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Use of sunscreen and risk of melanoma and non-melanoma skin cancer: a systematic review and meta-analysis

Background: The use of sunscreen is a key component of public health campaigns for skin cancer prevention, but epidemiological studies have raised doubts on its effectiveness in the general population. *Objectives:* This systematic review and meta-analysis aimed to assess the association between risk of skin cancer and sunscreen use. *Materials & methods:* We searched PubMed, BIREME and Google Scholar from inception to May 17, 2017, to identify observational studies and controlled trials. We used a random-effects model for conventional and cumulative meta-analyses. *Results:* We included 29 studies (25 case-control, two cohort, one cross-sectional, and one controlled trial) involving 313,717 participants (10,670 cases). The overall meta-analysis did not show a significant association between skin cancer and sunscreen use (odds ratio (OR) = 1.08; 95% CI: 0.91-1.28, I^2 = 89.4%). Neither melanoma (25 studies; 9,813 cases) nor non-melanoma skin cancer (five studies; 857 cases) were associated with sunscreen use, with a pooled OR (95% CI) of 1.10 (0.92-1.33) and 0.99 (0.62-1.57), respectively. The cumulative evidence before the 1980s showed a relatively strong positive association between melanoma and sunscreen use (cumulative OR: 2.35; 95% CI: 1.66-3.33). The strength of the association between risk of skin cancer and sunscreen use has constantly decreased since the early 1980s, and the association was no longer statistically significant from the early 1990s. *Conclusions:* While the current evidence suggests no increased risk of skin cancer related to sunscreen use, this systematic review does not confirm the expected protective benefits of sunscreen against skin cancer in the general population.

Key words: sunscreen, skin cancer, melanoma, systematic review, meta-analysis

Skin cancer is one of the most common malignancies in the world and is an important public health concern. The incidence of both melanoma and non-melanoma skin cancer has increased over the past decades [1, 2]. Globally, around 350,000 melanomas and 13 million non-melanoma skin cancers occur each year leading to approximately 81,000 deaths [3,4]. In the Unites States, the average annual number of adults treated for skin cancer increased from 3.4 million in 2002-2006 to 4.9 million in 2007-2011 [5]. During the same period, the average annual total cost for skin cancer increased from $3.6 billion to $8.1 billion.

Exposure to ultraviolet (UV) radiation from sunlight is considered a major modifiable environmental risk factor for skin cancer [6]. Therefore, primary prevention of skin cancer focuses on reducing UV exposure through sun protection behaviours. The use of sunscreen is thought to be an important adjunct to other types of protection against UV radiation from sunlight, and is a key component of public health campaigns for skin cancer prevention. However, epidemiological studies have yielded conflicting information about the relationship between risk of skin cancer and use of sunscreen. Some studies [7-11] show that regular sunscreen use could significantly reduce the risk of skin cancer while other studies [12-20] report an increased risk of skin cancer related to sunscreen application. Four previous systematic reviews have assessed the association between risk of melanoma and sunscreen use [21-24]. Despite the differences in the number of included studies and some inconsistencies in data extraction, all four reviews show no significant overall association between risk of melanoma and use of sunscreen. However, non-melanoma skin cancer, which represents more than 90% of all cases of skin cancer [4, 25], has not been addressed in previous reviews.

We conducted this systematic review and meta-analysis of observational and experimental epidemiological studies to assess the relationship between risk of skin cancer (melanoma and non-melanoma) and sunscreen use in adults and children. Besides the conventional meta-analysis, we

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performed cumulative meta-analysis to track how the body of evidence has shifted over time. We also explored the possible reasons for conflicting results across studies. We hypothesized that the strength and direction of the association between risk of skin cancer and sunscreen use may have changed significantly over the last three decades.

Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [26] to conduct and report this review. The review protocol was completed in 2015 and approved by a panel of experts, consisting of two epidemiologists and one dermatologist.

Databases and search strategy

We searched PubMed, Google Scholar, and the Virtual Health Library of the Latin American and Caribbean Center on Health Sciences Information (BIREME), which contains Medline, LILACS, and more than 20 other databases (http://bvsalud.org). All databases were initially searched from inception until November 30, 2015, with no language restrictions. We updated the literature search on May 17, 2017. We used the following search terms for PubMed: (sunscreen OR sunblock OR "suntan lotion" OR "sunburn cream" OR "sun cream" OR "block out" OR "solar protector") AND ("skin cancer" OR "skin tumor" OR "skin neoplasm" OR melanoma OR "basal cell carcinoma" OR "squamous cell carcinoma"). We used "human species" as a search limit. For Google Scholar and BIREME, we used the following search strategy: sunscreen AND ("skin cancer" OR melanoma OR "basal cell carcinoma" OR "squamous cell carcinoma"). Different types of articles (case-control, cross-sectional, cohort and controlled trial) were used as search limits on BIREME. Given the excessive number of records on Google Scholar, we searched only the titles of articles. We examined the reference lists of retrieved primary studies and systematic reviews to identify additional relevant studies.

Selection of studies

To be included in this review, studies had to meet all of the following criteria: (1) Study design: observational studies (case-control, cross-sectional or cohort) or controlled trials; (2) Participants: adults, children or both; (3) Exposure of interest: use of sunscreen classified into two or more categories according to frequency of use; (4) Outcomes: any type of skin cancer (melanoma, basal cell carcinoma or squamous cell carcinoma).
Three review authors independently assessed the titles and abstracts of all citations identified by the searches. The definitive inclusion of studies was made after reviewing the full-text articles.

Data extraction

Two review authors independently extracted the data from each study using a standardized data extraction form. We extracted the following data: (1) Study characteristics: name of the first author, year of publication, country and setting of study and study sponsor; (2) Participants: age, gender, inclusion and exclusion criteria, type of sampling and sample size; (3) Methods: study design, classification of exposure (sunscreen use), definition of outcomes (melanoma, basal cell carcinoma, and squamous cell carcinoma), instruments for data collection or data source, potential confounders, and statistical analysis methods; and (4) Results: for case-control studies: the number of cases, number of controls, number of exposed and non-exposed in each group, crude and/or adjusted odds ratio (OR), and 95% confidence intervals (95% CI); for cross-sectional studies and cohort studies: the total number of participants, number of participants in exposed and non-exposed groups, number of persons with skin cancer in each group, crude and/or adjusted relative risk (RR) and 95% CI; for randomized controlled trials: the number of participants in the intervention and control groups, number of persons with skin cancer in each group, RR, and 95% CI.
We obtained the altitude (meters from sea level) and latitude (degrees from the equator) of the study setting from MyGeoPosition.com (http://mygeoposition.com). For multicentre studies, we used only geographical data from the coordinating centre.

Study quality assessment

Two review authors independently assessed the quality of each study according to the criteria of the National Institutes of Health (NIH) [27, 28]. The study quality was rated good, fair or poor, mainly based on the potential risk of selection bias, information bias, measurement bias, and confounding factors.

