Sunbed use, sunscreen use, childhood sun exposure, and cutaneous melanoma

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Gebruik zonnebank, gebruik zonnecrèmes, blootstelling van de zon bij kinderen en melanoma van de huid

Thesis

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by

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For Anne, Anton and Gilles

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Abbreviations:

BCC:	Basal cell carcinoma
EORTC:	European Organization for Research on Treatment of Cancer
melanoma:	cutaneous malignant melanoma
nm:	nanometer
IARC:	International Agency for Research on Cancer
iPRI:	International Prevention Research Institute
SCC:	Squamous cell carcinoma
UV:	ultraviolet radiation
UVA:	ultraviolet A radiation
UVB:	ultraviolet B radiation
UVC:	ultraviolet C radiation

Section 1: Preface

Cancer registries established after World War II show that in most light-skinned populations, the incidence of malignant cutaneous melanoma (hereafter termed melanoma) has steadily increased. In the 1970s and 1980s, laboratory and epidemiological studies documented the possibility that solar radiation was the main environmental risk factor for most skin cancers, including melanoma, the basal cell carcinoma (BCC) and the squamous cell carcinoma (SCC).

In 1992 a Working Group on Solar and Ultraviolet Radiation convened by the International Agency for Research on Cancer (IARC, Lyon, France) first placed solar radiation in the IARC group 1 of sufficient evidence for carcinogenicity in humans (IARC, 1992).[1] At that time, UVB was known for its carcinogenic properties and its ability to cause sunburns. Epidemiological research found sunburns to be associated to all types of skin cancers. However, laboratory studies had not provided evidence that UVB was involved in melanoma occurrence. UVA was much less potent than the UVB for triggering DNA mutations in animal experiments but the relevance of these experiments to the human bare skin was uncertain. The Working Group did not consider there was sufficient evidence at the time to assign specific wavelengths to group 1, and both UVA and UVB were classified as "probably carcinogenic to humans" (group 2A). The Working Group also distinguished between the intermittent and the chronic sun exposure pattern, the former being associated with melanoma risk while the later exposure type was associated with SCC. Intermittent sun exposure is brisk sun exposure of usually sun-protected skin areas during leisure activities or holidays, while chronic sun exposure was typical of sun exposure accumulated over lifetime. The intermittent sun exposure concept better explained why melanoma often arose in usually sun protected skin areas (e.g. the trunk) of affluent people spending most of their time indoors. Chronic sun exposure was more typical of outdoor workers that developed squamous cell carcinoma on usually sun-exposed skin areas like the head and neck. In addition, studies often suggested that this type of exposure is associated with slightly decreased risk of melanoma.

[1] The sun emits the full ultraviolet radiation spectrum (100-400 nm), including the UVA (>315-400 nm), the UVB (>280-315 nm) and the UVC (100-280 nm). The stratospheric ozone layer completely blocks the UVC and filters out most of the UVB. The UVA, visible light and longer wavelengths do not interact with ozone.

The 1992 IARC Monograph made great use of studies in migrants indicating that childhood might be the most critical period for the occurrence of sun-induced biological events implicated in the genesis of melanoma. However, how childhood sun exposure influenced melanoma occurrence in adults was still insufficiently documented. The 1992 IARC Monograph did not significantly address issues associated with sunscreen use and exposure to sunlamps because limited epidemiological data existed on these two topics.

In this dissertation, we have outlined how our works contributed to exploring several issues about the aetiology and prevention of melanoma, raised after the 1992 IARC Monograph, in particular those related to the influence of sunbed and sunscreen use on melanoma occurrence and on childhood being a critical period for melanoma initiation.

Sun exposure, sunbed use, and sunscreen use are consequences of human behaviours and in this respect, these exposures represent some sort of "uncontrolled natural human experiments". Epidemiological studies are the main methods for capturing results of these "natural experiments". In some instances, as we will see with sunscreen use, it has been possible to verify hypotheses derived from epidemiological data via the conduct of randomised controlled trials.

In addition, during the 18 years of studies on acquired nevus and melanoma, we accumulated large sets of data that could help shed light on the way UV exposure was involved in this malignancy. Therefore, using several significant results from our works, we will briefly discuss the hypothesis that melanoma can be caused by different UV wavelengths resulting in cancers having different clinical behaviour.

Structure of the thesis

Four Sections will cover the following topics:

Section 2: Artificial UV tanning devices
Section 3: Sunscreens and wearing of clothes
Section 4: Childhood sun exposure
Section 5: Epidemiological evidence that UVA is involved in the genesis of melanoma

Sections 2 to 5 start with a brief introduction of the state of epidemiological knowledge on these issues at the time of the IARC Monograph of 1992, followed by a recall of main results of our studies. Epidemiological studies or human experiments by other groups that supported or challenged our methods and findings are then mentioned and discussed. The published articles most relevant to each section are displayed in chronological order.

A general discussion in Section 6 presents how our works contributed to the tailoring of public health policies and to the understanding of melanoma aetiology and outcome. The discussion outlines suggestions for future research directions in melanoma epidemiology. We also express our personal opinion on public health perspective regarding trends in the burden of melanoma.

References cited in the text in *italic* are studies we co-authored and studies in ***bold plus italicised*** we selected for display in the dissertation.

Section 2: Artificial UV tanning

Background as of 1992

Long fluorescent tubes emitting predominantly in the UVA range and allowing whole body UV sessions were marketed in the 1980s (*IARC, 2006*). Artificial UV tanning is often termed "UVA-tanning" as the spectrum of these machines contains 96 to 99% UVA and 1 to 4% UVB (this small amount of UVB is indispensable for triggering a deep long lasting facultative tan). The absence of firm data on UVA carcinogenicity in the 1980s and 1990s greatly contributed to the belief that "UVA-tanning" was safe, or at least safer than sunbathing in the midday sun that contains larger amounts of UVB.

Because UVA is one thousand times less potent than UVB in inducing a suntan, and because UV tanning sessions rarely exceed 20 minutes, high doses of UVA are necessary to provoke the synthesis of melanin. Therefore, the UV energy output of most powerful modern tanning machines may be five 10 to 15 times that the midday sun on the Mediterranean coast. Exposure of humans to such considerable UVA fluxes never existed before the advent of the "UVA-tanning" devices.

In 1992, knowledge of health hazards associated with sunbed use was limited to clinical reports regarding side effects (e.g. sunburns, itching) or rare but severe skin burns after intake of tanning activators (like the psoralens) taken before the sunbed session. The early epidemiological studies on exposure to artificial UV sources often explored the use of more dated types of both UV-lamps, whose emission spectrum was much richer in UVB, or of small size UVA lamps, before large size canopies were commercially available. These studies generally limited data collection to never/ever exposure to sunlamps and did not adjust for sun exposure or host characteristics (*IARC, 2006*).

The 1992 IARC Monograph did not expend much on the "UVA-tanning" because this fashion was just starting and too few epidemiological data were available. Irrespective, the use of sunlamps and sunbeds was classified as 'probably carcinogenic to humans' (group 2A), because it entailed exposure to UVA and UVB that were classified in group 2A.

In the absence of a valid animal model for human melanoma and given the ignorance of the ultraviolet wavelength implicated in melanoma genesis, the study of an eventual link between sunbed use and melanoma was left to epidemiological investigation.

Overview of ecological and observational studies

Ecological study in Belgium and Europe

In 1991-92, in order to substantiate applications for obtaining funds for studies, we first made an ecological description of patterns of sunbed use in Belgium (*Autier et al, 1991*) and found that melanoma patients reported greater use of sunbeds than the average Belgian population. Furthermore, the increasing melanoma incidence observed in various areas correlated with the increasing use of indoor tanning. Also, sunbed users were generally more inclined to engage in brisk sun exposure behaviours such as sunbathing.

Observational studies

The investigation of relationships between sunbed use and melanoma was the primary goal of the EORTC multicenter study we designed in 1991 (*Autier et al, 1994a,b*).[2] This case-control study, conducted in Belgium, Germany and France took place at a time when the public was not particularly aware of health hazards associated with sunbed use. It included 420 melanoma patients of all ages from hospital registries and 447 neighbourhood controls. The main finding was a positive association between sunbed use and melanoma occurrence, mainly when use had started before 1980 (i.e. first exposure distant in time). Statistical analysis using detailed data collected on sun exposure habits and host characteristics allowed to exclude that higher melanoma risk could be due to the known greater propensity of sunbed users to sunbathe.

We designed a second European multicentre case-control study that took place in 1999-2001 (*Bataille et al, 2005*).[3] This study focused on subjects aged 18 to 49 years old, as surveys showed that the vast majority of tanning salon visitors were under 40 years old. We therefore supposed that the impact of sunbed use on melanoma risk should be mainly visible in subjects under the age of 50.

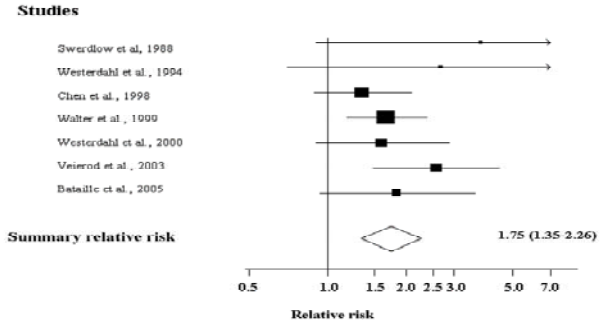
[2] Funded by the Europe Against Cancer Programme of the European Commission.
[3] Funded by the BIOMED II Programme of the Directorate General Research of the European Commission.

Recruitment of 597 melanoma patients and of 622 controls was done in France, Belgium, England, the Netherlands and Sweden (*Bataille et al, 2005*). This study failed to investigate the association between sunbed use and melanoma because ways by which controls were recruited in the different settings favoured subjects well aware of factors associated with melanoma occurrence, including sunbed use. This was the direct consequence of the growing dissemination of messages warning of the health hazards associated with sunbed use (*De Vries et al, 2005*). This unsuccessful study demonstrated that in the European context, the case-control design was no longer adequate for investigations of health hazards associated with sunbed use and that prospective cohort designs had to be adopted. Fortunately, such cohort studies were already underway in Norway and Sweden, two countries where the indoor tanning fashion was highly prevalent (Veierød et al, 2004).

Reviews and meta-analyses

We performed reviews of issues surrounding indoor tanning and skin cancer (***Autier, 2004;*** *Autier, 2005*), that played a role in the decision of the IARC to organize a systematic review with meta-analysis. An IARC Expert Group, convened in 2005, of which we were members. Our meta-analysis of epidemiological studies found a 75% (95% CI: 35 to 126%) increase in melanoma risk when sunbed use started before 30 years of age (Figure 2.1), as well as a higher risk for first exposure distant in time, i.e. 10 to 20 years before the diagnosis of melanoma (*IARC, 2006****; IARC, 2007***).

Fig 2.1 - Risk of melanoma in people < 30 years old at first sunbed use (IARC, 2006 & 2007)



These findings supported accumulating data showing that childhood and adolescence are periods of high susceptibility to carcinogenic effects of UV radiation. We therefore strongly advocated banning access of youths to tanning beds, suggesting 18 years as the minimum age for use as in most European countries, adulthood legally starts at this age (*Autier & Boyle, 2008*).

Further data from descriptive studies

In 2004, after the publication of the primary results from the Swedish-Norway cohort study (Veierød et al, 2004), we made the prediction that melanoma associated with solarium use would be predominantly localised to the trunk and particularly in women, because it allows exposure of the trunk to UV without protection (*Boniol et al, 2004*). We took advantage of collaborations with population-based cancer registries operating in countries with high prevalence of indoor tanning for monitoring melanoma incidence trends by sex, age and anatomic site.

A melanoma epidemic in Iceland following rapid spread of artificial UV tanning

Iceland is a Nordic country situated at 64-66° North latitude where bright, sunny days are rare. In a collaborative work with the Iceland Cancer Registry and Icelandic dermatologists, we described an epidemic of melanoma starting in 1995, that was most probably due to massive exposure of Icelandic youths to artificial tanning devices after 1985 (***Héry et al, 2010***). Sunbed use in Iceland expanded rapidly after 1985, mainly among young women. In 2000, it was approximately two and three times the levels recorded in Sweden and in the UK, respectively. A particular feature of that epidemic was that it mainly concerned melanoma occurring on the trunk of women under the age of 50. Around year 2000 the incidence of trunk melanoma in women had surpassed the incidence of lower limb melanoma. This latter aspect was in sharp contrast with the usual observations prior to 1995 whereby the greatest increase in melanoma incidence in women occurred on lower limbs (MacKie et al, 2002).

This study had an ecological design that is not appropriate for making causal inference. The question however, was to establish whether another cause could explain the dramatic increase in melanoma incidence, mainly observed on the trunk of young women. We carefully examined other possible causes of this dramatic increase of melanoma incidence, including changes in cancer registration and coding practice, changes in early detection by Icelandic doctors and travels abroad. None of these factors could explain the specific features of

the melanoma epidemic and the high prevalence of sunbed use was the only plausible explanation for the rapid increase in incidence of melanoma in Iceland (*Autier et al, 2010*).

Descriptive epidemiology of melanoma in Northern Ireland

In the UK, surveys have shown sunbed use to be most prevalent in Scotland and Northern Ireland (COMARE, 2009). A descriptive study we performed with the Northern Ireland Cancer Registry showed that the highest increase in incidence rates was observed on the female trunk (*Montella et al, 2009*).

Epidemiological or human experiment data supporting our findings

Epidemiological data published after the IARC report of 2006 (IARC, 2006) further documented the links between artificial UV tanning and cutaneous melanoma. It included three large case-control studies in the U.S.A, (Ting et al, 2007; Clough-Gorr et al, 2008; Lazovitch et al, 2010) the prospective U.S. Nurse's Health Study (Han et al, 2006) and confirmation of previous results of the Norwegian-Swedish cohort study (Veierød et al, 2010).

In areas such as the Nordic countries and Scotland where indoor UV tanning is popular, particularly amongst teenagers and young adults, sharp increases in melanoma incidence on the trunk have been described (Mowbray et al, 2007), sometimes surpassing the incidence on lower limbs (Dal et al, 2007). In the UK and the USA, rebounds of increase of melanoma incidence from 1998 onwards have been reported for women 20 to 39 years old (Diffey, 2007; Purdue et al, 2008), possibly due to the spread of the indoor tanning fashion.

Epidemiological or human experiment data challenging our findings

We found no published data from epidemiological studies or human experiments challenging the primary results of our studies.

Articles displayed as part of this section

Autier P. Perspectives in melanoma prevention: the case of sunbeds. *Eur J Cancer* 2004; 40: 2367-76.

International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with

cutaneous malignant melanoma and other skin cancers: A systematic review. *Int J Cancer* 2007; 120:1116-22. Review. Erratum in: *Int J Cancer* 2007; 120:2526.

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Current Perspective

Perspectives in melanoma prevention: the case of sunbeds

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Abstract

The incidence of cutaneous malignant melanoma (melanoma) and of basal cell carcinoma is still increasing in most fair-skinned populations. The fashion of intermittent exposure to solar ultraviolet (UV) radiations is considered the main cause of this increase. In 20 years time, tan acquisition through exposure to artificial sources of UV radiations has become frequent among fair-skinned adolescents and young adults. Modern sunbeds are powerful sources of UV radiations that do not exist in the nature, and repeated exposures to high doses of UVA constitute a new phenomenon in humans. A large prospective cohort study on 106,379 Norwegian and Swedish women conducted between 1991 and 1999 has provided evidence for a significant, moderate increase in melanoma risk among regular sunbed users. Failure of past case-control studies to document with consistency the sunbed-melanoma association was probably due to a too short latency period between sunbed use and melanoma diagnosis, and to too few subjects with high total durations of sunbed use. Regulations of sunbed installation, operation and use should become standardised across the 25 European Union countries. Enforcement of regulations in tanning parlours remains inadequate. In contrast, the existence of regulations is presented by many tanning salon operators as a guarantee that sunbed use is safe. We stress the need for the control of information disseminated by the ''tanning industry'' on suppositions that sunbed use is safer than sun exposure, and on the hypothetical health benefits of tanning. New fluorescent UV lamps are proposed that have a spectrum similar to the midday sun. Given the known association between intermittent sun exposure and melanoma, public-health authorities should reconsider the soundness of the commercialisation of these lamps.

Keywords: Melanoma; Skin cancer; Ultraviolet radiation; Epidemiology; Prevention

1. Introduction

The incidence of cutaneous malignant melanoma (melanoma) has steeply increased in the past 50 years in most fair-skinned populations. For instance, from 1970 until 1997, a 2.5-fold increase in melanoma incidence was observed in Finland, and a 3.6-fold increase in White Americans [1,2]. From 1979 until 1998, a 2.4-fold increase was observed in Scotland [3], and from 1980 and 2000, a 2.8-fold increase was estimated for France [4]. Risk factors for the basal cell carcinoma (BCC) are similar to risk factors for melanoma [5]. The incidence of BCC is also increasing sharply in most fair-skinned communities, mainly in females [6].

The fashion of intermittent sun exposure that took place after 1950 is considered as the main cause of the increases in melanoma and in BCC. The depletion in ozone observed in the stratospheric layers of the atmosphere is not likely to contribute to the raising incidence of these skin cancers. The ultraviolet (UV) radiation is deemed to represent the part of the solar spectrum involved in the genesis of melanoma [7]. In spite of increasing knowledge on the association between sun exposure and the considerable rise in skin cancer incidence, exposure to artificial sources of UV radiation has become popular in all fair-skinned populations around the world. These artificial sources of UV radiation have various

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denominations, e.g., tanning machines, UVA-tanning devices, indoor tanning, sunbeds, and solarium. The sunbed fashion could contribute to the increase in skin cancer occurrence, in particular, of melanoma [8].

In this paper, we delineate the public-health issues involved in sunbed use in 2004, and we stress the need to promote actions going beyond the regulations of sunbed use, especially actions aiming at controlling the information disseminated by the "tanning industry" on supposed safety and hypothetical health benefits of sunbed use.

2. Sunbed use is an intentional sun exposure behaviour

The melanoma epidemic affects mainly skin areas usually covered by clothes, like the trunk, shoulders and limbs, while lower increases in melanoma incidence are observed on the more chronically sun exposed body sites, like the head and neck [3,9]. Likewise, the increase in BCC incidence is mainly observed on body sites that are not chronically exposed to sunlight [6]. This epidemiological feature points to the role attributed to the intermittent sun exposure in the genesis of most melanoma and BCCs. The most intense form of intermittent sun exposure is the intentional sun exposure (ISE) that is essentially motivated by the acquisition of a tan or by the possibility to go uncovered in the sun [10]. During ISE, significant portions of the trunk and of the limbs are generally uncovered. Sunbathing and sunbed use are the most typical ISE behaviours, and people attracted to sunbathing activities are also more attracted to indoor tanning [11].

In Europe, the sunbed fashion follows a strong South-to-North gradient. The sunbed fashion started in the 1980s in the Nordic countries and extended in more Southern countries in the 1990s. Surveys in Europe and North America indicate that between 15% and 35% of women, and between 5% and 10% of men 15–30 years old have used sunbeds [12–14]. In Sweden, after 1995, 70% of females and 50% of males 18–50 years old reported sunbed use [15,16]. In the late 1990s, the indoor tanning fashion rapidly extended to Mediterranean areas like the north of Italy [17,18]. In the State of Victoria, Australia – a sunny area with high records of skin cancers – 9% of subjects 14–29 years old reported sunbed use in the past years [19]. A substantial proportion of sunbeds are used in private facilities. In Germany or Nordic countries, home-made solaria are not uncommon.

3. The role of UVA and UVB in melanoma occurrence is still unknown

At present, there are no scientific data indicating that intentional exposure to UV radiations emitted by sunbeds is less harmful than intentional exposure to sunlight.

The UV radiation reaching the earth's surface comprises UVB (280–319 nm) and UVA (320–400 nm) radiations. During a sunny day on the Mediterranean coast, the solar UV spectrum at noon contains approximately 5% of UVB and approximately 95% of UVA. UVB is far more efficient than UVA at inducing the synthesis of melanin, and producing a deep, persistent tan. UVB is also 1000 times more potent than UVA at inducing skin erythema (painless skin reddening) or sunburn (painful skin reddening, sometimes with blisters).

Until end of the 1980s, UVB was considered as the carcinogenic part of the solar spectrum, and a shift in usage occurred towards low pressure fluorescent tubes emitting essentially in the UVA range, yielding the so-called "UVA-tanning".

At the end of the 1980s, UVA was also suspected of having carcinogenic potential. In 1992, the International Agency for Research of Cancer classified UVB and UVA radiations, as well as sunbeds, as "agents that are probably carcinogenic to humans" (group 2A of the IARC classification of carcinogenic agents) [7].

Biological mechanisms by which chronic sun exposure causes squamous cell cancer (SCC) of the skin are better known (e.g., the UVB-induced mutations found in the *p53* gene). In contrast, we still have a poor knowledge of the biological mechanisms by which solar radiations are involved in the genesis of melanoma and BCC in humans.

3.1. Long-term health effects of high UVA doses are unknown

In large powerful tanning units, the UVA irradiation intensity may be 10–15 times higher than that of the midday sun [20]. When UV output is calculated in terms of biological activity, as estimated by the erythema-effective irradiance, the emission of many sunbeds is equivalent or surpasses the emission of the midday sun on the Mediterranean Sea [20,21]. Such powerful sources of UVA radiations do not exist in nature, and repeated exposures to high doses of UVA constitute a new phenomenon in humans. If the role of UVA in melanoma occurrence is uncertain, the UVA doses per unit of time received by the skin during a typical sunbed session are far higher than what is experienced during daily life or during sunbathing. We have little idea of the likely long-term medical consequences of such exposure. Worries are further reinforced by knowledge that UVA penetrates deeper than UVB into the skin. A recent study discovered DNA lesions typical of UVA action in the basal epithelial layer of the human skin, the skin region where most melanocytes are situated [22].

3.2. The questionable concept of "UVA-tanning"

The term "UVA-tanning" is misleading, as the output of a sunbed equipped with low pressure fluorescent lamps always contains some UVB, which is critical for the induction of a deep, persistent tan. In addition, most of the DNA damage observed in the skin of sunbed users is due to the fraction of UVB emitted by the fluorescent lamps [23].

In the 1990s, regulations in some countries (e.g., Sweden, France) limited the maximum proportion of UVB in the total UV energy output of sunbeds to 1.5%. However, in the real world, the UV output and spectral characteristics of sunbeds vary considerably. The proportion of UVB in UV energy output could vary from 0.5% to 4% [24,25], and may attain an emission spectrum similar to the sun spectrum in the UVB range [20]. These differences are due to sunbed design (e.g., the numbers and type of fluorescent tubes, the presence of high-pressure UV lamps, the materials of the filters, the distance from the canopy to the skin), to sunbed power, and to tube aging.

3.3. Sunbed-induced sunburns

Sunburn experience during childhood or during adulthood is a risk factor for melanoma, and the risk increases with increasing numbers of sunburns [26]. Skin erythema or burns are reported by 18–55% of sunbed users [12,13,16,27]. Although UVB is more potent than UVA for triggering sunburn, high fluxes of UVA are capable of inducing skin erythemal reactions after 10–20 min in a subject who is naturally susceptible to sunburns and having moderate tanning ability (i.e., Fitzpatrick skin phototype 2). The same subject engaging in unprotected sunbathing in the midday sun would incur an erythemal reaction after 20 min.

The high frequency of sunburn experience by sunbed users shows that sunbed use is very close in nature to sunbathing, and there is no reason to believe that sunburns experienced during sunbed sessions would convey less melanoma risk than sunburns experienced during sun exposure.

4. Epidemiological data on sunbed use and melanoma

As there is no valid animal model for human melanoma, and because we are still ignorant about the effects of UV radiation(s) and melanoma occurrence, the study of any eventual link between sunbed use and melanoma left to epidemiological investigations.

Seven epidemiological case-control studies specifically addressed the possible association between increasing amounts of sunbed use and melanoma [12,15,28–32]. Two reviews concerning six studies [33,34] concluded that some data raised the possibility of a moderate positive association between sunbed use and melanoma. However, overall, the results lacked consistency and no conclusive evidence could be drawn from these six studies on the influence of sunbed use on melanoma occurrence. A seventh case-control study conducted in the UK explored sunbed use before 1989 [32]. It showed no dose-response relationship between amounts of sunbed use and melanoma.

In 2003, MB Veierød and co-workers published the results of a prospective cohort study of 106,379 women in Norway and Sweden who were followed for an average of 8.1 years from 1991 until 1999 [26]. During the follow-up, 187 cases of melanoma were diagnosed. After adjustment for intermittent sun exposure and host characteristics, the study found a 55% increase in melanoma risk (95% Confidence Interval: 4–132%) among the 18% of women aged 10–39 years old who reported having used sunbed at least once a month when they were 10–19, 20–29 or 30–39 years old. An increase in melanoma risk was observed for all age groups, from 20 to 49 years old. Twelve sunbed sessions per year correspond to the 12-session tanning programme proposed by many commercial tanning facilities. Hence, the results of the Norwegian–Swedish study were consistent with the existence of a moderate association between regular sunbed use at least once a month and melanoma occurrence.

5. What are the differences between the Norway–Sweden and case-control studies?

5.1. Methodological limitations of case-control studies

In the seven case-control studies, exposure to sunbeds was assessed retrospectively, and compared between patients with melanoma (i.e., the cases) to subjects without melanoma (i.e., the controls). These case-control studies could suffer from three limitations:

1. Case-control studies are not optimal designs for demonstrating an increase in Relative Risk when additive risks are small, i.e., an estimated Relative Risk of between 1.00 and 1.99.
2. The answers of melanoma patients on their past sunbed use could be biased because, at the moment of the interview, they knew they had a melanoma (interview bias).
3. The selection of controls may have included subjects more inclined to have had more sunbed use than average (selection bias).

The Norwegian–Swedish study was a longitudinal cohort design. Sunbed use was assessed retrospectively, but before any diagnosis of melanoma. So, the

Norwegian–Swedish study was less prone to interview and selection biases at the inception of the cohort. In addition, prospective cohort studies on large numbers of subjects are more powerful designs than case-control studies, and are thus more appropriate to reveal the existence of moderately elevated risks.

5.2. Changing emission spectrum, latency period and accumulated UV doses

Apart from methodological issues, the negative results of the case-control studies could be due to the following factors:

1. The UV lamps changed over time. Up to the mid-1980s, arc mercury lamps having an emission spectrum rich in UVB (and even UVC) radiations were commonly used as a substitute to the absence of sunshine, e.g., for the synthesis of vitamin D in children. Hence, eventual carcinogenic effects could be attributable to exposure of children to these arc mercury UV lamps, and not to modern tanning devices.
2. The latency period between exposure to artificial UV sources and melanoma occurrence is probably several decades [11]. Five of the seven case-control studies examined sunbed use before 1990, and were conducted in countries where the indoor tanning fashion was still in its early phase. The latency period may be the main reason why case-control studies yielded inconsistent results, since sunbed use was not frequent before 1985.
3. Only a few subjects included in the case-control studies had more than 20 h of cumulative sunbed exposure.

How the Norway–Sweden study addressed these factors?

1. In 1983, commercialisation of arc mercury lamps was banned in Norway and Sweden. A further analysis of the Norway–Sweden study showed that the increased melanoma risk associated with sunbed use was not due to the use of UV lamps before 1983 [35].
2. Women who participated in the Norway–Sweden study were 30 years old or more at cohort inception. The highest melanoma risk was found in women who used sunbeds at least once per month when they were 20–29 years old [increase of 158% (95% CI: 48–350%)]. Lower melanoma risks were found for sunbed use at least once a month during the third or fourth decade of life. This result supports the hypothesis that there is a latency period. In the Nordic countries, the sunbed fashion is popular since the late 1970s, and rates of sunbed use in those countries are the highest in the world. Furthermore, women are approximately two times more inclined than men to utilise sunbeds. Hence, it is probable that the risk of melanoma associated with sunbed use started to become apparent in the Norway–Sweden study in women.
3. The Norway–Sweden study showed that before 1992 18% of the study women used sunbeds at least once a month over 10 years, what is equivalent to at least 40 h of cumulative sunbed use, if one assumes a duration of 20 min for a typical sunbed session.

In conclusion, the results of the Norway–Sweden study are consistent with the existence of a 55% (95% CI: 4–132%) increase in melanoma risk associated with 40 h or more of sunbed use. Further follow-up of the cohort will inform us about the trends in melanoma risk according to amounts of sunbed exposure.

5.3. Are 40 h of sunbed use equivalent to 40 h of sunbathing?

Over a 10-year period, the duration of sunbathing activities may exceed 400 h in suntan enthusiasts. So, how significant are 40 h of sunbed use, compared with 400 h of sunbathing? In fact, durations of sunbed use and of sunbathing are not readily comparable because:

- We do not know if sun exposure or sunbed use would influence melanoma occurrence by acting through the same biological mechanisms.
- If the UVA dose is the key element, then 20 min of sunbed exposure represents a UVA dose equivalent to 2–3 h of sun exposure in the summer midday sun, but the dose rate of UVA received per unit of time by skin cells is 5–10 times higher than that in the sun.
- The erythemal effectiveness of sunbed use is approximately two times that of the midday sun. If sunburns are key indicators of biological events implicated in the genesis of melanoma, then 20 min spent under a sunbed could have the biological significance of 40 min of sunbathing in the summer midday sun.
- Sunscreens are often used during sunbathing, with the net result for suntan worshippers that sunburn occurrence is delayed, and time spent in the sun is longer [36].
- Sunbathing may take place when the sun is less bright, for instance at the end of the afternoon.

So, with our current state of knowledge about the relationship between UV radiations and melanoma, one should be cautious when comparing durations of sunbathing with durations of sunbed use.

6. Skin cancers other than melanoma

Two case-control studies examined past exposure to sunbeds in patients with non-melanoma skin cancer.

One found no association [37]. Another found positive associations between sunbed use and SCC and BCC [38]. In the latter study, the estimated Relative Risk associated with sunbed use was 2.5 (95% CI: 1.7–3.8) for SCC and 1.5 (95% CI: 1.1–2.1) for BCC. These findings are in line with data on non-melanoma skin cancers in patients affected by severe psoriasis and treated with PUVA therapy (a combination of UVA irradiation and oral psoralen).

7. Regulations of commercialisation, installation, operation and use of artificial tanning devices

Since 1990, many countries have issued specific rules for sunbed installation, operation and utilisation. There is a wide variation in the content of these rules. In the European Union, there is no standardisation of regulations on sunbed commercialisation and use. In some countries (e.g., in the UK, Canada and the Netherlands), recommendations are formulated by, or in association with the sunbed industry, or organisations of professional sunbed operators. In the US, the Food and Drug Administration provides standards only for the manufacturing of tanning devices, and regulations for operation and utilisation vary considerably across the States.

An important achievement of regulations is the requirement for better information for consumers, as well as the wearing of protective eyewear to protect the eyes. Table 1 presents a list of criteria that should prevent individuals to use sunbeds. In some countries (e.g., in France), training of commercial tanning facilities is mandatory, and tanning machine operators are instructed to refuse access to the sunbed to the consumer meeting at least one criteria listed in Table 1. The need to have trained operators has prevented the multiplication of automated tanning parlours, working without the surveillance of an operator.

However, regulations and recommendations to consumers are not a panacea because:

1. Their enforcement remains a challenge.
2. They do not apply to the private use of sunbeds.
3. They do not reflect the numerous uncertainties we have on the association between UV exposure and skin cancers, or other UV-induced lesions like the premature skin aging and eye lesions.
4. Their potential impact on hazards associated with sunbed use is probably marginal because after all, they do not prevent individuals from receiving high doses of UV radiation.
5. Indoor tanning operators take advantage of the existence of regulations for asserting that sunbed use is secure.

8. The tanning industry and the concept of "safe tan acquisition"

8.1. The tanning industry

The "tanning industry" can be understood as all commercial activities developed around the behaviours of intentional sun exposure, for tan acquisition or for other reasons like the search of well-being. Products promoted and sold by the tanning industry comprise sunscreens, a variety of oral preparations deemed to increase the resistance to UV aggressions or to facilitate tan acquisition, swim suits permeable to UV radiations, and the use of non-solar sources of UV presented as safe

Table 1
Criteria that should prevent sunbed use*

1. To be less than 18 years of age.
2. To be pregnant.
3. To suffer from a febrile episode.
4. To suffer from significant eye vision impairment.
5. To have red hair.
6. To have melano-compromised skin, i.e., when the skin always sunburns with no ability to tan or has a high susceptibility to sunburn with a poor ability to develop a tan.
7. To have a family history of eye or cutaneous melanoma.
8. To have large numbers of naevus (mole), in the order of more than 30 moles $\geqslant$ 2 mm on the whole body, or one or more naevi larger than 5 mm.
9. To have a tendency to have freckling developing on the face when going in the sun.
10. To have a history of frequent sunburn during childhood or during adulthood.
11. To have pre-malignant (e.g., solar keratosis) or a history of malignant skin lesions.
12. To have a sun damaged skin (wrinkles on the face, or irregular pigmented skin areas on the face and arms).
13. To wear cosmetics. Cosmetics may enhance sensitivity to UV exposure.
14. To be taking medications. Medications may increase sensitivity to UV, and may sometimes lead to severe health complications (e.g., extensive skin burns). Individuals should seek advice from their physician to determine if the medication will make them UV-sensitive.

* After World Health Organisation (WHO) 2003 (60) and International Commission on Non-Ionizing Radiation Protection (ICNIRP) 2003 (8).

alternatives to sunlight. The tanning industry has elaborated a large part of its marketing strategies around the concept of "safe tan acquisition", that is the acquisition of a tan without incurring (or with incurring less) detrimental effects of UV exposure, mainly sunburns, skin cancers, and skin aging.

8.2. The dubious concept of "regulated" or "controlled" tan acquisition

For promoting the idea of the possibility of "safe (or safer) tan acquisition", the sunbed industry has invented the concept of "regulated" or "controlled tanning", as opposed to beach tanning that would be "unregulated" or "uncontrolled" [39,40]. "Controlled" tan acquisition would be safer than sunbathing because of the constancy of several UV-exposure criteria, like, for instance, a constant UV intensity in wavelength and in time. In hot countries, like Italy and Australia, the "controlled tan acquisition" concept is used for convincing consumers that sunbed use represents a good substitute to beach sunbathing.

But the perilous assertion that "controlled" tan acquisition would be less aggressive than 'uncontrolled' tan acquisition is not supported by laboratory experiments, it contradicts recent findings in basic science, and denies epidemiological and behavioural data:

1. Subjects attracted by indoor tanning are also attracted by sunbathing [11]. Hence, for most sunbed users, amounts of indoor UV add to amounts of outdoor UV, with possible interactive processes that could further increase the melanoma risk. In addition, the weak photoprotection against sunburns afforded by a sunbed-induced tan may encourage longer stays in the sun [41].
2. Surveys continually show the ignorance of tanning parlours operators and the lack of enforcement of basic utilisation rules [42–45].
3. DNA damage that is detectable after sunbed exposure is comparable to DNA damage induced by exposure to natural sunlight [46].
4. Tan induction is rather an indicator of skin aggression with DNA damage than a marker of skin photoprotection [47,48].
5. The recurring induction of melanin synthesis could be involved in skin carcinogenesis [49,50].
6. Sunbed use causes sunburns in 18–55% of users, and these acute skin reactions are associated with melanoma and BCC occurrence.
7. The UVB fraction present in the sunbed emission spectrum may still have detrimental effects on the skin.
8. We have no knowledge about the long-term effects of repeated exposures to high UVA doses mixed with some UVB.

8.3. The questionable photoprotection properties of "pre-vacation tan"

The tanning industry and many sun-enthusiasts allege that a "pre-vacation tan" acquired through sunbed use would confer protection against sunburns and other deleterious effects of the sun. But photoprotection against sunburns and DNA photodamage afforded by the facultative pigmentation induced by tanning under the sun is very low, just equivalent to a sun protection factor (SPF) 3 sunscreen [51]. The tan induced by UVA-tanning provides practically no photoprotection [52]. The moderate skin thickening induced by sunbed use would afford even less photoprotection than tanning [53]. Increasing numbers of laboratory data show that a pre-vacation tan offers only little protection against sun-induced DNA damage [41,54,55].

9. New threats on the horizon

9.1. The UV-lamps rich in UVB radiation

Recently, new fluorescent lamps that have an emission spectrum resembling the emission spectrum of the midday sun have been introduced into the market. Exposure to these lamps enables a faster acquisition of a deep tan. Exposure to UVB-rich lamps is similar to intentional sun exposure in the midday sun, and is thus likely to convey the same risk of skin cancer. Given the known association between intermittent sun exposure and melanoma, public-health authorities should reconsider the soundness of the commercialisation of these lamps.

9.2. Age of sunbed users

Age of sunbed users is a new concern: in Sweden, sunbed use is popular among adolescents 14–17 years old [56]. A large survey in 2004 in the schools of Lanarkshire (UK) showed that 7% of children 8–11 years old had used a sunbed [57]. This phenomenon is also observed in Australia [58]. Most countries do not have regulation on a minimal age for indoor tanning [59]. Childhood and adolescence are periods of greater biological vulnerability to UV radiations, and thus prohibition of the use of tanning devices before 18 years old seems wise [8,60].

9.3. The hypothetical health benefits of UV radiations

The subtlest position for the defence of indoor tanning is the recognition of good and bad effects of indoor tanning, but that finally, good effects would outweigh bad effects. The good health effects attributed by the tan-

ning industry to UV radiation are numerous, from the healing of seasonal depression to the prevention of breast, colon and prostate cancers. Advocacy texts issued by the tanning industry seems to come to the conclusion that everything being considered, finally, ''controlled skin damage'' is somehow good for health [61].

The generation of vitamin D is the main known benefit of UV radiation. Vitamin D synthesis is activated by UVB radiation, not by UVA radiation. In fair-skinned European subjects, if dietary intakes of vitamin D are inadequate, brief periods of exposure to summer sunlight in everyday life on hands and face is all that is needed to initiate vitamin D synthesis. Longer exposures provide no additional benefit in this respect.

UV radiations are used for treating various skin conditions such as psoriasis and dermatitis. Psoriasis patients treated over long periods of time with a combination of UVA and oral psoralen have an increased incidence in non-melanoma skin cancers [62,63], and a significant increase in melanoma incidence was found in one cohort of PUVA-treated psoriasis patients [64,65].

The role that UV radiation would have in the prevention of cancerous diseases is largely based on ecological data and on speculations on as yet unproven biological mechanisms. At present, there is no sound scientific data showing a protective effect of intentional exposure to UV radiation on any cancer in humans.

In North European countries, and in Canada, advertisements recommend sunbed use from November to March to combat the ''winter depression'' or ''seasonal depression'', attributed to the absence of days with bright sunshine and to long periods of obscurity. However, light therapy using white fluorescent lights is as effective for the treatment of seasonal depression [66]. Thus there is no reason to promote exposure to potentially harmful UV radiation to treat that condition.

