Sunscreen Use and the Risk for Melanoma: A Quantitative Review

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Background: **Originally developed to protect against sunburn, sunscreen has been assumed to prevent skin cancer. However, conflicting reports include claims that sunscreen increases risk for melanoma.**

Objective: **To examine the strength and consistency of associations between melanoma and sunscreen use in the published literature.**

Data Sources: **A comprehensive MEDLINE search of articles published from 1966 to 2003 that reported information on sunscreen use and melanoma in humans.**

Study Selection: **Analytic studies reporting data on sunscreen use before diagnosis of melanoma.**

Data Extraction: **Two independent reviewers extracted data. Inconsistencies were rereviewed until agreement was achieved. When necessary, a third party resolved discrepancies.**

Data Synthesis: **Odds ratios were pooled across studies by using standard meta-analytic techniques. Pooled odds ratios for ever use among 18 heterogeneous studies did not support an association between melanoma and sunscreen use. Variation among odds ratios was explained by studies that did not adjust for confounding effects of sun sensitivity. The lack of a dose–response effect with frequency of use (never, sometimes, or always) or years of use provided further evidence of a null association.**

Conclusions: **No association was seen between melanoma and sunscreen use. Failure to control for confounding factors may explain previous reports of positive associations linking melanoma to sunscreen use. In addition, it may take decades to detect a protective association between melanoma and use of the newer formulations of sunscreens.**

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In 2003, an estimated 54 200 cases (29 900 in men and 24 300 in women) of melanoma will be diagnosed in the United States, and 7600 people (4700 men and 2900 women) will have died of melanoma (1). The incidence of skin melanoma is increasing faster than that of any other type of cancer in the United States (2). The age-adjusted incidence of melanoma reported by the Surveillance Epidemiology and End Results (SEER) registries increased from 7.4 per 100 000 persons in 1973 to 20.1 per 100 000 in 1999 among white persons (3).

Melanoma occurs predominantly in white persons, and its incidence increases with age. The 2 major etiologic risk factors for melanoma are sun sensitivity (tendency to burn, inability to tan, light skin color, or tendency to develop freckles) and exposure to ultraviolet radiation through sun exposure. Additional risk factors include age, sex, family history of melanoma, many nevi, and possible exposure to artificial ultraviolet radiation (through tanning beds). Various other factors have also been examined, including oral contraceptive use, diet, smoking, and alcohol use, but no consistent associations have been established.

Sunscreens are thought to protect skin from many of the harmful effects of the sun. Consequently, some professionals suggest that limiting exposure to ultraviolet radiation through use of sunscreen during childhood can reduce the lifetime risk for nonmelanoma skin cancers by as much as 78% (4). In contrast, several recent reports (5–8) have suggested that sunscreen use may cause melanoma. Sun sensitivity probably positively confounds the association between sunscreen use and melanoma, yet few studies have stratified participants by sun sensitivity or appropriately controlled for this factor.

We sought to examine the strength and the consistency of the observed associations between melanoma and sunscreen use. Where possible, we examined sunscreen use stratified by sun sensitivity.

METHODS

Literature Search

To identify relevant studies for sunscreen use and melanoma, we searched the MEDLINE database by using *melanoma (epidemiology or etiology)* and *sunscreening agents* as Medical Subject Headings and *melanoma* and *sunscreen* as key words or text words. The search was repeated periodically to account for fluctuations in the results of searches. We also searched Cancerlit but found no additional articles. We checked the references of identified articles, including bibliographies of the review articles, for additional relevant studies. We also reviewed 70 articles from the first author's files that appeared to be related to melanoma and sunscreen use, sunburns, or sunlight.

Only cohort and case–control studies that measured sunscreen use in relation to melanoma were included. Of the eligible articles, 6 were not in the English language. These were reviewed by 1 person who was multilingual and trained in epidemiology; however, none reported on sunscreen use.

In May 2003, the MEDLINE search for articles published from 1966 through April 2003 was repeated by using *melanoma (epidemiology or etiology)* and *sunscreening agents* as Medical Subject Headings and *melanoma* and *sunscreen* as key words or text words (**Figure 1**). The latter search found 138 articles, including 14 case–control studies; 32 review articles on melanoma; 42 editorials or commentaries; 4 articles on melanoma trends; 41 articles on habits, behaviors, or prevention; 4 prevention trials that did not examine melanoma as an outcome; and 1 animal

study. Of the 14 case–control studies found, 12 had relevant data.

We then expanded our MEDLINE search to include *melanoma* and *sunburns* as Medical Subject Headings, key words, and text words, in an attempt to find additional studies not listed on key or text words for sunscreen. Of 183 articles found through this expanded search, we reviewed 67 in detail, which yielded 6 additional articles on sunscreen use. Three additional articles not found on MEDLINE were obtained from authors' files; 2 of these articles were also discussed in other reviews. Among 3 review articles, 17 studies were discussed, of which 13 were found on MEDLINE, 2 were found in the authors' files, and 2 were not found elsewhere. Two additional studies, 1 of which was an abstract and 1 an unpublished study, were found in the references of reviews on sunscreen use (9, 10) but not on MEDLINE. The authors were contacted but provided no additional data. In general, authors were not contacted because the response rate was low in a previous meta-analysis.

Of the 23 relevant analytic articles on sunscreen use and melanoma, 3 were duplicate publications, leaving 20 independent studies. One of the 20 studies reported only on tanning lotion.

Selection Criteria

Cohort, case–control, and cross-sectional studies that included adults or children were considered for this meta-analysis. However, we found no cohort or cross-sectional studies of sunscreen use and development of melanoma. One author and an assistant screened the titles and abstracts obtained from the literature review to exclude case reports; commentaries; and articles on melanoma trends, habits and behaviors, and other biological aspects of melanoma. If relevance was unclear, the study was reviewed in detail by 2 independent reviewers. Studies that reported use of what appeared to be tanning oils or tanning enhancers rather than sunscreen were independently reviewed and were later excluded from pooled analyses. We included studies that reported odds ratios and those that reported the percentage of cases and controls who used sunscreen. Because the diagnosis of melanoma is based on histologic examination, all studies were assumed to have included histologic confirmation, even if this was not explicitly stated.

Data Extraction

For each study and level of sunscreen use, the natural log of the odds ratio and its variance were required. Where available, the variances were calculated on the basis of the reported CIs (11). Otherwise, we calculated the variances of the natural log of the odds ratio from reported data. For studies that reported no association between melanoma and sunscreen and did not report an odds ratio, we assumed an estimated odds ratio of 1.0. We estimated corresponding variances on the basis of the number of participants, assuming an average exposure rate that was calculated from all other studies. When available, covariate-adjusted odds ratios were used.

