Title: A systematic review of studies investigating the association between dietary habits and cutaneous malignant melanoma

Running title: A systematic review on diet and melanoma

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ABSTRACT

Objective

Several papers have dealt with diet as a risk factor for cutaneous malignant melanoma (CMM). This study is aimed at synthesizing available data on the topic.

Study design

A systematic review of observational studies assessing the association between dietary habits and CMM was performed.

Methods

Electronic databases were used to identify eligible articles. Quality was evaluated through the NewCastle Ottawa scale. Case control and cohort studies assessing CMM occurrence in people with highest level of food and nutrient intake in comparison to lowest were considered eligible. Data from single studies were described qualitatively because combination of data was not possible.

Results

Sixteen articles were selected. Cohort studies showed a better quality than case-control ones. Most studies did not figure out any significant association between foods intake and CMM, except for few evidence of a protective role associated to fish, vegetables and fruit. Risk reduction was shown 35-37%, 40-57% and 34-46% respectively across studies releasing significant results. Beta-carotene, vitamin A, retinol, vitamin E, and vitamin D showed a protective role in single studies with a risk reduction of 64%, 49%, 37-43%, 50-66% and 39% respectively.

Conclusion

A trend in the reduction of CMM risk with higher intake of fish, vegetables and fruits, as well as beta-carotene and vitamins A, E and D has been shown but further research is needed to provide decisive data.

INTRODUCTION

Cutaneous malignant melanoma (CMM) is the most dangerous type of skin cancer and represents the leading cause of death from skin disease. CMM affects all ages from mid-teens to the elderly [1].

The incidence of melanoma skin cancer in people under the age of 55 years in Europe differs considerably between countries. Worldwide there are approximately 200,000 new CMM every year and 46,500 deaths due to it [2]. The American Cancer Society estimates 68,720 new cases of CMM in the United States in 2009 with 8,650 deaths, mostly male deaths, constituting a serious public health issue [3, 4]. In white population the incidence rate of CMM varies between 21.9 per 100,000 patient years in the United States and 55.9 per 100,000 patient years in Australian males [4, 5]. These variations are likely to be linked to specific behaviours (winter holidays, sun seeking) as well as to an improvement in diagnosis due to better detection of the disease [6].

The incidence of CMM is continuing to increase worldwide. Once a rare cancer, the incidence of CMM in most developed countries has risen faster than any other cancer type since the mid-1950s [7]; in particular, in white populations, CMM is the most rapidly increasing cancer [8].

All these data justify the public health concern on CMM.

Regarding the aetiology, CMM is primarily caused by exposure to ultraviolet (UV) radiation, either from the sun or from artificial sources, such as sunbeds. In particular,

acute, irregular and excess exposure to the sun, mainly during childhood, by people with fair skins is considered a major risk factor for CMM [9]. In the scientific literature a great number of publications support the causation of CMM by UV radiation exposure. The past 50 years have added both quantity and quality to epidemiological evidence and, most recently, provided direct evidence that sun exposure is the cause of mutations in critical tumor suppressor genes in melanoma [1, 10-18].

Although the relationship between CMM and UV exposure is well known and the evidence relating CMM to previous sun exposure is very strong, in recent years several studies have focused on the possible association between CMM and diet. In fact, CMM has continued to rise in incidence despite public efforts to promote sun protection behaviors. Considering that sunscreen use does not completely prevent skin cancer, additional chemo-preventive methods need evaluation. With this respect, recent years have brought increased interest in dietary factors for CMM prevention [19]. In particular, according to some Authors, nutritional approaches could play a beneficial role in skin cancer prevention. Dietary antioxidant vitamins, minerals and phytochemicals, in addition to n-3 polyunsaturated fatty acids, n-9 monounsaturated fatty acids and low pro-inflammatory n-6 polyunsaturated fatty acids, have demonstrated protective effects. The presence of these elements in the traditional Greek-style Mediterranean diet may contribute to the low incidence of CMM in the Mediterranean region, despite high levels of solar radiation [20]. Moreover, high intake of food containing beta-carotene and retinol may reduce the risk for cancer in general, while high intake of polyunsaturated fat has been suggested to increase the risk for CMM [21-24].

Nowadays some reviews have been published about the risk for CMM associated to UV exposure [10, 25-28]. Notwithstanding, only few reviews are actually available about the risk for CMM in relation to diet; moreover, some of these are specifically focused on particular nutrients, i.e. vitamin D, while some are related to all cutaneous disorders and not specifically to CMM [19, 29-31]. Furthermore, it is important to underline that results of existing studies are unclear, controversial and often inconsistent [32].

The aim of the present study is to collect available evidence on the association between diet and CMM and to summarize results by performing a systematic review of published studies according to PRISMA recommendations [33].

