Epidemiological data on exposure to artificial UV radiation for cosmetic purposes and skin cancers

As no valid animal model of human melanoma or other skin cancers exists, evidence of an association between indoor tanning facility exposure and skin cancer must be sought predominantly from epidemiological studies. Few studies have addressed this topic specifically, but most skin cancer studies have included one or more items about use of indoor tanning facilities. We systematically analysed the summary statistics compiled from the relevant studies in a meta-analysis. The results have also been discussed qualitatively, to allow for the large differences in study populations and study quality.

Since melanoma and other skin cancers differ somewhat in their aetiology, studies of melanoma were analysed separately from those of basal and squamous cell cancers. Epidemiological evidence from studies investigating other sources of exposure to artificial UV radiation has also been presented.

Methodology for literature search

The literature to April 2005 was searched using the following databases: Pubmed, ISI Web of Science (Science Citation Index Expanded), Embase, Pascal, Cochrane library, Lilacs and Medcarib. The following keywords and their corresponding French translations were used for search in the PASCAL database: "skin cancer", "squamous cell carcinoma", "SCC", "basal cell carcinoma", "BCC", "melanoma" for diseases. To define exposure, the following keywords were used: "sunbed", "sunlamp", "artificial UV", "artificial light", "solaria", "solarium", "indoor tanning", "tanning bed", "tanning parlour", "tanning salon" and "tanning booth".

We searched for keywords in the title and in the abstract, when available. We also performed a manual search of references cited in the selected articles, and in selected reviews or books on melanoma and skin cancer. All participants of the working group and some IARC staff were asked to report any additional published or submitted study. No language restriction was applied.

Primary inclusion criteria were developed for the selection of relevant articles, which were: case–control, cohort or cross–sectional studies published as an original article. Ecological studies, case reports, reviews and editorials were not considered eligible.

For the meta-analysis, we selected the articles fulfilling both of the following two criteria:

1. The article contained sufficient information to estimate the relative risk and 95% confidence intervals (odds ratios [OR], relative risks or crude data and corresponding standard errors, variance, confidence intervals or P-values of the significance of the estimates); and
2. The article reported an independent study (in order to avoid giving additional weight to some studies).

The selected articles were reviewed and data abstracted by means of a standardized data-collection protocol. When another article on the same study was published simultaneously, additional relevant or missing information was retrieved from the companion paper. For each study the following information was retrieved:

- General information: year of publication, recruitment years, study design, study location and latitude of the region;
- Exposure information: definition of type of exposure, age at first exposure, duration of exposure, year of exposure, place of exposure;
- Case–control information: inclusion or exclusion of specific histological types of melanoma, number and source of cases and controls, matching design, blinding of interviewers;
- Statistical information: statistical methods used, adjustment for confounding variables (demographic factors such as age and sex,

baseline host characteristics such as hair, eye and skin colour, inherent tendency to burn or tan easily, naevi, sunburns or sun exposure) and type of effect estimates (odds ratio, relative risk, standardized incidence ratio) with corresponding measures of precision, according to specific exposure category.

The minimal common information about exposure to indoor tanning devices for all studies was "ever exposed". For those studies where the definition of exposure "ever versus never exposed to indoor tanning facilities" was not present, we used the information closest to this category.

Since it has been suggested that age at exposure may influence the relative risk for skin cancer associated with UV exposure (Whiteman *et al.,* 2001), we extracted relative risks associated with use of indoor tanning facilities before the age of 35 years where available. Studies used different age categories for classifying age at first exposure, so odds ratios for the "young exposure" category were pooled without correction.

Melanoma

We identified 23 studies of use of indoor tanning facilities and melanoma (Klepp & Magnus, 1979; Adam *et al.,* 1981; Gallagher *et al.,* 1986; Holman *et al.,* 1986; Holly *et al.,* 1987; Swerdlow *et al.,* 1988; Osterlind *et al.,* 1988; Zanetti *et al.,* 1988; MacKie *et al.,* 1989; Beitner *et al.,* 1990; Walter *et al.,* 1990 (and 1999); Dunn-Lane *et al.,* 1993; Garbe *et al.,* 1993; Westerdahl *et al.,* 1994; Autier *et al.,* 1994; Holly *et al.,* 1995; Chen *et al.,* 1998; Westerdahl *et al.,* 2000; Naldi *et al.,* 2000; Kaskel *et al.,* 2001; Veierød *et al.,* 2003; Bataille *et al.,* 2004; Bataille *et al.,* 2005). All studies were case–control studies, except for one cohort study (Veierød *et al.,* 2003). No cross–sectional studies were identified. A case–control study was considered population-based when cases were derived from a population-based cancer registry and controls selected from the general population.

Description of studies

(a) Cohort study – Veierød et al. (2003): The only published prospective cohort study was conducted in Norway and Sweden, where 106 379 women aged 30–50 years at inclusion were recruited between 1991 and 1992. This population was selected from the National Population Register and followed for an average of 8.1 years. Among these, 187 cases of invasive melanoma were diagnosed during follow-up. The analysis was stratified by age at the time of exposure to sunbeds. Thirty-four cases occurred among the 14 377 women who were exposed at least once a month during one of three age periods (10–19, 20–29 or 30–39 years). The corresponding risk for melanoma for the entire cohort was 1.55 (confidence interval (CI), 1.04–2.32) when adjusting for age, region, hair colour, age-specific sunburns and annual number of weeks of summer vacations. For the age group 20–29 years, the risk for melanoma associated with solarium use more than once a month compared with rarely or never was 2.58 (CI, 1.48–4.50).

(b) Population-based case–control studies – Adam et al. (1981): A case–control study was conducted in Oxford and the south-western region of the United Kingdom between 1971 and 1976, recruiting 111 incident cases and 342 controls to study the association between the oral contraceptive and melanoma in women. Cases were selected from two cancer registries and when identified, were contacted through their General Practitioner (GP); controls were selected from the GP practice lists and matched to cases for age, marital status and GP practice. Nine cases and 10 controls had ever used sunlamps. The crude odds ratio calculated [by the Working Group] was 2.93 (CI, 1.16–7.40). [No estimate was reported for the exposure to sunlamps. The working group noted that 169 cases and 507 controls were selected from the registry, but only 111 cases and 342 controls completed questionnaires.]

Holman et al. (1986): A case–control study was conducted in Western Australia between 1980 and 1981 to evaluate constitutional traits, sunlight exposure, hormones, diet and other possible risk factors for cutaneous melanoma. This study recruited 511 incident cases and 511 controls, selected from the electoral roll and matched to cases for age and sex. Past use of sunlamps was

recorded, but only 9% of subjects had used them. The crude odds ratio for "ever use" compared to "never use" of sunlamps was 1.1 (CI, 0.6–1.8).

Osterlind et al. (1988): A case–control study conducted in East Denmark between October 1982 and March 1985 recruited 474 incident cases and 926 controls aged 20–79 years selected from the National Population Register to study risk factors for melanoma. Sixty-six cases and 168 controls had ever used sunbeds, and 50% of controls had used sunbeds less than 10 times. The crude odds ratio for ever versus never use [calculated by the Working Group] was 0.73 (CI, 0.53–1.01), and no trend was observed with number of sessions. Regarding exposure to sunlamps, 45% of cases and 42% of controls had used sunlamps, with 40% of both cases and controls having used sunlamps less than 10 times. [No estimate was reported for the use of a sunlamp.]

Zanetti et al. (1988): A case–control study investigating melanoma risk factors was conducted in Torino, Italy between May 1984 and October 1986. The authors identified 208 incident cases in the "Registro Tumori Piemonte" registry and selected 416 controls from National Health Service files. Of these, 15 cases and 21 controls had used UVA lamps for tanning purposes. The risk for melanoma from this exposure was 0.9 (CI, 0.4–2.0) after adjustment for age, hair colour, skin reaction, sunburn in childhood and education level. The use of sunlamp for tanning was very rare in Italy during the study period, and the authors warned about the consequent lack of power of the study.

Walter et al. (1990): A case–control study, designed specifically to investigate the melanoma risk associated with artificial UV exposure, was conducted in southern Ontario, Canada between October 1984 and September 1986. Recruitment included 583 incident cases identified from pathology reports and 608 controls selected from property tax assessment rolls. Controls were matched to cases for sex, age and place of residence; 152 cases and 109 controls had ever been exposed to sunlamps or sunbeds. The risk for melanoma, adjusted for skin reaction to initial summer exposure, was 1.54 (CI, 1.16–2.05). The relative risk in the youngest age group (20–34 years) was 1.51 (CI, 0.82–2.77). When duration of exposure to tanning appliances was analysed by category (never; <12 months; ≥ 12 months), a significant trend was observed both for men ($p < 0.01$) and for women ($p = 0.04$). [This study was initially published in 1990 (Walter *et al.,* 1990). Further calculations with new adjustments were published in 1999 (Walter *et al.,* 1999).]

Westerdahl et al. (1994): A case–control study was conducted in Sweden between July 1988 and June 1990. The authors recruited 400 incident cases selected from the regional tumour registry, and 640 controls selected from the National Population Registry, aged 15 to 75 years. Controls were matched to cases for age, sex and place of residence. Of these, 111 cases and 159 controls had ever used sunbeds or sunlamps. The relative risk, adjusted for sunburns, hair colour, naevi number and sunbathing habits during summer, was 1.3 (CI, 0.9–1.8). Among individuals aged ≤ 30 years, the relative risk was 2.7 (CI, 0.7–9.8). When exposure exceeded 10 sessions per year, the risk for melanoma was significantly increased over that of never-users (OR, 1.8; CI, 1.0–3.2).

Holly et al. (1995): A case–control study on melanoma risk factors was conducted in San Francisco, USA between January 1981 and December 1986. The study was restricted to women aged 25–59 years. The authors recruited 452 incident cases ascertained through the SEER Registry for the San Francisco Bay area and 452 controls ascertained using telephone random digit dialling. Controls were frequency-matched to cases for age in 5-year categories. Exposure to sunlamps was investigated. No association was observed for ever using a sunlamp (crude OR, 0.94; CI, 0.74–1.2). [The Working Group noted that use of sunlamps by 63% of cases and 62% of controls, as presented in the text, would result in an odds ratio of 1.05 (CI, 0.79–1.38). Despite this inconsistency, it was decided to use the estimate given in the table.]

