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Vitamin D and skin cancer: A meta-analysis

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ABSTRACT

A comprehensive bibliographic search of the literature was conducted to identify studies on Cutaneous Malignant Melanoma (CMM) and non-melanoma skin cancer (NMSC), Vitamin D receptor (VDR) polymorphisms, Vitamin D intake and 25(OH)D serum levels. Fully adjusted risk estimates were found and extracted for the two polymorphisms *FokI* and *BsmI* and Vitamin D intake. Ten studies were included in the meta-analysis, with a total of 6805 skin cancer cases.

We found an association with CMM for both polymorphisms. The summary relative risks (SRR) for the studies on CMM were: 1.21 (1.03–1.42) and 1.21 (0.95–1.54) for the *Ff* and *ff* versus wild-type of *FokI*, respectively. The SRR for *ff* versus wild-type became significant with the inclusion of NMSC. The SRR for the studies on CMM were: 0.78 (0.65–0.92) and 0.75 (0.59–0.95) for the *Bb* and *BB* versus wild-type of *BsmI*, respectively. There is also a slight indication of a role of dietary Vitamin D in CMM development.

In conclusion, this meta-analysis suggests a possible significant role of VDR *FokI* and *BsmI* polymorphism in CMM and NMSC risk. The association with Vitamin D intake is less clear and further studies could be useful to clarify the role of diet.

1. Introduction

There are three main types of skin cancers: the most common is basal cell carcinoma (BCC), followed by squamous cell carcinoma (SCC) and cutaneous malignant melanoma (CMM). In 2005, over 76,000 non-melanoma skin cancers (NMSC) were registered in the UK, but registration is known to be incomplete. One study estimated that at least 100,000 cases of NMSC are diagnosed each year.[1] Melanoma is the most lethal form of skin cancer and an increasingly common disease worldwide.[2] The incidence of melanoma has increased generally in western European countries during the last few years, and early detection owing to screening does not appear to be the only explanation for this fact.[3] The key environmental risk factor is exposure to the ultraviolet (UV) component in sunlight, with incidences of sunburn and intermittent sun exposure being particularly important, especially for white-skinned people.[4,5] The marked differences in melanoma incidence over time and between different populations suggest a key etiologic role of environmental factors, and diet is among these potential modifiable risk factors for CMM and NMSC.[6–8]

Vitamin D is a fat-soluble vitamin essential to bone development and the immune system and it also processes antiproliferative effects. Foods such as fortified milk or fat spreads may be the major dietary source of Vitamin D_2 and D_3, while in countries where fortification is not mandatory (e.g. Japan, Norway, and Italy) natural sources include sardines and other oily fish, meat and eggs.[9,10] Most Vitamin D

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is derived from the action of sunlight on the skin, converting 7-dehydrocholesterol to pre-Vitamin D_3. Vitamin D_3 from the skin and Vitamin D_2 and D_3 from the diet are metabolised in the liver to 25-hydroxyvitamin D (25(OH)D) (the best measure of Vitamin D status) and this is subsequently hydroxylated in the kidney to form the biologically active form of Vitamin D: 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$).

$1,25(OH)_2D_3$, or calcitriol, is the hormonal derivative of Vitamin D; through its activation by Vitamin D receptor (VDR), it suppresses proliferation and induces differentiation of cancer cells in tumour tissue, suggesting that high levels of Vitamin D metabolites may be protective against cancer.[11] More recently, it has also been established as a proapoptotic agent and an inhibitor of cell migration, which may imply an inhibitory effect in cancer. This is based on epidemiological studies related to diet, skin type and geographical factors, serum $1,25(OH)_2D_3$ levels and, recently, functionally significant polymorphisms of the VDR gene.