Reviewers were blinded to the authors, journal of publication, and introduction and discussion of each article. Two independent reviewers abstracted data from every article, and the 2 sets of results were compared for concordance and rereviewed if necessary. Inconsistencies were rereviewed until agreement was achieved. We sought third-party resolution of disagreements when necessary. We classified studies as hospital-based if they used hospital, clinic, or unidentified control groups. We considered studies that included neighborhood controls, community controls, and general population–based controls to be population based. The most adjusted odds ratios were abstracted, and we assumed that the authors had properly examined and adjusted for confounders. Because of heterogeneity, we examined subgroups of studies that reported adjustment for sun sensitivity, sunburns, and other sun exposure.

Study Quality

On the basis of our previous study of melanoma and meta-analyses, we developed a quality-assessment scoring system for articles reporting on melanoma and sunscreen use. Two reviewers applied the system to each of the 20 studies. Because selection of the control group is pertinent, we scored studies as follows: hospital, cancer, or outpatient dermatology controls, 0 points; hospital visitors, or other unclear group, 1 point; and population controls, 2 points. Studies were given credit for standardizing or pretesting the questionnaire in a sample similar to their study sample (2 points) or partial credit for using the same questions from a structured questionnaire (1 point). Interviewer-administered studies were assigned a score of 2 points if the

Context

Reports that sunscreen use increases risks for melanoma have led to controversy.

Contribution

This meta-analysis of 18 case–control studies found no good evidence for an increased risk for melanoma with sunscreen use. Several studies did not account for patients' sensitivity to sunlight, which could increase both sunscreen use and melanoma. A few studies found protective relationships between sunscreen use and melanoma.

Implications

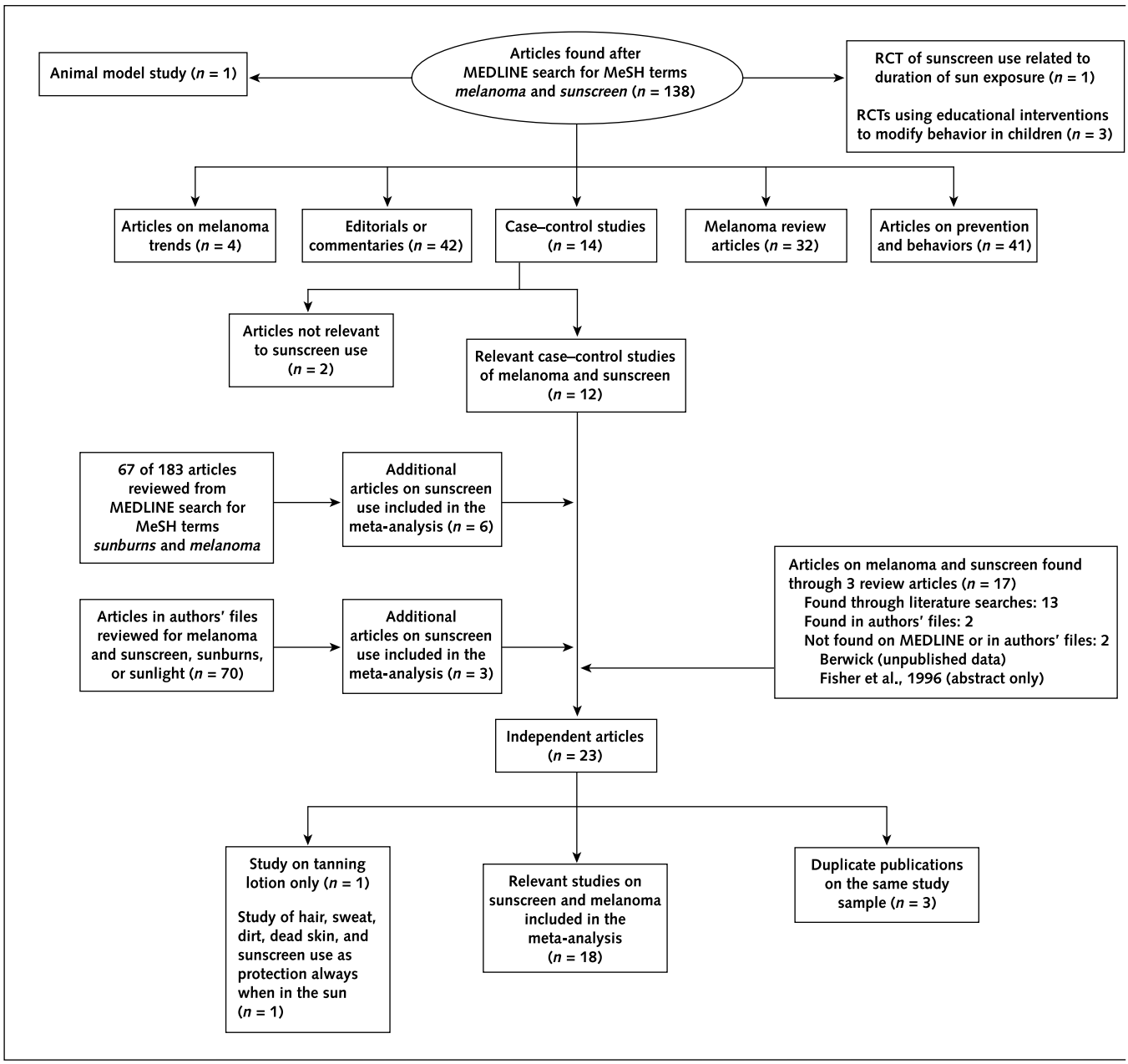
Previous reports of increased risk for melanoma with sunscreen use were misleading.

Cautions

Studies that were reviewed did not evaluate newer sunscreens with a sun protection factor greater than 15, protection against ultraviolet A radiation, or water resistance.

–The Editors

Figure 1. **Literature search for articles on risk for melanoma and sunscreen use.**



MeSH = Medical Subject Heading.

interviewer was blinded to the status of the patient and 1 point if he or she was not blinded; studies in which questionnaires were self-administered were assigned a score of 0 points. To help account for potential detection bias, we gave credit to studies in which the control group had a skin examination (1 point).

To address the potential confounding of sun sensitivity in the relationship between sunscreen and melanoma, we assigned several scores according to the method by which sun sensitivity was measured. A higher score was given to studies that adjusted for skin color, skin type, ability to tan, and tendency to burn (4 points), whereas a lower score was assigned to those that adjusted only for hair color, eye color, or freckling (2 points). We gave credit to studies that adjusted for the potential confounders of sunburn (2 points) and other sun exposure (2 points) and to those that partially adjusted for these confounders (1 point). In addition, points were assigned to studies that adjusted or matched for sex and age (2 points) or were frequency-matched only (1 point). In examining sunscreen use, credit was given to studies that reported more detail beyond ever use: for example, studies that reported years of use (2 points) and frequency of use (1 point). If any of the above information was unclear or not stated, the study received 0 points for that characteristic.

