25-Hydroxyvitamin D serum levels and melanoma risk: a case–control study and evidence synthesis of clinical epidemiological studies

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Introduction

Vitamin D, mostly derived from sunlight on the skin, is fat-soluble and essential for several physiological functions (Holick, 2007). Epidemiological and experimental studies have highlighted its role in cancer and mortality (Guerrieri-Gonzaga and Gandini, 2013; Pilz et al., 2013). Its biological active metabolites suppress tumor cell proliferation in different cell systems and induce differentiation of cancer cells in different tumor models in vitro and in vivo, suggesting that high levels of vitamin D metabolites may be protective against cancer. It has also been shown that populations with substantial deficiency of vitamin D are at a higher risk of neoplastic diseases (Teleni et al., 2013). The protective role played by 1,25-dihydroxyvitamin D [1,25(OH)2D] in different epithelial tumors (breast, colon, prostate) has been reported widely (Vuolo et al., 2012) and there is accumulating evidence that it may also be involved in melanoma (Eismann et al., 1987; Yudoh et al., 1999; Osborne and Hutchinson, 2002; Albert et al., 2004; Pandolfi et al., 2017; Spath et al., 2017).

1,25(OH)2D-mediated antitumor activity is mostly dependent on the abilities to regulate cell proliferation and differentiation, to induce apoptosis in different cellular systems, and to inhibit angiogenesis in human tumors (Chiang and Chen, 2013).

Recently, thanks to advances in molecular biology studies (Hutchinson et al., 2000; Li et al., 2007; Nemazannikova et al., 2014), more scientific evidence has been collected on the risk of developing melanoma (Egan, 2009) in the presence of vitamin D alterations, but the existing scientific literature provides conflicting results (Gandini et al., 2009; Cai ni et al., 2014) and additional research is needed.

Evaluation of 25-hydroxyvitamin D [25(OH)D] serum level is recommended as the best indicator of overall vitamin D status because it reflects total vitamin D from
dietary intake and sunlight exposure, as well as the conversion of vitamin D from adipose stores in the liver (Rosen, 2011).

Two categories are usually used in clinical practice to classify low levels of vitamin D: ‘vitamin D deficiency’ as a severe form and ‘vitamin D insufficiency’ as a mild form, without a clear consensus on the threshold levels that have not been subjected to a systematic, evidence-based development process.

Thus, in 2011, the Endocrine Society published a clinical practice guideline (Holick et al., 2011) not recommending but only suggesting that vitamin D deficiency, insufficiency, and sufficiency be defined as 25(OH)D less than or equal to 20 ng/ml, between 21 and 29 ng/ml, and between 30 and 100 ng/ml, respectively. These reference ranges were used in this study.

On the basis of these recent findings, we investigated the association between vitamin D status and the risk of cutaneous melanoma in patients and healthy controls.

**Patients and methods**

This case–control study, carried out at the Dermatology Clinic of ‘Sant’Andrea Hospital’ Rome, Italy, enrolled 137 incident cases of melanoma, diagnosed from 2007 to 2012 and histologically confirmed, and 99 healthy controls recruited, on a voluntary basis, from among the medical and paramedical staff of the hospital. Eligible criteria were age between 18 and 85 years and no history of cancer or acute/chronic diseases at the time of enrollment.

As the level of 25(OH)D may depend on BMI, other treatments, and supplementations, exclusion criteria for cases and controls were as follows: advanced age (>85 years); obesity (BMI > 30); and taking any of the following treatments: corticosteroids, calcium antagonists, bisphosphonates, calcium, or vitamin D supplementations because of their influence on vitamin D metabolism.

All patients affected by melanoma and healthy controls included in the study were resident in the Lazio region (Central Italy).

The study was reviewed and approved by the institutional review board of the Hospital and all study participants provided written informed consent.