10. How credible is the precautionary principle?

The precautionary principle is frequently evoked in the shaping of health or of environmental policies. In brief, that principle consists of regulating the general public use or the diffusion in the environment of a substance or of a device whose safety remains open to question. In Europe, the precautionary principle is frequently put forward to oppose the development of innovations, even though there is no evidence for a detrimental impact on health or on the environment.

In spite of the scientifically established association between the intermittent exposure to solar UV radiation and melanoma, and of the evidence that melanoma incidence is doubling every 10 or 20 years in many fair-skinned populations, the indoor tanning fashion has undergone a considerable growth in the past 20 years. Hence, although there was far more scientific evidence for possible harmful health effects due to sunbed use than for many other products, the precautionary principle has never been applied for protecting consumers against the many health uncertainties regarding the safety of artificial UV sources, and against the many unverified beliefs utilised for the marketing of the sunbed fashion.

11. The need to control information disseminated by the tanning industry

For most people, information and advertisements disseminated by the tanning industry are the main source of information regarding tan acquisition and sun protection. Behavioural studies in Europe [17,67,68] show that people know about skin cancer and the damaging affect of sunbathing, and about possible dangers associated with sunbed use, but that knowledge does not alter their tanning behaviours in general. In Europe and the USA, recommendations on sunbed

Table 2
Steps to be taken in the regulation of sunbed use and of information given to the general public*

1. Devise regulations for the installation, operation and utilisation, independently of those set by the tanning industry.
2. To prohibit sunbed use before 18 years old.
3. Rendering the use of protective eyewear (goggles) mandatory during sunbed sessions.
4. Use of and speculations on concepts such as ''safe'', or ''controlled'', or ''regulated'' tan acquisition'' should not be authorised.
5. Reference to hypothetical health benefits of outdoor or indoor ultraviolet (UV) exposures must be prohibited. The mention of preventive effects on cancers and other major health conditions should not be authorised.
6. The existence of legal regulations on indoor tanning should not be used for advertising purposes, or for issuing claims on the safety of indoor tanning.
7. Requirement to inform consumers visiting tanning parlours on the dangers associated with sunbed use and sun exposure, including, among other things:
   (a) Increased risk of skin cancer, especially melanoma and basal cell carcinoma (BCC).
   (b) Risk of sunburns and skin erythema.
   (c) Risk of premature wrinkles.
   (d) Risk of unpleasant and disgraceful pigmented skin lesions.

* The list should be included in information packages accompanying tanning devices that are acquired for private use.

use and regulations restricting indoor tanning do not make sunbed users more cautious, especially adolescents and young adults [67–71].

The most relevant strategy for curbing sunbed use is to obtain a change in attitudes toward sunbathing and having a tan. In that respect, the principal public health target should be to draw up regulations, independently of those set by the tanning industry, and the control of information and advertisements (Table 2). The tanning industry should no longer have the possibility to have recourse to claims on health benefits of outdoor or indoor tanning in order to convince consumers to use sunbeds.

Indeed, this strategy would concern other segments of the tanning industry, such as sunscreen companies that base their marketing strategy on the possibility of acquiring a healthy and safe tan, thanks to the use of their product.

12. Conclusions

The Norway–Sweden study [26] has provided epidemiological evidence that regular sunbed use is associated with a moderate increase in the risk of melanoma. Large numbers of people use sunbeds on a regular basis, and sunbed use often starts during adolescence. So, in 2004, UV doses accumulated by many people though sunbed use may be far higher than observed in the Norway–Sweden study.

Public-health efforts should continue to disseminate information on the dangers of UV radiations, and to discourage sunbed use.

Regulation of sunbed installation, operation and use is desirable, but enforcement of rules is by far the most difficult challenge. In addition, regulations should become harmonised in the European Union.

Advertisements and information disseminated by the tanning industry to the general public should be controlled. The sunbed manufacturers and operators should no longer be able to claim health benefits of any sort attributable to sunbed use, and to other forms of intentional sun exposure.

Close monitoring of sunbed use and of its immediate consequences (e.g., skin erythema and sunburns) is now well established in Sweden. There are signs of decreasing trends in sunbed use among adolescents and young adults in Sweden [68]. Is the sunbed fashion be levelling off in Sweden? Similar surveys should be conducted in other countries to monitor global exposure to privately owned or commercially operated tanning devises. Boldeman et al. [68] have proposed an international harmonisation of survey tools for the monitoring of sunbed use and sunburn experience. Such an instrument is highly desirable for comparing sunbed use habits and consequences across countries and to follow the impact of policies intended to discourage sunbed use or to combat the ''safe tan'' concept. The survey tool could also include the monitoring of sun exposure and sun protection habits.

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The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review

The International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer

Exposure to solar ultraviolet (UV) radiation is a known cause of skin cancer. Sunbed use represents an increasingly frequent source of artificial UV exposure in light-skinned populations. To assess the available evidence of the association between sunbed use and cutaneous malignant melanoma (melanoma) and other skin cancers, a systematic review of the literature till March 2006 on epidemiological and biological studies on sunbed use was performed in Pubmed, ISI Web of Science, Embase, Pascal, Cochrane library, Lilacs and Medcarib. Search for keywords in the title and in the abstract was done systematically and supplemented by manual searches. Only case–control, cohort or cross-sectional studies were selected. Data were abstracted by means of a standardized data-collection protocol. Based on 19 informative studies, ever-use of sunbeds was positively associated with melanoma (summary relative risk, 1.15; 95% CI, 1.00–1.31), although there was no consistent evidence of a dose–response relationship. First exposure to sunbeds before 35 years of age significantly increased the risk of melanoma, based on 7 informative studies (summary relative risk, 1.75; 95% CI, 1.35–2.26). The summary relative risk of 3 studies of squamous cell carcinoma showed an increased risk. For basal cell carcinoma, the studies did not support an association. The evidence does not support a protective effect of the use of sunbeds against damage to the skin from subsequent sun exposure. Young adults should be discouraged from using indoor tanning equipment and restricted access to sunbeds by minors should be strongly considered.

Key words: artificial UV; sunbeds; melanoma; skin cancer; meta-analysis

Sun exposure is the main environmental cause of skin cancer, and ultraviolet (UV) radiation is the solar wavelength involved in skin cancer, including the malignant cutaneous melanoma.[1] People may also be exposed to UV radiation through many artificial sources at home and in the workplace, with some individuals receiving high doses. Sources of artificial UV radiation include various lamps used in medicine, industry, business and research, as well as for domestic and cosmetic purposes. Sunbeds and sunlamps used for tanning purposes are the main source of deliberate exposure to artificial UV radiation.[†] Although the contexts of sun exposure and indoor tanning differ, both deliver UV radiation, and their health effects would therefore be expected to be similar.

UV radiation wavelengths range between 100 and 400 nm and are broadly categorized into UVA (>315–400 nm), UVB (>280–315 nm) and UVC (100–280 nm). Modern indoor tanning equipment mainly emits in the UVA range, but a fraction (*i.e.*, <5%) of this spectrum is in the UVB range.

Before 1990, UVB was usually considered the only carcinogenic part of the solar spectrum, but since then UVA as well has been suspected of having carcinogenic potential. In 1992, the International Agency for Research on Cancer (IARC) classified UVB and UVA radiation, as well as "use of sunlamps and sunbeds," as "probably carcinogenic to humans" (Group 2A of the IARC classification of carcinogenic agents).[1] More recently, the 10th Report on Carcinogens published by the National Toxicology Program in the USA classified UVA radiation as a "known to be a human carcinogen."[2] Biological mechanisms by which chronic sun exposure causes squamous cell cancer (SCC) of the skin have become better known and chronic exposure to high UVB doses is now considered as the main environmental cause of that skin cancer.[3] Biological mechanisms implicated in basal cell carcinoma (BCC) start to be better known. In contrast, we still have poor knowledge of the UV wavelength and the dose delivery pattern at skin level implicated in the genesis of melanoma and of BCC.[4]

Indoor tanning is widely practiced in most developed countries, particularly in Northern Europe and the USA, and is gaining popularity even in sunny countries such as Australia.[5,6] The likely impact of this fashion on skin cancer incidence is of substantial concern, mainly for cutaneous malignant melanoma (hereafter melanoma), a cancer of poor prognosis when diagnosed at an advanced stage.

This paper summarizes a systematic review of epidemiological and experimental studies on use of indoor tanning equipment and skin cancer developed by a Working Group convened by IARC.

UV spectra from sunlight and indoor UV tanning appliances

During a sunny day on the Mediterranean coast, the solar UV spectrum at noon contains 4–5% UVB and 95–96% UVA. When UV output of a typical indoor tanning appliance is calculated in terms of biological activity, as estimated by the erythema-effective irradiance, the emission of many tanning appliances is equivalent to or exceeds the emission of the midday sun in southern Europe.[7,8] The UV intensity of powerful tanning appliances may be 10–15 times higher than that of the midday sun,[8] leading to UVA doses per unit of time received by the skin during a typical tanning session that are well above those experienced during ordinary daily activities or even during sunbathing. As a result, the annual UVA doses received by frequent indoor tanners may be 1.2–4.7 times those received from the sun, in addition to those received from the sun.[9] This widespread repeated exposure to high doses of UVA constitutes a new phenomenon for human beings.

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[†]The device used for tanning may be referred to as sunbed, sunlamp, artificial UV, artificial light or tanning bed, among other terms. Also, a number of terms are used to define a place where indoor tanning may occur: solarium, tanning salon, tanning parlor, tanning booth, indoor tanning salon, indoor tanning facility. In addition, indoor tanning may also occur in non-commercial premises. For the purpose of this report, the term *indoor tanning equipment* has been used throughout.

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In the 1990s, regulations in some countries (*e.g.*, France, Sweden) limited to 1.5% the maximum percentage of UVB in the UV output of tanning appliances. However, in practice, the UV output and spectral characteristics (*i.e.*, amounts of UVA, UVB, visible light and infrared radiation) of tanning appliances vary considerably. The proportion of UVB in UV energy output could vary from 0.5 to 4%,[10,11] and may attain an emission spectrum similar to the sun spectrum in the UVB range.[8] These differences are due to sunbed design (*e.g.*, the numbers and type of fluorescent tubes, the presence of high pressure UV lamps, the materials composing filters, the distance from canopy to the skin), sunbed power and tube ageing.

Biological effects of exposure to artificial UV radiation relevant to carcinogenesis

A large body of experimental and epidemiological data strongly indicates that the spectrum of UV radiation reaching the Earth's surface causes skin cancer.[1,12,13] UVB is a complete carcinogen that is absorbed by DNA and can damage DNA directly.[13]

Evidence of the mutagenic properties of UVA in humans has been found in several studies.[12–14] UVA radiation does cause UVB-like cyclobutane pyrimidine dimers and 6-4 photoproducts, albeit with a much lower efficacy than does UVB radiation. Most of the DNA damage induced by UVA is indirect, through the absorption of UVA photons by other cellular structures (chromophores), with formation of reactive oxygen species that can transfer UVA energy to DNA *via* mutagenic oxidative intermediates.[15]

Skin of human volunteers exposed to UVA lamps used in tanning appliances show DNA damage, *p53* mutations induced by oxidative damage and alterations of the p53 protein similar to those observed after sun exposure or after exposure of experimental animals.[16–18]

UVA penetrates deeper into human skin than does UVB. Because UVA represents the largest proportion of the UV spectrum of tanning appliances and of solar radiation reaching the Earth's surface, far more UVA than UVB reaches the basal layers of the epidermis where melanocytes and early keratinocytic cells are located.

Both UVA and UVB radiation can affect the immune response that may be involved in the promotion of melanoma,[15,19,20] but the 2 types of radiation seem to act differently.[21,22] UVB induces immunosuppression at both the local and systemic levels, while UVA does not induce systemic immune suppression.[23]

To date, evidence obtained from experimental studies on the involvement of high UVB doses in the causation of SCC is consistent with observations in humans. In contrast, experimental studies give conflicting results regarding the roles of UVB and UVA in the induction of melanoma in humans. The same uncertainties hold true for BCC, a type of tumor that shares some epidemiological characteristics of melanoma.

Experiments carried out in animals cannot reproduce the complex interplay in individuals between highly variable natural susceptibilities to UV radiation, sun exposure behaviors and exposure to various sources of UV radiation. During indoor tanning, such interrelationships may be critical, as users are more inclined than the average population to engage in outdoor tanning activities,[24] and indoor tanning sessions often precede or follow active sun exposure or outdoor tanning.

Effects of artificial UV on human skin

Skin redness or burning are reported by 18–55% of users of indoor tanning equipment in Europe and North America.[25] Although UVB is far more potent than UVA in causing sunburn, high fluxes of UVA are capable of inducing skin redness in individuals sensitive to sunlight or with only moderate tanning ability.

In individuals who tan easily, exposure to tanning appliances will lead first to the oxidation of melanin already present in superficial keratinocytic layers of the skin, known as immediate pigment darkening.[26] A more permanent tan is acquired with accumulation of exposure, depending on tanning ability and on the amount of UVB present in the UV spectrum of the lamps.

Immediate pigment darkening has no photoprotective effect against UV-induced skin redness or sunburn.[27] Moreover a UVA-induced permanent tan provides little photoprotection[28,29] and the skin thickening caused by UVA affords only very little photoprotection.[30] Studies in humans show that a prevacation tan induced artificially offers virtually no protection against sun-induced DNA damage.[31–33]

Exposure to artificial UV for tanning purposes

Few people had used indoor tanning equipment before 1980 but by the end of the 1990s more than 60% of women and 50% of men aged 18–50 years in Northern Europe reported having ever used indoor tanning equipment.[34] Indeed, prevalence of indoor tanning is increasing so rapidly in many countries that current estimates may be outdated rapidly. The most frequent motivations for indoor tanning are the acquisition of a so-called safe tan and preparation of the skin before sun exposure.[25]

Use of indoor tanning equipment is more prevalent among women and among both men and women younger than 35 years. Earliest studies in Sweden and in the USA tended to find indoor tanning to be more prevalent among adolescents with fair skin types who are more prone to sunburn.[35–37] More recent studies in the USA found either the opposite[38–40] or no association.[41]

Few studies have assessed the compliance of indoor tanning facility operators or consumers with recommendations and regulations. Overall, information provided by tanning salon operators on health risks and on duration and frequency of exposure is often incomplete, and there is a lack of identification of highly sun-sensitive subjects or of subjects taking photosensitizing medications.[6,42–44]

About 17–35% sunbed users reported that they did not wear eye protection.[10,41,43] In some surveys, 16% of sunbed users may have had more than 100 sessions per year,[10] and most users tend to exceed the recommended exposure times.[41,44,45]

Since 1989, a total of 16 studies (18 reports) have examined prevalence of indoor tanning among children and adolescents aged 8–19 years in Australia, Europe and the USA.[46,47] All studies showed a frequent use by adolescents and children, sometimes at a very young age. According to the most recent studies, 30% of adolescents in Sweden and 24% of adolescents in the USA aged 13–19 years reported ever-use of indoor tanning equipment and 8 and 12% respectively were frequent users (10 times per year or more). In a recent survey in the United Kingdom, while 7% of children aged 8–11 years reported exposure to a sunbed in the past 6 months, as many as 48% expressed a desire to use a sunbed.[48]

Epidemiological studies on indoor tanning and skin cancer

As existing animal models of human melanoma are inconsistent, evidence of an association between indoor tanning and skin cancer must be sought predominantly from epidemiological studies. Few studies have addressed this topic specifically, but some studies included 1 or more secondary questions about indoor tanning. We systematically analyzed the results from the relevant studies and compiled them in a metaanalysis.

Methods

The methodology used for the literature search is summarized in Table I. The minimal common information about exposure to indoor tanning appliances for all studies was "ever exposed." For those studies wherein "ever exposed to indoor tanning appliances *versus* never" was not strictly assessed[49,50] we used the information closest to this category.

Most estimates included all subjects and combined sexes in the analysis. Some studies presented results separately for women and men, with no combined data, in which case both estimates were

included. Since the studies used different age categories for classifying age at first exposure, we considered as "young exposure" those exposures that started before 35 years of age.

Every measure of association adjusted for the maximum number of confounding variables, and corresponding confidence interval (CI), was transformed into logarithms of relative risk (log RR) and the corresponding variance was calculated.[51] Where no estimates were reported, the crude estimates were calculated from tabular data, using asymptotic Mantel-Haenszel methods to evaluate the 95% CI of the log odds ratio.

The homogeneity of the effects across studies was assessed using the large sample test based on the χ^2-test. The summary relative risk was estimated using random effects models even when heterogeneity was found to be not statistically significant, in order to be conservative. Publication bias was investigated by funnel plot regression.[52]

TABLE I – METHOD USED FOR THE LITERATURE SEARCH

The literature to March 2006 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 translation were used for search in the PASCAL database: skin cancer, squamous cell carcinoma, SCC, basal cell carcinoma, BCC and 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.
Search for keywords in the title and in the abstract was done systematically. Manual search was done of references cited in the selected articles, and in selected reviews or books on melanoma and skin cancer. All participants of the working group 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.
The selected articles were reviewed, and data were 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.

Studies on melanoma

We identified 23 studies on use of indoor tanning equipment and melanoma (Table II).[34,49,50,53–73] All studies used the case–control design, except for 1 cohort study.[50] A case–control study was considered population-based when cases were derived from a population-based cancer registry and controls were selected from the general population. Of these 23 studies, 4 studies were excluded from the metaanalysis because they did not include estimates of the relative risk for cutaneous melanoma associated with exposure to tanning appliances.[53,55,57,62]

Studies used for the metaanalysis included a total of 7,355 cases. The first study was published in 1981 and the last in 2005. Fifteen studies were carried out in European countries, 4 of which in Scandinavian countries, and 2 were in the United States, 1 in Canada and 1 in Australia.

Studies on basal cell and squamous cell carcinomas

Nine case–control studies have examined the association between indoor tanning and either BCC or SCC of the skin.[74–82] All studies reported a risk estimate except one,[74] which was therefore excluded. A further 3 studies that did not distinguish between

TABLE II – CHARACTERISTICS OF THE STUDIES CONSIDERED FOR THE METAANALYSIS ON MELANOMA

Reference	Country	Number		Relative risk[2]
		Cases	Controls	
Cohort study				
Veierød *et al*. (2003)[50]	Norway, Sweden	187	106,379[1]	1.55 (1.04–2.32)
Population-based case–control studies				
Adam *et al*. (1981)[54]	UK	169	207	2.93 (1.16–7.40)
Gallagher *et al*. (1986)[55]	Canada	595	595	[3]
Holman *et al*. (1986)[56]	Australia	511	511	1.1 (0.6–1.8)
Osterlind *et al*. (1988)[59]	Denmark	474	926	0.73 (0.53–1.01)
Zanetti *et al*. (1988)[60]	Italy	208	416	0.9 (0.4–2.0)
Beitner *et al*. (1990)[62]	Sweden	523	505	[3]
Walter *et al*. (1990)[63]	Canada	583	608	[4]
Westerdahl *et al*. (1994)[70]	Sweden	400	640	1.3 (0.9–1.8)
Holly *et al*. (1995)[68]	USA	452	930	0.94 (0.74–1.2)
Chen *et al*. (1998)[69]	USA	624	512	1.13 (0.82–1.54)
Walter *et al*. (1999)[64]	Canada	583	608	1.54 (1.16–2.05)
Westerdahl *et al*. (2000)[73]	Sweden	571	913	1.2 (0.9–1.6)
Other case-control studies				
Klepp and Magnus (1979)[53]	Norway	78	131	[3]
Holly *et al*. (1987)[57]	USA	121	139	[3]
Swerdlow *et al*. (1988)[58]	UK	180	120	2.94 (1.41–6.17)
MacKie *et al*. (1989)[61]	UK	280	180	1.3 (0.2–7.9) for men; 1.2 (0.5–3.0) for women
Dunn-Lane *et al*. (1993)[65]	UK	100	100	1.16 (0.54–2.47)
Garbe *et al*. (1993)[66]	Germany	280	280	1.5 (0.9–2.4)
Autier *et al*. (1994)[67]	Belgium, France, and Germany	420	447	0.97 (0.71–1.32)
Naldi *et al*. (2000)[71]	Italy	542	538	0.78 (0.45–1.37)
Kaskel *et al*. (2001)[49]	Germany	271	271	1.00 (0.6–1.8)
Bataille *et al*. (2004)[72]	UK	413	416	1.19 (0.84–1.68)
Bataille *et al*. (2005)[34]	Belgium, France, the Netherlands, Sweden, UK	597	622	0.90 (0.71–1.14)

ALM, acral lentiginous melanoma; HC, histologically confirmed; LMM, lentigo maligna melanoma; M, melanoma; MM, malignant melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.

[1]Cohort size.–[2]Values in parentheses are 95% CI .–[3]Because no estimate of risk was reported in these studies, we did not include them in the metaanalysis.–[4]The study by Walter *et al*. (1990)[63] was reanalyzed in the 1999 publication. We used the relative risk adjusted for potential confounders presented in the 1999 publication.

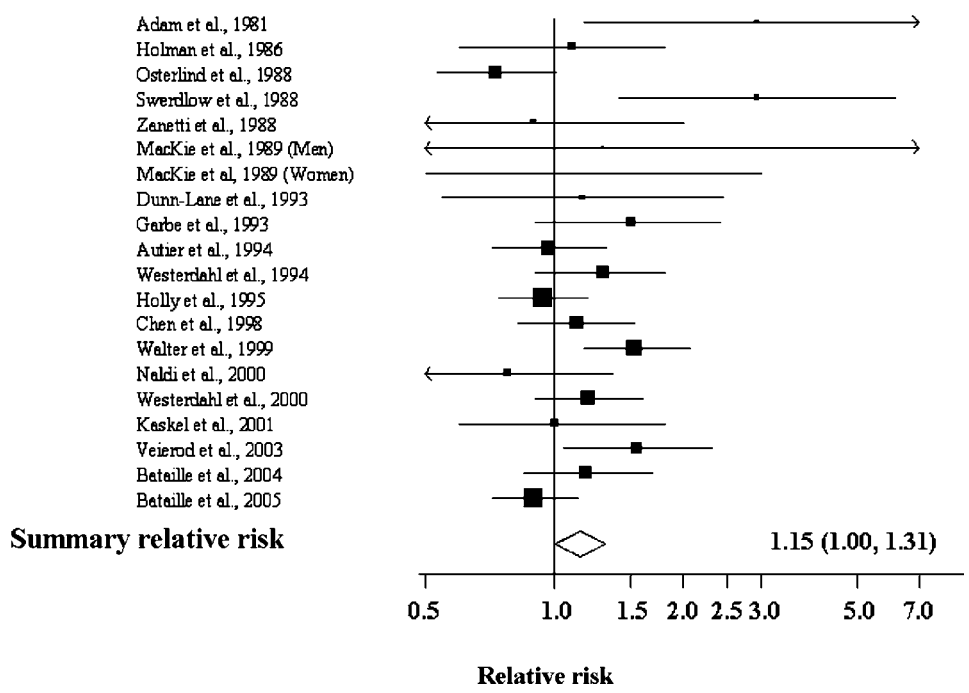

FIGURE 1 – Relative risk for cutaneous melanoma associated with ever use of indoor tanning equipment: estimates of 19 studies and summary estimate (relative risks were presented separately for men and women in the study by MacKie *et al.*[61]).

TABLE III – METAANALYSIS OF EPIDEMIOLOGICAL STUDIES ON INDOOR TANNING AND RISK FOR MELANOMA, SQUAMOUS CELL CARCINOMA AND BASAL CELL CARCINOMA

Exposure	Number of studies	Summary relative risk[1]	Heterogeneity[2] (p value)
Melanoma			
Ever use of indoor tanning equipment	19	1.15 (1.00–1.31)	0.013
First exposure in youth	7	1.75 (1.35–2.26)	0.55
Exposure distant in time	5	1.49 (0.93–2.38)	0.018
Exposure recent in time	5	1.10 (0.76–1.60)	0.81
Squamous cell carcinoma			
Ever use of indoor tanning equipment	3	2.25 (1.08–4.70)	0.10
Basal cell carcinoma			
Ever use of indoor tanning equipment	4	1.03 (0.56–1.90)	0.06

[1]Values in parentheses are 95% CI.–[2]χ^2-test: the degrees of freedom are given by the number of risk estimates included minus 1.

these 2 major types of skin cancer[75–77] were also excluded from review, leaving 5 studies for consideration.

Relative risk for melanoma

Thirteen of 19 studies presented positive estimates for "ever" *versus* "never" exposed to indoor tanning equipment, but only 4 were statistically significant[50,54,58,64] (Fig. 1). Seven of these studies reported only crude relative risks, and 1 adjusted for age and sex only. Results of the metaanalysis are shown in Table III. The summary estimate indicated a significant positive association between "ever" *versus* "never" indoor tanning and melanoma (RR, 1.15; CI, 1.00–1.31) and the χ^2-test for heterogeneity was statistically significant.

To decrease the influence of possible biases, estimates were calculated including only the cohort and the 9 population-based case–control studies. The summary relative risk was very similar apart from having wider CIs (RR, 1.17; CI, 0.96–1.42). In an analysis restricted to the 8 studies that adjusted for confounders related to sun exposure and sun sensitivity,[50,60,61,64,69–71,73] the summary relative risk remained similar to that obtained from all 19 studies, but the CI widened (RR, 1.19; CI, 0.33–4.30).

Seven studies presented estimates relevant for the evaluation of "first exposure in youth" *versus* "never" (Fig. 2). All relative risks were adjusted for confounders related to sun exposure or sun sensitivity, except in the study by Walter *et al.*[64] A significant 75% increase in risk was detected (Table III) and the χ^2-test for heterogeneity was nonsignificant.

Five studies investigated time since exposure and reported estimates that allowed comparisons between recent and more distant exposure.[34,58,63,67,69] Metaanalytic estimates were greater for exposures more distant in time when compared to those for more recent exposures (Table III).

There was some indication for a dose-effect relationship in 2 studies,[67,70] but not in the other two.[69,73] But metrics used for assessing duration were all different and therefore did not permit metaanalytic synthesis. Only 4 studies explored the role of natural sensitivity to sunlight on risk associated with indoor tanning, and overall, they found no consistent result.[34,64,72,73]

Type of indoor tanning equipment

No epidemiological study has been able to explore in a rigorous way amounts of UVA and UVB received by indoor tanning users. The study by Chen *et al.*[69] obtained information concerning the type of sunbed or sunlamp used (*e.g.*, desktop models, floor models, beds or walk-in booths). This information was obtained by showing to subjects pictures of various types of sunlamps and sun-

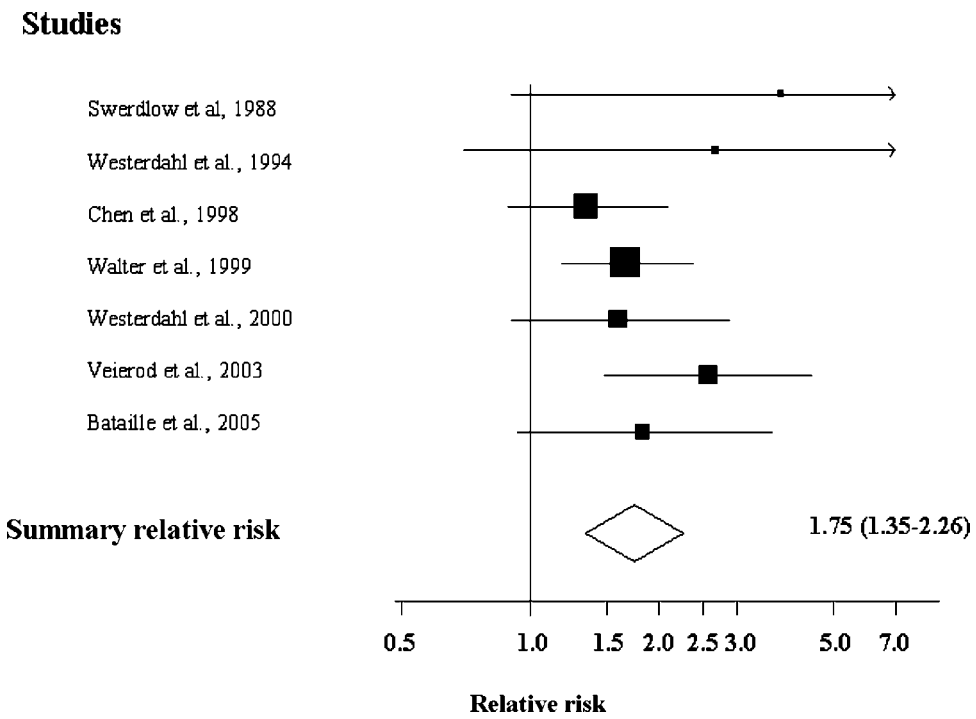

FIGURE 2 – Relative risk for cutaneous melanoma associated with first use of indoor tanning equipment at age <35 years: estimates of 7 studies and summary estimate.

beds. The study found a nonsignificant elevated risk of malignant 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 2 types of sunlamps, compared with no use of sunbeds. The study by Bataille *et al.*[34] reported no impact of the type of device used on melanoma risk.

The relative risks of melanoma associated with ever-use of sunbed/sunlamp reported in the studies did not vary with year of publication or first year of study period, and funnel plot regression gave no indication of publication bias (ever-use of sunbed/sunlamps, $p = 0.80$; first exposure in youth, $p = 0.10$). This observation suggests that the apparent increased risk for ever use and for age at first use were unlikely to be explained by the earlier types of indoor tanning appliance used.

Before 1980, exposure to artificial UV radiation was more likely to take place at home with devices that emitted greater amounts of UVB radiation, whereas exposure in the 1980s increasingly occurred in commercial salons using equipment that emitted mainly UVA. The Norway–Swedish 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.[83]

Relative risk for squamous cell carcinoma and basal cell carcinoma

The metaanalysis was based on the 5 studies[78–82] reporting type-specific risk estimates (Table III). Metaanalytic estimates suggested a significant effect of exposure to indoor tanning appliances for SCC, but not for BCC. Funnel plot regression gave no indication of publication bias ($p = 0.26$ and 0.77 for SCC and BCC, respectively).

The study by Karagas *et al.*[81] gave the most detailed results, and the trends were consistent with the results reported for melanoma. Results were adjusted for sun sensitivity but not for sun exposure, since adjustment for sun exposure did not change the risk estimates. Depending on age at first use, the 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 indoor tanning equipment.

Discussion

Investigation of the association between indoor tanning and skin cancers poses challenging problems, as indoor tanning has been in widespread use only recently. Based on our knowledge about the relationship between sun exposure and risk for melanoma, it could be stated that associations after long latency periods, such as would be expected for melanoma and BCC, may not be detectable yet. Also, since the fashion of indoor tanning has been increasing steadily, the failure to distinguish between distant and recent exposures in most epidemiological studies may mask an actual increase in risk with exposure early in life.

Our systematic review of published studies mainly from Europe and North America of the association of use of indoor tanning equipment with skin cancers revealed an association of age at first use of less than 35 years with melanoma risk. These studies consistently indicated a moderate strength of association, with a summary relative risk of 1.75 (1.35–2.26). This result suggests a greater vulnerability of younger people to the carcinogenic impact of indoor tanning. Also, it is in agreement with the knowledge that age at exposure may influence the relative risk for skin cancer associated with UV exposure, and that exposure to sunlight in childhood is an important contributing factor for melanoma risk in adults.[84,85]

The association with ever-use of such equipment, or use more than 15–20 years prior to diagnosis of melanoma, was weak, and evidence regarding a dose–response relationship was scant. The evidence is limited by concerns over characterization of exposure and recall of exposure by individuals, potential confounding by sun exposure or other variables and the low power to detect associations that become evident only following a prolonged lag period after exposure. Our results are similar to a previous metaanalysis,[86] but our systematic review is more exhaustive and included more studies.

In Scandinavian countries use of indoor tanning equipment has been popular since the late 1970s and the prevalence of use 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 equipment at least once per month when they were 20–29 years old. These results support the hypothesis that a certain lag 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 indoor tanning.

The positive association between use of indoor tanning equipment and melanoma risk reported here is consistent with the knowledge that melanoma is caused primarily by exposure to solar radiation. The limited evidence for a positive association between indoor tanning and SCC is consistent with its known dependence on dose of UV radiation to the skin. Thus the biological plausibility of a causal association between indoor tanning and risk for melanoma and SCC is strong.

On balance, the evidence pertaining to the strength, consistency, dose–response and temporal sequence of the association of the use of indoor tanning equipment with melanoma risk, and of the coherence and biologic plausibility of the association, leads us to conclude that there is convincing evidence to support a causal relationship, particularly with exposure before the age of 35 years. This evidence is strongly suggestive and further studies could clarify our understanding of this association and allow more definitive conclusions.

We are cognizant of the importance of this issue for the health of light-skinned populations. The strength of the existing evidence suggests that policy makers should strongly consider enacting measures such as restricting minors and discouraging young adults from using indoor tanning equipment, in order to protect the general population from additional risk for melanoma and squamous cell skin cancer.

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Original Contribution

A Melanoma Epidemic in Iceland: Possible Influence of Sunbed Use

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Since 1980, sunbed use and travel abroad have dramatically increased in Iceland (64°–66°N). The authors assessed temporal trends in melanoma incidence by body site in Iceland in relation to sunbed use and travel abroad. Using joinpoint analysis, they calculated estimated annual percent changes (EAPCs) and identified the years during which statistically significant changes in EAPC occurred. Between 1954 and 2006, the largest increase in incidence in men was observed on the trunk (EAPC = 4.6%, 95% confidence interval: 3.2, 6.0). In women, the slow increase in trunk melanoma incidence before 1995 was followed by a significantly sharper increase in incidence, mainly among women aged less than 50 years, resembling an epidemic incidence curve (1995–2002: EAPC = 20.4%, 95% confidence interval: 9.3, 32.8). In 2002, the melanoma incidence on the trunk was higher than the incidence on the lower limbs for women. Sunbed use in Iceland expanded rapidly after 1985, mainly among young women, and in 2000, it was approximately 2 and 3 times the levels recorded in Sweden and in the United Kingdom, respectively. Travels abroad were more prevalent among older Icelanders. The high prevalence of sunbed use probably contributed to the sharp increase in the incidence of melanoma in Iceland.

Iceland; melanoma; ultraviolet rays

Abbreviations: CI, confidence interval; EAPC, estimated annual percent change; UV, ultraviolet; UV-A, ultraviolet A; UV-B, ultraviolet B; UV-C, ultraviolet C.

Editor's note: *An invited commentary on this article appears on page* ***000****, and the authors' response is published on page* ***000****.*

Cutaneous malignant melanoma is a potentially deadly cancer that occurs predominantly in sun-sensitive subjects, that is, subjects with light skin and poor ability to tan (1). Intermittent exposure to ultraviolet (UV) radiation is the main environmental cause of cutaneous malignant melanoma (2). Intermittent sun exposure consists of intense exposure to UV radiation of skin areas normally sun protected, such as the trunk. UV radiation reaching the earth's surface contains ultraviolet A (UV-A) (>320–400 nm) and ultraviolet B (UV-B) (>280–320 nm) radiation. More recently, UV radiation (wavelength, 100–400 nm, encompassing ultraviolet C (UV-C), UV-B, and UV-A), as well as UV-emitting tanning devices, has been classified as carcinogenic to humans (group 1 carcinogens) by a Working Group of the International Agency for Research on Cancer (3).

Until about 1990, melanoma incidence in Iceland was below that of other Nordic countries (4), as expected from its northern latitude (between 64° and 66°N), frequent cloud cover, and consequent low natural UV radiation. However, melanoma incidence sharply increased in both genders during the 1990s and, in 2000, the incidence in Icelandic women was the highest of all Nordic countries (4). The indoor tanning fashion was suspected as a possible cause of this increase. A few years ago, we predicted that melanomas associated with solarium use would be preferentially localized to the trunk (5). We therefore performed a detailed analysis of temporal trends in melanoma incidence in

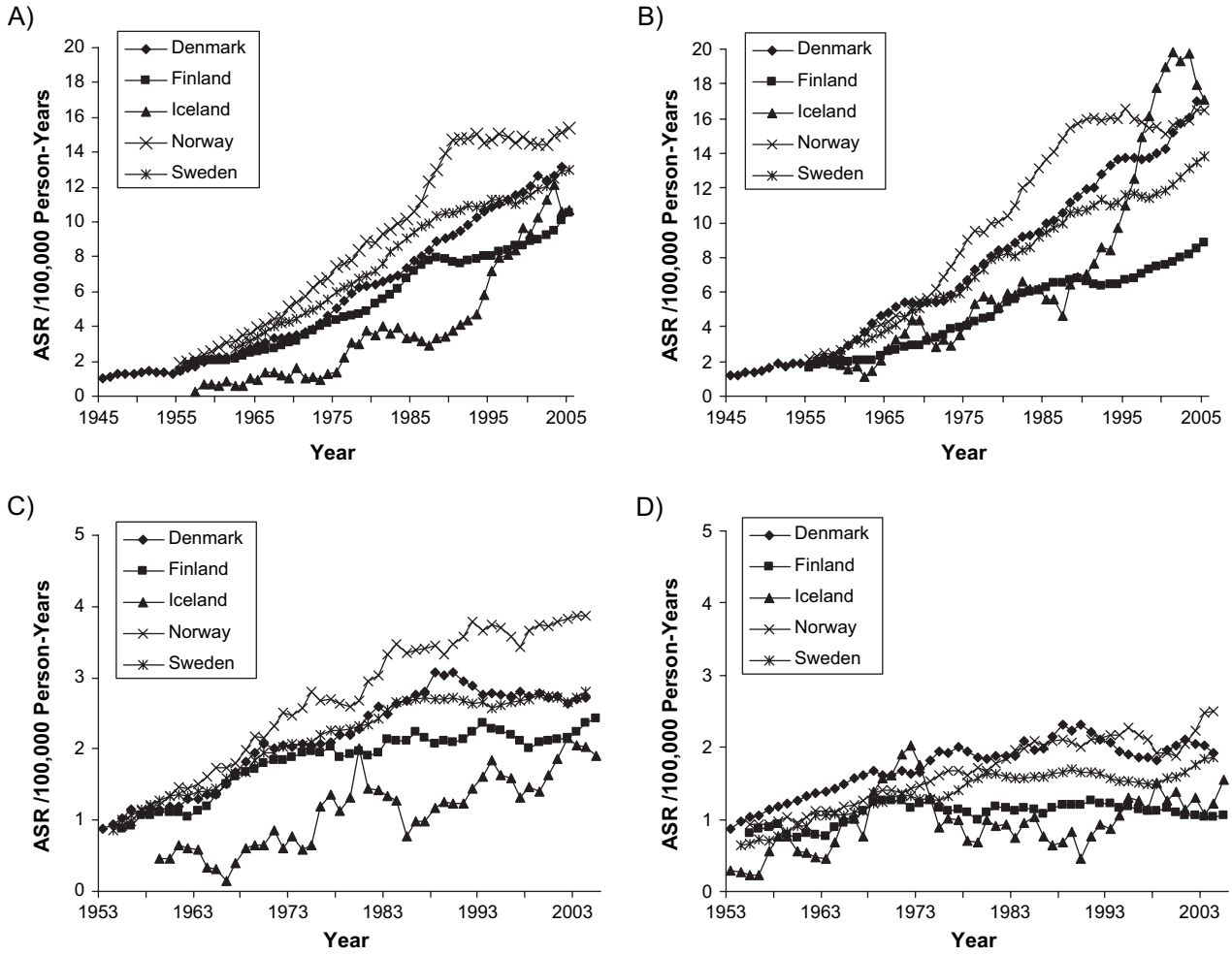

Figure 1. Trends in cutaneous melanoma incidence (1945–2007, men (A) and women (B)) and mortality (1953–2007, men (C) and women (D)) in Nordic countries. Incidence rates are 5-year moving averages with 2007 being the last possible year. The *y*-axis scale of mortality is approximately 4 times lower than that of incidence. ASR, age-standardized rate. Data source: NORDCAN (4), age adjusted on the World Standard Population.