Cultured melanoma cells can synthesise $1,25(OH)_2D_3$ from $25(OH)D_3$, express the VDR and proliferate more slowly in response to $1,25(OH)_2D_3$.[12–14] Moreover, $1,25(OH)_2D_3$ has been shown to suppress growth of human CMM-derived xenografts (expressing the VDR) in immune suppressed mice, but not in a VDR-negative CMM cell line. The $1,25(OH)_2D_3$ molecule has been shown to induce apoptosis in a human CMM cell line *in vitro*, and an inhibitory effect on the spread of CMM cells has recently been demonstrated *in vitro*.[15,16]

While activating the $1,25(OH)_2D_3$, the VDR mediates the effects of Vitamin D through regulating the transcriptions of other genes. VDR gene is located on chromosome 12q12-q14 and it has at least 196 single nucleotide polymorphisms, some of which seem to influence the activity of $1,25(OH)_2D_3$. Among VDR polymorphisms, the most frequently investigated for their association with various cancers are the *Fok*I (exon 2, rs10735810), which results in an altered translation start site and has been shown to be functionally relevant [17], and the *Bsm*I (intron 8, rs1544410), which seems to be associated with different diseases, although its function is still under debate.[18,19] The associations of VDR polymorphisms with skin cancer risk are relatively unknown. Only a few epidemiologic studies have directly addressed the relationship between VDR polymorphisms and the incidence or prognosis of CMM.

We performed a meta-analysis of published studies to assess the two most studied candidate polymorphisms of VDR gene (*Fok*I and *Bsm*I), 25(OH)D serum levels and the intake of Vitamin D in relation to skin cancer risk (CMM, SCC and BCC).

2. Material and methods

We conducted a comprehensive, systematic bibliographic search of the medical literature to identify relevant studies on CMM and NMSC. The literature search was performed upto February 2008 using the following databases: PubMed, ISI Web of Science (Science Citation Index Expanded) and Embase. We identified published papers and abstracts on CMM and/or NMSC and any of the two most studied VDR polymorphisms (*Fok*I and *Bsm*I) or those assessing $25(OH)D_3$ serum levels and/or Vitamin D intake. The publications were retrieved using the keywords 'Vitamin D', 'VDR', 'Vitamin D receptor', '25(OH)D', '25-Hydroxyvitamin D', 'cholecalciferol', 'calcidiol', 'calcitriol' in combination with 'melanoma', 'skin cancer', 'SCC' or 'BCC'. The computer search was supplemented by consulting the bibliographies of the articles and reviews. The search was limited to human studies but no language or time restrictions were applied.

We searched for publications with frequencies or estimates of the relative risk (RR) for CMM and/or NMSC, with 95% confidence intervals (CI), from:

- Genotype- or allele-based studies on VDR polymorphisms.
- Studies evaluating the intake of Vitamin D.
- Studies reporting results by $25(OH)D_3$ serum levels.

Among articles on VDR polymorphisms, four papers[20–23] presented overlapping data on *Fok*I; therefore, we only considered the study based on the largest number of subjects.[20,23] We extracted fully adjusted risk estimates, when available, from the selected studies for (1) variant allele, (2) subjects heterozygous for the studied polymorphism, (3) subjects homozygous with two variant alleles of the studied polymorphism.

For Vitamin D intake, we extracted fully adjusted risk estimates, when available, from the selected studies for (1) highest versus lowest intake, (2) dose–response model. One study[24] reported only RR for units of Vitamin D increase and it was included in the meta-analysis for dose–response. The estimates from one study[25] were not included because the data were not independent from Weinstock 1992[26] and the authors declared that the RR were 'extrapolated' and not estimated from the data and affirmed that the estimates for Vitamin D were quite variable. We did not find published papers reporting results by $25(OH)D_3$ serum levels.

The abstraction was performed independently by two readers. For each study we retrieved the following information:

- Study characteristics: publication year, study design, study location, exclusion of subjects among controls, adjustments for confounders;
- Exposure evaluation: laboratory methods to detect VDR polymorphisms, dietary assessment method used for Vitamin D intake, time of evaluation respect to diagnosis, values of Vitamin D intake, supplementation used;
- Study population: total number and source of cases and controls, sub-types of cases, history of familial melanoma or other cancers, gender, race;
- VDR estimates: number of cases and controls genotyped for the specific polymorphisms examined, case and control genotype frequency, and reported RRs with 95% CIs;
- Vitamin D intake: number of cases and controls for each category of Vitamin D intake and reported RRs with 95% CIs.