The maximum possible quality score was 19 points.

After we examined the reliability of the 2 reviews, the reviewers discussed the differences and created a final overall quality score for each study (**Appendix Table**, available at www.annals.org). Reliability was examined by using the κ statistic for categorical measures; total scores were compared by using interclass correlations (12). The reliability scores varied as follows. The κ value was correlated at 1.0 for whether the survey was completed by an interviewer or self-administered, selection of control groups, and whether the study adjusted for sunburns. All other categories had a κ value greater than 0.60 (**Table 1**). The quality scores, which have not been validated, are presented to provide an overall sense of each study's quality but were not used in any quantitative analyses.

Statistical Analysis

For dichotomous factors (ever use of sunscreen), we used fixed-effects and random-effects models to obtain pooled relative risk estimates (11, 13). Fixed-effects models provide inferences about the included studies. Random-effects models assume that the study samples were drawn from a larger set of possible studies and provide inferences about all studies in the hypothetical set of studies (11, 13). Statistical tests of homogeneity (11, 14) were performed to assess the consistency of associations. To quantify the extent of heterogeneity among the studies, we estimated the between-study variance (15). This analysis included reporting of the H statistic, which is calculated as the heterogeneity statistic Q divided by its expected value in the absence of heterogeneity. An H statistic of 1.0 indicates homogeneity. The I^2 statistic was also calculated to describe the proportion of total variation in estimates of the odds ratio that is due to the heterogeneity between studies (15). Unless otherwise stated, the reported odds ratios and CIs are based on random-effects models because of heterogeneity.

In addition, we stratified data by type of controls, adjustment for sun sensitivity, and sun sensitivity when available. For studies that did not report odds ratios and CIs, we estimated ever use on the basis of case and control distribution for frequency of sunscreen use. For 3 studies that did not report case and control distribution, we estimated the odds ratio and variance for ever use on the basis of an average of the odds ratios and variances reported for frequency of sunscreen use.

For multiple ordinal categories (frequency of sunscreen use and years of sunscreen use), we used a fixed-effects dose–response method to evaluate possible linear relationships (14). This method combines different levels of exposure in a linear regression of the natural log of the odds ratio while adjusting for correlated measures within studies. As suggested by Greenland and Longnecker (14), for years of sunscreen use, we used the median number of

Table 1. **Interrater Reliability and Final Distribution of the Quality Score, by Study Design, Analyses, and Reporting**

Item Assessed	κ Value for Interrater Reliability (95% CI)	Points Assigned to Items	Distribution of Final Summary Scoring, *n* (%)
Control group	1.0	0 = hospital, cancer, dermatology	9 (45)
		1 = hospital visitors	1 (5)
		2 = population based	10 (50)
Standardized questionnaire (same in cases as controls)	0.80 (0.58–1.02)*	0 = no, not clear, or not stated	7 (35)
		1 = same questions, structured questionnaire	9 (45)
		2 = standardized or piloted	4 (20)
Interviewer administered	1.0	0 = self	8 (40)
		1 = interviewer	12 (60)
Interviewer blinded to case status	1.0	0 = no, not applicable	18 (90)
		1 = yes	2 (10)
Control had skin examination	0.68 (0.35–1.01)	0 = no	12 (60)
		1 = yes	8 (40)
Adjusted for sun sensitivity	0.82 (0.61–1.02)*	0 = no adjustment	6 (30)
		2 = adjustment for hair color, eye color, or freckling only	5 (25)
		4 = skin color, skin type, ability to tan, tendency to burn	9 (45)
Adjusted for sunburn	1.0	0 = no	13 (65)
		2 = yes	7 (35)
Adjusted for other sun exposure	0.74 (0.54–0.93)*	0 = no	10 (50)
		1 = partial†	8 (40)
		2 = yes	2 (10)
Adjusted for age, sex matched	0.77 (0.46–1.09)*	0 = no	4 (20)
		1 = frequency matched only	1 (5)
		2 = yes	15 (75)
Measured more than ever use	0.75 (0.48–1.0)*	0 = only ever use	6 (30)
		1 = frequency of use	9 (45)
		2 = years of use, amount, duration	5 (25)
Total		19 possible points	

* Weighted κ value.
† Partial adjustment was considered for such items as age at migration, sunny vacations, and sunbathing. Full adjustment for sun exposure was recorded for adjustment for cumulative hours of sun exposure, recreational hours, occupational hours, or damage from ultraviolet radiation.

years of each category range in calculating an overall linear β for each study. The iterations required for estimating the linear β for each study were performed in SAS IML (SAS Software, Inc., Cary, North Carolina). Goodness-of-fit tests for linear and quadratic models were run to determine whether the linear models were appropriate. Linear models were appropriate unless otherwise stated. SAS software (SAS, Inc., Cary, North Carolina) was used for analyses and plots.

Role of the Funding Source

The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Table 2 describes the 20 studies from 23 published articles included in the meta-analysis. The earliest published case–control study (16) was excluded because it examined use of sun lotion or oil rather than sunscreen. One study (17) included hair, sweat, dirt, dead skin, and sunscreen use as measures of protection against ultraviolet radiation "always when in the sun" (**Table 2**). Therefore, we excluded it from the pooled odds ratio because it was not comparable to other studies. The remaining 18 studies included no cohort studies, 9 population-based case–control studies (5, 6, 8, 18–25) (including 1 population-based study of adolescents), 7 non–population-based studies (7, 26–32), and 2 case–control studies (9, 33) in which the control group was not clearly identified. Two of the 18 studies reported odds ratios for both sunscreen and sun lotions or oils (**Table 2**); however, only odds ratios for sunscreen use were pooled in the analyses.

Table 2 shows the period of data collection, location of the study sample, age range of participants, type of control group, other exposures measured in the studies, exposures for which the analyses adjusted, and overall measure of sunscreen use. Because the studies summarized here were case–control studies, recall bias of sunscreen use is open to misclassification that could differ between cases and controls.

Five studies used similar inclusion and exclusion criteria for cases and controls (8, 16, 20, 21, 25, 27), 1 did not have similar criteria (7), and the remaining 13 were unclear. Six of the studies stated that the controls had a skin examination (**Table 2**); therefore, they were unlikely to have undiagnosed melanomas. Five studies used mailed questionnaires (**Table 2**). The remaining 15 studies may have more complete data because of interviewer probing, but only 2 studies (20, 22) stated that the interviewers were blinded to case or control status, thus reducing differential probing by case status (22).

