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MELANOMA AND SUN EXPOSURE: AN OVERVIEW OF PUBLISHED STUDIES

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To assess the association between the incidence of cutaneous melanoma; intermittent, occupational and total sun exposure; and history of sunburn at different ages, we conducted a systematic review using results of all published case-control studies which have assessed incident melanoma, sun exposure and sunburn. Twenty-nine studies contributed data on sun exposure and 21 on sunburn. Overall, there was a significant positive association (odds ratio [OR] = 1.71) for intermittent exposure, a significantly reduced risk for heavy occupational exposure (OR = 0.86) and a small, marginally significant excess risk for total exposure (OR = 1.18). There was a significantly increased risk with sunburn at all ages or in adult life (OR = 1.91) and similarly elevated relative risks for sunburn in adolescence (OR = 1.73) and in childhood (OR = 1.95). There was significant heterogeneity with all of these estimates except that of all ages or adult sunburn. These results show the specificity of the positive association between melanoma risk and intermittent sun exposure, in contrast to a reduced risk with high levels of occupational exposure. The association with sunburn also is likely to reflect intermittent exposure; the results do not suggest any strong relationship to age at sunburn. These associations are similar to those reported for basal cell skin cancer but different from those reported for squamous cell cancer. The mechanisms by which intermittent exposure increases risk, while other patterns of exposure do not, remain to be elucidated. *Int. J. Cancer* 73:198–203, 1997.

Sun exposure has been accepted as the main cause of cutaneous melanoma in humans by reputable groups such as the International Association for Research on Cancer (1992). However, the evidence often is described as weak or conflicting. Descriptive epidemiological studies and clinical observations led in the early 1980s to the hypothesis that melanoma is related specifically to intermittent sun exposure, in contrast to other types of skin cancer, which were assumed to be related to continued or chronic exposure (Elwood and Hislop, 1982; Holman *et al.,* 1983). As randomised trials are not feasible and cohort studies are contra-indicated by the rarity of the condition and the lack of documentation on sun exposure, this hypothesis has been investigated by case-control studies. To date, 35 published case-control studies have reported results on this topic. We present an overview of these studies.

MATERIAL AND METHODS

Studies were identified by the IARC review up to 1992 (International Agency for Research on Cancer, 1992), Medline, studies referenced by other studies, proceedings of major conferences and meetings of the International Melanoma Epidemiology Group (IMAGE). We know of no completed but unpublished studies, though of course other studies are in progress.

Studies were reviewed independently by each of the current authors. Results were classified as relating to intermittent, occupational or total sun exposure or to sunburn history. The result used in the overview analysis is the published odds ratio (OR) for the highest reported category of the type of sun exposure documented compared to the reference group chosen by the authors, which was always the lowest exposure category. Where there was a choice of outcome variables for intermittent exposure, the variable likely to represent the most clearly ''intermittent'' type of sun exposure was chosen. Most studies had only one measure of occupational exposure, total exposure or sunburn. Where possible, a measure was used which was adjusted for demographic factors, such as age and sex, and for baseline host characteristics, such as ethnic origin, skin pigmentation and inherent tendency to burn or tan easily. Such a measure was used in preference to measures adjusted for factors which themselves could be related to sun exposure, such as number of naevi or sunburn history. The 95% confidence intervals (95% CIs) were those published by the authors or, when necessary, those which could be calculated from the published data. Most results were for all subjects, combining the sexes; some studies reported results separately by gender or body site with no combined data and were used in that form.

The overview analysis was based on the confidence interval method to give a summary estimate of ORs and 95% CIs, and a standard heterogeneity test was applied (Petitti, 1994). Thirty-five studies, based on 9,121 incident melanoma cases, which assessed sun exposure or sunburn were used in the analysis (several with more than one publication). One (Paffenbarger *et al.,* 1978) was a study ''nested'' within a defined cohort but used mortality data and, therefore, was excluded. Studies had to be excluded if no OR or 95% CI result was published or could be calculated from the information provided; this applied to only a few results.

RESULTS

There were 29 case-control studies identified with data on sun exposure.

Intermittent exposure

Twenty-three studies (6,934 cases) provided information on a measure of intermittent exposure, in terms of a specific recreational or vacation exposure, yielding an overall OR of 1.71, with 95% CIs of 1.54–1.90 (Table I). There were 26 data sets used as one study (Chen *et al.,* 1996) presented data for 4 anatomical subsites, but no total body estimates were given, though there were no significant differences in the subsite-specific estimates. Another publication (Berwick *et al.,* 1996) reported on the same cases but in much less detail and, therefore, was not included. A positive association was observed individually in 21 of the 23 studies, being statistically significant in 16. One study showed a significant reduction in risk. There was significant heterogeneity ($\chi^2 = 74.5$, df = 25, $P < 0.001$) due to the studies with outlying ORs of 0.62 (MacKie and Aitchison, 1982), 0.79 (Holly *et al.,* 1995) and 8.42 (Grob *et al.,* 1990). Exclusion of these reduced the heterogeneity ($\chi^2 = 29.4$, df = 22, $p > 0.1$) with a modest increase in the overall OR (1.87, 95% CI 1.67–2.09).