Chen et al. (1998): A case–control study was conducted in Connecticut, USA between January 1987 and May 1989. Using the population-based Rapid Case Ascertainment System, 624 incident cases were identified and 512 controls ascertained using telephone random digit dialling. Of these, 141 cases and 95 controls had ever used a sunlamp or sunbed. The risk for melanoma associated with sunlamp or sunbed exposure was 1.13 (CI, 0.82–1.54) after adjustment for age, sex, cutaneous phenotype index and recreational sun exposure index. In a stratified analysis, the relative risk associated with first exposure before age 25 years was 1.35 (CI, 0.88–2.08). No trend was observed in relation to duration of exposure to sunlamps or sunbeds.

Westerdahl et al. (2000): A case–control study was conducted in the South Health Care region of Sweden between January 1995 and June 1997. The authors recruited 571 incident cases identified in the regional tumour registry, and 913 controls matched for age and sex ascertained from the National Population Registry. Of these, 250 cases and 372 controls had ever used sunbeds. The risk for melanoma associated with sunbed exposure was 1.2 (CI, 0.9–1.6) after adjustment for age, sex, history of sunburn, hair colour, skin type and number of raised naevi. No change in the estimate was observed after adjustment for sunbathing habits. In a stratified analysis, there was a significant increase in risk when exposure took place before the age of 35 years (OR, 2.3; CI, 1.2–4.2). No trend relating to total duration of exposure was observed.

(c) Hospital- or clinic-based case–control studies

Klepp & Magnus (1979): A hospital-based case–control study was conducted in Oslo, Norway between January 1974 and May 1975. The authors enrolled 89 cases and 227 controls aged 20 years or more to evaluate possible etiological factors for melanoma. Cases were incident cutaneous melanomas from the Norwegian Radium Hospital; controls were other cancer patients in the same hospital. The self-administered questionnaire included a question about use of artificial UV lamps. No estimates were derived from the results because exposure to UV lamp was very rare, and there was no difference between cases and controls.

Gallagher et al. (1986): A case–control study was conducted in western Canada between April 1979 and March 1981. To study risk factors for melanoma, including host factors, sun exposure, and the use of oral contraceptive for women, 595 incidence cases from dermatology practice and 595 controls from provincial medical plans were recruited. Controls were matched to cases for age and sex. The recruitment was limited to individuals 20–79 years old. No estimate of the risk was presented. The study showed no association between sunlamp use and subsequent risk for melanoma (χ^2=6.1; 5 df; p=NS), including after stratifying by sex or by anatomical site exposed to the sunlamp.

Holly et al. (1987): A hospital-based case–control study was conducted in San Francisco (USA) between April 1984 and October 1987. To assess melanocytic naevi (dysplatic and non-dysplastic naevi) as risk factor for melanoma, 121 incident cases were recruited from a melanoma clinic at the University of California, San Francisco, and 139 controls were recruited among patients in another clinic at the same university. No estimate of the risk for melanoma associated with sunbed use was presented. The patients with cutaneous melanoma were similar to those in the control group with respect to their use of tanning salons.

Swerdlow et al. (1988): A hospital-based case–control study was conducted in Scotland (United Kingdom) between 1979 and 1984 to evaluate the role of fluorescent light and UV lamps on cutaneous melanoma risk. The authors recruited 180 incident cases from dermatology and plastic surgery units and 197 hospital inpatients and outpatients as controls excluding those with malignant disease. Analysis for exposure to tanning appliances was restricted to 120 controls without dermatological disease. Only 38 cases and 10 controls had ever used UV lamps or sunbeds (crude OR, 2.94; CI, 1.40–6.17). Data by age at first use (before and after age of 30 years) and by total number of hours of exposure (1–19 hours; ≥ 20 hours within the 5 years before presentation)

were also presented. A significant linear trend for duration of use was observed ($p<0.01$). Adjustment for hair colour, eye colour, skin type or sun exposure did not substantially change the estimates, while a small decrease was observed when adjusting for number of naevi.

MacKie et al. (1989): A hospital-based case–control study of melanoma was conducted in Scotland, United Kingdom in 1987. The authors identified 280 incident cases (99 men and 181 women) through the Scottish Cancer Registry; 280 controls (99 men and 181 women) were recruited at a hospital, excluding patients with dermatological illness. Controls were matched to cases for age and sex. In the questionnaire, one item investigated exposure to artificial UV radiation and use of sunbeds; 33 cases and 8 controls had been exposed to such sources. The odds ratio was stratified by sex and adjusted for total number of naevi, atypical naevi, freckling tendency, history of severe sunburns, tropical residence for more than 5 years and skin type. The adjusted odds ratios were 1.3 (CI, 0.2–7.9) for men and 1.2 (CI, 0.5–3.0) for women. Only 26 cases and 6 controls had used "modern sunbeds" once or twice weekly for at least 12 weeks. [Due to stratification by sex, two estimates from this study were used in the analysis.]

Beitner et al. (1990): A case–control study was conducted in Stockholm, Sweden between February 1978 and December 1983. The authors recruited 523 incident cases from the Department of Oncology at Karolinska Hospital and 505 controls selected from population registries. Controls were matched to cases for age and sex. No estimate of the risk was presented. No increase in the risk for developing cutaneous malignant melanoma was associated with frequent exposures to solaria.

Dunn-Lane et al. (1993): A hospital-based case–control study was conducted in Dublin, Ireland between 1985 and 1986. The authors recruited 100 incident cases from seven Dublin hospitals and 100 controls, admitted for limb injuries in the accident and emergency and orthopaedic departments, were recruited. Controls were matched to cases for age (within 5 years), sex and health broad area of residence. Seventeen cases and 15 controls had ever used sunbeds. The crude odds ratio [calculated by the Working Group] was 1.16 (CI, 0.54–2.47). [No estimates were reported by the authors.]

Garbe et al. (1993): A hospital-based case–control study evaluating risk factors for melanoma was conducted in Germany between 1984 and 1987. The authors studied 856 cases selected from the Central Malignant Melanoma Registry of the German Dermatology Society and 705 controls selected from outpatients presenting at dermatology clinics. Of these, 66 cases and 50 controls had ever used sunbeds. The relative risk for melanoma, adjusted for number of naevi, hair colour, skin type, age and study centre, was 1.5 (CI, 0.9–2.4). [The Working Group noted that the Central Malignant Melanoma Registry is a voluntary registry.]

Autier et al. (1994): A case–control study of melanoma was conducted in Europe (Germany, France, Belgium) from January 1991 onwards. The authors recruited 420 incident cases from dermatology practices and cancer centres; 447 controls were selected from neighbourhood by door-knock. Of these, 110 cases and 120 controls had ever been exposed to sunlamps or sunbeds. While there was no crude association with melanoma (OR, 0.97; CI, 0.71–1.32), in a stratified analysis total exposure to sunlamp or sunbed for tanning purposes for more than 10 hours and before 1980 showed an increased risk (OR, 2.12; CI, 0.84–5.37) after adjustment for age, sex, hair colour and number of holiday weeks per year. The risk for melanoma associated with sunlamp or sunbed use was significantly increased if exposures for more than 10 hours were accompanied by a burn to the skin (OR, 7.35; CI, 1.67–32.3).

Naldi et al. (2000): A hospital-based case–control study of melanoma was conducted in Italy between June 1992 and February 1995. The authors recruited 542 incident cases from oncology and dermatology centres, and 528 controls admitted to the hospital for a non-dermatologic or

non-neoplastic illness. Of these, 30 cases and 36 controls were ever exposed to sunbeds or sunlamps. The risk for melanoma, adjusted for age, sex, marital status, education, eye and skin colour, number of naevi, freckles density, sunburns and number of sunny vacations, was 0.78 (CI, 0.45–1.37).

Kaskel et al. (2001): A hospital-based case–control study of melanoma was conducted in Munich, Germany between June 1996 and April 1997. The authors recruited 271 prevalent cases (diagnosed from 5 years to 6 months before inclusion) from the Tumour Centre in Munich, and 271 controls from hospital departments of general surgery and ophthalmology. Controls were matched to cases for age (in 5-year categories), sex and place of residence. Among the 56 factors explored, one item investigated exposure to UV radiation or UV beds more than 5 times per year compared with 5 times per year or less. In the analysis of discordant pairs, the crude risk for artificial UV exposure was 1.0 (CI, 0.6–1.8).

Bataille et al. (2004): A hospital-based case–control study of melanoma was conducted in the North East Thames region (United Kingdom) between August 1989 and July 1993. The authors recruited 413 cases and 416 controls aged 16 to 75 years old. Incident cases of histologically confirmed melanomas were recruited from hospitals and general practices. Controls were also recruited through hospitals and general practices, excluding patients attending for a skin disease. One hundred cases and 110 controls had ever been exposed to sunbeds. The risk for melanoma associated with sunbed use was 1.19 (CI, 0.84–1.68), after adjusting for age and sex. Further adjustment for skin type and other sun exposure measures did not affect the results. In a stratified analysis, if sunbed exposure took place before the age of 45 years, the relative risk was 1.2 (CI, 0.76–1.90). No trend toward increased risk was observed with increasing lifetime duration of exposure.

Bataille et al. (2005): A case–control study designed specifically to investigate melanoma risk associated with sunbed exposure was conducted in Belgium, France, the Netherlands, Sweden and the United Kingdom between December 1998 and July 2001. The authors recruited 597 incident cases from dermatology or oncology clinics or identified through pathology laboratories. The method of recruitment of 622 controls differed according to each centre: population register in Sweden, neighbourhood controls in Belgium and France, and general practices in the Netherlands and the United Kingdom. Of these, 315 cases and 354 controls had ever used sunbeds. The risk for melanoma associated with sunbed use was 0.9 (CI, 0.71–1.14) when adjusting for age, sex and skin type. If exposure to tanning appliances occurred before age 15 years, the relative risk was 1.82 (CI, 0.92–3.62). No trends in risk for melanoma were observed with increasing lifetime exposure or with increasing time since first exposure. No association was observed when stratifying by type of sunbed. [A companion paper warned about potential biases that could have occurred in this study: selection bias of controls and misclassification of cases who tended to underreport their exposure (deVries *et al.,* 2005)].

