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Original Article

Analysis of association between sunscreens use and risk of malignant melanoma

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Abstract: Background: Epidemiological studies evaluating the association between sunscreens use and malignant melanoma risk have produced inconsistent results. Thus, we conducted a meta-analysis to summarize the evidence from epidemiological studies of sunscreens use with the risk of malignant melanoma. Methods: Pertinent studies were identified by a search in PubMed and Web of Knowledge up to October 2014. Random-effect model was used to combine the results. Publication bias was estimated using Egger's regression asymmetry test. Results: Twenty-one studies including 7150 malignant melanoma cases about sunscreens use with the risk of malignant melanoma were included in this meta-analysis. The combined relative risk (RR) of malignant melanoma associated with sunscreens use was 1.145 (95% CI=0.912-1.438). The association was significant neither in the case-control studies nor in the cohort studies. No publication biases were found. Conclusions: Our analysis indicated that sunscreens use is not associated with the risk of malignant melanoma.

Keywords: Sunscreens, malignant melanoma, meta-analysis

Introduction

The sustained increase in malignant melanoma incidence over the past few decades highlights the fact that this disease represents a major public health management issue worldwide [1]. Exogenous sun exposure and several host features such as light complexions, skin reactivity to sun exposure, presence of dysplastic nevi, family history of melanoma, history of cancer, and immunosuppression have been identified as major risk factors for this malignancy [2-4]. An understanding of other factors, in particular behavioral factors associated with melanoma risk is however less clear. Behavioral factors are modifiable, and so it is of particular importance to study their role in the etiology of cancer.

If solar radiation is a primary risk factor for malignant melanoma, it is reasonable to conclude that reducing sun exposure via topical sunscreen use would be associated with reduced disease risk. However, the available epidemiological data are contradictory. In fact, the majority of studies suggest that sunscreen use is associated with an increased melanoma risk [5-8]. To address this uncertainty, we designed the present study to systematically evaluate the available data using rigorous meta-analytic techniques.

Methods

Search strategy and study selection

Studies were identified by a literature search of PubMed and Web of Knowledge up to October 2014. The following search terms were used: (melanoma OR skin neoplasm OR skin cancer) AND (sunscreens OR sun OR sunblock) AND (cohort OR prospective OR nested OR case-control). Moreover, we reviewed the reference lists from retrieved articles to search for further relevant studies. Two investigators searched articles and reviewed of all retrieved studies independently.

For inclusion, studies had to fulfill the following criteria: (1) have a prospective or case-control study design; (2) the exposure of interest was sunscreens use; (3) the outcome of interest