Statistical analysis

We used the random-effects model for conventional and cumulative meta-analysis. The association between risk of skin cancer and sunscreen use was assessed by pooled OR and 95% CI. When RR and 95% CI were used as the measures of association in the primary studies, we estimated the OR and 95% CI by reconstructing a 2×2 contingency table. If there were no available data for reconstruction, we used the RR and 95% CI for the meta-analysis given that the RR is close to the OR when the outcome is a relatively uncommon event such as skin cancer. For the overall meta-analysis, we combined two or more categories of sunscreen use as a single category "sunscreen use", compared to the reference category "no or rare use.
We assessed the heterogeneity of results between studies using I^2 statistic that ranges from 0% to 100%, with values of 25%, 50%, and 75% corresponding to low, moderate, and high heterogeneity, respectively [29].
To investigate the possible sources of heterogeneity, we conducted a prior subgroup analyses based on type of skin cancer, study design, sampling method, control for confounding factors, age group, date of data collection, latitude of study location, and comparison of the frequency of sunscreen use. We also conducted a post-hoc subgroup analysis according to study quality. We conducted meta-regression to assess the influence of geographical factors (altitude and latitude) of study location on the sunscreen effects.

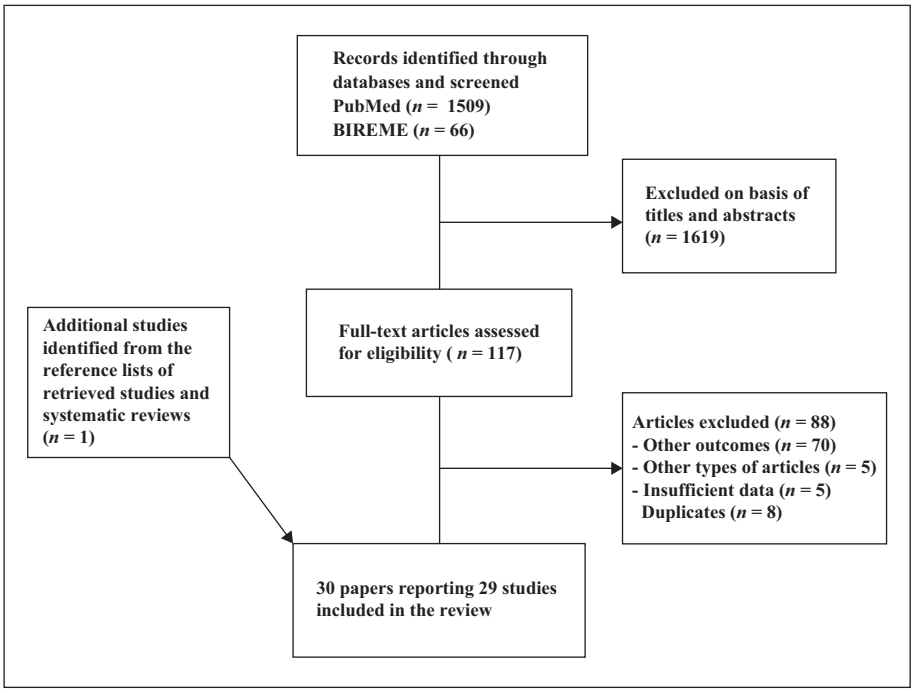

Figure 1. PRISMA flow diagram of study selection showing the process of identification, screening, assessment for eligibility, and inclusion of studies.

We assessed publication bias using a funnel plot and Egger's test. All meta-analyses were performed using Stata version 11.0 (Stata-Corp, College Station, TX, USA).

Results

The search strategy identified 1,736 records from PubMed, BIREME and Google Scholar, and 29 articles met the inclusion criteria. One additional paper was found through reviewing the reference lists of systematic reviews. Thus, a total of 30 papers [7-20, 30-45] reporting 29 studies were included in the review (*figure 1*). *Table 1* summarizes the characteristics of the 29 included studies, of which 28 were observational studies (25 case-control, two cohort, and one cross-sectional) and one was a randomized controlled trial. A total of 313,717 participants (10,670 cases of skin cancer) were recruited from 13 countries across three continents (11 studies from America, 12 studies from Europe, and six studies from Asia-Pacific).

The overall meta-analysis including all 29 studies showed no significant association between the risk of skin cancer and sunscreen use (OR = 1.08; 95% CI: 0.91-1.28; I^2 = 89.4%). The pooled OR was 1.11 (95% CI: 0.93-1.33; I^2 = 90.2%) for 28 observational studies.

Table 2 shows the results of subgroup analyses. The subgroup "melanoma" included 25 studies [7-10, 12-20, 31, 33-36, 38, 39, 41-45] involving a total of 203,948 participants (9,813 cases). Ten studies showed an increased risk of melanoma related to sunscreen use while five studies reported a protective effect of sunscreen use against melanoma. The pooled results of 25 studies revealed that the risk of melanoma was not significantly associated with sunscreen use (OR = 1.10; 95% CI: 0.92-1.33; I^2 = 89.4%).

The subgroup "non-melanoma skin cancer" included five studies [11, 30, 32, 37, 40] involving 110,914 participants (857 cases). Four studies showed no significant association, but one study revealed a protective effect of sunscreen against squamous cell carcinoma. The pooled results of five studies showed no significant association between the risk of non-melanoma skin cancer and sunscreen use (OR = 0.99; 95% CI: 0.62-1.57; I^2 = 87.3%). In the subgroup analysis according to latitude of study location, the pooled OR was 1.54 (95% CI: 1.23-1.92, I^2 = 90%) for 10 studies [13, 14, 16, 18-20, 30, 36, 39, 43] (3,933 cases) conducted at latitude $\geq 45^0$ from the equator, whereas it was 0.89 (95% CI: 0.71-1.10, I^2 = 79%) for 19 studies [7-12, 15, 17, 31-35, 37, 38, 40-42, 44, 45] (6,737 cases) conducted at latitude $<45^0$ (p = 0.001 for subgroup difference). There were no significant differences in the effect size of sunscreen between other subgroups. The substantial heterogeneity remained in all subgroups.

Figure 2 shows the results of cumulative meta-analysis. A relatively strong positive association between risk of melanoma and sunscreen use (cumulative OR = 2.35; 95% CI: 1.66-3.33) was observed when the analysis included only three studies [12,15,16] conducted before the 1980s, involving a total of 1,364 participants (619 cases of melanoma). The strength of the association between risk of skin cancer and sunscreen use has constantly reduced since the early 1980s, but the association remained statistically significant until the analysis included 13 studies [8, 10, 12-16, 18, 19, 30-33] with data collection completed until the early 1990s (119,756 participants, 4,841 cases of skin cancer; cumulative OR = 1.25; 95% CI: 1.0-1.56; p = 0.05). From then on, the association was no longer statistically significant, and the cumulative point estimate of OR has continued to move towards the null hypothesis value (OR = 1). The cumulative OR and 95% CI have

Table 1. Characteristics of included studies.