Of these 23 studies, 4 studies were excluded—in accordance with the selection criteria—because they did not include estimates of the relative risk for cutaneous melanoma associated with exposure to tanning appliances (Klepp & Magnus, 1979; Gallagher *et al.,* 1986; Holly *et al.,* 1987; Beitner *et al.,* 1990).

Another study (Walter *et al.,* 1990) which presented an evaluation of "ever" versus "never" exposed to artificial UV radiation was excluded because it involved the same population as a later publication (Walter *et al.,* 1999); moreover, it presented crude rather than adjusted relative risks. However, the estimate for "first exposure before age 35 years" from the early publication (Walter *et al.,* 1990) was included in the relevant section.

Quantitative approach: meta-analysis

(a) Evaluation of exposure: Four types of exposure to indoor tanning appliances were evaluated:
- "ever" versus "never";
- "first exposure before age 35 years" versus ''never".

In addition, another concept was considered in order to make a comparison between recent and distant exposures:

- "exposure distant in time" versus "never";
- "exposure recent in time" versus "never".

A dose-response model was not considered for this meta-analysis because of the heterogeneity among the categories of duration and frequency of exposure used by different authors.

(b) Study characteristics: Table 7 provides an overview of all the studies retrieved, including the 19 studies reporting estimates that could be included in the meta-analysis (for a total of 7 355 cases). The first (published in 1981) and the last (published in 2005) studies included were published more than 20 years apart. Three case–control studies presented a time lag between first recruitment year and publication of 10 years or more.

Fifteen studies were carried out in European countries, four of which were in Scandinavian countries; two were conducted in the United States, one in Canada and one in Australia. The mean latitude of the study centres was 50° (range 25º–59º); eight studies were conducted in countries with average latitude below 50°.

(c) Types of estimate presented: Since melanoma is a rare disease, we ignored the distinction between the various estimates of relative risk (i.e. odds ratio, rate ratio, risk ratio), and all measurements were interpreted as odds ratios.

Except for the studies by Kaskel *et al.* (2001) and by Veierød *et al.* (2003), all studies presented estimates for "ever" versus "never" exposed to artificial UV radiation (Table 8). Thirteen of 19 studies presented positive estimates for "ever" versus "never" exposed to sunbed/sunlamps, but only four were statistically significant. For seven of these studies it was possible to obtain only crude relative risks, one adjusted for age and sex only.

The cohort study (Veierød *et al.,* 2003) presented an estimate for the widest age interval included (10–39 years), only for the comparison "≥ 1 time per month" versus "never/rarely". One study (Kaskel *et al.,* 2001) presented an estimate only for the comparison ">5 times per year" versus "≤ 5 times per year".

Five studies (Swerdlow *et al.,* 1988; Walter *et al.,* 1990; Chen *et al.,* 1998; Westerdhal *et al.,* 2000; Bataille *et al.,* 2005) also presented an estimate for first exposure at age ≤ 35 years (Table 9). Veierød *et al*. (2003) presented relative risks for "≥ 1 time per month" versus "never" in the age period 20–29 years; Westerdhal *et al*. (1994) presented estimates of "ever" versus "never" for individuals younger than 30 years. All relative risks were adjusted for confounders related to sun exposure or sun sensitivity, except in the study by Walter *et al.* (1990). All these estimates were considered for the evaluation of "first exposure before age 35 years" versus "never".

Five studies investigated time since exposure (Table 10) and reported estimates that allowed comparisons between recent and distant exposure: number of years of exposure before presentation (Swerdlow *et al.,* 1988; Bataille *et al.,* 2005), number of years since last exposure (Walter *et al.,* 1990) and age at first exposure (Autier *et al.,* 1994; Chen *et al.,* 1998).

(d) Selection of data and methods of analysis: Every measure of association adjusted for the maximum number of confounding variables and corresponding confidence interval were transformed into log RR, and the corresponding variance was calculated using the formula proposed by Greenland (1987). Where no estimates were given, crude estimates were calculated from tabular data, using Asymptotic Mantel-Haenszel estimates to evaluate the 95% CI of the log odds ratio.

Most estimates included all subjects, combining sexes. One study presented results separately for women and men with no combined data; both estimates were included (MacKie *et al.,* 1989).

The homogeneity of the effects across studies was assessed using the large sample test based on the Chi-square statistic (Chi). Since the Chi-square test has limited power, we considered statistically significant heterogeneity at the P=0.10 level of association. A further measure of heterogeneity, H (the square-root of Chi-square divided by its degrees of freedom), has been considered in order to make comparisons between heterogeneities of pooled estimates summarizing

Table 7. Characteristics of studies considered for the meta-analysis on melanoma

Reference	Country	First Year	Number		Histological diagnosis	Participation of controls (%)
			Cases	Controls		
Cohort study						
[1]Veierød *et al*. (2003)	Norway, Sweden	1992	187	106 379[2]	HC invasive M	54.5[3]
Population-based case–control studies						
[1]Adam *et al*. (1981)	UK	1971	169	207	HCM	68
Gallagher *et al*. (1986)	Western Canada	1979	595	595	M excluding LMM and ALM	48
[1]Holman *et al*. (1986)	Australia	1982	511	511	HC pre-invasive/ invasive M	69
[1]Osterlind *et al*. (1988)	Denmark	1985	474	926	HCM excluding LMM	81.7
[1]Zanetti *et al*. (1988)	Italy	1984	208	416	M *in situ* and all other histology	68.2
Beitner *et al*. (1990)	Sweden	1978	523	505	HCM (SSM, NM, LMM, unclassif. MM)	96.2
Walter *et al*. (1990)	Canada	1984	583	608	HCM *in situ* and Hutchinson's freckle, LMM	81
[1]Westerdahl *et al*. (1994)	Sweden	1990	400	640	Invasive M	77.4
[1]Holly *et al*. (1995)	USA	1986	452	930	HCM	77
[1]Chen *et al*. (1998)	USA	1989	624	512	HC first primary invasive M	70
[1]Walter *et al*. (1999)	Canada	1986	583	608	HCM *in situ* and Hutchinson's freckle, LMM	81
[1]Westerdahl *et al*. (2000)	Sweden	1997	571	913	HC first primary invasive M	68
Other case–control studies						
Klepp & Magnus (1979)	Norway	1974	78	131	M	NR
Holly *et al*. (1987)	USA	1984	121	139	NM or SSM	NR
[1]Swerdlow *et al*. (1988)	UK	1988	180	120	Primary M	NR
[1]MacKie *et al*. (1989)	UK	1987	280	180	Invasive M	NR
[1]Dunn-Lane *et al*. (1993)	UK	1986	100	100	M excluding LMM and ALM	NR
[1]Garbe *et al*. (1993)	Germany	1987	280	280	M	NR
[1]Autier *et al*. (1994)	Belgium, France & Germany	1991	420	447	HCM	78
[1]Naldi *et al*. (2000)	Italy	1993	542	538	M	NR
[1]Kaskel *et al*. (2001)	Germany	1996	271	271	HCM	NR
[1]Bataille *et al*. (2004)	UK	1993	413	416	M including *in situ* and LMM	NR
[1]Bataille *et al*. (2005)	UK	1998	597	622	HC first primary invasive M excluding LMM	NR

[1]included in the meta-analysis; [2]cohort size; [3]response rate.

ALM, acral lentiginous melanoma; HC, histologically confirmed; LMM, lentigo maligna melanoma; M, melanoma; MM, malignant melanoma; NM, nodular melanoma; NR, not reported; SSM, superficial spreading melanoma.

Table 8. Estimates included in the evaluation of an association of ever use of indoor tanning facilities and risk for melanoma

Reference	Exposure comparison	Relative risk (95% CI)	Adjustment
Adam *et al*. (1981)	Ever use of sunlamps *vs* never	2.93 (1.16–7.40)	Crude
Holman *et al*. (1986)	Ever use of sunlamps *vs* never	1.1 (0.6–1.8)	Crude
Osterlind *et al*. (1988)	Ever use of sunbeds *vs* never	0.73 (0.53–1.01)	Crude
Swerdlow *et al*. (1988)	Ever use of UV lamps/ sunbeds *vs* never	2.94 (1.41–6.17)	Crude
Zanetti *et al*. (1988)	Use of UVA lamp for tanning purpose: yes/no	0.9 (0.4–2.0)	Age, hair colour, skin reaction, sunburn in childhood, education level
MacKie *et al*. (1989) (men)	Ultraviolet use: some *vs* none	1.3 (0.2–7.9)	Naevi, freckles, sunburns, tropical residence, phototype
MacKie *et al*. (1989) (women)	Ultraviolet use: some *vs* none	1.2 (0.5–3.0)	Naevi, freckles, sunburns, tropical residence, phototype
Dunn-Lane *et al*. (1993)	Ever use of sunbeds *vs* never	1.16 (0.54–2.47)	Crude
Garbe *et al*. (1993)	Use of sunbeds: yes/no	1.5 (0.9–2.4)	Age, naevi, hair colour, phototype, study centre
Autier *et al*. (1994)	Ever exposed to sunlamps/sunbeds *vs* never	0.97 (0.71–1.32)	Crude
Westerdahl *et al*. (1994)	Ever exposed to sunbeds/sunlamps *vs* never	1.3 (0.9–1.8)	Sunburns, hair colour, naevi, sunbathing
Holly *et al*. (1995) (women)	Ever use of sunlamps *vs* never	0.94 (0.74–1.2)	Crude
Chen *et al*. (1998)	Ever use of sunlamps *vs* never	1.13 (0.82–1.54)	Sex, age, phenotype, recreational sun exposure
Walter *et al*. (1999)	Ever use of sunbeds/sunlamps *vs* never	1.54 (1.16–2.05)	Sex, age, skin reaction to initial summer sun exposure
Naldi *et al*. (2000)	Ever use of sunbeds/sunlamps *vs* never	0.78 (0.45–1.37)	Sex, age, skin, hair, eye, naevi, freckles, sunburn, number of sunny vacations
Westerdahl *et al*. (2000)	Ever use of sunbeds *vs* never	1.2 (0.9–1.6)	Sunburns, hair colour, skin type, raised naevi
Kaskel *et al*. (2001)	Artificial UV radiation/UV beds: >5/year *vs* ≤5/year	1.00 (0.6–1.8)	Crude
Veierød *et al*. (2003) (women)	Solarium use : ≥1/month *vs* never/rarely	1.55 (1.04–2.32)	Age, region of residence, hair colour, sunburns, summer vacations
Bataille *et al*. (2004)	Ever use of sunbeds *vs* never	1.19 (0.84–1.68)	Sex, age
Bataille *et al*. (2005)	Ever use of sunbeds or sunlamps *vs* never	0.90 (0.71–1.14)	Sex, age, skin phototype