Occupational exposure

Twenty studies (6,517 cases and 23 data sets) provided information on occupational exposure, giving an overall OR of 0.86, a small protective effect which was significant (95% CI 0.77–0.96; Table I). There was significant heterogeneity ($\chi^2 = 69.7$, df = 22,

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TABLE I – RESULTS OF CASE-CONTROL STUDIES ON SUN EXPOSURE AND CUTANEOUS MELANOMA

Reference	Place	Intermittent exposure		Occupational exposure		Total exposure	
		Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Klepp and Magnus* (1979)	Norway	78	2.4 (1.0–5.8)	78	1.4 (0.6–3.5)		
Adam *et al.** (1981)	UK	111	1.5 (0.9–2.5)				
Mackie and Aitchison (1982)	Scotland	113	0.6 (0.2–1.2)	113	0.4 (0.1–0.7)		
Lew *et al.* (1983)	USA	111	2.5 (1.1–5.8)				
Rigel *et al.* (1983)	USA	114	2.4 (1.2–5.0)			114	1.6 (1.0–2.6)
Elwood *et al.* (1985)	Canada	595	1.7 (1.1–2.7)	595	0.9 (0.6–1.5)	595	1.2 (0.7–2.0)
Graham *et al.* (males) (1985)	USA			218	0.7 (0.3–1.3)	218	0.5 (0.2–1.0)
Graham *et al.* (females) (1985)	USA					186	0.6 (0.3–1.1)
Sorahan and Grimley (1985)	UK	58	6.5 (1.0–42.0)				
Dubin *et al.* (1986)	USA	1091	1.7 (1.2–2.3)	1096	2.5 (1.4–4.4)	1087	1.1 (0.8–1.6)
Elwood *et al.* (1986)	UK			83	1.7 (0.3–8.6)		
Green *et al.* (1986)	Australia	183	1.9 (0.5–7.4)			121	2.3 (0.9–6.1)
Holman *et al.* (1986)	Australia	267	1.1 (0.7–1.8)			494	0.7 (0.4–1.1)
Cristofolini *et al.* (1987)	Italy			103	0.9 (0.5–1.7)	103	0.6 (0.4–1.0)
Østerlind *et al.* (1988)	Denmark	474	1.8 (1.2–2.5)	474	0.7 (0.5–0.9)		
Zanetti *et al.* (1988)	Italy			73	2.1 (0.6–6.8)		
Garbe *et al.* (1989)	Germany			200	5.5 (1.2–25.3)		
Beitner *et al.* (1990)	Sweden	523	1.8 (1.2–2.6)	523	0.6 (0.4–1.0)		
Dubin *et al.* (1990)	USA	280	1.5 (1.0–2.4)	283	1.8 (0.9–4.0)	277	1.7 (1.1–2.8)
Grob *et al.* (1990)	France	207	8.4 (3.6–19.7)	207	2.5 (1.2–5.1)	207	3.8 (2.2–6.5)
Zanetti *et al.* (1992)	Italy	256	2.3 (1.4–3.8)				
Zaridze *et al.* (1992)	USSR	96	3.4 (0.6–17.4)				
Herzfeld *et al.* (1993)	USA	324	2.0 (1.3–3.3)	321	0.7 (0.5–1.0)		
Autier *et al.* (1994)	Belgium, France and Germany	420	6.1 (1.8–20.3)	420	0.3 (0.1–0.9)		
Nelemans *et al.* (1994)	Netherlands	128	2.4 (1.3–4.2)				
Westerdahl *et al.* (1994)	Sweden	400	1.2 (0.8–1.8)	400	0.8 (0.6–1.0)		
White *et al.* (1994)	USA			256	0.6 (0.3–1.2)	256	0.9 (0.5–1.6)
Holly *et al.* (females only) (1995)	USA	452	0.8 (0.6–1.1)	452	0.8 (0.5–1.5)		
Ródenas *et al.* (1996)	Spain	105	4.9 (2.2–10.9)	100	3.7 (1.7–7.5)	100	5.4 (2.4–12.0)
Chen *et al.* (head/neck) (1996)	USA	85	2.6 (1.2–5.6)	81	0.5 (0.2–1.1)		
Chen *et al.* (upper limb) (1996)	USA	101	2.4 (1.2–4.8)	96	0.6 (0.2–1.1)		
Chen *et al.* (lower limb) (1996)	USA	97	2.7 (1.2–5.8)	92	0.3 (0.1–0.9)		
Chen *et al.* (trunk) (1996)	USA	265	2.7 (1.6–4.5)	253	0.9 (0.6–1.3)		
Summary ORs			1.71 (1.54–1.90)		0.86 (0.77–0.96)		1.18 (1.02–1.38)
Number of studies		23		20		11	
Number of cases		6,934		6,517		3,540	
After excluding heterogenous results (see text)							
Summary ORs			1.87 (1.67–2.09)		0.76 (0.68–0.86)		1.20 (1.00–1.44)
Number of studies		20		16		7	
Number of cases		6,162		4,914		2,944	

OR, odds ratio for maximal category; CI, confidence interval.
*Data calculated by Armstrong (1988).