Source, location	Type of cancer	Study design and sampling	Cases/sample size (*n*) Age range (yr)	Overall association between skin cancer and "sunscreen use" (OR, 95% CI)	Association between skin cancer and frequency of sunscreen use (OR/RR*/HR**, 95% CI)	Confounding factors controlled	Study quality rating
Autier *et al.*, 1995 [13], Brussels, Belgium/ France /Germany	Melanoma	Hospital-based case-control	418/856 ≥20	1.50, 1.09-2.06	Never: 1.0 Regular use: 1.50, 1.09-2.06	Age, sex, hair colour, number of holidays, weeks spent every year in sunny resorts	Fair
Bakos *et al.*, 2002 [7], Porto Alegre, Brazil	Melanoma	Hospital-based case-control	103/309 20-84	0.52, 0.31-0.87 (SPF<8, SPF8-15, SPF15+; combined as "sunscreen use")	Never: 1.0 Use of sunscreens SPF<8: 0.4, 0.2-1.0 SPF8-15: 0.3, 0.1-0.7 SPF15+: 0.1, 0.0-0.5	Age, sex, race, eye colour, hair colour, phototype, number of nevi, sunburn episodes, use of physical protection	Fair
Beitner *et al.*, 1990 [14], Sweden	Melanoma	Population-based case-control	523/1028 ?	1.58, 1.19-2.11 (seldom, often, very often; combined as "sunscreen use")	RR, 95% CI Never: 1.0 Seldom: 1.4, 0.9-2.0 Often, very often: 1.8, 1.2-2.7	Age, sex, hair colour	Fair
Cress *et al.*, 1995 [8], San Francisco, United States	Melanoma	Population-based case-control	338/1210 25-59	0.86, 0.75-0.97 (2 x 2 contingency table reconstructed; 4 tan groups combined; almost always, sometimes; combined as "sunscreen use")	**Tan with no burn** Almost always: 1.0 Sometimes: 1.2, 0.50-2.8 Never: 2.1, 0.99-4.3 **Burn with moderate tan** Almost always: 1.0 Sometimes: 4.8, 1.7-13.2 Never: 4.2, 1.6-11.0 **Burn with light tan** Almost always: 1.0 Sometimes: 1.4, 0.78-2.6 Never: 1.4, 0.82-2.5 **Burn with no tan** Almost always: 1.0 Sometimes: 1.5, 0.76-3.1 Never: 1.7, 0.91-3.4	No	Fair

Table 1. (*Continued*)

Source, location	Type of cancer	Study design and sampling	Cases/sample size (*n*) Age range (yr)	Overall association between skin cancer and "sunscreen use" (OR, 95% CI)	Association between skin cancer and frequency of sunscreen use (OR/RR*/HR**, 95% CI)	Confounding factors controlled	Study quality rating
Espinosa Arranz *et al*., 1999 [9], **Madrid, Spain**	Melanoma	Hospital-based case-control	116/351 21-87	0.47, 0.34-0.71 (with OR converted to "no sunscreen use")	Use of sunscreen Yes: 1.0 No: 2.1, 1.4-2.9	Age, skin type, naevi count	Fair
Fargnoli *et al.*, 2004 [45], L'Aquila, Italy	Melanoma	Hospital-based case-control	100/300 18-74	0.92, 0.55-1.56	Use of sunscreen No: 1.0 Yes: 0.92, 0.55-1.56	Age, gender, ethnicity, hair colour, eye colour, skin type, number of melanocytic naevi	Fair
Ghiasvand *et al.*, 2016 [43], Oslo, Norway	Melanoma	Population-based cohort	543/109,886 40-75	1.25, 0.97-1.6 (2 x 2 contingency table reconstructed; consistently SPF <15, SPF ≥15 on at least one occasion, none/SPF <15-, SPF <15/none; combined as "sunscreen use")	Sunscreen use in high/low latitudes reported at both baseline and follow-up, HR, 95% CI SPF: <15/SPF < 15 (consistently SPF<15: 1.0 SPF ≥15 on at least one occasion: 0.69, 0.55-0.88 None/SPF <15, SPF <15/none: 0.92, 0.75-1.14 None/none: 0.63, 0.46- 0.86	Age, hair colour, freckling, ambient UV radiation of residence, cumulative number of weeks sunbathing, cumulative number of sunburns, indoor tanning	Good
Gon *et al*., 2011 [40], Londrina, Brazil	Basal cell carcinoma	Hospital-based case-control	127/407 18-80	1.69, 0.82-3.49 (with OR, converted to "never")	Sunscreen use Frequently: 1.0 Never or rarely: 0.59, 0.29-1.21	Age, sex, eye colour, hair colour, skin type, family history of skin cancer, presence of actinic keratosis	Fair
Graham *et al.*, 1985 [15], New York, United States	Melanoma	Hospital-based case-control	218/419 All	2.20, 1.2-4.1	Sun screening lotion No use: 1.0 Use: 2.20, 1.20-4.10	No	Poor

Table 1. (*Continued*)

Source, location	Type of cancer	Study design and sampling	Cases/sample size (*n*) Age range (yr)	Overall association between skin cancer and "sunscreen use" (OR, 95% CI)	Association between skin cancer and frequency of sunscreen use (OR/RR*/HR**, 95% CI)	Confounding factors controlled	Study quality rating
Green *et al*., 1999 [37], Queensland, Australia	Basal cell and squamous cell carcinomas	Randomized controlled trial	128 (basal cell carcinoma) + 47 (squamous cell carcinoma)/1,383 25-75	Basal cell carcinoma 1.03, 0.73-1.46 Squamous cell carcinomas 0.88, 0.50-1.55	Broad-spectrum sunscreen SPF 15+, RR, 95% CI Basal cell carcinoma No daily sunscreen: 1.0 Daily sunscreen: 1.03, 0.73-1.46 Squamous cell carcinoma No daily sunscreen: 1.0 Daily sunscreen: 0.88, 0.50-1.55	Randomization	Good
Green *et al*., 2011 [38], Queensland, Australia	Melanoma	10-year follow-up of the trial of Green *et al*. 1999	33/1,621 35-85	0.49, 0.24-1.02	Broad-spectrum sunscreen SPF 15+, HR, 95% CI No daily sunscreen: 1.0 Daily sunscreen: 0.49, 0.24- 1.02	Sex, skin type, numbers of nevi, previous history of skin cancer, sun exposure	Good
Grodstein *et al*., 1995 [32], Boston, United States	Squamous cell carcinoma	Population-based cohort	197/107,900 30-55	1.11, 0.83-1.66 (with RR, converted to "no sunscreen use")	RR, 95% CI Use sunscreen: 1.0 No sunscreen: 0.90, 0.60-1.20	Age, smoking, region, hair colour, reaction to sun, number of sunburns, tendency to tan, number of moles, time spent in the sun	Good
Herzfeld *et al*., 1993[12], United States	Melanoma	Population-based case-control	324/739 ≥ 18	2.60, 1.40-4.70	Suntan lotion Never: 1.0 Always: 2.60, 1.40-4.70	Age, sex, race, residence	Data not available

Table 1. (*Continued*)

Source, location	Type of cancer	Study design and sampling	Cases/sample size (*n*) Age range (yr)	Overall association between skin cancer and "sunscreen use" (OR, 95% CI)	Association between skin cancer and frequency of sunscreen use (OR/RR*/HR**, 95% CI)	Confounding factors controlled	Study quality rating
Holly *et al.*, 1995 [10], San Francisco, United States	Melanoma	Population-based case-control	452/1,382 25-59	0.47, 0.36-0.59 (3 groups combined; with OR, converted to "never")	Sunscreen use **Cutaneous malignant melanoma** Almost always: 1.0 Sometimes: 1.50, 1.10-2.20 Never: 2.10, 1.50-3.0 **Superficial spreading melanoma** Almost always: 1.0 Sometimes: 1.70, 1.20-2.60 Never: 2.20, 1.50-3.2 **Nodular melanoma** Almost always: 1.0 Sometimes: 0.8, 0.33-1.90 Never: 2.0, 1.0-4.0	Age, ethnicity, hair colour, skin colour, history of skin cancer, sunburns up to 12 yr, skin reaction to sun, number of large nevi	Fair
Holman *et al.*, 1986 [31], Perth, Australia	Melanoma	Population-based case-control	511/1,022 <80	1.10, 0.83-1.45 (2 groups combined as "sunscreen use")	**Duration of use** < 10 yr Never: 1.0 Sunscreen use: 1.06, 0.71-1.57 **Duration of use** ≥ 10 yr Never: 1.0 Sunscreen use: 1.15, 0.78-1.68	Age, sex, residence, hair colour, ethnicity, skin reaction to sunlight, age at arrival in Australia	Fair