Iceland and of changes in exposure to sources of UV radiation, mainly sunlight and artificial tanning devices.

MATERIALS AND METHODS

The population-based Icelandic Cancer Registry provided information on invasive melanoma incidence from 1955 to 2007 (6). Melanoma incidence rates for all body sites, by sex, were analyzed by using the Joinpoint Regression Program, version 2.7 (7), to identify periods with distinct trends between 1955 and 2007. The analysis was stratified by gender, by age (0–49 and $\geq$50 years of age), and by anatomic site. The NORDCAN online database provided Nordic incidence and mortality data on cancer from 1945 until 2006 (4). All rates were standardized to the World Standard Population.

Data on sunbed numbers were provided by the Icelandic Radiation Protection Institute (8). Further information on sunbed use came from surveys of melanoma risk factors in the Icelandic population conducted in 2001–2002 (8) and in 2002 (9). Information on travel abroad was provided by a survey done in 2001–2002 (10) and from the National Statistical Institute of Iceland (11).

RESULTS

Melanoma incidence

In 1955–2007, 861 melanoma cases (306 in men and 555 in women) were reported to the Icelandic Cancer Registry. In the period 1955–1959, the age-standardized incidence rate of melanoma in Iceland was less than 1/100,000 in men and 2.2/100,000 in women. Until around 1990, despite an annual increase of 4.1%, the melanoma incidence remained lower in Iceland than in the other Nordic countries (Figure 1), but during the period 1998–2002, the age-standardized incidence rate was 9.0/100,000 for men and 18.5/100,000 for women.

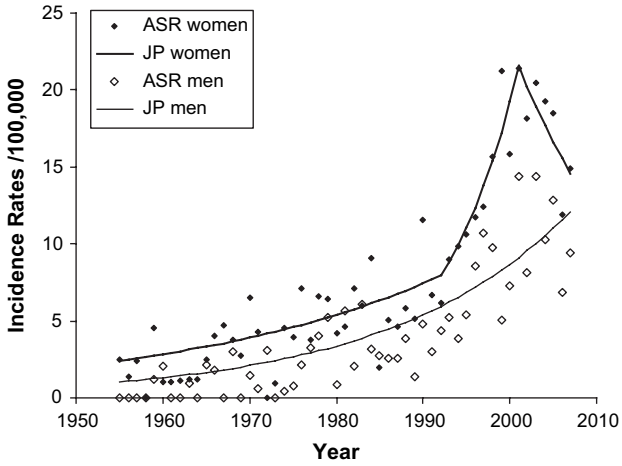

Figure 2. Joinpoint (JP) analysis of cutaneous melanoma incidence in Iceland (1955–2007) by sex. ASR, age-standardized rate.

Joinpoint analysis of incidence data from 1955 through 2007 for men showed a steady 4.8% estimated annual percent change (EAPC) (95% confidence interval (CI): 3.8, 5.9) without breakpoint, whereas for women a statistically significant breakpoint was observed in 1992 (Figure 2). Before 1992, the EAPC in incidence was 3.3% (95% CI: 1.9, 4.7) per year for women, but from 1992 until 2001, it was 11.8% (95% CI: 5.1, 18.8). A second breakpoint was observed in 2001, followed by a nonsignificant 6.3% (95% CI: −13.5, 1.4) decrease until 2007.

The age distribution of melanoma cases for men showed no significant change ($P = 0.85$) before and after 1992, with the number of cases tripling in men of both age groups (Table 1; Figure 3). In contrast, melanoma incidence rates increased by 3 times in women younger than 50 years and only slightly in women aged 50 or more years between 1955–1992 and 1993–2007 ($P < 0.001$) (Table 1; Figure 3). Moreover, using joinpoint analysis, we found that women younger than 50 years required 2 joinpoints ($P < 0.001$), with an EAPC of 2.3% (95% CI: 0.1, 4.6) from 1955 to 1991, an EAPC of 15.5% (95% CI: 6.8, 24.8) between 1991 and 2001, and an EAPC of −9.0% (95% CI: −18.1, 1.1) until 2007. For women 50 years of age or older, no joinpoint was required ($P = 0.63$), as the incidence increased steadily (EAPC = 2.6%, 95% CI: 1.7, 3.5).

The largest increase over the period was observed on the trunk in men (EAPC = 4.6%, 95% CI: 3.2, 6.0) and on the lower limbs in women (EAPC = 3.5%, 95% CI: 2.5, 4.6) (Figure 4). From the period 1955–1992 to the period 1993–2007, the frequency of melanoma on the trunk more than tripled in both sexes (Table 1). Although trunk melanoma increased steadily in men, in women the slow increase before 1995 was followed by a significantly sharper increase in incidence, resembling an epidemic incidence curve (1995–2002: EAPC = 20.4%, 95% CI: 9.3, 32.8) (Figure 4). As a consequence, in 2002 the incidence of trunk melanoma among women was higher than the incidence of melanoma on the lower limbs. The site with the largest percentage increase in incidence for women after 1992 was the trunk in younger women (Table 1).

Table 1. Numbers and Body Site Distribution of Cutaneous Melanomas Diagnosed in Iceland During the Time Period, 1955–2007

	Men				Women			
	1955–1992		1993–2007		1955–1992		1993–2007	
	No.	%	No.	%	No.	%	No.	%
All sites								
Age, <50 years	35	37.2	89	38.4	75	38.1	232	60.3
Age, ≥50 years	59	62.8	143	61.6	122	61.9	153	39.7
Age, <50 years								
Head and neck	5	14.3	8	9.0	8	10.7	10	4.3
Trunk	13	37.2	54	60.6	16	21.3	83	35.8
Upper limbs	6	17.1	7	7.9	12	16.0	26	11.2
Lower limbs	9	25.7	17	19.1	33	44.0	99	42.7
Others	2	5.7	3	3.4	6	8.0	14	6.0
Total		100		100		100		100
Age, ≥50 years								
Head and neck	17	28.8	45	31.5	33	27.0	30	19.6
Trunk	16	27.1	57	39.8	14	11.5	27	17.6
Upper limbs	8	13.6	16	11.2	22	18.0	29	19.0
Lower limbs	15	25.4	23	16.1	49	40.2	64	41.8
Others	3	5.1	2	1.4	4	3.3	3	2.0

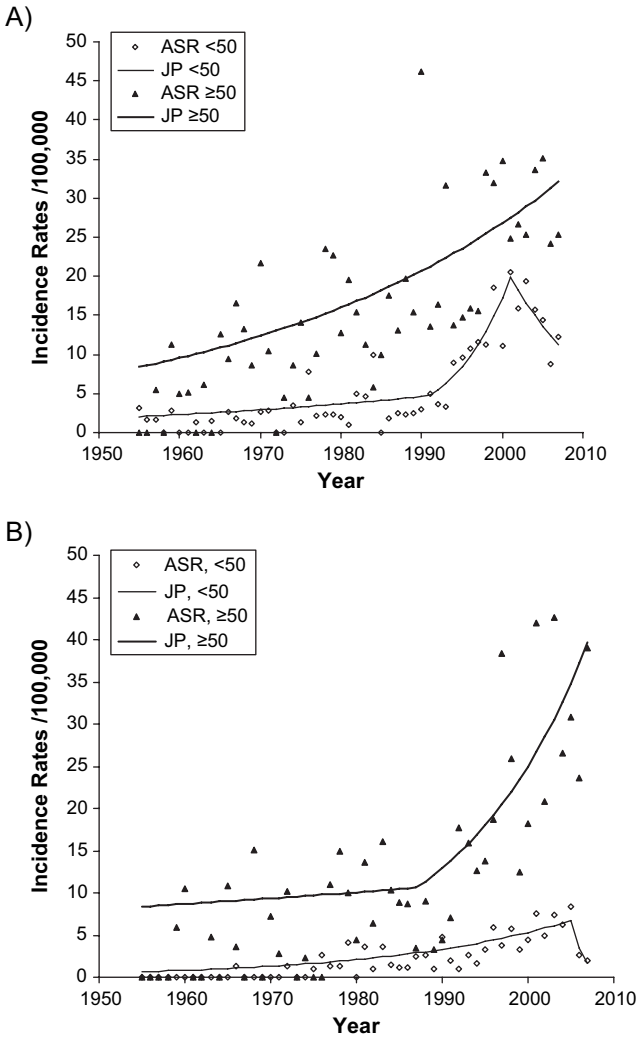

Figure 3. Joinpoint (JP) analysis of cutaneous melanoma incidence in Iceland (1955–2007) by age group for women (A) and for men (B). ASR, age-standardized rate.

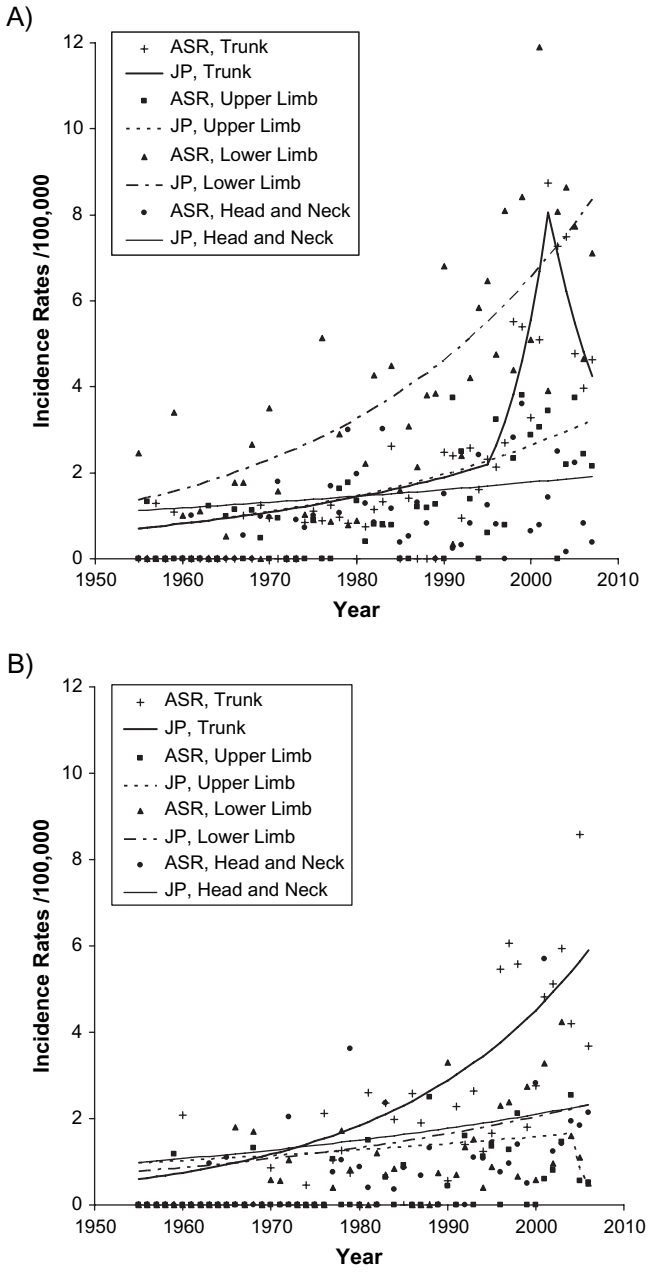

Figure 4. Joinpoint (JP) analysis of cutaneous melanoma incidence in Iceland (1955–2007) by morphologic site for women (A) and for men (B). ASR, age-standardized rate.

Melanoma mortality

Bearing in mind that, in Figure 1, the *y*-axis scale is 4 times lower than that of incidence, melanoma mortality from 1974 until 2007 did not parallel changes in incidence rates. Melanoma mortality in Iceland mostly stayed slightly below the rates observed in other Nordic countries and, from 1974 until 2007, remained quite stable around 1.0 and 1.4/100,000 in women and in men, respectively.

Sunbed use

In 1979, there were only 3 sunbed salons in Reykjavik, but their number increased rapidly and, in 1988, 56 facilities offered cosmetic tanning with 207 sunbeds (1.5 beds/1,000 inhabitants). In 2004, a campaign was launched by the Icelandic health authorities to discourage sunbed use, focusing particularly on teenage girls. In 2005, the number of publicly available sunbeds in the Reykjavik area decreased to 144 and further decreased to 97 in 2008 (T. Sigurdsson, personal communication, 2008).

The 2002 survey indicated that 70% of women and 35% of men had used a solarium (9). Among users, 42% of women and 30% of men reported a burn in a solarium. In the 2001–2002 survey (8), 16% of women and 12% of men aged 20–39 years had used a solarium more than 100 times during their lifetime. In contrast, these proportions were 2% and 1% among women and men aged 50 years or more.

Capacent-Gallup surveys done in the period 2004–2007 indicated that, on average, 26% of the Icelandic population had used a sunbed in the previous 12 months, representing 2.8 sessions per adult (16–75 years) per year (8). Among teenagers, each year about 50% of girls and 30% of boys used sunbeds in the last 12 months (T. Sigurdsson, B. Sigurgeirsson, and J. H. Olafsson, personal communication, 2008).

Sun exposure

Travel abroad to more southern areas represents an important source of sun exposure for Icelanders. In 1970, 65,941 voyages abroad by Icelanders were recorded, and this number steadily increased to 937,315 in 2006 (11). This increase went uninterrupted without slowing in recent years. In 2001–2002, 6% of women and 5% of men aged 20–39 years had travelled abroad 10 times or more during their lifetime (10). In contrast, these proportions were 17% among women and men aged 50 years or more.

DISCUSSION

This study had an ecologic design in which data were compared at the population level rather than at the individual level. The number of cases is relatively low, owing to the small population of Iceland. Ecologic correlation does not imply causation, but we found that sunbed use likely played an important role in affecting the melanoma incidence trends observed in Iceland. This hypothesis is supported by the sharp increase in incidence on the trunk in younger women who also had the highest records of sunbed use, which allows women to expose the trunk to UV radiation without protection. It is further supported by the decline in incidence in women observed after 2001, following the decline in sunbed use. Sunbed use in Iceland often started during the teen years, and the sharp increases in melanoma incidence are in agreement with the estimates of increased risk when sunbed use starts before approximately 35 years of age (risk = 1.75, 95% CI: 1.35, 2.26) (12, 13). As young Icelanders have fewer cumulative trips abroad but higher cumulative sunbed use than older Icelanders do, intermittent sun exposure in more southern latitudes alone is a less plausible explanation for increases in young men and women after 1994.

Compared with midday sunlight on the Mediterranean Sea, the UV radiation spectrum of sunbeds contains a greater proportion of UV-A, and the UV radiation intensity of powerful tanning units may be 10–15 times higher than that of the midday sun (14, 15), leading to UV-A doses per unit of time received by the skin during a typical tanning session well above those experienced during daily life or even during sunbathing. Such levels of repeated exposures to high UV-A doses constitute a new phenomenon for human beings. The whole UV radiation spectrum (including UV-A) and UV-emitting tanning devices are now considered as carcinogenic to humans (3). The Icelandic data also suggest that the time lag between exposure and melanoma occurrence may be relatively short, in the order of a few years. One possible hypothesis underlying a short lag time would be the stimulation, by repeated high UV-A doses, of melanocytes in preexisting nevi that developed earlier during life.

The average of 2.8 sunbed sessions per year in 2004–2007 in Iceland (8) is around 3 times higher than that estimated for the United Kingdom in 1996 (16) and around 2 times higher than that estimated for Sweden in 2005–2006 (17, 18). Before 2000, in most light-skinned communities, the increase in melanoma incidence in men was apparent mainly on the trunk, followed by the head and neck. In women, it was apparent mainly on the lower limbs (19). As in Iceland, the increase in melanoma incidence in Swedish women has been most pronounced on the trunk, and in 1996 the melanoma incidence on the trunk became equal to the incidence on the lower limbs (20). In Northern Ireland, incidence increases in men and women are more pronounced for trunk melanoma (21). In the United Kingdom, a rebound increase of melanoma incidence from 1998 onward has been reported for women 20–39 years of age (16).

Other reasons for the increases in incidence have been sought. No modification in cancer registration modalities has occurred that can explain changes in incidence. A fraction of the rising incidence may be due to markedly increased awareness and screening for melanoma in Iceland, initiated around 1990 by activities of the Icelandic Dermatological Association and the Icelandic Cancer Society. However, a screening effect is not likely to be specific to the female trunk.

The melanoma epidemic that occurred in 1987–1992 in the Hunter district of New South Wales, Australia, did not affect melanoma mortality, and it was concluded that the epidemic consisted mainly of a nonmetastasizing form of melanoma (22, 23). Likewise, because there is no efficient treatment for metastatic melanoma, the absence of change in melanoma death rates after 1974 in Iceland suggests that most of the epidemic was due to a non–life-threatening form of melanoma.

There is the possibility of synergistic effects between early detection and sunbed use: Intense exposure to UV radiation is known to induce changes in nevi appearance (24, 25) that could lead to more visits to dermatologists and to more excisions of suspicious pigmented skin lesions.

The low-background UV radiation and the high use of sunbeds make Iceland an interesting place for studying the effects of sunbed use on melanoma risk. A case-control study investigating the relations between melanoma and past sunbed use in Iceland has been envisioned, but the population has been well informed about the dangers of sun exposure and of indoor tanning (26, 27), which raises issues of selection and recall bias. A follow-up study is desirable, but several years will be needed before results become available.

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Chapter 3: Sunscreens and wearing clothes

Background as of 1992

In 1992, sunscreens were largely considered an efficient sun protection method. Animal experiments showed the ability of sunscreens to reduce the occurrence of UVB-induced skin damage, including cancers resembling the human SCC. Epidemiological studies consistently showed that a history of sunburn was a risk factor for all skin cancers. UVB is about one thousand more erythemogenic than the UVA. Although UVB represents less than 6% of the solar UV wavelengths reaching the Earth's surface, it contributes to 80% of sunburn occurrence. The sun protection factor (SPF) was introduced in the 1980s as the standard indicator informing of the ability of the sunscreen to delay sun-induced erythema. It was believed that the higher the SPF, the higher the ability to protect against UV-induced skin damage, including cancers.

Methoxypsoralens (MOPs) are part of the wider chemical class of furocoumarins that are potent tanning accelerators and known photocarcinogens (Kinley et al, 1997). When the carcinogenic properties of methoxypsoralens were unveiled in the 1980s (reviewed in *Autier et al, 1995*),[4] all cosmetic companies ceased to incorporate 5-MOP in their tanning lotions and the regulatory bodies of most countries banned commercialisation of such lotions. Notwithstanding, the French company Bergaderm succeeded in commercialising 5-MOP sunscreens in France, Belgium and Greece. The rationale for 5-MOP sunscreen was that the acceleration of tan acquisition was deemed to increase resistance against UV-induced DNA damage. Animal experiments tested this combination of UVB filters and 5-MOP termed "photochemoprotection" and found results supporting the claim that these products could decrease the risk of skin cancer (Young et al, 1988). Furthermore, sun protection provided by "photochemoprotection" seemed more efficient than when a regular sunscreen was used, especially in subjects with low ability to tan (Young et al, 1991). Surveys in 1989 indicated that about one third of French adolescents 13-14 years old used occasionally or regularly 5-MOP sunscreens to promote tanning (Grob et al, 1993).

The 1992 IARC Monograph briefly mentioned sunscreens in an appendix and remained rather vague on their usefulness for sun protection. One sentence

[4] The IARC classified the association of 8-MOP plus UVA in group 1 carcinogens for humans in 1987.

referred to 5-MOP sunscreens saying that their "role remained controversial". The appendix allocated only few sentences on findings by observational studies that sunscreen use was never associated with decreased melanoma risk, but rather often associated with moderate increases of melanoma risk. The 1992 IARC Monograph concluded that these findings were probably due to confounding by skin type and amount of exposure because subjects who easily burned or exposed their skin heavily were also more inclined to use sunscreens. Wearing clothes for sun protection was not examined.

Studies backing the public use of 5-MOP sunscreens were the target of many criticisms (e.g. Morrisson, 1990) but none impressed French, Belgian or Greek regulatory authorities. The puzzling results on higher melanoma risk associated with sunscreen were also the target of criticism, as the hypothesis that sunscreen use does not prevent malignant melanoma among those whose skin is highly exposed to sunlight is implausible on the basis of animal and human models (Marshall et al, 2003). On methodological grounds, the two major critiques were on the influence of "residual confounding" and the "confounding by indication". "Residual confounding" means that the apparent sunscreen-melanoma association could be due to the effect of sun exposure or characteristics of natural sun sensitivity that were not completely controlled in the statistical analysis, either because studies did not collected the appropriate data or because of a lack of adequate statistical analysis.

The confounding by indication remains an intractable threat to validity in observational studies (Boscoe et al, 2009) that refers to the fact that subjects taking or not taking a specific substance may differ in so many genuine ways that it is practically impossible to have the adequate data that would allow proper control of this confounding effect. In this respect, sunscreen users would be subjects at higher risk of melanoma than non-users, because of greater sun exposure habits or genetic background. The higher melanoma risk associated with sunscreen use would be the mere reflection of these characteristics.

Overview of observational studies on 5-MOP sunscreens

During the EORTC European multicentric case-control study of 1992-93, we showed that use of 5-MOP sunscreens was associated with higher melanoma risk than when using regular sunscreens, especially among poor tanners (***Autier et al, 1995***).

Many tourists from diverse origins could have used 5-MOP sunscreens when visiting France or Greece; we therefore issued a warning and a recommendation for proper skin surveillance of subjects who used these products (*Autier et al, 1997b*).

Overview of observational studies on sunscreens

Like many other observational studies, the EORTC European multicentric case-control study of 1992-93 found that the use of sunscreen was associated with higher melanoma risk (*Autier et al, 1995*). We performed more detailed statistical analyses than prior studies, which showed that whatever the level and type of sun exposure or of sun sensitivity characteristics, sunscreen use was invariably associated with increased melanoma risk. Hence, we could rule out the possibility of confounding by sun exposure or by natural sun sensitivity. However, the case-control design was unable to rule out the possibility of confounding by indication.

Most sunscreens are used when sun exposure takes place during leisure times and holidays, that is, during intermittent sun exposure sessions - the type of sun exposure typically associated with melanoma occurrence. Further thinking led us to notice that to date, most basic, clinical or epidemiological studies on sun protection did not reflect the actual conditions of sunscreen use by people spending their holidays in sunny areas, particularly engaging in sunbathing for tan acquisition or using these products to allow their child to go (almost) naked in the bright sunshine (*Autier et al, 1997c*). We therefore sought an observational study design closer to actual conditions of sunscreen use during intermittent sun exposure.

Acquire melanocytic nevi result from the monoclonal expansion of single melanocytes. Common acquired nevi develop after birth and their number peaks at 25-30 years of age. Risk factors for nevus acquisition are similar to those for melanoma occurrence. The nevus count is the best individual predictor of one's chance to be diagnosed with a melanoma during lifetime.

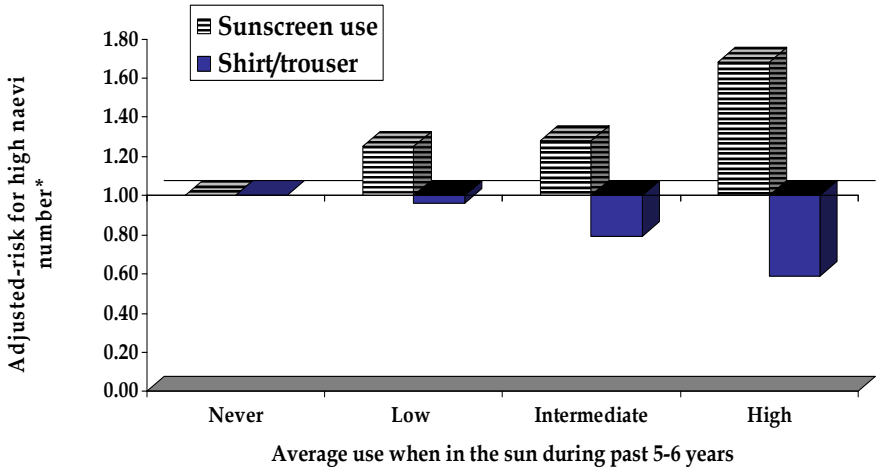
We designed a study on nevus count in 6-to-7-year-old schoolchildren, with the objective to assess how past sun exposure and the different types of sun protection influenced their nevus counts.[5] The study took advantage of the short

[5] The study was supported by a grant from the Europe Against Cancer programme of the European Commission.

time window between birth and counting of nevi and of the usually-good recall of mothers of holidays, behaviours and health ailments (e.g. sunburns) of their child. This study therefore had a retrospective cohort design and the data collection could go into great detail about sun exposure and sun protection after birth, exploring each holiday period and each sun protection method separately. In total, 631 children from Belgium, France, Italy, and Germany were included in the study.

The main finding as summarised in Figure 3.1 was that past sunscreen use was associated with higher nevus count, whilst wearing of clothes when in the sun was associated with lower nevus count; both relationships followed a dose-response curve (***Autier et al, 1998a***).

Fig. 3.1 - Sunscreen use, wearing clothes and nevi number in 631 6-to-7-year-old European children



Autier et al, JNCI, 1998a

This finding ruled out confounding by indication because subjects wearing clothes or using sunscreens when in the sun are likely to share similar genuine characteristics (*IARC, 2001*). Clothes constitute a physical barrier to UV and are thus a true sun protection method. If sunscreen use is actually sun protective, it is difficult to understand why results related to sunscreen use and to wearing of clothes were so divergent.

The study also found that in cases where higher quantities of sunscreen were used, generally fewer clothes were worn (*Severi et al, 2002*). An unexpected consequence of this study was that it substantiated the fact that studies that found a positive association between sunscreen use and melanoma were probably less likely to be published than studies that found a negative association. An example was the publication just after our own in 1998 of results from a Canadian study in 1979-81 showing increased melanoma risk with sunscreen use (Elwood & Gallagher, 1999).

Randomised controlled trials

The nevus study in schoolchildren convinced us that sunscreen use was a risk factor for melanoma and that the risk was tightly bound to conditions associated with their use. Sunscreens have no carcinogenic properties by themselves. The mechanism by which sunscreens could increase melanoma risk was suggested by H. Beitner and co-workers, who hypothesised that "[sunscreens] allow individuals with poor tanning ability to spend more time in the sun than otherwise possible"(Beitner et al, 1990). The likelihood of this hypothesis was supported by the common observation that sunscreen use during intermittent sun exposure behaviours was associated with exposure of longer durations without decreases in sunburn occurrence (*IARC, 2001**; Autier et al, 2009***). Indeed, nothing warns sunscreen users engaged in sunbathing that their extended exposure has reached UVB doses corresponding to their specific sunburning threshold.

For verifying this hypothesis we designed randomised controlled trials within the frame of the EORTC Melanoma Group, the objective of which was to assess the duration of sun exposure during holidays, according to use of a low or of a

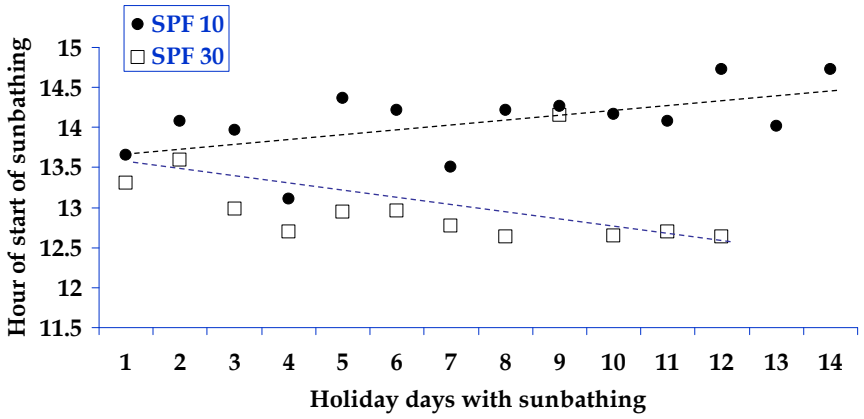
high SPF sunscreen (***Autier et al, 1999c;*** *Autier et al, 2000e*).[6] The first trial in 1997 included 89 French and Swiss paid volunteers, 18-25 years of age, who were willing to spend their holidays in sunny locations. The volunteers ignored the actual trial endpoint. They were randomly allocated to a group receiving a SPF 10 sunscreen and a group receiving a SPF 30 sunscreen. No sign on sunscreen bottles informed on the SPF, and the two sunscreens had the same consistency and flavour. The main finding was a 25 to 30% increase of sunbathing duration in SPF 30 volunteers as compared to SPF 10 volunteers, without any difference in sunburn experience. In 1998, we resumed a second trial using exactly the same protocol and including 48 Belgian and French volunteers selected in other locations. This trial found similar results (*Autier et al, 2000e*). The trial provided to volunteers simple individual UV-dosimeters that could measure UVA and UVB irradiation separately.[7]

In addition to extended sun exposure duration, a plethora of other changes in sun exposure behaviours was observed in the two trials, all consistently showing that the SPF 30 sunscreen allowed greater tolerance to high fluxes of UVB, for example sunbathing in the midday sun (Figure 3.2). Sunbathing typically entails brisk exposure of the trunk to sunlight and trial results showed that in the absence of sunscreen use, this usually sun protected site would not stand long exposure to UVB-rich sunlight. Hence, high SPF sunscreens proved to be powerful modifier of sun exposure behaviours towards longer stays in UVB-rich environments.

[6] The two trials were supported by grants of the Europe Against Cancer programme of the European Commission.

[7] The devise and manufacturing of the UV-dosimeters was funded by the European Melanoma Group (EMG), a Belgian non-governmental organisation that supported researches on melanoma.

Fig. 3.2 – EORTC Randomised trials of 1997 and 1998: Subjects who used a SPF 30 sunscreen tended to start earlier their sun exposure, while the reverse was true for subjects who used the SPF 10 sunscreen (Autier et al, 1999c; Autier et al, 2000e)



Reviews

Results of randomised trials led us to propose the concepts of *intentional* and *non-intentional sun exposure* (*IARC, 2001*; ***Autier et al, 2007; Autier, 2009***). The non-intentional sun exposure (NISE) pattern represents sun exposure during daily life activities, without a special willingness to acquire a tan or to be able to spend a long time in the sun. The so-called chronic sun exposure pattern usually equates to NISE. Examples of NISE are outdoor activities such as walking, hiking, gardening, skiing, construction and farming work. Lifetime accumulated NISE is mainly associated with solar keratoses and squamous cell carcinoma.

The intentional sun exposure (ISE) pattern is sun exposure with an intention to stay in the sun with large uncovered skin areas, or/and to acquire a tan. ISE is characteristic of light-skinned subjects who spend most of their daily life indoors but enjoy intense sun exposure during holidays. The so-called 'intermittent sun exposure pattern' is often intentional as subjects look for a biological effect. Sunbathing is the most typical ISE behaviour. Melanoma is commonly found on the usually-covered sites such as the trunk; this clinical evidence fits with the ISE patterns being the cause of most melanoma.

We recently performed two reviews that illustrated the relevance of the distinction between ISE and NISE for explaining results of epidemiological studies and of randomised trials with sunscreens. The first was a systematic

review of all observational and randomised studies on sunscreen use and sun exposure duration (***Autier et al, 2007***). This review showed that all studies we retrieved found that sunscreen use during ISE was associated with increased sun exposure duration and no change in sunburn occurrence. In contrast, sunscreen use during NISE was not associated with exposure of longer duration and could decrease sunburn occurrence.

The second review outlined in detail the main findings from studies on sunscreens and the proposed mechanisms by which sunscreen use for ISE could be involved in melanoma occurrence (***Autier, 2009***). We also improved the definition of the "compensation mechanism" as the extra amount of time spent in the sun resulting from sunscreen use, until sunburn occurrence. This extended period may lead to an accumulation of additional unfiltered UV that might be involved in melanoma occurrence. Compensation increases with increasing SPF and the quantity of sunscreen applied. Consequently, high SPF sunscreen during ISE may well be more hazardous for melanoma occurrence than low SPF sunscreens.

Epidemiological or human experiment data supporting our findings

1. The combination of oral intake of 8-MOP or of skin application of 5-MOP followed by whole body UVA irradiation was introduced in the 1970s for the treatment of severe psoriasis (Melsky et al, 1977; Fitzpatrick & Pathak, 1984). Many long-term follow-ups of PUVA treated psoriasis patients have shown increased risk for SCC. One cohort study found a significant increased incidence of melanoma among psoriasis patients treated with high doses of PUVA therapy (Stern et al, 1997). Other cohorts of PUVA treated patients found no increase in melanoma risk.

2. The associations we found between sunscreen use, wearing of clothes and nevus counts were confirmed by the majority of studies conducted in schoolchildren or adolescents in Europe, Israel and Australia (Luther et al, 1996, Azizi et al, 2000; Dulon et al, 2002; Darlington et al, 2002; Bauer et al, 2005; English et al, 2005; Waschmuth et al, 2005), with the exception of one study in the USA (Oliviera et al, 2006). The unique case-control study that assessed the influence of sunscreen use and wearing clothes on melanoma occurrence found a non-significant increased risk associated with sunscreen use and a significantly decreased risk associated with the wearing of clothes when in the sun (Holman et al, 1986).

Epidemiological studies or human experiments challenging our findings

1. Three randomised trials found that sunscreen use moderately decreased the development of solar keratoses (SK) and of SCC (thompson et al, 1993; Naylor et al, 1995; Green et al, 1999). These trials were performed among older subjects and were only relevant to NISE situations (***Autier, 2007; Autier 2009***).

2. A randomised trial conducted in Vancouver (Canada) found that children who used a broad-band sunscreen had a slightly (but statistically significant) lower count of nevi at the end of the trial (Gallagher et al, 2000). The effect however, was confined to those children with numerous freckles - a known hereditary characteristic associated with higher sun sensitivity. This trial did not typical of ISE situations. We expressed strong concern towards the statistical analysis used in this study, judging it to be flawed. The analysis had no adjustment for an imbalance in major confounding factors at baseline, no covariance analysis for adjusting for nevus count at initial visit (Vickers & Altman 2001; Barnett et al, 2005; ***Autier, 2005a; Autier et al, 2007***). It should be noted that at the time of the IARC meeting on sunscreens in 2000, this trial was accepted for publication and was known by experts participating in the meeting.

3. The randomized trial conducted by A Green and co-workers in Nambour (Queensland, Australia) demonstrated that regular sunscreen use by light-skinned middle-aged and older subjects living in sunny areas can decrease the risk to develop a cutaneous melanoma (Green et al, 2010). The trial intervention consisted in regular, generous application of sunscreen on body parts that cannot be protected by clothes (e.g., face, hands). These results were expected since first, subjects with solar keratoses or squamous cell cancer are at higher risk to develop a melanoma, that often occur in sun-damaged skin (Maitra et al, 2005). Second this trial had already shown that regular sunscreen use can decrease the risk of squamous cell cancer (Green et al, 1999). Solar keratoses, squamous cell cancer and melanoma in older subjects are caused by the accumulation of exposure to ultraviolet (UV) radiation and the Nambour trial documented that sunscreen generously and regularly applied on chronically sun exposed body sites of middle-aged and older subjects works like a "chemical piece of clothing" able to block transmission of the UV radiation.

The key questions are first, how robust are the Nambour trial results, and second up to which point the results of this trial are valid for all circumstances during which sunscreen is used. The first question was addressed by Goldenhersh & Koslowsky (2011) who underlined several methodological flaws, like for

instance, taking melanoma on the whole body as endpoint when the intervention was limited to sunscreen application son the face, arms and sometimes, the legs. For the second question, the Nambour trial was conducted among light skinned subjects of mainly Celtic ancestry living in a tropical area and thus experiencing high levels of daily sun exposure. This high ambient UV irradiation is the reason why melanoma and other skin cancer incidence is about 5 times higher in Queensland than in Northern European countries (Coory et al, 2006). The Nambour trial included subjects eager to protect their skin against harmful effects of the tropical sun, and most trial participants regularly adopted other sun protection method such as staying in the shade and wearing a hat when in the sun. In addition, sun exposure was similar between the daily and discretionary sunscreen groups. Hence, the Nambour trial took place in the context of non intentional sun exposure (NISE) and the key finding is that a sunscreen use is effective for skin cancer prevention when this use is not a mean to extend sun exposure. In this respect, the Nambour trial results are probably not valid for intentional sun exposure situations, that is, for most circumstances during which sunscreen is used by many Europeans and North Americans (Autier et al, 2011a).

Despite its limitations, the Nambour trial results strengthen the recommendation for sun protection with sunscreen of body parts usually not covered by clothes during non-intentional sun exposure. However, results of this trial should not represent a green light for suggesting that unrestricted intentional sun exposure is safe when a sunscreen is used. People should rather be warned about the possibility that extension of intentional sun exposure may increase the risk of melanoma. Institutions active in cancer prevention are urged to be cautious on the way results from the Nambour trial will be explained to the public and translated in public health recommendations.

4. A one-week randomised trial was organised in a French holiday resort for assessing sun exposure duration according to sunscreen use (Dupuy et al, 2005). Our re-assessment of data published on this trial found that in reality, the trial had also found that ISE duration increased with increasing SPF (***Autier et al, 2007***).

5. Three meta-analyses of observational studies on sunscreen use and melanoma (Denis et al, 2003; Huncharek & Kupelnick, 2002; Bastuji-Garin & Diepgen, 2002) found no increased risk of melanoma associated with sunscreen use and one meta-analysis found an increased risk (Geffeller et al, 2002). These four meta-analyses did not perform sensitivity analysis as we did for sunbed use and melanoma (IARC, 2006), with pooling of results from population and non-

population-based studies. Most non hospital-based observational studies, both case-control or prospective cohort studies, found no decrease or moderately increased risk of melanoma or basal cell cancer with sunscreen use. In contrast, the majority of hospital-based studies found decreased melanoma risk associated with sunscreen use. Finally, because of evidence that publication biases prevented the publication of unwanted results on sunscreen use and melanoma, the reliability of these meta-analyses is questionable (***Autier et al, 2007; Autier 2009***).