Using the information provided in the studies, we scored studies on the basis of several quality assessment items (**Table 1**). The 20 studies received scores ranging from 1 to 18 of 19 possible points. The study that was excluded from pooled analyses because it reported use of "sun lotion or oil" (16) received a score of 2. A second excluded study (17) received a score of 10, moderate to good quality, but measurement of sun protection included "hair, sweat, dirt, dead skin and sunscreen use as measures of ultraviolet radiation protection." Two studies (23, 32) adjusted for sun sensitivity and sunburns for some measure of sunscreen use. However, because we had to calculate the odds ratio for ever use for these studies in the pooled analysis, the odds ratio was not adjusted and these studies scored 6 fewer points than they might have otherwise.

Ever Use of Sunscreen

Five studies reported odds ratios and 95% CIs for "ever" sunscreen use. For the remaining studies, we estimated odds ratios on the basis of frequency of sunscreen use (**Table 2**). The pooled odds ratio for the 18 studies on ever use of sunscreen was 1.0 (95% CI, 0.8 to 1.2) (P value for heterogeneity, < 0.001). **Figure 2** shows the odds ratios and 95% CIs for the 18 studies, along with the pooled estimate. To examine heterogeneity among studies, we pooled data stratified by study design and by confounding factors that were adjusted for in the original articles. No difference in odds ratios was seen between type of control group. We did not believe that adjustment for hair or eye color without adjustment for skin color, tendency to burn, or inability to tan represented adequate adjustment for sun sensitivity. When the 5 studies that adjusted for hair color only were pooled with the studies that adjusted for sun sensitivity, no association was seen (odds ratio, 1.0). However, the odds ratio for melanoma and sunscreen use was smaller when these 5 studies were excluded. When studies were restricted to those that adjusted for sun sensitivity, the pooled odds ratio decreased to 0.8 (CI, 0.6 to 1.0).

Four of the 18 studies stratified participants by skin sensitivity. In 3 of the studies, sun sensitivity was defined as Fitzpatrick skin type I or II. In 1 study, persons with fair or pale skin color were considered sensitive to sun. When stratified by sun sensitivity, the available data for sun-sensitive persons were homogenous. Two of the 4 studies reported null associations (odds ratios, 1.14 and 1.17), 1 a marginally protective association (odds ratio, 0.77), and 1 a significantly protective association (odds ratio, 0.66). Overall, among sun-sensitive persons, who are more likely to use sunscreens and are at higher risk for melanoma, the association between sunscreen use and melanoma was homogeneous and nonsignificantly protective (odds ratio, 0.9 [95% CI, 0.7 to 1.2]; P value for heterogeneity, 0.13). For sun-resistant persons (those with medium or dark skin or Fitzpatrick skin type III or IV), 1 study reported a null association between sunscreen use and melanoma (odds ratio, 1.17), 2 reported increased associations (odds ratio, 1.3 and 1.7), and 1 reported a significant protective effect (odds ratio, 0.6), indicating heterogeneous associations (P value for heterogeneity, 0.002).

Table 2. **Characteristics of Study Methods Reported in Articles of Melanoma and Sunscreen Use, Ordered by First Year of Data Collection***

Dates of Data Collection	Setting	Study, Year (Reference)	Age Range, *y*	Controls
Studies included in the analysis				
1974–1980	New York State	Graham et al., 1985 (26)	All	Patients at the same hospital
1977–1979	New York State	Herzfeld et al., 1993 (19)	≥18	Population based using RDD
2/1978–12/1983	Stockholm, Sweden	Beitner et al., 1990 (18)		Population based from registrar
1/1/1980–11/5/1981	Western Australia	Holman et al., 1986 (20, 25)	<80	Population based from electoral rolls
1981–1986	San Francisco, California	Holly et al., 1995 (21, 24)	25–59	Population based using RDD
10/1/1982–3/31/1985	Eastern Denmark	Osterlind et al., 1988 (22)	20–79	Population based from registrar
1/1/1987–6/30/1994	Queensland, Australia	Whiteman et al., 1997 (8)	≤15	Population based; randomly selected from class lists
1987–1994	Queensland, Australia	Youl et al., 2002 (23)	15–19	Population based from electoral rolls
1987–1989	Connecticut	Berwick (unpublished)	Not stated	Not stated
1/1/1988–6/30/1990	Southern Sweden	Westerdahl et al., 1995 (5)	15–75	Population based from registrar
1989–1993	East Andalusia, Spain	Rodenas et al., 1996 (27)	20–79	Randomly selected from hospital visitors
Not stated	United States	Fisher et al., 1996 (33)	Not stated	Not stated
1/1990–1/1994	Madrid, Spain	Espinosa Arranz et al., 1999 (28)	21–87	Population based; patients with hospital emergencies
1991–1992	Belgium, France, Germany	Autier, 1995, 1998 (29, 30)	≥20	Not population based; unclear
6/1992–2/1995	Italy	Naldi et al., 2000 (31)	Not stated	Not population based; patients at the same hospital
6/1993–7/1994	Styria, Austria	Wolf et al., 1998 (7)	15–89	Not population based; patients at dermatology offices
1/1995–6/1997	Sweden	Westerdahl et al., 2000 (6)	16–80	Population based from registrar
1995–1998	Brazil	Bakos et al., 2002 (32)	20–84	Random patients at the same hospital
Studies of suntan lotion or other agents (excluded from analyses)				
1/1/1974–5/1/1975	Oslo, Norway	Klepp and Magnus, 1979 (16)	≥20	Controls with cancer in the hospital
1974–1980	New York State	Graham et al., 1985 (26)		See information in row 1 above.
1977–1979	New York State	Herzfeld et al., 1993 (19)		See information in row 2 above.
7/1/1979–6/30/1980	Queensland, Australia	Green et al., 1986 (17)	14–86	Population based from electoral rolls

* OR = odds ratio; RDD = random-digit dialing; SPF = sun protection factor; UV = ultraviolet.
† I = skin type (Fitzpatrick); II = tendency to burn; III = ability to tan; IV = skin color; V = freckles; VI = eye color; VII = hair color.
‡ 1a = sunburn in childhood; 1b = sunburn in adolescence; 1c = sunburn while an adult; 1d = sunburn during lifetime; 1e = sunburn ever; 2a = cumulative sun exposure; 2b = residential sun exposure; 3 = recreational sun exposure; 4 = occupational sun exposure; 5 = sunny vacations; 6 = sunbathing; 7 = sunlamps/beds.
§ The maximum possible quality score is 19 points.
‖ Calculated from data and therefore not adjusted for covariates.
¶ Estimated from frequency ORs.
** Estimated from the frequency of sunscreen use in cases and controls mentioned in text.
†† Also measured SPF.