**Laboratory examinations**

Serum samples were collected at the time of diagnosis in the patients and between October and April in the healthy controls to assess levels of calcium, 25(OH)D and parathyroid hormone (PTH). PTH was assayed using an electrochemiluminescence immunoassay kit (DPC Immulite 2000 intact PTH assay; Diagnostic Products Corporation (DPC), Los Angeles, California, USA) and 25(OH)D concentrations were determined using an automated chemiluminescence assay kit (Liaison 25-hydroxy vitamin D Total; Diasorin, Stillwater, Minnesota, USA); the intra-assay and interassay coefficients of variation were 8.1 and 10.2%, respectively. The Liaison 25(OH)D assay is cospecific for 25(OH)D₂ and 25(OH)D₃; thus, it reports a total 25(OH)D concentration. Participants were classified according to their 25(OH)D concentrations into three groups (‘deficient’ ≤ 20 ng/ml, ‘insufficient’ 21–29 ng/ml, and ‘sufficient’ ≥ 30 ng/ml) using cutoff values suggested by the Endocrine Society Clinical Practice Guideline published in 2011 (Holick et al., 2011).

**Statistical analysis**

We adhered to the recommendations issued by the Strengthening the Reporting of Observational Studies Initiative (von Elm et al., 2007).

Using an online sample size calculator to compute the sample size required to achieve a desired statistical power of 0.8 with an α level of 0.05, the recommended sample size per group was 97.

The distributions of the laboratory parameters among the cases and controls were examined, and their medians and interquartile ranges were compared using the Mann–Whitney test.

Percentages and the χ²-test were used to compare categorical variables.

Multivariate unconditional logistic regression models were used to assess the association between 25(OH)D serum levels and melanoma after adjusting for some possible confounders. Vitamin D deficiency was chosen as the reference group for vitamin D status. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were computed.

**Results**

There were 137 melanoma patients, aged between 21 and 85 years, and 99 control participants, aged between 25 and 69 years. There were 61 (44.5%) and 32 (32.3%) men in the patient and control groups, respectively (P = 0.58). Table 1 shows the demographic and biochemical results for both patients and controls, and Table 2 summarizes the histological features of the surgically resected primary melanomas. There was a statistically significant difference in the median levels of serum vitamin D between melanoma patients and healthy controls (18.0 vs. 27.8 ng/ml, P < 0.001). Histological type of melanoma had the following median levels of serum vitamin D (ng/ml): superficial spreading melanoma 18.4, nodular melanoma 17.4, and acral lentiginous melanoma 17.9 (differences were not statistically significant). No significant difference was found in age, PTH, and calcium serum levels, whereas we observed a small but statistically significant difference in BMI medians between melanoma patients and healthy controls (24.0 vs. 22.0, P < 0.001).

Figure 1 shows the distribution of serum 25(OH)D levels in melanoma patients and healthy controls. As shown in Table 3, 66.2% of melanoma patients showed vitamin D
deficiency and only 7.4% had vitamin D sufficiency compared with healthy controls, among whom, only 15.2% were vitamin D deficient whereas 37.4% were the sufficient \((P < 0.001)\). Vitamin D insufficiency was observed in 26.5% of melanoma patients and 47.5% of healthy controls.

ORs computed by logistic regression from a multivariate model including age, sex, and BMI are reported in Table 4. Age and sex were not associated significantly with melanoma. A statistically significant inverse association between melanoma and vitamin D sufficiency \((\geq 30 \text{ ng/ml})\) versus deficiency \((\leq 20 \text{ ng/ml})\) was observed \((\text{OR} = 0.04, \text{95\% CI: 0.02}–0.10, P < 0.001)\). Also, vitamin D insufficiency \((21–29 \text{ ng/ml})\) versus deficiency \((\leq 20 \text{ ng/ml})\) was found to be significantly inversely associated with melanoma \((\text{OR} = 0.13, \text{95\% CI: 0.06}–0.27, P < 0.001)\). These ORs imply that within the defined categories of levels of vitamin D, the following trend can be observed: the more vitamin D approaches normal values, the lower is the OR and thus the greater seems to be the protection.

BMI was also associated independently with melanoma \((\text{OR} = 2.34, \text{95\% CI: 1.09}–5.02, P = 0.030 \text{ for individuals with BMI between 25.0 and 30.0})\).

**Discussion**

Our study shows that the median value of 25(OH)D is significantly lower in melanoma patients than in controls and that the distribution of 25(OH)D in melanoma patients is shifted toward lower values compared with the controls.

Also, over 90% of melanoma patients have deficient or insufficient 25(OH)D serum levels at the time of diagnosis, whereas only 7.4% had sufficient values \((\geq 30 \text{ ng/ml})\). Both sufficiency and insufficiency are associated significantly with a lower risk of melanoma compared with vitamin D deficiency.