Other considerations

1. The group of AR Young performed new experiments and found that epidermal tanning with or without furocoumarin (the chemical family of psoralens) is not effective in preventing skin cancer in the nude mouse model (Kipp et al, 1998; IARC 2001).

2. There is mounting evidence that facultative tanning induction is mainly a consequence of UV-induced DNA photodamage (Pedeux et al, 1998; Gilchrest & Eller, 1999; Cui et al, 2007). The rapid suntan acquisition after use of 5 or 8-MOP is most probably due to their unique mechanisms of action that considerably enhance the DNA damage induced by UVA wavelength. The respective role of UV and 5 or 8-MOP in melanoma risk is impossible to assess in epidemiological studies. Nonetheless, taken together with the mechanism of action of these molecules, the epidemiological data demonstrates that UVA may react with natural photocarcinogenic compounds in increasing the melanoma risk. Our results on 5-MOP sunscreen use constitute an indirect proof that UV-induced DNA damage is a potent inducer of facultative tanning and this DNA damage is specifically related to biological events possibly leading to melanoma.

3. Sunscreen supporters typically argue that new sunscreen formulations can effectively filter out both the UVA and the UVB radiation. The vast majority of sunscreen products are sold to subjects willing to enjoy ISE. Thus, the question is whether the generalisation of UVA-UVB blocking agents in sunscreen formulation is likely to reduce the melanoma risk associated with ISE. The answer is likely to be negative because the compensatory behaviour induced by sunscreen use (***Autier, 2009***) will ultimately lead to accumulation of UV doses capable of triggering a facultative tan, which is an indisputable marker that UV-induced DNA damage has taken place. Sunscreens would be able to decrease melanoma risk if their use was correlated with absence (or near absence) of tan and absence (or drastic reduction) of sunburns at the end of the holiday period.

In conclusion, it remains to be demonstrated that sunburn incidence, nevus development and melanoma occurrence are actually reduced thank to the use of these newly formulated products during ISE.

Articles displayed as part of this section:

Autier P, Doré JF, Cattaruzza MS, Renard F, Luther H, Gentiloni-Silverj F, et al. for the EORTC Melanoma Group. Sunscreen use, wearing clothes and number of nevi in 6- to 7-year-old European children. *J Nat Cancer Inst* 1998; 90: 1873-81.

Autier P, Doré JF, Négrier S, Liénard D, Panizzon R, Lejeune FJ, Guggisberg D, Eggermont AMM. Sunscreen use and duration of sun exposure : A double blind randomized trial. *J Natl Cancer Inst* 1999; 91: 1304-9.

Autier P, Boniol M, Doré JF. Sunscreen use and increased duration of intentional sun exposure: Still a burning issue. *Int J Cancer* 2007;121: 1-5.

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ARTICLES

Sunscreen Use, Wearing Clothes, and Number of Nevi in 6- to 7-Year-Old European Children

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Background: **Previous epidemiologic studies have suggested that sunscreen use is associated with an increased risk of melanoma skin cancer. Because high nevi (mole) count in adults is a strong predictor of melanoma, we conducted a study examining the number of nevi in 6- to 7-year-old European children, according to their sunscreen use.** ***Methods:*** **Whole-body and site-specific counts of nevi 2 mm or larger were performed in 631 children in their first year of primary school in four European cities. Independently, parents were interviewed regarding sun exposure, sunscreen use, and physical sun protection of their child.** ***Results:*** **After adjustment for sun exposure and host characteristics (e.g., skin phototype, eye color), the relative risk for high nevus count on the trunk was 1.68 (95% confidence interval [CI] = 1.09–2.59) for the highest level of sunscreen use and 0.59 (95% CI = 0.36–0.97) for the highest level of wearing of clothes while in the sun. The sun protection factor had no effect on nevus counts despite a high median value of 17.4. Sunburn number was not associated with nevus count. The highest risk associated with sunscreen use was found among children who had never experienced sunburn.** ***Conclusions:*** **In white, European children, sunscreen use appears to be associated with development of nevi, probably because it allows longer sun exposures. Wearing clothes may be an effective way to prevent proliferation of nevi. Since a high nevus count is a strong predictor of melanoma, sunscreen use may be involved in melanoma occurrence because it may encourage recreational sun exposure. [J Natl Cancer Inst 1998;90: 1873–80]**

Since 1982, evidence has developed about the association between sunburn and skin cancers *(1,2).* Sunscreens are able to delay sunburn occurrence, and experiments in rodents and in humans have shown that sunscreens could prevent solar-induced skin lesions, including nonmelanoma cancers *(3–7).* Therefore, these products have been widely advocated for the prevention of skin cancers *(8).* The ability of sunscreens to retard ultraviolet-induced skin reddening is called the sun protection factor (SPF). It is believed that the higher the SPF, the more efficient the protection against cancer. Also, high SPF sunscreens (i.e., 15 or higher) are capable of removing some of the ultraviolet A radiation; now, specific blocking agents for ultraviolet A radiation are incorporated in many sunscreens, mainly in those recommended for children.

In contrast, epidemiologic studies have not only failed to show any decrease in melanoma risk associated with sunscreen use but also suggested sunscreen use to be a determining factor for an increased risk of melanoma *(9).* That increased risk was also found with basal cell carcinoma of the skin *(10–12).* Hence, doubts have been cast on the efficacy of sunscreens to prevent melanoma. However, most epidemiologic studies reported before have collected data mainly related to earlier sunscreens of low SPF, and assessment of past sunscreen use may not have been accurate.

Most nevi are acquired *(13),* and their development in children is influenced by sun exposure *(14–16).* Because high nevus count in adults is a strong predictor of melanoma *(17),* we conducted a study examining the number of nevi in 6- to 7-year-old European children according to sunscreen use. Studying young children should enable a better examination of the latest generation of high-SPF sunscreens and help to reduce memory bias, since only a few recent years of exposure are considered. Furthermore, sun exposure during early life seems to represent a key determinant for melanoma occurrence during adulthood *(18).*

Subjects and Methods

Study Design

The study was conducted during the period from October 1995 through February 1997 in elementary schools of Brussels, Bochum, Lyons, and Rome.

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See ''Notes'' following ''References.''

Brussels is situated in a temperate climate, Bochum and Lyons in a semicontinental climate, and Rome in a Mediterranean climate. The protocol was accepted by ethics committees of the Jules Bordet Institute (Brussels, Belgium), St. Josef Hospital (Bochum, Germany), Centre Léon Bérard (Lyon, France), and Institute of Hygiene, University ''La Sapienza'' (Rome, Italy). The study design has been described elsewhere *(9)*. The study comprised the following two independent components: 1) count of nevi in Caucasian children during their first year of primary school (6–7 years old) and 2) interview of parents about sun exposure history, physical protection, sunscreen use, and sunburn history of their child.

Skin examiners and interviewers had no contact and remained unaware of the findings of each other. School administrators, teachers, parents, and interviewers were carefully blinded about the study hypothesis and about nevus counts of children.

In each city, schools of different socioeconomic profile were chosen to avoid clustering of risk factors. In schools where directors gave permission, parents of all children in their first year of primary school were invited to participate in the study, regardless of their ancestry and ethnic background. Written informed consent from the parents was obtained before children were examined.

Count of Melanocytic Nevi

Skin examinations took place in schools. Hair and eye color were assessed by examiners. Counting of nevi followed guidelines developed by English et al. *(19)*. In each study site, all children were examined by the same physician trained for the recognition of skin pigmented lesions. A nevus was defined as any brown or black pigmented macula or papule darker in color than the surrounding skin, having one dimension of at least 2 mm. Counting of nevi was done by use of transparent plastic slides pierced with a 2-mm hole. Like other researchers *(20)*, we made no special effort to differentiate between nevi and solar lentigines, which are rare in children and generally of small size. The scalp was not explored, but attention was given to the border between head and neck skin and the hair. The genital area and buttocks were not examined. Because some children wore large underclothes ample enough to hide nevi, the upper limit for nevus counting was set at the anterosuperior iliac spine and the lower limit at the bend of the buttocks. The density of freckles on the face, on both arms, and on the shoulders was assessed by use of standard freckling charts.

Interviews of Parents

Home interviews of parents were performed by nonmedical, trained, female interviewers. The principal goal of the interview was to reconstruct the history of sun exposure, sun protection, and sunburn experience from birth to the moment of the skin examination. The most frequent setting for sun exposure and sunscreen use was holidays. A ''holiday period'' was defined as any period of 5 days or more outside the parents' home(s). For each holiday period, the following questions were systematically asked: *(a)* During which year(s) and month(s) did holidays take place? *(b)* How many weeks did they last? *(c)* Place and latitude? [Latitude was derived from a geographical map inserted in the questionnaire.] *(d)* Was the weather sunny? *(e)* Did the child go in the sun? *(f)* Did the child go outside during the hot hours of the day? *(g)* When in the sunlight, did the child wear a shirt? *(h)* When in the sunlight, did the child wear trousers? *(i)* Could the child go naked or almost naked in the sun? *(j)* Was a sunscreen applied on the child's skin? *(k)* What was the SPF indicated on the sunscreen bottles? If different sunscreens were used during a holiday period, SPFs of initial, second, and eventual third sunscreen were recorded.

For questions *(d)* to *(j)*, answers were collected in a semiquantitative way according to four or five categories, e.g., from ''never'' to ''always.'' Another section of the questionnaire inquired about the sun exposure, the sunscreen use, and other sun protection methods during periods that were not holidays (e.g., when at home in the garden).

Questions on sunburns were in a separate section, inquiring about all sunburn episodes from birth to the moment of the skin examination. A sunburn episode could occur during a holiday period or during a sunny day in the garden. For each sunburn episode, body sites involved as well as sunburn-induced pain or fever were recorded. Questions about the country of birth of both parents and grandparents were asked, so that the Caucasian origin of the children could be assessed. During the course of the interview, the skin phototype of the child, according to the Fitzpatrick classification *(21)*, was determined as follows: Children with skin phototype I were those who never tanned but always sunburned when going unprotected in the sun for the first time during the year; children with skin phototype II were those who first sunburned but got a tan after; children with skin phototype III were those who rarely sunburned and always got a deep tan after; and children with skin phototype IV were those who always tanned and never sunburned.

Construction of Exposure Indexes

Synthesis of data was done by the construction of exposure indexes. For sun exposure, we first made a selection between holiday periods, excluding those during which there had been no sunny weather or those during which the child did not go outside. All reported holiday periods represented a total of 15 026 7-day weeks, 14 512 (97%) of which satisfied both conditions, which represented a mean of 23 sunny holiday weeks per child (range = 0–138 weeks).

The sun exposure during a given holiday period was computed as the duration multiplied by the intensity of sun exposure. Duration was calculated as the ''number of holiday weeks'' multiplied by the ''amount of sunny weather.'' Intensity was calculated as ''the latitude of holiday area'' multiplied by the ''child having been in the sun'' multiplied by ''the child could go outside during the hot hours of the day.'' Then, for each child, the sun exposure experiences were summed across all holiday periods in order to yield the ''sun exposure index'' that was then divided in tertiles.

The sunscreen use during a given holiday period was reported as ''never,'' ''sometimes,'' ''often,'' and ''always.'' An arbitrary value of 0, 1, 2, and 3 was given to each reported sunscreen use, respectively, and these values were summed across all holiday weeks to yield the ''total sunscreen use.'' Children who never used sunscreens were set as the referent category. The remaining children were classified in tertiles. ''Total sunscreen use'' encompassed the time dimension of exposure to sunscreens but did not provide information about the amount of sunscreen used during a typical holiday week. Thus, we also computed the ''average sunscreen use'' as the total sunscreen use divided by the total number of holiday weeks. Children were classified in the categories ''never,'' ''rare,'' ''sometimes,'' ''often,'' and ''always'' when their average sunscreen use was equal to 0, greater than 0 and less than 1, greater than 1 and less than 2, greater than 2 and less than 3, and equal to 3, respectively.

SPF of sunscreens was averaged across all holiday weeks during which sunscreens were used. The SPF of the first sunscreen used was utilized, since the SPFs of first, second, and eventual third sunscreen used were highly correlated (Pearson's product–moment correlation coefficient $r > .90$). When a responder did not remember the exact SPF of a sunscreen used but only if the sunscreen had a low, moderate, or high ability to protect against ultraviolet radiation, the SPF of ''low or moderately protective'' sunscreen was set to 8, and the SPF of a ''highly protective'' sunscreen was set to 15. If, for a given holiday period, a responder reported sunscreen use but could not remember if it was a low, moderate, or highly protective sunscreen, then the average SPF used by the child was assigned a default value.

Wearing a shirt was almost always accompanied by the wearing of trousers (Pearson's product–moment correlation coefficient $r = .90$). Similar to average sunscreen use, the wearing of clothes was computed as the summation across all holiday weeks of the reported wearing of shirt or trousers and then divided by the total number of holiday weeks. Categories were defined according to possible answers in the questionnaire.

Statistical Analysis

Similar to other studies of nevi in children *(14–16)*, the distribution of nevi was skewed to the right. Therefore, univariate analysis used the nonparametric Kruskal–Wallis test.

The adjustment for confounders was done by use of Poisson regression. However, a Poisson distribution assumes equal mean and variance. The mean and variance of the distribution of nevi were not equal. We, therefore, used Poisson models with extra-Poisson variation. Taking into account extra-Poisson variation does not modify parameter estimates (i.e., the relative risks [RRs]) but confidence intervals (CIs) are wider. In a first step, modeling considered partial regression equations that included the sex, the study place, the skin phototype, and the eye color together with one of the three following variables: sun exposure, total sunscreen use, and wearing of clothes. In a second step, full models that included all of the seven aforementioned variables were fitted. Modeling was done by use of the GENMOD module of the SAS statistical package (SAS Institute Inc., Cary, NC; 1997).

The Pearson's product–moment correlation coefficient was used to provide a numerical indicator of the strength of the relationship between exposure variables. All P values resulted from use of two-sided statistical tests.

RESULTS

Parents who agreed to participate represented 682 (55%) of the 1234 apparently eligible children approached. Fifty-one children were eliminated from the study because the child was not of Caucasian origin, the skin examination was not performed (e.g., the child was not willing to be examined), or the parents could not be reached for the interview. The participation rate was about the same in all schools, and there was no difference in sex distribution between participants and nonparticipants. The final sample comprised 631 children (321 boys and 310 girls). Mothers were present during 93% of interviews, and the responder was not the mother or the father for four children.

The median number of nevi 2 mm or larger was six (range = 0–82). Propensity to get sunburns was the host characteristic that best predicted the nevus count; the median numbers for skin phototypes IV, III, II, and I were 4, 8, 8, and 8.5, respectively (Kruskal–Wallis test; $P<.001$). Nevus count was not associated with hair color (data not shown); however, for eye color, the median total nevus count was five in children with dark eyes, seven if their eyes were hazel or green, and seven if their eyes were blue or gray (Kruskal–Wallis test; $P<.001$).

Determinants of Sunscreen Use

Thirty-four (5%) of 631 children had never used sunscreens. Half of the children who ever used a sunscreen received a product of higher SPF than that used by their parents, and one quarter of the parents stated that they had bought sunscreens specifically recommended for children.

If sunscreens were used during 12 965 (89%) of the 14 512 holiday weeks, the quantity of sunscreen used during holiday weeks could greatly vary; i.e., the best predictor of average sunscreen use was the possibility to go naked (or almost naked) in the sun, whereas there was an inverse relationship between average sunscreen use and wearing clothes when being in the sun. Because of the highly variable quantity of sunscreen used during the holiday weeks, there was a poor association between the sun exposure index and average sunscreen use. Average sunscreen use was associated with the skin phototype (with increasing use from skin phototype IV to I) and a positive history of sunburn episode.

SPF of sunscreens was not known for 2% of holiday periods during which sunscreens were used. For children who ever used sunscreens, the median SPF was 17.4. That median SPF remained constant over the past 6 years. The median SPF increased with higher susceptibility to sunlight, from 15.0 in children with skin phototype IV to 19.5 in children with skin phototype I (Kruskal–Wallis test; $P<.001$).

Sunscreen Use and Nevus Count

In all study places, the median numbers of nevi tended to increase with total or average sunscreen use during holiday periods, whereas the reverse was true for wearing clothes while in the sun (Table 1).

Median nevus counts increased with both increasing sun exposure and average sunscreen use (Table 2). Adjusted RRs derived from Poisson regression models allowed us to remove the effect of skin phototype and of eye color on nevus counts. An RR indicates the likelihood of having an increased number of nevi as compared with a referent category in which the exposure of interest is minimal. Risk for higher nevus count increased with both increasing sun exposure and sunscreen use, and the increase in risk was more pronounced on the trunk. When the sun exposure index was high, children who often or always used sunscreens had a nevus number about two times greater than children who never used a sunscreen. In contrast, when sun exposure index was low, the increase in nevus count with increasing sunscreen use was much less pronounced and never reached statistical significance. The effect of a given amount of sun exposure (i.e., low, intermediate, or high) on nevus number was dependent on the amount of sunscreen use.

Table 3 displays results from Poisson regression models applied on nevus counts on the trunk (an intermittently sun-exposed body area) and on the head and neck (a chronically sun-exposed body area). In partial models, the sun exposure index was a marked risk factor for trunk nevus counts. Head and neck nevus numbers seemed unaffected by sun exposure. Total sunscreen use was positively associated with trunk nevus counts. A trend was noticeable between sunscreen use and head and neck nevus counts, although no RR reached statistical significance (i.e., unity not included in the 95% CI). A negative relationship between nevus count and wearing clothes emerged, with the highest effect on the trunk. The changes in RRs between the partial and the full models provided the most important information; i.e., on the trunk, the risks associated with total sunscreen used decreased but remained significant with consistent dose–response trends. The effect of the sun exposure index substantially decreased and was no longer significant. The protective effect of wearing clothes became more apparent with maximal effect on the trunk and the apparition of a consistent dose–response trend. Because wearing clothes while in the sun was inversely correlated to sunscreen use, this latter variable negatively confounded the association between physical sun protection and lower nevus count.

The joint influence of sunscreen use and SPF is examined in Table 4. RRs increased with increasing average sunscreen use, but no change was observed with increasing average SPF.

We also examined the influence of sunscreen use during periods other than the holidays. Habits of sun exposure, sunscreen use, and other sun protection methods during holiday and nonholiday periods were highly correlated. To minimize the effects of sunscreen use and of sun exposure during holidays, we restricted the analysis to the 189 children who reported a total of fewer than 12 sunny holiday weeks. In those children, the use of a sunscreen during recreational sun exposure at home was associated with a higher risk of whole-body nevus count (RR = 1.46; 95% CI = 1.14–1.89) after adjustment for sex, eye color, skin phototype, study site, and average sunscreen use during the holiday weeks. Last, after adjustment for skin phototype and recent sun exposure, the density of freckles on the face, the arms, and the shoulders was statistically significantly higher (i.e., unity not included in the 95% CI) in children who had used sunscreens during the last year.

Sunburns and Nevus Count

Sunburns were reported in 340 children (54%), who experienced a total of 583 sunburn episodes. Eighty-eight percent of these episodes occurred during the holiday periods. Table 5

Table 1. Median total body number of nevi 2 mm or larger according to sunscreen use and wearing of clothes while in the sun

	No. of children 6–7 y old	Study location				All places (n = 631)
		Brussels (n = 228)	Bochum (n = 147)	Lyons (n = 104)	Rome (n = 152)	
Total sunscreen use*						
Never	34	6.0	2.0	2.0	4.0	3.5
Low	180	11.0	6.0	4.0	7.0	6.0
Intermediate	213	12.0	8.0	2.0	8.0	6.0
High	204	11.0	10.0	4.5	9.0	8.0
P†		.045	.004	.095	.062	<.0001
Average sunscreen use‡						
Never	34	7.0	1.0	2.0	4.0	3.5
Rare	84	9.0	4.0	3.0	7.5	5.0
Sometimes	157	9.0	4.0	2.0	9.0	6.0
Often	214	11.0	3.0	2.5	9.0	6.0
Always	142	13.0	3.0	7.0	8.5	9.5
P		.023	.032	.093	.23	.0003
Average wearing of clothes§						
Never	17	12.0	—‖	—‖	8.0	8.0
Rare	124	15.0	7.0	4.0	9.0	8.0
Sometimes	438	11.0	3.0	2.5	8.0	6.0
Often	52	9.0	2.0	1.0	0.0	6.0
P		.31	.13	.33	.033	.01

*Estimate of the total quantity of sunscreen used from birth to the moment of the skin examination. This esimate was computed as the summation across all holiday weeks of the reported sunscreen use, using an arbitrary value of 0, 1, 2, and 3 attributed to the possible answers to that question, i.e., ''never,'' ''sometimes,'' ''often,'' and ''always.'' Children who ever used sunscreens were classified in tertiles.

†*P* values were determined from Kruskal–Wallis statistical test.

‡Estimate of the average quantity of sunscreen used during a typical holiday week from birth to the moment of the skin examination. This estimate was computed as the ''total sunscreen use'' divided by the total number of holiday weeks. Children were classified in the categories ''never,'' ''rare,'' ''sometimes,'' ''often,'' and ''always'' when their ''average sunscreen use'' was equal to 0, greater than 0 and less than 1, greater than 1 and less than 2, greater than 2 and less than 3, and equal to 3, respectively.

§Estimate of the average wearing of shirt or trousers during a typical holiday week from birth to the moment of the skin examination. Similar to ''average sunscreen use,'' it was computed as the summation across all holiday weeks of the reported wearing of clothes and then divided by the total number of holiday weeks. Categories were defined according to possible answers in the questionnaire.

‖No children in these categories.

shows site-specific risk for nevus number according to number of site-specific sunburns. Although shoulders were by far the most frequently affected area, nevus count in that area was minimally influenced by the number of sunburns. The same lack of influence holds true for the head and neck. Only nevus count on the trunk (shoulders not included) seemed to increase with sunburn experience, but successive adjustments decreased the effect of sunburns on that body site. The first sunburn episode occurred before 3 years of age in 20% of children with a positive sunburn history; 23% of all episodes were painful, and fever occurred in 3%. No association was found between nevus count and these last three factors (data not shown).

Sunburns, Sunscreen Use, and Nevus Count

Fig. 1 suggests a more complex relationship between sunburns and nevi. Positive sunburn history first seemed to increase nevus count; however, as sunburns became numerous, the nevus count tended to decrease. To explore this phenomenon, we cross-tabulated total sunscreen use with sunburn experience (Table 6). Compared with the results in Table 3, the risk levels associated with sunscreen use were highest if there was no sunburn experience. Among children with low total sunscreen use, an increased number of sunburns seemed to increase nevus count. Among children with numerous sunburns, increasing sunscreen use was associated with lower nevus count. For children with both high sunscreen use and at least three sunburn episodes, the RR for higher nevus count was about the same as for children without sunburn experience and who never used a sunscreen. These results indicated a strong negative interaction between the effect of sunscreen use and sunburn experience on nevus count, on both additive and multiplicative scales ($P<.001$ for the multiplicative interaction).

Table 7 helps to interpret these intriguing data. Relative to children free of sunburn experience, children with a history of at least three sunburn episodes were more sun sensitive (i.e., skin phototype I–II), had less occasions to go naked in the sunlight, and were more likely to wear clothes when in the sun. Children with highest RRs in Table 6 presented a similar high frequency of having gone naked in the sun and of low physical sun protection. In contrast, children with both high sunscreen use and at least three sunburn episodes seemed less likely to have gone naked in the sunlight and tended to benefit more from physical protection.

Discussion

Our results provide evidence that sunscreen use is involved in proliferation of nevi, whereas wearing clothes in the sun prevents the sun-induced development of nevi. Similar associations between nevus counts and sunscreen use in children were previously reported *(16,22)*, but no adjustment for sun exposure had been made.

Our participation rate was comparable to the rates reported by

Table 2. Sun exposure, sunscreen use, and number of nevi in 631 European children 6–7 years old

Average sunscreen use when in the sun during holidays*	Sun exposure index†		
	Low	Intermediate	High
No. of children in each category			
Never	16	10	8
Rare/sometimes‡	76	72	93
Often	56	79	79
Always	57	52	33
Median whole-body No. of nevi, RR of higher nevus count, and 95% CI§			
Never	3.0	1.5	5.5
	1.00‖	0.57	1.05
	—	0.21–1.55	0.47–2.38
Rare/sometimes	4.0	6.5	7.0
	1.15	1.49	1.26
	0.70–1.92	0.91–2.44	0.77–2.06
Often	4.0	6.0	8.0
	1.13	1.20	1.70
	0.67–1.92	0.73–1.98	1.01–2.70
Always	9.0	9.0	10.0
	1.32	1.44	2.13
	0.80–2.19	0.87–2.39	1.28–3.54
Median No. of nevi on the trunk, RR of higher nevus count, and 95% CI§			
Never	1.0	1.0	2.5
	1.00‖	0.61	1.29
	—	0.20–1.87	0.54–3.05
Rare/sometimes	2.0	2.0	3.0
	1.16	1.36	1.42
	0.65–2.09	0.77–2.50	0.81–2.51
Often	2.0	2.0	4.0
	1.22	1.24	1.96
	0.67–2.22	0.69–2.21	1.12–3.44
Always	3.0	4.0	4.0
	1.39	1.55	2.44
	0.77–2.50	0.86–2.78	1.36–4.39

*Estimate of the average quantity of sunscreen used during a typical holiday week from birth to the moment of the skin examination. This estimate was computed as the ''total sunscreen use'' divided by the total number of holiday weeks. Children were classified in the categories ''never,'' ''rare,'' ''sometimes,'' ''often,'' and ''always'' when their ''average sunscreen use'' was equal to 0, greater than 0 and less than 1, greater than 1 and less than 2, greater than 2 and less than 3, and equal to 3, respectively.

†Computed as the duration (in weeks) multiplied by the intensity of sun exposure during the different holiday periods, summed across all holiday periods, and then divided in tertiles.

‡Categories ''rare'' and ''sometimes'' of Table 1 were collapsed to allow sufficient numbers of children in each ''average sunscreen use'' by ''sun exposure index'' category.

§Adjusted for sex, study site, skin phototype, and eye color; RR = relative risk; CI = confidence interval.

‖Referent category.

Table 3. Relative risk (RR) for number of nevi 2 mm or larger associated with variables related to sun exposure in 631 European children 6–7 years old

Variable	Trunk		Head and neck	
	Partial model†	Full model‡	Partial model	Full model
Sun exposure index§				
Low‖	1.00	1.00	1.00	1.00
	—	—	—	—
Intermediate	1.09	0.98	1.13	1.06
	0.90–1.31	0.80–1.19	0.91–1.41	0.84–1.34
High	1.45	1.20	1.09	0.98
	1.21–1.74	0.97–1.49	0.86–1.37	0.75–1.29
Total sunscreen use¶				
Never‖	1.00	1.00	1.00	1.00
	—	—	—	—
Low	1.26	1.25	1.33	1.28
	0.83–1.92	0.81–1.93	0.80–2.22	0.75–2.17
Intermediate	1.36	1.28	1.41	1.32
	0.90–2.06	0.83–1.97	0.85–2.35	0.77–2.26
High	1.91	1.68	1.56	1.48
	1.27–2.88	1.09–2.59	0.94–2.60	0.86–2.54
Average wearing of clothes¶				
Never‖	1.00	1.00	1.00	1.00
	—	—	—	—
Rare	1.13	0.96	1.08	0.97
	0.76–1.70	0.64–1.45	0.63–1.85	0.55–1.70
Sometimes	0.90	0.79	0.99	0.92
	0.60–1.35	0.53–1.20	0.58–1.68	0.53–1.59
Often	0.61	0.59	0.73	0.72
	0.37–1.01	0.36–0.97	0.40–1.37	0.38–1.35

*Estimate of the total quantity of sunscreen used from birth to the moment of the skin examination. This estimate was computed as the summation across all holiday weeks of the reported sunscreen use, using an arbitrary value of 0, 1, 2, and 3 attributed to the possible answers to that question, i.e., ''never,'' ''sometimes,'' ''often,'' and ''always.'' Children who ever used sunscreens were classified in tertiles. Trunk includes shoulders.

†Partial model: RRs and 95% confidence intervals (CIs) were derived from a Poisson regression model including one of the three variables (sun exposure index or total sunscreen use or average wearing of clothes) plus sex, study place, eye color, and skin phototype.

‡Full model: RRs and 95% CI were derived from a Poisson regression model including all three variables plus sex, study place, eye color, and skin phototype.

§Computed as the duration (in weeks) multiplied by the intensity of sun exposure during the different holiday periods, summed across all holiday periods, and then divided in tertiles.

‖Referent category.

¶Estimate of the average wearing of shirt or trousers during a typical holiday week from birth to the moment of the skin examination. Similar to ''average sunscreen use,'' it was computed as the summation across all holiday weeks of the reported wearing of clothes and then divided by the total number of holiday weeks. Categories were defined according to possible answers in the questionnaire.

most other studies of nevi in children *(15,16,22–24).* Because parents, teachers, and school administrators were blind to the study hypothesis, it is highly improbable that the decision to participate in the study could have been influenced by the amounts of sunscreen used or the nevus count. It is, thus, hardly credible that all presumed protective properties of sunscreens would have been concentrated in the nonparticipants. Interobserver variability could account for a portion of the differences in nevus counts between study places. However, nevus counts in Bochum were equivalent to those obtained during a previous study *(22)* in a similar population of children. Interobserver variability is unlikely to have changed the trends observed because 1) in each study place, data were consistent with sunscreen use being associated with higher nevus number and, 2) there is no reason to believe that correct ranking of children according to their nevus count was not preserved.

We also performed statistical analysis with the use of logistic regression methods (using children in the second or third tertile of the nevus distribution as an end point) or least-square regression approaches (logarithm of the nevus number as end point). The Poisson regression method yielded more conservative results than did the two other methods.

Did our study correctly assess sun exposure? In European populations, intermittent sun exposure is regarded as the sun exposure pattern most implicated in melanoma occurrence *(25),* and sunburns are indicators of intermittent sun exposure pattern

Table 4. Relative risk (RR) for number of nevi 2 mm or larger on the trunk according to sunscreen use and sun protection factor*

Average sunscreen use during holidays†	Average sun protection factor (SPF) (No. of children)					
	Never (34)	4–9‡ (53)	10–14 (139)	15–19 (201)	20–24 (151)	⩾25 (53)
Never	1.00§					
Rare		1.05	1.10	1.33	1.03	0.37
Sometimes		1.33	1.66‖	1.29	0.88	1.22
Often		1.10	1.93‖	1.29	1.39	1.98‖
Always		2.03‖	1.21	2.24‖	1.39	1.90‖

*Adjusted for sex, study place, skin phototype, eye color, sun exposure index, wearing of clothes while being in the sun, and number of sunburns.

†Estimate of the average quantity of sunscreen used during a typical holiday week from birth to the moment of the skin examination. This estimate was computed as the ''total sunscreen use'' divided by the total number of holiday weeks. Children were classified in the categories ''never,'' ''rare,'' ''sometimes,'' ''often,'' and ''always'' when their ''average sunscreen use'' was equal to 0, greater than 0 and less than 1, greater than 1 and less than 2, greater than 2 and less than 3, and equal to 3, respectively.

‡Average SPF was never lower than 4.

§Referent category.

‖Lower bound of 95% confidence interval does not include 1.00.

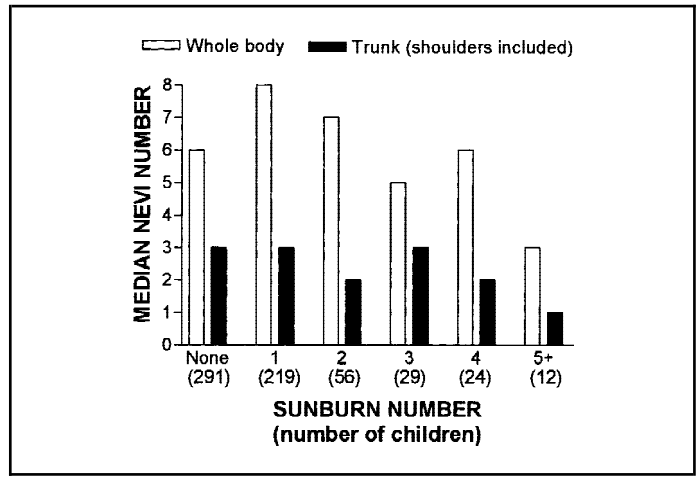

Fig. 1. Sunburn number and nevi count.

(2). In our study, each year, a child had an average of 4 weeks of sunny holidays, during which 88% of the sunburn episodes occurred. Thus, it seems that the greater part of the intermittent sun exposure experienced by European children takes place during these holiday periods. Also, sun exposure and sun protection attitudes during holiday and non-holiday periods were highly correlated. Hence, the sun exposure index that we used may be considered as a valid reflection of the sun exposure experienced by young, European children.

The effects of sunscreen use on nevus number cannot be explained by underlying host characteristics fostering both sunscreen use and proliferation of nevi. There is always the possibility of an unknown confounder. But given the magnitude of the observed effect of sunscreen use on nevus counts, such a confounder should be strongly associated with both sunscreen use and nevus number and would have been identified by the numerous epidemiologic studies performed on skin cancers and nevi during the past 20 years.

The marked effect of sunscreen use on RRs associated with sun exposure in Tables 2 and 3 indicates that a substantial part of all sun exposure was rendered possible by the use of sunscreens. Reciprocally, the decrease in RRs associated with sunscreen use observed in Table 3 indicates that the risk conveyed by sunscreen use proceeds from the possibility of longer sun exposure. Because nevus count is the strongest host factor predicting melanoma and because nevi share many common epidemiologic and biologic similarities, our findings could apply to melanoma.

As suggested by Bech-Thomsen and Wulf *(26),* could our results be due to application of insufficient quantities of sunscreens? If so, it is difficult to understand why nevus counts increased with increasing average sunscreen use. Also, this argument would assume that if an insufficient quantity of sunscreen is present on the skin, the ultraviolet-induced development of nevi is not inhibited. We are aware of no experimental data supporting the plausibility of such a hypothesis.

The SPF had no effect on occurrence of nevi. SPF measure-

Table 5. Site-specific relative risk (RR) for number of nevi 2 mm or larger according to site-specific number of sunburns*

	Head and neck	Shoulders	Arms	Trunk	Legs
No. (%) of children with ⩾1 sunburn on the site	114 (18)	238 (38)	48 (8)	60 (9)	29 (5)
Total No. of sunburns on the site	187	351	69	85	41
Sunburn episodes in which the site was involved, %	32	60	12	15	7
Variables in the Poisson regression model					
Site-specific sunburns, sex, study place	1.16† 0.93–1.46	1.19 0.97–1.45	1.16 0.94–1.43	1.41 1.08–1.83	0.92 0.67–1.27
Site-specific sunburns, sex, study place, sun exposure index, total sunscreen use	1.11 0.89–1.40	1.15 0.94–1.40	1.15 0.92–1.42	1.36 1.04–1.77	0.91 0.66–1.26
Site-specific sunburns, sex, study place, sun exposure index, total sunscreen use, skin phototype	1.00 0.80–1.27	1.05 0.86–1.30	1.09 0.88–1.35	1.26 0.97–1.64	0.84 0.61–1.17

*583 sunburn episodes were reported, but one episode could involve more than one body site.

†RRs and 95% confidence intervals associated with body site-specific number of sunburns included in the model as a continuous variable. The referent category are children without sunburn on the site.

Table 6. Sunscreen use, sunburn, and relative risk for number of nevi 2 mm or larger on the trunk*

Total sunscreen use†	Sunburn episodes on the trunk‡		
	Never	1–2	⩾3
No. of children in each category			
Never	25	9	0
Low	89	77	14
Intermediate	87	98	28
High	90	91	23
Relative risk and 95% confidence interval for nevi count			
Never	1.00§	1.77‖	—
	—	0.80–3.95	
Low	1.32	1.57	3.91
	0.78–2.22	0.91–2.71	1.92–7.96
Intermediate	1.59	1.41	2.22
	0.94–2.66	0.83–2.40	1.16–4.26
High	2.21	1.89	1.21
	1.33–3.67	1.11–3.22	0.59–2.49

*Shoulders included for both sunburn and nevus counts.

†Estimate of the total quantity of sunscreen used from birth to the moment of the skin examination. The estimate was computed as the summation across all holiday weeks of the reported sunscreen use, using an arbitrary value of 0, 1, 2, and 3 attributed to the possible answers to that question; i.e., ''never,'' ''sometimes,'' ''often,'' and ''always.'' Children who ever used sunscreens were classified in tertiles.

‡Number of sunburn episodes experienced from birth to the moment of the skin examination.

§Referent category.

‖Adjusted for sex, study place, skin phototype, eye color, sun exposure index, and average wearing of clothes.

ment in the European community follows standardized protocols. Although errors may have occurred in SPF reporting, it is difficult to consider misclassification of SPFs as the only responsible factor for the total absence of effect on nevus counts when large quantities of high-SPF sunscreens were used. The most probable explanation is that SPF is not related to the biologic phenomena implicated in formation of nevi and, by extension, to occurrence of melanoma.

Armstrong et al. *(27)* found quite a similar association pattern between sunburns and nevus count as described in Fig. 1. In our study, highest nevus counts were found among children free of sunburn experience and who used large quantities of sunscreens or among children with numerous sunburns and low sunscreen use. We already described such a negative interaction in a study on melanoma *(28)*. In that study, melanoma risk was highest when sunscreen use was coupled with absence of sunburn experience. A possible explanation for the negative interaction observed in children is that some parents confronted with the high sunburn frequency of their children adopted the whole sun protection panoply. It is difficult to ascertain whether these parents made a difference between the various sun-protection methods; however, in view of the data, it seems that, in that subgroup of children, high sunscreen use represented a marker of adoption of effective sun-protection methods, such as wearing clothes or avoiding going naked in the sun. In contrast, it is probable that the children with numerous sunburns who did not benefit from effective sun-protection methods experienced further ultraviolet irradiation that resulted in higher nevus counts. These findings

Table 7. Factors associated with sunscreen use and sunburn experience

Total sunscreen use*	Sunburn episodes†		
	Never	1–2	⩾3
Highest study degree obtained by the father‡			
Never	3.0	3.0	—§
Low	4.0	4.0	5.0
Intermediate	5.0	4.0	5.0
High	5.0	5.0	6.0
Skin phototype I–II, %			
Never	4	38	—
Low	15	27	29
Intermediate	20	39	27
High	27	42	48
Children who sometimes or often went naked in the sunlight during holidays, %‖			
Never	60	13	—
Low	67	62	57
Intermediate	48	57	46
High	58	48	39
Children who, during last-year holidays, were sun protected with clothes, %			
Never	20	13	—
Low	34	42	36
Intermediate	56	55	75
High	37	51	70

*Estimate of the total quantity of sunscreen used from birth to the moment of the skin examination. Computed as the summation across all holiday weeks of the reported sunscreen use, using an arbitrary value of 0, 1, 2, and 3 attributed to the possible answers to that question; i.e., ''never,'' ''sometimes,'' ''often,'' and ''always.'' Children who ever used sunscreens were classified in tertiles.