Table 2—**Continued**

Reference	Standardized Questionnaire?	Interviewer Administered?	Skin Examination among Controls?	Measurement of Sun Sensitivity†	Measurement of UV and Other Exposures‡	Quality Score§	Cases/Controls, *n/n*
26	No	Yes	No	III, IV, V, VI, VII	2a, 2b, 4	1	404/521
19	Yes	Yes	No	II, IV, V, VI, VII	3, 4, 6	6	324/415 men
18	Partial	No	No	I, VI, VII	1e, 4, 5, 6, 7	8	523/505
20, 25	Yes	Yes	Yes	II, III, IV, VI, VII	1d, 2a, 2b, 3, 4, 6, 7	18	494/494 (511/511)
21, 24	Yes	Yes	No	II, III, IV, V, VI, VII	1a, 1b, 1c, 1d, 2a, 7	14	452/930 women
22	Partial	Yes	No	V, VII	1a, 1b, 1c, 2b, 3, 4, 5, 6, 7	11	474/926
8	No	No	Yes	II, III, V, VI, VII	1a, 1b, 1d, 2a, 5	10	52/156
23	Partial	Yes	Yes	I?, II, III, V, VI, VII	1d, 2a, 2b, 4, 6	8	201/205
Unpublished	–	–	–		2a	6	Not stated
5	Partial	No	No	V, VI, VII	1a, 1b, 1c	11	400/640
27	Partial	Yes	Yes	IV, V, VI, VII	1a, 1b, 1c, 1d, 2a, 3, 4, 5, 7	13	105/138
33	–	No	–	Constitutional	Solar	3	70/109
28	Partial	Yes	Yes	II, III, IV, V, VI, VII	2a, 2b, 3, 4, 5, 6, 7	9	116/235
29, 30	No	Yes	No	I, VII	1a, 1b, 1c, 2a, 3, 5, 7	10	418/438 (412/445)
31	Partial	Yes	Yes	II, IV, V, VI, VII	1d, 3, 4, 5, 7	15	542/538
7	–	–	No	I, IV, V, VI, VII	1e, 1d, 2b, 3, 4, 5, 6, 7	10	193/319
6	Partial	No	No	I, V, VI, VII	1c, 2b, 4, 5, 6, 7	12	558/891
32	No	Yes	Yes	I, V, VI, VII	1d	6	103/206
16	Partial	No	No	II, III, V, VI, VII	3, 4, 5, 6, 7	2	78/131
26							
19							
17	Yes	Yes	Yes	II, III, IV, V, VI, VII	1a, 1b, 1c, 1d, 2a, 3, 4, 5	10	183/183

Table 2—**Continued**

OR for Association between Melanoma and Ever Use (95% CI)	OR for Association between Melanoma and Frequency of Use (95% CI)	Adjustments Reported
Men: 2.2 (1.2–4.1) Women: 1.0 (0.7–1.6)‖		Crude
0.8 (0.6–1.1)‖		Crude (restricted to men)
Sun protection agents: 1.6 (1.1–2.3)¶	Never: 1.0 Seldom: 1.4 (0.9–2.0) Often/very often: 1.8 (1.2–2.7)	Age, sex, hair color
1.1 (0.8–1.6)¶	Never: 1.0 <1/2 of the time: 1.12 (0.74–1.71) >1/2 of the time: 1.10 (0.76–1.58)	Fair pigment, sensitivity to sunlight, ethnic origin, age at arrival to Australia (sun exposure) (matched on age, sex, and residence; study examined confounding due to sunburns)
0.8 (0.6–1.0)‖	Never: 2.1 (1.5–3.0) Sometimes: 1.5 (1.1–2.2) Almost always: 1.0	Childhood sunburns, ability to tan, hair color, large nevi, complexion, maternal ethnicity, history of skin cancer, and age (women only)
0.8 (0.7–1.0)**	Never: 1.0 Occasionally: 1.3 (1.0–1.6) Always: 1.1 (0.8–1.5)	Constitutional factors, sex, and age
Sunscreen use on holiday: 1.9 (0.7–5.2)‖	Never/rarely: 1.0 Sometimes: 1.5 (0.3–8.2) Often: 1.5 (0.3–7.4) Always: 2.2 (0.4–11.6)	Sex, school, grade, tanning ability, freckling, number of nevi (matched on age, sex, and residence)
1.0 (0.7–1.5)‖	Average lifetime use at home Often/always: 1.0 Sometimes: 0.9 (0.5–1.7) Rarely/never: 0.9 (0.5–1.7)	Crude (matched on age, sex, and residence)
1.2 (0.9–1.6)¶	Never: 1.0 Sometimes: 1.1 (0.8–1.5) Almost always: 1.3 (0.9–1.6)	Sun sensitivity and sun exposure
1.6 (1.1–2.2)	Never: 1.0 Sometimes: 1.3 (0.9–1.9) Almost always: 1.8 (1.1–2.8)	Host factors (nevi, hair and eye color, freckling), sunburns, frequency of sunbathing, outdoor employment (matched on age, sex, and residence)
0.4 (0.2–0.7)‖	Never: 1.0 Sometimes: 0.6 (0.26–1.42) Always: 0.2 (0.04–0.79)	Age, skin color, skin type, number of hours of recreational sun exposure, hours of occupational sun exposure, number of nevi (no difference by sex)
Regular lifelong use: 0.3 (0.1–0.8)		Constitutional risk and solar exposure
0.5 (0.3–0.7)		Age, skin type, nevi (matched on age and sex)
1.50 (1.09–2.06)		Age, sex, skin type, hair color, holiday weeks in sunny resorts, tropical sunbathing, and adult sunburns
1.1 (0.9–1.4)‖	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 color; number of freckles; large nevi; history of sunburns; tanning pattern; sunny holidays
1.0 (0.6–1.6)‖	Never: 1.0 Rarely: 1.30 (0.70–2.39) Often: 3.47 (1.81–6.64)	Skin color, sunbathing, sunburns, age, and sex
1.3 (1.0–1.6)‖	Never: 1.0 Sometimes: 1.3 (0.9–1.9) Always/sometimes: 0.9 (0.6–1.5) Always first, then sometimes: 1.8 (1.1–2.9)††	Hair color, sunburns, frequency of sunbathing, duration of sunbathing (matched on age, sex, and residence)
0.5 (0.3–0.9)‖	Measured use of sunscreen as never, SPF <8, SPF 8–15, or SPF ≥15	Crude (matched on age, sex, and residence)
Sun lotion or oil: 2.1 (1.1–3.8)‖	Sun lotion or oil Almost never: 1.0 Very rarely: 1.5 (0.7–3.0)‖ Sometimes: 2.5 (1.1–6.0)‖ Quite often: 1.5 (0.4–5.8)‖ Almost always: 3.6 (1.5–8.9)‖	Crude
Suntan lotion, men: 1.7 (1.1–2.7)		Crude
	Suntan lotion Always use: 2.58 (1.42–4.69)	Restricted to men and adjusted for decade of birth
	UV radiation–blocking agents (hair, sweat, dirt, dead skin and sunscreen use) always when in sun: 0.8 (0.4–1.7)	UV radiation dosage and nevi (matched on age, sex, and residence)