Table 1. (*Continued*)

Source, location	Type of cancer	Study design and sampling	Cases/sample size (*n*) Age range (yr)	Overall association between skin cancer and "sunscreen use" (OR, 95% CI)	Association between skin cancer and frequency of sunscreen use (OR/RR*/HR**, 95% CI)	Confounding factors controlled	Study quality rating
Klepp *et al*., 1979 [16], Montebello, Norway	Melanoma	Hospital-based case-control	77/206 ≥ 20	2.26, 1.25-4.09 (2 x 2 contingency table reconstructed; sometimes, quite often, almost always, combined as "sunscreen use")	Sun lotion/oil, RR Almost never/very rarely: 1.0 Sometimes /quite often/almost always: 2.27	No	Poor
Klug *et al*., 2010 [33], United States	Melanoma	Hospital-based case-control	717/1,662 20-79	0.90, 0.7-1.19	Sunscreen: No use: 1.0 Sunscreen use: 0.90, 0.70-1.19	Age, gender, study site, UVB intensity at site of residency, hours outdoors as an adult, tan-type, number of sunburns	Fair
Kricker *et al*., 1995 [30], Nedlands, Australia	Basal cell carcinoma	Population-based case-control	192/892 40-64	1.51, 0.99-2.31 (half the time or more: 1-9 years, 10+ years, combined as "sunscreen use")	Sunscreen, SPF10+ Never, <half of the time: 1.0 half the time or more: 1-9 years: 1.92, 1.17-3.13 10+ years: 1.25, 0.82-1.90	Age, sex, ability to tan and site	Fair
Lazovich *et al*., 2011 [41], Minnesota, United States	Melanoma	Population-based case-control	1167/2,268 25-59	1.07, 0.86-1.34 (Middle, frequent in both decades, combined as "sunscreen use")	Sunscreen SPF15+ during outdoor activities Non-user in both decades: 1.0 Middle: 1.06, 0.80-1.40 Frequent in both decades: 1.10, 0.77-1.57	Age, gender, phenotypic risk score, moles, high income, college education, family history of melanoma, lifetime sunburns, routine sun exposure, activity leading to sun exposure, occasional indoor tanning	Fair

Table 1. (*Continued*)

Source, location	Type of cancer	Study design and sampling	Cases/sample size (*n*) Age range (yr)	Overall association between skin cancer and "sunscreen use" (OR, 95% CI)	Association between skin cancer and frequency of sunscreen use (OR/RR*/HR**, 95% CI)	Confounding factors controlled	Study quality rating
Luiz *et al.,* 2012 [42], São Paulo, Brazil	Melanoma	Hospital-based case-control	202/424 15-79	0.32, 0.11-0.97 (with OR, converted to "never/almost never")	Lifetime sunscreen use Often: 1.0 Occasionally: 3.53, 0.59-21.21 Never/almost never: 3.08, 1.03-9.22	Age, sex, educational level, ethnicity, eye colour, sunburn at 15-19 yr, lifetime severe sunburn	Fair
Naldi *et al.,* 2000 [36], Milan, Italy	Melanoma	Hospital-based case-control	542/1,080 ?	0.89, 0.69-1.15 (Sometimes, often, combined as "sunscreen use")	Never: 1.0 Sometimes: 0.97, 0.69-1.35 Often: 0.80, 0.54-1.17	Age, sex, geographic area, education, skin, eye, and hair colour, number of freckles, large nevi, history of sunburns, tanning pattern, sunny holidays	Fair
Olsen *et al.*, 2015 [17], Queensland, Australia	Melanoma	Population-based cross-sectional	1433/40,172 40-69	1.56, 1.41-1.73 (2 x 2 contingency table reconstructed)	Prevalence proportion ratio No regular sunscreen use: 1.0 Regular sunscreen use: 1.77, 1.59-1.97	Age, sex, educational level	Fair
Osterlind *et al.*, 1988 [18], Copenhagen, Denmark	Melanoma	Population-based case-control	474/1,400 20-79	1.22, 1.01-1.47 (Occasional/always used, combined as "sunscreen use")	RR, 95% CI Never: 1.0 Occasional use: 1.30, 0.99 = 1.60 Always: 1.10, 0.8-1.50	Constitutional factors, sex, age	Fair

Table 1. (*Continued*)

Source, location	Type of cancer	Study design and sampling	Cases/sample size (*n*) Age range (yr)	Overall association between skin cancer and "sunscreen use" (OR, 95% CI)	Association between skin cancer and frequency of sunscreen use (OR/RR*/HR**, 95% CI)	Confounding factors controlled	Study quality rating
Ródenas *et al*., 1996 [44], Granada, Spain	Melanoma	Hospital-based case-control	105/243 20-29	0.41, 0.15-1.15 (Sometimes, always, combined as "sunscreen use")	Never: 1.0 Sometimes: 0.60, 0.26-1.42 Always: 0.20, 0.04-0.79	Age, skin colour, skin type, hours of sun exposure, number of nevi	Fair
Sànchez and Nova, 2013 [11], Bogota, Colombia	Squamous cell carcinoma	Hospital-based case-control	166/332 32-94	0.43, 0.33-0.56 (Failure to use sunscreen before age 15 yr, age 15-30 yr, after age 30 yr; combined as "no use"; with OR, "no use")	Use sunscreen: 1.0 Failure to use sunscreen before age 15 yr: 2.96, 0.15-176.9 Failure to use sunscreen aged: 15-30 yr 0, 0-3.25 Failure to use sunscreen after age: 30 yr 1.74, 0.22-13.6	No	Poor
Westerdahl *et al*., 1995 [19], Lund, Sweden	Melanoma	Population-based case-control	400/1,040 15-75	1.48, 1.08-2.03 (Sometimes, almost always, combined as "sunscreen use")	Never: 1.0 Sometimes 1.30, 0.90-1.90 Almost always 1.80, 1.10-2.80	Sunburn, sunbathing, outdoor employment, eye and hair colour, freckling, naevi	Fair
Westerdahl *et al*., 2000 [39], Lund, Sweden	Melanoma	Population-based case-control	571/1,484 16-80	1.28, 0.89-1.84 (Sometimes, always initially + sometimes, always, combined as "sunscreen use")	Never 1.0 Sometimes: 1.30, 0.90-1.90 Always initially + sometimes: 0.90, 0.60-1.50 Always: 1.80, 1.10-2.90	Hair colour, sunburns, sunbathing, duration of each episode of sunbathing	Fair

Table 1. (*Continued*)