†Number of sunburn episodes experienced from birth to the moment of the skin examination.

‡Median level of highest study degree obtained by the father: 3.0 = secondary school, inferior level (studies up to ±15 years old); 4.0 = secondary school, superior level (studies up to ±18 years old); 5.0 = high school, nonuniversity; 6.0 = university studies.

§No children in that category.

‖Proportions were derived from individual averages computed across all weeks of sunny holidays.

Sunscreen Use and Duration of Sun Exposure: a Double-Blind, Randomized Trial

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Background: **In epidemiologic studies, sunscreen use is associated with increased risk of cutaneous melanoma, basal cell skin cancer, and higher numbers of nevi. It has been proposed that sunscreens may encourage prolonged sun exposure because they delay sunburn occurrence. We examined whether, under habitual conditions of sunscreen use, the sun-protection factor (SPF) had an influence on sun-exposure duration.** ***Methods:*** **Before the 1997 summer holidays, we randomly assigned 87 French and Swiss participants who were 18–24 years of age to receive an SPF 10 or an SPF 30 sunscreen. Neither medical personnel nor study participants were aware of their sunscreen assignment. Participants were asked to complete daily records of their sun exposure. To avoid influencing the recreational sun-exposure habits of the study participants, no recommendation was made about sun exposure or sun protection. Furthermore, participants were told that the trial end point was the number of pigmented skin lesions before and after the holidays. One subject was lost to follow-up. All statistical tests were two-sided.** ***Results:*** **The SPF 10 (n = 44) and SPF 30 (n = 42) groups had equivalent mean holiday durations (19.4 days versus 20.2 days) and mean quantities of sunscreen used (72.3 g versus 71.6 g). The mean cumulative sun exposures for the two groups were 58.2 hours and 72.6 hours, respectively (*P* = .011). The mean daily durations of sunbathing were 2.6 and 3.1 hours, respectively (*P* = .0013), and, for outdoor activities, they were 3.6 and 3.8 hours, respectively (*P* = .62). There was no difference in sunburn experience between the two groups.** ***Conclusions:*** **Use of higher SPF sunscreen seems to increase the duration of recreational sun exposure of young white Europeans. [J Natl Cancer Inst 1999;91:1304–9]**

Sun exposure is believed to be the main environmental determinant of skin cancers *(1),* and sunburn experience is associated with skin cancer occurrence *(2).* Sunscreens are able to delay sunburns and to reduce some UV-induced skin lesions, such as nonmelanoma tumors in rodents, local immunologic depression, mutations of the p53 (also known as TP53) gene in keratinocytes, and the incidence of actinic keratoses in humans *(2–7).* As a consequence, sunscreen use has become recommended as a sun-protection method, and that protection is deemed to increase with increasing sun-protection factor (SPF). The SPF indicates the ability of a sunscreen to delay the skin erythemal reaction induced by the solar radiation.

In contrast to the results of experimental studies, observational studies have repeatedly found sunscreen use to be associated with higher risk of cutaneous melanoma and basal cell skin cancer and with higher counts of nevi *(8–16).* By way of explaining this difference, it has been hypothesized that, because they delay sunburn occurrence, sunscreens could allow prolonged sun exposure, a situation that could lead to increased skin cancer risk *(1,9).*

If the hypothesis that sunscreen use encourages longer sun exposure is correct, then higher SPF should lead to greater sun-exposure duration *(17).* We conducted a two-center, double-blind, randomized study to determine whether, in the habitual conditions of sunscreen use by European young adults, the SPF had an influence on duration of sun exposure.

Subjects and Methods

Study Subjects

Study subjects were healthy, paid volunteers 18–24 years old recruited in universities in Lyon (France) and Lausanne (Switzerland) and from nonmedical disciplines. Participants had to have a positive history of sunburn in the past and to be regular sunscreen users intending to have at least 15 days of holidays in sunny areas during the next 2 months. Volunteers with a current skin disease, even minor, or who had a history of a skin disease that lasted for 1 year or more were not eligible. Pregnant women, subjects with a chronic physical illness, or subjects taking a photosensitizing medication were also ineligible.

Participants were randomly assigned to receive an SPF 10 or an SPF 30 sunscreen. The two sunscreens used in this study were broad spectrum, commercially available, high-quality preparations from the same brand. The two sunscreens were prepared with the same chemical absorbents and mineral–oxide reflectants active in the UV A and B wavelengths, but the SPF 30 sunscreen contained a higher concentration of these substances. Both sunscreens had the same appearance, fragrance, color, and texture. They were bought from a local retailer and repackaged in unidentifiable tubes. Five tubes of 60 mL per participant were prepared by an experienced pharmacist (average, 373-g gross weight).

The study was conducted in accordance with the principles of the Helsinki declaration and was submitted for approval to an Ethical Review Committee of the Centre Léon Bérard (Lyon) and of the Centre Hospitalier Universitaire Vaudois (Lausanne). Each participant signed a written informed consent before randomization.

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See "Notes" following "References."

Study Design

The trial design is shown in Fig. 1. The study end point was the duration of recreational sun exposure. Recreational sun exposure included sunbathing and other outdoor activities, such as walking, playing, and enjoying sport (e.g., swimming or boating) in the sun. To avoid the possibility that knowledge of the actual end point could influence sun-exposure behavior, the stated study end point for participants and all persons in contact with them was the influence of different types of sunscreens on pigmented lesions of the skin. Since nevus counting and the assessment of the freckling index merely served to distract subjects from the real study objective, data on pigmented skin lesions are not presented.

Data from a 1992 survey in Connecticut *(18)* suggested a difference of 0.33 hour in daily sun exposure (standard deviation of 2 hours) between sunscreen users and nonusers. Assuming an average of 10 days with sun exposure per participant, to detect a 0.33-hour difference in daily sun exposure, with 90% power and a two-sided alpha error of 5%, at least 80 subjects had to be included.

A person who had no contact with the participants or the medical personnel involved in the study performed the randomization on an individual basis. By use of a table of random numbers, a five-digit random number was assigned to each set of five sunscreen tubes. Next the sets were ordered by successive random numbers.

Potential participants were invited to attend a medical examination. Following eligibility checking, the freckling index (face, arms, and shoulders) was assessed and the numbers of nevi were counted on both arms and on the back. A photograph of the back was also taken. Randomized sets of five sunscreen tubes were given to participants on a consecutive basis. To keep the trial close to participants' habitual conditions of recreational sun exposure, no recommendation was made either about sun exposure or about sunscreen use. Participants were asked to complete a standard daily diary recording detailed data on their sun exposure: hours and type of sun exposure (e.g., sunbathing, swimming, and boating), amount of clothing (e.g., nude, naked breasts, and one- or two-piece swimming suit), number of sunscreen applications, time of application (i.e., before or after starting sun exposure), and sunburn or skin-reddening experience (sunburn was defined as an episode of painful skin erythema; skin reddening was defined as an episode of painless skin erythema). If another sunscreen was used, the participant was asked to record the day and time of day the other sunscreen was used, the commercial name, the SPF, and the motive for changing to another product.

In September, the participants attended a second medical examination during which all sunscreen tubes were taken back and weighed. The daily diaries were collected and verified for completeness. In case there were missing data, the participants were directly asked to provide the missing information during that second medical examination. Participants also completed a questionnaire on their lifetime sun-exposure habits, sunburn experience, and sunscreen use. Their skin phototype was determined according to their propensity to sunburn or to get a tan when going unprotected in the mid-day sun *(19):* The skin phototype I subject always burns and never tans, the skin phototype II subject always burns first and tans after, and the skin phototype III subject sometimes burns but always gets a deep tan. In this study, there were no skin type IV subjects, i.e., subjects who never burn and always get a deep tan.

Statistical Analysis

Sun-exposure durations were calculated from the daily record diaries. Missing or imprecise data on sun-exposure hours remained for 5 (0.4%) of the 1312 days with sun exposure. Sun exposures during these 5 days could thus not be included in the calculations of sun-exposure duration. After data entry, the randomization code was broken and the analysis was performed. Student's t test, the uncorrected χ^2, and the Wilcoxon rank sum test were used for testing univariate statistical associations. Least-squares regression multivariate analysis was used to assess the influence of different factors on study end point. All statistical tests were two-sided.

RESULTS

In June through July 1997, 87 healthy participants who were 18–24 years old (51 females; 36 males) were recruited in Lyon and Lausanne for the trial. One participant was considered lost to follow-up (French, female, skin type III, SPF 30 group) after she did not attend the second medical examination in September and did not return the daily record diary to study investigators. This subject could not be included in the analysis.

There was no major imbalance in the distribution of baseline characteristics between the two groups (Table 1), who showed similar patterns of skin phototype, skin complexion, past sun-exposure habits, sunburn experience, and sunscreen use. SPF 10 participants spent their holidays in 139 different areas, of which 47% were countrysides or lakes, 26% were very sunny areas (e.g., the Mediterranean coast), and 27% were other places (e.g., swimming pools in cities). SPF 30 participants spent their holidays in 127 different areas, of which 50% were countrysides or lakes, 28% were very sunny areas, and 22% were other places.

In both groups, the duration of holidays and the number of sunny days during which they either sunbathed or had outdoor activities were equivalent (Table 2). Participants used nearly equal quantities of sunscreen, and none exhausted the sunscreen received at the initial medical visit. The average quantity of sunscreen used represented 20% of the quantity received, ranging from 0% to 65% (one participant in the SPF 30 group did not use any sunscreen at all). Sunscreen use was associated more with sunbathing activities than with outdoor activities (data not shown).

The use of the SPF 30 sunscreen was associated with a greater number of hours

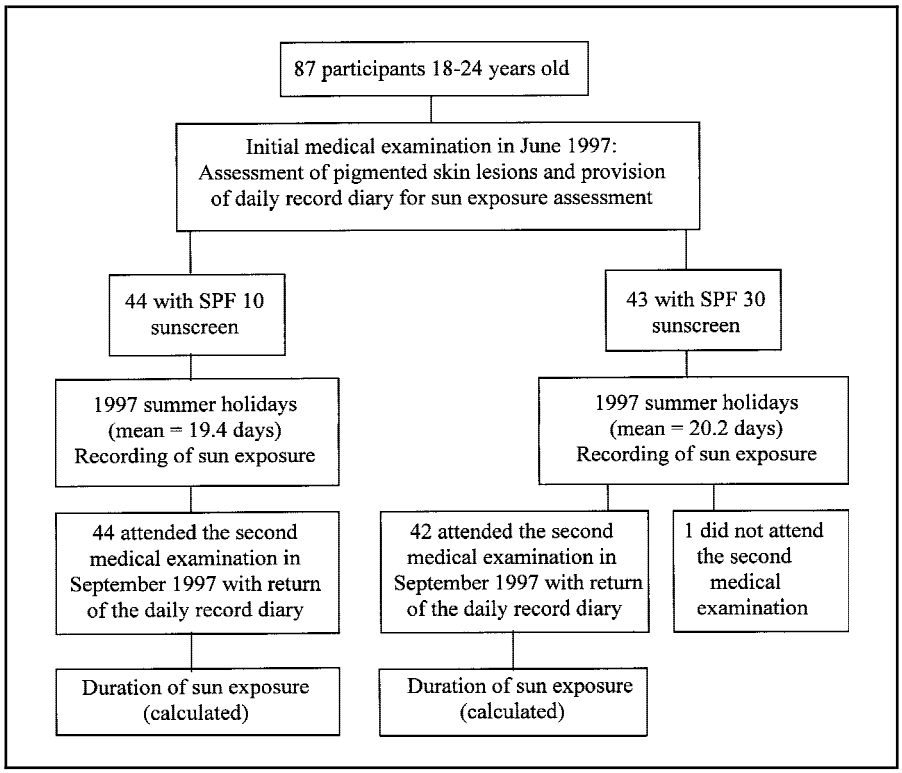

Fig. 1. Trial design.

Table 1. Baseline characteristics of participants

Characteristic	No. (%) of participants	
	SPF* 10 (n = 44)	SPF* 30 (n = 42)
French	33 (75)	32 (76)
Swiss	11 (25)	10 (24)
Females	27 (61)	23 (55)
Males	17 (39)	19 (45)
Skin phototype†		
I	1 (2)	1 (3)
II	14 (32)	14 (33)
III	29 (66)	27 (64)
Skin complexion‡		
Pale	8 (18)	8 (19)
Medium	25 (57)	26 (62)
Dark	11 (25)	8 (19)
Average No. of holiday weeks spent each year in sunny areas since 15 y old		
None	1 (2)	1 (3)
1–2	15 (34)	11 (26)
3–4	18 (41)	22 (52)
5–6	6 (14)	5 (12)
⩾7	4 (9)	3 (7)
Likes to sunbathe	32 (73)	33 (78)
Before study, sunbathed during the hot hours of the day since age 15 y	18 (41)	17 (40)
Before study, use of a sunscreen during sunny holidays or during leisure times in the sun		
Rarely	11 (25)	9 (21)
Sometimes	8 (18)	10 (24)
Often	18 (41)	16 (38)
Always	7 (16)	7 (17)
History of sunburn before age 15 y	33 (75)	30 (71)
History of sunburn after age 14 y	35 (79)	32 (76)

*SPF = sun-protection factor.

†When going in the sun, a skin phototype I subject always burns and never tans, a skin phototype II subject always burns first and tans after, and a skin phototype III subject sometimes burns but always gets a deep tan *(19)*. In this study, there were no skin phototype IV subjects (i.e., who never burn and always get a deep tan).

‡Determined by examining the inner side of upper arms.

spent in the sun (Table 2). Sun exposure of participants who used the SPF 30 sunscreen was, on average, 25% longer than that of participants who used the SPF 10 sunscreen. The higher sun exposure associated with the SPF 30 sunscreen was observed in both study sites. To verify that the observed difference was not due to exceptional sun exposure of some SPF 30 participants, we analyzed the data after elimination of one participant in the SPF 10 group and two participants in the SPF 30 group having total sun-exposure duration three standard deviations above the mean. The difference in the number of hours spent in the sun remained about the same.

The mean daily duration of sun exposure, sunbathing, or outdoor activities was calculated by use of the number of days on which these activities occurred. The increase in daily sun exposure associated with the SPF 30 sunscreen was observed mainly for sunbathing activities. The increase in sunbathing duration was retrieved in the three subgroups of skin color at initial medical examination, despite the small numbers of participants in the skin color categories.

The starting hour of sunbathing activities was identical in both groups during the first holiday day with sunbathing (Fig. 2). As the holidays progressed, however, SPF 30 participants tended to start sunbathing systematically earlier than SPF 10 participants, resulting in more sun exposure during the middle of the day.

The numbers of sunburns or of skin-reddening episodes were comparable in both groups (Table 2). Despite the use of potent sunscreens, 45% of the participants reported one or more sunburns and 81% reported one or more skin-reddening episodes. There was no association between the quantities of sunscreen used and the number of sunburn or skin-reddening episodes (data not shown). Body sites involved in skin-reddening or sunburn episodes were similar in the two groups (data not shown), except for the anterior part of the trunk, where nine women in the SPF 10 group and three in the SPF 30 group reported at least one skin-reddening or sunburn episode ($P = .075$).

Because clothes normally cover them during time spent outdoors, women's breasts are highly sensitive to the sun. Five women in the SPF 10 group and eight in the SPF 30 group sunbathed with naked breasts (Table 3). All sunbathing sessions with naked breasts were preceded by sunscreen applications to the trunk. While duration of holidays and numbers of skin erythemal episodes were identical in the two groups of women, the use of the SPF 30 sunscreen was associated with five times longer sunbathing with naked breasts. Also, while women in the SPF 30 group were more inclined to sunbathe with naked breasts in the early days of their vacation, most women in the SPF 10 sunscreen group waited at least 1 week before exposing their breasts to the sun.

To verify that our results were not the consequence of multiple small confounding effects, we fitted a least-squares regression model using accumulated hours of sun exposure as the dependent variable. The model included number of days of holidays, number of sunscreen applications, randomization group, number of sunburns, sex, and study site. The main predictors of accumulated sun exposure were the duration of holidays ($P<.001$) and the number of daily sunscreen applications ($P = .008$). These results are not surprising, since duration of sun exposure is positively associated with duration of holidays and staying in the sun encourages sunscreen use. The SPF of the sunscreen used was a statistically significant predictor of duration of total sun exposure ($P = .010$), independent of the effect of other variables. The remaining variables were not associated with sun-exposure duration ($P>.20$ for all).

Eleven French participants, seven in the SPF 10 group and four in the SPF 30 group, used another sunscreen than that provided. Alternative products were used, for a total of 18 days in the SPF 10 group and 7 days in the SPF 30 group. The SPFs of the alternative sunscreens were 5, 6, 6, 10, 10, 20, and 20 in the SPF 10 group and 8, 30, 30, and 60 in the SPF 30 group (Wilcoxon rank sum test for the difference in SPF: $P = .070$), suggesting that alternative products used by SPF 30 participants were of higher SPF than alternative products used by SPF 10 participants.

DISCUSSION

The results of this randomized trial demonstrate that recreational sun exposure is of longer duration when a high SPF sunscreen is used than when a low SPF sunscreen is used. Similar results were found in two independent study sites and mainly concerned sunbathing activities. Two findings in particular attest

Table 2. Sun exposure and sunburn experience during holidays*

	SPF 10 (n = 44)	SPF 30 (n = 42)	P†
Total No. of holiday days	854	848	
Mean No. of holiday days (range)	19.4 (12–43)	20.2 (14–46)	.57
No. of days (% of total No. of holiday days) during which			
Participant did not go outside‡	146 (17)	107 (13)	
Participant went outside but did not become exposed to the sun	65 (8)	77 (9)	
There was sun exposure	643 (75)	664 (78)	
There was sunbathing	328 (38)	347 (41)	
There were outdoor activities	467 (55)	514 (60)	
There were sunbathing and outdoor activities	152 (18)	197 (23)	
Mean (95% CI) quantity of sunscreen used, g	72.3 (60.2–84.4)	71.6 (53.7–89.5)	.95
Range, g	12–167	0–244§	
Accumulated hours of			
Sun exposure	2559	3048	
Sunbathing	852	1075	
Outdoor activities	1707	1973	
Mean (95% CI) total hours of sun exposure per participant	58.2 (52.0–64.4)	72.6 (63.5–81.7)	.011
French participants	62.3 (55.2–69.4)	74.9 (63.6–86.2)	.063
Swiss participants	45.8 (35.4–56.2)	65.1 (52.9–77.3)	.027
Exclusion of three participants with highest exposure‖	56.6 (51.0–62.2)	68.0 (61.5–74.5)	.010
Range for all participants	17–126	30–199	
Mean (95% CI) hours of daily			
Sun exposure¶	4.0 (3.3–4.7)	4.6 (3.9–5.3)	<.0001
Outdoor activities¶	3.6 (2.9–4.3)	3.8 (3.0–4.6)	.62
Sunbathing¶	2.6 (2.1–3.1)	3.1 (2.5–3.7)	.0013
Skin complexion pale at initial examination, h	1.9 (1.2–2.6)	3.0 (1.9–4.2)	<.001
Skin complexion medium at initial examination, h	2.6 (2.1–3.2)	3.0 (2.4–3.5)	.034
Skin complexion dark at initial examination, h	2.8 (1.9–3.7)	2.9 (1.9–3.9)	.73
No. of sunburn or of skin-reddening episodes	159	159	.99
No. of sunburn episodes	42	34	.90
No. of skin-reddening episodes	117	125	.85

*SPF = sun-protection factor; 95% CI = 95% confidence interval.

†Student's *t* test for testing of difference between means, χ^2 statistics for testing of difference between numbers; *P* values are two-sided.

‡Because of bad weather, or of absence of eagerness to go outside, or of a sunburn in the previous days.

§One participant in SPF 30 group did not use any sunscreen.

‖Exclusion of participants with total sun exposure three standard deviations above the mean: one participant in the SPF 10 group (126 hours of total sun exposure) and two participants in the SPF 30 group (127 and 199 hours of total sun exposure).

¶Accumulated hours of sun exposure, outdoor activities, or sunbathing divided by the number of days during which there was sun exposure, outdoor activities, or sunbathing.

to the sense of security conferred by potent sunscreens. First, the use of the SPF 30 sunscreen led to a greater amount of sunbathing during hours of the day during which the UV radiation usually reaches its peak value. Second, women using the SPF 30 sunscreen sunbathed longer with naked breasts while incurring a lower number of sunburns or skin-reddening episodes on that part of the body.

Participants in the two study arms were similar in terms of natural susceptibility to sunlight, history of sun exposure and sunburn, duration of holidays, and the types of places they vacationed. Furthermore, our data suggest that those participants who used SPF 30 sunscreen actually increased their sun exposure over the course of the holidays (Fig. 2). Therefore, it is unlikely that the difference in sun-exposure duration stemmed from differences in baseline characteristics and choice of holiday location; rather, it appears to be related to protection from burning conferred by the stronger sunscreen.

Data collection was done prospectively by use of standard diaries completed on a daily basis. Therefore, biases in the recording of sun-exposure duration have probably been minimal. If some bias was present, however, it is reasonable to assume that it has been equally distributed among the two study groups.

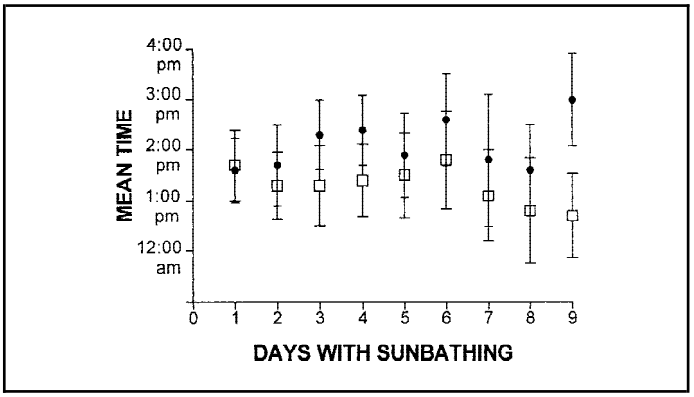

Fig. 2. Mean hour of start of sunbathing activities in days with sunbathing. Days without sunbathing were skipped. The time in the figure is the so-called "summer hour" in Continental Europe, equivalent to the solar hour plus 2 hours. **Blank squares** represent sun-protection factor (SPF) 30 participants; **black circles** represent SPF 10 participants. **Error bars** represent 95% confidence intervals. Student's *t* test for the difference in mean hour: *P*>.90 for the first day; *P*<.050 for days 2–9 (*P* values are two-sided).

Table 3. Sunbathing with naked breasts in female participants

Woman No.	Skin phototype*	Duration of holidays, days	No. of skin-reddening or sunburn episodes during the holidays	Hours of sunbathing with naked breasts	Day of first exposure with naked breasts
			SPF 10 group		
1	II	24	1	6.00	1st
2	II	20	2	4.75	10th
3	II	25	9	3.00	15th
4	III	43	4	4.00	30th
5	III	15	0	5.00	12th
Total hours of sunbathing with naked breasts				22.75	
Mean (95% confidence interval) duration of sunbathing with naked breasts				4.55 (3.15–5.95)†	
			SPF 30 group		
1	I	16	10	11.50	2d
2	II	21	1	5.00	11th
3	II	28	2	28.50	2d
4	III	28	3	47.00	1st
5	III	28	1	3.50	4th
6	III	16	0	38.00	5th
7	III	16	3	31.00	1st
8	III	23	3	18.00	2d
Total hours of sunbathing with naked breasts				182.50	
Mean (95% confidence interval) duration of sunbathing with naked breasts				22.81 (9.57–36.06)†	

*For definition, *see* footnote in Table 1.

†Wilcoxon rank sum test for the difference in median hours of sunbathing with naked breasts; two-sided $P = .030$.

We thus consider that the reported sun-exposure durations in this study are a valid reflection of the true sun exposure of participants during their holidays and that our findings are unlikely to be due to bias.

An adult should use roughly 35 mL of sunscreen per single whole-body application to correspond to the doses used by laboratories for measuring the SPF of a sunscreen *(20)*. In that respect, our study participants should have consumed at least three to four times the quantities actually used, and it is thus probable that, in most participants, the effective SPF of the sunscreens used was about three to four times lower. However, our study shows that an increased ability to delay sun-induced skin erythemal reactions is sufficient to cause longer sun exposure, even when moderate quantities of sunscreen are used.

The increase we observed in sun-exposure duration may explain why sunscreen use has been reported to be a risk factor for melanoma, basal cell cancer, and nevus development. It also demonstrates that the longer sun exposure allowed by sunscreen use is an unconscious phenomenon, which makes individual control difficult, particularly where children are concerned.

Sunburn or skin-reddening experience among participants was independent of the SPF and of the quantity of sunscreen used. This observation suggests that sunscreen use during recreational sun exposure does not imply protection against sunburns. Sunburns are essentially due to the UV B radiation *(1)*. Equivalence of sunburns and skin-reddening experiences in the two groups suggest that doses of UV B radiation received by skin cells were probably similar in the two groups. However, the delivery of these doses to skin cells of SPF 30 participants would have taken a longer time than that to skin cells of SPF 10 participants.

The issue addressed by this study is common to all sunscreens. Because we did not want to single out the products of a specific company, we chose not to disclose the commercial name and the exact composition of the sunscreens used in this trial.

From our results, it is reasonable to infer that equivalent or greater differences in sun-exposure duration would have been observed if one had compared subjects using a sunscreen with subjects not using any sunscreen. One could have considered a placebo-controlled trial using as placebo a lotion without any chemical or physical substance able to block UV radiation. In this study, a placebo group was not possible. First, it was ethically difficult to allow a placebo sunscreen when the sun-protection virtues of sunscreens are widely acknowledged. Second, it was not easy to provide a placebo sunscreen without informing subjects of both study groups that they should be careful in their sun exposure to avoid severe sunburns. Third, many subjects in the placebo group would have rapidly changed to a real sunscreen, which would have endangered the trial.

Experiments that tested the ability of sunscreens to reduce the incidence of UV-induced lesions have not examined the possibility that these products could modify the sun-exposure behaviors of subjects eager to acquire a tan or to stay in the midday sun with large parts of the body uncovered. The two human placebo-controlled trials that showed the ability of sunscreen use to reduce the incidence of actinic keratoses *(6,7)* enrolled subjects having a mean age of 64 years who had a history of nonmelanoma skin cancer or of other sun-induced skin lesions, who were highly aware of the hazards of sun exposure, who were not keen to acquire a suntan, and who apparently never had sunburn during the trials. Clearly, these trials did not reproduce the normal or reasonably foreseeable conditions of sunscreen use in North America and Europe, where sunscreen use by younger people remains largely driven by the desire to enjoy the sun and to acquire a "safe suntan" *(21–24)*.

The protective effect of sunscreen use against skin cancer, particularly melanoma, has not been demonstrated in the general population, but there are compelling data that show a strong relationship between duration of recreational sun exposure and skin cancer. It is therefore desirable that people should be warned against the danger that using a sunscreen may inadvertently prolong recreational sun exposure.

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are in agreement with the concept that sunburns would be markers of both susceptibility to sunlight and of exaggerated sun exposure rather than cause nevi or melanoma per se.

Our findings do not contradict results from experiments that showed the ability of sunscreens to prevent ultraviolet-induced lesions. Rather, they stress that these experiments did not reproduce actual sun exposure and sunscreen use habits of fair-skinned populations. For instance, clinical trials *(6,7)* that showed decreased incidence of solar keratoses or of nonmelanoma skin cancers among subjects using high-SPF sunscreens intentionally included subjects at high risk for actinic skin lesions, who were fully aware of the hazards associated with sun exposure (many had a history of nonmelanoma skin cancer). Thus, results from these trials are not generalizable to usual populations.

There is no satisfactory animal model that mimics melanoma occurrence in humans. Hence, results obtained while studying the keratinocytic system may not be directly transposable to the melanocytic system. However, if sunscreen use acts by allowing prolonged sun exposure, then consequences would affect both keratinocytic and melanocytic systems, and sunscreen use could also be responsible for a part of the increase in nonmelanoma skin cancers in white populations. The increased incidence of basal cell carcinoma among sunscreen users observed in several studies *(10–12)* supports this hypothesis.

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MINI REVIEW

Sunscreen use and increased duration of intentional sun exposure: Still a burning issue

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Sunscreen use is often proposed for sun protection because of their ability to block UV-induced sunburns (the sun protection factor – SPF). Among suntan seekers, however, risk of cutaneous melanoma may be increased because of extended sun exposure duration. We made a systematic review of the evidence linking sunscreen use to sun exposure duration. Five observational studies found that when sun exposure was associated with willingness to get a tan or to stay longer in the sun (*i.e.*, intentional sun exposure), sunscreen use was associated with duration of sun exposure 13–39% longer. Paradoxically, sunburns tend to be more frequent among sunscreen users, probably because of greater natural sun sensitivity. When sun exposure was not intentional, sunscreen use did not increase time spent in the sun. Two European double-blind randomized trials conducted among young sun seekers found daily sun exposure duration, especially sunbathing, 19–25% longer with use of SPF 30 than with use of SPF 10 sunscreens. One randomized trial in a holiday resort in France found a 3–13% increase in sun exposure duration with use of SPF 12 versus SPF 40 sunscreen. But, the SPF 12 groups used 3.6–4.2 more sunscreen than the SPF 40 group, and thus the actual SPF in the SPF 12 group was higher than in the SPF 40 groups. In conclusion, sunscreen use leads to longer duration of sun exposure when sun exposure is intentional, but not when sun exposure is non intentional.

Key words: sun protection; sunscreens; behavior; skin cancer; melanoma; epidemiology; randomized controlled trial

Sunscreens were primarily designed for sunburn prevention, but animal and human experiments showed their ability to reduce UV-induced skin lesions such as solar keratoses and squamous cell carcinoma (SCC).[1,2] The protection afforded increases with the sun protection factor (SPF), *i.e.*, the ability of a sunscreen to retard UV-induced skin erythemal reaction. Consequently, high SPF sunscreens (*i.e.*, SPF $\geq$ 15) have often been recommended for sun protection.

Sunscreen use for sun protection has been challenged by repeated observation that not only sunscreen use (including recent high-SPF broad-band sunscreens) did not protect against cutaneous malignant melanoma (melanoma), basal cell carcinoma (BCC), and higher nevus counts, but that it was often associated with increased risk of these tumors, whereas wearing of clothes was associated with no change or with decrease of these tumors.[3–5]

An alternative hypothesis was that sunscreen use could encourage sun exposures of longer duration, possibly leading to increased risk of melanoma and of BCC. In this article, we review observational and randomized studies that examined sunscreen use and sun exposure duration, according to the sun exposure type associated with sunscreen use.

Intentional and nonintentional types of sun-exposure

Substantial proportions of melanoma and BCC are associated with intermittent sun exposure rather than with lifetime accumulated sun exposure,[6] *i.e.*, light-skinned subjects spending most of their daily life time indoor but enjoying intense sun exposure during holidays, and often eager to acquire a sun tan. Intermittent sun exposure is thus often intentional as subjects look for a biological effect.[1,2] During intentional sun exposure (ISE), significant portions of the trunk, shoulders, and of the upper parts of limbs are frequently uncovered. Sunbathing is the most typical ISE behavior.

Nonintentional sun exposure (NISE) represents sun exposure during daily life activities, without special willingness to acquire a tan or to being able to spend long time in the sun. During NISE, skin areas most usually sun exposed are the head and neck, the hands, and the forearms. Examples of NISE are outdoor activities such as walking, hiking, gardening, skiing, or work on building construction sites or in farming fields. Lifetime accumulated NISE is mainly associated with occurrence of solar keratoses and of squamous cell carcinoma (SCC).

Methods for literature search

We started the literature search with materials gathered for the IARC Handbook on Sunscreens[1] and with bibliography gathered by authors. We then performed a systematic literature search in the MEDLINE until August 2006 without restriction on type and language of article. Use of variable combinations of MeSH terms ''sunscreen agent'', ''sunscreening agents'', ''sunlight'', ''sunburns,'' and ''time'' until March 2006 conducted to a selection of 155 articles including words in the title or in the abstract (when available) suggesting relevance for the study. Full copies of these articles were obtained and independently revised by P.A. and M.B. We made a similar search in the ISI Web of Knowledge, Science Citation Index Expanded, covering the science literature from 1945 until August 2006. Examination of title and available abstracts of articles did not conduct to finding further articles than those found using the MEDLINE. Data from relevant articles were abstracted in a table summarizing key variables and results. Reported data had to provide or to allow the calculation of time spent in the sun during parts of day or during days during which there was effective sun exposure, with knowledge of sunscreen use before or during effective sun exposure. Relevant information of methods or on results were sometimes found in the Discussion section of articles, *e.g.*, time spent in the sun in 1 Danish study,[7] or the notion that during a randomized trial in France, an investigator was permanently present in holiday villages and had daily contacts with trial participants.[8]

Results

Observational studies on sunscreen use during ISE

We identified 6 observational studies conducted during predominantly ISE situations that measured time spent in the sun according to sunscreen use, and published in 7 articles.[7,9–14] A cross-

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TABLE I – OBSERVATIONAL STUDIES ON SUNSCREEN USE AND DURATION OF SUN EXPOSURE OR OF EXPOSURE TO ULTRAVIOLET (UV) RADIATION

Study,[1] year of publication (ref.)	Study design	Place, season and year of study	Type of subjects	Method for data collection	Assessment of time in the sun or of UV dose received	Sunscreen use	Time spent in the sun or UV dose	% difference	% with 1 sunburn or more
Berwick *et al.*, 1992[9]	Cross-sectional survey	Participants to a skin screening campaign in Connecticut, USA, 1988	153 Adults of all ages	Questionnaire on summer of previous year	Average sun exposure duration per weekend day[2]	Never Always	2.57 hr[2] 2.90 hr[2]	Ref. 13% $p = 0.06$	NR NR
Stender *et al.*, 1996[10]; Wulf *et al.*, 1997[11]	Cross-sectional survey	Beaches and parks in Denmark in July 1994	805 Sunbathing Caucasians (mean age: 28) on 4 beaches and in a park	(1) Questionnaire during one sunny day	Difference in minutes between time of arrival at location and time for expected departure	No Yes	197 min 206 min	Ref. 5% $p = 0.186$	34%[3] 42%[3] NR
				(2) Single UV-dosimeter installed on the location	UV dose (SED[5]) recorded between time of arrival at location and time for expected departure	No Yes	4.5 SED 4.8 SED	Ref. 7% $p = 0.035$	– –
McCarthy *et al.*, 1999[12]	Cross-sectional survey	Beaches in Texas, USA, in July 1997	55 Beachgoers 16–59 years old	Questionnaire on sunbathing activities of the day to subjects preparing to leave the beach	Time (hr) of sunbathing	None SPF 2-15 SPF > 15	2.8 3.2 3.5	Ref. 15% 25% NR	54% 50% 73% NR
Robinson *et al.*, 2000[14]	Nationwide cross-sectional survey	Representative sample of families in USA, in July-August 1997	503 children <13 years	Questionnaire to parents on Mondays following a weekend	Mean time outdoor between 10 am and 4 pm	No Yes	4.6 hr 5.7 hr	Ref. 23% $p < 0.05$	7% 20% $p < 0.05$
Thieden *et al.*, 2005[7]	Prospective study of subjects	Danish citizens 4 to 68 years old during 3 summer seasons, 1999–2001		(1) Daily diaries	Number of sun exposure hours per risk behaviour day[4]	No Yes	4.1 5.7	Ref. 39% NR	4.8%[6] 9.5%[6] NR
				(2) Recordings of individual UV dosimeters during risk behaviour days in Southern Europe	Median SED per risk behaviour days[4]				
			93 Subjects			No Yes	3.5 SED 7.8 SED	Ref. 223% NR	NR NR
			19 Children			No Yes	1.5 SED 7.4 SED	Ref. 393% $p < 0.05$	NR NR
			22 Sun worshipper			No Yes	1.8 SED 9 SED	Ref. 400% NR	NR NR
			8 Gardeners			No Yes	8.1 SED 10.2 SED	Ref. 26% NR	NR NR

NR: test for difference between groups not reported.

[1]Study of Wichstrom, 1994[13] not included in table, see text.–[2]Averages conservatively approximated by us, from data in published article, and *t*-test calculated by us (p for trend = 0.07 in published article).–[3]Sunburn reported as ''redness'' by a subsample of 102 subjects the day after interview.–[4]Days during which there was sunbathing or exposure of the upper body or shoulders.–[5]SED is standard erythemal dose. The SED is equivalent to an erythemally weighted dose of 100 J/m^2 (Commission Internationale de L'Eclairage 1988).[15]–[6]Sunburn occurrence during days with risk behaviors.

TABLE II – RANDOMISED TRIALS ON USE OF SUNSCREENS HAVING DIFFERENT SUN PROTECTION FACTOR (SPF) AND DURATION OF SUN EXPOSURE OR OF EXPOSURE TO ULTRAVIOLET (UV) RADIATION

Study, year of publication (ref.)	Study design	Place, season and year of study	Type of subjects	Method for data collection	Assessment of time in the sun or of UV dose received	Sunscreen used by randomized group	Time spent in the sun or UV dose	% difference	% with 1 sunburn or more	Quantity of sunscreen used in g
Autier *et al*., 1999[16]	Double-blind controlled randomized trial	Sunny resorts where students spent their holiday in July–August 1997	87 French and Swiss students 18 to 24 years old taking holidays in sunny resorts in July–August	Self-administered daily diaries	Mean hours of sun bathing per day with sunbathing (average of 11 days)	SPF 10	2.6 hr	Ref.	47%	72.3 (mean)
						SPF 30	3.1 hr	19% $p = 0.0013$	43% p=0.90	71.6 (mean) $p = 0.95$
Autier *et al*., 2000[17]	Double-blind controlled randomized trial	Sunny resorts where students spent their holiday in July–August 1998	48 French and Belgian students 18 to 24 years old taking holidays in sunny resorts in July–August	(1) Self-administered daily diaries	Mean hours of sun bathing per day with sunbathing (average of 9 days)	SPF 10	2.4 hr	Ref.	38%	67 (mean)
						SPF 30	3.0 hr	25% $p = 0.054$	41% $p = 0.46$	77 (mean) $p = 0.22$
					Test for difference between groups					
				(2) Individual UVB and UVA dosimeters		SPF 10	UVB: 841 J/m^2; UVA: 727 KJ/m^2	Ref.	–	–
						SPF 30	UVB: 984 J/m^2; UVA: 812 KJ/m^2	UVB: +17%; UVA: +11%	–	–
								UVB: $p = 0.15$; UVA: $p = 0.70$	–	–
Dupuy *et al*., 2005[8]	Randomized trial with sunscreen tubes labelled as ''basic'' or ''high protection''	Summer villages located on the sea in France in July–August 2001	367 adults 18 to 78 years old (mean = 39) during one week of holidays in July–August	Daily diaries and questionnaires completed with help of on-site investigator	Duration (hr) of sun exposure over one week while wearing a swimming suit or equivalent	SPF 12, ''basic protection''	14.6 hr	Ref.	24%	109 (median)
						SPF 40 ''basic protection''	12.9 hr	−12%	14%	30 (median)
						SPF 40 ''high protection''	14.2 hr	−3%	16%	26 (median)
								$p = 0.06$ (*)	$p = 0.049$*	$p < 0.001$*

*Test for difference between SPF 12 ''basic protection'' and SPF 40 ''basic protection.''

sectional study among Norwegian adolescents[13] could not be used because data on sunbathing time were not reported according to sunscreen of to sun protection factor (SPF) used, and skin lotions with SPF 0–2 were incorrectly considered as sunscreens. Table I summarizes the 5 studies with relevant data.