$p < 0.001$). In individual results, 8 studies showed increased ORs, statistically significant in 4 instances; 12 studies showed reduced ORs, significant in 4. The results fall into 2 groups. The studies contributing to the heterogeneity were the 4 showing the highest ORs (Dubin *et al.*, 1986; Grob *et al.*, 1990; Garbe *et al.*, 1989; Ródenas *et al.*, 1996). These showed a significantly increased OR of 2.86 (95% CI 1.98–4.13; heterogeneity $\chi^2 = 1.6$, df = 3, $p > 0.5$). Their exclusion left 16 studies, 19 data sets, showing a significantly reduced OR (0.76, 95% CI 0.68–0.86; heterogeneity $\chi^2 = 22.2$, df = 18, $p > 0.1$).

Comparison of intermittent and occupational exposure

To compare intermittent and occupational exposure, the 14 studies providing estimates on both were selected (5,605 cases). They showed a significantly elevated OR for intermittent exposure of 1.67 (95% CI 1.48–1.88) and a significantly reduced OR for occupational exposure of 0.85 (95% CI 0.76–0.96), though there was significant heterogeneity in both estimates. Two studies (Grob *et al.*, 1990; Ródenas *et al.*, 1996) contributed to the heterogeneity of both, while 2 (MacKie and Aitchison, 1982; Holly *et al.*, 1995) were heterogenous for intermittent exposure and one (Dubin *et al.*, 1986) for the occupational estimate. Exclusion of these 5 still left an overall increased risk for intermittent exposure (OR 1.86, 95% CI 1.60–2.16) and a decreased risk for occupational exposure (OR 0.76, 95% CI 0.66–0.86).

Total sun exposure

Eleven studies (with 12 data sets as one study reported on males and females separately, 3,540 cases) gave data on total sun exposure, giving an overall marginally significant OR of 1.18 (95% CI 1.02–1.38). Seven studies showed increased ORs, significant in 4, while 4 studies (5 data sets) showed decreases, significant in 2. Again, there was significant heterogeneity ($\chi^2 = 62.1$, df = 11, $p < 0.001$) due to 2 studies with high ORs (Grob *et al.*, 1990; Ródenas *et al.*, 1996) and 2 with low ORs (Graham *et al.*, 1985; Cristofolini *et al.*, 1987). Excluding these gave an overall OR of 1.20 (95% CI 1.00–1.44) with no significant heterogeneity over 7 studies ($\chi^2 = 11.3$, df = 6, $p > 0.05$).

Sunburn in adult life or lifelong

Nineteen studies with 23 data sets (4,771 cases) (Table II) gave information on the association with a previous history of sunburn either at any age or in adult life. These yielded a significant overall OR of 1.91, 95% CI of 1.69–2.17. Each of these studies showed an increase in OR, it being significant in 14. Heterogeneity was not significant ($\chi^2 = 25.8$, df = 22, $p > 0.25$).

TABLE II – RESULTS OF CASE-CONTROL STUDIES ON SUNBURN AND CUTANEOUS MELANOMA

Reference	Place	All ages/adult		Adolescence		Childhood	
		Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
MacKie and Aitchison (1982)	Scotland	113	2.8 (1.1–7.4)				
Lew *et al.* (1983)	USA			111	2.1 (1.2–3.6)		
Elwood *et al.* (1984)	Canada					595	1.3 (0.9–1.8)
Green *et al.* (1985)	Australia	183	2.4 (1.0–6.1)				
Elwood *et al.* (1986)	UK	83	3.2 (1.7–5.9)				
Holman *et al.** (1986)	Australia	507	1.7 (1.0–2.9)			507	1.2 (0.6–2.3)
Cristofolini *et al.* (1987)	Italy	103	1.2 (0.7–2.1)	103	0.7 (0.4–1.2)		
Holly *et al.* (1987)	USA	121	4.4 (1.9–10.0)				
Østerlind *et al.* (1988)	Denmark	474	3.0 (1.6–5.4)	474	2.4 (1.6–3.6)	474	3.7 (2.3–6.1)
MacKie *et al.* (males) (1989)	Scotland	99	7.6 (1.8–32.0)				
MacKie *et al.* (females) (1989)	Scotland	181	2.3 (0.9–5.6)				
Weinstock *et al.* (1989)	USA	123	1.1 (0.6–2.3)	124	1.9 (1.1–3.4)		
Dubin *et al.* (1990)	USA	132	1.6 (1.0–2.6)				
Elwood *et al.* (1990)	UK	195	1.8 (0.9–3.7)	195	1.0 (0.6–2.0)	187	2.4 (0.8–7.3)
Grob *et al.* (1990)	France	207	3.7 (1.8–7.9)				
Zanetti *et al.* (1992)	Italy	254	1.5 (0.8–2.7)			248	6.5 (3.4–12.3)
Dunn-Lane *et al.* (1993)	Ireland	100	1.9 (1.1–3.3)				
Autier *et al.* (1994)	Belgium, France and Germany	420	1.9 (1.2–2.5)			420	1.5 (1.0–2.3)
Westerdahl *et al.* (1994)	Sweden	376	1.9 (1.2–3.1)	367	1.6 (1.0–2.5)	339	1.6 (1.0–2.6)
Holly *et al.* (females only) (1995)	USA	452	2.0 (1.1–3.8)	452	2.4 (1.6–3.5)	452	2.0 (1.4–2.9)
Ródenas *et al.* (1996)	Spain	105	2.4 (1.1–5.1)			105	3.6 (1.5–8.4)
Chen *et al.* (head/neck) (1996)	USA	84	1.9 (1.0–3.4)				
Chen *et al.* (upper limb) (1996)	USA	100	1.5 (0.8–2.6)				
Chen *et al.* (lower limb) (1996)	USA	96	1.7 (0.9–3.0)				
Chen *et al.* (trunk) (1996)	USA	263	1.6 (1.0–2.3)				
Summary ORs			1.91 (1.69–2.17)		1.73 (1.44–2.07)		1.95 (1.66–2.31)
Number of studies		19		7		9	
Number of cases		4,771		1,826		2,732	
After excluding heterogenous results (see text)							
Summary ORs			NS heterogeneity		1.95 (1.60–2.36)		1.62 (1.35–1.95)
Number of studies				5		7	
Number of cases				1,723		2,010	