When adjusted estimates were not available we included in the meta-analysis crude estimates. Since the reference group for each VDR polymorphism varied among the studies, we made the most common allele for each polymorphism (b for *Bsm*I, and F for *Fok*I) and the correspondent wild-type genotype the reference allele and genotype, respectively, for our analyses.

Table 1 – Description of the studies included.

Risk factor	Cancer	First author, PY	Country	Study design	Source of controls	Tot *n.* cases	RR 95%CI	Exp.	Ref.	Adjustment	VD Suppl.
FockI	CMM	Hutchinson, 2000[a20]	UK	CC	Hospital	316	1.60 (0.99, 2.57)	*Ff*	FF	.	.
							1.90 (0.93, 3.89)	*ff*	FF		.
		Santonocito, 2007 [45]	Italy	CC	Population	101	0.78 (0.41, 1.47)	*Ff*	FF	*Fock*I, A-1012G, skin type, gender and age	.
							0.81 (0.31, 2.09)	*ff*	FF		.
		Han, 2007 [33]	USA	NCC	Population	215	0.96 (0.67, 1.37)	Ff	FF	Total VD intake, calcium intake, multivitamin	.
							1.40 (0.86, 2.27)	*ff*	FF	use, susceptibility, family history, sunburns, sun lump, geographic region	.
		Li, 2008 [23]	USA	CC	Hospital	805	1.3 (1.05, 1.6)	*Ff*	FF	Age and sex	.
							1.08 (0.78, 1.49)	*ff*	FF		.
	SCC	Han, 2007[33]	USA	NCC	Population	278	0.91 (0.66, 1.24)	*Ff*	FF	Total VD intake, calcium intake, multivitamin	.
							1.41 (0.92, 2.17)	*ff*	FF	use, susceptibility, family history, sunburns, sun	.
	BCC	Han, 2007[33]	USA	NCC	Population	285	1.02 (0.74, 1.41)	*Ff*	FF	lump, geographic region	.
							1.50 (0.98, 2.30)	*ff*	FF		.
BsmI	CMM	Santonocito, 2007 [45]	Italy	CC	Population	101	0.74 (0.40,1.40)	*Bb*	*bb*	*Fock*I, A-1012G, skin type, gender and age	.
							0.29 (0.12,0.71)	BB	BB		.
		Han, 2007 [33]	USA	NCC	Population	215	0.85 (0.60, 1.22)	*Bb*	*bb*	Total VD intake, calcium intake, multivitamin	.
							0.89 (0.54, 1.48)	*BB*	*BB*	use, susceptibility, family history, sunburns, sun lump, geographic region	.
		Li, 2008 [23]	USA	CC	Hospital	805	0.75 (0.60, 0.93)	*Bb*	*bb*	Age and sex	.
							0.78 (0.59, 1.05)	*BB*	*bb*		.
	SCC	Han, 2007[33]	USA	NCC	Population	278	1.05 (0.76, 1.45)	*Bb*	*bb*	Total VD intake, calcium intake, multivitamin	.
							1.51 (1.00, 2.28)	*BB*	*bb*	use, susceptibility, family history, sunburns, sun	.
	BCC	Han, 2007[33]	USA	NCC	Population	285	0.90 (0.65, 1.23)	*Bb*	*bb*	lump, geographic region	.
							1.01 (0.66, 1.56)	*BB*	*bb*		.
Vitamin D intake[b]	CMM[e]	Weinstock, 1992 [26]	USA	CC	Hospital	165	1.80 (0.90, 3.50)	395	105	Age, hair colour, family history of CMM	Yes
		Millen, 2004 [36c]	USA	CC	Hospital	497	0.61 (0.40, 0.95)	158	58	Age, sex, dysplastic nevi, education, skin type	No
							0.66 (0.42, 1.02)	262	63		Yes
		Vinceti, 2005[f35]	Italy	CC	Population	59	0.76 (0.23, 2.50)	117.6	81.6	Energy, sex and age match	No
	BCC	Hunter, 1992 [34]	USA	Cohort	.	771	1.02 (0.81, 1.27)	288.5	45.2	Age, region, time, time spent outdoors,	No
							1.08 (0.86, 1.35)	601.2	53.6	sunscreen, hair colour, sunburns, BMI	Yes
		van Dam, 2000 [32]	USA	Cohort	.	3190	1.10 (0.94, 1.30)	752	98	Age, ancestry, BMI, energy, hair colour, smoking, solar radiation of region, frequency physical examination, vitamins	Yes
		Davies, 2002[d 24]	UK	NCC	Population	123	1.07 (0.85, 1.35)			BMI, red hair and diet	No