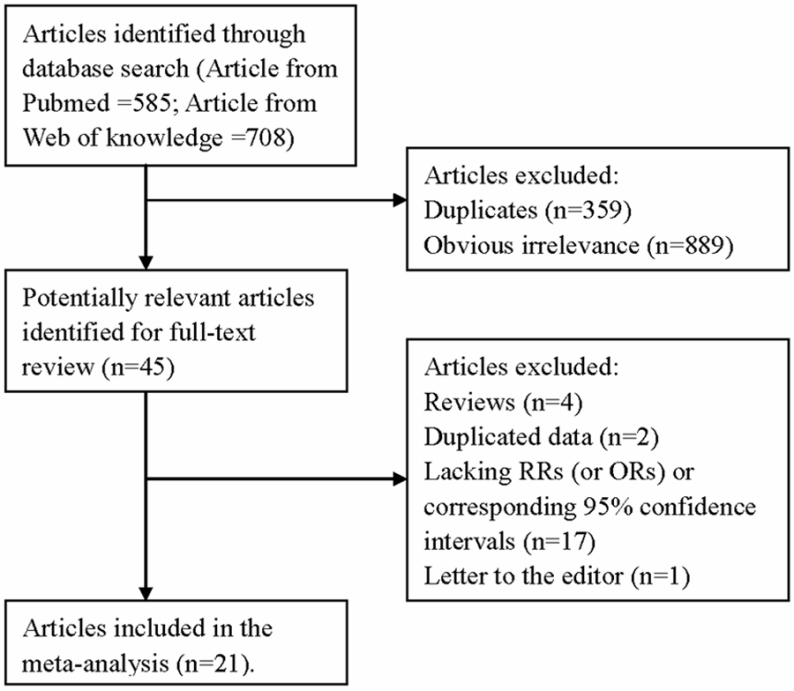

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

was malignant melanoma; and (4) relative risk (RR) or odds ratio (OR) with 95% confidence interval (CI) was provided (or data available to calculate them).

Data extraction

Two researchers independently extracted the following data from each study that met the criteria for inclusion: the first author's last name, year of publication, geographic locations, study design, sample source, the age range of study participants, the number of cases and participants. From each study, we extracted the RR that reflected the greatest degree of control for potential confounders.

Statistical analysis

The pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI, to assess the association between sunscreens use and risk of malignant melanoma. Random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [9]. The I^2 was used to assess heterogeneity, and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity [10], respectively. Meta-regression with restricted maximum likelihood estimation was performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity [11]. Publication bias was evaluated using Egger regression asymmetry test [12]. A study of influence analysis [13] was conducted to describe how robust the pooled estimator was to removal of individual studies. An individual study was suspected of excessive influence if the point estimate of its omitted analysis lay outside the 95% CI of the combined analysis. All statistical analyses were conducted with STATA version 11.0 (StataCorp LP, College Station, Texas, USA). Two-tailed p-value ≤ 0.05 was accepted as statistically significant.

Results

Search results and study characteristics

The search strategy identified 585 articles from PubMed and 708 from the Web of Knowledge, and 45 articles were reviewed in full after reviewing the title/abstract. Twenty-four of these 45 articles were subsequently excluded from the meta-analysis for various reasons. Hence, 21 articles (2 prospective studies and 19 case-control studies) [5-8, 14-30] involving 7150 malignant melanoma cases and 23434 participants were used in this meta-analysis. The detailed steps of our literature search are shown in **Figure 1**. The characteristics of these studies are presented in **Table 1**. Ten studies come from Europe, 6 from America and 5 from Oceania.

High versus low analyses

Data from 21 articles including 7150 malignant melanoma cases were used in this meta-analysis. Eight studies reported that sunscreens use could increase the risk of malignant melanoma, while no significant association was reported in

Table 1. Characteristics of studies on sunscreens use and risk of malignant melanoma

