An epidemiological review of diet and cutaneous malignant melanoma

Running title: epidemiology of diet and melanoma

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Abstract

Incidence of cutaneous malignant melanoma has continued to rise despite public efforts to promote sun protection behaviors among populations at risk. However, dietary factors may also affect the development of melanoma. In the past few decades, findings from epidemiological and experimental research have linked consumption of several foods and other nutrients to the risk of melanoma. Caffeine has been associated with a lower risk of melanoma, and citrus fruits and alcohol with increased risk. Associations between polyunsaturated fatty acid, niacin/nicotinamide, folate and Vitamin D with melanoma remain controversial. Diet likely influences melanoma development through several potential mechanisms, such as enhancing UV-induced apoptosis and increasing photosensitivity. We conducted a narrative review to summarize recent epidemiological studies of diet and melanoma based on published literature. Given the high prevalence of the food items and nutrients covered in this review and the decades-long rising melanoma incidence worldwide, the associations we discuss may have important public health implications in terms of reducing melanoma incidence through dietary modification.

Keywords: diet; melanoma; prevention

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Introduction

Cutaneous malignant melanoma is the fifth most common cancer in the United States and one of the deadliest forms of skin cancer because of its high metastatic potential (1). The U.S. is estimated to have 91,270 new melanoma cases in 2018, which will account for approximately 5.3% of all new cancers; the number of deaths from melanoma in 2018 is estimated at 9,320, or approximately 1.5% of all cancer deaths. Incidence rates for new melanoma cases have been rising an average of 1.5% per year over the past decade; mortality rates have been falling on average 1.2% per year during 2006-2015; and the five-year survival rate has climbed from 81.8% in 1975-1977 to 91.8% in 2008-2014 (1).

Excess exposure to ultraviolet radiation (UVR) from natural sunlight or tanning devices is the most important risk factor for melanoma. Other common risk factors include family history of melanoma, number of atypical moles, history of severe sunburns, as well as phenotypic characteristics such as low tanning ability, light skin, light eye color, and red/blonde hair (2). Animal studies have shown promising results supporting the role of some natural compounds in the chemoprevention of melanoma. Epidemiological studies have also suggested that some dietary factors and nutrients might play roles in affecting melanoma risk (3), though the significance of many of those associations is still controversial. Diet likely influences melanoma development through several potential mechanisms, such as lowering melanoma risk by enhancing UV-induced apoptosis (4) and increasing melanoma risk by enhancing photosensitivity (5).

A few reviews of diet and melanoma have been published; however, most have focused specifically on some natural compounds of the diet with antioxidant properties, such as vitamins A, C, and E, and selenium (3,6-8). Herein, in this paper, we provide a comprehensive review of

the relationship between diet and melanoma risk from the perspective of epidemiology. Our paper includes a list of updated references and a large coverage of dietary factors that may have a role in melanoma, including coffee and caffeine, citrus fruits, alcohol, polyunsaturated fatty acid, niacin/nicotinamide, folate, and vitamin D. Additionally, we also discussed the underlying biological mechanisms and outlined some possible future directions in the field. Since some dietary factors emerged as promising candidates for chemoprevention, through summarizing current evidence, we also hope our review could encourage further efforts in both research and practice in this field.

Methods

We conducted a narrative review based on literature published in English (up to January 2018). Relevant articles were identified by searching the keywords “diet melanoma”, “nutrition melanoma”, “melanoma chemoprevention”, “coffee melanoma”, “citrus melanoma”, “alcohol melanoma”, “niacin melanoma”, “nicotinamide melanoma”, “fatty acid melanoma”, “folate melanoma”, and “vitamin D melanoma” in PubMed.

Diet and cutaneous malignant melanoma

1. Coffee and caffeine

Coffee is quite widely consumed. Animal studies have shown that caffeine may inhibit UV-induced sunburn lesions in the epidermis of mice and may mimic the effect of a sunscreen (4). Though caffeinated coffee is the major source of caffeine, other foods high in caffeine include tea, cola, and chocolate. Epidemiologic evidence for the association between coffee consumption and risk of melanoma has been ambiguous. Some studies suggested an inverse association (9,10), whereas others showed no significant association (11-13); though the latter

did not distinguish caffeinated coffee from decaffeinated coffee (9,10,12).

Most evidence on this topic comes from cohort studies. Data from the Norwegian Women and Cancer (NOWAC) Study (1.7 million person-years of follow-up) showed reduced melanoma risk associated with a moderate intake of filtered coffee but not with instant, boiled, or total coffee consumption (14). Song *et al*. (11) analyzed pooled data from the Nurses' Health Study (NHS) (24 years of follow-up from 1984) and the Health Professionals Follow-up Study (HPFS) (22 years of follow-up from 1986); they found that neither caffeinated nor decaffeinated coffee—nor even total caffeine intake from all dietary sources—was significantly associated with melanoma risk. However, NHS and HPFS used different cutoffs for caffeine intake levels, which may have produced heterogeneity in the estimates of higher-intake groups versus reference groups over the total study populations (15). Therefore, Wu *et al*. further regrouped participants from the NHS (1980-2008) and the HPFS (1986-2008) using caffeine intake quintiles in the Nurses' Health Study II (NHS II) (1991-2009) (15). They found that melanoma risk among those with higher caffeine intake (≥393 mg/day) was significantly lower than among those with lower caffeine intake (<60 mg/day) [HR (95% CI)=0.78 (0.64-0.96)]. Among women, caffeinated coffee consumption was significantly associated with lower melanoma risk [>2/Day vs. never: HR (95% CI)=0.76 (0.64-0.89)], though the association between decaffeinated coffee consumption and melanoma risk was not significant. Moreover, Wu *et al.* (15) also found that the inverse association between caffeine and melanoma was significant for melanoma on the head, neck, and extremities [≥393 mg/day vs. <60 mg/day: HR (95% CI) = 0.71 (0.59-0.86)] but insignificant for melanoma on the trunk, including shoulder, back, hip, abdomen, and chest [≥393 mg/day vs. <60 mg/day: HR (95% CI) = 0.90 (0.70-1.20)].