Table 9. Estimates included in the evaluation of an association of first use of indoor tanning facility in youth and risk for melanoma

Reference	Definition	Relative risk (95% CI)	Adjustment
Swerdlow *et al.* (1988)	Age at first exposure <30 years *vs* never	3.8 (0.9–16.5)	Naevi, skin type, hair and eye colour, sun exposure
Walter *et al.* (1990)	Age at first use <30 years *vs* never	1.67 (1.17–2.39)	Age
Westerdahl *et al.* (1994)	Ever use of sunbed at age younger than 30 years	2.7 (0.7–9.8)	Sunburns, hair colour, naevi, sunbathing
Chen *et al.* (1998)	Age at first use of sunlamp < 25 years *vs* never	1.35 (0.88–2.08)	Sex, age, phenotype index, recreational sun exposure
Westerdahl *et al.* (2000)	Age at first exposure ≤ 35 years *vs* never	1.6 (0.9–2.9)	Sunburns, hair colour, skin type, naevi
Veierød *et al.* (2003)	Exposure at age 20–29: ≥ 1 time/month *vs* never	2.58 (1.48–4.50)	Age, region of residence, sunburns, summer vacations
Bataille *et al.* (2005)	Ever sunbed use before age 15 years *vs* never	1.82 (0.92–3.62)	Age, sex, skin type

Table 10. Estimates included in the evaluation of an association of distant and recent exposure and risk for melanoma

Reference	Definition	Relative risk (95% CI)	Adjustment
Swerdlow *et al.* (1988)	Less than 5 years before presentation *vs* never	1.9 (0.6–5.6)	Age, sex, residence
	More than 5 years before presentation *vs* never	9.1 (2.0–40.6)	
Walter *et al.* (1990)	Less than 5 years since last use *vs* never	Men, 1.52 (0.56–4.25) Women, 1.24 (0.67–2.31)	Age
	More than 5 years since last use *vs* never	Men, 2.00 (1.21–3.34) Women, 1.53 (0.96–2.46)	
Autier *et al.* (1994)	First use in 1980 or later (≥ 10 hr of exposure for tanning purposes)	0.99 (0.49–2.00)	Age, sex, hair colour, holiday weeks spent in sunny resorts
	First use before 1980 (≥ 10 hr of exposure for tanning purposes)	2.12 (0.84–5.37)	
Chen *et al.* (1998)	First use after 1970	1.15 (0.64–2.07)	Sex, age, phenotype index, recreational sun exposure
	First use before 1970	1.33 (0.84–2.12)	
Bataille *et al.* (2005)	< 6 years between first sunbed use and interviews	0.91 (0.58–1.42)	Sex, age, skin type
	≥ 15 years between first sunbed use and interviews	0.97 (0.70–1.34)	

different numbers of studies. Greater values of H indicate larger heterogeneity (Higgins & Thompson, 2002).

The summary relative risk was estimated by pooling the study-specific estimates by random effects models even when heterogeneity was found to be not significant and H was very low, in order to be conservative and to enable generalization of the results. For mixed effects models, SAS was used (SAS Institute Inc. SAS Windows version 8.02, 1999, Cary, NC) with PROC MIXED (van Houwelingen *et al.,* 2002). These models allowed taking into account between-study variability and non-independence of estimates originating from the same study.

Subgroup analyses and meta-regressions were carried out to investigate inter-study heterogeneity (Colditz *et al.,* 1995). Heterogeneity was investigated by looking at all factors concerning the type of study, analysis, exposure and features of the population that could influence the estimates. Studies conducted in different populations living at substantially different latitudes were not included in the heterogeneity analysis that evaluated latitude.

A sensitivity analysis was conducted to evaluate the stability of the pooled estimates and the influence of individual studies. To verify whether publication bias might affect the validity of the estimates, funnel plots were plotted using Copas and Shi's method (Copas & Shi, 2001) and the funnel plot regression of Ln(RR) on the sample size, weighted by the inverse of the pooled variance (Macaskill *et al.,* 2001).

(e) Pooled estimates: Results of the meta-analysis of all studies included are shown in Table 11 and Figure 2. Between-study heterogeneity was found significant for being "ever" versus "never" exposed to artificial UV (Chi=35.40, degrees of freedom (d.f.) =19, P=0.013). The pooled estimate indicated a borderline-significant positive association between "ever" versus "never" use of sunlamps/sunbed and melanoma (RR, 1.15; CI, 1.00-1.31).

When "first exposure before age 35 years" was analysed, a significant 75% increase in risk was detected (Table 11; Figure 3) and the Chi-square testing heterogeneity was non-significant (Chi = 4.95, d.f . = 6, P = 0.55) and H (= 0.91) was smaller than the value obtained for "ever" versus "never" (H = 1.37).

The number of studies presenting an assessment of time since exposure was low (n = 5); however all studies presented greater estimates for exposures more distant in time compared to more recent exposures. Heterogeneity was greater for "distant exposure" (H = 1.65 and Chi =13.63, d.f. = 5, P = 0.018) than for "recent exposure" (H = 0.67 and Chi = 2.52, d.f. = 5, P = 0.81).

It is interesting to note that exposures more distant in time led to an increased risk compared with recent exposures, consistently with the higher risk for "first exposure before age 35 years" versus "never" compared to "ever" versus "never".

In order to decrease the influence of biases, estimates were calculated including only the cohort and population-based case–control studies (Table 12). The pooled relative risks were very similar apart from wider confidence intervals.

Table 11. Meta-analysis of all studies included

Exposure	Number of studies	Summary relative risk (95% CI)	Heterogeneity[1]	
			P-value χ^2	H
Ever use of indoor tanning facility	19	1.15 (1.00–1.31)	0.013	1.37
First exposure in youth	7	1.75 (1.35–2.26)	0.55	0.91
Exposure distant in time	5	1.49 (0.93–2.38)	0.018	1.65
Exposure recent in time	5	1.10 (0.76–1.60)	0.81	0.67

[1]The degrees of freedom for the Chi-square are given by the number of databases included minus one, not by the number of studies.

Figure 2. Relative risk for cutaneous melanoma associated with ever use of indoor tanning equipment: estimates of 19 studies and summary estimate

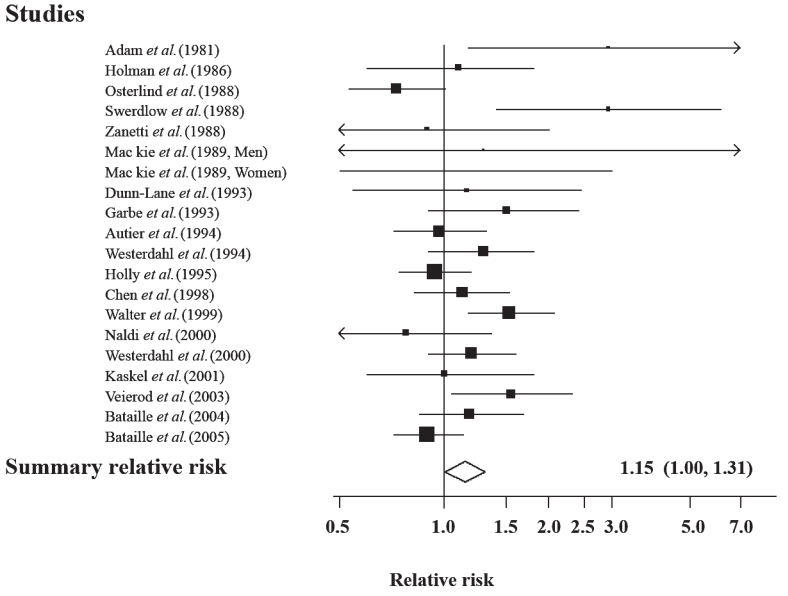


Figure 3. Relative risk for cutaneous melanoma associated with first use of indoor tanning equipment at age <35 years: estimates of 7 studies and summary estimate

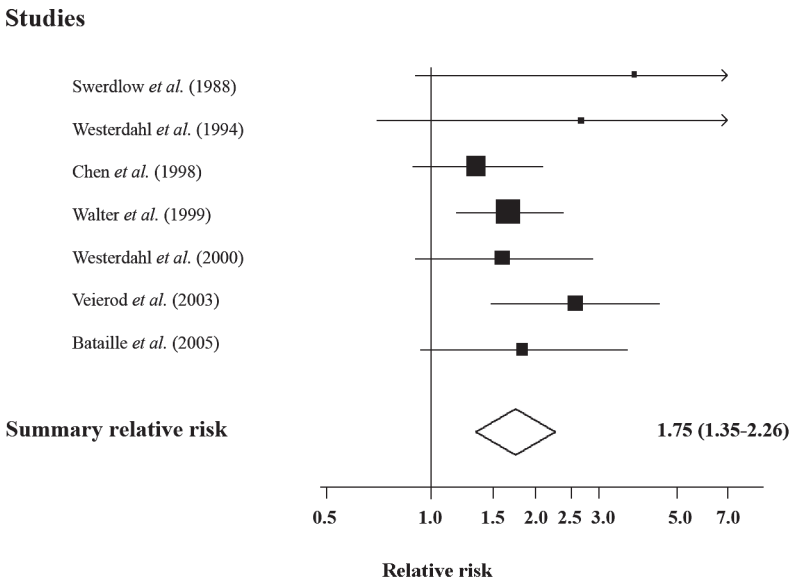


Table 12. Meta-analysis of the cohort and population-based case–control studies included

Exposure	Number of studies	Summary relative risk (95% CI)	Heterogeneity	
			P-value χ^2	H
Ever use of indoor tanning facility	10	1.17 (0.96–1.42)	0.011	1.540
Age at first exposure in youth	5	1.71 (1.25–2.33)	0.435	0.973
Exposure distant in time	2	1.58 (0.25–9.98)[1]	0.502	0.830
Exposure recent in time	2	1.24 (0.52–2.94)	0.762	0.521

[1]The confidence interval is very wide because this analysis includes only 2 studies, one of which has two estimates.