METHODS

Identification of relevant studies

The electronic databases PubMed, OvidSP and the Cochrane Library were used for the search; key words were “Melanoma”, “CMM”, “Diet”, “Dietary behaviour”, “Dietary pattern”, “Dietary habit”, “Food frequency questionnaire”, FFQ, “Diet history”. The following MESH terms were also used in order to perform the search on PubMed: "Melanoma"[Mesh] and "Diet"[Mesh].

The identification of relevant studies was carried out from January 1st 1990 to January 13st 2015 and it was not restricted to English language.

Eligibility criteria for studies being included were related to:

- study design (either case-control or cohort studies);
- study population (studies examining dietary factors in in-vitro conditions or using lab animals, such as mice, rodents, etc., were eliminated; as a consequence, only studies conducted in human population were considered eligible);

- exposure: only studies dealing with dietary habits were considered. Studies on serum levels of nutrients or supplements were excluded.

Eligible studies were selected through a two steps approach by two researchers independently: abstract and title reading and full text assessment.

Quality assessment and data extraction

Studies were reviewed by two researchers in order to assess their quality, according to the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies [34].

This tool is composed of sixteen items in total: four items which allow assessing selection of the sample, one item about comparability and three items about exposure, for case-control studies, and by four items which allow assessing selection of the sample, one item about comparability and three items about outcome, for cohort studies. For each item, a star is assigned if the study accomplishes the requisite defined as the best in the scale.

Data extraction was performed by two researchers with respect to first author, year of publication, study design, country, sample size, age of the sample (mean with Standard Deviation - SD - or min-max), gender (M/F), setting (hospital, general population), methods for exposure assessment, diet items (foods, nutrients) and methods for outcome assessment.

Furthermore, data about the association between CMM and the following dietary factors were extracted:

- foods: fish, vegetables and fruit. Any significant associations concerning food other than the abovementioned were reported too.

- nutrients: carotenoids (beta-carotene), vitamin A, other vitamins (B, C, D, E), fats, carbohydrates, proteins.

Results were expressed by means of Odds Ratio (OR) or Relative Risk (RR) with 95% Confidence Intervals (95%CI): for the aim of this review fully adjusted data were collected and highest levels of intake were compared to lowest ones. Adjustment factors were reported alongside results.

RESULTS

Identification of relevant studies

We found 301 articles in Medline, 341 articles in OvidSP and 14 in Cochrane Library. Out of 301 articles in Medline, 26 satisfied inclusion criteria according to title and abstract reading [35-60]. Four of them were excluded because full texts were not available [38, 50, 52, 55], while the design of other two papers was judged inappropriate [35, 39]. Another one [43] was either excluded because it was a reply to a study already included [45].

In Ovid SP, out of 341 articles, 17 [36, 37, 40-42, 45-51, 53, 59, 61, 62] were identified as potentially relevant for our review. Fifteen of them were overlapped with findings from Medline search, thus remaining two eligible studies only [57, 62]. None of the studies retrieved in Cochrane Library was judged relevant for our review.

In conclusion, sixteen articles [36, 37, 40-42, 44-49, 51, 53-54, 56, 61] were considered in the review (Figure 1). Anyway, articles by Vinceti et al. published in 2005 and 2008 [40, 42] were considered as a single study, because the sample was exactly the same. Indeed, for the following description, fifteen studies will be considered.

Quality assessment and studies characteristics

The design of thirteen out of the fifteen studies was case-control [36, 37, 40-42, 44, 45, 47, 49, 51, 53, 54, 56, 61], while the remaining two [46, 48] were cohort studies. Studies characteristics are shown in Table 1.

Studies quality is shown in Tables 2A and 2B. The minimum score for case-control studies was five out of nine stairs, achieved by most studies, compared to a maximum of eight out of ten achieved only by Naldi et al [44]. Cohort studies were shown to be very good, reaching Feskanich et al. [46] the highest score (nine out nine) and Veierød et al. [48] eight out nine stars.

One of the most common lacks detected in case-control studies was the non-response rate in cases and controls, which was similar only in four studies [37, 44, 49, 61]. With respect to selection of cases and controls, all paper satisfied at least three out of four items except for Fortes et al. [37] and Weinstock et al. [51] which were able to meet just two out of four. Every paper considered the comparability of cases and controls controlling the analysis for the most important confounding factors. About the exposure, the ascertainment was given by secure records or structured interview blind to case/control status in four studies [37, 40, 42, 44, 54] but methods of ascertainment were the same for cases and controls in all papers.

Regarding cohort studies, Veierød et al. [48] did not achieve an adequate follow-up of the two cohorts.

Seven studies (46.7%) [36, 37, 40, 42, 48, 54, 61] out of fifteen were conducted in Europe, mostly Italy; only one (6.6%) was conducted in Australia [56]; the remaining seven (46.7%) were carried out in United States [41, 45-47, 49, 51, 53].

Sample size ranged from 108 (59 cases and 59 controls) [36] to 1,400 (474 cases and 926 controls) [54] in case-control studies and from 50,757 [48] to 162,078 [46] in cohort ones.