In addition, after a median follow-up of 10.5 years among 447,357 non-Hispanic white

subjects in the NIH-AARP Diet and Health Study, Loftfield *et al.* (16) also detected a modest decrease in melanoma risk among people with higher coffee intake [≥4 cups/day vs. None: HR (95% CI) = 0.80 (0.68-0.93)]; the association was significant for caffeinated [≥4 cups/day vs. None: HR (95% CI) = 0.75 (0.64-0.89)] but not for decaffeinated coffee. Similarly, Caini *et al.* (17) reported an inverse association between caffeinated coffee consumption and melanoma risk among men [4^{th} quartile vs. none: HR (95% CI) = 0.31 (0.14-0.69)], but not in women, and no association with decaffeinated coffee consumption among either men or women, after a median follow-up of 14.9 years among 476,160 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The associations reported in these cohort studies were adjusted for age, sex, body mass index (BMI), potential lifestyle confounders such as physical activity, smoking, and alcohol consumption, as well as known melanoma risk factors (11,15-17). Finally, significant inverse associations between caffeinated coffee and melanoma were also reported by two recent meta-analyses of observational studies (18,19).

Taken together, current epidemiological evidence suggests that higher caffeine intake and caffeinated coffee consumption may help reduce melanoma risk. Evidence from biomedical research lends biological plausibility to the possible beneficial role of caffeine intake in protecting against UVB-induced carcinogenesis. Animal studies have demonstrated that oral administration of caffeine may eliminate sunburned cells by enhancing UV-induced apoptosis, thus preventing UV-induced carcinogenesis (4,20). Further, research indicated that the ability of caffeine to promote the apoptosis of DNA-damaged cells could be related to the inhibition of the ataxia telangiectasia and Rad3-related (ATR) kinase or its downstream target checkpoint kinase 1 (Chk1) (ATR/Chk1 pathway) (21,22). It has been shown that irradiation of mouse skin with UVB activated the ATR/Chk1 pathways, induced phosphorylation of Chk1 on Ser^{345}, and further

decreased the number of mitotic keratinocytes with cyclin B1. Administration of caffeine enhanced the removal of DNA-damaged cells by inhibiting the ATR-mediated phosphorylation of Chk1 and abrogating the UVB-induced decrease in mitotic cells with cyclin B1 (22,23). Moreover, considering the biological evidence for caffeine's beneficial effect against UV-induced skin cancer (24) and the hypothesis that the role of sunlight in melanoma differs according to anatomic site (25), it is plausible that caffeine may have a stronger beneficial effect in reducing risk of sun-induced cutaneous carcinogenesis on body sites receiving higher continuous UV radiation (e.g., head, neck) compared with body sites receiving lower continuous UV radiation (e.g., trunk); this was observed in Wu *et al.*'s study (15).

2. Citrus fruit

A limited number of epidemiological studies have examined the relationship between citrus fruit consumption and melanoma. In 2003, Feskanich *et al.* (26) reported an unexpected higher risk among the NHS (1984-1998) and NHS II (1991-1999) cohorts of US women who consumed more orange juice and derived vitamin C from foods, but not from supplements; compared to no orange juice consumption, consumption ≥ 1 serving per day was associated with an elevated risk of melanoma [RR=1.61, 95% CI=0.92-2.84, *P* for linear trend=0.008]. Since vitamin C has preferential toxicity for melanoma cells (26), the increased melanoma risk associated with dietary vitamin C was likely the effect of other components (e.g., photoactive compounds such as psoralens and furocoumarins (5), a group of naturally occurring chemicals that, through sensitizing the skin to UV radiation, may have photocarcinogenic properties) in vitamin C–rich foods (e.g., citrus fruits).

Using data from the NHS (1984-2010) and HPFS (1986-2010) cohorts, Wu *et al.* (5) found that citrus consumption was associated with increased risk of melanoma, and the

association between overall citrus consumption and melanoma risk appeared to depend upon the frequency of exposure in their pooled analysis; consumption of citrus fruits ≥ 1.6 times per day was associated with higher risk for developing melanoma compared to consumption of citrus fruits < 2 times per week [HR (95% CI)=1.36 (1.14-1.63), *P*-trend <0.001]. The positive association was strongest between grapefruit consumption and melanoma risk [≥ 3 times per week vs. never, HR (95% CI)=1.41 (1.10-1.82)]; the association was significant but weaker between orange juice consumption and melanoma risk [≥ once per week vs. < once per week, HR (95% CI)=1.25(1.07-1.47)]. Consumption of grapefruit juice and oranges was generally not associated with melanoma risk. This may be because psoralens and furocoumarins are more abundant in grapefruit than in grapefruit juice, and the much more prevalent consumption of orange juice compared with oranges themselves would counterbalance the lower levels of psoralens and furocoumarins in orange juice (5). However, conflicting findings were reported by one hospital-based case-control study in Italy (304 cases vs. 305 controls); that study found that high citrus consumption seemed to have a beneficial effect against melanoma risk [≥ 5 times per week vs. ≤ 2 times per week, OR (95% CI)=0.51(0.32-0.80)] (27).

Citrus products are widely consumed foods that are rich in psoralens and furocoumarins. The mechanism underlying the association between consumption of citrus and the development of melanoma could be based on the presence of psoralens and furocoumarins in citrus fruits, particularly grapefruit. Photochemotherapy using oral psoralen (methoxsalen) and ultraviolet (UV) A radiation (PUVA) is a highly effective therapy for severe psoriasis: psoralen is taken orally to sensitize the skin before UVA light treatment. Both epidemiological and experimental studies suggested that long-term PUVA therapy increases the risk of melanoma (28,29).

Research has also shown that psoralens and furocoumarins can interact with ultraviolet (UV) light to stimulate proliferation of melanoma cells (30).

Generally, evidence regarding the association between dietary consumption of psoralen-rich foods and melanoma risk remains inconclusive. Considering that citrus fruits are widely consumed and that their consumption has long been advocated for its potential benefits in reducing risk of disorders such as coronary heart disease, additional investigations are needed to confirm current findings before making further dietary suggestions to the public (31).

3. Alcohol

It has been suggested that alcohol intake increases sunburn severity, a major risk factor for melanoma skin cancer. In 1977 Williams and Horm first reported a positive association between alcohol consumption and risk of melanoma based on Third National Cancer Survey data (32). Since then, several epidemiological studies have investigated the relationship between alcohol consumption and melanoma, but the evidence is inconsistent (12,33-37).