(f) Heterogeneity analysis: For the comparison of "ever" versus "never", which included the largest number of studies, several factors that could influence the variability among estimates were investigated. This analysis revealed that studies with a longer time lag between the first year of recruitment and publication (≥ 10 years) presented higher estimates (Table 13). (The cohort study was excluded from this analysis because of the nature of the study design.)

Studies carried out in countries at higher latitudes presented higher relative estimates than did studies carried out at lower latitudes (Table 13 and Figure 4).

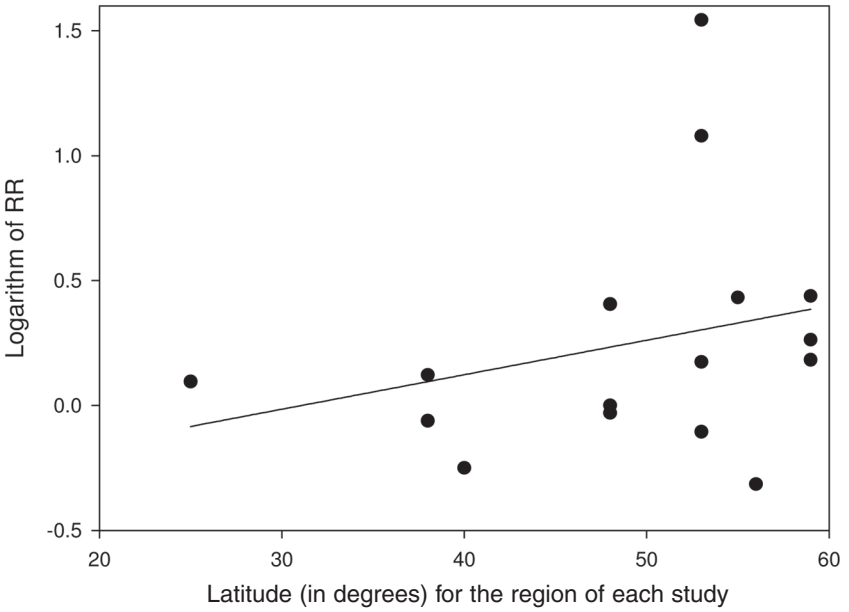
Adjustment for confounders related to sun exposure and sun sensitivity led to a higher pooled estimate compared with studies considering only crude relative risks or relative risks adjusted only for age and sex (Table 13). In the analysis restricted to the eight studies that adjusted for confounders related to sun exposure and sun sensitivity, the pooled relative risk remained similar to the summary estimate for all 19 studies but the confidence interval widened (RR, 1.19; CI, 0.33–4.30). The difference between adjusted and crude pooled relative risks may not be due to the adjustment in itself but to the fact that well-conducted studies usually adjust for sun exposure and sun sensitivity, which could be an indicator of the quality of the analysis.

(g) Sensitivity analysis: A series of analyses were performed to test the stability and sensitivity of the analysis (Table 14). Inclusion criteria were tested by including the estimates reported by Walter and colleagues in 1990 instead of those reported in 1999. Also, the studies that did not report any relative risk (Klepp & Magnus, 1979; Gallagher *et al.,* 1986; Holly *et al.,* 1987; Beitner *et al.,* 1990) were included by imputing the

Table 13. Heterogeneity analysis

Parameter analysed	Number of studies	Pooled relative risk (95% CI)	Heterogeneity
			P-value χ^2
Number of years between recruitment and publication ≥ 10	3	1.38 (0.25–7.46)	0.16
Number of years between recruitment and publication <10	15	1.06 (0.50–2.27)	0.14
Estimate adjusted for phototype/sun exposure/sunburns	10	1.19 (0.45–3.12)	0.17
Crude estimate or estimate adjusted for age and sex only	9	1.03 (0.31–3.40)	0.018
Latitude of study centre <50°	8	1.08 (0.31–3.78)	0.73
Latitude of study center >50°	11	1.20 (0.41–3.46)	0.003

Figure 4. Correlation between latitude of study centre and relative risk for melanoma associated with use of indoor tanning facilities



missing estimates from data available in the reports. Where no data at all were presented but an indication of non-significant effect was given, a relative risk of 1 and a standard error equal to the mean standard error of the other studies was considered. The pooled relative risks did not change considerably (Table 14).

In order to verify the stability of the results, a new analysis was carried out taking out the estimate from the cohort study (Veierød *et al.,* 2003). The pooled relative risk showed a wider confidence interval.

The definitions used to evaluate the risk for "first exposure before age 35 years" differed for two studies: one study presented an estimate of "ever" versus "never" for individuals aged ≤ 30 years (Westerdahl *et al.,* 1994); the other study (Veierød *et al.,* 2003) presented two estimates: "ever" versus "never" at age 10–19 years and "≥ 1 time/month" versus "never" at age 20–29 years. For the latter study, the estimate including a larger number of individuals (age group 20–29 years) was used for the main analysis of "first exposure before age 35 years" (only 4 cases were in the exposed group for the estimate at age 10–19 years). When both studies were excluded, the pooled estimate did not change considerably (Table 14).

For the evaluation of recent and distant exposures, Autier et al. (1994) reported estimates by several substrata; for the main analysis we selected the adjusted relative risk evaluating exposure for tanning purposes and for a duration of 10 hr or more. Crude relative risks obtained by merging all categories were: for "distant exposure", 1.22 (CI, 0.79–1.88) and for "recent exposure", 0.82 (CI, 0.56–1.19). Thus the pooled relative risk for "distant exposure" remained greater than that for "recent exposure" (data not shown).

Analysis by Funnel plot regression gave no indication of publication bias ("ever used sunbed/sunlamps", P = 0.80; "first exposure before age 35 years", P = 0.10). In addition, analysis by the Copas and Shi method of trends in the funnel plots (Figures 5 and 6) gave an indication of non-significant asymmetry ("ever used sunbed/sunlamps", P = 0.37; "first exposure before age 35 years", P = 0.15).

Discussion

To establish a causal link between exposure to tanning appliances and melanoma occurrence, studies should show whether there are dose–effect relationships and whether exposures distant in time are

Table 14. Sensitivity analysis

Parameter analysed	Inclusion criteria	Number of studies	Summary relative risk (95% CI)	P-value χ^2 Heterogeneity
Ever use of indoor tanning facility	Including study by Walter *et al.* (1990)	19	1.15 (1.00–1.32)	0.007
	Including all studies considered	23	1.14 (1.00–1.30)	0.045
	Excluding the cohort study by Veierød *et al.* (2003)	18	1.11 (0.97–1.26)	0.019
First exposure in youth	Excluding the cohort study by Veierød *et al.* (2003)	6	1.64 (1.22–2.20)	0.743
	Including only those studies with a specific definition of first exposure (studies by Veierød *et al.* 2003 and Westerdahl *et al.,* 2000 excluded)	5	1.65 (1.17–2.32)	0.709

more strongly associated with melanoma than are recent exposures. The latter point is important, as there is most probably a latency period between exposure and melanoma, thus the carcinogenic effect of more recent exposures would not yet be detectable. Also, since the fashion of using indoor tanning facilities has been increasing steadily, a lack of distinction between distant and recent exposures may mask an actual increase in risk.

Experimental and epidemiological studies provide evidence that susceptibility to UV radiation is greater at younger ages (mainly in childhood and adolescence) than at older ages (see page 8; Autier & Doré 1998; Whiteman *et al.,* 2001). Hence, data analysis should identify whether exposure to tanning appliances starting at younger ages was more strongly associated with melanoma than exposure starting at older ages.

The UV emission spectrum of UV lamps in indoor tanning appliances has changed over time: before 1980, many UV lamps produced large amounts of UVC and UVB, whereas most UV tanning appliances used after 1985 mainly emitted in the UVA range (see page 3).

(a) Case–control studies: Case–control studies of melanoma providing results on use of indoor tanning facilities have been of variable study design, and many of them only included one question on exposure to tanning appliances. Some positive or negative associations between exposure to tanning appliances and risk for melanoma may have been due to statistical fluctuations (i.e. alpha or beta errors) or to design effects.

In some studies, melanoma patients (i.e. cases) were derived from a small number of dermatologic clinics, and subjects without melanoma (i.e. controls) were derived from hospital wards or outpatient clinics. This way of selecting cases and controls is prone to many biases: for instance, control subjects could suffer from a disease associated with higher or lower propensity to engage in indoor or outdoor tanning.

