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INFLUENCE OF SUN EXPOSURES DURING CHILDHOOD AND DURING ADULTHOOD ON MELANOMA RISK

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Sun exposure in both childhood and adult life represents the main environmental risk determinant for cutaneous melanoma. However, little is known about the joint effects of sun exposure during early and later life on melanoma risk. A case-control study in Belgium, Germany and France conducted in 1991–1992 suggests that the melanoma risks attached to indicators related to sun exposure appear to combine their effects in an additive way. We therefore constructed composite indices of sun exposure during childhood and during adulthood, assuming additive combinations of melanoma risk associated with each indicator of sun exposure. Logistic regression modeling showed that the melanoma risk associated with a given level of sun exposure during adulthood increased with higher sun exposure during childhood, but the increase in risk was higher than the simple addition of melanoma risk associated with sun exposure during childhood or adulthood. In turn, high sun exposure during childhood constituted a significant risk factor for melanoma only if there was substantial sun exposure during adult life. We thus suggest that sun exposure during childhood and during adulthood would be interdependent as far as their impact on melanoma risk is concerned. Our results support the hypothesis by which the important contribution of sun exposure during childhood in melanoma occurrence is not properly assessed by retrospective epidemiologic studies. Sun avoidance during childhood would have a greater impact on melanoma risk than sun avoidance during adulthood. *Int. J. Cancer* 77:533–537, 1998.
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Sun exposure is now recognized as the most important environmental risk determinant of cutaneous melanoma (International Agency for Research on Cancer, 1992). Some 29 published studies reviewed by Elwood and Jopson (1997) have shown an increase in melanoma risk with increasing sun exposure during adult life, mainly when sun exposure is of the intermittent type, *i.e.*, brutal exposures to solar radiation of skin areas normally covered by clothes, usually during outdoor recreational activities or sunbathing sessions.

Although cutaneous melanoma is very rare before the age of 20 years, early life is considered a period of considerable importance for the biological events leading to later melanoma. The most compelling evidence of childhood being a crucial period for melanoma initiation comes from studies that have shown a higher melanoma risk in subjects who spent their childhood in sunny areas, compared to subjects who spent their childhood in areas with low ambient ultraviolet irradiation (Autier *et al.*, 1997; Khlat *et al.*, 1992; Mack and Floredus, 1991; Steinitz *et al.*, 1989; Holman and Armstrong, 1984). Other evidence for the role of sun exposure in early life comes from the association between sunburn experience during childhood and melanoma. One study suggests that sun exposures taking place before the age of 20 years are more influential on melanoma occurrence than sun exposures later in life (Weinstock *et al.*, 1989), and another suggests that sun protection during childhood could reduce melanoma risk during adulthood (Autier *et al.*, 1996).

However, since practically all studies on risk determinants of melanoma are retrospective studies performed among adults, we still have a poor idea of the actual amounts and patterns of sun exposure during early life possibly influencing the risk of melanoma. Because of the difficulty of exploring sun exposure during childhood with the same indicators used for assessing sun exposure during adulthood, combining data on sun exposure that took place during different periods of life has been impossible, and the joint effect on melanoma risk of sun exposure at different moments of life has seldom been examined.

Here we attempt to explore the mutual influences of sun exposures during childhood and during adulthood on melanoma risk, using data gathered during a case-control study conducted by institution members of the European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Cooperative Group.

MATERIAL AND METHODS

In 1991–1992, a case-control study was conducted in Belgium, France and Germany, which included 412 melanoma cases and 445 controls. Previous analyses of these data identified several relevant indicators related to sun exposure and sun protection during childhood and adulthood (Autier *et al.*, 1994*a*,*b*, 1995, 1996, 1997). Table I lists the indicators relating to sun exposure that emerged as associated with an increased melanoma risk at the $p = 0.10$ level in a logistic model, as recommended when proceeding to stepwise multivariate analysis (Kleinbaum *et al.*, 1982).

Three indicators described sun exposure during childhood: (1) residence in areas next to the Mediterranean coast and in tropical or subtropical areas before the age of 10 years, (2) sunburn experience and (3) having been protected against solar radiation during holidays with parents in sunny resorts. Six indicators were related to sun exposure in adulthood. History of non-malignant skin disease that lasted for 1 year or more was associated with a reduced risk of melanoma, probably because subjects who suffered from serious skin disease were generally more inclined to adopt sun protection behavior patterns. For the sake of coherence in the presentation of the results, sun protection indicators (*i.e.*, indicators 3 and 9 in Table I) were converted into sun exposure risk factors by considering their symmetric counterpart. Sunbed use (coded as never/ever use) has been discarded since it did not reach a statistical significance at the $p = 0.10$ level. For the same reason, we discarded the question about ''sunbathing during leisure times, outside the holiday periods''. Indicators for which the highest melanoma risk were attained also included the fewest subjects; therefore, their confidence intervals (CIs) are larger than for the other indicators.