A case-control study in Montreal (107 cases vs. 507 controls) found no significant association between lifetime consumption of alcoholic beverages and melanoma risk [≥ 7 drinks/week vs. never, OR (95%CI)=1.21(0.68-2.18)] (33). Similarly, a case-control study in Italy (542 cases vs. 538 controls) also failed to find any association [≥ 28 drinks/week vs. never, OR (95% CI)=0.83 (0.49-1.40)] (12). On the other hand, high alcohol consumption was associated with elevated risk of melanoma [alcohol accounts for ≥ 10% of total calories vs. None, OR (95% CI)=1.65 (1.09-2.49)] in another case-control study with 502 cases and 565 controls (34). Recently, Miura *et al.* (35) conducted a pooled analysis of eight case-control studies (1886

cases vs. 2113 controls) that found a positive association between ever consuming alcohol and melanoma risk among women [adjusted pooled OR (95% CI)=1.3 (1.1-1.5)].

Large cohort studies have consistently associated increased melanoma risk with alcohol consumption. Kubo *et al.* (36) examined the association among 59,575 white postmenopausal women in the Women's Health Initiative (WHI) Observational Study (OS). They noted a significant relationship between the amount of alcohol consumed and risk of melanoma [7+ drinks/week vs. nondrinkers, HR (95% CI)=1.64 (1.09-2.49)] after 10.2 means years of follow-up; compared to nondrinkers, those who consumed either white wine or liquor were at increased melanoma risk [white wine: HR (95% CI)=1.52 (1.02-2.27); Liquor: HR (95% CI)= 1.65 (1.07-2.55)] (36).

Rivera *et al.* (37) then examined the association in the NHS (1984-2012), NHS II (1991-2011), and HPFS (1986-2012) cohorts; they found that higher alcohol intake was associated with elevated invasive melanoma risk [pooled multivariate HR (95% CI)=1.14 (1.00–1.29)] per drink/day; *P*-trend < 0.04] over 18.3 means years of follow-up. Similar to findings from the WHI (36), white wine consumption was also associated with an increased risk of melanoma in NHS, NHS II, and HPFS, after adjusting for other alcoholic beverages [pooled multivariate HR (95% CI)=1.13 (1.04-1.24) per drink/ day; *P*-trend <0.01]. Moreover, Rivera *et al.* (37) found that the association between alcohol consumption and melanoma risk was stronger for melanoma in relatively UV-spared sites (trunk) versus more UV-exposed sites (head, neck, or extremities). As evidence suggests that etiologies of melanoma differ by anatomic site (25), the authors (37) explained the finding by positing that alcohol consumption may affect those etiologic pathways differently; alcohol's carcinogenic effect may be more relevant to melanomas at relatively UV-spared sites. Similarly, in the previously discussed pooled analysis of eight case-control studies,

the positive association between alcohol intake and melanoma was also found to be slightly stronger with melanomas on the trunk compared with other body sites (35).

Finally, one meta-analysis of 14 case-control and 2 cohort studies encompassing a total of 6251 cases of melanoma showed that alcohol consumption was positively associated with the risk of melanoma [any alcohol drinking vs. no/occasional drinking, RR (95% CI)= 1.20 (1.06-1.37)]. The association was attenuated but remained marginally significant when only the 10 studies that adjusted for sun exposure were included [any alcohol drinking vs. no/occasional drinking, RR (95% CI)= 1.15 (0.94-1.41)] (38).

Generally, alcohol causes carcinogenesis via acetaldehyde by creating DNA adducts. Alcohol may also act as a photosensitizer, and the combination of UV radiation and alcohol consumption may potentiate skin carcinogenesis (39). Specifically, ethanol is converted to acetaldehyde soon after its ingestion; the metabolite may act as a photosensitizer, generating reactive oxygen species and related intermediates, which may further induce oxidative DNA damage, enhance the binding of acetaldehyde to DNA, and activate signal-transduction cascades and prostaglandin synthesis (39). However, the potential synergistic effect between UV radiation and alcohol on skin carcinogenesis needs further exploration, as stronger associations were detected between alcohol consumption and melanoma on UV-spared body locations in cohort studies (35,37). In addition, epidemiological evidence consistently showed that among all alcoholic beverages (36,37), white wine has the strongest association with increased melanoma risk. This may because of the far-higher levels of pre-existing acetaldehyde in wine than in beer or spirits. In some cases, the pre-existing acetaldehyde alone exceeds carcinogenic levels (40).

4. Niacin/Nicotinamide

Niacin, also known as nicotinic acid or vitamin B3, together with its water-soluble amide form nicotinamide, makes up the group called vitamin B3 complex. Both niacin and nicotinamide are widely available in plant and animal foods; breakfast cereal, multivitamins, and B vitamin supplements often contain nicotinamide as niacin (41).

Nicotinamide is the primary precursor of nicotinamide adenine dinucleotide (NAD+), an essential coenzyme in ATP production. Increased skin sensitivity to sun exposure is a well-known symptom of severe niacin deficiency (pellagra) in humans, which is related to low nicotinamide-adenine dinucleotide (NAD) status and deficiencies in responding to UV damage (42). Niacin and nicotinamide have been shown to reduce UV-induced immunosuppression (a risk factor for skin cancer) in mice and humans when used topically or orally (43). Nicotinamide may also have a beneficial protective role against DNA damage and mutagenesis through facilitating DNA repair (44).

However, few epidemiological studies have investigated the association between niacin intake and melanoma risk. Recently, Park *et al.* (45) prospectively evaluated whether total, dietary, or supplemental niacin intake was associated with skin cancer risk among 72,308 women in the NHS (1984-2010) and 41,808 men in the HPFS (1986-2010). They found the association between total niacin intake and melanoma was not statistically significant [top vs. bottom quintiles, adjusted-pooled HR (95% CI)=1.18 (0.77-1.81); *P*-trend=0.07]. Still, higher total niacin intake was marginally and positively associated with melanoma risk in men [top vs. bottom quintiles, adjusted-pooled HR (95% CI)=1.48 (1.07-2.05); *P*-trend=0.05], but not in women [top vs. bottom quintiles, adjusted-pooled HR (95% CI)=0.96 (0.73-1.27); *P*-trend=0.67] (45). More epidemiological studies are needed to evaluate the effect of niacin intake on skin cancer risk.

5. Polyunsaturated fatty acid

Omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs) are both essential for human health. PUFAs are important structural components of membrane phospholipids and precursors of families of signaling molecules (e.g., eicosanoids). Eicosanoids derived from omega-6 (n-6) and omega-3 (n-3) PUFAs are functionally distinct; some even have important but opposing physiological functions (46).

