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To identify the association between dietary vitamin D intake and serum levels and risk or prognostic factors for melanoma-systematic review and meta-analysis

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ABSTRACT

Objective To evaluate the association of serum vitamin D levels and dietary intake with melanoma risk and prognostic factors.

Methods Two independent investigators systematically searched PubMed, Embase and ISI Web of Knowledge (Thomson Scientific Technical Support, New York) databases for eligible studies published between January 1992 and September 2020 using the following combinations of search terms: (vitamin D, or 25-hydroxyvitamin D) AND (melanoma, malignant melanoma, cutaneous melanoma, or cutaneous malignant melanoma). Articles not written in English but with English titles and abstracts were also checked. We obtained the full text of all potentially eligible articles, and reference lists of all studies retrieved at the first stage were also checked to identify other eligible papers. Review articles not reporting original data were excluded, but their reference lists were inspected.

Results Six studies including 212 723 cases reported the association between dietary intake of 25(OH) D serum levels and melanoma risk. The total relative risk for the comparison between the highest and lowest quantiles of the distribution of vitamin D intake was 1.10 (95% CI 0.96 to 1.26) with I^2=56%. Another six studies including 12 297 cases evaluated the association between serum vitamin D levels and melanoma risk. The total relative risk for the comparison of serum vitamin D levels between the highest and lowest quantiles was 1.12 (95% CI 0.53 to 2.35) with I^2=91%. Four studies with 2105 cases investigated the association between serum 25(OH)D (nmol/L) and Breslow thickness, three of which found an inverse association between serum 25(OH)D (nmol/L) and melanoma thickness.

Conclusions Vitamin D intake and serum 25(OH)D levels were not closely related with melanoma risk, but an inverse association between serum 25(OH)D levels with melanoma thickness was discovered. As the positive correlation between melanoma thickness and melanoma mortality has been recognised, hence it is concluded that a moderate dietary vitamin D supplement to avoid the serum 25(OH)D deficient might be beneficial to the long-term survival of patients with melanoma.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first systematic review that comprehensively identified, assessed and summarised the evidence regarding the association between vitamin D deficiency and the risk and prognosis of melanoma.
⇒ This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
⇒ In case of disagreements, a third independent researcher was consulted to reduce the risk of observer bias.
⇒ First, the exact data on the vitamin D intake and serum 25(OH)D levels of individuals were not available from all studies, which may lead to less accurate estimates of risk.
⇒ Second, the number of studies included was relatively small; therefore, some subgroup analyses were difficult to perform.
⇒ Third, the heterogeneity and deficiencies of the included studies limited the extraction of accurate and conclusive information for quantitative analysis in some cases.

BACKGROUND

Cutaneous malignant melanoma is the most dangerous type of skin cancer and represents the most important cause of death from skin diseases, occurring in all age groups.[1] The incidence of melanoma has been increasing, despite the efforts to improve sun protection; thus, there is a demand on additional preventive treatments or measures.

Vitamin D is a prohormone following conversion to calcitriol and exhibits a wide range of biological functions in the human body. In addition to bone and calcium metabolism disorders, many illnesses have been linked with vitamin D deficiency in recent epidemiological studies.[2–4] As vitamin D is either synthesised in the skin or obtained from dietary sources, optimal sun exposure

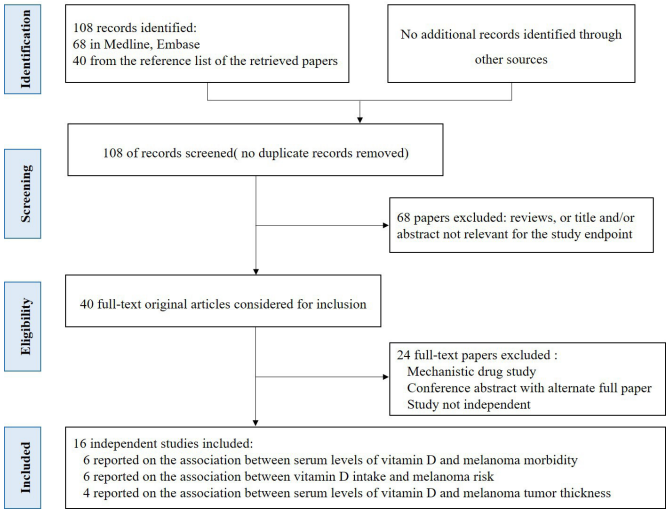

Figure 1 Flow chart of the selection process of the studies included in the meta-analysis.