OR, odds ratio for maximal category; CI, confidence interval; NS, not significant.
*Data calculated by Armstrong (1988).

Sunburn in adolescence

Seven studies (1,826 cases) specifically reported on sunburn in adolescence, *i.e.*, approx. age 12 up to 20 years, with an overall OR of 1.73 (95% CI 1.44–2.07); 6 studies showed increased risks, significant in 5. Heterogeneity ($\chi^2 = 20.0$, df = 6, $p < 0.01$) was mainly due to one study with a low OR of 0.70 (Cristofolini *et al.*, 1987); with this excluded, the overall OR was 1.95 (95% CI 1.60–2.36; heterogeneity $\chi^2 = 7.5$, df = 5, $p > 0.25$).

Sunburn in childhood

Nine studies (2,732 cases) reported specifically on childhood sunburn, giving an OR of 1.95 (95% CI 1.66–2.31); an increased risk was seen in each study, significant in 5. Heterogeneity ($\chi^2 = 31.6$, df = 8, $p < 0.001$) was due primarily to the ORs of 6.5 and 3.7 in 2 studies (Zanetti *et al.*, 1992; Østerlind *et al.*, 1988); exclusion of these gave an overall OR of 1.62 (95% CI 1.35–1.95), with no significant heterogeneity ($\chi^2 = 11.6$, df = 6, $p > 0.05$).

Heterogeneity

Table III summarizes the overall results and the studies which gave results showing heterogeneity with the overall summary estimate of each association. For intermittent exposure, 1 study had a higher and 2 a lower OR than the summary result. For occupational exposure, there are 4 studies giving ORs considerably higher than the summary result for the remaining 14 studies. For total sun exposure, 2 studies gave lower and 2 gave higher ORs than the summary estimate. For adult or lifetime sunburn, there was no significant heterogeneity. For adolescent sunburn, 1 study gave a lower OR than the others; for the association with childhood sunburn, 2 studies gave ORs considerably higher than the summary value for the other 7 studies.

DISCUSSION

Our report is based on an analysis of the published data from 35 studies. A meta-analysis based on the original data from each study would be much more informative but is an extremely challenging task. Meta-analyses of melanoma case-control studies, restricted to the major studies, have been published for family history and for the number of naevi as risk factors (Bliss *et al.*, 1995; Ford *et al.*, 1995); work on a meta-analysis of sun-exposure variables is continuing (Coldman and Gallagher, 1993). It is, however, extremely difficult as the data items assessed as sun exposure and the methods of recording and coding the data vary between studies. Moreover, unlike other exposures, such as diet, the physical dose of solar radiation received from a given exposure will vary with geographical location and the absorbed dose will vary with personal skin characteristics as well as clothing (Elwood and Diffey, 1993; Diffey and Elwood, 1994).

The overview analysis of these case-control studies is dependent on the choice of results used. We chose the measure of exposure which appeared to fit most clearly the definition of either intermittent, occupational or total sun exposure and of sunburn, and we used the result for the most extreme category from each study. For example, from Holman *et al.* (1986) we used swimming rather than boating or fishing as the index of intermittent exposure; from Autier *et al.* (1994) we used time on vacation with sunbathing, rather than time on vacation without sunbathing. In the former study, the alternative measures gave higher ORs; in the latter study, the alternative OR was lower. Where there was a choice of result with different degrees of control for confounders, we selected results which were controlled for the major true confounders, such as demographic and fixed host factors, but not over-controlled by