Source, location	Type of cancer	Study design and sampling	Cases/sample size (*n*) Age range (yr)	Overall association between skin cancer and "sunscreen use" (OR, 95% CI)	Association between skin cancer and frequency of sunscreen use (OR/RR*/HR**, 95% CI)	Confounding factors controlled	Study quality rating
Whiteman *et al.*, 1997 [34], Queensland, Australia	Melanoma	Population-based case-control	52/208 ≤15	1.21, 0,69-2.14 (Sunscreen on holiday and at school; sometimes, often, always; combined as "sunscreen use")	**Sunscreen use on holiday** Never/rarely: 1.0 Sometimes: 1.50, 0.30-8.20 Often: 1.50, 0.30-7.4 Always: 2.20, 0.40-11.6 **Sunscreen use at school** Never/rarely: 1.0 Sometimes: 0.80, 0.30-2.10 Often: 1.60, 0.50-5.50 Always 0.70, 0.10-6.0	Sex, school, grade, tanning ability, freckles, number of nevi	Fair
Wolf *et al.*, 1998 [20], Graz, Austria	Melanoma	Hospital-based case-control	193/512 15-89	3.47, 1.81-6.64 (Often vs. never)	Never: 1.0 Rarely: 1.30, 0.70-2.39 Often: 3.47, 1.81-6.64	Age, sex, hair and skin colour, skin phototype, sun sensitivity, sunbathing, sunburns	Fair
Youl *et al.*, 2002 [35], Queensland, Australia	Melanoma	Population-based case-control	201/406 15-19	0.97, 0.71-1.34 (2 x 2 contingency table reconstructed; sunscreen use at home and on holiday; often/always, sometimes; combined as "sunscreen use")	**Lifetime sunscreen use at home** Often/always: 1.0 Sometimes: 0.90, 0.50-1.70 Never/rarely: 0.90, 0.50-1.70 **Lifetime sunscreen use on holidays** Often/always: 1.0 Sometimes: 1.30, 0.80-2.00 Never/rarely: 1.0, 0.50-1.80	Age, sex, residency	Fair

**RR: relative risk (risk ratio, rate ratio, relative risk); **HR: hazard ratio; SPF: sun protection factor.*

Table 2. Subgroup analyses of the association between risk of skin cancer and sunscreen use.

Subgroups	Number of studies	Number of cases	OR (95% CI)	I^2 (%) for heterogeneity
Type of skin cancer				
Melanoma	25	9813	1.11 (0.93-1.33)	89.3
Non-melanoma	5	857	0.99 (0.62-1.57)	87.3
Study design				
Retrospective (case-control, cross-sectional)	26	9722	1.08 (0.90-1.30)	89.8
Prospective (cohort and randomized trial)	3	948	1.09 (0.67-1.76)	86.1
Study quality				
Good	3		1.08 (0.67-1.75)	86.1
Fair	23		1.06 (0.89-1.27)	88.3
Poor	3		1.25 (0.36-4.45)	95.2
Sampling method				
Population-based	16	7586	1.17 (0.97-1.42)	87.5
Hospital- or clinic-based	13	3084	0.96 (0.69-1.35)	87.5
Control for confounding factors				
At least one factor	18	6585	0.99 (0.78-1.27)	87.1
Factors including skin colour/type and/or hair colour	12	3983	1.00 (0.76-1.34)	86.1
No	11	4807	1.25 (0.99-1.57)	89.9
Date of data collection				
Before 1990	9	3109	1.30 (0.95-1.78)	90.1
1990-1999	13	3823	0.98 (0.79-1.21)	77.0
2000 and thereafter	7	3738	1.06 (0.68-1.65)	94.4
Latitude of study location				
$< 45^0$ from the equator	19	6737	0.89 (0.72-1.11)	90.2
$\geq 45^0$ from the equator	10	3933	1.54 (1.23-1.92)	79.0
Frequency of sunscreen use				
Maximum frequency (always/almost always vs. never/rarely)	10	2995	1.14 (0.78-1.68)	83.1
Occasional vs. never/rarely	29	10670	1.08 (0.92-1.29)	89.3
Age groups				
Adults and adolescents	27	10417	1.08 (0.90-1.29)	90.0
Children and adolescents	2	253	1.02 (0.78-1.35)	0

remained almost unchanged since the early 2000s, even though seven studies [11, 17, 40-43, 45] involving a total of 187,747 participants (3,738 cases of skin cancer) were added to the analysis.

The meta-regression analysis showed an inverse relationship between the OR (log scale) and the altitude of study setting (coefficient of -0.0004; $p = 0.02$). However, the results were not statistically significant after adjusting for covariates ($p = 0.69$). The meta-regression analysis revealed a significant positive association between the OR (log scale) and the latitude of study setting (coefficient of 0.02; $p = 0.003$), *i.e.* the higher the absolute latitude from the equator, the greater the odds ratio, and the less the protective effect of sunscreen against skin cancer, or even the higher the risk of skin cancer associated with sunscreen use. The results remained statistically significant after adjusting for altitude, type of cancer, study design, sampling method, control of confounding factors (skin type/colour and/or hair colour), and date of data collection (coefficient of 0.023; $p = 0.01$).

The funnel plot and Egger's test did not reveal a significant publication bias (*figure 3*).

Discussion

This systematic review and meta-analysis of 28 observational studies and one community-based randomized trial, with a total of 313,717 participants (10,670 cases), showed no significant overall association between the risk of melanoma and non-melanoma skin cancers and use of sunscreen. The geographical latitude seemed to influence the effects of sunscreen, that is, the higher the latitude where people live, the less the protective effect of sunscreen against skin cancer.

The cumulative evidence before the 1980s revealed a relatively strong positive association between the risk of melanoma and sunscreen use. However, the strength of the association between risk of skin cancer and sunscreen use

Study	Type of cancer	Dates of data collection	Cumulative number of cases	Cumulative sample size	Cumulative odds ratio ES (95% Cl)
Klepp 1979	Melanoma	1974-1975	77	206	2.26 (1.25, 4.09)
Herzfeld 1993	Melanoma	1977-1979	401	945	2.42 (1.58, 3.70)
Graham 1985	Melanoma	1974-1980	619	1364	2.35 (1.66, 3.33)
Holman 1986	Melanoma	1980-1981	1130	2386	1.85 (1.14, 3.01)
Beitner 1990	Melanoma	1978-1983	1653	3414	1.72 (1.24, 2.39)
Osterlind 1988	Melanoma	1982-1985	2127	4814	1.56 (1.21, 2.00)
Cress 1995	Melanoma	1981-1986	2465	6024	1.43 (1.08, 1.90)
Holly 1995	Melanoma	1981-1986	2917	7406	1.26 (0.91, 1.75)
Kricker 1995	Basal-cell carcinoma	1987-1988	3109	8298	1.28 (0.95, 1.74)
Grodstein 1995	Squamous-cell carcinoma	1982-1990	3306	116198	1.26 (0.95, 1.66)
Westerdahl 1995	Melanoma	1988-1990	3706	117238	1.28 (0.98, 1.65)
Autier 1995	Melanoma	1991-1992	4124	118094	1.29 (1.01, 1.65)
Klug 2010	Melanoma	1991-1992	4841	119756	1.25 (1.00, 1.56)
Ródenas 1996	Melanoma	1989-1993	4946	119999	1.21 (0.97, 1.51)
Espinosa Arranz 1999	Melanoma	1990-1994	5062	120350	1.13 (0.90, 1.42)
Whiteman 1997	Melanoma	1987-1994	5114	120558	1.14 (0.91, 1.41)
Wolf 1998	Melanoma	1993-1994	5307	121070	1.20 (0.96, 1.50)
Youl 2002	Melanoma	1987-1994	5508	121476	1.18 (0.96, 1.46)
Naldi 2000	Melanoma	1992-1995	6050	122556	1.15 (0.95, 1.40)
Green 1999	Basal- & Squamous-cell carcinoma	1992-1996	6225	124177	1.14 (0.95, 1.38)
Green 2011	Melanoma	1992-1996	6258	124177	1.11 (0.92, 1.34)
Westerdahi 2000	Melanoma	1995-1997	6829	125661	1.12 (0.94, 1.34)
Bakos 2002	Melanoma	1995-1998	6932	125970	1.09 (0.91, 1.30)
Fargnoli 2004	Melanoma	2000-2001	7032	126270	1.08 (0.91, 1.28)
Gon 2011	Basal-cell carcinoma	2006-2007	7159	126677	1.09 (0.92, 1.29)
Lazovich 2011	Melanoma	2004-2007	8326	128945	1.09 (0.93, 1.28)
Luiz 2012	Melanoma	2004-2008	8528	129369	1.07 (0.91, 1.25)
Ghiasvand 2016	Melanoma	1997-2010	9071	273213	1.11 (0.94, 1.31)
Olsen 2015	Melanoma	2011	10504	313385	1.12 (0.95, 1.32)
Sànchez 2013	Squamous-cell carcinoma	2010-2011	10670	313717	1.08 (0.91, 1.29)