Our previous analyses suggested that indicators related to sun exposure combined in an additive way their effects on melanoma risk. For instance, the increase in melanoma risk associated with

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TABLE I – MELANOMA RISK ASSOCIATED WITH SUN EXPOSURE INDICATORS IN BELGIUM, FRANCE AND GERMANY (1991–1992)[1]

Sun exposure risk factors	Adjusted OR	95% CI
Risk factors during childhood (0–14 years old)[2]		
1. Residency ≥1 year in Mediterranean, tropical or subtropical area starting before 10 years old	4.3	1.7–11.1
2. Ever sunburn between 5 and 10 years, and between 10 and 14 years old	1.5	1.0–2.3
3. Never been protected against sunlight during holidays in sunny resorts	1.4	1.0–1.9
Risk factors during late adolescence and adulthood[3]		
4. On average, >2 holiday weeks spent each year in sunny resorts	1.7	1.3–2.3
5. During holidays, sun exposure during the hot hours of the day	1.6	1.0–2.5
6. Search for suntan during residence of ≥1 year in Mediterrannean, tropical or subtropical area	4.1	1.3–13.4
7. Ever sunburn after 14 years old	1.4	1.0–1.8
8. Sunscreen use		
Ever regular sunscreen only	1.5	1.1–2.0
Ever psoralen sunscreen	2.4	1.3–4.2
9. Never suffered from non-malignant skin disease that lasted for ≥1 year	1.6	1.0–2.5

[1]References: Variables 2, 4, 5 and 7: Autier *et al.* (1994*a*); variables 8 and 9: Autier *et al.* (1995); variable 3: Autier *et al.* (1996); variables 1 and 6: Autier *et al.* (1997). OR = odds ratio; CI = confidence interval.–[2]Logistic model included exact age, gender, skin phototype (I–II *vs.* III–IV), hair color (blond/red *vs.* black/brown) and indicators of sun exposure during childhood listed in the table.–[3]Logistic model included exact age, gender, skin phototype (I–II *vs.* III–IV), hair color (blond/red *vs.* black/brown) and indicators of sun exposure during adulthood listed in the table.

sunbathing during the hot hours of the day added to the melanoma risk conveyed by duration of holidays in sunny areas (Autier *et al.*, 1994*a*). Another example was the addition of the risk associated with sunscreen use to the risk associated with duration of holidays in sunny areas (Autier *et al.*, 1996). In view of these apparently additive combinations of effects, we constructed 2 composite indices of sun exposure with the indicators listed in Table I:

1. *Index of sun exposure during childhood.* Subjects were classified according to 4 levels of sun exposure during childhood, from no experience of any of the 3 types of exposure up to having experienced all 3 types of exposures. There were, however, no subjects in the latter category.
2. *Index of sun exposure during adulthood.* Subjects were classified according to 8 levels of sun exposure during adulthood, from no experience of any of the risk factors up to having experienced all exposures. The indicator ''sunscreen use'' comprised 2 levels of risk because psoralen sunscreens were a mixture of regular sunscreen and 5-methoxypsoralen, and thus the melanoma risk associated with the presence of 5-methoxypsoralen had to be considered supplementary to the risk associated with the use of regular sunscreens (Autier *et al.*, 1995). Since some score values of the composite index comprised few subjects, we collapsed index levels to yield exposure levels corresponding to 0 or 1, 2, 3, 4, and 5–7 risk factors.

After the construction of the sun exposure indices, we looked at the joint effect of sun exposure during childhood and during adulthood on melanoma risk by cross-tabulating the 2 sun exposure indices. Melanoma risk was assessed through logistic regression models which systematically included as adjustment variables exact age, gender, hair color, ability to tan and propensity to sunburn when going unprotected in the sunlight. The latter variable was classified according to skin phototypes (Melski *et al.*, 1977).