and dietary intake are related to optimal vitamin D status. However, vitamin D insufficiency remains as a global health problem, the major causes of which are insufficient exposure to sunlight, decreased dietary intake, skin pigmentation, obesity and advanced age. To overcome or avoid these causes, vitamin D supplementation has been considered to be the most convenient and effective means.

Some studies have suggested an inverse relationship between vitamin D levels and cancer risk, especially in the risks of breast, pancreatic, prostate and colon cancers.[5–8] However, several studies have reported a null association or even an increase in cancer risk with higher vitamin D levels.

Vitamin D is a fat-soluble steroid hormone, which binds to the vitamin D receptor (VDR), thereby mediating its genetic effects. The relationship of serum levels with melanoma risk and mortality remains unclear. In vivo studies have found that vitamin D could inhibit the metastatic ability of lung cancer cells in animal models, and in vitro studies have showed that vitamin D could result in a decrease in cell proliferation and induce apoptosis in lung cancer cell lines. In fact, UV radiation is not among the main causes of non-sun-exposed melanomas; systemic immunosuppression and physiological features in these special sites may contribute to the development of the disease. Additionally, some studies have reported that higher serum levels of vitamin D are associated with a better prognosis in patients with melanoma.[9]

Vitamin D binds to the VDR, resulting in the transcription of many genes that play roles in the inhibition of MAPK signalling pathway, induction of apoptosis, and cell-cycle inhibition.[10] Vitamin D also has suppressive effects on adaptive immunity and has been reported to promote innate immunity.[11] Recently, several cohort studies have addressed the associations of vitamin D status with incidence and survival of patients with melanoma. However, the strength of the associations and their statistical significance varied among these studies. We therefore conducted a systematic review and meta-analysis to provide a comprehensive overview of the evidence on the potential protective role of high 25(OH)D level, the main form of vitamin D in the body, on the incidence and prognosis of melanoma.

METHODS

This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12 13]

Patient and public involvement

No patient involved.

Search

Two reviewers searched PubMed, Embase and ISI Web of Knowledge (Thomson Scientific Technical Support, New York) databases for eligible studies published between January 1992 and September 2020. The following search terms related to vitamin D and melanoma were combined for a main search: “vitamin D” OR “25-hydroxyvitamin D” AND “melanoma” OR “malignant melanoma” OR “cutaneous melanoma” OR “cutaneous malignant melanoma”. See online supplemental appendix A for the full search for all databases.

Eligibility and exclusion criteria

Literature inclusion criteria: (1) cohort studies or case-control studies; (2) assessing the association between vitamin D intake and melanoma risk or serum vitamin D levels and melanoma risk, or serum vitamin D levels and melanoma tumour thickness; (3) the outcomes were melanoma incidence or tumour thickness. Exclusion criteria: (1) reviews, case-only studies, independent studies, case reports and editorials were all excluded. (2) The association between vitamin D intake and the risk of melanoma could not be calculated. (3) The results are repeatedly reported in the literature.

When several articles reported results from the same participants, only the study with the largest sample of subjects was considered. Regarding the effect of vitamin D on the prognosis of melanoma, we focused on tumour thickness only, as this is the most frequently reported and the most important prognostic factor in early-stage melanoma. Therefore, we also included studies reporting on the average vitamin D intake or blood level across categories of tumour thickness.

Procedures

All references were imported into the bibliographic management software Mendeley and duplicates were identified and removed. Two independent authors screened the remaining results by title and abstract. Two reviewers screened the full texts of the selected articles to identify those that satisfied the eligibility criteria. A third reviewer was consulted in case of any disagreements.