These results are in agreement with Gambichler et al. (2013), who found that only 7.2% of patients in a large German cohort of 764 melanoma patients had sufficient vitamin D values \((\geq 30 \text{ ng/ml})\).

In our logistic model, vitamin D sufficiency is associated inversely with melanoma, but also insufficient levels imply significantly lower risk compared with vitamin D deficiency (reference group).

Previous studies have found both conflicting and similar results to ours (Table 5).
Some studies found an increased risk of melanoma associated with the highest 25(OH)D serum levels.

The study by van der Pols et al. (2013) was prospective and involved 1191 Australian adults who participated from 1992 to 1996 in the Nambour Skin Cancer Prevention Trial of daily sunscreen use and β-carotene supplementation; they were followed for 11 years to assess the association between baseline serum 25(OH)D levels and the risk of skin cancer. In the subgroup of 17 patients with melanoma, dichotomizing 25(OH)D serum concentration as less than 30 ng/ml and at least 30 ng/ml, the authors reported a nonsignificant increased risk of melanoma (OR = 2.71, 95% CI: 0.98–7.48) for the only eight patients with baseline 25(OH)D levels above or equal to 30 ng/ml (75 nmol/l) after adjustment for several factors (Table 5).

In a nested case–control study of 50-69-year-old Finnish male smokers (within the α-Tocopherol β-Carotene Cancer Prevention Study), Major et al. (2012) found no overall association between serum 25(OH)D and melanoma. Modeling serum 25(OH)D as a categorical variable (<25, 25, 37.50, and 50+ nmol/l), a lower risk of melanoma was suggested for serum vitamin D levels between 15 and 19.9 ng/ml (37.50–49.99 nmol/l) (OR = 0.60, 95% CI: 0.25–1.44), and an increased risk for serum vitamin D levels of at least 20 ng/ml (≥50 nmol/l) (OR = 1.32, 95% CI: 0.64–2.72), compared with men whose prediagnostic levels were less than 10 ng/ml (< 25 nmol/l). These results were not statistically significant. It is noteworthy that these findings cannot be extended to the whole population because the study only included male smokers from Finland.

In the prospective study by Afzal et al. (2013), 10 060 White individuals from the Danish general population were followed up for 28 years; 78 individuals developed melanoma. Multivariable adjusted hazard ratios for melanoma were 4.72 (95% CI: 0.96–23.3) for serum 25(OH)D of at least 20 ng/ml (50 nmol/l) versus less than 10 ng/ml (25 nmol/l) and 6.3 (95% CI: 1.38–28.8) for the top (67th–100th) versus the bottom (0th–34th) percentile. Despite the large cohort, the study found only 78 melanoma patients and thus the 95% CI are wide and the results are inconsistent.

In contrast, other studies have found an inverse association with high 25(OH)D levels, as we have.

In a sun exposure and melanoma risk, case–control study in Northern England (Newton-Bishop et al., 2011), the authors also investigated the correlation between reported sun exposure and serum vitamin D levels in a subsample of the cases (n = 805) and population controls (n = 187). They found that serum vitamin D level was not independently protective (OR = 0.89, 95% CI: 0.76–1.04 ng/ml, 20 nmol/l increase), but comparing cases and matched siblings (n = 128) using conditional logistic regression adjusting for age, sex, season, and hair color, significant protective effects for serum vitamin D levels were observed (OR = 0.64, 95% CI: 0.46–0.87 ng/ml increase, 20 nmol/l).

From the study of Nürnberg et al. (2009), calculating risk estimates from their published raw data, we found a significant inverse association with melanoma risk on comparing more than 20 ng/ml versus less than or equal to 20 ng/ml categories (OR = 0.48; 95% CI: 0.29–0.80).

In a case–control study investigating vitamin D receptor polymorphisms and melanoma susceptibility, Randerson-Moot et al. (2009) compared serum vitamin D levels for the 941 cases and 114 controls from North England and found a nonsignificant adjusted OR of 0.94 (95% CI: 0.79–1.12) for an increment of 8 ng/ml (20 nmol/l) of 25(OH)D serum level.