People of all ages were recruited, from adolescents to elderly. Mean age was approximately 50 years in most studies and females were generally more represented than men.

Nine studies (60%) [40-42, 46-49, 54, 56, 61] out of fifteen had a population setting, one (6.7%) [36] included both a population- and a hospital-based research while the remaining [37, 44, 45, 51, 53] were performed at population level.

Assessment of dietary habits

Selected studies differed greatly with regard to the assessment of dietary habits, especially because of the tools used. From the evaluation of methods for exposure assessment, it came out that:

- all Authors used a questionnaire, mostly self-administered and not standardized with a number of items varying from 14 to 188 (if reported). In particular, as far as the type of questionnaire is concerned, studies were performed as follows: a semi-quantitative food-frequency questionnaire was administered in five studies [36, 40, 42, 48, 51, 53]; in two studies a food-frequency questionnaire was used [46, 49]; in only one study the "Dobson short fat questionnaire" was used [56]; in four studies trained interviewers administered a structured questionnaire [37, 44, 54, 61]; the study subjects were requested to complete a reduced version of the "Block-food-frequency questionnaire" in another study [45]; in only one study each participant completed a telephone survey and a questionnaire was administered during the phone interview [47]; last, in only one

study in-persons interviews were conducted at subject's homes by trained interviewers [41];

- methods used in order to quantify servings were both qualitative (e.g. pictures or images) and quantitative (e.g. grams, cups, spoons);
- there were many differences between foods included in questionnaires, depending on geographical origin of the study population: prevalent dietary habit was the Mediterranean one, based principally on vegetables and fruits, followed by the Scandinavian one, based on fish and dairy products;
- the time span of dietary habits assessment ranged from one to four years before questionnaire administration.

Because of the heterogeneity between studies, only a qualitative summary of results was considered suitable without any combination of data. Tables 3A and 3B reported the results yielded by included studies with respect to considered foods and nutrients.

Studies results: a qualitative summary

Seven studies [37, 40, 41, 44, 45, 48, 53] dealt with fish consumption, nine [37, 40, 41, 44-47, 53, 54] with vegetables and eight [37, 40, 41, 44-48] with fruit. Most studies did not identify any significant association between foods intake and CMM, except for two studies [37, 45] out of seven (28.6%) demonstrating a significant reduction of about 35-37% associated to a higher fish consumption, three [37, 45, 47] out of nine (33.3%) showing a 40-57% risk reduction with a higher vegetables intake and two [37, 47] out of eight (25%) highlighting a significant reduction ranging from 34% to 46% with respect to fruit.

With regard to nutrients, most attention was paid to carotenoids and vitamin A which were considered by seven studies [41, 42, 44-46, 49, 53], vitamin C and E which were assessed in six [41, 42, 45, 46, 49, 53], and fats which were investigated in eight studies [41, 42, 45, 48, 49, 53, 54, 56].

With respect to vitamin A, two [44, 45] out seven (28.6%) studies released significant results. Total vitamin A and retinol intake showed both a protective role with respect to the CMM in the same study (49% reduction for total vitamin A and 43% for retinol, both for the highest quartile of intake compared with the lowest one) [44]. Retinol was also shown to be associated to a 37% risk reduction by Millen et al [45]. Also vitamin E appeared to be a protective factor in two [49, 53] out of six studies (33.3%) (OR 0.34; 95%CI: 0.16-0.72; OR 0.5; 95%CI 0.3-0.9). As far as beta-carotene and vitamin D are concerned, they were shown to be protective factors in only one study [45] out of seven (14.3%) and four (25%) respectively. In particular, the OR was 0.36 (95%CI 0.22-0.56) for beta-carotene and 0.61 (95%CI 0.40-0.95) for vitamin D.

Finally, one [61] out of eight studies (12.5%) indicated fats as a protective factor (OR 0.61; 95%CI: 0.40-0.92).

Foods/nutrients were not shown a risk factor for CMM in any study,

DISCUSSION

Our review is suggesting that the evidence on the association between dietary habits and CMM is still too weak to be conclusive. In particular, the most important threat is represented by the differences in assessing foods and nutrients intake which may be responsible, alongside confounding factors, for contrasting results for single foods or nutrients. Notwithstanding, dietary pattern may play a role in the natural history of cancer both increasing and decreasing the risk [63]. In particular, with respect to food

classes consumption, it has been estimated that worldwide up to 50% of gastric cancer and up to 29% of colorectal cancer may be prevented with the increase in vegetable consumption and up to 45% of esophageal cancer and 50% of gastric cancers might have been prevented if fruit consumption had increased [64]. In fact, specific dietary components may play a role in cell cycle progression and proliferation [65, 66]. Fruits and vegetables have been studied also with respect to CMM because of their content in apigenin and carotenoids; these last, together with retinoids, seem to be responsible for proliferation inhibition [65, 66]. Furthermore, dietary antioxidants, such as beta-carotene and vitamins A, C and E which are contained in vegetables and fruits, may have a protective role in the early phase of CMM development [67]. In fact, Meyskens et al. [68] have hypothesized that CMM pathogenesis encompasses the early oxidation of melanin to the pro-oxidant quinone-imine which may play a role in accumulation of metals and other chemicals. This process is contrasted by cellular antioxidants whose depletion is indeed considered a feature of CMM pathogenesis [69, 70].