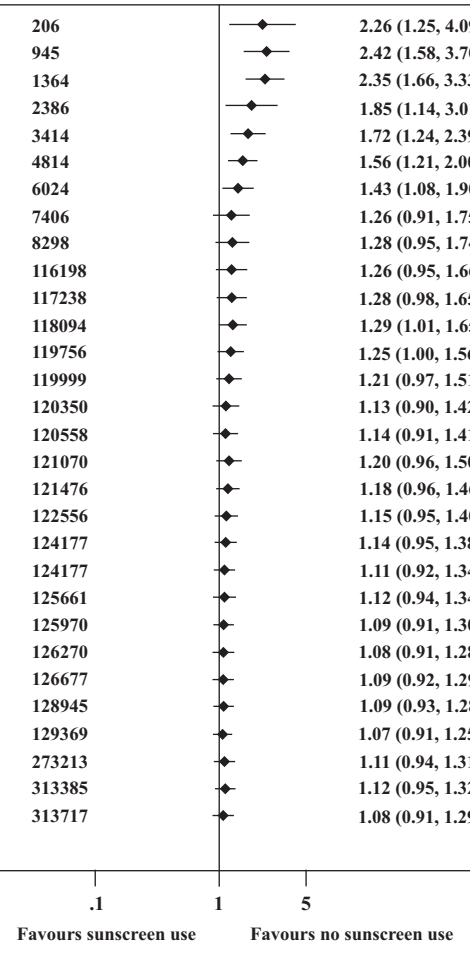

Figure 2. Cumulative meta-analysis of the association between skin cancer and sunscreen use. The solid squares represent point estimates of cumulative odds ratio and the *horizontal lines represent 95% CIs.*

has constantly reduced since the early 1980s, and the association was no longer statistically significant from the early 1990s. Several hypotheses have been proposed to explain the positive association between risk of skin cancer, especially melanoma, and use of sunscreen, as shown by earlier observational studies, including compensation hypothesis, inconsistent use, vitamin D deficiency, and lack of control for confounding factors [46-49]. The median Sun Protection Factor (SPF) of commonly used sunscreens in the 1970s and 1980s was 4-10 [48], and these sunscreens incorporated active UV filters, limited largely to the UVB waveband. People who use low SPF/UVB sunscreens may stay longer in the sun because of reduced risk of sunburn, and thus increase their exposure to UVA radiation which may lead to an increased risk of carcinogenesis.

The constant shift of the cumulative point estimate of the association between skin cancer and sunscreen use towards the null hypothesis value through the 1990s may be partly explained by the improved efficacy of sunscreens in protecting against solar UV radiation, particularly UVA rays, and the growing public awareness of the risk of excessive sun exposure. These results may alleviate public concern about the increased risk of skin cancer related to sunscreen use, as reported by earlier epidemiological studies. However, the expected protective benefits of sunscreen against skin cancer were not revealed by the cumulative meta-analysis, even though seven new studies conducted in the 2000s, involving a large number of participants and cases of skin cancer, were added to the analysis. This may raise the question as to whether the use of sunscreens really protects against skin cancer.

A 4.5-year community-based randomized controlled trial conducted at Nambour, Australia, has been widely cited to show the efficacy of daily use of a broad-spectrum SPF15+ sunscreen in protecting against skin cancers in adults [37, 38, 50]. However, caution should be taken when extrapolating the results of this trial to the general population. This trial was conducted in the low-latitude township of Nambour, situated at 26° south latitude, where cumulative sun exposure may affect the risk of skin cancer. The

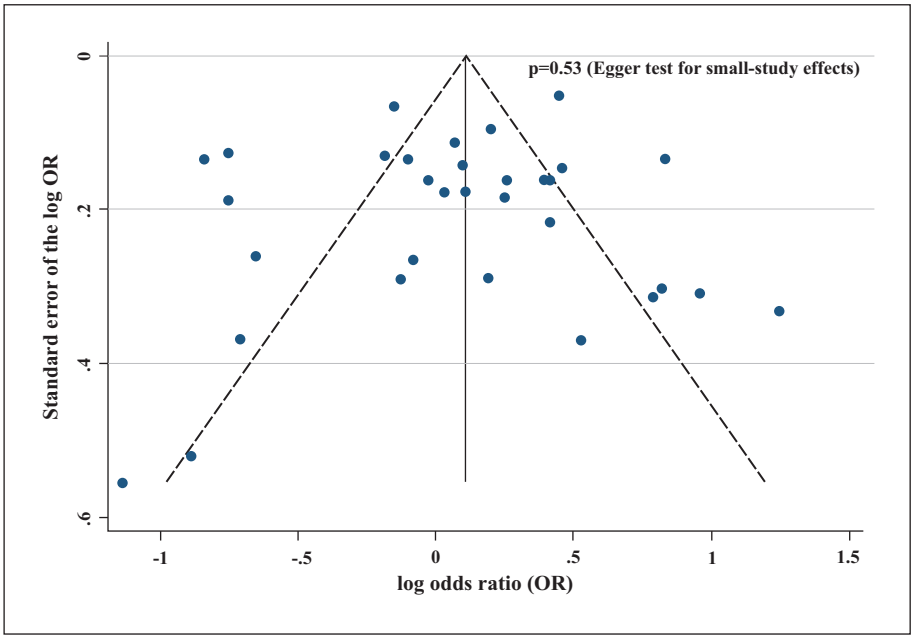

Figure 3. Funnel plot with pseudo 95% confidence limits, with log odds ratio (OR) against its standard error. The circles represent risk estimates for each study. The vertical line represents the pooled effect estimate expressed as a log OR. Dashed lines represent pseudo-95% confidence limits. The Egger test (p = 0.53) suggests no small-study effects.

practicality and the cost of daily application of sunscreen should also be considered.