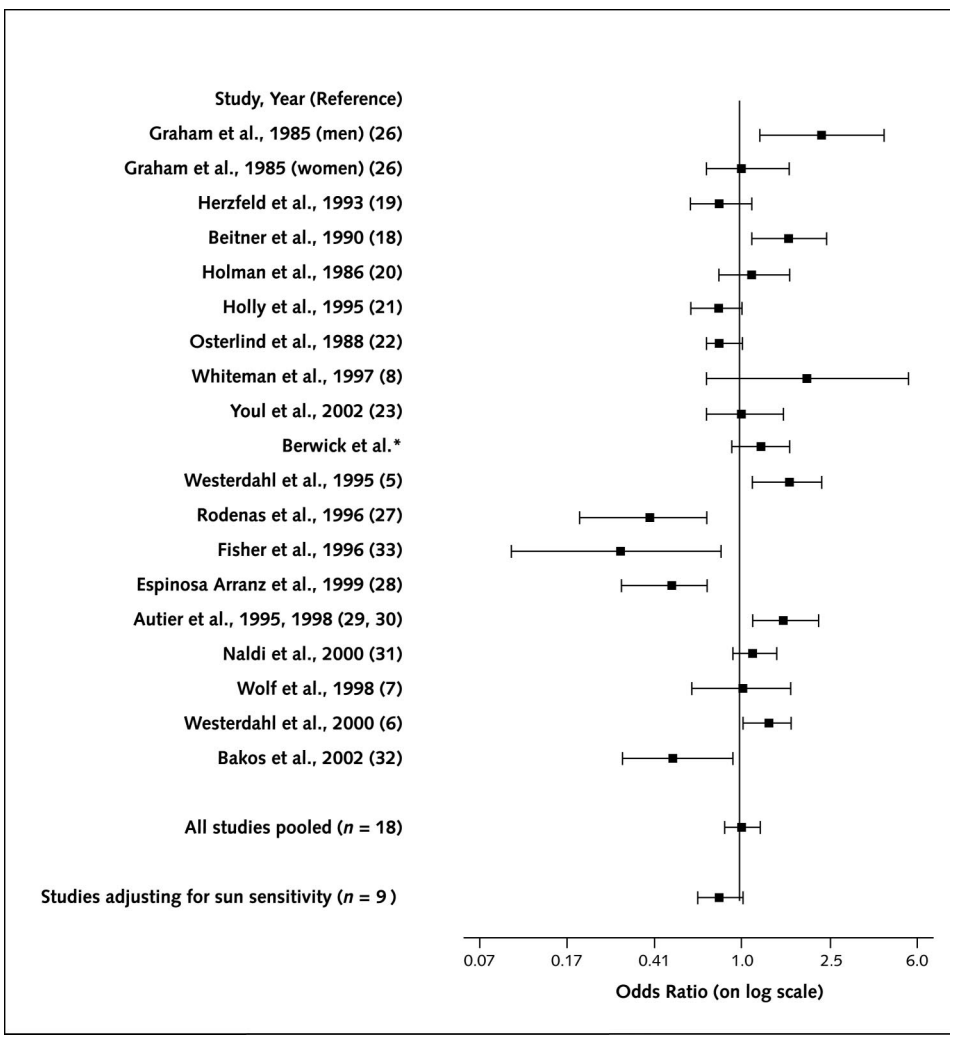
Dose–Response Analyses

Unlike investigators in previous reviews (34), we did not believe that it was appropriate to pool ever use of sunscreen with always-use or use for more than 10 years, because these categories differ markedly in their description of sunscreen use. Therefore, we conducted detailed dose–response analyses. Frequency of sunscreen use is typically reported in ordered categories of "never or rarely," "sometimes," or "almost always." Although such data are not optimal for accurately quantifying sunscreen use, they are ordered categories that provide supplemental information on sunscreen use beyond "ever use."

Using a linear model that assumed equal distance between the above categories, we pooled data on ordered categories from the 12 case–control studies and found that they were heterogeneous, with no apparent association (odds ratio, 1.1; $P = 0.09$) between melanoma and frequency of sunscreen use. Among these 12 studies, 84% of variation was due to between-study variation (15). However, 4 of the 12 studies did not adjust for the confounding effects of sun sensitivity or adjusted only for hair color. When these 4 studies were excluded, the odds ratio for the relationship decreased to 0.93 (CI, 0.81 to 1.07). An additional 3 studies did not adjust for the potential confounding effects of previous sunburns. When the 5 studies that adjusted for sun sensitivity and sunburns were pooled, a significant protective association was observed (odds ratio, 0.76 [CI, 0.65 to 0.90]). However, in each of these analyses, the pooled studies remained heterogeneous: The variation due to between-study variation remained at 84% (15). This finding may indicate that the ordered categories for frequency of sunscreen use may not be comparable across studies. More likely, however, it reflects differences in how people quantify their sunscreen use.

Years of sunscreen use may provide a more quantitative measure of the dose of sunscreen used. However, "years of use" is an imprecise measure that does not account for how often sunscreen is used. Four studies reported data on years of sunscreen use. Although the data fit a linear model, there was no association with increasing years of sunscreen use. **Table 3** shows data from the 4 studies and the pooled estimates. The 4 studies that measured years of use reported homogeneous odds ratios ($P >$ 0.2).

Figure 2. **Odds ratios and 95% CIs for ever use of sunscreen for the 18 studies, sorted by first year of data collection; overall pooled estimate, based on a random-effects dose–response model; and pooled estimate including only studies that adjusted for sun sensitivity ($n = 9$).**



*Unpublished.