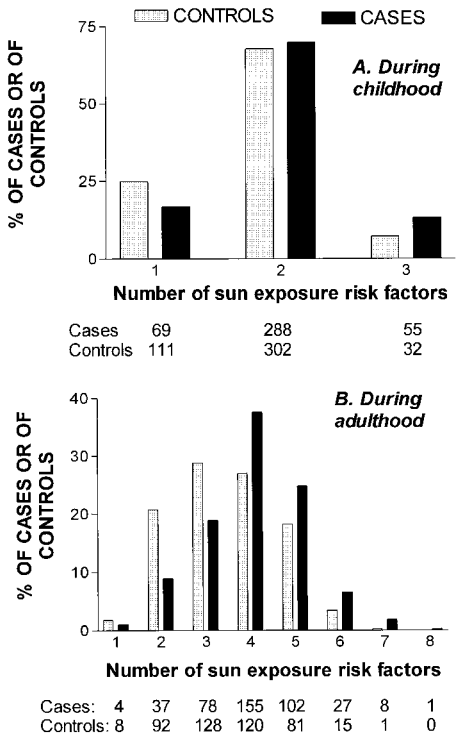

FIGURE 1 – Distribution of indices of sun exposure during (*a*) childhood and (*b*) adulthood in 412 melanoma cases and 445 controls.

Skin phototype I subjects where those who declared to never tan but to always burn; skin phototype II subjects to first always burn, but tan after; skin phototype III subjects rarely burned, and always got a deep tan after; skin phototype IV subjects always tanned, never burned.

Risk estimates for melanoma were calculated as odds ratios (ORs), with their 95% CIs calculated using the method of Gart (1970). All statistically significant values were 2-sided. Unless otherwise specified, the uncorrected chi-square or Student's *t*-test was used to test univariate hypotheses. Logistic regression modeling was accomplished using GLIM software (Numerical Algorithms Group, 1977, Oxford, UK). Exploration of interactions was done on both additive and multiplicative scales (Kleinbaum *et al.*, 1982; Rothman, 1986).

RESULTS

The number of sun exposure factors during childhood and during adulthood for which the study subjects provided positive answers were higher for cases than for controls (Fig. 1). The index of sun exposure during childhood reached higher values among cases than among controls, yielding a χ^2 for trend value of 14.7 for 1 degree of freedom ($p = 0.0001$). During adulthood, the distributions of sun exposure risk factors tended toward normality for both cases and controls, with the curve of the cases shifted toward higher numbers of sun exposure factors. As a consequence, the index of sun exposure during adulthood had a mean value of 4.1 (SD = 1.2) among cases and 3.5 (SD = 1.2) among controls ($p < 0.001$).

In Table II, the relationship between the sun exposure indices during childhood and during adulthood was first considered separately, then included together in the same logistic model. The melanoma risk increased as subjects accumulated sun exposure experiences throughout childhood or adult life. These relationships were more pronounced among skin phototype I–II subjects (*i.e.*, subjects with poor tanning ability), but were nonetheless present among skin phototype III–IV subjects (*i.e.*, subjects with good

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TABLE II – MELANOMA RISK ASSOCIATED WITH INDICES OF SUN EXPOSURE DURING CHILDHOOD AND DURING ADULTHOOD

Indices added to basic model[1]	All subjects		Skin phototype III–IV		Skin phototype I–II	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Sun exposure during childhood						
Low (no risk factor)[3]	1.0[2]	—	1.0[2]	—	1.0[2]	—
Medium (1 risk factor)	1.5	1.1–2.2	1.2	0.7–1.9	2.3	1.3–4.1
High (2 risk factors)	2.5	1.4–4.3	2.4	1.1–5.0	2.8	1.3–6.2
Sun exposure during adulthood						
Low (no or 1 risk factor)	1.0[2]	—	1.0[2]	—	1.0[2]	—
Moderate (2 risk factors)	1.5	1.0–2.5	1.5	0.8–2.7	1.7	0.8–3.7
High (3 risk factors)	3.4	2.0–5.5	2.9	1.6–5.3	4.2	2.0–9.1
Very high (4 risk factors)	3.4	2.1–5.4	3.0	1.6–5.6	4.0	1.8–8.9
Extreme (5–7 risk factors)	6.9	3.3–14.2	5.7	2.4–13.8	9.2	2.5–34.4
Sun exposure during childhood and during adulthood						
During childhood						
Low (no risk factor)	1.0[2]	—	1.0[2]	—	1.0[2]	—
Medium (1 risk factor)	1.8	1.2–2.5	1.3	0.8–2.1	2.9	1.6–5.5
High (2 risk factors)	2.5	1.4–4.2	2.3	1.1–4.9	3.0	1.3–6.9
During adulthood						
Low (no or 1 risk factor)	1.0[2]	—	1.0[2]	—	1.0[2]	—
Moderate (2 risk factors)	1.6	1.0–2.5	1.4	0.8–2.6	1.9	0.9–4.1
High (3 risk factors)	3.5	2.2–5.6	2.8	1.6–5.1	5.0	2.3–11.0
Very high (4 risk factors)	3.5	2.1–5.8	3.0	1.6–5.7	4.6	2.0–10.3
Extreme (5–7 risk factors)	7.4	3.6–15.5	5.7	2.4–13.9	12.1	3.1–47.5

[1]Basic model for all subjects includes exact age, gender, skin phototype and hair color. Basic model by skin phototype category includes exact age, gender and hair color.–[2]Referent category.–[3]Risk factors from Table I.