While randomized trials assess the efficacy of an intervention under "ideal" circumstances, epidemiological studies can provide valid insights into the effectiveness of the intervention in the "real" world. Why have most epidemiological studies, even recently conducted ones, not demonstrated the expected effects of sunscreens in protecting against skin cancer in the general population? The inappropriate application of sunscreen has been postulated as the major cause for the lack of protective benefits of sunscreen, even broad-spectrum ones [48, 51, 52]. People usually do not apply enough sunscreen to achieve the claimed SPF, and the actual SPF received may be only 20% to 50% of the labelled SPF marked on the bottle. Additionally, reapplication is generally considered a key element for obtaining the most effective protection from sunscreen [52, 53], but many people do not regularly reapply sunscreen [54]. Vitamin D deficiency and confounding factors may also have contributed to the lack of protective effects of sunscreen use, as shown by epidemiological studies.

The meta-regression analysis revealed an inverse relationship between protective effect of sunscreen against skin cancer and latitude of study location. Additionally, the subgroup analysis showed that use of sunscreens was associated with a non-significant decreased risk of skin cancer at latitude $<45^\circ$ from the equator, whereas use of sunscreens could significantly increase the risk of skin cancer at latitude $\geq 45^\circ$. The influence of latitude on the association between the risk of melanoma and sunscreen use has previously been reported by Gorham *et al.* [23]. The authors hypothesized that the influence of latitude on the effect of sunscreen could be explained by differences in skin type, rather than geophysical effects of ultraviolet radiation at higher latitudes. However, the findings of the present systematic review do not totally support this hypothesis given that the latitudinal dependence of the effect of sunscreen on the risk of skin cancer remains after adjusting for several covariates, including skin type and hair colour. We believe that the influence of the latitude on the effect of sunscreen could be mediated by UV radiation levels. It has been reported that, within some countries, the incidence rates of melanoma and non-melanoma skin cancers increase with decreasing latitude, *i.e.* higher UV radiation levels [55-58]. It seems reasonable that regular sunscreen use would have a greater protective effect for persons at higher risk of skin cancer because they live at lower latitudes and are exposed to higher levels of UV radiation. In contrast, for people who live at higher latitudes where UV radiation is weaker and less constant, regular sunscreen use may provide less protection against skin cancer, or even increase the risk of carcinogenesis.

While the current evidence suggests no increased risk of skin cancer related to sunscreen, this systematic review and meta-analysis does not confirm the expected protective benefits of sunscreen use against skin cancer in the general population. These results support a wide range of strategies besides sunscreen use for primary prevention of skin cancer. These strategies include wearing hats and protective clothing, seeking shade, limiting exposure during peak sun hours, and avoiding tanning beds and other artificial UV radiation sources [59-61].

Meta-analyses of observational studies are generally prone to heterogeneity and bias [62, 63]. In this study, there was substantial heterogeneity with regards to the overall meta-analysis and the heterogeneity remained high in subgroup analyses according to study design, study quality, sampling method, control for confounding factors, age group, frequency of sunscreen use, and date of data collection. As many of these factors could simultaneously affect the study results, it is difficult to identify the independent contribution of each factor to the heterogeneity. Moreover, other covariates may also influence the effects

of sunscreens and contribute to the heterogeneity. These may include genetic predisposition, behaviour and lifestyle habits, socioeconomic status, sun exposure habits, use of other sun protection methods, components of sunscreens, and techniques of sunscreen application. Unfortunately, these covariates have rarely been taken into account in primary studies.

The quality of evidence provided by this review could only be graded as low, mainly due to inconsistency of the results between studies, retrospective design, and potential risk of bias (selection bias, information bias, and confounding factors) in most of the primary studies. Given that the quality of current evidence is low and new sunscreen products that efficiently block both UVA and UVB have been available on the market for more than two decades, it is time to investigate the effects of new broad-spectrum sunscreens on protecting against skin cancer in the general population. Randomized controlled trials are considered the "gold standard" for assessing the efficacy of an intervention. However, such design requires large sample size and long trial duration. Moreover, the applicability of the trial results to the general population is limited. Prospective, real-world, population-based observational studies would be good options. Future studies should involve collection of data on both sunscreen use and appropriateness of application (amount of sunscreen applied and reapplication). The data on confounding factors, such as genetic predisposition, behaviour and lifestyle habits, socioeconomic status, sun sensitivity, sun exposure, and use of other sun protection methods, should be collected and taken into account in the analysis. The potential impact of latitude on the effects of sunscreen on skin cancer risk should also be assessed in further studies. ■

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References

1. Merrill SJ, Ashrafi S, Subramanian M, Godar DE. Exponentially increasing incidences of cutaneous malignant melanoma in Europe correlate with low personal annual UV doses and suggests 2 major risk factors. *Dermatoendocrinol* 2015; 7: e1004018.

2. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol* 2012; 166: 1069-80.

3. Lucas R, McMichael T, Smith W, Armstrong B. Solar ultraviolet radiation: global burden of disease from solar ultraviolet radiation. In: *Environmental Burden of Disease Series No. 13*. Geneva: WHO Public Health and the Environment, 2006.

4. Karimkhani C, Green AC, Nijsten T, *et al*. The global burden of melanoma: results from the Global Burden of Disease Study 2015. *Br J Dermatol* 2017; 177: 134-40.

5. Guy GP Jr., Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med* 2015; 48: 183-7.

6. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B* 2001; 63: 8-18.

7. Bakos L, Wagner M, Bakos RM, Leite CS, Sperhacke CL, Dzekaniak KS, *et al*. Sunburn, sunscreens, and phenotypes: some risk factors for cutaneous melanoma in southern Brazil. *Int J Dermatol* 2002; 41: 557-62.

8. Cress RD, Holly EA, Ahn DK. Cutaneous melanoma in women. V. Characteristics of those who tan and those who burn when exposed to summer sun. *Epidemiology* 1995; 6: 538-43.

9. Espinosa Arranz J, Sanchez Hernandez JJ, Bravo Fernandez P, *et al*. Cutaneous malignant melanoma and sun exposure in Spain. *Melanoma Res* 1999; 9: 199-205.

10. Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. *Am J Epidemiol* 1995; 141: 923-33.

11. Sánchez G, Nova J. Risk factors for squamous cell carcinoma, a study by the National Dermatology Centre of Colombia. *Actas Dermosifiliogr* 2013; 104: 672-8.

12. Herzfeld PM, Fitzgerald EF, Hwang SA, Stark A. A case-control study of malignant melanoma of the trunk among white males in upstate New York. *Cancer Detect Prev* 1993; 17: 601-8.

13. Autier P, Doré JF, Schifflers E, *et al*. Melanoma and use of sunscreens: an Eortc case-control study in Germany, Belgium and France. The EORTC Melanoma Cooperative Group. *Int J Cancer* 1995; 61: 749-55.

14. Beitner H, Norell SE, Ringborg U, Wennersten G, Mattson B. Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. *Br J Dermatol* 1990; 122: 43-51.

15. Graham S, Marshall J, Haughey B, *et al*. An inquiry into the epidemiology of melanoma. *Am J Epidemiol* 1985; 122: 606-19.

16. Klepp O, Magnus K. Some environmental and bodily characteristics of melanoma patients. A case-control study. *Int J Cancer* 1979; 23: 482-6.

17. Olsen CM, Thompson BS, Green AC, Neale RE, Whiteman DC, & QSkin Sun, Health Study Group. Sun protection and skin examination practices in a setting of high ambient solar radiation: a population-based cohort study. *JAMA Dermatol* 2015; 151: 982-90.