Table 1 Main features of studies included in this meta-analysis on the association between dietary intake (from food and/or supplements) of 25(OH)D and melanoma risk

First author, Year	Study location	Sample size, n, T/C	% Male participants, T/C	Source of vitamin D	Reported estimate	Relative risk (95% CI)	Adjustment for covariates	Study quality (max. 9 points)*
Weinstock *et al*[14] 1992	US	165/209	44%/43%	Food+supplements	>9.9 versus<2.6 µg/day Yes versus no	1.8 (0.9 to 3.5) 1.3 (0.8 to 2.2)	Age, family history of melanoma, hair colour	7
Millen *et al*[15] 2004	US	502/565	54%/57%	Food+supplements	≥6.55 versus ≤1.58 µg /1000 kcal†	0.66 (0.42 to 1.02)	Age, sex, study site	9
Asgari *et al*[16] 2009	US	68 611	48%	Food supplements	>7.1 versus ≤3.0 µg/day >9.9 versus none	1.31 (0.94 to 1.82) 1.13 (0.89 to 1.43)	Age, gender, education	8
Vinceti *et al*[17] 2011	Italy	380/719	46.1%/44.4%	Food	≥3.67 versus <1.62 µg/day	0.53 (0.31 to 0.88)	Age, sex, province of residence, total energy, and calcium intake, phototype, skin sun reaction, history of sunburns, education	9
Tang *et al*[18] 2011	US	36 282	0	Supplements	10 µg/day versus none	0.86 (0.64 to 1.16)	Age, sun exposure, anthropometry	8
Park *et al*[19] 2016	US	105 290	39.4%	Food supplements	≥10 µg/day versus none †	1.06 (0.96 to 1.39) 1.04 (0.87 to 1.26)	Family history of melanoma, hair colour, number of arm moles, sun exposure, body mass index, physical activity, smoking status, intakes of total energy, alcohol, coffee, and citrus intake	8

*Study quality was judged based on the Newcastle-Ottawa Scale (1–9 stars).
†Reported as IU/day in the text and transformed into µg/day by using the equivalence: 1 µg=40 IU.
T/C, cases /controls.

Table 2 Main features of papers included in this meta-analysis on the association between serum vitamin D levels and melanoma risk

First author, Year	Study location	Study design	Sample size, *n* T/C	Age, years, T/C	% men, T/C	Reported estimate	Relative risk (95% CI)	Adjustment for covariates	Study quality (max. 9 points)*
Nürnberg *et al*[20] 2009	Germany	Case-control study	205/141	14–34 (4.9%/28.4%) 35–64 (52.7%/46.8%) ≥65 (42.4%/24.8%)	44%/43%	>50 versus <25 nmol/L*	0.82 (0.46 to 1.49)	None†	8
Major *et al*[21] 2012	Finland	Nested case-control study	92/276	Median 65/66	Not available	≥50 versus <25 nmol/L	1.32 (0.64 to 2.72)	Age, date of blood draw, height, weight, dietary cholesterol, skin behaviour	7
Afzal *et al*[22] 2012	Denmark	Cohort study	10 060	Median 59/57	43.8%	≥50 versus <25 nmol/L	4.72 (0.96 to 23.3)	Age, gender, pack years, body mass index, income, occupational physical exertion, intensity of leisure-time activities, regular cycling or running	8
van der Pols *et al*[23] 2012	Australia	Cohort study	1191	Mean 58/54	45%	<75 versus ≥75 nmol/L	2.71 (0.98 to 7.48)	Age, sex, β-carotene, sun exposure, family history of skin cancer, skin colour, other	8
Eun Joo Lee[24] 2017	Korea	Case-control study	40/56	Mean 48.5/48.4	37.5%/37.5	<50 versus ≥75 nmol/L	0.54 (0.13 to 2.18)	None*	7
Cattaruz *et al*[25] 2019	Italy	Case-control study	137/99	Mean 52.0/51.6	44.5%/32.3%	≥ 75 versus≤ 50 nmol/L*	0.04 (0.02 to 0.10)	Age, sex, BMI	7

*Reported as ng/mL in the text and transformed into nmol/L by using the equivalence: 1 ng/mL=2.5 nmol/L.
†Unadjusted ORs were calculated from raw data.
T/C, cases/controls.