TABLE III – SUN EXPOSURE HABITS OF 445 CONTROL SUBJECTS ACCORDING TO SUNNY HOLIDAYS WITH PARENTS AND SUN EXPOSURE DURING CHILDHOOD[1]

Indicators of sun exposure during adulthood	Holidays in sunny areas with parents			Index of sun exposure during childhood		
	No (N = 249)	Yes, and were sun protected (N = 130)	Yes, but were not sun protected (N = 66)	Low: no risk factor (N = 111)	Medium: 1 risk factor (N = 302)	High: 2 risk factors (N = 32)
% spending each year >2 holiday weeks in sunny resorts	33	54	56	56	38	38
% exposing to the sun during the hot hours of the day when on holiday	6	12	21	14	7	22
% who ever used sunscreens	42	73	53	64	40	50

[1]Data are the percentages of the number of control subjects in a given column.

tanning ability). A peculiarity of the results on skin phototype I–II subjects was the somewhat increased risk estimates obtained when sun exposures during childhood and adulthood were included in the same model, compared to estimated risk when they were considered separately. Such a shift in estimated risk denoted negative confounding effects between sun exposure during childhood and adulthood. To elucidate this point, we concentrated on relationships between sun exposure and sun protection factors at different periods of life.

Table III shows that among control subjects, the offspring tended to adopt the sun exposure behaviors of their parents. However, when children benefited from sun protection when being on holiday with their parents, this parent-offspring induction was somewhat attenuated (*i.e.,* the lower propensity for sunbathing during the hot hours: 12% *vs.* 21%), accompanied by a more pronounced tendency to use sunscreens (73% *vs.* 53%). The most probable explanation for these observations is that sun protection during childhood induced a better awareness of the dangers associated with exaggerated exposure to sunlight (Autier *et al.,* 1994*a*). Table III also shows that high levels of sun exposure during childhood did not necessarily translate in higher adult sun exposure or higher level of sunscreen use. The last features were more marked for the skin phototype I–II subjects (data not shown). Finally, the controls who spent most of their childhood in sunny climates appeared more inclined to beware of the sun during their adult life (data not shown). Thus, although potential and actual sun exposure during childhood may have been high, it did not necessarily imply a high level of sun exposure during adulthood. This imperfect proportionality between amounts of sun exposure during childhood and during adulthood is most probably at the source of the negative confounding effects observed in Table II.

To examine the joint influence of child and adult sun exposure on melanoma risk, we cross-tabulated the sun exposure indices during childhood and adulthood (Table IV). To avoid too few subjects in some cells of Table IV, categories of indices displayed in Table II were collapsed. Overall, within a given category of sun exposure during childhood, there was a consistent increase of melanoma risk with increasing sun exposure during adulthood, and *vice versa.* At first sight, these data suggest that both childhood and adult sun exposure have independent effects on melanoma risk. However, sun exposure during childhood and during adulthood did not simply add their effects on melanoma risk. If this were the case, then the estimated risk for the ''high'' sun exposure categories would be $1.4 + 2.0 - 1.0 = 2.4$. The observed estimated risk was 4.2, suggesting a relative excess risk due to interaction of $4.2 - 2.4 = 1.8$ (Rothman, 1986). A relative excess risk due to interaction was also found for the other levels of increased child and adult sun exposure in Table IV.

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TABLE IV – JOINT EFFECT ON MELANOMA RISK OF SUN EXPOSURE DURING CHILDHOOD AND DURING ADULTHOOD[1]

Indice of sun exposure during adulthood[1]	Indice of sun exposure during childhood[2]		
	Low	Medium	High
Low/moderate	16/37	92/180	11/11
	1.0[3]	1.1	2.0
	—	0.6–2.0	0.7–5.6
High	25/41	103/66	27/13
	1.4	3.4	4.2
	0.6–3.0	1.7–6.6	1.7–10.3
Very high/extreme	28/33	93/56	17/8
	2.0	3.6	4.5
	0.9–4.5	1.8–7.1	1.6–12.5

[1]Data are number of cases/controls, adjusted OR and 95% CI; adjustment for exact age, gender, skin phototype (I–II *vs.* III–IV) and hair color (blond/red *vs.* black/brown).–[2]See Tables I and II for significance of the indices.–[3]Referent category.