Four studies (Nürnberg et al., 2009, Major et al., 2012, Afzal et al., 2013, van der Pols et al., 2013, for a total of 392 cases overall) were included in the meta-analysis by Caini et al. (2014), yielding a nonsignificant summary relative risk of 1.46 (95% CI: 0.60–3.53) for the highest versus the lowest categories (I² = 54%). However, Caini et al. (2014) calculated the OR for the study by
<table>
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<tr>
<th>References</th>
<th>Country</th>
<th>Characteristics of studied population</th>
<th>Study design</th>
<th>Time elapsing from blood draw to diagnosis</th>
<th>Number of melanoma cases</th>
<th>Number of controls</th>
<th>Vitamin D serum levels</th>
<th>Risk (95% confidence interval)</th>
<th>Adjustments</th>
<th>Statistical significance</th>
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<td><strong>Studies which found an increased risk of melanoma associated with highest 25(OH)D serum levels</strong></td>
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<td>Van der Pols et al. (2013)</td>
<td>Australia</td>
<td>1191 adults (range: 29–79 years) from NAMBOUR skin cancer prevention trial of daily sunscreen use and β-carotene supplementation from 1992 to 1996</td>
<td>Prospective cohort study</td>
<td>All blood samples in 1996 (in August = end of winter in Australia). Follow-up for detecting incident cases from 1996 to 2007.</td>
<td>17</td>
<td>–</td>
<td>≥ 30 vs. &lt;30 ng/ml</td>
<td>OR = 2.71 (0.98–7.48)</td>
<td>OR from logistic regression adjusted for: age, sex, β-carotene, and sunscreen allocations during the trial, personal history of skin cancer before 1996, family history of skin cancer, skin color, usual time spent outdoors</td>
<td>NS</td>
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<td>Major et al. (2012)</td>
<td>Finland</td>
<td>368 Finnish male smokers (range: 50–69 years) from the α-Tocopherol β-Carotene Cancer Prevention study from 1986 to 2005</td>
<td>Nested case–control study</td>
<td>Median time from baseline blood draw to diagnosis was 8.9 years. Median follow-up time for controls was 18.2 years. Serum collected at study entry and stored at −70°C. Incident cases from 1986 to 2005.</td>
<td>92</td>
<td>276</td>
<td>10–14.9 vs. &lt;10 ng/ml</td>
<td>OR = 1.04 (0.52–2.12)</td>
<td>OR from conditional logistic regression model adjusted for age at randomization, date of blood draw, height, weight, dietary cholesterol, and skin behavior (e.g. skin burns easily in prolonged direct sunlight (no/yes/missing). Serum 25(OH)D was modeled as distinct clinically-defined categories (&lt;25, 25–37.49, 37.50–49.99, and 50 + nmol/l).</td>
<td>NS</td>
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<td>Afzal et al. (2013)</td>
<td>Denmark</td>
<td>10 060 White individuals from the Danish general population (range: 20–100 years) – Copenhagen City Heart study from 1981 to 1983</td>
<td>Prospective cohort study</td>
<td>Plasma samples collected at baseline in 1981–1983 and stored at −20°C until 2009–2010. Patients developed melanoma during up to 28 years of follow-up.</td>
<td>78</td>
<td>–</td>
<td>15–19.9 vs. &lt;10 ng/ml</td>
<td>OR = 0.60 (0.25–1.44)</td>
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<td>≥ 20 vs. &lt;10 ng/ml</td>
<td>HR = 4.72 (0.96–23.3)</td>
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<td><strong>Studies which found a decreased risk of melanoma associated with highest 25(OH)D serum levels</strong></td>
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<td>Newton-Bishop et al. (2011)</td>
<td>UK</td>
<td>1647 individuals from North England (range: 18–76 years). Incident melanoma cases and two different types of controls:</td>
<td>Case–control study</td>
<td>–</td>
<td>805</td>
<td>187 (population)</td>
<td>Increase by 8 ng/ml</td>
<td>OR = 0.89 (0.76–1.04)</td>
<td>OR from unconditional logistic regression adjusted for age, sex, weekend sun exposure</td>
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<td>Nürnberg et al. (2009)</td>
<td>Germany</td>
<td>346 individuals (range: 14–65 + years). Patients from Departments of Dermatology, University of Homburg and Mannheim, from 1997 to 2007 and healthy controls.</td>
<td>Case–control study</td>
<td>–</td>
<td>205</td>
<td>141</td>
<td>&gt; 20 vs. &lt;10 ng/ml</td>
<td>OR = 0.82 (0.44–1.55)</td>
<td>OR from conditional logistic regression adjusted for age, sex, season of year sampled and hair color</td>
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<td>86</td>
<td>91</td>
<td>&gt; 20 vs. ≤20 ng/ml</td>
<td>OR = 0.48 (0.29–0.80)</td>
<td>This OR was calculated by the authors of this study from Nürnberg et al. (2009) published raw data to make comparison with our results</td>
<td>Significant</td>
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<td>Randerson-Moor et al. (2009)</td>
<td>UK</td>
<td>1451 Individuals from North England (range: 18–75 years). Incident melanoma cases from 2000 to 2006 and controls matched by age and sex.</td>
<td>Case–control study</td>
<td>–</td>
<td>941</td>
<td>114</td>
<td>Increase by 8 ng/ml</td>
<td>OR = 0.94 (0.79–1.12)</td>
<td>OR from logistic regression adjusted for age, sex, BMI</td>
<td>NS</td>
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<td>This study</td>
<td>Italy</td>
<td>236 individuals (range: 21–85 years). Incident melanoma cases from Dermatology Unit, Sant'Andrea Hospital, from 2007 to 2012 and healthy controls.</td>
<td>Case–control study</td>
<td>–</td>
<td>137</td>
<td>99</td>
<td>≥30 vs. ≤20 ng/ml</td>
<td>OR = 0.04 (0.02–0.10)</td>
<td>ORs from logistic regression adjusted for age, sex, BMI</td>
<td>Significant</td>
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<td>21–29 vs. ≤20 ng/ml</td>
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<td>OR = 0.13 (0.08–0.27)</td>
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<td>Significant</td>
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CI, confidence interval; HR, hazard ratio; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.
Nünnberg et al. (2009) from raw data, comparing serum levels less than 10 ng/ml with more than 20 ng/ml, obtaining a conservative estimate, whereas considering at least 20 ng/ml versus less than 20 ng/ml in 205 cases and 141 controls, we found an OR of 0.48 (95% CI: 0.29–0.80), implying a 50% significant reduction in risk.