Generally speaking it has to be considered that around 24% and 26% of all cancers may be prevented through nutrition and body fatness control and physical activity in United States and UK respectively according to the 2007 World Cancer Research Fund/American Institute for Cancer Research Diet and Cancer Report. The percentage of cancers which may be prevented is increased at 34% and 39% considering the twelve most common cancer types [71].

A lot of efforts in quantifying the association between dietary pattern and cancer are still going on. Magalhães et al. [63] have analysed eight cohort and eight case-control studies in order to assess the risk for colorectal cancer and demonstrated that an "healthy" dietary pattern, characterised by high fruit/vegetables consumption, is

associated to a 20% reduction of the risk (RR 0.80; 95%CI: 0.70-0.90); on the contrary, a "western" pattern, characterised by high red/processed meat consumption is associated to a 29% increase of risk (RR 1.29; 95%CI: 1.13-1.48). The attention is mainly paid to colon cancer as well as breast cancer, because of their burden of disease. At the same time, evidence is growing also in prognostic research: in fact, a low-fat, high-fibre diet might be protective against cancer recurrence and progression even though the mechanism of benefit could be due to body weight control [72].

Our review seems to be useful in order to provide evidence about a cancer type - CMM - which is lacking of information about the association with dietary habits. This is relevant in the view of the increasing incidence of CMM [7, 8]. Similar evidence have been already produced for non-melanoma cancer; in particular, McNaughton et al. [73] suggested a relationship between fat intake and basal and squamous cell cancer with inconsistent results on beta-carotene, carotenoids, retinol, vitamin E, vitamin C and selenium [73].

Our review highlights a potential role of fish, fruit and vegetables consumption. Another important result is concerning the association between single nutrients, such as carotenoids and vitamin A, and CMM. This is in accordance with other evidence. Zhang et al. [74] have released an OR for cervical cancer of 0.59 (95%CI: 0.49-0.72) for total vitamin A and 0.51 (95%CI: 0.35-0.73), 0.60 (95%CI: 0.43-0.84) and 0.80 (95%CI: 0.64-1.00) for carotene, other carotenoids and retinol intake respectively. Retinoic acid, a metabolite of vitamin A, has been also used as a chemopreventive and therapeutic agent in cervical cancer [75]. With respect to dietary fat, our review is in accordance to already existing evidence which have pointed out a not significant relationship between

level of total dietary fat and colorectal cancer, independently by source (animal or plant) [76].

The knowledge of dietary habits impact could be beneficial in the view of promoting health education and preventative interventions and improving therapeutic approach. From the preventative viewpoint, antioxidant vitamins, minerals, phytochemicals, n-3 polyunsaturated fatty acids, n-9 monounsaturated fatty acids and low pro-inflammatory n-6 polyunsaturated fatty acids may be involved in the low incidence of CMM in the Mediterranean region despite high levels of solar radiation [20]. The chemoprevention of melanoma is envisaged also in the light of increasing incidence rate albeit sunscreen use [19]. In fact, the possibility to prevent cancer through dietary intervention is relevant: Soerjomataram et al. [77] estimated 212,000 fruit/vegetables related cancer in 2050 in France, Germany, The Netherlands, Spain and Sweden being 0.19% preventable if the 500 g/die fruit and vegetable intake was achieved. The knowledge of single food/nutrients involved in cancer development may help promoting dietary interventions [78].

Our review has several limitations. First of all, selection bias may not be excluded in the process of selection of eligible articles because of the use of only three databases for the search. Furthermore the review is not thorough with respect to single food and nutrients because it was focused on dietary habits as all. Notwithstanding, attention was paid to foods/nutrients which have been already investigated in other types of cancer [79]. Another limit is represented by the impossibility to make a quantitative synthesis of results. In fact, the heterogeneity in the assessment of dietary habits and classification of food and nutrients consumption/intake has prevented us to combine data. Indeed, conclusions were based on a qualitative synthesis of results delivered by case-control

and cohort studies even though their quality was different. In particular, cohort studies scored better than case-control studies. This may be due to the fact that cohort studies are generally free for several bias, such as misclassification in particular, which are more commonly observed in case-control studies. In fact, more than half of case-control studies included in this review showed concerns with respect of exposure assessment. Because of the importance of a proper exposure assessment in etiological research it may be concluded that cohort studies could be more appropriate in this field. This is also supported by the fact that, through a cohort study, it could be possible to properly assess duration of exposure and its change in time which are important aspects in a long process such as that of carcinogenesis. In order to assess exposure, in that dietary assessment, several tools are available, such as dietary records, 24-hour dietary recalls, food frequency questionnaires, brief dietary assessment instruments, dietary history and blended methods [80]. The choice of the method depends on the population's characteristics, on aspects of diet/dietary behaviour which are being considered [81] and on study design [80]. In particular, food frequency and diet history methods are suitable for both case-control and cohort studies. In fact this two methods allowed assessing past diet [80]. Notwithstanding, considering the ease of administration, food frequency questionnaires are generally used even though several versions exist. In consideration of that, it would be desirable to identify one single version which may be used worldwide in order to assess diet/dietary habits in etiological cancer research.