First author, year	Country	Study design	Cases, age	Frequency of Sunscreen Use	RR (95% CI)	Adjustment or matched for
Autier et al. 1995	Germany, Belgium and France	Case-control	418, ≥20	Regular use vs. never	1.50 (1.09-2.06)	Age, sex, hair color, no. of holiday weeks spent in sunny climate.
Bakos et al. 2002	Brazil	Case-control	102, 20-84	SPF15+ vs. never	0.2 (0.1-0.8)	Age, sex, race, and residence.
Beitner et al. 1990	Sweden	Case-control	523, Na	Very often/often vs. never	1.80 (1.20-2.70)	Age, sex, hair colour.
Espinoza Arranz et al. 1999	Spain	Case-control	116, 21-87	Ever vs. never	0.48 (0.34-0.71)	Skin type, nevi count, age.
Gandini et al. 2014	Italy	Prospective	139, Na	Ever vs. never	0.82 (0.70-0.96)	Place of residence, interview location, age, sex, socio-economic features.
Graham et al. 1985	United States	Case-control	404, Na	Use vs. never used	2.20 (1.20-4.10)	Na.
Green et al. 2011	Australia	Prospective	33, 25-75	Use vs. never used	0.50 (0.24-1.02)	Age, sex, phenotype, sun exposure, and history of skin cancer.
Herzfeld et al. 1993	United States	Case-control	324, ≥18	Always vs. never	2.6 (1.4-4.7)	Age, sex, race, and residence.
Holly et al. 1995	United States	Case-control	452, 25-59	Almost always vs. never	0.48 (0.33-0.67)	Age, complexion, maternal ethnicity, history of skin cancer, and sunburns up to 12 yrs of age, skin reaction to sun, host factors.
Holman et al. 1986	Australia	Case-control	507, <80	Ever vs. never	1.15 (0.78-1.68)	Host factors, age at arrival in Australia, ethnic origin.
Klepp et al. 1979	Norway	Case-control	78, ≥20	Often vs. rarely or never	2.27 (1.26-4.12)	Na.
Klug et al. 2010	United States	Case-control	349, Na	Ever vs. never	0.90 (0.70-1.19)	Ambient residential UV intensity, number of hours outdoors, tan type, number of sunburns, gender, age group, and study site.
Lazovich et al. 2011	United States	Case-control	1167, 25-59	High vs. no used	1.10 (0.77-1.57)	Gender, age at interview, phenotypic risk score, moles, high income, college education, family history of melanoma, lifetime sunburns, routine sun exposure, activity sun exposure, and ever use of indoor tanning.
Naldi et al. 2000	Italy	Case-control	542, Na	Often vs. never used	0.80 (0.54-1.17)	Age, sex, geographic area, education, skin, eye and hair colour, number of freckles and naevi ≥2 mm, history of sunburns, tanning pattern and sunny holiday weeks per year.
Osterlind et al. 1988	Denmark	Case-control	474, 20-79	>10 yrs vs. never	1.2 (0.9-1.5)	Constitutional factors, sex, age.
Rodenas et al. 1996	Spain	Case-control	105, 20-79	Always vs. never	0.6 (0.26-1.42)	Age, skin color, skin type, total number of hours of recreational sun exposure, total number of hours of occupational sun exposure, and total number of nevi.
Westerdahl et al. 1995	Sweden	Case-control	400. 15-75	Almost always vs. never	1.80 (1.10-2.80)	History of sunburn, history of sunbathing, employment, host factors.
Westerdahl et al. 2000	Sweden	Case-control	571, 16-80	Often vs. never used	1.8 (1.1-2.9)	Hair colour, history of sunburns, frequency of sunbathing during the summer and the duration of each sunbathing occasion.
Whiteman et al. 1997	Australia	Case-control	52, <21	Always vs. never	2.2 (0.4-11.6)	Sex, school, grade, tanning ability, freckling and number of naevi.
Wolf et al. 1998	Australia	Case-control	193, 18-83	Often vs. never	3.34 (1.81-6.64)	Age, sex, sunbathing, host factors.
Youl et al. 2002	Australia	Case-control	201, Na	Often vs. never	2.2 (0.7-7.1)	Age, sex, total nevi, hair color, eye color, tanning ability, facial freckling, family history.

Abbreviations: RR: relative risk; CI: confidence interval; SPF: solar protection factor; Na: not available; vs.: versus.