TABLE III – SUMMARY OF RESULTS OF OVERVIEW, WITH HETEROGENOUS RESULTS

Exposure	Low results	Summary result excluding outliers (95% CI)	High results
Intermittent exposure			
Number of studies	2	20	1
Number of cases	565	6,162	207
OR	0.75	1.87	8.42
Studies	MacKie and Aitchison (1982) Holly *et al.* (1995)	(1.67–2.09)	Grob *et al.* (1990)
Occupational exposure			
Number of studies		16	4
Number of cases		4,914	1,603
OR		0.76	2.86
Studies		(0.68–0.86)	
			Dubin *et al.* (1986) Garbe *et al.* (1989) Grob *et al.* (1990)
Total exposure			
Number of studies	2	7	2
Number of cases	289	2,944	307
OR	0.56	1.20	4.23
Studies	Graham *et al.* (1985) Cristofolini *et al.* (1987)	(0.00–1.44)	Grob *et al.* (1990) Ródenas *et al.* (1996)
Sunburn: adult/lifetime			
Number of studies		19	
Number of cases		4,771	
OR		1.91	
Studies		(1.69–2.17)	
Sunburn: adolescence			
Number of studies	1	6	
Number of cases	103	1,723	
OR	0.70	1.95	
Studies	Cristofolini *et al.* (1987)	(1.60–2.36)	
Sunburn: childhood			
Number of studies		7	2
Number of cases		2,010	722
OR		1.62	4.55
Studies		(1.35–1.95)	Østerlind *et al.* (1988) Zanetti *et al.* (1992)

adjustment for factors which themselves may be related to sun exposure. While we believe our choice of measures is defensible, for many studies results from other measures of sun exposure could have been selected. We assessed the overall risk ratios using these alternative measures; for each category of sun exposure, these did not produce substantially different results from those shown.

There was statistically significant heterogeneity in regard to most of the exposure measures used, when all results were included. For occupational exposure and childhood sunburn, several studies gave results with considerably higher ORs than the overall summary estimate. This may indicate that these higher results are valid for those study populations or that those studies may have some advantages over the others. Review of the methods of all studies did not reveal any particular characteristics of the studies which gave disparate results, which would clearly explain them. The measurement of sun exposure is extremely complex, and there are no accepted definitions of different types of exposure, different categorizations of level of exposure or even consistency on the use of particular reference groups. If, *e.g.*, there is a true positive relationship with a certain type of exposure, the size of the association seen will be increased if the measure used is a closer indicator of the exposure of biological importance, if the degree of non-differential misclassification error is less, if the reference group used is more extreme towards the low end of the scale, if the maximum exposure category is more extreme or if confounding effects are dealt with in a different way. Analysis of the original data from the studies may help to deal with some of these issues. The ideal solution would be to conduct new studies using compatible protocols in different populations with different levels of sun exposure, using agreed upon definitions and methods of ascertainment. Such approaches would require a major investment in internationally co-ordinated studies.

The overview analysis shows a significant positive association between cutaneous melanoma incidence and high levels of intermittent solar exposure; this is clear both in the overview result and in the results of the great majority of the individual studies. The variation in ORs is likely to be related to the considerable variation in the choice of measures of intermittent exposure. The results confirm those of the most powerful individual studies, in Canada, Europe and Australia, which have reported both general measures of intermittent exposure and results for many specific recreational activities and for vacations (Elwood *et al.*, 1985; Holman *et al.*, 1986; Østerlind *et al.*, 1988).

In contrast, the overall result for occupational exposure shows a small, though significant, reduction in risk. Occupational exposure in general should be easier to document than intermittent exposure, so this provides strong evidence against there being a clear increase in risk at maximum levels of occupational exposure. The best way to assess the contrast between intermittent and occupational exposure is to concentrate on the studies which provide estimates of both as this brings some consistency to the choice of measures used by the authors and the study methods; this comparison also shows a significant increase in risk with intermittent exposure, and a significant decrease in risk for occupational exposure. More detailed analysis of some of the individual large studies suggests that the association with occupational exposure may be non-linear, with an increase in risk related to small amounts of occupational exposure and a decrease in risk with long continued heavy exposure (Elwood *et al.*, 1985). The first component of this may be due to intrmittent exposure related to small amounts of outdoor

work, and the decreased risk at high exposures may suggest that a constant solar irradiation pattern results in an adequate protection mechanism and ultimately in a decreased risk. We were not able to assess this more subtle issue of dose response to occupational exposure in the overview analysis.

If intermittent exposure increases risk and long-term occupational exposure is neutral or decreases risk, it is understandable that the association with total sun exposure is weaker than with intermittent exposure, as seen here. One large study in Queensland, Australia, shows a strong positive effect of total exposure, with a similar result for intermittent exposure, and the conclusion that intermittent and occupational exposures could not be distinguished clearly (Green *et al.,* 1986). This study relates to a white population in the highest solar exposure environment of any of the studies which have been done and suggests that at very high exposure levels the distinction between an intermittent and a chronic exposure pattern is lost. Similar results are seen in 2 European studies, in southern France (Grob *et al.,* 1990) and Spain (Ródenas *et al.,* 1996). The overall conclusion of a positive association with intermittent exposure and a protective or uncertain result for occupational and total exposure is consistent with the detailed results of large studies in moderate-incidence areas, such as Denmark (Østerlind *et al.,* 1988) and Canada (Elwood *et al.,* 1985). The current result is also consistent with a previous, more limited meta-analysis of published studies (Nelemans, 1993) and preliminary work being carried out using the original data from major studies (Coldman and Gallagher, 1993).