Despite limitations, a trend in the reduction of risk for CMM with higher intake of fish, vegetables and fruits has been shown and this may be fundamental for future public health initiatives. Furthermore the review highlights the need for further research aimed at avoiding heterogeneity in assessing dietary habits.

CONCLUSION

In our study a trend in the reduction of CMM risk was shown with higher intake of fish, vegetables and fruits as well as higher intake of beta-carotene vitamin A, retinol, vitamin E, and vitamin D. Considering the growing in CMM incidence, so that it was termed an "epidemic cancer" and a major public health concern, the results of our review appear promising for strengthening nutritional prevention campaigns and for developing tailored initiatives.

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Figure 1 - Flow chart of studies selection.

Table 1. Studies characteristics

Article	Study design	Country	Sample size	Age* in years	Gender (M/F)	Setting	Methods for exposure assessment	Diet items	Outcome assessment
Feskanich et al. [46]	Cohort study	United States	162,078	56	Only females were enrolled	Population setting	Baseline food frequency questionnaire	Micronutrients	Medical records
Fortes et al. [37]	Case-control study	Italy	304 cases and 305 controls	53.0 (15.3) for cases and 51.1 (16.1) for controls	0.89	Hospital setting	Self-administered food frequency questionnaire	Foods intake	Histologically confirmed diagnosis
Gogas et al. [57]	Case-control study	Greece	55 cases and 165 controls	52.7 (range: 23–88) in cases and 53.2 (range: 23-87) in controls	1.38	Population setting	Condensed and validated version of an extended questionnaire comprising items related to the consumption of the basic food groups	Foods intake	Histologically confirmed diagnosis
Granger et al. [56]	Case-control study	Australia	245 cases and 468 controls	46.1 (10.0) and 44.7 (9.8) in male cases and controls; 44.0 (10.0) and 45.3 (9.7) in female cases and controls	0.88	Population setting	Fat-frequency questionnaire (Dobson short fat questionnaire)	Fat intake	Notifications to the Tasmanian Cancer Registry (histopatological confirmed)
Kirkpatrick et al. [49]	Case-control study	United States	234 cases and 248 controls	Range: 25-65	N.A.	Population setting	Food frequency questionnaire and telephone interview	Micro and macro nutrients	Notifications to the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry

Le Marchand et al. [41]	Case-control study	United States	278 cases and 278 controls	53.7 (15.0) in cases and 52.1 (15.0) in controls	1.5	Population setting	Quantitative food frequency questionnaire	Micro and macro nutrients	Histologically confirmed diagnosis notified to the reporting system of the Hawaii Tumor Registry
Malagoli et al. [36]	Case-control study	Italy	41 cases and 82 controls	Range: 28-78 for cases, 26-80 for population controls and 30-80 for hospital controls	0.71 among cases	Population and Hospital setting	Self-administered validated semi-quantitative food-frequency questionnaire	Micro and macro nutrients	Medical records
Millen et al. [45]	Case-control study	United States	497 cases and 561 controls	50 (SE 0.7) for cases and 50 (SE 0.6) for controls	1.17 among cases, 1.33 among controls	Hospital setting	Reduced version of the Block Food Frequency Questionnaire	Micro and macro nutrients	Histologically confirmed diagnosis
Naldi et al. [44]	Case-control study	Italy	542 cases and 538 controls	Median: 54 (range: 15-87) for cases and 54 (range: 15-92) for controls	0.73	Hospital setting	Structured questionnaire administered by trained interviewers	Micro and macro nutrients	Histologically confirmed diagnosis
Osterlind [54]	Case-control study	Denmark	474 cases and 926 controls	52 (range: 20-79) for cases	0.72	Population setting	Usual diet intake questions	Foods intake	Notifications to the Danish Cancer Registry (histopatological confirmed)
Shors et al. [47]	Case-control study	United States	386 cases and 727 controls	Range: 35-74	0.71	Population setting	Questionnaire administered during a phone interview	Fruit and vegetables	Data from hospitals, pathologists and death certificates
Stryker et al. [53]	Case-control study	United States	204 cases and 248 controls	48 and 41 for male cases and controls; 42 and 38 for female	0.74	Hospital setting	Self-administered semi-quantitative food frequency questionnaire	Micro and macro nutrients	Histologically confirmed diagnosis