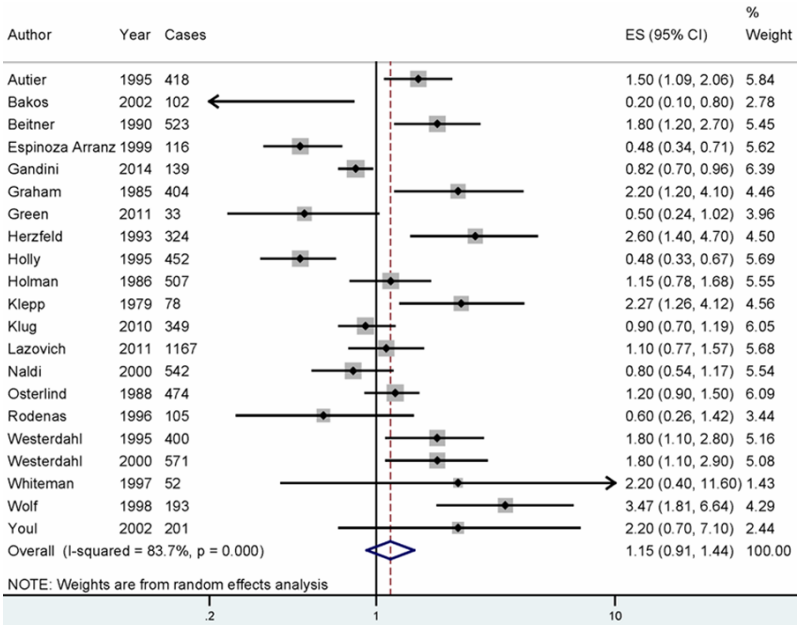

Figure 2. The forest plot between sunscreens use and malignant melanoma risk. White diamond denotes the pooled RR. Black squares indicate the RR in each study, with square sizes inversely proportional to the standard error of the RR. Horizontal lines represent 95% CI.

9 studies. However, four studies reported that sunscreen is a protective factor for malignant melanoma. Pooled results indicating no association between sunscreen use and development of malignant melanoma [summary RR=1.145, 95% CI=0.912-1.438, I^2=83.7%] (**Figure 2**).

Meta-regression and subgroup analysis

As seen in the pooled results, high heterogeneity (I^2=83.7%, $P_{heterogeneity}$=0.000) was found in the analysis. In order to explore the high between-study heterogeneity founded in several analysis, univariate meta-regression with the covariates of publication year, location where the study was conducted, study design (case-control or prospective), number of cases and source of controls was performed. No significant findings were found in the above-mentioned analysis.

For the subgroup analyses by study design, the association was significant neither in the case-control studies [RR=1.219, 95% CI=0.942-1.576], nor in the cohort studies [RR=0.730, 95% CI=0.484-1.101] for the sunscreen use and risk of malignant melanoma. In subgroup analyses of geographic locations, when we restricted the analysis to America, Europe and Oceania, no significant associations were found in the subgroup analysis. The main results are summarized in **Table 2**.

Influence analysis and publication bias

Influence analysis showed that no individual study had excessive influence on the association of sunscreens use and risk of malignant melanoma (**Figure 3**). Egger's test (*P*=0.192) showed no evidence of significant publication bias between sunscreens use and malignant melanoma risk.

Discussion

Finding from this meta-analysis suggested that sunscreens use is not associated on malignant melanoma risk. The associations were not significant both in cohort studies and in case-control studies.

Sunscreens are able to delay sunburns and to reduce some ultraviolet-induced skin lesions, such as non-melanoma tumors in rodents, local immunological depression, and the incidence of actinic keratoses in humans. As a consequence, sunscreen use is often recommended as a sun protection method, although its true impact on melanoma prevention remains obscure. Despite uncertainties in the available epidemiological data, experimental evidence using both animal models and humans suggests that sunscreen preparations capable of reducing exposure to ultraviolet-B radiation from the sun can prevent melanoma [31]. Regrettably, this finding has not been universal. In fact, some investigators suggest that sunscreen use could be a risk rather than a protective factor for malignant melanoma [32]. Although it is considered unlikely that available sunscreen preparations contain compounds with carcinogenic effects, other factors may account for this observed relationship; they include uncontrolled confounding caused by

Table 2. Summary risk estimates of the association between sunscreens use and risk of malignant melanoma

Sub-groups	Cases	Studies	RR (95% CI)	I^2 (%)	$P_{heterogeneity}$
All studies	7150	21	1.145 (0.912-1.438)	83.7	0.000
Study design					
Case-control	6978	19	1.219 (0.942-1.576)	83.3	0.000
Prospective	172	2	0.730 (0.484-1.101)	41.7	0.190
Geographic locations					
America	6	2798	0.958 (0.567-1.618)	87.9	0.000
Europe	10	3366	1.162 (0.870-1.552)	84.8	0.000
Oceania	5	986	1.477 (0.727-2.998)	76.5	0.002