Users of indoor tanning facilities have been shown to have a greater-than-average propensity to engage in intentional sun exposure (Autier *et al.,* 1991), and may have characteristics of inherited sun sensitivity different from the rest of the population (see page 9). Hence, a possible association between exposure to tanning

Figure 5. Investigation by Funnel plot representation of a possible publication bias in the studies of risk for melanoma associated with use of indoor tanning facilitites included in the meta-analysis

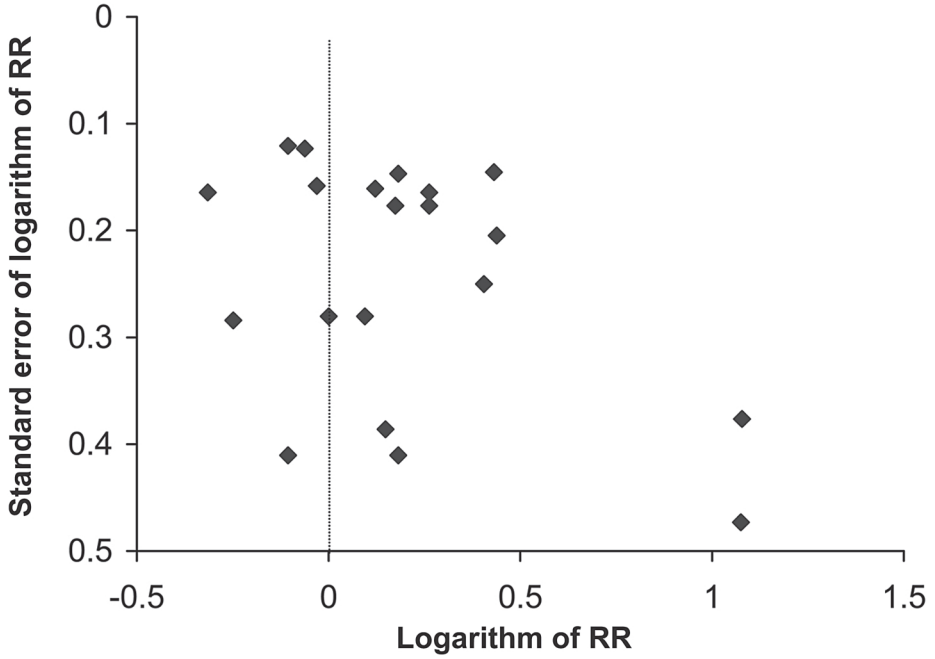
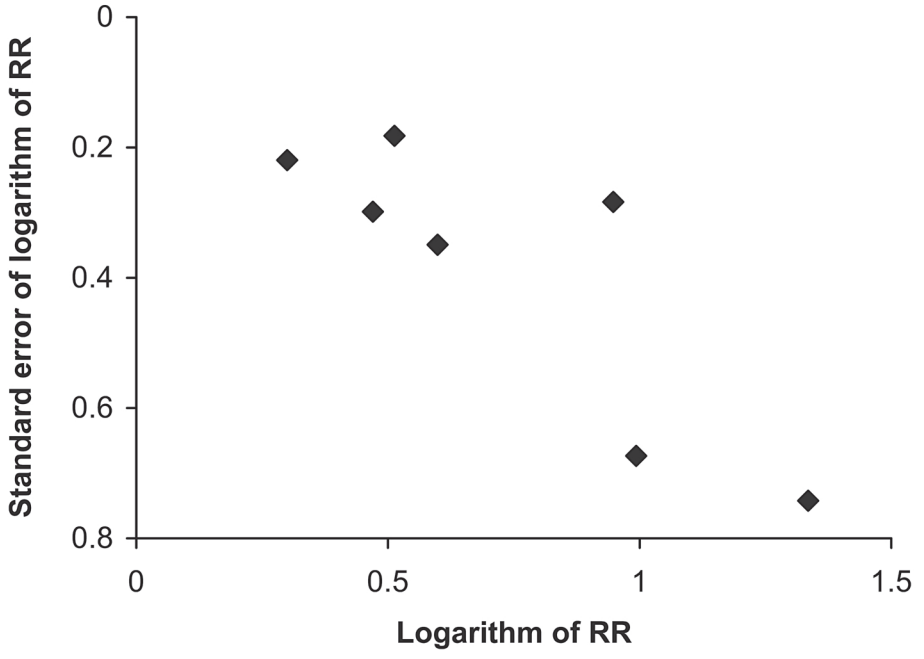


Figure 6. Investigation by Funnel plot representation of a possible publication bias in the studies of risk for melanoma associated with first use of indoor tanning facilities in youth



appliances and risk for melanoma could in fact be due to greater sun exposure than average, or to greater use of indoor tanning facilities by subjects naturally more prone to melanoma. To reduce the effect of these confounding factors on risk estimates, it was necessary to adopt statistical methods (e.g. a multivariate logistic regression model) allowing the calculation of estimated risks adjusted for both sun exposure history and host characteristics.

In order to examine the consistency of the data on exposure to tanning appliances and risk for melanoma provided by case–control studies, we selected those studies among the 19 studies included in the meta-analysis (see Tables 7 and 8) that had a section specifically exploring exposure to tanning appliances and results adjusted for (intermittent) sun exposure and sun sensitivity (Autier *et al.,* 1994; Westerdahl *et al.,* 1994; Chen *et al.,* 1998; Westerdahl *et al.,* 2000).

Table 15 presents adjusted relative risks for melanoma associated with exposure to tanning appliances, showing some statistically significant dose–effect relationship for two studies (Autier *et al.,* 1994; Westerdahl *et al.,* 1994), a borderline statistically significant dose–effect relationship in one study (Chen *et al.,* 1998), and one study with a non-significant dose–effect relationship (Westerdahl *et al.,* 2000).

Two of the four studies (Autier *et al.,* 1994; Chen *et al.,* 1998) showed that the highest risk for melanoma was associated with exposure to tanning appliances more distant in time (Table 10). Three studies (Westerdahl *et al.,* 1994; Chen *et al.,* 1998; Westerdahl *et al.,* 2000) showed that melanoma risk was highest when exposure to tanning appliances started at younger ages, i.e. before approximately 35 years old (Table 9). However, most associations with exposure distant in time and with younger age at start did not reach statistical significance because of the low number of subjects in the relevant categories of exposure. Statistical significance first emerged when all data were combined in a meta-analysis, resulting in a greater number of subjects in relevant categories of exposure and thus higher statistical power (see page 30).

(b) Prospective study: The Norwegian-Swedish study (Veierød *et al.,* 2003) is the only published prospective cohort study of environmental risk factors for melanoma. Women in Norway and Sweden (N=106 379) were followed for an average of 8.1 years from 1991 until 1999. The study showed consistent associations between host characteristics of inherited sun susceptibility, sunburn history, sun exposure, exposure to tanning appliances and cutaneous melanoma. During follow-up, 187 cases of melanoma were diagnosed. After adjustment for intermittent sun exposure and host characteristics, the adjusted relative risk for melanoma was 1.55 (CI, 1.04–2.32) among the 18% of women aged 10–39 years who reported having used sunbeds at least once a month when they were 10–19, 20–29 or 30–39 years old. Twelve sunbed sessions per year correspond to the typical tanning programme proposed by many commercial tanning facilities. Thus the 55% increase in melanoma risk was related to 40 hours or more of exposure to tanning appliances, assuming an average of 20 minutes per session. In that respect, the levels of exposure to tanning appliances reported in this prospective study were more comparable with levels reported in surveys carried out in European countries than those reported in case–control studies.

In the Scandinavian countries, use of indoor tanning facilities has been popular since the late 1970s, and the prevalence of use of indoor tanning facilities in those countries is the highest in the world. In the Norwegian-Swedish prospective study, the highest risk for melanoma was found in women who used indoor tanning facilities at least once per month when they were 20 to 29 years old (RR, 2.58; CI, 1.48–4.50), and the lowest risks were found for exposure to tanning appliances at least once a month during the third (RR, 1.42; CI, 0.93–2.16) or the fourth decade of life (RR, 1.67; CI, 0.93–2.99). These results support the hypothesis by which a latency period is needed before the impact of exposure to tanning appliances on melanoma incidence becomes apparent. It also underlines the greater vulnerability of younger subjects to harmful effects of sunbeds.

Table 15. Duration of exposure to indoor tanning facilities and risk for melanoma in selected case–control studies[1]

Reference Place & years of study Numbers of cases/control		Duration of exposure	Cases	Controls	Estimated risk	95% CI
Autier *et al.* (1994)		Never used	310	327	1.00	Ref.
Belgium, France, Germany,	Exposure starts	< 10 hours	36	45	0.75	0.46–1.25
1991–92	≥ 1980	≥ 10 hours	19	18	0.99	0.49–2.00
420/447[2]	Exposure starts	< 10 hours	16	15	1.00	0.47–2.13
	< 1980	≥ 10 hours	18	7	2.12	0.84–2.12
Westerdahl *et al.* (1994)		Never used	282	479	1.0	Ref.
Sweden, 1988-90		1–3 sessions/year	44	67	1.1	0.7–1.9
400/640		4–10 sessions/year	30	55	1.1	0.7–1.9
		>10 sessions/year	41	33	1.8	1.0–3.2
Chen *et al.* (1998)		Never used	483	417	1.00	Ref.
Connecticut, USA, 1987–89		< 10 sunlamp uses	76	50	1.25	0.84–1.84
624/512		≥ 10 sunlamp uses	63	40	1.15	0.60–2.20
Westerdahl *et al.* (2000)		Never used	319	538	1.0	Ref.
Sweden, 1995–97		1–125 uses	22	32	2.8	1.0–7.8
571/913		126–250 uses	34	31	3.1	1.3–7.1
		> 250 uses	31	37	1.5	0.7–3.2

[1] Duration of exposure, relative risk, and 95% confidences as in published reports. All estimated risks are adjusted for age, sex, natural sun sensitivity and recreational sun exposure.

[2] The 21 cases and 35 controls who were exposed to sunlamp or sunbed for non-tanning purposes are not reported in this Table.

(c) Methodological aspects of case–control and prospective cohort studies: Case–control studies are prone to two biases inherent in the design. First, since data are collected retrospectively (when cases already know they have a melanoma), the associations found could be the result of recall bias, as melanoma patients might have been more likely to remember past exposures to artificial UV sources (Walter *et al.,* 1990). Second, the selection of controls may have included subjects more (or less) inclined to have had more frequent exposure to tanning appliances than average (selection bias).

