tanning, sunburns and the use of sun protection methods (subsection II). Information on sun exposure and related behaviours also includes data on intermittent sun exposure (during childhood, adolescence and adulthood, as well as during a 10-year period prior to melanoma diagnosis). The number and age of occurrence (<18 years or ≥18 years) of severe (grade 2) sunburns are also recorded, as is their site with respect to melanoma (where applicable). The use of sunscreen is categorized as never, <50% or >50% of the time during sun exposure, always, or not known, over four periods of life. Additional questions focus on lifestyle habits, specifically, vitamin intake and smoking history (subsection III).

Section C includes clinical examination, detailed medical history and family history of melanoma/other cancers for both cases and controls. This section is designed to be completed by a health care professional. The clinical examination part aims at recording the presence of multiple and/or clinically atypical melanocytic nevi, congenital melanocytic nevi, blue nevi, actinic keratoses and keratinocyte skin cancer KSC (basal cell carcinoma and squamous cell carcinoma) (subsection I). Nevi >2 mm in size are recorded as a continuous variable by site and by laterality. Clinically, atypical nevi are defined as having a macular component in at least one part of the lesion (mandatory), and having at least 3 of the following criteria: >5 mm diameter, colour variegation, irregular borders or erythema.[22,23] Congenital nevi classified as medium-sized (>1.5–19.9 cm), large (≥20 cm), or giant (≥40 cm) are recorded as present or absent and their site is noted. The presence of actinic keratoses is also recorded

specifying site and distribution and recommending the use of recently described scoring systems such as the AKASI or AK-FAS scores.[24,25] Information about the presence of KSC at the time of physical examination (subsection I) or of any history of previous KSC (subsection II) is also recorded, in the latter case with details on tumour type, number of tumours and time of appearance with respect to melanoma diagnosis. Additional questions in this section focus on medical history, reproductive history and medications (subsection II). Finally, subsection III collects information about family history of melanoma and other cancers. A positive family history of melanoma is considered relevant in the presence of ≥2 first- to third-degree relatives affected by *in situ* or invasive melanoma. This definition takes into account the generally lower incidence of melanoma in the Mediterranean basin compared to other geographical regions, and the specific features of the Mediterranean populations.[26] If possible, a family pedigree for each subject reporting a positive family history of melanoma should be added to the collected information.

Section D is the diagnostic section of the questionnaire designed for patients with a confirmed diagnosis of melanoma. It should be completed by a health care professional and aims to collect data on clinical presentation, including site of primary melanoma, Breslow thickness (and other major histopathologic features), American Joint Committee on Cancer (AJCC) stage, date of diagnosis and somatic mutational data (if available) (subsection I). All thirteen items should be recorded separately for each melanoma if the patient received multiple melanoma diagnoses. Notably, MelanoQ includes twelve items, which are marked as optional, that is to be collected only for the purpose of more detailed analyses.

We have tested MelanoQ in a total of 62 patients at five MelaNostrum centres in Italy, Spain, Greece. The time required for completion ranged from 22 to 60 minutes (average 40 min). Although the completion time of the medical sections (C and D) was similar across physicians and centres (15–20 min), the self-administered part (Section B) was more variable in duration (12–30 min). In particular, questions 6–9 and 11 in subsection II (Section B) required a longer time especially in more senior patients/controls or patients with lower educational background. When we added the assistance of an interviewer for these people, the completion time decreased and the quality of the information increased substantially. We thus have added a separate evaluation section (questions #19, 20 in Section B and questions #17, 18 in Section C) that enables to score the degree of difficulty in responding to the self-administered questions in section B as well as to the phenotypical/clinical information in Section C by the physician/nurse.

Discussion

Upon establishment of the MelaNostrum Consortium, one of the major issues that members had to deal with (and solve) was the incomplete or heterogeneous recording of the information on melanoma patients' specific risk factors, especially skin phototype, sun exposure patterns and nevus assessment, collected at each participating centre. We report herein on the development of a standardized tool that expedites collection of epidemiologic and clinical data on CM from diverse case–control datasets to allow association analyses across different centres. MelanoQ also provides a template for data compilation for prospective studies, clinical research projects or trials. Even though it has been designed more as a research tool for epidemiologic studies and may not be suitable for completion in the context of the rapid pace of daily clinical practice, it may also serve as database for collection of pertinent clinico-pathological information on newly diagnosed patients in melanoma centres.