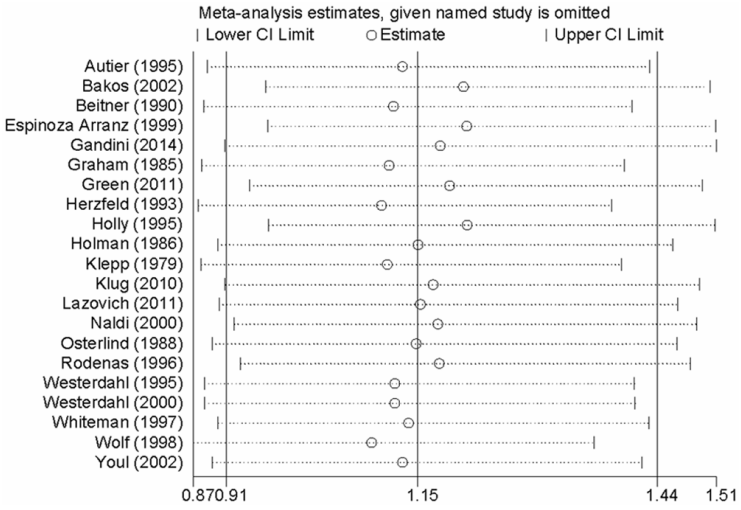

Figure 3. Analysis of influence of individual study on the pooled estimate in sunscreens use and malignant melanoma risk. Open circle, the pooled OR, given named study is omitted. Horizontal lines represent the 95% CIs.

host factors and behavioral factors, such as increased sun exposure among patients who use sunscreen preparations. By pooling data from 21 studies meeting protocol inclusion criteria (yielding a statistically non-significant summary RR of 1.145), we demonstrated that sunscreen use is not associated with an increased risk of developing malignant melanoma. Unfortunately, further evaluation showed the data to be highly heterogeneous.

Between-study heterogeneity is common in meta-analysis [33], and exploring the potential sources of between-study heterogeneity is the essential component of meta-analysis. For sunscreens use on the risk of malignant melanoma, evidence of heterogeneity was found in the pooled results. The between-study heterogeneity might arise from publication year, location where the study was conducted, study design (case-control or prospective), number of cases and source of controls. Thus, we used meta-regression to explore the causes of heterogeneity for covariates. However, no covariate having a significant impact on between-study heterogeneity for the above mentioned covariates. Considering the pooled meta-analysis was fraught with the problem of heterogeneity, subgroup analyses by the type of study design and geographic locations were performed to explore the source of heterogeneity. However, the between-study heterogeneity persisted in some subgroups.

This is a comprehensive meta-analysis between sunscreens use and malignant melanoma risk. Our study included a larger number of participants and cases, allowing a much greater possibility of reaching reliable conclusions about the association between sunscreens use and malignant melanoma risk. However, our study has some limitations. First, most studies included in this meta-analysis were case-control studies. Overstated association may be expected from the case-control studies because of recall or selection bias, and early symptoms in patients may have resulted in a change in dietary habits. Further studies with cohort design are wanted to confirm this association between sunscreens use and malignant melanoma risk. Second, although we combined the results with sunscreens use and malignant melanoma risk, we did not do a dose-response analysis because of the limited data in the reported articles. Third, as a meta-analysis of observational studies, we cannot rule out that individual studies may have failed to control for potential confounders, which may introduce bias in an unpredictable direction. Fourth, between-study heterogeneity was found in some analysis in this meta-analysis, but the between-study heterogeneity was not successfully explained by the subgroup analysis and

meta-regression. However, other genetic and environment variables, as well as their possible interaction may be potential contributors to this disease-effect unconformity.

Conclusion

In summary, results from this meta-analysis suggested that sunscreens use is not associated with the risk of malignant melanoma. Further studies with more participants and more cases are wanted to confirm this result.

Disclosure of conflict of interest

None.

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