Among the four case–control studies selected in Section (a) of this section, three studies (Autier *et al.,* 1994; Westerdahl *et al.,* 1994, 2000) used measures to control for recall bias. Autier *et al.* (1994) focused on recall bias in the training of the interviewers: neither interviewers nor subjects were informed of the study's objective. Westerdahl *et al.* (1994) used a questionnaire with many variables and stated that at the time of the interview (1988 to 1990), the population was unaware of the relationship between exposure to artificial UV radiation for tanning purposes and malignant melanoma. Westerdahl *et al.* (2000) used identical procedures of data collection for cases and controls, and collected information from melanoma patients shortly after diagnosis.

Selection bias of controls was not likely to have occurred in any of the four selected case–control studies: three studies (Westerdahl *et al.,* 1994, 2000; Chen *et al.,* 1998) were based on population-based melanoma registries and sampling of control subjects. The study by Autier *et al.* (1994) selected cases from multiple sources (hospital, clinics and melanoma registries), and controls were chosen in the neighbourhood of cases according to rigorous contact procedures (Grimes & Schulz, 2005).

The prospective cohort study assessed exposure to tanning appliances retrospectively

but before diagnosis of melanoma. Thus, this study was less prone to interview and selection biases at the inception of the cohort.

Taken together, the four case–control studies selected and the prospective study offer the conclusion that the increased melanoma risk was associated with exposure to tanning appliances (mainly when exposure started before the age of approximately 35 years) and the observed positive associations are not entirely due to recall or selection biases.

(d) Type of artificial UV light: Only one study (Chen *et al.,* 1998) collected information concerning the type of appliance used by showing subjects pictures of various types of indoor tanning appliances (e.g. desktop models, floor models, beds, walk-in booths). The study found a non-significant elevated risk for melanoma associated with the use of desktop sunlamps and heavyweight floor-model sunbeds and a statistically significant tripled risk associated with use of more than two types of sunlamps, compared with no use of sunlamps.

Before 1980, exposure to artificial UV radiation was more likely to take place at home with appliances that emitted large amounts of UVB radiation, whereas exposure in the 1980s increasingly occurred in commercial salons using appliances that emitted mainly UVA. The prospective study provided evidence that the increased melanoma risk associated with exposure to tanning appliances was not due to the type of UV lamps used before 1983 (Veierød *et al.,* 2004).

Basal cell and squamous cell carcinomas

Description of studies

Nine case–control studies have addressed the possible association of artificial UV exposure with either BCC or SCC of the skin. All studies reported a risk estimate, except one (Boyd *et al.,* 2002), which was therefore excluded. A further three studies that did not distinguish between these two major types of skin cancer (O'Loughlin *et al.,* 1985; Herity *et al.,* 1989; Hogan *et al.,* 1991) were also excluded from review because BCCs and SCCs have different aetiologies, thus leaving five studies under consideration (Table 16).

Aubry & MacGibbon (1985): The earliest case–control study that addressed the possible

Table 16. Characteristics of case–control studies included in the meta-analysis on non-melanoma skin cancers

Reference	Country	Number of cases	Number of controls	Source	
				Cases	Controls
Aubry & McGibbon (1985)	Canada	SCC: 92	174	Hospital	Hospital
Bajdik *et al.* (1996)	Canada	BCC: 226 SCC: 180	404	Cancer registry	Population, health insurance
Corona *et al.* (2001)	Italy	BCC: 166	158	Hospital	Hospital
Karagas *et al*. (2002)	USA	BCC: 601 SCC: 292	539	Dermatology department	Population, Dept. of Transportation, Medicare
Walther *et al.* (2004)	Germany	BCC: 213	411	Hospital	Hospital

BCC, basal cell carcinoma; SCC, squamous cell carcinoma

association of artificial UV exposure and squamous cell carcinoma was conducted in Montreal, Canada. Its overall aim was to assess risk factors for SCC of the skin with a particular focus on potential carcinogenic occupational exposures. Eligible cases were histologically diagnosed with primary invasive cutaneous SCC in 1977–78 in 12 hospitals in the Montreal region; 2 controls per case with no known history of skin cancer, matched for sex, age and hospital of case diagnosis, were selected from those diagnosed in the same period with specified dermatologic conditions. Data on standard risk factors for skin cancer were collected including skin type, occupational and nonoccupational sun exposure as well as ever-use of long- and round-tube sunlamps. The final study population, aged 65 years on average, comprised 30% of all eligible patients. There were 92 SCC cases, 4 of whom reported any exposure to a long-tube sunlamp, and 174 dermatological controls, one of whom was so exposed, giving an odds ratio of 13.4 after adjusting for age, sex, eye and hair colour, ethnicity, and nonoccupational sun exposure ($p < 0.008$). (Round-tube sunlamp results were not reported.) [This study was conducted almost 30 years ago among elderly people; the Working Group noted major drawbacks, including a hospital-based study population, controls with skin conditions and a very low response rate. The risk estimates were based on a single exposed control, and no details of artificial UV exposure were obtained.]

Bajdik et al. (1996): Another study carried out in Canada that aimed to assess phenotypic, solar and non-solar risk factors for BCC and SCC of the skin in men in the province of Alberta also asked about exposure to non-solar UV light. Cases were men with a first BCC or SCC histologically diagnosed in 1983–84 and ascertained through the Alberta Cancer Registry. Controls were matched for age within 2 years from the Alberta health insurance plan subscriber list. Through personal interviews, information about non-solar UV exposure such as exposure to welding torches, UV lights and sunlamps was obtained, as well as standard risk factors. Results were based on 226 BCC cases (72% of those ascertained), 180 SCC cases (80%), and 406 eligible controls (71%). Ever-use of a sunlamp was reported by 8% of controls (33 of 404) and 9% of BCC cases (23 of 226), giving an odds ratio of 1.2 (CI, 0.7–2.2); ever-use was reported by 10% of SCC cases (18 of 180), with odds ratio of 1.4 (CI, 0.7–2.7). Risk estimates were adjusted for age, skin and hair colour, ethnicity and lifetime occupational sun exposure. [While this study was population-based, it was conducted 20 years ago, was restricted to men of unreported but likely older ages, and no details of artificial UV exposure were available.]

Corona et al. (2001): A more recently conducted hospital-based case–control study of causes of BCC in Italy assessed non-solar factors as well as phenotypic and solar factors. Cases of histologically-confirmed BCCs diagnosed in 1995–1997 were ascertained on random days of the week through a hospital for skin diseases in Rome. Controls diagnosed with minor skin disorders (e.g. warts, naevi) were drawn from the same hospital but excluded if they had a history of skin cancer or UV therapy. Questionnaire data collected face-to-face included artificial UV exposure as well as standard risk factors regarding phenotype and patterns of sun exposure. Ever-use of a sunbed or sunlamp was reported by 20% of controls (31 of 158) and 11% of BCC cases (17 of 166). After adjustment for age, sex, family history of skin cancer, outdoor work and beach exposure in youth, the relative risk estimate for BCC was 0.6 (CI, 0.3–1.2). [This study, carried out 10 years ago, had major shortcomings through its design, namely a convenience sampling frame of adult dermatologic patients. No details of exposure to tanning appliances were obtained.]

Karagas et al. (2002): A case–control study conducted in the USA among New Hampshire residents assessed risk for BCC and SCC in relation to exposure to artificial UV tanning appliances, among other factors. Cases of skin cancer diagnosed in 1993–1995 were ascertained through a network of dermatologists and pathology laboratories. Controls were a frequency-matched sample of residents drawn from the Department of Transportation listing (< 65 yrs) or Medicare program list (> 65 yrs). Sunlamp/tanning bed use

and age at first and last use as well as standard skin-cancer risk factor data were obtained through personal interviews. The study population comprised 603 BCC cases and 293 SCC cases (78% of those eligible) and 540 (60%) eligible controls. Fourteen percent of controls (75 of 539), 21% (127 of 601) of BCC cases and 22% (63 of 229) of SCC cases reported any exposure to tanning appliances. After adjustment for age, sex and sun sensitivity, risk estimates associated with ever-use of a sunlamp in relation to BCC were 1.5 (CI, 1.1–2.1) and to SCC, 2.5 (1.7–3.8), and were similar in men and women. There was a non-significant trend toward increased risk with younger age at first use for SCC. Risks were increased for both BCC (OR, 1.6; CI, 1.1–2.3) and SCC (OR, 2.9; CI, 1.8–4.7) for first use more than 20 years previous to enrolment (before 1975). [The strengths of this study conducted 10 years ago were its population-based design and its availability of some quantitative data regarding sunlamp use. It lacked power to explore the associations with age at first use versus years since first exposure, and no data were available about frequency of use.]

Walther et al. (2004): The most recently published study of the association of artificial UV radiation and BCC was conducted in Germany, based on 213 patients with BCC diagnosed in the previous 5 years and 411 controls from the same dermatology department as the cases or the general surgery department of the same hospitals. During an interview patients were asked about number of times a year they used indoor tanning facilities. On crude analysis there was no association between recent history of BCC and use of indoor tanning facilities more than 5 times a year (OR, 0.7; CI, 0.3–1.5).

Meta-analysis

The meta-analysis was based on the five studies reporting type-specific risk estimates (Table 17). Chi-squared test and random effect models were used to assess heterogeneity, as described on page 26. Pooled relative risks suggested a significant effect of exposure to indoor tanning facilities for SCC, but not for BCC (Table 18).

The effect estimate seen for BCC was not much influenced by the estimate reported by Corona *et al.* (2001), which indicated a protective effect of artificial UV radiation for BCC (the weight of this study was the lowest [w = 8.0]). As above, this study was not specifically designed to investigate exposure to artificial UV radiation, thus radiation exposure data were not detailed. Excluding this publication from the analysis changed the pooled relative risk for BCC, although not substantially (pooled RR, 1.39; CI, 0.14–13.51).

Regarding SCC as an outcome, the study by Aubry & MacGibbon (1985) reported findings for only one type of sunlamp (long-tube type) and was hospital-based. The weight of this study was the lowest of this group (w=0.74); nevertheless, the pooled relative risk for SCC excluding this study was neither stronger not more significant (pooled RR, 2.16; CI, 0.24–19.53).

Funnel plot regression gave indication of no publication bias (P=0.77 and 0.26 for BCC and SCC, respectively) but results based on so few estimates are not reliable.