The beneficial impact of long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs) on human health have been widely observed and primarily attributed to the two LC n-3 PUFAs, i.e., eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3) (47). EPA and DHA are abundant in fish and other seafood. The possible antineoplastic effect of dietary LC n-3 PUFAs has been supported by many basic science studies that have identified a number of molecular factors and pathways involved in cell growth, apoptosis, invasion, and angiogenesis and are affected by these fatty acids (48). Recent evidence regarding the potential of LC n-3 PUFAs to abrogate photo-immunosuppression in human skin has provided additional support for their chemopreventive role against skin cancers (49). Direct evidence from animal studies has shown that n-3 PUFAs inhibit UV-induced carcinogenesis (50). Additionally, emerging evidence suggests that it is actually the n-6/n-3 fatty acid ratio, rather than the absolute levels of the two classes of PUFAs, that plays the principal role in the antitumor effects of n-3 PUFAs (46).

Though the biological plausibility of the antitumor effect of n-3 PUFAs has been well established through preclinical research, epidemiological evidence to date regarding melanoma remains both limited and inconsistent. Early case-control studies showed no association between PUFA-rich food consumption and melanoma risk (51,52). The beneficial effect was suggested by an epidemiological study that showed relatively low rates (estimated by standardized incidence

ratios) of melanoma in the Inuit, an Eskimo population whose fish-based diet results in a high daily intake of LC n-3 PUFAs compared to rates in Connecticut, Denmark, and Canada (53). One hospital-based case-control study in Italy (304 incident melanoma cases and 305 controls) showed an inverse association between consumption of fish rich in n-3 fatty acids and melanoma risk [low vs. high intake, OR (95% CI)=0.52 (0.34-0.78)] (27). However, actual PUFA intakes were not calculated based on food frequency questionnaire (FFQ), nor were serum PUFA levels tested (27,51-53). Bain *et al.* (54) conducted a population-based case-control study of 41 women with melanoma and 297 controls from the same community (Brisbane, Australia). Diet was assessed by a comprehensive FFQ. Results indicated a strong inverse relation between high intakes of polyunsaturated fatty acids and melanoma ($P < 0.01$). Recently, Donat-Vargas *et al.* (55) examined the association between dietary EPA-DHA intake (FFQ based) and melanoma risk using data from the Swedish Mammography Cohort (follow up: 4.5 years); they found that higher dietary EPA-DHA intake was significantly associated with lower melanoma risk [highest vs. lowest tertiles, HR (95% CI)=0.2 (0.1-0.8), *P*-trend=0.03]. Results from Nurses' Health Study (NHS, 1984-2012) and the Health Professionals Follow-up Study (HPFS, 1986-2012) showed that higher n-6 PUFA intake was associated with an increased risk of melanoma (highest vs. lowest quintiles, HR (95% CI)=1.20 (1.02-1.41), *P*-trend=0.03); no other fats were significantly associated with melanoma risk (56).

Taken together, observational studies published to date have not clearly explained the role of PUFAs in the development of melanoma. Recently, to explore the causal link of PUFA levels and melanoma risk, Liyanage *et al.* conducted a mendelian randomization analysis using 12,874 cases and 23,203 controls from the largest melanoma genome-wide association study (GWAS) meta-analysis; their results showed that the effect of increased PUFA levels on

melanoma risk is either zero or very small (57). As observational studies are always subject to residual confounding, which makes it difficult to interpret observed findings, further studies are needed to explore the causality of PUFAs and melanoma risk.

It is worth mentioning that, in basic research, animals or cells are treated with purified LC n-3 PUFAs. However, PUFA intake in most epidemiological studies is evaluated based on the amounts/frequency of fish ingested. This information is usually obtained through FFQ, in which the actual levels of different types of PUFAs (n-3/n-6) and consumption of different types of fish are difficult to estimate. Some fish (e.g., lean fish) actually contain very low levels of LC n-3 PUFAs. In addition, subjects considered "high consumers" in one region might be described as "low consumers" in other regions, causing further confusion in the interpretation of results. However, few epidemiological studies published to date have examined the associations between biomarkers such as erythrocyte or serum levels of LC n-3 PUFA with melanoma risk. Therefore, studies applying both biomarkers and FFQ would be needed to better explore the relationships between fatty acids and the risk of cancers in population groups (48).

6. Folate/folic acid

Folate (vitamin B9), along with vitamins B2, B12, and B6 are the sources of coenzymes participating in the one-carbon metabolism (58). Folic acid is a synthetic form of folate. Due to the confirmed protective effect of folate against neural tube defects (59), folic acid supplementation is now recommended for women during the periconceptional period, and nationwide folate fortification of flour has been mandatory in US (60) and Canada (61) for around two decades. However, folate fortification is still not mandatory in many European, Asian, and African countries (62). One of the biggest concerns for adults is the potential elevated cancer risk related to folate intake.

Epidemiological evidence regarding the relationship between folate and overall/site-specific cancer risk is quite inconsistent; positive, inverse, as well as null associations have all been reported (63-66). Recently, increased risks of overall skin cancer [third vs. first tertiles: HR (95% CI)= 1.79 (1.07-2.99)] associated with dietary folate intake were reported in a prospective cohort study (follow-up: 1994-2007) in France (67). In terms of folate intake and melanoma risk, epidemiological studies are limited. One meta-analysis of randomized controlled trials showed no significant effect of folic acid supplementation on the risk of melanoma skin cancer (63). However, an inverse association between folic acid supplementation and melanoma risk was found by another meta-analysis of three trials [RR (95% CI)=0.47 (0.23-0.94)] (64). There were no any published prospective cohort analyses specifically examining the relationship between dietary folate/folic acid and melanoma.

Some animal studies have suggested that folate might have a dual effect on cancer, i.e., high folate intakes could suppress the development of early lesions in normal tissue (i.e., protect against cancer initiation) but facilitate the growth of pre-neoplastic cells and subclinical neoplasms (68). Research has also shown that folic acid is associated with cellular phototoxicity and photogenotoxicity (69); this finding could provide further clues in explaining the relationship between folate and skin cancer risk.

7. Vitamin D

Vitamin D has long been known to be essential for human bone health. Ultraviolet radiation (UVR) exposure, diet, and supplements are the sources of Vitamin D, of which UVR is the major source. Emerging evidence suggests that vitamin D also plays an important role in reducing the risk of heart disease, autoimmune disease, and cancer, and in supporting cognitive function (70). Paradoxically, vitamin D deficiency has been linked to increased melanoma risk

and progression with conflicting results, although sun exposure is an established risk factor for melanoma (71).