There was some evidence for multiplicative relations, as for the same ''high'' categories of exposure, 4.2 is greater than the product (1.4 * 2.0) = 2.8. However, a multiplicative relation was not clear for the highest categories of sun exposure (''high'' during childhood and ''very high/extreme'' during adulthood) since the product (2.0 * 2.0) = 4.0 is quite close to the observed value of 4.5. Also, adding to the logistic model containing the sun exposure indices as displayed in Table IV a cross-product term formed with the 2 indices yielded a change in deviance of 3.6, for 4 degrees of freedom, corresponding to $p = 0.46$.

Restricting the analysis to subjects less than 50 years old tended to increase the interaction observed (data not shown), but the data in several categories were too sparse and prevented drawing specific conclusions for younger age groups.

DISCUSSION

We have attempted to disentangle complex intricacies of sun exposure and sun protection at different periods of life. Our way to combine information from various questions may appear to be an oversimplification of the reality, and the actual importance of each risk factor may not be reflected by the dichotomous classification applied. Our index of sun exposure during childhood was based on broader data, and thus, probably that lesser recall bias was associated with that index than when relying only upon the sunburn experience. Nonetheless, our assessment of sun exposure during early life certainly suffered from memory biases, and the indicators used did certainly not capture the full sun exposure experience during childhood. This may partly explain the lower estimated melanoma risk we found for sun exposure during that period of life (Table II). The best method for quantifying the association between sun exposure during childhood and melanoma would be a large prospective study starting data gathering on sun exposure and sun protection from birth. Such a study is unlikely ever to be done.

Results in Table IV are not an expression of lifetime exposure to solar radiation. If this were the case, the melanoma risk associated with sun exposure during childhood and during adulthood would simply add their effects, and there would not be a relative excess risk due to interaction. The results observed in Table IV suggest that highest melanoma risk during adulthood is found among those adults who were intensely sun exposed during childhood. On the other hand, adults with low or moderate sun exposure but high sun exposure during childhood may well be at higher risk to develop a melanoma than adults with high sun exposure, but with low sun exposure during childhood. Hence, there seems to be a relationship of interdependence between sun exposure during childhood and during adulthood as far as their impact on melanoma risk is concerned. Given the consistency of the results, this finding is not likely to be an artifact. However, because of the above-mentioned limitations, the type of interaction found in these data is difficult to define, and at this stage, we cannot assert whether additive or multiplicative models would be more appropriate.

The important contribution of sun exposure during childhood has remained underestimated in many epidemiological studies because of the difficulties in assessing sun exposure during that period of life. This may explain some of the inconsistencies encountered among publications about the impact of sun exposure on melanoma occurrence. For instance, some studies done in countries with year-round high ambient ultraviolet irradiation and high melanoma incidence, such as Australia, found low melanoma risk associated with sun exposure, with risk levels situated between 1.0 and 2.0 (Elwood and Jopson, 1997). In contrast, melanoma risk associated with sun exposure was often found to be above 2.0 in countries with less sunny weather year-round, *e.g.,* Canada or Northern Europe (Elwood and Jopson, 1997). Our findings suggest a potential explanation for these contrasting results: in some areas with year-round high ambient sun exposure, when they reach adulthood, fair-skinned subjects may have already accumulated an enormous amount of sun exposure that will substantially contribute to melanoma occurrence later in life, as indicated by studies in migrants. Therefore, in those areas, the extra amount of intermittent sun exposure needed to accomplish the ultimate steps for melanoma occurrence would be small compared to populations living in Northern Europe or Canada. In the latter areas, intermittent sun exposure during childhood must be supplemented with higher amounts of intermittent sun exposure during adulthood to achieve the carcinogenic processes leading to melanoma. As a result, and because of the difficulty in assessing sun exposure during early life, in Australia, the melanoma risk associated with intermittent sun exposure during adulthood may have appeared as relatively low, whereas it was found to be higher in Northern Europe or Canada.

The higher melanoma risk for an equivalent value of sun exposure indices among skin phototype I–II subjects underlines the sharp difference in melanoma risk according to melanocompetency (''tannability''). The higher the genetically determined susceptibility to sunlight, the less sun exposure episodes would be necessary for accomplishing biological events involved in melanoma occurrence. However, in good tanners, the melanoma risk also increases with increasing sun exposure during childhood and during adulthood, and thus, the natural ability to acquire a deep tan by no means represents a ''protection'' against melanoma.

In conclusion, our results underline the important role played by sun exposure during childhood, and support the hypothesis by which sun protection during childhood would have a greater impact on melanoma risk than sun protection during adulthood.

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