18. Osterlind A. Epidemiology on malignant melanoma in Europe. *Acta Oncol* 1992; 31: 903-8.

19. Westerdahl J, Olsson H, Måsbäck A, Ingvar C, Jonsson N. Is the use of sunscreens a risk factor for malignant melanoma? *Melanoma Res* 1995; 5: 59-65.

20. Wolf P, Quehenberger F, Müllegger R, Stranz B, Kerl H. Phenotypic markers, sunlight-related factors and sunscreen use in patients with cutaneous melanoma: an Austrian case-control study. *Melanoma Res* 1998; 8: 370-8.

21. Dennis LK, Beane Freeman LE, VanBeek MJ. Sunscreen use and the risk for melanoma: a quantitative review. *Ann Intern Med* 2003; 139: 966-78.

22. Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case-control studies. *Am J Public Health* 2002; 92: 1173-7.

23. Gorham ED, Mohr SB, Garland CF, Chaplin G, Garland FC. Do sunscreens increase risk of melanoma in populations residing at higher latitudes? *Ann Epidemiol* 2007; 17: 956-63.

24. Xie F, Xie T, Song Q, Xia S, Li H. Analysis of association between sunscreens use and risk of malignant melanoma. *Int J Clin Exp Med* 2015; 8: 2378-84.

25. Perera E, Sinclair R. An estimation of the prevalence of non-melanoma skin cancer in the U.S. *F1000Res* 2013; 2: 107.

26. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.

27. National Heart, Lung, and Blood Institute. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Available at: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort.(accessed 09 May 2016).

28. National Heart, Lung, and Blood Institute. Quality Assessment of Case-Control Studies. Available at: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case-control.(accessed 09 May 2016).

29. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-60.

30. Kricker A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. *Int J Cancer* 1995; 60: 489-94.
31. Holman CD, Armstrong BK, Heenan PJ, *et al*. The causes of malignant melanoma: results from the West Australian Lions Melanoma Research Project. *Recent Results Cancer Res* 1986; 102: 18-37.
32. Grodstein F, Speizer FE, Hunter DJ. A prospective study of incident squamous cell carcinoma of the skin in the nurses' health study. *J Natl Cancer Inst* 1995; 87: 1061-6.
33. Klug HL, Tooze JA, Graff-Cherry C, *et al*. Sunscreen prevention of melanoma in man and mouse. *Pigment Cell Melanoma Res* 2010; 23: 835-7.
34. Whiteman DC, Valery P, McWhirter W, Green AC. Risk factors for childhood melanoma in Queensland, Australia. *Int J Cancer* 1997; 70: 26-31.
35. Youl P, Aitken J, Hayward N, *et al*. Melanoma in adolescents: a case-control study of risk factors in Queensland, Australia. *Int J Cancer* 2002; 98: 92-8.
36. Naldi L, Gallus S, Imberti GL, Cainelli T, Negri E, La Vecchia C. Sunscreens and cutaneous malignant melanoma: an Italian case-control study. *Int J Cancer* 2000; 86: 879-82.
37. Green A, Williams G, Neale R, *et al*. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 1999; 354: 723-9.
38. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol* 2011; 29: 257-63.
39. Westerdahl J, Ingvar C, Måsbäck A, Olsson H. Sunscreen use and malignant melanoma. *Int J Cancer* 2000; 87: 145-50.
40. Gon A, Minelli L. Risk factors for basal cell carcinoma in a southern Brazilian population: a case-control study. *Int J Dermatol* 2011; 50: 1286-90.
41. Lazovich D, Vogel RI, Berwick M, Weinstock MA, Warshaw EM, Anderson KE. Melanoma risk in relation to use of sunscreen or other sun protection methods. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 2583-93.
42. Luiz OC, Gianini RJ, Gonçalves FT, *et al*. Ethnicity and cutaneous melanoma in the city of Sao Paulo, Brazil: a case-control study. *PLoS One* 2012; 7: e36348.
43. Ghiasvand R, Weiderpass E, Green AC, Lund E, Veierød MB. Sunscreen use and subsequent melanoma risk: a population-based cohort study. *J Clin Oncol* 2016; 34: 3976-83.
44. Ródenas JM, Delgado-Rodríguez M, Herranz MT, Tercedor J, Serrano S. Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma: a case-control study in a Mediterranean population. *Cancer Causes Control* 1996; 7: 27-83.
45. Fargnoli MC, Piccolo D, Altobelli E, Formicone F, Chimenti S, Peris K. Constitutional and environmental risk factors for cutaneous melanoma in an Italian population. A case-control study. *Melanoma Res* 2004; 14: 151-7.
46. Garland CF, Garland FC, Gorham ED. Rising trends in melanoma. An hypothesis concerning sunscreen effectiveness. *Ann Epidemiol* 1993; 3: 103-10.
47. Weinstock MA. Do sunscreens increase or decrease melanoma risk: an epidemiologic evaluation. *J Investig Dermatol Symp Proc* 1999; 4: 97-100.
48. Diffey BL. Sunscreens and melanoma: the future looks bright. *Br J Dermatol* 2005; 153: 378-81.
49. Planta MB. Sunscreen and melanoma: is our prevention message correct? *J Am Board Fam Med* 2011; 24: 735-9.
50. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2546-8.
51. Stenberg C, Larkö O. Sunscreen application and its importance for the sun protection factor. *Arch Dermatol* 1985; 121: 1400-2.
52. Petersen B, Wulf HC. Application of sunscreen-theory and reality. *Photodermatol Photoimmunol Photomed* 2014; 30: 96-101.
53. Diffey BL. When should sunscreen be reapplied? *J Am Acad Dermatol* 2001; 45: 882-5.
54. Pruim B, Wright L, Green A. Do people who apply sunscreens, re-apply them? *Australas J Dermatol* 1999; 40: 79-82.
55. Auerbach H. Geographic variation in incidence of skin cancer in the United States. *Public Health Rep* 1961; 76: 345-8.
56. Bulliard JL, Cox B, Elwood JM. Latitude gradients in melanoma incidence and mortality in the non-Maori population of New Zealand. *Cancer Causes Control* 1994; 5: 234-40.
57. Moan J, Dahlback A, Setlow RB. Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem Photobiol* 1999; 70: 243-7.
58. Cicarma E, Juzeniene A, Porojnicu AC, Bruland ØS AC, Moan J. Latitude gradient for melanoma incidence by anatomic site and gender in Norway 1966-2007. *J Photochem Photobiol B* 2010; 101: 174-8.
59. Moyer VA, & U.S., Preventive Services Task Force. Behavioral counseling to prevent skin cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012; 157: 59-65.
60. National Institute for Health and Care Excellence. Public Health Guideline (PH32): Skin Cancer Prevention. Available at: https://www.nice.org.uk/guidance/ph32.(accessed 20 June 2017).
61. Cancer Council Australia. Preventing skin cancer. Available at: http://www.cancer.org.au/preventing-cancer/sun-protection/preventing-skin-cancer.(accessed 20 June 2017).
62. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998; 316: 140-4.
63. Dwyer T, Couper D, Walter SD. Sources of heterogeneity in the meta-analysis of observational studies: the example of SIDS and sleeping position. *J Clin Epidemiol* 2001; 54: 440-7.