No definite conclusion can be drawn from these studies, but some aspects need consideration.

First, there is no universal agreement on the choice of the cutoffs for defining vitamin D deficiency and insufficiency, and the lack of a shared definition confuses the comparisons among the studies (International Agency for research on Cancer, 2008; Ross et al., 2011).

Second, the studies reviewed did not primarily aim to assess the association between vitamin D status and melanoma.

Third, as the incidence of melanoma is low, even large prospective studies identify only a few patients (Afzal et al., 2013; van der Pols et al., 2013) and thus conclusions may not reach statistical significance.

Fourth, case–control studies cannot verify that the relationship between 25(OH)D and melanoma patients is causal. There is an intense debate on this topic. Indeed, because of the discrepancies observed between observational and intervention studies, vitamin D was hypothesized to be a marker, not a cause, of ‘ill health’ because of the ‘reverse causation’ bias (Robshahm et al., 2013; Autier et al., 2014; Guessous, 2015).

A limitation of our study is that we have not adjusted for sun exposure, skin phototype, and season, even though the entire spectrum of ultraviolet is recognized as a risk factor for melanoma (El Ghissassi et al., 2009). However, sun exposure and season are correlated with vitamin D levels. To adjust for sun exposure is, at least partially, adjusting for vitamin D. Furthermore, if melanoma patients are sun seekers, they should have high levels of vitamin D, which is not observed. Individuals from the same small geographical area (in this study, Latium region, Central Italy) should be highly homogeneous with respect to skin phototype, avoiding this bias. Furthermore, comparisons with other studies should take account of the heterogeneous prevalence of different phototypes in Europe. Current evidence is still contradictory about whether skin pigmentation influences vitamin D photosynthesis (Xiang et al., 2015).

We collected all our control serum samples between October and April and all patient serum samples at the time of diagnosis. Therefore, even in the worst possible scenario in which vitamin D levels could be overestimated in all patients, because of summer season collection, we still found lower vitamin D levels in cases than in controls; thus, lack of adjustment for season should not confound the results.