7.1 Vitamin D intake and melanoma risk

In vitro research has found that vitamin D has anti-proliferative effects on cultured melanoma cells (72). However, epidemiological data supporting the chemopreventive effect of vitamin D intake against melanoma remains inconsistent. One U.S. case-control study found that higher energy-adjusted vitamin D intake from food was significantly associated with lower melanoma risk [highest versus lowest quintiles, OR (95% CI)= 0.61 (0.40-0.95)]; however, the association became only marginally significant when combined vitamin D intake from both food and supplements was considered [highest versus lowest quintiles, OR (95% CI)= 0.66 (0.42-1.02)] (34). An inverse association between dietary vitamin D intake and melanoma risk was also reported in a population-based case-control study (380 cases vs. 719 controls) in a northern region of Italy [highest versus lowest quintiles, OR (95% CI)= 0.53 (0.31-0.88)] (73).

On the other hand, most cohorts found null results. For example, 10-year follow-up of the Vitamins and Lifestyle cohort study, a large prospective US cohort study, found no significant difference in melanoma risk among the highest quartiles of dietary vitamin D intake [RR (95% CI)=1.31 (0.94-1.82)], supplemental vitamin D intake [RR (95% CI)=1.13 (0.89-1.43)], and combined dietary and supplemental intake [RR (95% CI)=1.05 (0.79-1.40)], compared with the lowest quartile (74). Also, null associations between total, dietary, and supplemental vitamin D intake with melanoma risk were found in cohort analyses based on 63,760 women in the Nurse's Health Study (1984-2010) and 41,530 men in the Health Professionals Follow-up Study (1986-2010) (75). Finally, post hoc analyses of the Women's Health Initiative Randomized Controlled Trial (mean follow-up: 7 years) found no difference in melanoma incidence between the

treatment group (1,000 mg of elemental calcium plus 400 IU of vitamin D3 daily) and the placebo group [HR (95% CI)=0.86 (0.64-1.16)]; however, subgroup analysis showed a beneficial role of vitamin D supplementation against melanoma risk among women with a history of NMSC [HR (95% CI)=0.43 (0.21-0.90)] (76).

7.2 Serum vitamin D level and melanoma risk/survival

Serum 25-hydroxyvitamin D [25(OH)D] level is a general reflection of vitamin D stored in the human body and obtained from UV exposure, diet, and supplements. Newton-Bishop *et al.* (77) reported an inverse relationship between serum vitamin D levels and melanoma risk in a case-control study in the UK [OR (95% CI)=0.64 (0.46-0.87) per 20 nmol/L increase across seasons]. The associations between insufficient and deficient serum levels of vitamin D and melanoma risk were also reported by a recent case-control study in Italy (137 cases vs. 99 controls) (78). Meta-analysis of four studies including 392 melanoma cases did not indicate a significant association between 25(OH)D serum levels and melanoma risk [highest vs. lowest, RR (95% CI)=1.46 (0.60-3.53)] (79). However, a marginally significant and positive association was found between melanoma and serum 25(OH) D level in an 11-year prospective study in Australia [OR (95% CI)=2.71 (0.98-7.48) for 25(OH)D level ≥ 75 vs. <75 nmol/L, OR (95% CI)=2.70 (0.83-8.77) for every 50 nmol/L increase in 25(OH)D concentration] (80). A prospective cohort study of 10,060 Danish participants also found that increasing levels of plasma 25(OH)D were associated with elevated risk of melanoma after 28 years' follow-up [HR (95% CI)=4.72 (0.96-23.3) for 25(OH) D level ≥ 50 vs. <25 nmol/L, HR (95% CI)=9.58 (2.37-38.7) for 25(OH) D level ≥ 100 vs. <25 nmol/L] (81). The positive association between serum vitamin D level and melanoma risk may be because serum vitamin D levels are strongly

associated with increased sun exposure, and thus may simply act as a surrogate for excess sun exposure (77).

Existing epidemiological evidence indicates that serum vitamin D levels are also related to melanoma outcomes. Gambichler et al. reported that lower serum 25(OH)D levels are associated with greater tumor thickness and more-advanced tumor stage in a German cohort of 764 patients with melanoma (82). In the Leeds Melanoma Cohort of 872 melanoma patients, Newton-Bishop et al. found that higher 25-hydroxyvitamin D3 levels were significantly associated with lower Breslow thickness at diagnosis and better survival [For relapse-free survival, HR (95% CI) = 0.79 (0.64-0.96) for a 20 nmol/L increase in serum vitamin D level], after a median follow-up of 4.7 years (83). Saiag et al. found that in melanoma patients, 25(OH)D3 levels at diagnosis were inversely correlated with prognostic factors including ulceration, cancer staging, and Breslow's thickness, but not with risk of relapse; however, changes in 25(OH)D3 levels in both directions during follow-up were associated with worse prognosis (84). Recently, a retrospective pilot study also found that high serum vitamin D level was correlated with better prognostic indicators among patients diagnosed with primary melanoma (85). Taken together, those lines of evidence suggest that correction of low vitamin D levels after diagnosis may be beneficial for melanoma-specific survival; however, the findings of observational studies need to be confirmed in randomized controlled trials, and additional studies are needed to establish optimal serum levels for melanoma patients.

Conclusion and Future directions

In conclusion, major epidemiological evidence so far suggests that caffeine intake may have beneficial protective effects against cutaneous malignant melanoma, while citrus fruits and alcohol consumption may play detrimental roles. Though experimental studies have suggested

biological mechanisms for these links, few conclusions are possible based on data from RCTs supporting the efficacy of dietary modification for the prevention of melanoma. Findings regarding the associations between polyunsaturated fatty acid, niacin/nicotinamide, folate intakes, and Vitamin D with melanoma are still quite inconsistent. These associations require additional explorations through prospective studies. Noteworthily, observational studies are subject to limitations such as residual confounding and reverse causality. In addition, the assessment of diet intakes based on food frequency questionnaire may result in recall bias in case-control studies. These points may somewhat help explain the inconsistent results observed in cohort and case-control studies regarding certain associations. Therefore, more randomized trials are needed to confirm the results from observational studies. Moreover, development of more-robust dietary biomarkers using high-throughput technologies would be highly recommended. For dietary factors with potential beneficial impact, further efforts are needed to identify the main molecular targets in melanoma. Additionally, the role of gene-diet interaction in melanoma development could also be explored. These efforts are crucial for understanding the underlying mechanism and developing precision chemoprevention strategies for melanoma.