Table 3. **Years of Sunscreen Use in 4 Studies, and Pooled Risk for Melanoma**

Author, Year (Reference)	Age Range	Type of Controls	Geographic Location	Period of Data Collection	Cases/ Controls	Odds Ratio (95% CI) for Duration of Sunscreen Use	Duration of Sunscreen Use	Linear Pooled Odds Ratios (95% CI)
	y				*n/n*		*y*	
Holman et al., 1986 (20, 25)	<80	Population based	Western Australia	1/1/1980–11/5/1981	494/494	1.0, never 1.06 (0.71–1.57), <10 y 1.15 (0.78–1.68), ≥10 y	0	1.0
Naldi et al., 2000 (31)	Unclear	Non–population based	Italy	6/1992–2/1995	542/538	1.0, never 0.97 (0.59–1.61), 1–9 y 1.01 (0.64–1.58), 10–19 y 0.86 (0.58–1.29), ≥ 20 y	10	1.06 (0.96–1.17)
Westerdahl et al., 2000 (6)	16–80	Population based	Sweden	1/1995–6/1997	558/891	1.0, never 4.3 (0.8–21.9), 1–20 y 1.7 (0.5–5.6), ≥ 20 y	20	1.12 (0.92–1.37)
Osterlind et al., 1988 (22)	20–79	Population based	Eastern Denmark	10/1/1982–3/31/1985	474/926	1.0, never 1.3 (0.9–1.7), <10 y 1.2 (0.9–1.5), ≥10 y		*P* value for linear trend >0.2 *P* value for heterogeneity >0.2

Discussion

Our results do not support a positive association between sunscreen use and melanoma. No association was seen between melanoma and ever use of sunscreen in this meta-analysis of 18 heterogeneous studies. The heterogeneity across studies limits the validity of the pooled results and must be considered when interpreting the analyses. However, no association was seen among the homogenous odds ratios reported for sun-sensitive persons (those with fair or pale skin color, or Fitzpatrick skin type I or II). The heterogeneity seen among sun-resistant persons (those with medium to dark skin color or Fitzpatrick skin type III or IV) should be explored further but may be related to prolonged exposure to sun after maximal tanning.

The inconsistent findings and heterogeneity among dose–response analyses for frequency of use are not surprising. Most studies ask participants how often they use sunscreens according to such categories as "never," "sometimes," "often," or "always," but they are not asked about duration of use or reapplication of sunscreens. Data on years of use were not heterogeneous and had low or inconsistent odds ratios across increasing categories of use in all 4 studies. The lack of a dose–response effect for years of use supports a null association between sunscreen use and melanoma. However, additional studies that properly adjust for confounding effects of sun sensitivity and sunburns are needed to confirm any reduction in melanoma risk with sunscreen use. A better exploration of differences in risk by skin type is also needed.

Previous reports of an increased risk for melanoma with sunscreen use are misleading. Sun-sensitive persons typically are more likely to use sunscreens (35) and are at higher risk for melanoma (9, 20, 25, 36). Thus, reports of increased risk for melanoma among sunscreen users may reflect an increased risk among sun-sensitive persons rather than an increased risk solely due to sunscreen use. Therefore, lack of control for the confounding effects of sun sensitivity would provide crude odds ratios that are larger than odds ratios adjusted for sun sensitivity. Evidence for such confounding is supported by a decrease in the linear odds ratio for frequency of use seen in the analyses when studies that did not control for sun sensitivity were excluded. In addition, pooled results from the 4 studies that reported data stratified by sun sensitivity suggest no effect of sunscreen use. Thus, the lack of overall association in most of the analyses does not support an increased risk for melanoma with use of sunscreen.

Sunscreen use may be higher among persons with a history of sunburns. Sunscreens were initially developed to reduce erythema or sunburns. Evidence for confounding due to sunburn history is supported by a decrease in the linear odds ratio for melanoma and frequency of sunscreen use when studies that did not control for sunburns were excluded from analyses. Some people may use sunscreen to allow prolonged sun exposure by preventing sunburns, thus receiving a higher amount of cumulative ultraviolet radiation. Minimal erythema may only be a marker for damaging effects of sun exposure. Therefore, prevention of sunburns without reduction in sun exposure may not reduce risk for skin cancer (37). Clinically, sunscreen use may help prevent melanoma by preventing sunburns; however, people must be warned that sunscreens do not protect the skin during prolonged exposure to sun.

Sun exposure is a complex confounding factor of sunscreen use because it can be intermittent or chronic. Sun-resistant persons may incur risk for melanoma with cumulative sun exposure after maximal tanning (38). Sun-resistant persons may use sunscreen to protect against sunburn, thus allowing them to spend longer amounts of time in the sun. It is unclear whether such persons would be protected from an increased risk for melanoma owing to lack of sunburn and sufficient ultraviolet protection from the sunscreens.

A double-blind, randomized trial of sunscreen use and

duration of sun exposure (39) illustrates the potential for prolonged sun exposure among sunscreen users. Participants 18 to 24 years of age randomly received sunscreen with a sun protection factor (SPF) of 10 or 30 but no recommendations about sun protection or sun exposure. The group that received sunscreen with an SPF of 30 had higher cumulative exposure to sun and longer daily sunbathing than did the group that used sunscreen with an SPF of 10 (39). This finding suggests that sun exposure is an important confounder of the association between sunscreen use and melanoma (9, 40, 41).

Although intermittent exposure to sun appears to be a major risk factor for melanoma (18, 21, 22, 27), some research suggests that chronic or cumulative exposure (7, 22, 27, 28) is also an important risk factor. In this review, the odds ratios pooled across sun-sensitive persons were homogeneous ($P = 0.13$), whereas those among sun-resistant persons were heterogeneous ($P = 0.002$). The heterogeneity suggests a wider variation in the odds ratios and CIs among sun-resistant persons in the reviewed articles and must be considered a limiting factor in interpreting these analyses. Some sun-resistant or dark-skinned persons may use sunscreen to prevent sunburns (potentially reducing their risk for melanoma), whereas others use sunscreen to prolong their exposure to sun (potentially increasing their risk for melanoma). The strong correlation between sun exposure and sunscreen use makes adjustment and interpretation difficult (40).

Differences in sunscreen use patterns and formulations may also affect any association between sunscreen use on melanoma development. Since sunscreen was developed in 1928 (42), the type of ultraviolet protection has changed dramatically, with the evolution of new active ingredients. A standardized SPF rating system was proposed in 1978 (43). The SPF is the ratio of the minimal erythema dose needed to induce minimal sunburn to skin protected by a standard dose of sunscreen (2 mg/cm) compared with unprotected skin (44). Studies of ultraviolet radiation in the fish genus *Xiphophorus* have suggested that ultraviolet A radiation is more important than ultraviolet B in development of cutaneous malignant melanoma (45, 46). Historically, most sunscreens were inadequate to protect against ultraviolet A radiation (41, 47). Partial, short-wave, ultraviolet A radiation–absorbing compounds were added to selected sunscreens only starting in 1989. Relative protection against long-wave ultraviolet A radiation was eventually achieved with the development of Avobenzone and Parsol 1789 and inclusion of physical blocking agents, such as titanium dioxide (48). Since the ultraviolet protection afforded by sunscreens has changed dramatically in the past 50 years, some of the variability seen in the studies analyzed may reflect changes in specific ultraviolet protection. Thus, studies reporting no effect between sunscreen use and melanoma should be interpreted cautiously if effective sunscreen agents were not widely available when most study participants received the majority of their sun exposure (20, 49).