CC: case-control; NCC: nested case-control; Exp.: exposure; Ref.: reference category; VD: Vitamin D; Suppl.: food intake including supplementation.

a Presented data only for *Fok*I.

b Categories indicate lowest values of the upper categories and upper values of the lowest categories in IU/day evaluated with the RRs.

c Units: IU/1000 kcal.

d RR per 1 μg/day.

e CMM cases with relapse.

f Units transformed from μg to IU.

Pooled estimates of the dose-response effect of Vitamin D intake on the risk were based on a two-step procedure. In the first-step, a linear model was fitted, within each study, to estimate the relative risk, per one unit of IU intake of increase. When sufficient information was published (the number of subjects at each category of Vitamin D intake), the model was fitted according to the method proposed by Greenland and Longnecker.[27] When the number of subjects at each category of Vitamin D intake was not available from the papers, coefficients were calculated ignoring the correlation between the estimates of risk in the separate exposure levels. In the second step, the summarised RR was estimated pooling the study–specific estimates.[27]

We used random effects models and fixed effects models fitted using SAS (Proc Mixed)[28] with maximum likelihood estimate, to evaluate summary estimation of associations with CMM and NMSC development. When more than one risk estimate were provided in a single study (i.e. for basal cell carcinoma and squamous cell carcinoma, separately), the model took into account the two sources of variation (within and between studies).

Homogeneity of effects across studies was assessed using the Chi-square statistic and I^2, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance.[29] Since the Chi-square test has limited power, we applied random effects models when p-value was $\leqslant 0.09$.[30] Investigation of publication bias was carried out to evaluate stability of pooled results.

To evaluate the influence of individual studies on the summary RR, sensitivity analyses were performed by excluding each study individually and recalculating the pooled RR for each allele or genotype comparison. Publication bias was graphically evaluated by funnel plots and assessed by Macaskill's regression method.[31]

The departure of frequencies of each VDR polymorphism from expectation under Hardy–Weinberg (H–W) equilibrium was assessed by Chi-square test in controls.

Forest plots presented the risk estimates for CMM of heterozygous and variant homozygous versus wild-type of *Fok*I and *Bsm*I polymorphisms and for highest versus lowest intake of Vitamin D.

3. Results

Overall, we included data from ten studies that published data for VDR or Vitamin D intake. For VDR we extracted data for a total of 1437 CMM and 563 NMSC cases from four independent studies. For Vitamin D intake we extracted data for 721 CMM and 4084 NMSC from six independent studies (Table 1).

Overall, six studies presented results for CMM, three for BCC and one for CMM, BCC and SCC. All studies presented results for Caucasian populations, except for one study which included less than 10% of non-white subjects.[32] Six were carried out in USA, two were realised in the UK and two in Italy. Except for two cohort studies, all of them were case-control studies. Two were nested case-control studies (NCC)[24,33]: in the Nurse Health Study and in the EPIC. Hunter et al. (1992)[34] published data from the Nurse Health Study but for a previous period. The cohorts and the two NCC were able to obtain data for NMSC (Table 1).

Vinceti et al. (2005)[35] reported the estimate for Vitamin D from food consumption only while the other studies reported the estimate including supplementation.[26,32] Hunter et al. (1992)[34] and Millen et al. (2004)[36] reported two estimates for Vitamin D, from foods and supplements. All papers reported the Vitamin D intake using International Unit; only Vinceti[35] reported the estimate in micrograms, and in this case the conversion was made (1 μg calciferol = 40 IU Vitamin D). Millen et al. (2004)[36] expressed the estimate for Vitamin D intake in IU/1000 kcal.

For Vitamin D intake when the authors presented estimates both from food only and supplementation the former was chosen, but the differences in the estimates were narrow (Table 1). In the analysis on CMM, Weinstock et al. (1992)[26] is the only study included with estimates on food and supplementation; however, values of Vitamin D intake were quite low, taking into account that they included supplementation.