In addition, emerging data has suggested that a combination of nutrients and foods may demonstrate stronger associations with cancer risk compared with specific nutrients or food types; healthy dietary patterns have been associated with lower risk of cancers including pancreatic, colorectal and breast cancer (86,87). However, to date, few epidemiological studies have examined dietary patterns and melanoma risk. Fortes *et al.* found the Mediterranean diet may have protective effects against melanoma (27). Malagoli *et al.* found an inverse association between melanoma risk with the Healthy Eating Index 2010 (HEI-2010) and Dietary Approaches to Stop Hypertension (DASH) index, which both assess diet quality (88). These lines of evidence

suggested that dietary patterns could affect risk of melanoma. Therefore, more epidemiological studies investigating possible associations between dietary pattern and melanoma risk should be encouraged, since they are crucial before incorporating dietary interventions into clinical and nutritional practice.

Given the high prevalence of food items and nutrients covered in this review, along with rising melanoma incidence over recent decades worldwide, the associations we discuss may have important public health implication, and may eventually be useful for the prevention of cutaneous malignant melanoma.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: a cancer journal for clinicians 2018;68(1):7-30.
2. Gandhi SA, Kampp J. Skin Cancer Epidemiology, Detection, and Management. The Medical clinics of North America 2015;99(6):1323-35.
3. Tong LX, Young LC. Nutrition: the future of melanoma prevention? Journal of the American Academy of Dermatology 2014;71(1):151-60.
4. Lu YP, Lou YR, Xie JG, Peng QY, Zhou S, Lin Y, et al. Caffeine and caffeine sodium benzoate have a sunscreen effect, enhance UVB-induced apoptosis, and inhibit UVB-induced skin carcinogenesis in SKH-1 mice. Carcinogenesis 2007;28(1):199-206.
5. Wu S, Han J, Feskanich D, Cho E, Stampfer MJ, Willett WC, et al. Citrus Consumption and Risk of Cutaneous Malignant Melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33(23):2500-8.
6. de Waure C, Quaranta G, Gualano MR, Cadeddu C, Jovic-Vranes A, Djikanovic B, et al. Systematic review of studies investigating the association between dietary habits and cutaneous malignant melanoma. Public health 2015;129(8):1099-113.
7. Miura K, Green AC. Dietary Antioxidants and Melanoma: Evidence from Cohort and Intervention Studies. Nutrition and cancer 2015;67(6):867-76.
8. Jensen JD, Wing GJ, Dellavalle RP. Nutrition and melanoma prevention. Clinics in dermatology 2010;28(6):644-9.
9. Veierod MB, Thelle DS, Laake P. Diet and risk of cutaneous malignant melanoma: a prospective study of 50,757 Norwegian men and women. International journal of cancer Journal international du cancer 1997;71(4):600-4.
10. Fortes C, Mastroeni S, Boffetta P, Antonelli G, Pilla MA, Botta G, et al. The protective effect of coffee consumption on cutaneous melanoma risk and the role of GSTM1 and GSTT1 polymorphisms. Cancer causes & control : CCC 2013;24(10):1779-87.
11. Song F, Qureshi AA, Han J. Increased caffeine intake is associated with reduced risk of basal cell carcinoma of the skin. Cancer research 2012;72(13):3282-9.
12. Naldi L, Gallus S, Tavani A, Imberti GL, La Vecchia C. Risk of melanoma and vitamin A, coffee and alcohol: a case-control study from Italy. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2004;13(6):503-8.
13. Wu H, Reeves KW, Qian J, Sturgeon SR. Coffee, tea, and melanoma risk among postmenopausal women. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2015;24(4):347-52.
14. Lukic M, Jareid M, Weiderpass E, Braaten T. Coffee consumption and the risk of malignant melanoma in the Norwegian Women and Cancer (NOWAC) Study. BMC cancer 2016;16:562.
15. Wu S, Han J, Song F, Cho E, Gao X, Hunter DJ, et al. Caffeine Intake, Coffee Consumption, and Risk of Cutaneous Malignant Melanoma. Epidemiology 2015;26(6):898-908.
16. Loftfield E, Freedman ND, Graubard BI, Hollenbeck AR, Shebl FM, Mayne ST, et al. Coffee drinking and cutaneous melanoma risk in the NIH-AARP diet and health study. Journal of the National Cancer Institute 2015;107(2).

17. Caini S, Masala G, Saieva C, Kvaskoff M, Savoye I, Sacerdote C, et al. Coffee, tea and melanoma risk: findings from the European Prospective Investigation into Cancer and Nutrition. International journal of cancer Journal international du cancer 2017;140(10):2246-55.
18. Liu J, Shen B, Shi M, Cai J. Higher Caffeinated Coffee Intake Is Associated with Reduced Malignant Melanoma Risk: A Meta-Analysis Study. PloS one 2016;11(1):e0147056.
19. Yew YW, Lai YC, Schwartz RA. Coffee Consumption and Melanoma: A Systematic Review and Meta-Analysis of Observational Studies. American journal of clinical dermatology 2016;17(2):113-23.
20. Lu YP, Lou YR, Li XH, Xie JG, Brash D, Huang MT, et al. Stimulatory effect of oral administration of green tea or caffeine on ultraviolet light-induced increases in epidermal wild-type p53, p21(WAF1/CIP1), and apoptotic sunburn cells in SKH-1 mice. Cancer research 2000;60(17):4785-91.
21. Kawasumi M, Lemos B, Bradner JE, Thibodeau R, Kim YS, Schmidt M, et al. Protection from UV-induced skin carcinogenesis by genetic inhibition of the ataxia telangiectasia and Rad3-related (ATR) kinase. Proceedings of the National Academy of Sciences of the United States of America 2011;108(33):13716-21.
22. Lu YP, Lou YR, Peng QY, Xie JG, Nghiem P, Conney AH. Effect of caffeine on the ATR/Chk1 pathway in the epidermis of UVB-irradiated mice. Cancer research 2008;68(7):2523-9.
23. Lu YP, Lou YR, Peng QY, Nghiem P, Conney AH. Caffeine decreases phospho-Chk1 (Ser317) and increases mitotic cells with cyclin B1 and caspase 3 in tumors from UVB-treated mice. Cancer prevention research (Philadelphia, Pa) 2011;4(7):1118-25.
24. Conney AH, Lu YP, Lou YR, Kawasumi M, Nghiem P. Mechanisms of Caffeine-Induced Inhibition of UVB Carcinogenesis. Frontiers in oncology 2013;3:144.
25. Whiteman DC, Stickley M, Watt P, Hughes MC, Davis MB, Green AC. Anatomic site, sun exposure, and risk of cutaneous melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24(19):3172-7.
26. Feskanich D, Willett WC, Hunter DJ, Colditz GA. Dietary intakes of vitamins A, C, and E and risk of melanoma in two cohorts of women. British journal of cancer 2003;88(9):1381-7.
27. Fortes C, Mastroeni S, Melchi F, Pilla MA, Antonelli G, Camaioni D, et al. A protective effect of the Mediterranean diet for cutaneous melanoma. International journal of epidemiology 2008;37(5):1018-29.
28. Stern RS, Nichols KT, Vakeva LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study. The New England journal of medicine 1997;336(15):1041-5.
29. Aubin F, Donawho CK, Kripke ML. Effect of psoralen plus ultraviolet A radiation on in vivo growth of melanoma cells. Cancer research 1991;51(21):5893-7.
30. Sayre RM, Dowdy JC. The increase in melanoma: are dietary furocoumarins responsible? Medical hypotheses 2008;70(4):855-9.
31. Berwick M. Dietary Advice for Melanoma: Not Ready for Prime Time. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33(23):2487-8.

32. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. Journal of the National Cancer Institute 1977;58(3):525-47.
33. Benedetti A, Parent ME, Siemiatycki J. Lifetime consumption of alcoholic beverages and risk of 13 types of cancer in men: results from a case-control study in Montreal. Cancer detection and prevention 2009;32(5-6):352-62.
34. Millen AE, Tucker MA, Hartge P, Halpern A, Elder DE, Guerry Dt, et al. Diet and melanoma in a case-control study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2004;13(6):1042-51.
35. Miura K, Zens MS, Peart T, Holly EA, Berwick M, Gallagher RP, et al. Alcohol consumption and risk of melanoma among women: pooled analysis of eight case-control studies. Archives of dermatological research 2015;307(9):819-28.
36. Kubo JT, Henderson MT, Desai M, Wactawski-Wende J, Stefanick ML, Tang JY. Alcohol consumption and risk of melanoma and non-melanoma skin cancer in the Women's Health Initiative. Cancer causes & control : CCC 2014;25(1):1-10.
37. Rivera A, Nan H, Li T, Qureshi A, Cho E. Alcohol Intake and Risk of Incident Melanoma: A Pooled Analysis of Three Prospective Studies in the United States. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2016;25(12):1550-58.
38. Rota M, Pasquali E, Bellocco R, Bagnardi V, Scotti L, Islami F, et al. Alcohol drinking and cutaneous melanoma risk: a systematic review and dose-risk meta-analysis. The British journal of dermatology 2014;170(5):1021-8.
39. Saladi RN, Nektalova T, Fox JL. Induction of skin carcinogenicity by alcohol and ultraviolet light. Clinical and experimental dermatology 2010;35(1):7-11.
40. Lachenmeier DW, Kanteres F, Rehm J. Carcinogenicity of acetaldehyde in alcoholic beverages: risk assessment outside ethanol metabolism. Addiction (Abingdon, England) 2009;104(4):533-50.
41. Lang R, Yagar EF, Eggers R, Hofmann T. Quantitative investigation of trigonelline, nicotinic acid, and nicotinamide in foods, urine, and plasma by means of LC-MS/MS and stable isotope dilution analysis. Journal of agricultural and food chemistry 2008;56(23):11114-21.
42. Benavente CA, Jacobson MK, Jacobson EL. NAD in skin: therapeutic approaches for niacin. Current pharmaceutical design 2009;15(1):29-38.
43. Surjana D, Halliday GM, Damian DL. Nicotinamide enhances repair of ultraviolet radiation-induced DNA damage in human keratinocytes and ex vivo skin. Carcinogenesis 2013;34(5):1144-9.
44. Surjana D, Halliday GM, Damian DL. Role of nicotinamide in DNA damage, mutagenesis, and DNA repair. Journal of nucleic acids 2010; pii: 157591.
45. Park SM, Li T, Wu S, Li WQ, Weinstock M, Qureshi AA, et al. Niacin intake and risk of skin cancer in US women and men. International journal of cancer Journal international du cancer 2017;140(9):2023-31.
46. Xia S, Lu Y, Wang J, He C, Hong S, Serhan CN, et al. Melanoma growth is reduced in fat-1 transgenic mice: impact of omega-6/omega-3 essential fatty acids. Proceedings of

the National Academy of Sciences of the United States of America 2006;103(33):12499-504.
47. Ruxton CH, Calder PC, Reed SC, Simpson MJ. The impact of long-chain n-3 polyunsaturated fatty acids on human health. Nutrition research reviews 2005;18(1):113-29.
48. Serini S, Fasano E, Celleno L, Cittadini A, Calviello G. Potential of long-chain n-3 polyunsaturated fatty acids in melanoma prevention. Nutrition reviews 2014;72(4):255-66.
49. Pilkington SM, Watson RE, Nicolaou A, Rhodes LE. Omega-3 polyunsaturated fatty acids: photoprotective macronutrients. Experimental dermatology 2011;20(7):537-43.
50. Black HS, Rhodes LE. Potential Benefits of Omega-3 Fatty Acids in Non-Melanoma Skin Cancer. Journal of clinical medicine 2016;5(2): pii: E23.
51. Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. IV. No association with nutritional factors, alcohol, smoking or hair dyes. International journal of cancer Journal international du cancer 1988;42(6):825-8.
52. Kirkpatrick CS, White E, Lee JA. Case-control study of malignant melanoma in Washington State. II. Diet, alcohol, and obesity. American journal of epidemiology 1994;139(9):869-80.
53. Miller AB, Gaudette LA. Cancers of skin, bone, connective tissues, brain, eye, thyroid and other specified and unspecified sites in Inuit. Acta oncologica (Stockholm, Sweden) 1996;35(5):607-16.
54. Bain C, Green A, Siskind V, Alexander J, Harvey P. Diet and melanoma. An exploratory case-control study. Annals of epidemiology 1993;3(3):235-8.
55. Donat-Vargas C, Berglund M, Glynn A, Wolk A, Akesson A. Dietary polychlorinated biphenyls, long-chain n-3 polyunsaturated fatty acids and incidence of malignant melanoma. European journal of cancer (Oxford, England : 1990) 2017;72:137-43.
56. Park MK, Li WQ, Qureshi AA, Cho E. Fat intake and risk of skin cancer in US adults. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2018. doi: 10.1158/1055-9965.EPI-17-0782.
57. Liyanage UE, Law MH, Ong JS, Cust AE, Mann GJ, Ward SV, et al. Polyunsaturated fatty acids and risk of melanoma: A Mendelian randomisation analysis. International journal of cancer Journal international du cancer 2018. doi: 10.1002/ijc.31334.
58. Selhub J. Folate, vitamin B12 and vitamin B6 and one carbon metabolism. The journal of nutrition, health & aging 2002;6(1):39-42.
59. Li K, Wahlqvist ML, Li D. Nutrition, One-Carbon Metabolism and Neural Tube Defects: A Review. Nutrients 2016;8(11).
60. Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. Jama 2001;285(23):2981-6.
61. De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, et al. Reduction in neural-tube defects after folic acid fortification in Canada. The New England journal of medicine 2007;357(2):135-42.