Figure 2 Forest plot comparing the risk of melanoma in the highest versus lowest categories of vitamin D intake (through diet and/or supplementation).

Data extraction and quality assessment

A standardised protocol for data collection was used for data extraction. For each study, we extracted information on the first author, publication year, country where the study was conducted, number of participants, sex distribution, study design, exact definition of dietary intake of vitamin D, serum vitamin D levels, cases of incident melanoma and risk estimates for melanoma risk. Two authors independently performed the quality of included studies and data collection, and any initial disagreements were checked by another author and resolved by consensus after a further review of the studies. Since melanoma is a relatively rare disease, we ignored the distinction between the various estimates of relative risk (ie, OR, risk ratio, rate ratio), and all measures were interpreted as relative risk.

We used the Newcastle–Ottawa Scale to evaluate the quality of the included studies. The evaluation criteria consisted of the following three parts: the selection method of the case and the control groups, the comparability of the case and the control groups, and the exposure assessment method. The semiquantitative principle of the star system was adopted to evaluate the literature quality, with a full score of 9 stars and a score of≥7 stars considered as high-quality studies; studies with a score of≤4 stars were not included.

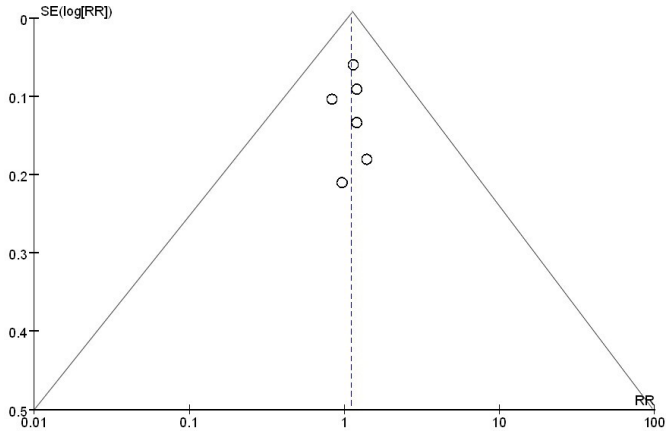

Figure 3 Begg's funnel plot. The funnel plot was used to evaluate publication bias. All studies are within the limits determined by the graphic, indicating low bias.

Data synthesis and statistical analysis

All the statistical analyses were performed using the R software, V.R-3.5.1. (https://cran.r-project.org), and the library (metafor), library (meta), library (rmeta) packages were loaded for data collection and analysis. The pooled *RR*s and 95% CIs were calculated to assess the strength of the association between vitamin D intake (or serum vitamin D levels) and melanoma risk. Serum vitamin D concentrations are presented as in nmol/L. Concentrations reported in ng/mL were accordingly converted based on the following equivalence: 1 ng/mL=2.5 nmol/L. The summary *RR* with 95% CI was used to assess melanoma risk. The *RR* comparing high levels of vitamin D with low levels of vitamin D was used in this meta-analysis. Between-study heterogeneity was assessed using Cochrane's Q test, and p<0.1 indicated obvious heterogeneity in the included studies. A further assessment of heterogeneity was performed using the I^2 statistic method, and an I^2<50% was acceptable of the variability level, I^2>50% indicated that there was heterogeneity among the included studies Heterogeneity was also investigated by considering all the possible factors that could influence the estimates, including country, type of controls, adjustment for confounding factors, and study design. Random effect model was adopted to calculate the pooled *RR* when the heterogeneity was obvious; otherwise, a fixed effect model was used.

Sensitivity analysis was conducted by removing one study by turns to evaluate the reliability and validity of the pooled *RR*s. Publication bias was evaluated using the funnel plot, and asymmetry in the funnel plot indicated possible risk of publication bias. Egger's test was also used to assess publication bias.