A clear and significant positive association is seen with a history of sunburn. Sunburn is caused by unaccustomed severe sun exposure and is, therefore, another indicator of an intermittent exposure pattern. The strength of the association is similar to that of intermittent exposure. The ORs for sunburn in childhood (1.95), in adolescence (1.73) and in adulthood or lifelong (1.91) are similar, though a comparison of ORs for different exposure variables needs to allow for differences in reliability of the questions used. No major studies have reported on the reliability or reproducibility of measures on sun exposure; Westerdahl *et al.* (1996) showed that the reproducibility of responses on sunscreen use and history of sunburn was somewhat lower than for the use of sunbeds or ever having had freckles. Other studies of reliability deal with sunburn, freckling and ability to tan (Berwick and Chen, 1995; Weinstock *et al.,* 1991). No clear difference is seen when the individual results of studies reporting measures at different ages are assessed (Table II). No major difference in effects by age was seen in another recent review of sunburn exposure (Whiteman and Green, 1994).

Thus, these results are consistent with the intermittent exposure hypothesis, that cutaneous melanoma is increased primarily by intermittent unaccustomed sun exposure. The summary results, after the exclusion of heterogenous results, also show a small increase in risk with total sun exposure and a reduction in risk with occupational exposure.

Increased melanoma risk is strongly related to the number of naevi, and naevi are increased in populations and in individuals with high levels of sun exposure (Armstrong and English, 1988). The mechanism for the associations between sun exposure and melanoma remains unknown but may relate to the induction and/or transformation of naevi. It seems likely that the neutral or protective effect of heavy chronic exposure is related to protective mechanisms such as tanning and skin thickening, but this may not be the total explanation. While all the evidence suggests that it is the UV portion of the solar spectrum which is relevant, the contribution of specific wavelength bands and the action spectrum for melanoma induction in humans remains unknown, and the only non-human models are in species very different from humans (International Agency for Research on Cancer, 1992). However, while this mechanism still requires exploration, the empiric evidence that intermittent exposure is a major factor in melanoma production appears clear. The associations with intermittent exposure and sunburn give scientific justification for programmes to reduce individual sun exposure, by concentrating on the reduction of intermittent unaccustomed exposure.

There is now substantial evidence that intermittent sun exposure is the major causal factor in basal cell skin cancer, with major studies showing little or no evidence for a relationship with chronic or total sun exposure (Kricker *et al.,* 1995*a,b*). Squamous cell skin carcinoma, however, does appear to be related to total chronic sun exposure (Strickland *et al.,* 1989). The contrast between the different associations with melanoma and basal cell carcinoma, as compared to squamous cell carcinoma, may be a fruitful area for further work. In particular, if the lack of positive association between chronic exposure and melanoma and basal cell carcinoma is due to protective mechanisms in the skin, the failure of such mechanisms to protect against squamous cell carcinoma needs to be explained (Armstrong and Kricker, 1996).

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REFERENCES

ADAM, S.A., SHEAVES, J.K., WRIGHT, N.H., MOSSER, G., HARRIS, R.W. and VESSEY, M.P., A case-control study of the possible association between oral contraceptives and malignant melanoma. *Brit. J. Cancer,* **44,** 45–50 (1981).

ARMSTRONG, B.K., Epidemiology of malignant melanoma: intermittent or total accumulated exposure to the sun? *J. Dermatol. surg. Oncol.,* **14,** 835–849 (1988).

ARMSTRONG, B.K. and ENGLISH, D.R., The epidemiology of acquired melanocytic naevi and their relationship to malignant melanoma. *In:* J.M. Elwood (ed.), *Melanoma and naevi, pigment cell,* vol. **9,** pp. 27–47, Karger, Basle (1988).

ARMSTRONG, B.K. and KRICKER, A., UV radiation and skin cancer—are melanoma and non-melanocytic skin cancers really different [Abstract]? *In: Third Symposium on the Epidemiology of Melanoma and Non-Melanocytic Skin Cancer,* **1,** British Columbia Cancer Agency, Vancouver (1996).

AUTIER, P., 13 OTHERS and EORTC MALIGNANT MELANOMA COOPERATIVE GROUP, Recreational exposure to sunlight and lack of information as risk factors for cutaneous malignant melanoma. Results of a European Organization for Research and Treatment of Cancer (EORTC) case-control study in Belgium, France and Germany. *Melanoma Res.,* **4,** 79–85 (1994).

BEITNER, H., NORELL, S.E., RINGBORG, U., WENNERSTEN, G. and MATTSON, B., Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. *Brit. J. Dermatol.,* **122,** 43–51 (1990).

BERWICK, M., BEGG, C.B., FINE, J.A., ROUSH, G.C. and BARNHILL, R.L., Screening for cutaneous melanoma by skin self-examination. *J. nat. Cancer Inst.,* **88,** 17–23 (1996).