62. Garrett GS, Bailey LB. A public health approach for preventing neural tube defects: folic acid fortification and beyond. Annals of the New York Academy of Sciences 2018. 1414(1): 47-58.
63. Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet 2013;381(9871):1029-36.
64. Qin X, Cui Y, Shen L, Sun N, Zhang Y, Li J, et al. Folic acid supplementation and cancer risk: a meta-analysis of randomized controlled trials. International journal of cancer Journal international du cancer 2013;133(5):1033-41.
65. Ebbing M, Bonaa KH, Nygard O, Arnesen E, Ueland PM, Nordrehaug JE, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. Jama 2009;302(19):2119-26.
66. Gibson TM, Weinstein SJ, Pfeiffer RM, Hollenbeck AR, Subar AF, Schatzkin A, et al. Pre- and postfortification intake of folate and risk of colorectal cancer in a large prospective cohort study in the United States. The American journal of clinical nutrition 2011;94(4):1053-62.
67. Donnenfeld M, Deschasaux M, Latino-Martel P, Diallo A, Galan P, Hercberg S, et al. Prospective association between dietary folate intake and skin cancer risk: results from the Supplementation en Vitamines et Mineraux Antioxydants cohort. The American journal of clinical nutrition 2015;102(2):471-8.
68. Smith AD, Kim YI, Refsum H. Is folic acid good for everyone? The American journal of clinical nutrition 2008;87(3):517-33.
69. Butzbach K, Epe B. Photogenotoxicity of folic acid. Free radical biology & medicine 2013;65:821-7.
70. Stechschulte SA, Kirsner RS, Federman DG. Vitamin D: bone and beyond, rationale and recommendations for supplementation. The American journal of medicine 2009;122(9):793-802.
71. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. European journal of cancer (Oxford, England : 1990) 2005;41(1):45-60.
72. Field S, Davies J, Bishop DT, Newton-Bishop JA. Vitamin D and melanoma. Dermato-endocrinology 2013;5(1):121-9.
73. Vinceti M, Malagoli C, Fiorentini C, Longo C, Crespi CM, Albertini G, et al. Inverse association between dietary vitamin D and risk of cutaneous melanoma in a northern Italy population. Nutrition and cancer 2011;63(4):506-13.
74. Asgari MM, Maruti SS, Kushi LH, White E. A cohort study of vitamin D intake and melanoma risk. The Journal of investigative dermatology 2009;129(7):1675-80.
75. Park SM, Li T, Wu S, Li WQ, Qureshi AA, Cho E. Vitamin D Intake and Risk of Skin Cancer in US Women and Men. PloS one 2016;11(8):e0160308.
76. Tang JY, Fu T, Leblanc E, Manson JE, Feldman D, Linos E, et al. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011;29(22):3078-84.
77. Newton-Bishop JA, Chang YM, Elliott F, Chan M, Leake S, Karpavicius B, et al. Relationship between sun exposure and melanoma risk for tumours in different body sites

in a large case-control study in a temperate climate. European journal of cancer (Oxford, England : 1990) 2011;47(5):732-41.
78. Cattaruzza MS, Pisani D, Fidanza L, Gandini S, Marmo G, Narcisi A, et al. 25-Hydroxyvitamin D serum levels and melanoma risk: a case-control study and evidence synthesis of clinical epidemiological studies. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2018. doi: 10.1097/CEJ.0000000000000437.
79. Caini S, Boniol M, Tosti G, Magi S, Medri M, Stanganelli I, et al. Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: a comprehensive review and meta-analysis. European journal of cancer (Oxford, England : 1990) 2014;50(15):2649-58.
80. van der Pols JC, Russell A, Bauer U, Neale RE, Kimlin MG, Green AC. Vitamin D status and skin cancer risk independent of time outdoors: 11-year prospective study in an Australian community. The Journal of investigative dermatology 2013;133(3):637-41.
81. Afzal S, Nordestgaard BG, Bojesen SE. Plasma 25-hydroxyvitamin D and risk of non-melanoma and melanoma skin cancer: a prospective cohort study. The Journal of investigative dermatology 2013;133(3):629-36.
82. Gambichler T, Bindsteiner M, Hoxtermann S, Kreuter A. Serum 25-hydroxyvitamin D serum levels in a large German cohort of patients with melanoma. The British journal of dermatology 2013;168(3):625-8.
83. Newton-Bishop JA, Beswick S, Randerson-Moor J, Chang YM, Affleck P, Elliott F, et al. Serum 25-hydroxyvitamin D3 levels are associated with breslow thickness at presentation and survival from melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27(32):5439-44.
84. Saiag P, Aegerter P, Vitoux D, Lebbe C, Wolkenstein P, Dupin N, et al. Prognostic Value of 25-hydroxyvitamin D3 Levels at Diagnosis and During Follow-up in Melanoma Patients. Journal of the National Cancer Institute 2015;107(12):djv264.
85. Lim A, Shayan R, Varigos G. High serum vitamin D level correlates with better prognostic indicators in primary melanoma: A pilot study. The Australasian journal of dermatology 2017; doi: 10.1111/ajd.12648.
86. Zheng J, Guinter MA, Merchant AT, Wirth MD, Zhang J, Stolzenberg-Solomon RZ, et al. Dietary patterns and risk of pancreatic cancer: a systematic review. Nutrition reviews 2017;75(11):883-908.
87. Grosso G, Bella F, Godos J, Sciacca S, Del Rio D, Ray S, et al. Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. Nutrition reviews 2017;75(6):405-19.
88. Malagoli C, Malavolti M, Agnoli C, Crespi CM, Fiorentini C, Farnetani F, et al. Diet Quality and Risk of Melanoma in an Italian Population. The Journal of nutrition 2015;145(8):1800-7.