RESULTS

Search results and characteristics of the included studies

The flow diagram of the systematic literature search process and results are depicted in figure 1. A total of 108 abstracts of possible studies were identified from Medline, Embase and ISI Web of Knowledge up to September 2020. After an initial screening, 40 papers were preliminarily considered for inclusion, 24 studies were excluded

Figure 4 Forest plot comparing the risk of melanoma in the highest versus lowest categories of vitamin D serum levels.

based on the inclusion criteria. Among the 16 studies remaining, 3 were prospective cohort studies, 8 were case-control studies, 4 were retrospective studies and 1 was a randomised controlled trial. They were conducted in the US (n=5) and in European (n=7) and Asian (n=4) regions and published from 1992 to 2019. The main features of these studies are shown in table 1. All studies provided risk estimates of melanoma according to the levels of vitamin D. There were six studies that assessed the association between vitamin D intake and melanoma risk (table 1) and another six studies that assessed the association between serum vitamin D levels and melanoma risk (table 2).

The Newcastle-Ottawa Scale mentioned above was adopted to evaluate the quality of the studies included. All studies had scores of≥7 and were thus considered to be high-quality studies. This demonstrates the rationality of the selection method and the comparability between the case and the control groups.

Meta-analysis

Table 1 shows the main features of the six included studies[14–19] with 212 723 cases overall reporting on the association between dietary intake of 25(OH) D serum levels and melanoma risk. The total relative ratio for the comparison between the highest and lowest quantiles of the distribution of vitamin D intake was 1.10 (95% CI 0.96 to 1.26) with I^2=56% (figure 2). As the number of studies was limited so we did not carry out subgroup analyses. Sensitivity analyses did not identify any significant factor influencing the summary results. The funnel plot showed that all the included studies were evenly distributed, with no study located out of the funnel (figure 3).

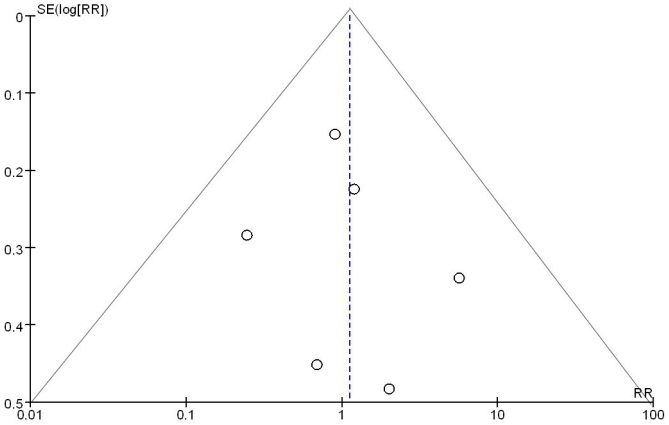

Figure 5 The funnel plot was adopted to evaluate publication bias. All included studies are within the limits determined by the graphic, indicating no obvious bias.

Table 2 shows the main characteristics of the other six studies[20–25] with 12 297 cases overall reporting the association between serum vitamin D levels and melanoma risk. The total relative ratio for the comparison of serum vitamin D levels between the highest and lowest quantiles was 1.12 (95% CI 0.53 to 2.35) with I^2=91% (figure 4). The funnel plot showed no publication bias in these studies (figure 5).

Table 3 summarises descriptive statistics of four studies[26–29] with 2105 cases overall reporting on the association between serum 25(OH) D (nmol/L) and Breslow thickness. All studies found an inverse association between serum 25(OH) D (nmol/L) and melanoma thickness. With the exclusion of the small study by Candy Wyatt,[28] the inverse association in all the other studies was significant (figure 6).

DISCUSSION

Serum 25(OH) D levels are positively correlated with the prognosis of patients with melanoma

This meta-analysis summarises the results of prospective and retrospective studies, including 6 studies on vitamin D intake comprising 211 230 patients and 1493 controls and 6 studies on serum 25(OH) D levels comprising 11 725 patients and 572 controls, 4 studies on serum 25(OH) D levels and melanoma thickness including 2105 patients with melanoma. Our results indicate that vitamin D intake and serum 25(OH) D levels are not strongly associated with melanoma risk; however, we found an inverse association between serum 25(OH)D levels and melanoma thickness, which was identified as a prognostic factor.