Table 2 – Summary and heterogeneity estimates for the association between VDR, Vitamin D intake and skin cancer.

Risk factor	Cancer	Comparisons	SRR and 95%CI	Q test p-value
VDR *Bsm*I	CMM	*Bb* versus *bb*	0.78 (0.65, 0.92)	0.74
		BB versus *bb*	0.75 (0.59, 0.95)	0.09
	CMM or NMSC	*Bb* versus *bb*	0.80 (0.6, 1.06)	0.53
		BB versus *bb*	0.87 (0.63, 1.21)	0.01
VDR *Fok*I	CMM	*Ff* versus *FF*	1.21 (1.03, 1.42)	0.16
		ff versus *FF*	1.21 (0.95, 1.54)	0.39
	CMM or NMSC	*Ff* versus *FF*	1.11 (0.95, 1.31)	0.16
		ff versus *FF*	1.30 (1.03, 1.63)	0.56
Vitamin D intake	CMM	High versus low	0.92 (0.25, 3.44)	0.03
		DR by 100 IU	1.00 (0.76, 1.30)	0.01
	Excluding Weinstock, 1992 [26]	High versus low	0.63 (0.42, 0.94)	0.73
		DR by 100 IU	0.92 (0.55, 1.54)	0.98
	CMM or NMSC	High versus low	1.04 (0.87, 1.24)	0.06
		DR by 100 IU	1.01 (0.98, 1.03)	0.06

SRR: summary relative risk; CMM: cutaneous malignant melanoma, NMSC: non melanoma skin cancer; VDR: vitamin D receptor; DR: Dose-response estimates; Q test = Chi-square test for heterogeneity.

In the sensitivity analysis this study was excluded to evaluate the change in the summary RR (SRR).

3.1. *VDR meta-analysis*

Departure from the H–W equilibrium in controls was never observed.

Summary Relative risk (SRR) and 95% CI for heterozygous and homozygous versus wild-type genotype, are presented in Table 2 along with *p*-values for the Chi-square Q statistic. The *FokI f* allele showed a positive association with CMM, SRR: 1.13 (1.01–1.25) and $I^2 = 25$. The SRR for the studies on CMM were: 1.21 (1.03–1.42) and 1.21 (0.95–1.54) for the *Ff* and *ff* genotypes versus wild-type genotype, with $I^2 = 42$ and 1, respectively. The *FokI f* allele showed a significant positive association with CMM or NMSC; SRR: 1.14 (0.99–1.31) and $I^2 = 0$. For the association of *FokI Ff* and *ff* genotypes versus wild-type genotype in CMM or NMSC risk, the SRR were: 1.11 (0.95–1.31) and 1.30 (1.03–1.63) with $I^2 = 38$ and 0, respectively (Fig. 1a and b).

The *BsmI B* allele showed a significantly negative association with CMM, SRR: 0.84 (0.75–0.94) and $I^2 = 35$. The SRR for the studies on CMM were: 0.78 (0.65–0.92) and 0.75 (0.59–0.95) for the *Bb* and *BB* genotypes versus wild-type genotype, with $I^2 = 0$ and 58, respectively. When we considered CMM or NMSC, the SRR for *BsmI B* allele was: 0.88 (0.59–1.34) with $I^2 = 72$. For the association of *Bb* and *BB* genotypes, the SRR were: 0.80 (0.60–1.06) and 0.87 (0.63–1.21) with $I^2 = 0$ and 70, respectively (Fig. 1c and d).

Heterogeneity was statistically significant for *BsmI* and NMSC ($p = 0.01$ Table 2): we observed that both the estimates for SCC with *Bb* and *BB* genotypes versus wild-type were in the opposite direction compared with the other estimates for CMM: 1.05 (0.76–1.44) and 1.51 (1.00–2.28).

We did not find any indication of publication bias. Makaskill's regression test[31] was not significant.