In some studies, statistical tests for some results were not reported, or data reporting precluded statistical analysis. In all 5 studies, for adults and for children, sunscreen use was associated with duration of sun exposure 13–39% longer than if no sunscreen was used. One study found that UV doses received were considerably higher when sunscreens were used.[7] Four studies recorded sunburns and found higher proportions of subjects with sunburn when a sunscreen was used, especially when the SPF was high. According to reports, differences in sun sensitivity between sunscreen users and nonusers were not likely reasons for explaining results on durations and on sunburns, although these results were never statistically adjusted on sun sensitivity of study participants. Interestingly, 1 study[7] examined also gardeners (a NISE behavior), and found no difference in UV dose received according to sunscreen use. This study did not report data on sunburn occurrence during NISE.

These observational studies could however not assess whether longer duration was a result of sunscreen use that sunscreen users were not aware of, or a result of the willingness of sunscreen users to spent long time in the sun without (did they believe) incurring sunburn. Qualification of the exact cause-effect chain of events could only be determined by randomized trials.

The European randomized trials

The European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group conducted 2 double-blind randomized trials among students 18–24 years of age eager to engage in intentional sun exposure during their summer holidays (Table II).[16,17] These trials were representative of sun exposure behaviors of millions of light-skinned young subjects eager to acquire a tan during holidays or during leisure times. The 2 trials demonstrated that sun exposure, mainly sunbathing, was 19–25% longer duration with use of SPF 30 than with use of SPF 10 sunscreens. High SPF susncreens also allowed more hazardous sun exposure behaviors that would not be possible otherwise, like for instance sunbathing with naked breasts. Average quantity of sunscreen used was similar in randomization groups and the in-holiday sunburn experience was identical for participants regardless of the SPF of the sunscreen used. For many participants, sunburn occurrence was the factor limiting sun exposure duration, but sunburn occurred later in the high SPF group than in the low SPF group. Hence, it was sunscreen use during ISE that led to longer sun exposure sessions, without affecting sunburn occurrence, and trial participants were not aware of this increase in sun exposure duration.

In 2001, a Working Party convened by the IARC concluded that ''use of sunscreen can extend the duration of intentional sun exposure, such as sunbathing. Such an extension may increase the risk for cutaneous melanoma.''[1,2] The US National Cancer Institute and the US Preventive Services Task Force came to similar conclusions.[18,19]

The French randomized trial

A randomized trial funded by a major sunscreen manufacturer appeared to contradicted results of European trials, finding no significant difference in the duration of time spent in the sun according to sunscreen SPF.[8] However, this trial involved a population with low interest in sunbathing. Also the way this trial, was designed and conducted was likely to produce a negative result, *i.e.*, no difference in sun exposure duration according to SPF of sunscreen used.

Notwithstanding study design issues, interpretation of results may be different than that provided by authors. The French trial reported that the SPF 12 and SPF 40 sunscreens especially made for the study had different textures, SPF 12 being easier to spread, which may partly explain the 3.6- to 4.2-fold difference in amount of sunscreen used in the SPF 12 group as compared with the 2 SPF 40 groups (Table II). Taking into account data on sunscreen use in European randomized trials[20] and differences in average daily sunbathing duration in European and in the French trials, participants in the SPF 40 groups may have applied between 0.25 and 0.5 mg/cm^2 of sunscreen onto their skin. With a 0.25 or 0.5 g/cm^2 sunscreen application, the actual SPF is about the eighth and the fourth square root of the SPF indicated on the bottle,[12] *i.e.*, 1.6 or 2.5. Assuming no difference in sun exposure duration according to SPF used and of exposed skin areas, use of 3.6- to 4.2-fold more SPF 12 sunscreen than of SPF 40 may have resulted in an actual sun protection potency 2–3 times higher in the SPF 12 group than in the SPF 40 groups. The consequence was probably the borderline statistically significant 12% increase in sunbathing duration observed in 1 of the SPF 12 groups (Table II). Hence, results from this French randomized trial were in fact quite similar to results of the European randomized trials.[16,17]

Sunscreen use for protection against solar keratoses and squamous cell carcinoma

Trials with solar keratoses and squamous cell carcinoma (SCC) as endpoint were conducted among older subjects whose sun exposure was not intentional but due to normal circumstances of daily-life. Two trials in volunteers relatively aged and having a history of sun-induced skin damage showed the ability of sunscreen use to reduce new solar keratoses.[21,22] The Nembour trial showed that sunscreen use can reduce the incidence of SCC.[23] This trial was performed in Queensland, Australia, in a population living in an area with high ambient sunshine all the year round, and where skin cancer incidence is the highest in the World. In these 3 trials, sun exposure was essentially nonintentional, and sunscreens (or placebo lotions) were mainly used during daily life and applied essentially on the face, ears, neck, and hands. Apparently, subjects did not experience sunburn or the number of sunburns was significantly lower in the intervention group.[23,24] None of the 3 trials reported measurements of in-trial sun exposure durations, but the Nembour trial stated there was no evidence of differences in the time spent in the sun among subjects allocated to the intervention group.[23]

Randomized trials on sunscreen use and numbers of acquired nevi

In 1998 until 2001, 2 randomized trials tested the ability of broadband sunscreen use on the development of nevi in schoolchildren.[25,26] The Vancouver trial in Canada found a reduction in the development of new nevi in children with dense facial freckling and found no effect in children without dense facial freckling.[25] The German trial failed to change patterns of sunscreen use between the randomization groups because apparently, sunscreen use was already highly prevalent in all groups at study start.[26] The Vancouver trial reported estimations of the total amounts of time spent in the sun during the 3-year trial duration but did not report duration of sun exposure per day with or without sunscreen use.

Discussion

All available observational and experimental data in humans provided evidence that intentional sun exposure tends to be of longer duration when a sunscreen is used or when SPF increases. Results of the European randomized trials suggest that sunscreen users are unaware of the impact sunscreen use has on their sun exposure behaviors.

A paradoxical result of observational studies was the higher numbers of subjects reporting sunburns when a sunscreen was used, mainly when the SPF was high. It is well known that the majority of sunscreen users apply only a fifth to a third of quantities of sunscreens used in laboratory for testing their SPF.[11,20] Also,

thickness of sunscreens of a same commercial brand does not change much with SPF, and 1 study showed that quantities of sunscreen applied onto the skin did not vary much with SPF.[27] Observational studies did not perform adjustment of their results on natural sun sensitivity of study participants. Hence, the higher number of sunburns among (high SPF) sunscreen users in observational studies could have been due to greater sun sensitivity.

In contrast to what happens during ISE, during NISE, observational and experimental data in humans provide evidence that sunscreen use would not increase time spent in the sun, and would decrease sunburn occurrence. In this respect, impact of sunscreen use during NISE situations would meet expectations raised by laboratory experiments that showed the ability of sunscreens to decrease the incidence of UV-induced skin erythemal reactions and nonmelanocytic skin cancers.[1] In ISE situations, these expectations are not met because of the influence sunscreen use has on behaviors of humans eager to get a tan or to stay long in the sun.

During the second half of the nineteenth century, the sun tanning fashion exploded among light-skinned populations and growth of sunscreen commercialization paralleled that fashion.[28–30] Sunscreen are often considered as tanning aid,[1,31] and advertising sometimes persuade sun seekers that sunscreens may ensure acquisition of a ''safe tan''. In spite of uncertainties about their exact role in melanoma and BCC occurrence, and in spite of recommendations that sunscreen use should just be an adjunct to other more natural forms of protection, such as use of hats, shirts, and search for shade, sunscreens remain the most frequently used sun protection method, mainly among adolescents and young adults, while in the same time, younger adults declare to be more likely to sunbathe deliberately than other people.[32] In Australia sun protection no longer relies on sunscreen use.[33]

In conclusion, examination of studies on sun protection methods should always take into account the type of sun exposure that was addressed. Also, information on sunscreens should make a clear difference between situations of intentional or of nonintentional sun exposure. When intentional sun exposure is concerned, information to the general public should be closer to uncertainties on their efficacy and to knowledge of the possible impact they may have on sun exposure behaviors, and on melanoma risk.

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REVIEW ARTICLE

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Sunscreen abuse for intentional sun exposure

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Summary

Skin cancer is caused by exposure to ultraviolet radiation (UV) and the sun is the main source of this radiation. Sunscreens were initially formulated to prevent sunburns; laboratory studies later revealed that in rodents they could reduce UV-induced skin cancer which resembles human squamous cell carcinoma. Three randomized trials in older adults showed the ability of sunscreens to moderately reduce the occurrence of solar keratoses and of squamous cell carcinoma. However, no effect was observed for basal cell carcinoma. There is no animal model for human melanoma and observational studies often found sunscreen use associated with a higher risk of nevus, melanoma and basal cell carcinoma. These higher risks were found when sun exposure appeared to be intentional, that is, with the desire to acquire a tan, a healthy look or simply to spend as long as possible in the sun with as much skin exposed as possible. Three randomized trials showed that sunscreen use by sun sensitive subjects engaging in intentional sun exposure could increase the duration of exposure without decreasing sunburn occurrence. This increased duration could be the reason why melanoma risk is increased when sunscreen is used. Hence, sunscreen abuse may extend sun exposure duration thus allowing sun exposure behaviours that would not be possible otherwise. Advertising for sunscreens and labeling of sunscreen bottles should inform consumers of the carcinogenic hazards associated with sunscreen abuse. It would be good to use a personal UV dosimeter which would give an alert when one's individual sunburn threshold in the absence of sunscreen use is nearing. The combination of sunscreen and a UV dosimeter may be an option for reducing the melanoma risk among sun worshippers.

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The advent of sunscreens paralleled the tanning fashion that spread in light skinned populations starting in the 1930s.[1] Their initial formulation was designed to block ultraviolet (UV) B radiation (UVB, 280–320 nm), which causes most sunburns. Epidemiological studies in the 1980s found a strong link between sunburn history and skin cancer, including melanoma. At the same time many laboratory experiments showed that besides delaying the erythemal reaction, sunscreens could reduce a variety of other UV-induced skin lesions, including squamous cell cancer. As a result, these products have been advocated for the prevention of skin cancers, including melanoma despite the absence of a good animal model mimicking human skin melanoma. Until recently, it was generally assumed that the greater the ability of a sunscreen to delay sunburn (i.e., its sun protection factor – SPF), the higher the protection against deleterious effects of the sun. In the 1990s the carcinogenic properties of ultraviolet A radiation (UVA, 320–400 nm) began to be suspected, and a new generation of broad-band sunscreens has emerged, having high SPF (30 and more) and containing agents specifically blocking the UVA.

However, contrary to the expectations based on laboratory experiments, population-based case-control studies often found an increased risk of melanoma associated with sunscreen use (revised in ref. 2). Prospective and retrospective cohort studies found sunscreen use to be associated with increased risk of basal cell cancer in adult women,[3] and higher numbers of acquired melanocytic nevi among school children and adolescents.[4,5] Concerns raised by epidemiological studies were emphasized by laboratory experiments showing that sunscreens could enhance the stimulation of melanoma growth by UV radiation.[6]

After 1995, epidemiological studies and randomized trials found that the most probable reason why sunscreen use increased the risk of melanoma was that by delaying sunburn occurrence, these products extended the time spent in the sun.[7] In this paper, we review the evidence backing this finding and propose a model for explaining why sunscreen extended sun exposure may increase melanoma risk. Based on this model, we propose a way to control time spent in the sun when a sunscreen is used.

Sunscreens and intentional or non-intentional patterns of sun-exposure

Understanding the sunscreen-melanoma association requires distinguishing between two different types of sun exposure patterns.

The non-intentional sun exposure (NISE) pattern represents sun exposure during daily life activities, without a special willingness to acquire a tan or to be able to spend a long time in the sun. The so-called chronic sun exposure pattern usually equates to NISE. Examples of NISE are outdoor activities such as walking, hiking, gardening, skiing, or construction and farming work. Lifetime accumulated NISE is mainly associated with solar keratoses and squamous cell carcinoma.

The intentional sun exposure (ISE) pattern is sun exposure with an intention to stay in the sun with large uncovered skin areas, or/and to acquire a tan. ISE is characteristic of light-skinned subjects who spend most of their daily life indoors but enjoy intense sun exposure during holidays. The usually called intermittent sun exposure pattern is often intentional as subjects look for a biological effect. Sunbathing is the most typical ISE behaviour. Melanoma is commonly found on the usually covered sites such as the trunk, and this clinical evidence fits with the ISE patterns being the cause of most melanoma.

Reasons for the increased melanoma risk associated with sunscreen use

It was first hypothesized that the increased risk of melanoma or high nevi numbers was found in populations not using modern high SPF, anti-UVA broad-band sunscreens. However, many of these studies are quite recent and included people who already used the broad-band type of sunscreens.[2]

Secondly, it was argued that because sunscreen users were generally more sun sensitive than non-users, the increased risk of melanoma observed in sunscreen users merely reflected their inherently greater risk of melanoma. The epidemiological literature describes this phenomenon as 'bias by indication'. However, this bias can likely be excluded because of the 'sunscreen-clothes paradox' found in many studies: sunscreen use and wearing of clothes when in the sun are more prevalent in sun sensitive subjects.[2,8] The study on nevi in European schoolchildren showed that during sunny holidays, an inverse correlation existed between sunscreen use and sun protection through the wearing of clothes (Fig. 1): the more sunscreens were used, the fewer clothes protected the skin against the sun. This and other studies found that while sunscreen use was associated with higher nevus counts, wearing clothing was associated with decreasing numbers of nevi.[4,5] Only one population-based case-control study examined the risk of melanoma with sunscreen use and wearing of clothes, and found a melanoma risk reduced by 52% ($P < 0{\cdot}001$) when the primary site of the tumour was usually covered with clothes during outdoor work in the summer.[9] In contrast, the melanoma risk associated with sunscreen use was 1·15 (95% CI 0·78–1·68) in subjects who used sunscreens for 10 years or more.

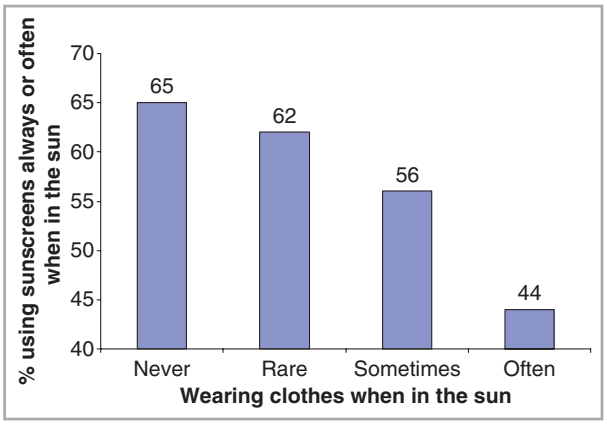

Fig 1. Correlation between sunscreen use and wearing clothes in 623 5- to 7-year-old European schoolchildren (R-square = 0·92, $P < 0{\cdot}0001$) (Ref. 4).

If wearing clothing and using sunscreen represent real barriers against the transmission of UV to the skin, then why does the former actually protect against melanoma and nevus formation, while the latter seems unable to protect against melanoma and rather increases nevus development. This paradox made credible the hypothesis that sunscreen use could be involved in nevus and melanoma occurrence.

The third hypothesis was that due to their ability to delay sunburns, sunscreen use would encourage sun exposures of longer duration; this would be especially true when sun exposure is motivated by a desire to tan or to remain in the sun for longer periods. This hypothesis was supported by the common observation that in NISE situations, sunscreen use can reduce sunburn occurrence. In contrast, in ISE situations, sunscreen use did not change the risk of sunburn.[2,8]

Sunscreen use and duration of sun exposure

Three randomized trials demonstrated that during ISE, use of relatively small amounts of sunscreen (i.e., amounts 3–4 times smaller that those used for measuring the SPF) was able to increase time spent in the sun. Two trials were conducted in France, Switzerland and Belgium with sun-sensitive volunteers 18–24 going to sunny areas for summer holidays.[10,11] These volunteers were randomized in a double blind design to receive SPF 10 or SPF 30 sunscreen. These trials showed that high SPF sunscreen extended sunbathing time by 19–25%, while there was no difference in sunburn experience and no difference in quantity of sunscreen used. Another key finding of these two trials was that as their holiday progressed, subjects using the SPF 30 sunscreen usually started sunbathing around noon, whereas those using the SPF 10 sunscreen tended to start sunbathing steadily later in the day. Hence, sun exposure duration of sun sensitive subjects engaged in ISE is limited by sunburn acquisition, and delaying sunburn occurrence leads to profound changes in sun behaviours.

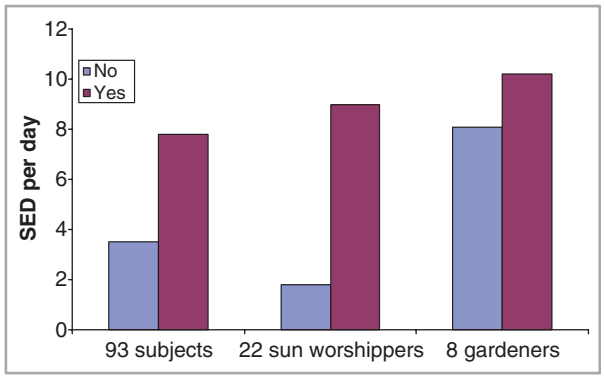

Fig 2. UV doses [in standard erythemal dose (SED) per day] received by volunteers wearing personal UV dosimeters, Denmark (Ref. 14).

The third trial took place in 2003 in a French holiday village and randomized 308 adults 18–78 years of age into three groups using sunscreen of different SPF and having different labelling.[12] Results of this trial indicated that after 1 week of use, higher SPF was associated with longer ISE duration.[7]

What about sunscreen use and sun exposure duration during NISE? The few available data suggest that in NISE situations, there is no increased duration of sun exposure associated with sunscreen use. The Australian randomized trials for prevention of squamous and basal cell carcinoma found no evidence for increased duration of time spent in the sun when high SPF sunscreen was used.[13] A Danish group with great experience in individual UV dosimetry monitored time spent in the sun and UV doses experienced during various types of outdoor activities (Fig. 2).[14] Although samples were relatively small, sunscreen use during a NISE activity like gardening did not increase the UV dose received, while among sun worshippers sunscreen use was associated with a considerable increase in UV dose received.

ISE, NISE, sunscreens and skin cancer

Three randomized controlled trials (two in Australia and one in the U.S.A.) in subjects over 50 years old, many of whom had a history of actinic skin lesions, have shown that when used during NISE, sunscreen use (moderately) decreases the incidence of squamous cell carcinoma and of solar keratoses, but not of basal cell carcinoma.[15–17]

Essentially because of intractable practical and ethical difficulties, no randomized trial has ever tested the ability of sunscreen use to protect against skin cancer and melanoma in particular during ISE situations. The trial in Vancouver, Canada tested the ability of a broad-band sunscreen to limit nevi numbers in schoolchildren.[18] It is not clear whether the Vancouver trial was representative of ISE situations. Results of this trial are difficult to interpret, as, for yet unknown reasons, all the effect of sunscreens was confined to children with high freckling. Furthermore, the statistical analysis did not adjust for nevi counts at baseline.

Epidemiological data relevant to the associations found between sunscreen use and skin cancer is summarized in the Table 1. Studies conducted during NISE situations were close to conditions encountered in laboratory experiments that demonstrated the cancer prevention properties of sunscreens, e.g., application of high doses of sunscreens, subjects eager to protect themselves from harmful effects of the sun and not attracted by tan acquisition. These laboratory experiments did not at all reflect sunscreen use during ISE situations.

These data led a Working Group convened by the IARC in 2000 to conclude that:[2]

1 Sunscreen use may decrease occurrence of SCC.
2 Sunscreen use has no demonstrated influence on BCC.
3 In ISE situations, sunscreen use may increase the risk of melanoma.

The traditional and alternative view on the biological effects of sunscreen use in humans

The traditional view is that the greater the SPF of the sunscreen actually applied onto the skin (usually 2–4 times lower than doses used for measuring the SPF), the greater the sun protection. This view schematized in Figure 3a suggests that the application of a potent sunscreen will decrease the UV

Table 1 Likely effects of sunscreen use in sun sensitive subjects during non-intentional and intentional sun exposure

	Non-intentional sun exposure	Intentional sun exposure
Examples	Outdoor professional activities, gardening, skiing, walking	Sunbathing, outdoor sport with naked trunk
Type of subjects in studies	Old adults or elderlies not sun to tan attracted, often with history of actinic skin damage	Young adults, suntan seekers
Sunburn occurence	Decrease	No difference[a]
Time spent in the sun	No change	Increase
Influence on risk of		
Squamous cell carcinoma	Decrease	No data
Basal cell carcinoma	No change	No difference or increase
Cutaneous melanoma	No data	No difference or increase

[a]The increase reported in some studies was probably due to lack of control for sun-sensitivity (ref. 7).

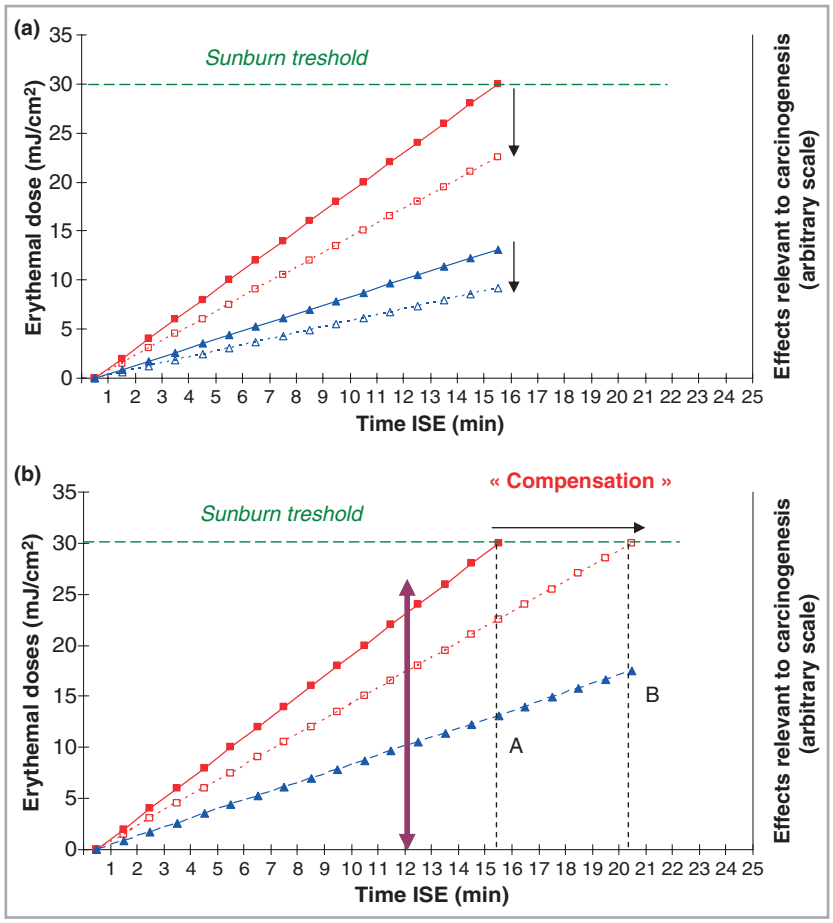

Fig 3. Schematic representation of traditional and alternative views on effects of use (continuous lines, plain squares and triangles) or no use (doted lines, open squares and triangles) of sunscreens in humans. Squares refer to sunburn occurrence according to UV dose received in mJ cm^{-2} on the left Y-axis. Triangles refer to carcinogenic effects, with an arbitrary scale of Y-axis on the right. For simplification, sunburn occurrence and carcinogenic effects are assumed to linearly increase with time spent in the sun. In this example, a sunburn threshold of 30 mJ cm^{-2} was chosen, but this threshold varies from subject to subject according to skin complexion and phototype. Black arrows indicate effects of sunscreens, and the large double arrow indicates the threshold for the alert displayed by an individual UV dosimeter.

dose delivered to the skin. The immediate consequence is the prevention of sunburn. In this case, the decrease in erythemal effect is paralleled by a proportional decrease in carcinogenic effects. This view assumes that the duration of sun exposure remains equivalent with or without sunscreen use. This traditional view mirrors the results from laboratory studies during which exposure duration parameters are controlled.

The assumption that duration of sun exposure remains equivalent with or without sunscreen use is not tenable as nothing indicates to sunscreen users that without the sunscreen, they would already be sunburned. So, the alternative view schematized in Figure 3b is based on evidence that sunscreen use will just delay sunburn occurrence but not prevent it, and lead to increased duration of sun exposure. This increased duration is sometimes labelled 'compensatory behaviour'.[2] Also, the alternative view assumes that the ability to prevent sunburns (as measured by the SPF) probably does not imply the ability to prevent melanoma or basal cell carcinoma. This view agrees with results of randomized trials on sunscreen use and sun exposure duration during ISE and also agrees with laboratory data suggesting that wavelengths other than the UVB may be involved in melanoma initiation and growth.[6,19] Extension of sun exposure duration induced by sunscreen use will result in the increase from point A to point B of the carcinogenic effects.

So, the traditional view would apply to typically UVB-induced skin lesions, including squamous cell cancer and solar keratoses. The alternative view would apply to cutaneous melanoma, mainly for melanoma occurring on usually sun protected sites such as the trunk.

Adding specific UVA filters to sunscreens is now common, and is deemed to improve their anti-cancer properties. But there is still disagreement on the standard test for evaluating their anti-UVA properties.[20] Indeed, filtering out some of the UVA may affect biological pathways other than those involved in erythema but possibly involved in skin carcinogenesis. However, because the quantity of sunscreen typically applied to the skin is small and sunlight is very rich in UVA, it is quite possible that the anti-carcinogenic defences provided by UVA filters might be overwhelmed during sunbathing in the midday sun, especially if exposure time is increased due to a high SPF. We thus do not think that the schematic view we outlined would be fundamentally different if sunscreens did or did not contain specific UVA filters. Our reasoning is supported by studies in volunteers using sunscreen of the same SPF formulated with essentially UVB filters or with essentially UVA filters.[21] No difference between the two types of sunscreens was found in their capacity to decrease UV induced DNA damage or erythema.

Sunscreen abuse

Sunscreen abuse has two complementary facets. The first is that most subjects engaging in ISE use a sunscreen in order to best take advantage of their sun exposure without, do they believe, incurring side effects, mainly sunburns. The second, less obvious facet is that sunscreen use during ISE allows sun exposure behaviors that would not be possible otherwise. The recommendation to re-apply sunscreen after a certain length of sun exposure probably represents a form of abuse.

Many studies and prevention campaigns have been conducted with the belief that recreational sun exposure, specially sunbathing, is safer when a sunscreen is used. When there is no control of sun exposure duration, that belief is questionable. So, the basic question is, 'what is most dangerous: sunbathing with or without using a sunscreen?' Until a method is found to prevent subjects unable to refrain from ISE from extending the time they spend in the sun, they should be advised not to use sunscreen but rather to let their skin adapt and set strict limits on the time they spend in the sun. This may be somewhat shocking but it follows the logic outlined in the alternative view in Figure 3b, because not using a sunscreen would prevent the stimulation of carcinogenic processes induced by unfiltered radiation.

Sunscreen abuse is encouraged by the false sense of security promoted by sunscreen advertisements, claiming or suggesting that these products protect against carcinogenic processes when used during ISE, and especially during tan acquisition. Such advertising encourages sunscreen abuse during ISE and thus contributes to increasing the risk of melanoma. This raises consumer protection issues. One day, melanoma patients could sue sunscreen makers because they were not warned against excessive sun exposure induced by sunscreen use and rather lulled by messages promoting sunscreen use during sunbathing as a way to safely acquire a nice, deep tan. This is not science fiction as in 2006 in the U.S.A., a class action suit was filed at the Los Angeles Superior Court for misleading advertising and fraudulent misrepresentation in the labelling of sunscreen bottles that, according to the plaintiffs, did not correctly indicate the hazards associated with the absence or low UVA blocking capacity of sunscreens.[22]

How to avoid sunscreen abuse and its deleterious consequences?

Trying to discourage tan acquisition and deliberate sun exposure during the holidays is not very cost effective, especially among teenagers and young adults.

Consumer information on sunscreens should better reflect current knowledge of potential health hazards associated with their use during ISE. Cosmetic companies should not pretend that 'safe tanning' exists when using sunscreen.

Sunscreen bottles could bear messages on the hazards associated with ISE, mainly the longer stay in the sun that may end up in sunburn and the possibility of higher melanoma risk. However, such labelling of sunscreen products is not likely to be well understood, especially if on the other hand, it is rightly claimed that sunscreen use during non-intentional sun exposure may decrease skin cancer risk. Sunburns would remain frequent and no one would understand why lotions preventing sunburns during NISE would be discouraged during ISE.

A wiser approach would be to avoid excess sun exposure thanks to information on individual UV exposure. Referring back to Figure 3b, if a subject engaged in ISE is informed after say 12 min that he or she is nearing his or her specific sunburn threshold in the absence of sunscreen use, and if that subject covers up or moves to a shaded area, then the erythemogenic UV dose and the carcinogenic effect would be lower than if no information was provided.

Practically speaking, UV dosimeters could inform sunscreen users engaged in ISE. The dosimeter could be worn as a watch [22] or inlayed in the caps of the sunscreen bottle. Indeed, dosimeters should be calibrated according to individual sun sensitivity in the absence of sunscreen use. The technology for cheap individual UV dosimeters already exists that could be adapted for controlling sun exposure duration.[23–25]

This approach would reconcile sunscreen and educational efforts. If feasible such a method would transform an ISE situation into a NISE situation and sunscreen use could then decrease skin cancer risk, and probably also melanoma.

Users of dosimeters and sunscreens will surely complain that tan acquisition is longer, and that they would like to stay longer in the bright sunshine than allowed by the dosimeter, but at the end of the day, subjects complying with the method will understand their health benefit.

Testing this approach may first be done though randomized trials on sunburn occurrence comparing sunscreen users vs. sunscreen and dosimeter users. Normally, the latter group should experience fewer sunburn episodes. A second, test would be the assessment of changes in nevi count and shape on the trunk of young adults spending holidays in sunny areas, again with randomization of sunscreen alone vs. sunscreen combined with dosimeters.

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Chapter 4: Childhood sun exposure

Background as of 1992

In the 1970s and 1980s, studies of migrants in Australia, New Zealand, Israel and the USA showed that subjects born in sunny areas have a higher risk of melanoma and to die from this cancer than subjects who migrated to these sunny after birth (reviewed in Whiteman et al, 2001).

Together with studies on childhood sunburns, studies in migrants provided the most compelling epidemiological evidence to the 1992 Monograph for sunlight being causally associated with melanoma. They also corroborated the notion that childhood may be the most critical period for the occurrence of sun-induced biological events implicated in the genesis of melanoma.

However, a number of questions remained unanswered, such as the influence of sun exposure at different periods of life on melanoma risk. For instance, melanoma is very rare before 20 years of age, so it needs to be established how sun exposure in early life could influence melanoma occurrence in adult life.

We performed two studies on childhood sun exposure and nevus count or melanoma. The first study was linked to the 1992-93 case-control study in Belgium, France and Germany (*Autier et al, 1994*). The second study was associated with the large quantity of data we had gathered during the study on Sunscreen use, wearing clothes and number of nevi in 6 to 7-year-old European children (*Autier et al, 1998a*).

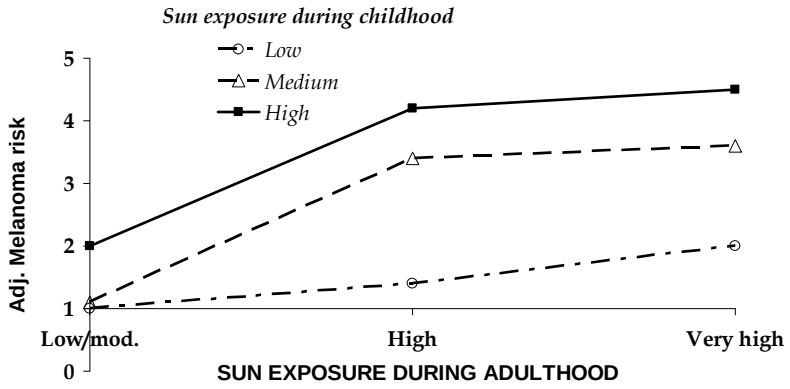
Overview of studies on childhood sun exposure and melanoma

A more detailed analysis of the 1992-93 case-control study showed that melanoma risk decreased with decreasing sun exposure (including fewer sunburns) and increasing sun protection during childhood (*Autier et al, 1996*).

A further analysis showed that melanoma risk was much greater in European subjects who were born in or spent part of their life in much sunnier areas (*Autier et al, 1997a*). Younger age at migration to sunnier areas had a stronger effect on melanoma risk than duration of residence in these areas.

We then examined the respective contribution of sun exposure during childhood and during adult life, using the data collected on sun exposure and sun protection during these two periods of life (*Autier & Doré, 1998*). The main finding was that regardless of the level of sun exposure as an adult, the development of a melanoma appeared unlikely in the absence of significant sun exposure during childhood (Figure 4.1). In addition, sun exposure during adulthood was mandatory for the development of melanomas initiated by heavy sun exposure during childhood.

Fig. 4.1 -Melanoma risk and sun exposure during childhood and adulthood (Autier & Doré, 1998)



These results reinforced the notion that being heavily exposed to the sun during childhood would be a necessary step for melanoma genesis. They also suggested that epidemiological studies underestimated the importance of sun exposure in melanoma occurrence because of the difficulty for studies in adults of all ages to explore accurately the sun exposure habits before 20 years of age.

Overview of studies on childhood sun exposure and nevus development

As mentioned in Section 3, the best single predictor of one's chance of being diagnosed with a melanoma is the number of nevi of any size and the number of large or atypical nevi. The study on nevi in schoolchildren amassed detailed data on past sun exposure and included the number, location and duration of holiday periods between birth and the study and any sunburn history.

Studies on anatomic distribution of nevi in children and of melanoma in adults helped greatly in understanding the complex aetiology of this cancer (e.g., Fritischi et al, 1984; Elwood & Gallagher, 1998). We first performed an analysis of body-site distribution of nevi in schoolchildren using statistical methods similar to those used for adult melanoma. We found that body site distribution of nevi in children correlated fairly well with body site distribution of melanoma in adults (*Autier et al, 2001a*).

We then examined determinants of nevus counts in children using statistical methods allowing multiple adjustments for the various host characteristics and sun exposure factors involved in nevus development. We found that the sharp gender differences in body site distribution of adult melanoma are already visible for nevi in children (***Autier et al, 2004***). However, the nevus density in young girls was lower on lower limbs than on other body sites, although girls tended anyway to have more nevi on the lower limbs than boys (*Autier et al, 2003a*).

There were about 20 times less nevi ≥ 5mm than nevi 2 to 4.9 mm. Like in adults, three-quarters of large nevi were located on the trunk. Although the number of nevi 2 to 4.9 mm was a strong predictor of numbers of nevi ≥ 5mm, there was no gender difference in the body site distribution of large nevi.

The natural propensity to burn or to tan when in the sun (the skin phototype), and pigmentary traits (the eye colour) were risk factors for higher numbers of small nevi but not for numbers of large nevi. These host factors had more influence on small nevi counts than sun exposure factors. We further found that the number and duration of holiday periods were moderately associated with increasing numbers of nevi 2 to 4.9 mm, but not with nevi ≥ 5mm (*Autier et al, 2003a*). In contrast, sunburn history and holiday location latitudes were not associated with numbers of nevi 2 to 4.9 mm, but were well associated with nevi ≥ 5mm. Sunburns and latitude are known to be more associated with UVB than with UVA (IARC, 1992). We thus hypothesised that wavelengths other than the UVB could be involved in the development of small nevi in children, while radial growth phase leading to large (and possibly atypical) nevi was inducible by exposure to significant doses of UVB.

Epidemiological or human experiment data supporting our findings

1/ Our study in subjects who spent part of their life in sunnier areas prompted the review by D Whiteman et al on migrations and melanoma (Whiteman et al, 2001) in which they confirmed that both melanoma incidence and mortality were higher when migration took place at young ages than if it took place at older ages. According to Whiteman et al (2001) our study on migration from "high to low'' ambient sunlight "provided the most persuasive evidence that high levels of sun exposure in childhood are associated with increased risks of melanoma, notwithstanding any additional effects of exposure in later life".

2/ The findings on determinants of small and large nevi in schoolchildren were consistent with studies in twins showing that genetic factors would account for the majority of the variability in numbers of nevi < 5mm in diameter but not for the variability in numbers of nevi ≥ 5 mm (dysplastic or not) whose development would depend more on environmental factors (Easton et al, 1991; Bataille et al, 2000; Wachsmuth et al, 2001; Zhu et al, 1999).

3/ Our results on body site distribution of nevi 2 to 4.9 mm and nevi ≥ 5 mm in children were similar to studies in Australia, Canada and Sweden (McLennan et al, 2003; Gallagher et al, 1990; Harrison et al, 1999; Synnerstad et al, 2004; Valiukeviciene et al, 2007). All these studies found that the anatomic distribution of nevi in children and young adolescents was close to that of melanoma in adults, except for female lower limbs. In fact, nevus numbers on female lower limbs rise fast during adolescence (Nichols 1973; Gallagher et al, 1990) and around 18 years of age, nevus density on female lower limbs surpasses that of other body sites. Our additional contribution was that that young girls tended anyway to have more nevi on the lower limbs than young boys (*Autier et al, 2003a*).

Epidemiological or human experiment data challenging our findings

1/ We found no study challenging our findings on migrants or on the necessity of sun exposure during both childhood and adulthood for melanoma occurrence.

2/ We found no study challenging our findings on nevus counts and nevus anatomic distribution.