				cases and controls					
Veierod et al. [48]	Cohort study	Norway	50,757	43 (range: 16–56)	1.03	Population setting	Self-administered dietary semi-quantitative questionnaire	Micro and macro nutrients	Cancer Registry of Norway
Vinceti et al. [40, 42]	Case-control study	Italy	59 cases and 59 controls	58.1 and 53.9, among male and female cases respectively – controls were age matched (±5 years)	0.90 among cases	Population setting	Self-administered validated semi-quantitative food-frequency questionnaire	Micro and macro nutrients[42] and foods intake[40]	Histologically confirmed diagnosis
Weinstock et al. [51]	Case-control study	United States	165 cases and 209 controls	Median: 43 for cases and 35 for controls	0.77	Hospital setting	Self-administered semi-quantitative food-frequency questionnaire	Vitamin D and calories	Histologically confirmed diagnosis

SE, standard error; N.A., Not Available; *Mean (SD) if no otherwise reported

Table 2A – Quality assessment of case-control studies by NOS.

	SELECTION				COMPARABILITY		EXPOSURE			TOTAL
	1. Case definition is adequate	2. Consecutive or obviously representative series of cases	3. Community controls	4. No history of disease in controls	1. Study controls for the most important factor	Comparability for any additional factor	1. Secure record / structured interview blind to case/control status	2. Same method for ascertainment for cases and controls	3. Non-response rate same for both groups	
Fortes et al. [37]	*			*	*	*	*	*	*	7
Gogas et al. [57]	*	*	*	*	*	*		*		7
Granger et al. [56]	*	*	*		*	*		*	*	7
Kirkpatrick et al. [49]	*	*	*		*	*		*	*	7
Le Marchand et al. [41]	*	*	*		*	*		*		5
Malagoli et al. [36]	*	*	*		*	*		*		6
Millen et al. [45]	*	*	*	*	*	*		*		7
Naldi et al. [44]	*	*		*	*	*	*	*	*	8
Osterlind [54]	*	*	*		*		*	*		6
Shors et al. [47]	*		*	*	*	*		*		6
Stryker et al. [53]	*	*		*	*	*		*		6
Vinceti et al. [40, 42]	*	*	*		*		*	*		6
Weinstock et al. [51]	*			*	*	*		*		5

NOS, NewCastle Ottawa Scale

Table 2B – Quality assessment of cohort studies by NOS.

	SELECTION				COMPARABILITY		OUTCOME			TOTAL
	1. Exposed cohort truly or somewhat representative of community	2. Non exposed cohort drawn from the same community of the exposed cohort	3. Secure record / structured interview to ascertain exposure	4. Outcome of interest not present at the start of the study	1. Comparability of cohorts on the basis of the design of analysis	Comparability for any additional factor	1. Independent blind assessment/record linkage to assess the outcome	2. Follow up long enough for outcome of interest	3. Adequacy of follow up of the two cohorts	
Feskanich et al. [46]	*	*	*	*	*	*	*	*	*	9
Veierod et al. [48]	*	*	*	*	*	*	*	*		8

NOS, NewCastle Ottawa Scale

Table 3A – Foods intake and risk for CMM: data from studies included in the review

Article	Adjustment	Fish	Vegetables	Fruits	Other significant results
Feskanich et al. [46]	Skin reaction after sun exposure during childhood, n. sunburns, n. moles, natural hair colour, family history of melanoma, state of residence, menopausal status, oral contraceptive use, postmenopausal hormone use, parity, height, body mass index	/	RR 1.01 (0.68 – 1.50) [≥ 5 daily servings compared to < 2]	RR 1.37 (0.86 – 2.20) [≥ 3.5 daily servings compared to < 1]	
Fortes et al. [37]	Gender, age, education, hair color, skin phototypes, number of nevi, presence of freckles in childhood and sunburns in childhood	**OR 0.65 (0.43–0.97)** [weekly and more vs. less than weekly]	**OR 0.50 (0.31–0.80)** [>5 times/week compared to up to 2 times/week]	**OR 0.54 (0.33–0.86)** [daily and more vs. up to 4 times/week]	Protective role of tea (**OR 0.42; 0.18–0.95)** [daily and more vs. less than weekly]
Le Marchand et al. [41]	Height, education, hair color, n. of blistering sunburns, ability to tan, n. of moles	No association (data not shown)	No association (data not shown)	No association (data not shown)	
Millen et al. [45]	Age, gender, study site, presence of dysplastic nevi, education, and skin response to repeated	**OR 0.63 (0.43-0.94)** [0.3-1.0 frequency/day vs. no assumption]	**OR 0.43 (0.26-0.70)** f[3.1-8.7 frequency/day vs. 0-1 frequency/day]	OR 0.76 (0.54-1.08) [2.1-7 frequency/day vs. 0-1 frequency/day]	