Vitamin D deficiency is an important risk factor for many types of solid cancers, such as colorectal cancer. The prevalence of vitamin D deficiency is higher in patients with colorectal cancer (approximately 90%) than in those of other types of cancer.[30] Vitamin D may decrease the risk of cancer through several mechanisms,

Table 3 Summary descriptive statistics of papers reporting on the association between serum 25(OH)D (nmol/L) and melanoma thickness

First author, Year	Study location	Study design	Recruitment of subjects	Sample size, *n*	Age at diagnosis, years	Male participants, n (%)	Tumour thickness, mm	Mean serum vitamin D level, nmol/L	P value
Newton-Bishop *et al*[26] 2009	UK	Retrospective study	The patients were population-ascertained incident patients with melanoma (stages I to IIIA) recruited in a geographically defined area of northern England from September 2000 to March 2008.	1132	Not available	Not available	<1 versus>3	55.8 versus 48.5	0.002
Gambichler *et al*[27] 2013	Germany	Retrospective study	The study involved 764 patients with melanoma who were prospectively recruited from December 2009 to March 2012.	764	% <40 (18.1%) 40–60 (36.7%) >60 (45.2%)	47%	<1 versus >4	37.8 versus 23.5*	<0.05
Wyatt *et al*[28] 2015	Australia	Retrospective study	Participants were patients aged≥18 years with histologically confirmed cutaneous melanoma. Recruitment took place between 1 July 2010 and 27 July 2011.	100	Mean (SD) 61 (13)	56%	<0.75 versus ≥0.75	59.7 versus 50.7	0.08
Lim *et al*[29] 2018	Australia	Retrospective study	A total of 109 primary melanomas diagnosed between 2001 and 2013 were retrospectively identified from the institutional database. The corresponding 25-hydroxyvitamin D3 levels were estimated within 6 months of diagnosis.	109	Mean (SD) 57.7 (18.05)	46.8%	≤1.0 versus >1	67.0 versus 57.6	0.04

*Reported as ng/mL in the text and transformed into nmol/L by using the equivalence as follows: 1 ng/mL = 2.5 nmol/L.