BERWICK, M. and CHEN, Y., Reliability of reported sunburn history in a case-control study of cutaneous malignant melanoma. *Amer. J. Epidemiol.,* **141,** 1033–1037 (1995).

BLISS, J.M. and 13 OTHERS, Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. *Int. J. Cancer,* **62,** 367–376 (1995).

CHEN, Y., DUBROW, R., HOLFORD, T.R., ZHENG, T., BARNHILL, R.L., FINE, J. and BERWICK, M., Malignant melanoma risk factors by anatomic site: a case-control study and polychotomous logistic regression analysis. *Int. J. Cancer,* **67,** 636–643 (1996).

COLDMAN, A.J. and GALLAGHER, R.P., Re-analysis of four epidemiologic studies of malignant melanoma. *Melanoma Res.,* **3,** 59 (1993).

CRISTOFOLINI, M., FRANCESCHI, S., TASIN, L., ZUMIANI, G., PISCIOLI, F., TALAMINI, R. and LA VECCHIA, C., Risk factors for cutaneous malignant melanoma in a northern Italian population. *Int. J. Cancer,* **39,** 150–154 (1987).

DIFFEY, B.L. and ELWOOD, J.M., Tables of ambient solar ultraviolet radiation for use in epidemiological studies of malignant melanoma and other diseases. *In:* R.P. Gallagher and J.M. Elwood (eds.), *Epidemiological*

aspects of cutaneous malignant melanoma, pp. 81–105, Kluwer, Boston (1994).

DUBIN, N., MOSESON, M. and PASTERNACK, B.S., Epidemiology of malignant melanoma: pigmentary traits, ultraviolet radiation, and the identification of high risk populations. *In:* R.P. Gallagher (ed.), *Epidemiology of malignant melanoma. Recent results in cancer research*, pp. 56–75, Springer-Verlag, Berlin (1986).

DUBIN, N., PASTERNACK, B.S. and MOSESON, M., Simultaneous assessment of risk factors for malignant melanoma and non-melanoma skin lesions, with emphasis on sun exposure and related variables. *Int. J. Epidemiol.*, **19,** 811–819 (1990).

DUNN-LANE, J., HERITY, B., MORIARTY, M.J. and CONROY, R., A case control study of malignant melanoma. *Irish med. J.*, **86,** 57–59 (1993).

ELWOOD, J.M. and DIFFEY, B.L., A consideration of ambient solar ultraviolet radiation in the interpretation of studies of the aetiology of melanoma. *Melanoma Res.*, **3,** 113–122 (1993).

ELWOOD, J.M., GALLAGHER, R.P., HILL, G.B. and PEARSON, J.C.G., Cutaneous melanoma in relation to intermittent and constant sun exposure: the Western Canada Melanoma Study. *Int. J. Cancer,* **35,** 427–443 (1985).

ELWOOD, J.M., GALLAGHER, R.P., HILL, G.B., SPINELLI, J.J., PEARSON, J.C.G. and THRELFALL, W., Pigmentation and skin reaction to sun as risk factors for cutaneous melanoma: Western Canada Melanoma Study. *Brit. med. J.*, **288,** 99–102 (1984).

ELWOOD, J.M. and HISLOP, T.G., Solar radiation in the etiology of cutaneous malignant melanoma in Caucasians. *Monogr. nat. Cancer Inst.*, **62,** 167–171 (1982).

ELWOOD, J.M., WHITEHEAD, S.M., DAVISON, J., STEWART, M. and GALT, M., Malignant melanoma in England: risks associated with naevi, freckles, social class, hair colour, and sunburn. *Int. J. Epidemiol.*, **19,** 801–810 (1990).

ELWOOD, J.M., WILLIAMSON, C. and STAPLETON, P.J., Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. *Brit. J. Cancer,* **53,** 65–74 (1986).

FORD, D. and 12 OTHERS, Risk of cutaneous melanoma associated with a family history of the disease. *Int. J. Cancer,* **62,** 377–381 (1995).

GARBE, C., KRÜGER, S., STADLER, R., GUGGENMOOS-HOLZMANN, I. and ORFANOS, C.E., Markers and relative risk in a German population for developing malignant melanoma. *Int. J. Dermatol.*, **28,** 517–523 (1989).

GRAHAM, S., MARSHALL, J., HAUGHEY, B., STOLL, H., ZIELEZNY, M., BRASURE, J. and WEST, D., An inquiry into the epidemiology of melanoma. *Amer. J. Epidemiol.*, **122,** 606–619 (1985).

GREEN, A., BAIN, C., MCLENNAN, R. and SISKIND, V., Risk factors for cutaneous melanoma in Queensland. *In:* R.P. Gallagher (ed.), *Epidemiology of malignant melanoma. Recent results in cancer research*, pp. 76–97, Springer-Verlag, Berlin (1986).

GREEN, A., SISKIND, V., BAIN, C. and ALEXANDER, J., Sunburn and malignant melanoma. *Brit. J. Cancer,* **51,** 393–397 (1985).