	sun exposure				
Naldi et al. [44]	Age, gender, education, body mass index, history of sunburns, propensity to sunburns, n. of nevi, n. of freckles, skin, hair and eye color and tobacco smoking	OR 1.04 (0.74-1.46) [≥ 2 portions/week compared to < 1 portion/week]	OR 1.04 (0.76-1.42) [≥ 8 portions/week compared to < 7 portions/week]	OR 0.95 (0.65-1.38) [≥ 14 portions/week compared to < 7 portions/week]	Carrots: **OR 0.66 (0.44-0.99)** [≥ 1 portion/week vs. no consumption; butter: **OR 0.52 (0.32-0.87)** for high vs. low score
Osterlind [54]		/	Consumption of green vegetables was very similar in cases and controls	/	/
Shors et al. [47]	Age, gender, hair color, lifetime days in which the participant spent more than 4 hour in the sun	/	Fruit-Vegetable Index: **OR 0.6 (0.34-1.0)** [highest vs. lowest fruit-vegetable index quartile]	Fruit-Vegetable Index: **OR 0.6 (0.34-1.0)** [highest vs. lowest fruit-vegetable index quartile]	/
Stryker et al. [53]	Age, gender, hair color and ability to tan	Tuna fish: OR 1.3 [high vs. low use]	Mixed vegetables: OR 0.7 [high vs. low use]	/	
Veierod et al. [48]	Gender, age at inclusion, time-scale variable-attained age and country of residence	The consumption of fish sandwich spread and main meals with fish liver and fish was not associated with		The consumption of oranges, apples and pears was not associated with melanoma	Cod liver oil: IRR 1.1 (0.5-2.6) in men and **2.9 (1.7-5.1)** in women (comparison to no assumption)

		melanoma			
Vinceti et al. [40]	Total energy intake, melanoma family history, skin type, history of sunlight exposure and sunburns (for selected food)	RR 0.97 (0.82–1.16) for 10-g increments of daily intake	RR 1.02 (0.97–1.06) for 10-g increments of daily intake (leafy vegetables, root vegetables, fruiting vegetables, mixed salad, mushrooms, stalk vegetables and sprouts)	RR 1.00 (0.97–1.03) for 10-g increments of daily intake of fruits other than citrus	Vegetables oils: **RR 6.23 (1.08–35.84)** [III vs. I tertile]

Table 3B – Nutrients intake and risk for CMM: data from studies included in the review

Article	Adjustment	Energy intake	Carotenoids (Beta –carotene)	Vitamin A	Other vitamins	Fats	Carbohydrates	Proteins
Feskanich et al. [46]	Skin reaction after sun exposure during childhood, n. of sunburns, n. of moles, natural hair colour, family history of melanoma, state of residence, menopausal status, oral contraceptive use, postmenopausal hormone use, parity, height, body mass index	/	RR 1.22 (0.86–1.74) [≥ 6000 µg compared to < 2400 µg]	Retinol RR 0.85 (0.63–1.16) [≥ 1800 µg compared to < 400 µg]	Vitamin C: RR 1.33 (0.74–2.38) [≥ 400 mg compared to < 110 mg]. Vitamin E: RR 1.11 (0.66–1.85) [≥ 50 mg compared to < 9 mg]	/	/	/
Granger et al. [56]	Age, density of cutaneous melanin at the upper inner arm, reported usual sun	/	/	/	/	OR: 0.90 (0.61–1.33) and **0.61 (0.40–0.92)** for medium and high fat intake respectively	/	/

Kirkpatrick et al. [49]	Age, education, and total energy intake	OR 1.05 (0.61-1.82) [>2567 kcal/day compared to < 1527 kcal/day]	OR 1.43 (0.80-2.54) [>9712 IU/day compared to < 3528 IU/day]	OR 1.15 (0.67-2.00) [>14997 IU/day compared to < 6521 IU/day]	Vitamin C: 0.91 (0.51-1.64) [>153 mg/day compared to < 78 mg/day]. Vitamin E: **OR 0.34 (0.16-0.72)** [>10 mg/day compared to < 5 mg/day]	OR 0.46 (0.17-1.21) [>115 g/day compared to < 58 g/day]	/	/
Le Marchand et al. [41]	Height, education, hair color, n. of blistering sunburns, ability to tan, n. of moles	Males: OR 1.0 (0.5-1.9) [high vs. low intake]. Females: OR 1.0 (0.4-2.4) [high vs. low intake]	Males: OR 1.0 (0.5-2) [high vs. low intake]. Females: OR 1.1 (0.4-2.5) [high vs. low intake]	Males: OR 1.1 (0.5-2.5) [high vs. low intake]. Females: OR 0.9 (0.4-2.7) [high vs. low intake]	Vitamin C - Males: OR 0.9 (0.5-1.6) [high vs. low intake]. Females: OR 1.7 (0.8-3.7) [high vs. low intake]. Vitamin E: - Males: OR 1 (0.4-2.3) [high vs. low intake]. Females: OR 1 (0.4-2.8) [high vs. low intake]	Males: OR 1 (0.6-1.8) [high vs. low intake]. Females: OR 1 (0.4-2.1) [high vs. low intake]	/	/