Sex Differences in Numbers of Nevi on Body Sites of Young European Children: Implications for the Etiology of Cutaneous Melanoma

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Abstract

Background: **Since 1950, the greatest increase in cutaneous melanoma incidence in fair-skinned males took place on the trunk and on the head and neck, whereas in females, it took place on the limbs, mainly on the lower limbs. We examined the influence of sex on numbers and size of nevi on different body sites in white European schoolchildren.**

Methods: **Information about each holiday period since birth to interview was recorded from parents of six hundred twenty-eight 6- to 7-year-old children in four European cities (Brussels (Belgium), Bochum (Germany), Lyons (France), and Rome (Italy)). Number and anatomic location of small (2-4.9 mm) and large (≥5 mm) nevi and individual susceptibility to sunlight were independently assessed.**

Results: **After adjustment for host characteristics, sun exposure, and sun protection habits, males had 7% [95% confidence interval (95% CI), −7 to 19] more small nevi than females. However, compared to females, numbers of small nevi were increased by 17% (95% CI, 1-31) on the head and neck and by 16% (95% CI, 2-27) on the trunk and shoulders. In contrast, in males, the number of small nevi on upper limbs was decreased by −5% (95% CI, −26 to 13), and on lower limbs by −8% (95% CI, −34 to 13). The number of large nevi was 6% higher in males than in females (95% CI, −26 to 30).**

Conclusions: **The sex differences in small nevus distribution in schoolchildren reflect the sex differences in the anatomic distribution of melanoma in adults. Sex differences in sun exposure behaviors, dressing, and clothing would just add their effects to the sex-dependent inherited propensity to develop nevi on a given body site. These results reinforce the hypothesis by which childhood would be a decisive period for the occurrence of sun-induced biological events implicated in the genesis of cutaneous melanoma.** (Cancer Epidemiol Biomarkers Prev 2004;13(12):2003–5)

Introduction

In most fair skinned populations, the incidence of cutaneous malignant melanoma (melanoma) has considerably increased in the past 50 years, most probably because of the increase in intermittent sun exposure that took place after World War II (1). In many populations, the incidence of melanoma is slightly higher in females than in males. But gender differences in melanoma incidence are more pronounced when anatomic sites are considered: in males, the greatest increase in melanoma incidence over time took place on the trunk and the head and neck, whereas in females, the greatest increase in incidence over time took place on the limbs, mainly the lower limbs (2-4).

The number of nevi is the best predictor of melanoma occurrence in adults (5). The increase in nevus density (i.e., the number of nevi per unit of skin surface) is maximal before 15 years old (6-8). After nevus density stabilization at around 30 to 35 years old, nevus frequency steadily decreases with age. Nevus development is strongly genetically determined, but sun exposure would be necessary for complete phenotypic expression of the nevus genotype (9, 10).

Little is known of association between gender and nevus development. In this work, we examined the influence of sex on numbers and size of nevi on different body sites in white European 6- to 7-year-old children.

Methods

The study design has been described in a previous report (11). Briefly, 6- to 7-year-old Caucasian children were recruited between October 1995 and February 1997 in elementary schools of Brussels (Belgium), Bochum (Germany), Lyons (France), and Rome (Italy).

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Total Body Nevus Count. In each city, a physician trained for the recognition of skin pigmented lesions examined the entire skin of children in the primary schools. The scalp, the genital area, and the buttocks were not examined. Counting of nevi was done using transparent plastic slides pierced with 2- and 5-mm holes. We thus directly distinguished nevi with dimensions in the range 2 to 4.9 mm (hereafter referred as small nevi) from nevi with dimensions ≥5 mm (hereafter referred as large nevi).

Statistical Analysis. Examination of the influence of gender on nevus counts took into account the influence of other host and environmental factors that could be associated with gender. Details of the analysis procedures have been reported in previous article (12). In brief, two Poisson regression models were constructed, one having as end point the number of small nevi, and the other the number of large nevi. For small nevi, models were applied separately to four body sites (trunk and shoulders, upper limbs, lower limbs, and head and neck).

Poisson regression models for small nevi included variables related to host characteristics and sun exposure or sun protection habits. Models for large nevi were further adjusted for number of small nevi. A result was labelled as statistically significant if zero was not comprised in the 95% confidence interval.

Results

Parents who agreed to participate represented 682 (55%) out of the 1,234 apparently eligible children approached. Fifty-one children were excluded from the study because the child was not of Caucasian origin, or the skin examination was not done (e.g., the child was not willing to be examined), or the parents could not be reached for the interview. Three children were further excluded because of missing data in adjustment variables. The final sample for statistical analysis comprised 628 children (319 boys and 309 girls).

The median was 6 nevi ≥2 mm per child (range, 0-77). Detailed body distribution of nevi has been published elsewhere (13). In brief, of 5,933 nevi, 5,638 (95%) were small nevi (i.e., with one dimension between 2 and 4.9 mm), and 295 (5%) were large nevi (i.e., with one dimension ≥5 mm). Thirty-nine percent of small nevi were located on the trunk and shoulders, compared with 69% of large nevi, implying that large nevi are more likely than small nevi to develop on trunk and shoulders than on other body sites.

Table 1 shows that the total of small nevi was similar for boys and girls. In males, small nevi were somewhat more numerous on trunk and shoulders, and on head and neck, but less numerous on limbs. Large nevi were more numerous in males.

After multiple adjustments, small nevus numbers on trunk and shoulders and on the head and neck became significantly more associated with male than with female gender. A positive association (although not significant) with female gender was found in the upper limbs and in the lower limbs.

Apparently, males had more large nevi than females. But because (i) the number of small nevi is a strong predictor of the number of large nevi (12) and (ii) that most large nevi are located on the trunk and shoulders (13), adjusting for small nevi decreased the apparent association between male gender and the number of large nevi. No gender difference was apparent when the analysis of large nevus numbers was restricted to the trunk and shoulders (data not shown).

Discussion

Our study assessed the predictors of nevus counts in European young children according to body site, with multiple adjustments for host characteristics, sun exposure, and sun protection habits. Boys ages 5 to 6 years had significantly more small nevi (2-4.9 mm) on the back and shoulders, and on the head and neck than girls of same age. In contrast, in girls, there was a tendency for more small nevi on the limbs. Our results are comparable to those from studies in Australian adolescents and schoolchildren that found significantly larger numbers of small nevi on the back (14, 15) and on the head and neck (14) of males, whereas larger number numbers of small nevi were observed on female lower limbs (15). Alike the Australian study in schoolchildren (15), we found a larger number of large nevi in boys than in girls, but because the number of large nevi is strongly linked to the

Table 1. Numbers of nevi on body sites of 628 European children 6 to 7 years old

Body site	Males (n = 319)		Females (n = 309)		% Difference males/females		
	Mean	Range	Mean	Range	Unadjusted*	Adjusted†	95% Confidence interval
Nevi, 2 to 4.9 mm (n = 5,638)							
All sites	9.1	0-65	8.9	0-77	2	7	−7 to 19
Head and neck	1.5	0-16	1.3	0-9	14	17	1-31
Trunk and shoulders	3.7	0-25	3.2	0-29	13	16	2-27
Upper limb	1.9	0-3	2.1	0-3	−9	−5	−26 to 13
Lower limb	1.9	0-2	2.2	0-3	−16	−8	−34 to 13
Nevi, >5 mm (n = 295)	0.5	0-10	0.4	0-8	19	6‡	−26 to 30

NOTE: Buttocks, genital area, and scalp not included. Surface of selected body areas represent 86.5% of total body surface area.

*No unadjusted ratio reached statistical significance.

†Mean adjusted difference between males and females, with females being the reference category, expressed in %, and 95% confidence interval. % differences are derived from coefficients of a Poisson regression models, including variables related to sun exposure, the skin phototype, the eye color, the average number of holiday periods, the average total duration of sun exposure, the average difference in latitude, the number of sunburn episodes, the study place, the average wearing of trousers and shirt, the average wearing of hat, and the average sunscreen use during holidays.

‡Same model as for nevi 2 to 4.9 mm, with inclusion of numbers of nevi 2 to 4.9 mm as a continuous variable.

number of small nevi, adjustment on small nevus numbers cancelled most of the gender influence on large nevus counts.

The gender difference we found in numbers of nevi 2 to 4.9 mm according to body site in school children is similar to the gender difference in body site distribution of melanoma found in adults (16-18). Studies with the Swedish Cancer Registry showed that before 20 years old, melanoma occurrence is more frequent on upper and lower limbs in females, whereas in males, it is more frequent on the trunk (19).

For explaining the gender difference in anatomic distribution of melanoma, gender differences in sun exposure behaviors and in dressing and clothing styles have been evoked (e.g., longer hair in females, or wearing of miniskirt by women versus pants by males; ref. 16). However, previous reports on data used in this study showed no significant gender difference in sun exposure, sunburn history (during and outside holiday periods), sun protection habits, sunscreen use, and wearing of clothes when in the sun (11, 12, 20). Moreover, that explanation cannot address the substantial gender differences observed on the trunk and shoulders.

A study done in Canadian Hutterite children found similar gender-specific differences in the body site distribution of nevi (21). The traditional religious costume of Hutterite children protects them from sun exposure, and thus in this population, gender difference in clothing or in sun exposure habits can hardly explain gender differences observed in body site nevus distribution.

Our results suggest that anatomic location of melanoma diagnosed during adult life would be already determined during the first years of life. Sex differences in sun exposure behaviors, dressing, and clothing would just add their effects to the inherited proneness to develop nevi on a given body site.

Studies on migrants have provided the most compelling evidence that childhood was a decisive period for sun-induced biological lesions involved in the genesis of melanoma (22). The results of this study reinforce the likelihood of the childhood hypothesis. The biological lesions acquired at these ages would survive during all life.

The numbers of small nevi and of large nevi are independent predictors of melanoma occurrence (23, 24). The fact that we found gender to be a predictor of the body site development of small, but not of large nevi, supports the hypothesis by which small nevi and large nevi would be related to different biological events involved in the genesis of melanoma.

The genetic information is identical in all melanocytes of an individual, and a nevus is a monoclonal expansion of a single melanocyte (25, 26). From a study on body site variations in benign melanocytic nevi adjacent to melanoma, Green (27) proposed the hypothesis of site-specific susceptibility to sunlight and to malignant transformation. Studies in European and in Australian children confirmed the site-specific differences in proliferation potential of melanocytes (13, 15). We further hypothesize that the likelihood for a melanocyte situated in a given anatomic site to develop into a small nevus is also influenced by gender. Thus, whatever happens in sun exposure in later life, sex-linked genetic factors acting during early life influence the likelihood that a melanoma would occur on a given body site.

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Section 5: Epidemiological evidence that UVA is involved in the genesis of melanoma

Background

This Section exploits parts of our works suggesting that the UVA may be involved in melanoma occurrence. The article ***Autier et al (2011)*** details arguments derived from studies on sunbed and sunscreen use. We present in this Section additional arguments from studies on nevi in children and unpublished results from our melanoma-sunbed studies.

Since about thirty years, the role of UVA and UVB in the genesis of melanoma is the centre of a controversy. Nearly all UV sources are a mixture of both UVA and UVB and human exposure to pure UVA or UVB sources is rare.[1] So why have scientific activities and public health discussions been so involved with trying to distinguish damages specific to UVA and UVB? The main reason is that the quest for establishing the biological effects specific to UVA and UVB has considerable public health and economic implications.

On the public health side, if UVB is the wavelength involved in melanoma occurrence, then sun protection should aim at maximising the reduction in the amounts of UVB reaching the skin; this philosophy is at the origin of the manufacturing of high SPF sunscreens. If UVA is the relevant wavelength, then sunscreens prepared with UVB filters may not be protective and indoor "UVA-tanning" is a real health hazard. The glass blocks the UVB but not the UVA. Hence, staying behind a glass would not be that protective if UVA is involved in melanoma genesis. If both the UVA and UVB are implicated in melanoma, sun protection needs to target reducing exposure to the entire UV spectrum.

On the economic side, the scientific activities surrounding UVA and UVB research has been heavily influenced by the antagonism between the sunscreen and the indoor tanning industries. The sunscreen industry considers UVA as the main culprit for melanoma occurrence, explaining the failure of UVB-sunscreens to protect against this cancer. In contrast, the indoor tanning industry considers UVB as the carcinogenic wavelength and UVA having no demonstrated carcinogenic properties in humans.

[1] Examples of sources of pure UVB are TL2 lamps for phototherapy of psoriasis. Examples of pure UVA sources are lamps used for PUVA treatments of severe psoriasis.

We did not measure UV wavelengths in our studies, with the exception of the second randomised trial on sunscreen use and sun exposure duration (Autier et al, 2000c). Exposure data collected by epidemiological studies are thus by no means reflecting exposure to pure sources of UVA or UVB. However, some results of our studies can inform on the type of wavelength possibly involved in nevus and melanoma occurrence. Indeed, wavelength boundaries in our hypotheses may be different than ranges defined by physicists and in the remainder of this section, the terms "UVA" and "UVB" are purely indicative of the wavelength range likely to be associated with a specific epidemiological result.

Five lines of results suggest a role of UVA in the genesis of melanoma, the first three of which are detailed in ***Autier et al, 2011***.

First, the association between artificial "UVA-tanning" and melanoma provides evidence that exposure of sun-susceptible individuals to high UVA fluxes can trigger melanoma. Indeed, some UVB is always present in the UV spectrum of sun-tanning lamps but the genuine characteristics of the majority of modern canopy-like UV-tanning units is to deliver UVA dosages that are much higher than what is delivered, for example, by the summer midday sun on a Mediterranean beach.

Second, the raised melanoma risk associated with increased ISE duration induced by sunscreen use would be due to greater exposure to the UVA radiation (***Autier 2009***; ***Autier et al, 2011***).

Third, high SPF sunscreens enabled subjects to withstand high UVB fluxes, which in turn probably led to greater exposure to high UVA fluxes (***Autier et al, 1999b;*** *Autier et al, 2000c****; Autier et al, 2011***).

Fourth, the randomised trial during which individual UVA and UVB dosimeters were used (*Autier et al, 2000c*) revealed that during their holidays, volunteers in the SPF 30 group had greater accumulation of UVA over the entire holiday period, but higher exposure to UVB during days with sunbathing. Retrospectively, we consider that these seemingly contradictory results are attributable to dosimeters measuring UVA and UVB exposure but not the amounts of UVA or UVB passing through the sunscreen layer and reaching the skin. As high SPF sunscreens are probably better at blocking UVB than UVA and because sunburn experience was identical in both SPF groups, we can

hypothesise that over the entire holiday period, amounts of UVB that reached the skin were similar in both groups, whilst amounts of UVA that reached the skin were higher in the SPF 30 group.

Fifth, we found sunburn history and lower latitude holidays were associated with large nevi (≥5mm) in children but not with small nevi (2 to 4.9 mm) (Autier et al, 2003a). In contrast, quantities and durations of holidays were associated with numbers of small but not of large nevi. UVB is approximately one thousand times more potent than UVA in triggering sunburn (IARC, 1992). UVA and UVB fluxes reaching the earth's surface increase with decreasing latitude but UVB increases more rapidly than UVA fluxes. Hence, latitudinal differences reflect more differences in UVB than in UVA fluxes (IARC, 1992). These results suggest that the UVB would be the main trigger of the radial growth phase of nevi, leading to their enlargement and probably also to acquisition of clinical features of "atypia". UV wavelength other than the UVB, i.e., the UVA, would be involved in the initial steps triggering nevus formation.

We view these five sets of results as providing indirect evidence that UV wavelengths in the UVA range might be involved in the genesis of melanoma.

The effect of sunburn and of latitudinal differences between place of residence and holiday locations indicate that the radial growth of nevi would compare with animal experiments that showed the capacity of UVB to trigger nevus or melanoma-like skin lesions in young suckling nude mice or in human newborn foreskin grafted in mice. The key question is to establish what triggers initiation of the vertical growth phase (VGP). Animal studies favour the UVB radiation hypothesis but it still needs to be proven that the UVB can trigger potentially deadly melanoma in humans.

Are UVA-induced melanomas less life threatening?

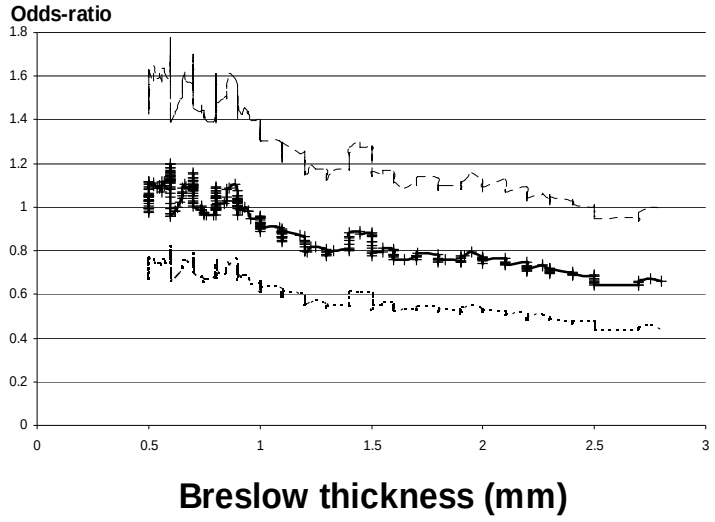
The sunbed-induced melanoma epidemic we described in Iceland developed without concomitant increase in melanoma mortality. This major discrepancy between incidence and mortality suggests that the rapid increase in incidence in the 1990s was confined to melanoma of limited capacity to disseminate in distant organs (***Autier et al, 2011***).

The European multicenter case-control of 1999-2001 (*Bataille et al, 2005*) provided additional clues to the Icelandic observations. The Breslow thickness is the measure of the vertical growth phase of a melanoma, i.e. the length of the

tumour that has invaded the dermis. The Breslow thickness is a strong predictor of survival - the thicker a melanoma, the greater the probability of distant metastases in lymph nodes or in distant organs and thus the greater the likelihood to die from it (Balch et al, 2009). Because of a multiplicity of biases (see section 2), this European multicenter could not conclude on existence or absence of an association between sunbed use and melanoma. Figure 5.1 displays an intriguing unpublished statistical analysis: the thicker the melanoma, the lower the risk associated with sunbed use. In the light of the Icelandic melanoma epidemic, we now interpret the Figure 5.1 as an indication that melanoma associated with "UVA-tanning" are generally thin.

Fig. 5.1 - Risk of being diagnosed with thin or a thick melanoma according to past sunbed use (European Multicentre study 1999-2001, unpublished data)

Odds-ratio bootstrap (1000 simulations per point) of melanoma risk associated with sunbed use according to Breslow thickness, adjusted for sex and for age. Odds ratios are in bold and dotted lines represent the 95% CI.



The UVA hypothesis and melanoma incidence and mortality

Melanoma incidence is still on the rise in most light-skinned populations, while mortality stabilised in the 1980s and 1990s and even started to decrease slightly, mainly among younger female subjects (particularly in the Nordic countries, Australia and USA) (Giles et al, 1996; *Severi et al, 2000*; de Vries et al, 2003; Linos et al, 2009;). The Iceland epidemic would represent an extreme example of the discrepancy in incidence and mortality trends. The UVA hypothesis for indolent invasive melanoma could partly explain the persistent rise in incidence observed in most light-skinned populations, without concomitant rise in mortality. Sunbed and sunscreen use, as well as recommendations to prefer sun exposure outside

hot hours, would lead to a "UVA-shift" in UV exposure that would result in increasing numbers of nevi, in situ melanoma and thin invasive melanoma having little potential for distant dissemination.

Epidemiological or experimental data supporting our findings

1/ Ecological studies (e.g., Moan et al, 1999) have found that country-specific incidence of non-melanoma skin cancer correlated with the UVB latitude gradient. However, these studies found that melanoma incidence correlated better with the UVA latitude gradient than with the UVB latitude gradient. These data proceeding from ecological considerations were considered as speculative and not at all capable to control for the multiple confounding factors possibly involved in these relationships.

2/ An experiment on Xiphophorus fish by D Setlow and co-workers showed that UVA was as effective as UVB in triggering non-metastasising melanomas in the fish (Setlow et al, 1993). This unique experiment has fuelled the UVA/UVB controversy during nearly two decades. In 2009, the same experiment was repeated, using a much larger number of Xiphophorus fish in stringently controlled experimental conditions (Mitchell et al, 2010). It showed no impact of UVA on melanoma development in the fish

3/ In vitro data have accumulated over the recent years on the capacity of the UVA to induce DNA mutations and affect DNA repair, immune function, cell integrity, cell cycle regulation, and other critical biological functions [e.g., Ridley et al, 2009; Rünger & Kappes, 2008; Mouret et al, 2006; Petra et al, 2009; von Thaler et al, 2009). These studies showed that the carcinogenic mechanisms of UVA and UVB differ but sometimes overlap.

Epidemiological or experimental data challenging our findings

1/ Numerous experiments failed to show that irradiation of animals with UVA could trigger a tumour resembling a human nevus or melanoma (reviewed in Zaidi et al, 2008, and summarised in ***Autier et al, 2011***). An important finding of animal experiments is the greater vulnerability of newborn animals or of human skin from babies to carcinogenic effects of UVB. In contrast, UVB irradiation of adult animals or on skin from adult humans has a very low ability to induce melanocytic lesions (Noonan et al, 2001; Berking et al, 2002) The overall concern

regarding these experiments is to establish how their results apply to humans. The bare human skin is very different from rodent skin and laboratory experiments cannot reproduce the complex human sun behaviours.

Articles displayed as part of this section:

Autier P, Doré JF, Eggermont AMM, Coebergh JW. Epidemiological evidence that the UVA radiation is involved in the genesis of cutaneous melanoma. *Curr Opinion Oncol* 2011; 23:189–196.

Epidemiological evidence that UVA radiation is involved in the genesis of cutaneous melanoma

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Purpose of review

Epidemiological data have contributed to the classification in 2009 of the full ultraviolet (UV) radiation spectrum as carcinogenic to humans. We reviewed the epidemiological evidence that UVA could be involved in the genesis of cutaneous melanoma.

Recent findings

Use of artificial UV tanning devices (sunbeds) consists mainly of repeated exposure to high UVA doses. Epidemiological studies published over the last years confirmed the association between sunbed use and melanoma. Sunbed use is the most probable cause of an epidemic of melanoma that took place in Iceland from 1990 to 2006. The four-fold increase in melanoma incidence was not followed by an increase in melanoma mortality. Sunscreens were primarily devised for the prevention of sunburn, and UVB is the wavelength causing most sunburns. All observational studies and randomized trials show that sunscreen use may extend sun exposure intended for getting a tan, while it does not necessarily decrease sunburn occurrence. Sunscreen use for tan acquisition would thus lead to similar exposure to UVB and greater exposure to UVA, which could explain the slightly higher melanoma risk often found among sunscreen users.

Summary

UVA could be involved in the occurrence of nonlife-threatening melanoma. The increasing use of sunbeds and of sunscreens may partly explain why melanoma incidence increases in most light-skinned populations without concomitant increase in mortality.

Keywords

indoor tanning, melanoma, sunscreens, ultraviolet radiation

Curr Opin Oncol 23:189–196

1040-8746

Introduction

The burden of melanoma is still rising in most light-skinned populations. There is now a large body of scientific evidence that the ultraviolet (UV) wavelength is the main environmental cause of skin cancer, including melanoma. In 2009, the International Agency for research on cancer classified the full UV spectrum [including the UVA (>315–400 nm), UVB (>280 to 315 nm) and UVC (200–280 nm)], as well as artificial UV tanning devices (sunbeds) as carcinogenic to humans (group 1 carcinogens) [1•]. In support of this classification, the full sequencing of the genome of a malignant melanoma showed that the dominant mutational signature in melanoma cells reflects DNA damage due to UV light exposure [2••]. However, the UV-induced biological mechanisms critical for initiating the development of this potentially life-threatening cancer are still largely unknown.

The UV radiation reaching the Earth's surface is composed of 2–10% UVB and of 90–98% UVA. By the end of the 1980s, the carcinogenic properties of UVB were already well documented and it was recognized as the main environmental factor involved in squamous cell carcinoma (SCC) [3]. Basic research data have accumulated over the recent years on the capacity of UVA to induce DNA mutations and affect DNA repair, immune function, cell integrity, cell cycle regulation, and other critical biological functions (e.g., [4–6,7•]). These studies showed that the carcinogenic mechanisms of UVA and UVB differ but sometimes overlap.

Despite basic research findings, animal experiments failed to show that irradiation with UVA could trigger a tumour resembling a human nevus or melanoma (reviewed in [8]). An experiment on Xiphophorus fish by Setlow *et al* [9]. showed that UVA was

as effective as UVB in triggering nonmetastasizing melanomas in the fish. This unique experiment has fuelled the UVA/UVB controversy during nearly two decades. In 2009, the same experiment was repeated, using a much larger number of Xiphophorus fish in stringently controlled experimental conditions [10]. It showed no impact of UVA on melanoma development in the fish.

The overall concern regarding these experiments is to establish how their results apply to humans. The bare human skin is very different from rodent skin and laboratory experiments cannot reproduce the complex human sun behaviours.

Epidemiological data have contributed to the IARC classification of the full UV range and of artificial UV devices as carcinogenic to humans. In this paper, we review the evidence provided by epidemiological studies that UVA can be involved in the genesis of cutaneous melanoma. We also present a hypothesis as to the type of melanoma induced by UVA, and how this hypothesis may explain epidemiological features of this cancer.

Sunbed use is associated with melanoma occurrence

The majority of modern canopy-like UV-tanning units are equipped with low-pressure fluorescent lamps with a spectrum mainly emitting in the UVA range plus some UVB (which is necessary for inducing a deep long-lasting tan). High-pressure lamps producing large quantities of long-wave UVA (>335–400 nm) per unit of time are also marketed. Sunbeds deliver UVA dosages that are 5–15 times higher than what is delivered by the summer mid-day sun on a Mediterranean beach. Compared with the summer midday sunlight, these machines emit much higher fluxes of UVA and lower fluxes of UVB.

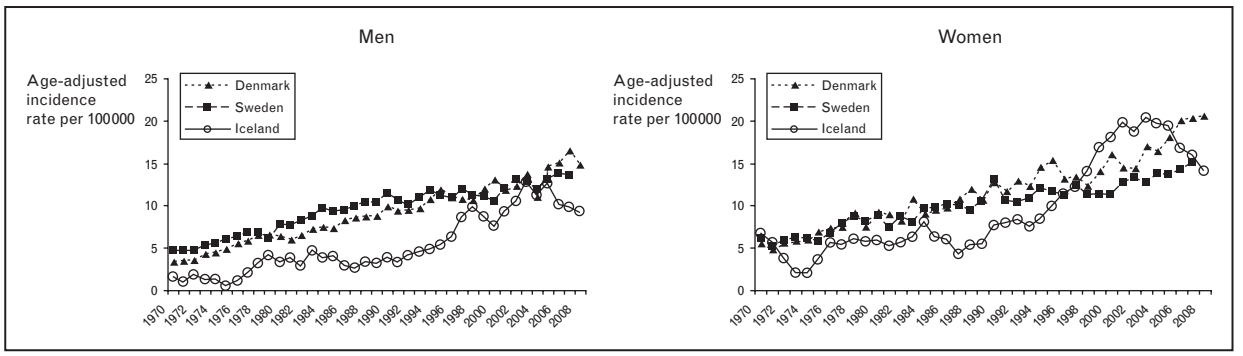
Observational studies

Observational studies from 1994 to 2005 have documented that exposure of sun-susceptible individuals to sunbed can trigger melanoma, mainly when this exposure started before 30 years of age [11••,12]. Epidemiological data published after the IARC report of 2006 [11••] further documented the links between artificial UV tanning and melanoma. They included three large case–control studies in the USA [13•,14,15], the prospective U.S. Nurse's Health Study [16] and the confirmation of previous results of the Norwegian–Swedish cohort study [17••]. Even in Australia where sunshine is abundant, a case–control study organized within the Australian Melanoma Family Study found sunbed use to be associated with increased risk of early-onset melanoma [18].

The melanoma epidemic in Iceland

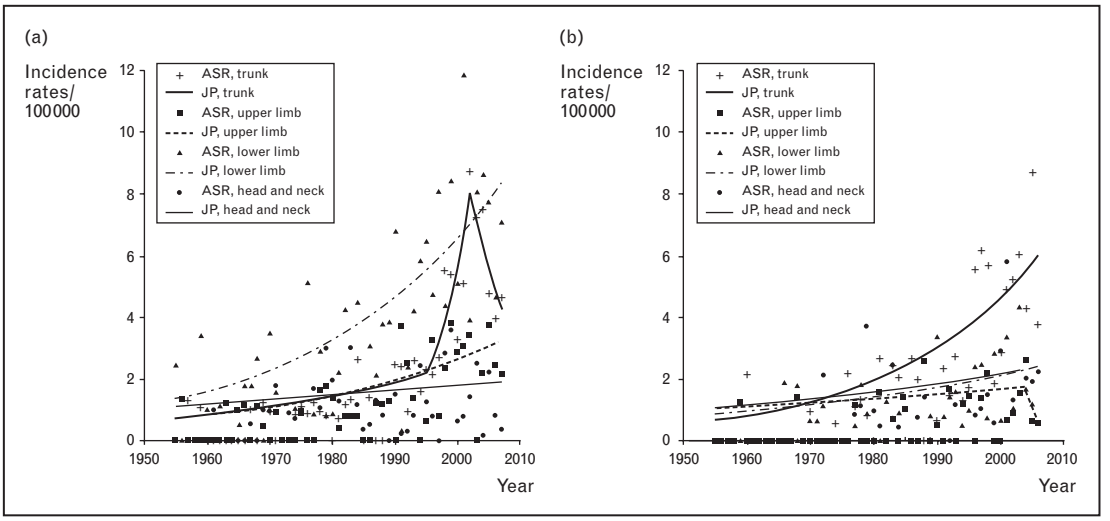
A few years ago, we predicted that melanomas associated with solarium use would be preferentially localized to anatomic sites that are usually only intermittently sun exposed such as the trunk [19]. This phenomenon should be mainly noticeable among women because sunbed use allows unrestricted UV exposure of the trunk. Iceland is a Nordic country situated at 64–66° north latitude where bright, sunny days are rare. In a collaborative work with the Iceland Cancer Registry and Icelandic dermatologists, we described an epidemic of melanoma starting in 1995 [20••]. Before 1995, the melanoma incidence in Iceland was lower than in Denmark and Sweden (Fig. 1) [21]. In the 1990s, it started to rise steeply and after 2000, it surpassed the incidence in other Nordic countries. This phenomenon was mainly noticeable among women. A particular feature of that epidemic was that it mainly concerned melanoma occurring on

Figure 1 Incidence of cutaneous melanoma in Iceland, Denmark and Sweden, 1970–2008



Age-adjusted (World Standard population) incidence of cutaneous melanoma in Iceland, Denmark and Sweden, 1970–2008 (Nordcan database [21]; 3-year moving average for Iceland).

Figure 2 Analysis of cutaneous melanoma incidence in Iceland (1955–2007)



Join-point analysis of age-standardized (ASR, World Standard population) cutaneous melanoma incidence in Iceland (1955–2007) by morphologic site for women (a) and for men (b). Adapted with permission from [20••].

the trunk of women under the age of 50. Around the year 2000, the incidence of trunk melanoma in women had surpassed the incidence of lower limb melanoma (Fig. 2). This latter aspect was in sharp contrast with the usual observations prior to 1995 whereby the greatest increase in melanoma incidence in women occurred on lower limbs [22].

Our investigation concluded that the only plausible explanation for this epidemic was the massive exposure of Icelandic youths to artificial tanning devices after 1985 [23]. The decrease in incidence after 2001 in women and 2004 in men (Fig. 1) is most probably due to campaigns initiated by the Icelandic health services at the end of the 1990s to discourage sunbed use.

Sunbed use and recent changes in melanoma incidence in women

The Icelandic data are not a unique story. In the UK and the USA, rebounds of increase of melanoma incidence from 1998 onwards have been reported for women 20–39 years old [24,25], possibly due to the spread of the indoor tanning fashion. In Northern Ireland and Scotland, the UK areas where sunbed use is most prevalent [26], the highest increase in incidence rates was observed on the female trunk [27,28]. In the USA, after 1996, trunk melanomas among younger women are increasing relative to all other anatomic body sites [29]. Sunbed use has been popular in Sweden since the beginning of the 1980s. Over the last 20 years, the incidence of trunk melanoma in Swedish women has caught up the incidence of lower limb melanoma [30].

Sunscreen use during intentional sun exposure may increase the risk of melanoma

Sunscreens have the ability to prevent sunburn occurrence, and the higher the sun protection factor (SPF) of a sunscreen, the greater the protection against sunburns. Modern sunscreens contain both organic filters and mineral oxides and may hence also filter a variable proportion of UVA, but SPF is a UVB-dependent characteristic since this wavelength is one thousand times more efficient than UVA for triggering sunburn. Because of the known association between sunburn and melanoma, it was believed that prevention of sunburns through sunscreen use would also prevent melanoma.

The sunscreen-melanoma quagmire

Retrospective and prospective population-based epidemiological studies often found that sunscreen use during intentional sun exposure (ISE, i.e., sunscreen use for sunbathing or for allowing longer stays in the sun) increased the risk of melanoma or of high nevus count [31–33]. Various explanations, including residual confounding or bias by indication were proposed for these unexpected results, as well as the possibility that sunscreens would allow individuals with poor tanning ability to spend more time in the sun than otherwise possible [34].

Randomized trials on sunscreen use and sun exposure duration

In 1997 and 1998, two randomized controlled trials we conducted within the frame of the EORTC Melanoma Group showed that sunscreen use by young populations during their holidays in sunny resorts increased the

Table 1 Comparison of sun behaviours of young sun-sensitive populations using a SPF 30 vs. a SPF 10 sunscreen during their holidays in sunny resorts

Trial outcome	Use of SPF 30 vs. SPF10 sunscreen
Quantity of sunscreen used	Similar
Time spent in the sun during each day with sun exposure	Increased
Time in the day for sun exposure	More often around solar noon, when sunlight is richer in UVB
For women, sunbathing with naked breasts	Increased
Number of sunburns	Similar
Numbers of skin reddening episodes	Similar

SPF, sun protection factor. Data from [35,36].

duration of sun exposure [35,36] (Table 1), a phenomenon likely to explain the association found between sunscreen use and melanoma risk. These trials contributed to the conclusion of the International Agency for Research on Cancer that 'in intentional sun exposure situations, sunscreen use may conduct to increasing the risk of melanoma' [32,33].

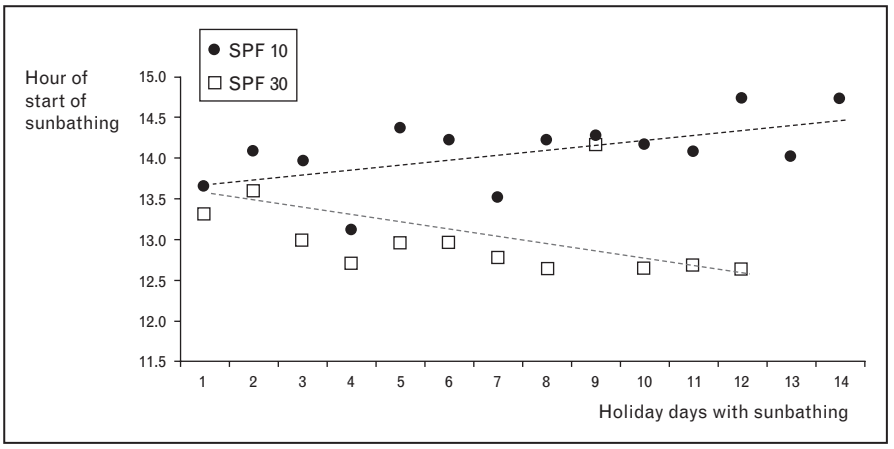
In addition to extended sun exposure duration, a plethora of other changes in sun exposure behaviours was observed in the two trials, further documenting that sunscreen use may allow sun exposure behaviours that would not be possible otherwise [37,38•]. For example, the two randomized trials consistently showed that as a holiday progressed, populations using high SPF sunscreen tended to start sunbathing earlier in the day, while populations using a low SPF sunscreen tended to start sunbathing later in the afternoon (Fig. 3) [35,36]. During the day, UVA and UVB fluxes peak around solar noon but the solar spectrum in the morning and in the late afternoon is poor in UVB [3]. Sunbathing typically entails brisk exposure of the trunk to sunlight and trial results suggested that in the absence of sunscreen use, this usually sun protected site would not stand long exposure to UVB-rich sunlight.

Sunscreen use increases sun exposure duration and UVA

Table 1 summarizes the main results of the randomized trials on sunscreen use by suntan worshippers. The number of sunburns reported was similar for populations using low or high SPF sunscreens, while sun exposure duration was greater among high SPF sunscreen users. In support of results of these two trials, all observational studies and randomized trials studies that examined sun exposure duration in relation to sunscreen use found increased ISE and no change in sunburn occurrence [33,37].

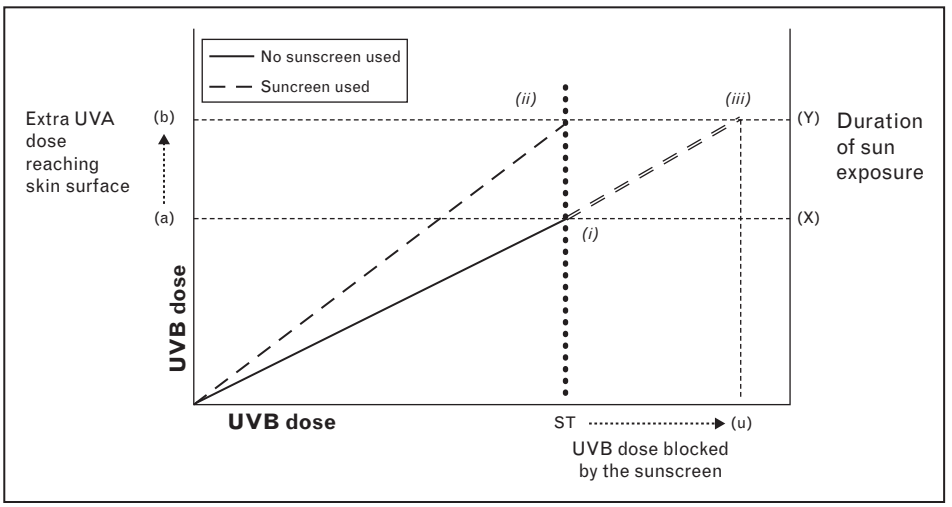
The apparent paradox of sunscreen use not associated with decreasing sunburn occurrence suggests that during ISE, amounts of UVB reaching the skin are similar when a sunscreen is used or not. The only difference is that with sunscreen use, more time is needed to accrue the amount of UVB necessary to tan or to burn (to tan or to burn first depends on the skin phototype of sunscreen user). During that extra time of ISE, more unfiltered UV wavelength can pass through the sunscreen layer. These additional amounts of UV presumably mainly consist in UVA. Would presence of UVA filters in the sunscreen avoid the greater

Figure 3 Hour of start of sunbathing activities



Mean hour of start of sunbathing activities in days with sunbathing. Days without sunbathing were skipped. The time in the figure is the so-called 'summer hour' in Continental Europe, equivalent to the solar hour plus 2 h. Adapted with permission from [36].