The study by Karagas *et al*. (2002) gave the most detailed results and the trends were consistent with the results reported for melanoma. The weight of this study was the highest (w = 23.8 for SCC and w = 36.8 for BCC) and therefore its results were the most influential.

Quality of studies

Only one case–control study (Karagas *et al.,* 2002) had a section designed specifically to explore sunlamp/sunbed use in more detail than never/ever use. Results were adjusted for sun sensitivity but not for sun exposure since adjustment for sun exposure did not change the risk estimates. Study participants who reported using sunlamps or sunbeds were more likely to be women, to be aged under 50 years, to have sun-sensitive skin, more painful sunburns and a history of frequent sunbathing (> 4 times per year) than non-users. Based on age at first use, the relative risks for BCC and SCC were found to increase by 10% (OR, 1.1; CI, 0.9–1.5) and 20% (OR, 1.2; CI, 0.9–1.6) respectively, for each decade younger the person was at first use of an indoor tanning facility. The effects of age at first use could

Table 17. Estimates included in the evaluation of an association of ever use of indoor tanning facilities and risk for non-melanoma skin cancers

Reference	Exposure	Diagnosis	Relative risk (95% CI)	Adjustment
Aubry & McGibbon (1985)	Long-tube sunlamp use	SCC	13.4 (1.4–130.5)	Age, sex, eye and hair colour, ethnicity, non-occupational sun exposure
Bajdik *et al.* (1996)	Ever use of sun-lamps	BCC SCC	1.2 (0.7–2.2) 1.4 (0.7–2.7)	Age, ethnic origin, skin and hair colour, occupational sun exposure
Corona *et al.* (2001)	Sun bed or sun-lamp use	BCC	0.6 (0.3–1.2)	Age, sex, pigmentary traits, family history skin cancer, outdoor work, number of weeks spent at beach before age 20 years
Karagas *et al.* (2002)	Any tanning device use	BCC SCC	1.5 (1.1–2.1) 2.5 (1.7–3.8)	Age, sex, sun sensitivity
Walther *et al.* (2004)	Exposure ≥ 5 times/year to artificial UV radiation/-UV sunbeds	BCC	0.7 (0.3–1.5)	Crude

BCC, basal cell carcinoma; SCC, squamous cell carcinoma

not be distinguished from years since first use because of the relatively small number of cases in the study, and there were no semi-quantitative measurements of artificial UV exposure (e.g. number of sessions per month, duration of use).

Other sources of exposure to artificial UV radiation

Medical Use

Light treatment has been used for a large number of medical conditions (see page 4), most particularly for psoriasis.

(a) PUVA therapy in psoriasis patients: Most long-term studies looking at risk for skin cancer resulting from exposure to UV treatment collected data from a significant number of psoriasis patients treated with PUVA (see page 4 (b)). There is clear evidence that PUVA increases the risk for SCC with a relatively short latency period, although it is difficult to distinguish the contribution of PUVA from other factors, given that treated patients have usually received multiple carcinogenic treatments. For example, SCC in psoriatic patients treated with PUVA commonly have UV signature mutations rather than PUVA signature mutations (Kreimer-Erlacher *et al.,* 2003), suggesting that PUVA may act as a promoter rather than an initiator.

Two large cohorts of psoriasis patients have been followed up since the 1970s: one of 4799 patients in Sweden (Lindelof *et al.,* 1999) and another of 1380 patients in the USA (Stern, 2001). In the Swedish cohort the relative risk for SCC was 5.6 in men (CI, 4.4–7.1) and 3.6 in women (CI, 2.1–5.8). In the cohort in the USA, one fourth of patients who received more than 2000 J/cm^2 developed an SCC (Stern & Laird,

Table 18. Meta-analysis of studies of exposure to artificial UV radiation and risk for non-melanoma skin cancers

Diagnosis	Number of studies	Summary relative risk (95% CI)	P-value χ^2 Heterogeneity
SCC	3	2.25 (1.08–4.70)	0.10
BCC	4	1.03 (0.56–1.90)	0.06

BCC, basal cell carcinoma; SCC, squamous cell carcinoma

1994). The same authors subsequently carried out a meta-analysis of their own data and all published studies with more than 150 patients (Stern & Lunder, 1998), and found that patients exposed to high doses of PUVA (more than 200 treatments or more than 2000 J/cm^2) had a 14-fold higher risk for SCC than those with <100 treatments or <1000 J/cm^2 exposure. The risk is further increased when the patients have also received methotrexate at some time (Stern & Laird, 1994) and is greater still with the use of cyclosporine (Marcil & Stern, 2001). There is no evidence to date that bath PUVA increases the risk for SCC (Hannuksela-Svahn *et al.,* 1999) but the data available relate to only 944 patients who received relatively low total PUVA doses.

The risk for melanoma after PUVA treatment is more controversial. In the cohort in the USA, discussed above, an increased risk for melanoma has been reported (Stern, 2001). Of the 822 participants with long-term follow-up, 44% had at least 200 PUVA treatments and therefore are called high exposure patients. Sixteen of the 1380 patients developed an invasive melanoma and 6 developed a melanoma in situ. The authors reported a 10-fold increase in the incidence of invasive melanoma compared with population rates in the 27 months prior to publication of the article. Within the cohort, the risk for melanoma was greater in those with fair skin (Fitzpatrick skin type) and those who received high doses of PUVA (incidence rate ratio, 2.6; CI, 1.0–6.6) for more than 200 treatments compared with less than 200. The risk also appeared to have a long latency in that an elevation in risk appeared only after 15 years. There did not appear to be any increased risk in patients who were also treated with ionizing radiation or methotrexate.

The Swedish cohort (Lindelof *et al.,* 1999) reported no increased risk for melanoma. This study was much larger than the study in the USA and the patients were tracked using the Swedish Cancer Registry, thereby allowing "complete" follow-up. Of the 2343 men in the cohort, 8 developed a melanoma compared with the 7.3 expected, and of the 2456 women, 7 developed a melanoma compared with the 6.3 expected. The length of follow-up was impressive in this cohort, as the average length was 16 years and 1038 patients had been followed for more than 19 years.

Given the considerable size and the duration of follow-up of the Swedish cohort, the findings from this cohort are the more persuasive of the two studies. The difference in findings, however, remains unexplained. In the Swedish cohort a proportion of patients had had bath PUVA, which tends to be associated with lower UVA doses. There were differences in the treatment protocols as well (Honigsmann, 2001), in that in Europe schedules are individualized after light testing, more commonly resulting in reduced time to clearing and lower doses per treatment course. These differences may explain the discrepant risk estimates, but it cannot be excluded that the data from the study in the USA are subject to bias, not least because follow-up was substantially incomplete.

Overall, there is a postive association between PUVA and risk for SCC and there appears to be a dose–response effect. The risk was greater for fair-skinned people. The risk for melanoma is much less clear, even in fair-skinned populations. The positive dose-response relationship in the study in the USA supports the interpretation that the association is causal. It seems likely, however, that the risk is associated with high doses of PUVA, is relatively small and is observed after a long latency.

The data from PUVA studies are important in that they include large numbers of people who were studied prospectively. They cannot however be extrapolated to exposure to tanning appliances because of the presence of psoralen. Furthermore, the total UV dose received by psoriasis patients is considerably less than that received by long-term users of indoor tanning facilities.

(b) Broadband and narrow-band UVB in psoriasis patients: The evidence relating to long-term risk for skin cancer after UVB therapy is scanty. In the PUVA cohort study from the United States, there was no discernible additional effect of exposure to UVB (Stern & Laird, 1994). In a study of psoriatics treated with coal tar and UVB in the 1950s followed up for 25 years, there was no demonstrable increased risk for skin cancer, though the numbers treated were relatively small (n = 280) (Pittelkow *et al.,* 1981). In a small study of 195 German psoriatics treated with broadband (n = 69) or narrow-band UVB (n =126) from 1994 to 2000 only one skin cancer had occurred by 2004. This was an in-situ melanoma which developed in the same year that narrow-band UVB therapy was begun (Weischer *et al.,* 2004). Though these data are reassuring they cannot exclude a small increased risk nor a large increased risk in patients treated with high doses.

(c) UV treatment of other skin diseases: The immunomodulatory effects of UV radiation are utilized in the treatment of a variety of skin diseases other than psoriasis. Many of the patients treated are at increased risk for skin cancer even without PUVA because of the nature of their dermatosis (e.g. vitiligo). Others are at further increased risk because of immunosuppression which may both characterize the skin disease and its treatment, such as graft versus host disease (GVHD) (Furlong *et al.,* 2002) or cutaneous T-cell lymphoma.

A series of 103 patients with steroid-resistant GVHD treated with PUVA received a mean dose of 41 J/cm^2 between 1994 and 2000. Only one SCC has developed in this cohort to date (Furlong *et al.,* 2002).

PUVA is also very useful, although not curative, in the treatment of cutaneous T cell lymphoma (CTCL) when it is commonly used as part of multi-modality treatment programmes with other drugs contributing to risk such as cytotoxics (McGinnis *et al.,* 2003). Narrow-band UVB has been reported to be as effective as PUVA in the treatment of early CTCL in one retrospective study (Diederen *et al.,* 2003). There is no doubt that in this patient population there was an increased risk for SCC but it is difficult to apportion risk to PUVA. The risk for melanoma was reported in a very small series of patients and therefore cannot be assessed (McGinnis *et al.,* 2003).

Lighting

(a) Fluorescent tubes: Household lights emit significant amounts of UV radiation (Sayre *et al.,* 2004) and several case–control studies have addressed risk for melanoma associated with such exposure. The earliest study suggested an elevated risk associated with exposure to fluorescent lights at work (Beral *et al.,* 1982) but all subsequent studies failed to identify such a risk (Rigel *et al.,* 1983; Osterlind *et al.,* 1988; Walter *et al.,* 1992; Holly *et al.,* 1995).

(*b) Full spectrum lamps:* No data were available to the Working Group regarding exposure to full-spectrum lamps intended for domestic and public use and risk for skin cancer.