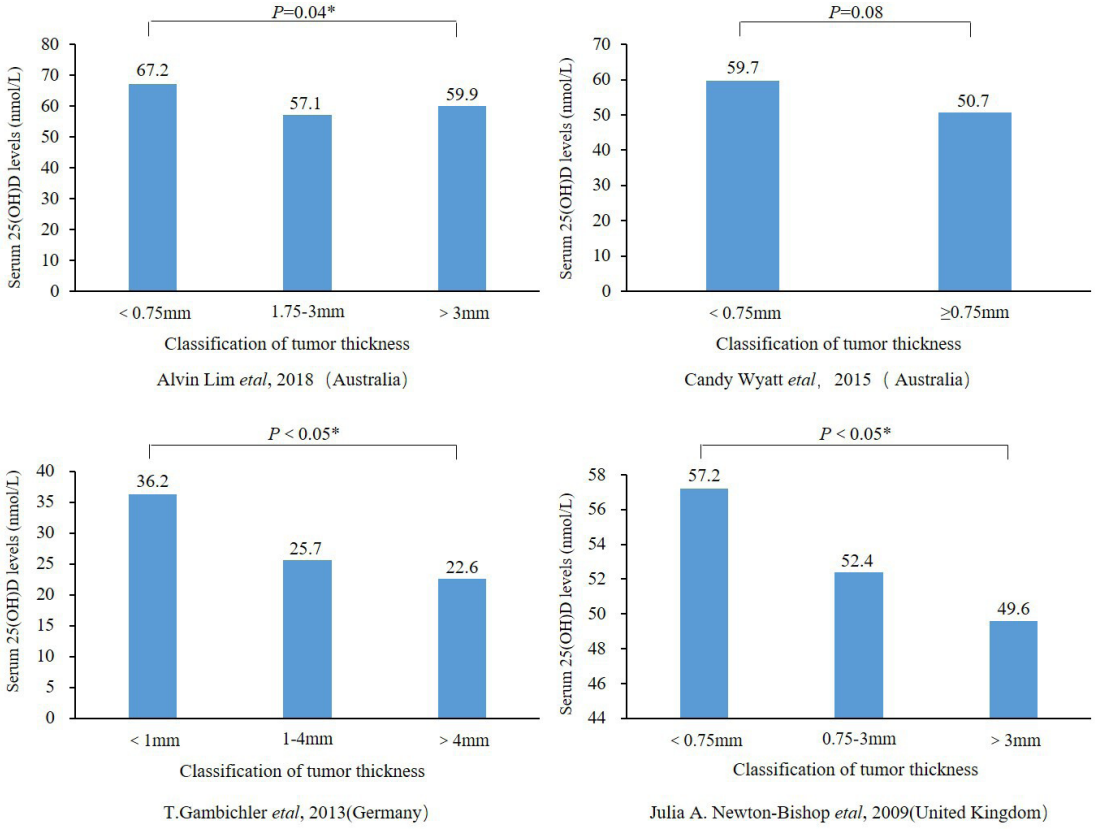

Figure 6 Melanoma thickness is slightly negatively related with serum 25(OH)D levels.

including the regulation of proliferation and differentiation, the induction of apoptosis, and the inhibition of angiogenesis.[31]

As melanoma is the most aggressive malignant disease among skin tumours, studies on the aetiological factors of melanoma have attracted much attention. The synthesis of vitamin D requires UV radiation, an important factor in melanoma incidence; thus, the relationship between vitamin D and melanoma seems more complex and significant. A few studies have provided information on vitamin intake and melanoma incidence; however, their conclusions remain controversial. Meta-analysis is an important tool to reveal trends that are not apparent in a single study. Pooling of similar but independent studies increases precision and therefore increases the confidence level of the findings.

Limitations of this meta-analysis directions for future research

This meta-analysis had some strengths. First, the number of total cases and controls included was substantial, thus significantly increasing the statistical power of the analysis. Second, our quantitative assessment was mainly based on prospective studies, thereby minimising selection or recall bias. Third, the publication biases were small, indicating that the entire pooled result may be unbiased.

Nevertheless, thus study had some limitations. First, the exact data of the vitamin D intake and serum 25(OH) D levels of individuals were not available from all studies, which may lead to less accurate estimates of risk. Second, the number of studies involved was relatively small; thus, some of the subgroup analyses were difficult to perform. Third, the controls were not uniformly defined. Although most participants in the control groups were healthy, some may have had benign disease. Therefore, there might be non-differential misclassification because the included control participants may have different risks of developing melanoma. Fourth, the range of values for the cut-off points for these categories for both the plasma 25(OH) D levels and the vitamin D intake in the studies was wide, thus affecting the analysis. Therefore, large randomised clinical trials should be conducted with uniform criteria for vitamin D intake and plasma 25(OH) D levels in several countries and regions. Finally, although there was no clear indication of major publication bias in the formal evaluation, potential publication bias is difficult to completely exclude because small studies with negative results may not be published.

In summary, the results of this meta-analysis demonstrated that vitamin D intake and serum 25(OH) D level were weakly associated with the risk of melanoma, but positively correlated with an improved prognosis of patients with melanoma. However, in-depth analyses of the assessed associations using longitudinal studies are required to enable more precise estimates of the role of vitamin D in melanoma; further investigations are needed to ulteriorly demonstrate the benefits and to suggest the implications of dietary vitamin D supplements, prospective studies with large samples are especially demanded

to set up a clear and convictive guideline for vitamin D supplement.

Correction notice This article has been corrected since it published online to update author contribution.

Contributors All authors contributed to the study design. YS and HL searched and screened the articles. All authors contributed to data analysis and interpretation of the data. YS drafted the manuscript, HL and YC revised it critically, and all authors contributed to revisions and approved the final manuscript. YS is responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data included in this study are available upon request by contact with the corresponding author.

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