Millen et al. [45]	Age, gender, study site, presence of dysplastic nevi, education, and skin response to repeated sun exposure	OR 1.07 (0.68-1.69) [≥2021 kcal/day compared to ≤1063 kcal/day]	**OR 0.36 (0.22-0.56)** [≥3048 µg/1000kcal compared to ≤942 µg/1000kcal]	Retinol: **OR 0.63 (0.40-0.99)** [≥482 µg/1000kcal compared to ≤223 µg/1000kcal]	Vitamin C: OR 0.66 (0.43-1.01) [≥117 mg/1000kcal compared to the ≤49 mg/1000kcal]. Vitamin D: **OR 0.61 (0.40-0.95)** [≥158 IU/1000kcal compared to ≤58 IU/1000kcal]. Vitamin E: OR 0.64 (0.41-1.01) [≥8 mgEq/1000kcal compared to ≤4 mgEq/1000kcal]	OR 1.47 (0.95-2.27) [≥41% kcal compared to ≤28%kcal]	**OR 0.55 (0.35-0.87)** [≥53%kcal compared to ≤39%kcal]	**OR 0.50 (0.33-0.78**) [≥19% kcal compared to ≤13%kcal]
Naldi et al. [44]	Age, gender, education, body mass index, history of sunburns, propensity to sunburns, n. of nevi, n. of freckles, skin, hair and eye color and tobacco smoking	/	OR 0.71 (0.50-1.02) [the highest vs. lowest quartile]	Total vitamin A: **OR 0.51 (0.35-0.74)** [highest vs. lowest quartile]. Retinol: **OR 0.57 (0.39-0.83)** [highest vs. lowest quartile]	/	/	/	/

Osterlind [54]		/	/	/	/	The risk of melanoma was not increased in high fat consumers	/	/
Stryker et al. [53]	Age, gender, hair color and ability to tan	/	Carotene: OR 0.7 (0.4-1.2) [highest vs. lowest quintile]	Preformed vitamin A, food: OR 0.9 (0.5-1.5) [highest vs. lowest quintile]	Vitamin E, food: **OR 0.5 (0.3-0.9)**; vitamin B1, food: OR 0.8 (0.5-1.4); vitamin B2, food: OR 1.2 (0.7-2.1); vitamin B12, food: OR 1.1 (0.8-1.4); vitamin C, food: OR 1.0 (0.6-1.8); vitamin D, food: OR 1.2 (0.7-2.0) [highest vs. lowest quintile]	Vegetable fat: OR 0.7 (0.4-1.1); animal fat: OR 1.6 (0.9-2.8) [highest vs. lowest quintile]	OR 0.6 (0.3-1.0) [highest vs. lowest quintile]	OR 1.2 (0.7-2.0) [highest vs. lowest quintile]
Veierod et al. [48]	Gender, age at inclusion, attained age and country of residence	/	/	/	/	Total fat did not influence the risk of melanoma	/	

Vinceti et al. [42]	Energy intake	Total energy intake was not associated with melanoma	OR 1.60 (0.42–6.12) [III vs. I tertile]	Retinol: OR 1.94 (0.33–11.54) [III vs. I tertile]	Vitamin E: OR 1.16 (0.26-5.07); vitamin C: OR 0.71 (0.13-4.03); vitamin D: OR 0.76 (0.23-2.50); vitamin B1: OR 0.62 (0.11-3.57); vitamin B2: OR 0.84 (0.13-5.37); vitamin B3: OR 0.31 (0.05-1.93); vitamin B6: OR 1.82 (0.42-7.93); vitamin B9: OR 1.25 (0.18-8.60) [III vs. I tertile]	OR 1.21 (0.09–15.28) [III vs. I tertile]	OR 0.42 (0.03-5.90 [III vs. I tertile]	OR 0.83 (0.14–4.71) [III vs. I tertile]
Weinstock et al. [51]	Age, family history for melanoma and hair color	Energy intake was not associated with melanoma	/	/	Calorie-adjusted vitamin D intake: RR 1.8 (0.9-3.5) [highest vs. lowest quintile]	/	/	/

In the study from Gogas et al., one quintile more of plant food monthly consumption was associated to an **OR of 0.49 (95%CI 0.34-0.71)** whereas one quintile more of animal food monthly consumption showed an OR of **2.28 (95% CI 1.52-3.43)**. Malagoli et al. shows that total and animal proteins, total and animal fats, total saturated, monounsaturated and polyunsaturated fatty acids and vitamin D were associated to an increased risk in the case of hospital controls as references. The replacement of hospital controls with population referents

did not yield any relation between the risk of melanoma and dietary factors, with the exception of a newly detected association between riboflavin intake and risk for CMM.