Previous questionnaires for melanoma studies include the Q-skin,[27] the Sun Exposure Behaviour Inventory (SEBI),[17] and the Sun Exposure and Protection Index (SEPI),[18] among others.[19–21] The Q-skin questionnaire is considered one of the most complete tools. However, its test–retest reliability for the measurement of phenotypic characteristics, sun exposure and nevus-related variables was not high.[27] Similarly, the repeatability of the SEBI instrument, which was limited in scope, since it was designed to assess current and prior sun exposure, was found to be only satisfactory.[17] MelanoQ has the advantage of allowing collection of data on individual risk assessment for epidemiologic purposes, but it can also be used as an entry tool by clinical centres managing melanoma patients. At the same time, although certain items in MelanoQ should be collected by clinicians or specialized personnel, several parts can be self-administered.

In designing this data collection tool, we first identified the most relevant questions to be used for investigating disease aetiology and progression. We also strove to clearly formulate simple questions for the lay public and precoded the responses for statistical analyses. In order to facilitate data collection, we added charts for eye colour, hair colour, freckling and nevus density, lists of ethnicities, examples of outdoor occupations and recreational activities and online tools for residency and occupation recording. Finally, we added an evaluation section to identify the most challenging self-administered questions that may need follow-up by the investigators.

An important part of MelanoQ relates to the collection of information on pigmentation characteristics. Fair skin type (Fitzpatrick I or II),[28] red or blond hair and the presence of freckles have all been associated with a higher risk of melanoma.[2915,16,30–34] Eye colour has also shown an association with melanoma risk in numerous studies.[15,16,35–38] In MelanoQ, we have reproduced the categorization of pigmentary features that has been used for melanoma studies, with a larger spectrum of phototypes for subjects with relatively dark complexion, like those in the Mediterranean population.

The importance of recreational/intermittent sun exposure for melanoma risk has been well documented, while the role of occupational/continuous sun exposure remains unclear.[13,39] A standardized way of recording these two types of exposure by self-administered questionnaires has been proposed, which aims at capturing the amount of exposure time during daylight hours for both recreational and occupational activities.[40] Previous studies with existing standardized tools have shown reasonable reproducibility although the validity of the responses is unclear.[41,42] The items specifically related to sun exposure in MelanoQ have been designed as simple, closed-ended questions. For instance, for intermittent sun exposure, a short description is included (i.e. in spring and summer time) and the case/control subject is requested to provide an answer for four predesignated time periods (section B-II, question 8). We also included questions to record sunscreen use and sun protection methods over time.[43,44]

The identification and recording of common melanocytic and atypical nevi–two well-established risk factors associated with a high risk of melanoma–proved to be one of the most difficult tasks in the epidemiologic investigation of melanoma.[12,45] Although the issues associated with the identification of melanocytic lesions were partially addressed by the implementation of dermoscopy in the daily clinical practice, the need for a harmonized way to record nevus counts still exists. Before deciding how to collect nevi data, the MelaNostrum clinicians discussed the diagnosis and measurement criteria, reviewed the abundant literature on the topic[12,22,23,45–47] and addressed the inter-observer differences in nevus count.[48,49] The group also performed joint patient examinations to reach a consensus on how to report, easily and precisely, nevus counts and relevant risk factors. The questions in MelanoQ are in agreement with the International Agency for Research on Cancer (IARC) protocol for the identification and recording of nevi,[47,50] which has been implemented in previous studies.[51–54] Items that can help one to collect information on the presence of congenital nevi sized >1.5 cm, and particularly those with diameter ≥20 cm or giant nevi, which are considered at risk of malignant transformation, have also been included in our tool.[55–59]

Section D of MelanoQ contains highly structured questions regarding patient melanoma diagnosis, including anatomical site of the lesion, tumour histopathologic features and tumour mutational status information (if applicable). The completeness of the clinical and histopathological data collected by the SEER registries and their impact on the transition from the AJCC 6th to the 7th edition with regards to stage distribution has been previously assessed.[60] It was reported that about 10% of cases were coded as unknown for measured thickness, ulceration and lymph node metastasis, suggesting the need for enhanced data capture for staging purposes.[60] We created a specific checklist for melanoma diagnosis data collection to reduce the possibility of incomplete data recording as a result of human error.

MelanoQ can be enriched with additional items to generate hypothesis-driven questions and to include new information that may prove to be associated with melanoma risk in the future. Our tool may expedite ongoing efforts to compile high-quality data for pooled analyses or meta-analyses and offer a solid base for the design of clinical, epidemiologic and translational studies on melanoma. We have already tested MelanoQ across different clinical centres, languages and cultures in Greece, Italy and Spain and plan, as a future step, to verify its validity and repeatability by applying it to other populations.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Tanning ability chart.
Figure S2. Eye colour chart.
Figure S3. Hair colour chart.
Figure S4. Freckle density chart (Chart adapted by the Q-questionnaire tool - by permission).
Figure S5. Nevus density chart.
Table S1. Centres and members of the MelaNostrum Consortium.
Table S2. The complete MelaNostrum questionnaire.
Appendix S1. List of ethnicities.