3.2. *Vitamin D intake analysis*

SRR indicates a possible protective effect for CMM only when we compare highest versus lowest intake: 0.92 (0.25–3.44). However, we found a high heterogeneity (*p* of Chi-square = 0.03 and $I^2 = 71$) mainly due to the oldest study.[26] Excluding this study the heterogeneity disappeared (*p* of Chi-square = 0.73 and $I^2 = 0$) and the SRR shows a significant protective effect: 0.63 (0.42–0.94). Similarly, dose–response estimates suggest a protective effect for CMM only when we excluded Weinstock et al. (1992)[26] and the heterogeneity disappeared (*p* of Chi-square = 0.98 and $I^2 = 0$). When we included NMSC we do not have any indication of an association with Vitamin D intake (Table 2) (see Fig. 2).

4. Discussion

Solar UV-exposure, particularly intensive short-time and recreational sun exposure, is considered to be the major etiologic risk factor for melanoma.[4] On the other hand, 90% of all requisite Vitamin D has to be formed in the skin through

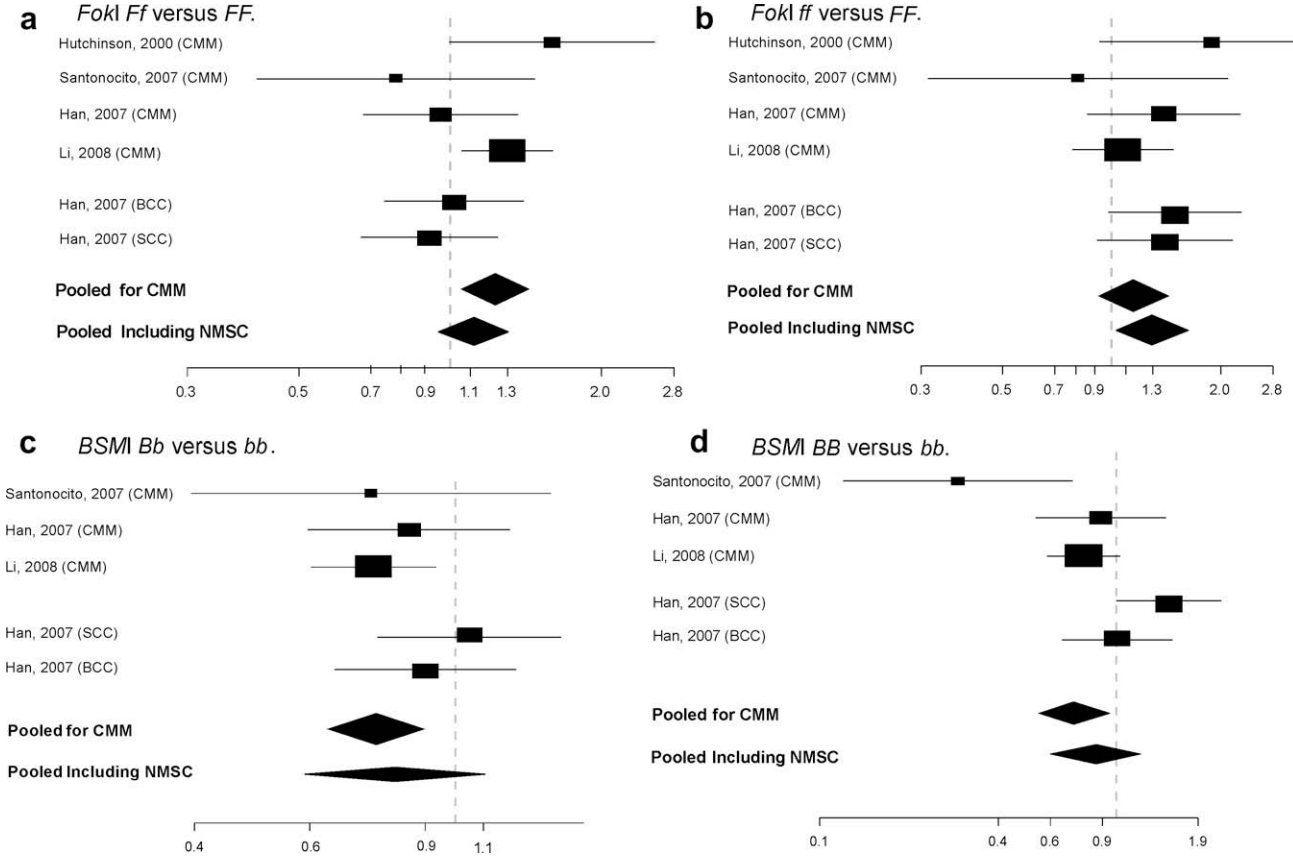

Fig. 1 – (a) *FokI Ff* versus *FF*, (b) *FokI Ff* versus *FF*, (c) *BsmI Bb* versus *bb*, (d) *BsmI BB* versus *bb*.