The interpretation of the results of case–control studies requires caution because of the possible occurrence of ‘reverse causation’ bias, but also that of cohort studies is difficult because the exposure (the level of vitamin D) is measured long before the onset of the disease. Indeed, the cohort studies produced little evidence of an association with vitamin D unless evaluated during follow-up. The well-designed cohort study by Saiag et al. (2015) showed that 25(OH)D variation during follow-up is an independent melanoma prognostic marker.

The association between serum vitamin D levels and melanoma was only noted for BMI as serum vitamin D levels vary with the proportion of body fat and vitamin D has complex metabolic interactions with fat cells (Li et al., 2008; Sun and Zemel, 2008). The significant difference between the means of BMI patients and controls is small. In the multivariate logistic regression, the inverse association between vitamin D and the risk of melanoma remained after adjustment for BMI. Furthermore, BMI of at least 25 was found to be independently and significantly associated with melanoma risk. Excess body weight has been investigated as a potential risk factor for melanoma in a meta-analysis. A significant pooled effect estimate (1.31, 95% CI: 1.18–1.45) was reported for overweight men (Sargentanis et al., 2013). To explain the role of BMI in melanoma pathogenesis, some investigators (de Giorgi et al., 2013) have hypothesized that chronic hyperinsulinemia, hyperestrogen levels, high plasma leptin levels, and low level of vitamin D may be risk factors for tumor growth. Inflammation, fibrosis, and neangiogenesis, typical of adipose tissue, constitute microenvironments that could promote the development and progression of cancer.

Recent studies (Newton-Bishop et al., 2015; Fang et al., 2016) have shown that lower vitamin D levels are associated independently with poorer outcomes even after controlling for systemic inflammation.

To conclude, even if no clear conclusions can be drawn, several epidemiological studies support a protective effect of ‘normal’ vitamin D levels not only on melanoma risk but also on prognosis, stage, and survival. Several authors have reported an association between low levels of vitamin D and higher Breslow thickness. Wyatt et al. (2015) found that serum 25(OH)D less than 20 ng/ml (50 nmol/l) was associated with a statistically significant quadrupling risk of the thicker tumor; Newton-Bishop et al. (2009), in a prospective study of survival, reported that higher 25(OH)D3 levels were associated with lower Breslow thickness at diagnosis (P=0.002) and were independently protective against relapse and death. Randerson-Moor et al. (2009) showed that thinner tumors were associated with higher serum levels of vitamin D at recruitment, after adjusting for age, sex, season of serum collection, deprivation score, and BMI. Nünnberg et al. (2009) confirmed that there was a trend toward greater
tumor thickness in patients with lower vitamin D levels, that these patients had earlier metastatic diseases, and that vitamin D levels are reduced in stage IV melanoma patients.

Several cell-based studies investigated the molecular events that may account for the role of vitamin D in melanoma growth and progression (Ahonen et al., 2000; Spath et al., 2017). These showed as plausible vitamin D-induced mechanisms growth arrest, apoptosis of tumor cells or their non-neoplastic progenitors, chemoprotective and immunomodulation. Finally, the Women’s Health Initiative Randomized Controlled Trial (Tang et al., 2011) showed that in women with a history of no-melanoma skin cancer (NMSC), vitamin D supplementation reduced melanoma risk, suggesting a role for vitamin D supplements in this high-risk group. Although these data are from post-hoc subgroup analyses, the results suggest that increasing vitamin D serum levels may prevent the development of melanoma in women at high risk. A role for vitamin D supplementation in preventing melanoma in women with a history of NMSC warrants further investigation. Patients with a history of NMSC should avoid sun exposure and have very low 25(OH)D levels; therefore, this subgroup of patients could benefit from vitamin D supplementation.

Some evidence supports the hypothesis that low vitamin D increases melanoma risk and other tumors (Garland et al., 1989; Ahonen et al., 2000; Engel et al., 2010). Our study highlights ‘normal’ vitamin D status as a favorable condition to reduce the risk of melanoma (Zittermann et al., 2012). However, more rigorous and randomized clinical trials are necessary to shed more light on the association between 25(OH)D and melanoma risk and prognosis (Raimondi et al., 2016).

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References