Figure 4 Schematic representation of likely impact of sunscreen use on amounts of UVA reaching the skin surface



ST, sunburn threshold. See text for explanations.

UVA exposure? Probably not if the goal of sunscreen use is to acquire a tan or to stay long in the sun, as tan acquisition is the signature that UV-induced DNA damage occurred [39].

Figure 4 illustrates the relationships between sunscreen use, UVB, sun exposure duration, sunburns and UVA in sun-sensitive populations. Figure 4 assumes that the sunscreen has no ability to block the UVA, and that sun exposure is (definitely or temporally) discontinued after sunburn occurrence. When no sunscreen is used, populations engaging in ISE (e.g., in sunbathing) will reach their specific sunburn threshold after (x) minutes, (x) depending on their inherited sun sensitivity. The UVB dose will thus be equivalent to sunburn threshold and the UVA dose to (a). When a sunscreen is used, more time [(y) – (x)] is needed for reaching sunburn threshold. During that extra time, an extra dose of UVA [(b) – (a)] will go through the sunscreen and reach the skin. The quantity [(u) – sunburn threshold] is the amount of UVB blocked by the sunscreen.

UVA has a greater ability than UVB to penetrate deep into the dermis and induce DNA damage in inner skin layers [40], which would explain the increased risk of higher nevus count and of melanoma associated with sunscreen use.

In conclusion, sunscreen use enables populations to withstand high UVB fluxes, which in turn probably leads to greater exposure to high UVA fluxes. This situation would be mainly true for the trunk, the body site typically intermittently exposed.

There are indications that sunbed-induced melanomas are less life threatening

The sunbed-induced melanoma epidemic we described in Iceland developed without concomitant increase in melanoma mortality. The steepest increases in melanoma incidence were observed in young subjects and for trunk melanoma. Trunk melanoma is known to be more dangerous than limb melanoma. However, Fig. 5 shows no appreciable change over time of melanoma mortality in Icelandic men and women, with rare cases of death before age 50.

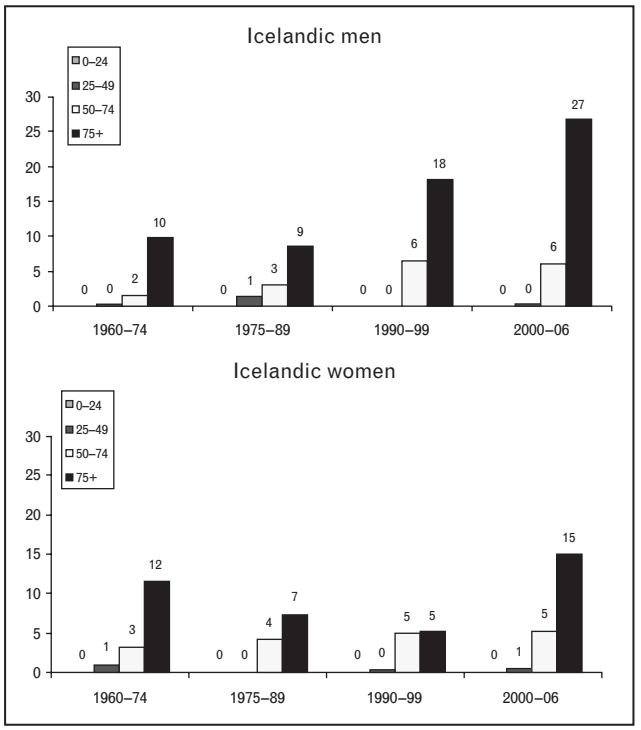
Given the short-term poor prognosis of advanced melanoma and in view of the formidable increase in incidence that took place between 1990 and 2006, it is unclear why mortality remained stable at younger ages. Nonetheless, the contrast between incidence and mortality trends suggests that the rapid increase in incidence in the 1990s was confined to melanoma of limited capacity to disseminate in distant organs.

The first epidemic of melanoma was described in the Hunter District (New South Wales, Australia) in 1987–1992 [41]. The cause of this sudden rise in melanoma incidence remains unknown. Similarly to Iceland, the sharp rise in incidence did not affect melanoma mortality, and it was concluded that the epidemic mainly consisted of a nonmetastasizing form of melanoma [42].

Formulation of the 'UVA-shift' hypothesis

We view the results on sunbed and sunscreen studies as providing indirect evidence that UV wavelengths in the

Figure 5 Annual age-adjusted (World Standard population) melanoma mortality rates in Iceland 1960–2006, by age group



From Nordcan database [21].

UVA range might be involved in the genesis of melanoma. Also, time between 'UVA exposure' and melanoma occurrence would be a few years. One possible hypothesis underlying a short lag time would be the stimulation, by repeated high UVA doses, of melanocytes in preexisting nevi that developed earlier during life.

The main limitation is that UV wavelength was rarely measured during epidemiological studies on sunbeds and sunscreens. Exposure data collected by epidemiological studies are thus by no means reflecting exposure to pure sources of UVA or UVB. However, these results can inform on the type of wavelength possibly involved in melanoma occurrence.

Melanoma incidence is still on the rise in most light-skinned populations, in particular in young women. In contrast, melanoma mortality stabilized in the 1980s and 1990s and even started to decrease slightly, mainly among younger female populations in the Nordic countries, Australia, UK and USA [27,43•,44–47]. The incidence rise was essentially due to thin melanoma less than 2 mm thickness. In contrast, the incidence of thick melanoma (i.e., 2 mm and more) has remained quite stable [27,43•,44,48•]. The epidemics in the Hunter district and in Iceland would represent extreme examples of the discrepancy between incidence and mortality.

We hypothesize that sunbed and sunscreen use would lead to a 'UVA-shift' in UV exposure that would contribute to increasing the number of thin invasive melanoma having little potential for distant dissemination. Sunbed use and sunscreen use are more common in younger age groups, predominantly in women. This hypothesis could partly explain why in most light-skinned populations less than 60 years of age, and in women in particular, melanoma incidence is still rising without a concomitant rise in mortality.

Conclusion

If the UVA hypothesis is grounded, the main question to be solved is the nature of deadly melanoma: do they have same risk factors as the thin, nonlife-threatening melanoma? Which wavelength is involved in their occurrence? One clue may come from earlier studies on migrants. Melanoma mortality is greater for populations born in sunny areas than for those who migrated at later age [49]. Hence, probably deadly melanoma that occurs mainly in older ages would develop from melanocytes initiated during early life, whereas the major part of the rising incidence would be due to melanocytes exposed to high UVA doses during adolescence and adulthood that would take less time to develop into thin melanomas.

In conclusion, growing epidemiological evidence suggests that at least two different forms of melanoma exist, that would have different clinical course. 'UVA-induced' melanoma would be caused by intermittent exposure to high UVA doses. These melanomas would develop rapidly but usually, they would not be aggressive. The environmental causes of more aggressive melanoma, most of which occur in older ages, remain to be defined.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 232).

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Section 6: General discussion

Contribution of our works to changes in legislation towards consumer products and public health policies

Sunbeds

Our works on sunbeds contributed to the strengthening of regulations on sunbed installation and operation and towards providing guidance and warnings to consumers. The most significant outcome was the classification in June 2009 of the entire UV spectrum and all UV-emitting tanning devices as carcinogenic to humans by an IARC Working Group, of which we were members [8] (*El Ghisazi et al, 2009*; Monograph No. 100 publication planned for 2010). In many countries, this new classification encouraged new regulatory moves towards greater control of the indoor tanning market, culminating with the national ban on tanning salons decreed in November 2009 by the Brazilian National Health Surveillance Agency (ANVISA).

Sunscreens prepared with 5-MOP

In April 1993, we sent the report on the 1992-93 EORTC study to the "Europe Against Cancer Programme". The half a page section dedicated to 5-MOP sunscreens received immediate attention and was made public by the Belgian League Against Cancer (BLAC),[9] a charity that at that time partly supported our work. In June 1993, Bergaderm, the company that manufactured these products sued ourselves and the BLAC for compensation of 400,000€ (1993 value). In July 1994 the Belgian justice dismissed Bergarderm's suit.

In 1995 the European Commission issued a ban on products incorporating psoralens at concentrations exceeding 1mg/kg of product. Such a low concentration (sometimes found in natural products and fragrances) has no

[8] In June 2009, Ph Autier was IARC staff member and therefore his name did not appear in the summary published in the Lancet Oncology (*El Ghissassi et al, 2009*). The full list of participants will be displayed in the IARC Monograph No. 100D to appear in 2011. Other experts for human effects of UV exposure were: Bruce Armstrong, Jean-Francois Doré, Adèle Green. Other participants had expertise in basic research on UV, including animal experiments.

[9] Oeuvre Belge du Cancer (OBC) in French, Belgishe Werk tegen Kanker (BWK) in Dutch.

biological effect and equates to forbidding the commercialisation of 5-MOP sunscreens.[10]

Sunscreens

In 2000, a Working Group convened by the IARC made a systematic review of the value of sunscreen for skin cancer prevention (Vaino et al, 2000; IARC, 2001). The final evaluation was:

- Sunscreen use may decrease occurrence of SCC;
- Sunscreen use has no demonstrated influence on BCC;
- In intentional sun exposure situations, sunscreen use may conduct to increasing the risk of melanoma.

The IARC Handbook on sunscreens contributed to shifting the focus of sun protection towards sun avoidance and the wearing of clothes, with sunscreens to be used in NISE situations and in cases where sun exposure is unavoidable, on skin areas that cannot be protected by clothes (e.g., MacCarthy, 2004).

Studies on sun exposure during childhood

These studies contributed to reinforcing public health messages on sun protection for children and stressed the need to consider that protection of children would be the best way for curbing down the melanoma burden.

Sun protection with wearing clothes

Our works added data on the ability of wearing clothes to reduce nevus development in children and probably also, to reduce the risk of melanoma.

Contribution to the understanding of melanoma aetiology

Nevus development is strongly related to one's genetic background, but sun exposure is necessary for complete phenotypic expression of the nevi genotype (Zhu et al, 1999; Bataille et al, 2000; Wachsmuth et al, 2001). Subjects with large or atypical nevi are at increasing risk of melanoma risk, and this risk is independent from the number of small nevi (Gandini et al, 2005b). Large or atypical nevi are

[10] Commission Directive 95/34/DC of 10 July 1995.

about fifty times less common than small nevi, and in both children and adults, they are most usually located on the trunk. Their number directly depends on numbers of smaller nevi.

Several studies have illustrated the good correlation between site-specific distribution of nevi in adults and of melanoma in adults (See Section 4). In contrast, studies in adults, including meta-analyses, showed practically no correlation between the anatomical distribution of nevi (according to whole-body counting) and of melanoma (older papers reviewed in Autier et al, 2000a; Caini et al, 2009; Randi et al, 2006; Chang et al, 2009). Furthermore, with aging, the gender differences in the distribution of nevi tends to fade away (Randi et al, 2006). After 30 years of age, the nevi body distribution in adults does no longer parallel the gender differences in body distribution of nevi in children (Autier et al, 2001a) and of melanoma in adults (Randi et al, 2009).

Altogether, results of migrant studies and studies on anatomic distribution of nevi and of melanoma, strongly support the notion that key UV-induced biological events for melanoma occurrence and death in adult life take place during childhood. The incidence-mortality contrast further suggests that if melanocytes in adults were not UV-initiated during childhood, sun exposure could still induce nevus formation or non life-threatening melanoma (i.e., *in situ* melanoma or thin indolent melanoma), but no longer melanoma that could be life threatening.

Differences in gene expression (phenotype) of melanocytes in response to UV irradiation according to anatomic location was initially formulated by A Green (1992). Our data on nevi in children suggests the existence of site-specific biological pathways that combine their effects with sex-specific biological events. The trunk for instance, would be most susceptible to UV carcinogenic effects. Although it is usually sun protected, the density of small nevi is high and associated with recreational sun exposure; large nevi are influenced by UVB-rich environments and tend to develop more on this site than on any other site. In addition to site-specific factors, male sex would amplify the influence UV exposure on trunk melanocytes (or nevocytes). In contrast, the development of nevi on lower limbs would take place mainly during the adolescence, and be amplified by female gender. Chronic sun exposure of head and neck melanocytes would explain why densities of nevus and of melanomas are highest on this site. However, the rarity of large nevi on this site would be a marker of the resistance of melanocytes or of their microenvironment against the type of biological lesions not directly associated with the development of small nevi, for instance,

the type of cellular damage due to UVB radiation. Male gender probably also plays a role in the UV susceptibility of the head and neck melanocytes but it might be less direct than on the trunk and rather linked to differences in hairstyle or baldness. These site-specific and gender differences would explain why trunk melanomas tend to occur earlier during adulthood and than are often associated to a pre-existing nevus. In contrast, UV doses required for triggering a melanoma on the head and neck would be more important. Age, skin aging (e.g., wrinkles) and chronic sun damage (solar keratoses, dermal elastosis) would be markers of cumulative doses of UV received by the head and neck skin over lifetime. Because nevi number decreases with age, and because sun exposure accumulation is probably involved in the involution and disappearance of nevi (Bouwes-Bavinck et al, 1996), melanoma of elderly and of the head and neck would be less associated with a pre-existing nevus, and more with chronic sun damage.

What ought to be future research directions?

Recent statistics from the USA (Criscione & Weinstock, 2009) summarised in Table 5.1 show that the diagnosis of a thin melanoma is associated with a low probability to die from it. However, approximately one quarter of melanoma deaths occur in patients diagnosed with melanoma less than 1 mm thick and another quarter with melanoma 1 to 1.99 mm thick.

Table 5.1 - Melanomas numbers and deaths in the USA, 1988-2008 in 17 SEER cancer registries, by Breslow thickness (Criscione & Weinstock, 2009)

	Incident melanomas			
Breslow thickness	**Numbers**	**% of total**		
<1.01	91,174	70.0		
1.01–2.00	20,424	15.7		
2.01–4.00	11,702	9.0		
>4	6,894	5.3		
Total	*130,194*	*100.0*		
	Fatal melanomas			
			% of incident melanomas	**Ratio of death probability**
<1.01	2,472	27.1	2.7	ref.
1.01–2.00	2,142	23.5	10.5	3.9
2.01–4.00	2,474	27.1	21.1	7.8
>4	2,041	22.4	29.6	10.9
Total	*9,129*	*100.0*	*7.0*	

We believe that at present, the focus for epidemiology research on melanoma ought to be the search for reasons why some patients are diagnosed with indolent cancers, whilst others are diagnosed with aggressive cancer.

This may seems surprising, but for instance, we still do not know whether red haired subjects known to harbour germ line mutation(s) in the MC1R gene and to be at higher risk of melanoma, also have a higher risk of being diagnosed with a potentially deadly melanoma. The same question holds true for sunburn history and sun exposure. We still have a poor understanding as to why melanoma is so deadly in the elderly, especially in men.

In this dissertation we did not go over data that we published which was relevant to early detection and screening (i.e. the generalisation of early detection to the general population or to high-risk subjects). It is however worth outlining that a number of data indicate that early detection is probably not that efficient for decreasing melanoma mortality:

1. Lack of skin surveillance is not a sufficient explanation for the elderly often displaying thick melanoma. Nodular melanoma (the most aggressive type of melanoma) occurs in greater frequency in the elderly and its occurrence has nothing to do with early detection.

2. Delays in presentation to doctors of suspicious pigmented spots seem to be unassociated with more advanced disease (Richard et al, 1999).

3. In the classic multistep model of melanoma growth (Miller and Mihm, 2006), decreasing incidence of advanced melanoma would represent the best evidence that early detection contributes to decreasing melanoma mortality. However to date, no quality population-based cancer registry operating in areas where early detection is widespread (e.g., Queensland, the USA) has shown a decrease in the incidence of advanced melanoma (Coory et al, 2006; Criscione and Weinstock, 2009; Linos et al, 2009).

4. As shown in Table 5.1, a sizeable fraction of melanoma deaths are caused by thin tumours. Early detection is unlikely to change the fatality associated with such thin but aggressive melanoma.

Hence, it appears that many deadly melanomas grow too fast to be detectable at an early stage.

The question on why some individuals develop fatal melanoma and others do not needs to be well defined. Studies of melanoma in immune depressed organ transplant recipients show that melanoma can metastasize in distant organs without being able to expand in these organs (Strauss & Thomas, 2010). Hence, local and systemic environment exerts a strong control on melanoma tendency to invade the surrounding skin and on the metastases. In addition, age and to a lesser degree, sex, are associated with occurrence of deadly melanoma.

Therefore, on the one hand, UV-initiated melanocytes may have highly variable malignant potential according to the type of underlying biological lesion and capacity to escape from cancerous transformation (e.g. apoptosis and senescence). On the other hand, host resistance against invasion, migration and successful growth in distant organs is critical for counteracting the cancer spread. Thus, the question may be formulated as follows: What are the factors associated with the development of weakly aggressive or with deadly melanoma ? Are these factors linked to :

- The genetic make-up of patients;
- The phenotype of melanocytes and of local skin environment according to anatomical location;
- Lifestyle factors;
- Yet unknown environmental factors;
- Bad luck (stochastic determinism);
- A combination of two or of more of these factors.

The second question that immediately follows is how factors presumably associated with deadly melanoma would be associated with aging and with gender.

For the sake of operational and time efficiency, research may focus on intermediary outcome markers (e.g., Breslow thickness, ulceration, mitotic activity, sentinel node status) and combine multidisciplinary designs involving pathologists, clinicians and basic scientists.

Improved knowledge of the characteristics associated with advanced melanoma may help to better define subjects diagnosed with melanoma that are at high risk of dying from it. It may also help in better targeting primary and secondary prevention efforts. The primary goal of early detection is to decrease melanoma mortality. If in present time, early detection seems ineffective for curbing the

incidence of advanced disease, perhaps the surveillance of individuals identified as at high risk to develop deadly melanoma may be effective. For substantiating the relevance of this approach, another research area for epidemiology is the evaluation of growth patterns of melanoma with attempts to estimate the sojourn time (i.e., the time between detectability by any mean and clinically evidence lesion) of indolent and of aggressive melanoma.

Public health perspectives

The melanoma epidemic is still ongoing in most light-skinned populations. The good news is the existence of levelling-off and in some cases the decrease in melanoma mortality, mainly among women. We do not however understand the reasons underpinning the decrease in melanoma mortality in these younger age groups.

In 2010, certain treatments seem to increase the survival of patients with disseminated melanoma. These improvements in treating a cancer that has resisted to all other forms of therapy are near miraculous. However, at present, they only delay fatal outcome by a few months. Hopefully, these first significant progresses in treatment are a sign of more important therapeutic breakthroughs in the near future. In the meantime, controls of the melanoma epidemic and of melanoma mortality are part of the duties of primary (reduction of exposure to environmental risk factors) and secondary (early detection) prevention.

Control of melanoma mortality through primary prevention will only become possible when we have good knowledge of factors associated with the occurrence of deadly melanoma. This is still a very new area of research we outlined in the previous section.

Regarding incidence, four factors will contribute to further increases:

1. The indoor tanning fashion will probably somewhat decline after the numerous works that lead to tougher regulations and better information of the public. However, this industry is very active and the fashion will maintain at a certain level and continue to cause new melanoma cases in younger age groups.

2. Sunscreens are still largely perceived by the public and many health professionals as the most efficient sun protection method during leisure or

holidays in sunny locations, including for children. As long as sunscreen use is associated with "safe tan", sunscreens use during ISE will continue to boost the incidence of melanoma. Indeed, we do not expect many initiatives in the near future for better regulation of information provided to consumers on the pros and cons of sunscreen use.

3. There is a strong parallel between rising melanoma incidence and the number of travels abroad (Bentham et al, 1996; Westherdahl et al 1992; Agredano et al, 2000) and travel statistics show that holidays in distant sunny resorts are increasingly popular.

4. The increasing awareness of skin cancer will stimulate early detection activities that will contribute to the increase in the diagnosis of non life-threatening in situ and thin invasive melanoma (Rees, 2008; Welsh et al, 481; Edman & Klaus, 2000).

We therefore believe that for melanoma incidence, the perspectives are quite dismal. However, we have now sufficient knowledge on the environmental causes of melanoma to pursue public health action towards reducing the impact of these factors on the melanoma burden. Establishing why some subjects develop deadly melanoma represents a new scientific quest susceptible to helping combat the death toll due to this cancer.

Section 6: Summary in English and in Dutch – Samenvatting in het Engels en in het Nederlands.

Summary

The objectives of this dissertation was to outline our works on environmental risk factors for cutaneous melanoma and on sun protection, including exposure to artificial UV tanning devices, sunscreen use for melanoma prevention, and on childhood being a critical period for melanoma initiation.

Our works took the IARC Monograph on Solar and ultraviolet radiation of 1992 as starting point. This Monograph classified the solar radiation as carcinogenic to humans (group 1). However, the UVA, UVB and the sunlamps and sunbeds were classified as probably carcinogenic to humans (group 2A), essentially because too few data specific to these issues existed at the time.

In Section 2 we presented studies on sunbed use and melanoma. The first European case-control study in 1992-93 showed the increased risk associated with artificial UV tanning, mainly when exposure started about ten years earlier. A second European case-control study in 1999-2001 failed to investigate the sunbed-melanoma association because prevention campaigns had started warning about health hazards associated with indoor tanning. Knowledge of these hazards by melanoma patients and controls led to biases that made results impossible to interpret. We then turned to meta-analyses of observational studies that showed substantial increase in melanoma risk when sunbed use started before around 30 years old, a result in line with the known susceptibility of youths to carcinogenic effects of UV radiation. More recently, we described an epidemic of melanoma in Iceland that took place after 1990, a rare epidemiological phenomenon most probably triggered by the considerable spread of indoor tanning among Icelandic youngsters after 1985. Sunbed use was the most likely cause of the epidemic because it mainly affected the trunk of young women. Also, travels abroad were more prevalent among older than among younger Icelandic subjects.

In Section 3, we presented studies on sunscreen use and melanoma. Because of their ability to delay sunburn and to decrease the occurrence of UV-induced keratinocytic cancers in rodents, sunscreens were considered as a method of choice for skin cancer prevention. However, contrary to expectations, population-based epidemiological studies showed moderate increased risk of melanoma associated with sunscreen use, and rarely a decreased risk. These intriguing findings were deemed to be due to

inappropriate control of confounding by sun exposure or by host characteristics. In addition, in 1992, some sunscreens sold in France, Belgium and Greece were prepared with 5-methoxyprosralen (5-MOP), a potent tanning activator also known for its carcinogenic properties when activated by the UVA.

In the case-control study of 1992-93, we showed that poor tanner using 5-MOP sunscreens had a risk of melanoma higher than subjects using normal sunscreens. This study also showed that the higher melanoma risk of sunscreen users was not due to lack of control of the confounding effects of sun exposure or of host characteristics.

The number of nevus is the main individual predictor of melanoma. Nevus development is influenced by the same environmental and host factors than melanoma. In 1995-97, we performed a retrospective cohort study in 6-to-7-year-old schoolchildren in Belgium, France, Germany and Italy that showed higher numbers of nevi when sunscreens were used. In contrast, wearing clothes when in the sun was associated with decreasing number of nevi. Sunscreen use and wearing clothes when in the sun were more frequently adopted by children having characteristics of higher nevus count or of higher melanoma risk. The sharp contrasts in results obtained for wearing clothes and sunscreen use excluded an explanation by confounding.

Probably that the higher melanoma risk observed when sunscreens were used was due to longer stays in the sun. For verifying this hypothesis, we organized two randomized controlled trials during the summers of 1997 and 1998. In these trials, students 18 to 25 years old willing to spend their holidays in sunny areas were randomly assigned to a group that received a potent sunscreen (i.e., a sunscreen with good ability to prevent sunburns) and in a group that received a less potent sunscreen. Both trials demonstrated that use of potent sunscreens increased the duration of sunbathing but did not decrease sunburn occurrence. Hence, extension of intentional sun exposure duration (e.g., for tan acquisition) until sunburn occurred anyway, was the most plausible reason underlying the higher risk of melanoma often observed among sunscreen users. Further systematic reviews we made showed that all observational studies and human experiments done on the subject invariably showed longer duration of intentional sun exposure when sunscreens are used. However, this is not the case when sunscreens are used during sun exposures not associated with willingness to acquire a tan or to stay long in the sun (the non-intentional sun exposure (NISE) like for instance, gardening or skiing). Sunscreen use during NISE prevents sunburn and decreases the risk of squamous cell carcinoma and of melanoma.

In Section 4, we outlined case-control studies on melanoma in adults and the retrospective cohort study in children that allowed exploring in more depth the relationships between sun exposure and sun protection during childhood and melanoma occurrence during adulthood. We found that melanoma occurrence in adults was unlikely in the absence of sun exposure during childhood. Conversely, melanoma initiated by sun exposure in childhood necessitated further sun exposure during adult life for it s occurrence. We also found that the anatomic distribution of nevi in children was correlated with the anatomic distribution of melanoma in adults. Also, sex differences in nevus body distribution in children were similar to those found in adults. These similarities between nevi in children and melanoma in adults were in sharp contrast with the near absence of correlation between the anatomic distributions of nevi and of melanoma in adults. These data further documented the knowledge that initial steps in melanoma genesis take place early in life.

In Section 5, we formulate two hypotheses based on the data we gathered during 18 years of epidemiological research on sunbeds, sunscreens and childhood sun exposure. The first hypothesis is that the UVA might be involved in melanoma occurrence. Epidemiological evidence comes from studies on sunbeds, on sunscreens and on nevus counts in small children.

The second hypothesis is that invasive melanoma mainly induced by UVA exposure would have low potential for invading surrounding skin layers and dissemination in distant organs. This hypothesis was prompted by the sunbed-induced melanoma epidemic in Iceland that was not paralleled by an increase in melanoma mortality. This hypothesis is also supported by data from studies on indoor tanning and Breslow thickness, and on sunscreen use.

Our works on indoor tanning and melanoma contributed to the reinforcement of regulations on installation and operation of tanning salons, and to the formulation of recommendations to the public. They also contributed to the classification by the IARC in 2009 of artificial UV tanning devices as carcinogenic to humans (group 1). Our works on sunscreens led an IARC Working Group to conclude that sunscreen use during intentional sun exposure could increase the risk of melanoma. Our works provided decisive data to regulatory bodies and in 1995, the European Commission put a ban on the commercialization of 5-MOP sunscreens.

Synopsis

De twee doelstellingen van dit proefschrift waren een overzicht te geven van ons werk rond enerzijds de omgevingsfactoren die het risico op melanoma verhogen, en anderzijds over zonnebeschermingsmaatregelen. Dit omvat zonnebanken die werken met kunstmatige ultraviolette straling (artificiële UV) zonnebanken, zonnecrèmes gebruikt ter bescherming tegen melanoom en onderzoeken gedaan naar de kindertijd gezien deze periode kritiek is voor het ontstaan van melanoma.

De monografie van het Internationale Agentschap voor Kankeronderzoek, IARC, "Solar and ultraviolet radiation" uit 1992 werd gebruikt als uitgangspunt. Deze monografie categoriseerde zonnestraling als kankerverwekkend voor de mens (groep 1). Desondanks werden UVA, UVB, zonnelampen en zonnebanken ingedeeld als waarschijnlijk kankerverwekkend voor de mens (groep 2A), hoofdzakelijk omdat er toen te weinig specifieke gegevens waren omtrent deze materie.

In Sectie 2 presenteren we enkele studies over het gebruik van zonnebanken en melanoma. Het eerste Europese patiënt-controle-onderzoek uit 1992-93 toonde een verhoogd risico aan geassocieerd met artificieel UV zonnen, voornamelijk wanneer de blootstelling ongeveer tien jaar eerder begon. Een tweede Europees patiënt-controle onderzoek uit 1999-2001 naar de relatie tussen het gebruik van zonnebanken en melanoma mislukte, omdat preventiecampagnes opgezet waren die waarschuwden voor de gezondheidsrisico's verbonden aan binnenshuis zonnen met kunstmatig UV licht. De kennis over deze gezondheidsrisico's bij patiënten met melanoom en gezonde controlepersonen leidden waarschijnlijk tot aanzienlijke vertekeningen, waardoor de resultaten onmogelijk geïnterpreteerd konden worden. We zijn hierna overgegaan op meta-analyses van observationele studies die een aanzienlijke verhoging aantoonden van de prevalentie van melanoma wanneer het gebruik van zonnebanken startte rond de leeftijd van 30 jaar. Dit resultaat stemt overeen met de bekende gevoeligheid van jongeren voor de kankerverwekkende effecten van UV-straling. Recent bestudeerden we een epidemie van melanoom in IJsland die plaatsvond na 1990, een zeldzaam epidemiologisch fenomeen dat waarschijnlijk veroorzaakt werd door de grote verspreiding van indoor zonneapparatuur bij IJslandse jongeren na 1985. Het regelmatig gebruik van zonnebanken is de meest waarschijnlijke oorzaak van de epidemie, aangezien voornamelijk de romp van jonge vrouwen getroffen werd. Bovendien waren buitenlandse reizen frequenter bij oudere dan bij jongere IJslandse vrouwen.

In Sectie 3 presenteren we studies over het gebruik van zonnecrèmes en melanoom. Dankzij hun vermogen om zonnebrand uit te stellen en het optreden van door UV-straling geïnduceerde keratinocyten-kankers in knaagdieren te verminderen, werden zonnecrèmes gedurende lange tijd beschouwd als de beste methode ter preventie van huidkanker. In tegenstelling tot de verwachtingen, toonden epidemiologische studies in populaties echter een matig verhoogd risico op melanoom geassocieerd met het gebruik van zonnecrèmes, en zelden een verminderd risico. Er werd aangenomen dat deze intrigerende resultaten het gevolg waren van onjuist corrigeren voor blootstelling aan de zon of voor specifieke eigenschappen van de proefpersoon. Bovendien waren sommige zonnecrèmes verkocht in Frankrijk, België en Griekenland in 1992 bereid met 5-methoxypsoralen (5-MOP), een sterke bruinend middel, ook bekend vanwege zijn kankerverwekkende eigenschappen wanneer het geactiveerd wordt door UVA.

In de patiënt-controle studie uit 1992-93 toonden we aan dat proefpersonen die langzaam bruinden en die zonnecrèmes met 5-MOP gebruikten een hoger risico hadden op melanoom dan proefpersonen die normale zonnecrèmes gebruikten. Dit onderzoek toonde ook aan dat het hoger risico op melanoom bij gebruikers van zonnecrèmes niet te wijten was aan het gebrek aan controle voor storende factoren zoals zonneblootstelling of van de specifieke eigenschappen van de gastheer.

Het aantal moedervlekken (naevi) is de belangrijkste individuele voorspeller van de kans op het krijgen van melanoom. De ontwikkeling van naevi wordt beïnvloed door dezelfde omgevingsfactoren als melanoom. Tussen 1995 en 1997, voerden we een retrospectief cohort onderzoek uit bij schoolkinderen van 6 en 7 jaar in België, Frankrijk, Duitsland en Italië. Een groter aantal naevi werd aangetoond wanneer zonnecrèmes werden gebruikt, terwijl het dragen van kleding bij zonnen geassocieerd werd met een daling van het aantal naevi. Het gebruik van zonnecrèmes en het dragen van kleding in de zon werd frequenter toegepast door kinderen die een hoger aantal naevi hadden of een hoger melanoom risico. De scherpe contrasten in de verkregen resultaten voor het dragen van kleding en het gebruik van zonnecrèmes sloot een andere verklaring door storende variabelen uit.

Het was waarschijnlijk dat het hogere risico op melanoom bij gebruik van zonnecrèmes gevonden werd doordat de personen die de zonnecrèmes gebruikten langer in de zon verbleven. Om deze hypothesis te controleren, voerden we twee gecontroleerde en gerandomiseerde onderzoeken uit tijdens de zomers van 1997 en 1998. In deze onderzoeken werden studenten tussen 18 en 25 jaar oud, die hun vakanties gingen doorbrengen in zonnige oorden,

willekeurig ingedeeld in een groep die goede zonnecrèmes kreeg (i.e. een zonnecrème die het risico op zonnebrand beperkt) en een groep die minder goede zonnecrèmes ontving. Beide onderzoeken toonden aan dat het gebruik van goede zonnecrèmes de duur van het zonnen verhoogde, maar het risico op zonverbranding niet verminderde. De opzettelijke verlenging van de duur van de expositie aan de zon tot zonverbranding ontstond is de meest aannemelijke oorzaak voor de verhoging van het risico op melanoom dat vaak waargenomen werd bij gebruikers van zonnecrèmes. Systematisch onderzoek dat wij uitvoerden binnen observationele onderzoeken en bij experimenten met proefpersonen toonde onveranderlijk een langere duur van de opzettelijke zonneblootstelling aan wanneer zonnecrèmes werden gebruikt. Dit was echter niet het geval wanneer zonnecrèmes gebruikt werden tijdens zonneblootstelling die niet geassocieerd is met het willen bruinen of tijdens langere verblijven in de zon zoals tuinieren of skiën (non-intentional sun exposure, NISE). Het gebruik van zonnecrèmes tijdens NISE voorkomt zonverbranding en vermindert het risico op plaveisecelcarcinoom en melanoom.

In Sectie 4 vatten we de resultaten van enkele patiënt-controle studies over melanoom bij volwassenen samen, evenals een retrospectieve cohortstudie bij kinderen. Dit stond ons toe in meer detail de relatie tussen zonneblootstelling en zonnebescherming bij kinderen en het optreden van melanoom bij volwassenen te onderzoeken. We constateerden dat het optreden van melanoom bij volwassenen onwaarschijnlijk was als er geen zonneblootstelling was tijdens de jeugd. Bovendien zal melanoom geïnitieerd tijdens zonneblootstelling tijdens de jeugd verdere zonneblootstelling nodig hebben om zich tijdens het volwassen leven te ontwikkelen. We stelden ook vast dat de anatomische verspreiding van naevi bij kinderen in verband staat met de anatomische verspreiding van melanoom bij volwassenen. Bovendien waren de geslachtsverschillen in verdeling van de naevi over het lichaam van kinderen gelijk aan deze gevonden bij volwassenen. Deze overeenkomsten tussen naevi bij kinderen en melanooma bij volwassenen stonden in scherp contrast met de bijna afwezige correlatie tussen de anatomische verspreidingspatronen van naevi en melanoom bij volwassenen. Deze gegevens toonden aan dat de initiële stappen in het ontstaan van melanoom vroeg in het leven optreden.

In Sectie 5 formuleren we twee hypotheses gebaseerd op de data verzameld tijdens het 18-jarig epidemiologisch onderzoek over zonnebanken, zonnecrèmes en zonneblootstelling bij kinderen. De eerste hypothese stelt dat UVA betrokken zou kunnen zijn bij het optreden van melanoom. Epidemiologische aanwijzingen voor deze hypothese komen uit de

onderzoeken over zonnebanken, zonnecrèmes en het aantal naevi bij kleine kinderen.

De tweede hypothesis stelt dat invasieve melanomen die hoofdzakelijk veroorzaakt worden door UVA-blootstelling een laag potentieel zouden hebben om de omringende huidlagen binnen te dringen en zich te verspreiden in afgelegen organen. Deze hypothese werd ondersteund door de IJslandse melanoma epidemie door het gebruik van zonnebanken. Deze epidemie ging niet gepaard met toenames in de melanoom-sterfte. Deze hypothese wordt ook ondersteund door data uit onderzoeken over indoor zonnen en de Breslow-dikte, en door het gebruik van zonnecrèmes.

Onze onderzoeken over indoor zonnen en melanoom droegen bij aan de bekrachtiging van de wetgeving over de installatie en het management van zonnebankcentra, en tot de formulering van aanbevelingen voor het publiek. Deze onderzoeken vormden ook een bijdrage bij de classificatie van de artificiële UV zonneapparatuur als kankerverwekkend voor de mens (groep 1) door IARC in 2009. Onze onderzoeken over zonnecrèmes leidden ertoe dat een IARC werkgroep concludeerde dat het gebruik van zonnecrèmes tijdens opzettelijke zonneblootstelling het risico op melanoom kan verhogen. Ons werk leverde doorslaggevende data voor de regulerende instanties, en in 1995 verbood de Europese Commissie de verdere commercialisatie van 5-MOP zonnecrèmes.

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Short Curriculum Vitae

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Philippe Autier, born in 1956, is a Belgian medical doctor and epidemiologist with broad international experience.

Philippe Autier received his medical degree from the Free University of Brussels in 1982 and a diploma in tropical medicine from the Prince Leopold Institute of Tropical Medicine, Antwerp in 1983. He started his professional life by joining the humanitarian non-governmental organization *Médecins Sans Frontières (MSF)*, where he helped in Honduras (1982 and 1983), and later in Chad (1984-85). In Chad, he became the *medical coordinator* of all health projects runned by MSF. From 1985 unilt 1988, he was the *head of the medical department* of MSF headquarters in Brussels and was a founder of the European Agency for Health and development (AEDES, Brussels, www.aedes.be), an agency specialized in international health. In 1988, he received a Fulbright fellowship with a grant from the *Frank Boas Foundation* to study at Harvard School of Public Health, Boston, Massachusetts, where he was awarded a Masters in Public Health (MPH) in 1989.

Philippe Autier began his scientific career as expert in international health, mainly in disaster medicine, working with the WHO and the World Bank. His main achievements in this area were studies on nutritional surveillance and the quality of drugs supplied to disaster areas. [1]

In 1989, Philippe Autier joined the Jules Bordet Institute (a main cancer centre in Belgium) in Brussels where he became *head of the Epidemiology and Prevention department*. From 1995 to 2000, he was deputy director of the Epidemiology and Biostatistics department of the European Institute of Oncology in Milan (Italy). In

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2000-2004, he was back at the Jules Bordet Institute in Brussels (Belgium). In 2005-2009, he was *Group Head* of the Prevention Group at the International Agency for Research on Cancer in Lyon, (France). Since December 2009, he is Vice President Population Research at the International Prevention Research Institute in Lyon (France)(iPRI, www.i-pri.org), and he has been nominated as Honorary Professor at the University of Dundee (UK).

Philippe Autier has broad scientific and international experience. Since 1990, his main research area is the epidemiology of skin cancer and sun protection, for which he has coordinated major research activities within the Melanoma Group of the European Organization for Research on Cancer (EORTC). He is greatly involved in the evaluation of cancer screening activities and in the use of descriptive data for assessing the impact of health activities on cancer incidence and mortality. Philippe Autier is also involved in health technology assessment, especially for the evaluation and clinical testing of new methods for cancer early detection. He is author and co-author of 150 articles published in peer-reviewed journals, being the only or the first author in 65 articles and the senior author in 21.[2]

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