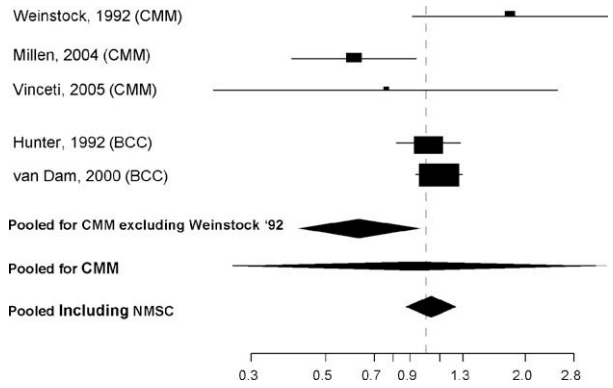

Fig. 2 – Vitamin D intake: high versus low.

the action of the sun - a serious problem due to the fact that new scientific findings convincingly demonstrate Vitamin D deficiency to be associated with a variety of severe diseases including various types of cancer (e.g. colon, prostate and breast cancer).[10] Sun exposure is associated with a relatively favourable prognosis and increased survival rate in various malignancies, including malignant melanoma.[37–40] It has been speculated that these findings were related to UV exposure–induced relatively high serum levels of Vitamin D, which may lead to a more favourable course of melanoma.

We have postulated that polymorphisms in the VDR gene are important in CMM and NMSC development. This hypothesis is supported by data showing that $1,25(OH)_2D_3$ inhibits cell proliferation and stimulates differentiation and apoptosis in several cell types expressing the VDR. In this meta-analysis, the *f* allele at the *Fok*I restriction sites was associated with a significant increased risk for CMM, with a risk increase attributable to the *ff* genotype estimated at 21% more than the *FF* genotype. The increased risk for the *f* allele was borderline significant for NMSC and the risk increase attributable to the *ff* genotype was estimated at 30%. The *B* allele at the *Bsm*I restriction site was associated to a significant decrease of CMM, with a risk decrease attributable to the *BB* genotype estimated at 25% less than the *bb* genotype. The decrease for carriers of *B* allele was not significant for NMSC.

A recent meta-analysis investigated the association between five VDR polymorphisms (*Taq*I, *Fok*I, *Bsm*I, *Eco*RV, and *Cdx*2) and the risk of melanoma.[41] A free-model approach has been applied and the DerSimonian and Laird method was used to pool the crude estimates. They found a significant association between the *Bsm*I VDR polymorphism and melanoma risk (pooled odds ratio for *BB*+*Bb* versus *bb* was 1.30; 95%CI: 1.11–1.53) but they did not pool the estimates for *Fok*I. We confirm the results of the *Bsm*I VDR polymorphism, adopting the maximum likelihood approach, which achieved the best coverage probabilities when the number of studies is modest.[28] Moreover, we included fully adjusted RRs to take into account the main confounding factors. The inclusion of NMSC and the choice to analyse separately heterozygous versus wild-type and variant homozygous versus wild-type allow us to also find an association with *Fok*I.

Data on Vitamin D intake suggest a protective effect for CMM only, excluding the oldest of the three studies. Weinstock et al. (1992)[26] reported estimates on food and supplementation but the values of Vitamin D were quite low. At that time, available data for Vitamin D content in food were scarce and made with unreliable bioassays. In any case, the data are too limited to draw any reliable conclusions. Nowadays data on Vitamin D content are not generally standardised; therefore, many studies do not calculate Vitamin D intake.[9] National fortification and supplementation practices are very different between countries included in this meta-analysis. Fortification of staple foods, such as milk and margarine and spreads, plus other optional fortifications (orange juice, ready-to-eat breakfast cereals, sliced American cheese and yogurt) are mandatory in the United States, while there is no required fortification of foods in Italy. The overall Vitamin D intake is doubled in the United States, compared to Italy, due to fortification and supplementation practice.