Furthermore, none of the reviewed studies considered or controlled for possible inconsistencies in sunscreen factors, such as substantivity (the ability of a sunscreen to adhere to the skin) or water resistance, and only a few accounted for SPF. Substantivity and water resistance also influence the relative protection afforded by various sunscreen products. Because of inconsistencies in sunscreen substantivity, the amount of protection provided after application can vary greatly despite similar SPF ratings. Similarly, water resistance can also determine the relative protection provided by sunscreens with the same SPF (50). The efficacy of sunscreen is contingent on the adequacy and proficiency of its application. However, numerous studies have documented poor compliance with recommendations of regular sunscreen application (35, 51). Thus, patient education is of clinical importance. Patients must understand that sunscreen products must be applied both evenly and in sufficient amounts to achieve adequate protection (52). Sunscreens with an SPF greater than 15 are recommended by most experts.

Other biases in retrospective case–control studies may include increased reporting of sunscreen use among patients with melanoma. This phenomenon reflects patients' current concern about sun protection (49). A recent case–control study of melanoma in Iowa in which participants were asked about current sunscreen use when outside on a sunny day supports this idea. At the time of the survey, which occurred 2 to 3 years after diagnosis, 45.9% of patients with melanoma reported using sunscreen at least half the time when in the sun compared with only 25.1% of controls (53). Current concern about sun protection in patients after diagnosis of melanoma could bias the reporting of sunscreen use, especially if care is not taken to ensure that only prediagnosis use is ascertained (49). Furthermore, sunscreen use means different things to different persons (54). The survey instruments used to measure sunscreen use must therefore be examined for reliability and validity. Details are needed on how much sunscreen is applied, frequency of application, and whether it is applied before sun exposure.

Studies to date do not provide evidence of an increased risk for melanoma with sunscreen use. A few studies suggest a protective effect of sunscreen use against melanoma. Yet, most of the studies reviewed were conducted before protection against ultraviolet A radiation was developed and other sunscreen variables, such as substantivity and water resistance, were standardized. It will probably take decades to see the potential protective effect of regular use of sunscreens with SPF greater than 15, protection against ultraviolet A radiation, or use according to recommended technique of application on risk for melanoma.

The effects of prolonged exposure to sun due to use of sunscreens to prevent sunburns are unclear, and further study is needed. Future studies of sunscreen and melanoma

also must obtain detailed measurement of sunscreen use and confounding factors. Studies that do not attempt to reduce bias or do not account for confounding factors will only contribute to the misinformation and confusion about sun-safe habits.

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Appendix Table. **Quality Assessment Scoring of the Melanoma and Sunscreen Studies***

Author, Year (Reference)	Geographic Location	Coding of Items		
		Type of Controls†	Standardized Questionnaire‡	Interviewer Administered§
Graham et al., 1985 (26)	New York State	0	0	1
Herzfeld et al., 1993 (19)	New York State	2	2	1
Beitner et al., 1990 (18)	Stockholm, Sweden	2	1	0
Green et al., 1986 (17)	Queensland, Australia	2	2	1
Holman et al., 1986 (20, 25)	Western Australia	2	2	2
Holly et al., 1995 (21, 24)	San Francisco, CA	2	2	1
Osterlind et al., 1988 (22)	Eastern Denmark	2	1	2
Whiteman et al., 1997 (8)	Queensland, Australia	2	0	0
Youl et al., 2002 (23)	Queensland, Australia	2	1	1
Berwick et al., (Unpublished data)	Connecticut	0	0	0
Westerdahl et al., 1995 (5)	Southern Sweden	2	1	0
Rodenas et al., 1996 (27)	Eastern Andalusia, Spain	1	1	1
Fisher et al., 1996 (33)	United States	0	0	0
Espinosa-Arranz et al., 1999 (28)	Madrid, Spain	0	1	1
Autier et al., 1995 and 1998 (29, 30)	Belgium, France, and Germany	0	0	1
Naldi et al., 2000 (31)	Italy	0	1	1
Wolf et al., 1998 (7)	Styria, Austria	0	0	0
Westerdahl et al., 2000 (6)	Sweden	2	1	0
Bakos et al., 2002 (32)	Brazil	0	0	1
Klepp and Magnus, 1979 (16)	Oslo, Norway	0	1	0

* See Table 2 for a description of individual studies.
† 0 = hospital based or unclear; 1 = hospital visitors; 2 = population based.
‡ 0 = no, not stated; 1 = same questions, structured; 2 = standardized or piloted.
§ 0 = self; 1 = nonblinded interviewer; 2 = blinded interviewers.
‖ 0 = no; 1 = yes.
¶ 0 = no adjustment; 2 = hair color, eye color, or freckling; 4 = skin color, skin type, ability to tan, tendency to burn.
** 0 = no; 2 = yes.
†† 0 = no; 1 = partial; 2 = yes. Partial adjustment was recorded for such items as age at migration, sunny vacations, and sunbathing. Full adjustment was recorded for adjustment for cumulative hours of sun exposure, recreational hours, occupational hours, or ultraviolet radiation damage.
‡‡ 0 = no; 1 = frequency matched; 2 = yes.
§§ 0 = only ever use; 1 = frequency of use; 2 = years of use, amount, or duration.
‖‖ Maximum possible score is 19 points.

Appendix Table—**Continued**

Coding of Items						
Skin Examination among Controls‖	Adjusted for Sun Sensitivity¶	Adjusted for Sunburns**	Adjusted for Sun Exposures††	Adjusted for Age and Sex‡‡	Reported Measurements of Sunscreen Use§§	Total Quality Score‖‖
0	0	0	0	0	0	1
0	0	0	0	1	0	6
0	2	0	0	2	1	8
1	0	0	2	2	0	10
1	4	2	1	2	2	18
0	4	2	0	2	1	14
0	2	0	0	2	2	11
1	4	0	0	2	1	10
1	0	0	0	2	1	8
0	4	0	1	0	1	6
0	2	2	1	2	1	11
1	4	0	2	2	1	13
0	2	0	1	0	0	3
1	4	0	0	2	0	9
0	4	2	1	2	0	10
1	4	2	1	2	2	14
0	4	2	1	2	1	10
0	2	2	1	2	2	12
1	0	0	0	2	2	6
0	0	0	0	0	1	2