Han et al.[33] found a significant interaction between both polymorphisms and total Vitamin D intake on SCC risk. The significantly positive association with SCC risk was limited to women with high intake (OR: 2.38 (1.22–4.62) and 2.46 (1.23–4.90) for *BB* and for *ff* genotypes, respectively).

Some studies have demonstrated that diet is a significant independent predictor of plasma $25(OH)D_3$ levels. This is evident when indigenous inhabitants, often in extreme northern or southern latitudes, change from traditional foods naturally rich in vitamin D, such as fish and blubber, to westernised diets.[42] However, the link between dietary intake of Vitamin D and the anticancer effect of $25(OH)D_3$ needs to be studied and further assessment is needed. Only two abstracts were found evaluating serum levels of $25(OH)D_3$ and skin cancer risk.[43,44] Both reported basal $25(OH)D_3$ levels lower in melanoma patients than in the control group, although this difference was statistically not significant. Newton Bishop et al. (2006)[44] evaluated the risk of relapse for CMM patients taking Vitamin D supplementation and found a significant reduced risk: 0.54 (0.32–0.92). Moreover, Nürnberg[43] found that progression of malignant melanoma was associated with statistically significantly reduced $25(OH)D_3$ serum levels. Two other studies found an association of VDR polymorphisms with Breslow thickness[20,45] suggesting a role for Vitamin D in the CMM prognosis.

Some epidemiologic studies have suggested that adequate Vitamin D levels may provide protection against several chronic diseases, including cancer, and could improve cancer prognosis. A prospective study examined the association between pre-diagnosis $25(OH)D_3$ levels and mortality in patients diagnosed for colorectal cancer within the the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS). This study showed that higher prediagnosis plasma 25(OH)D levels were associated with a significant improvement in overall survival.[46] A meta-analysis of published randomised trials showed a significant reduction in total mortality in subjects taking Vitamin D.[47] Berwick et al.[40] showed a fatality reduction of 40–60% in melanoma patients with a history of high sun exposure independently of body site, thickness, mitotic rate and early detection behaviour. The study by Berwick et al.[40] involved mostly patients with early stage melanoma, and it is plausible that the known antiproliferative and antiangiogenic properties of Vitamin D may be inversely associated with melanoma progression. How-

ever, its protection against skin cancer is a complex issue. Ultraviolet light exposure not only promotes Vitamin D_3 (cholecalciferol) synthesis in the skin but also increases the risk of skin cancer. UV radiation has a wide range of carcinogenic effects on skin tissue, such as causing DNA and tissue damage, oxidative stress and inflammation. Intermittent patterns of sun exposure and sunburn are especially well known risk factors for CMM[4] and NMSC.[48]

The analysis of gene–environment interactions could give further clues in the epidemiology of skin cancers. Hutchinson et al.[20] found that the *Fok*I polymorphism interacted with the known melanoma risk factors of skin colour, moles and family history of cancer.[5,49] Hutchinson et al.[20] also identified an association between VDR genotypes and red hair in patients with CMM. Although the mechanism for this association is not known, other studies have identified links between polymorphisms at other loci and hair colour in MM.[50–52] These data suggest that the molecular route by which patients with red hair develop CMM may differ from patients with other hair colours, supporting the view that these patients represent a high-risk subgroup. However, these data require confirmation in independent studies, including healthy individuals.

In conclusion, this meta-analysis should be added to the growing body of evidence that Vitamin D may be of importance for pathogenesis of CMM. In particular, VDR *Fok*I and *Bsm*I polymorphisms result in an association, even if in different directions, with CMM and NMSC risk. There is also a slight indication of a role of dietary Vitamin D in CMM development but further studies should be carried out to clarify this association and to validate possible gene–environment interactions and the relationship with incidence and prognosis.

Conflict of interest statement

None declared.

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