GROB, J.J., GOUVERNET, J., AYMAR, D., MOSTAQUE, A., ROMANO, M.H., COLLET, A.M., NOE, M.C., DICONSTANZO, M.P. and BONERANDI, J.J., Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. *Cancer,* **66,** 387–395 (1990).

HERZFELD, P.M., FITZGERALD, E.F., HWANG, S. and STARK, A., A case-control study of malignant melanoma of the trunk among white males in upstate New York. *Cancer Detect. Prev.*, **17,** 601–608 (1993).

HOLLY, E.A., ASTON, D.A., CRESS, R.D., AHN, D.K. and KRISTIANSEN, J.J., Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. *Amer. J. Epidemiol.*, **141,** 923–933 (1995).

HOLLY, E.A., KELLY, J.W., SHPALL, S.N. and CHIU, S., Number of melanocytic nevi as a major risk factor for malignant melanoma. *J. Amer. Acad. Dermatol.*, **17,** 459–468 (1987).

HOLMAN, C.D.J., ARMSTRONG, B.K. and HEENAN, P.J., A theory of the etiology and pathogenesis of human cutaneous malignant melanoma. *J. nat. Cancer Inst.*, **71,** 651–656 (1983).

HOLMAN, C.D.J., ARMSTRONG, B.K. and HEENAN, P.J., Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits. *J. nat. Cancer Inst.*, **76,** 403–414 (1986).

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, *IARC monographs on the evaluation of carcinogenic risks to humans; ultraviolet radiation*, vol. **55,** IARC, Lyon (1992).

KLEPP, O. and MAGNUS, K., Some environmental and bodily characteristics of melanoma patients. A case-control study. *Int. J. Cancer,* **23,** 482–486 (1979).

KRICKER, A., ARMSTRONG, B.K., ENGLISH, D.R. and HEENAN, P.J., A dose-response curve for sun exposure and basal cell carcinoma. *Int. J. Cancer,* **60,** 482–488 (1995*a*).

KRICKER, A., ARMSTRONG, B.K., ENGLISH, D.R. and HEENAN, P.J., Does intermittent sun exposure cause basal cell carcinoma? A case-control study in Western Australia. *Int. J. Cancer,* **60,** 489–494 (1995*b*).

LEW, R.A., SOBER, A.J., COOK, N., MARVELL, R. and FITZPATRICK, T.B., Sun exposure habits in patients with cutaneous melanoma: a case control study. *J. Dermatol. surg. Oncol.*, **9,** 981–986 (1983).

MACKIE, R.M. and AITCHISON, T., Severe sunburn and subsequent risk of primary cutaneous malignant melanoma in Scotland. *Brit. J. Cancer,* **46,** 955–960 (1982).

MACKIE, R.M., FREUDENBERGER, T. and AITCHISON, T.C., Personal risk-factor chart for cutaneous melanoma. *Lancet,* **2,** 487–490 (1989).

NELEMANS, P., Cutaneous melanoma and sunlight exposure: an attempt to meta-analyse the results of case-control studies [Abstract]. *Melanoma Res.*, **3** (suppl. 1), 59 (1993).

NELEMANS, P.J., RAMPEN, F.H.J., GROENENDAL, H., KIEMENEY, L.A.L.M., RUITER, D.J. and VERBEEK, A.L.M., Swimming and the risk of cutaneous melanoma. *Melanoma Res.*, **4,** 281–286 (1994).

ØSTERLIND, A., TUCKER, M.A., STONE, B.J. and JENSEN, Ø.M., The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. *Int. J. Cancer,* **42,** 319–324 (1988).

PAFFENBARGER, R.S.J., WING, A.L. and HYDE, R.T., Characteristics in youth predictive of adult-onset malignant lymphomas, melanomas, and leukemias: brief communication. *J. nat. Cancer Inst.*, **60,** 89–92 (1978).

PETITTI, D.B., *Meta-analysis decision analysis and cost-effectiveness analysis: methods for quantitative synthesis in medicine*, p. 246, Oxford University Press, New York (1994).

RIGEL, D.S., FRIEDMAN, R.J., LEVENSTEIN, M.J. and GREENWALD, D.I., Relationship of fluorescent lights to malignant melanoma: another view. *J. Dermatol. surg. Oncol.*, **9,** 836–838 (1983).

RÓDENAS, J.M., DELGADO-RODRIGUEZ, M., HERRANZ, M.T., TERCEDOR, J. and SERRANO, S., Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma: a case-control study in a Mediterranean population. *Cancer Causes Control*, **7,** 275–283 (1996).

SORAHAN, T. and GRIMLEY, R.P., The aetiological significance of sunlight and fluorescent lighting in malignant melanoma: a case-control study. *Brit. J. Cancer,* **52,** 765–769 (1985).

STRICKLAND, P.T., VITASA, B.C., WEST, S.K., ROSENTHAL, F.S., EMMETT, E.A. and TAYLOR, H.R., Quantitative carcinogenesis in man: solar ultraviolet B dose dependence of skin cancer in Maryland watermen. *J. nat. Cancer Inst.*, **81,** 1910–1913 (1989).

WEINSTOCK, M.A., COLDITZ, G.A., WILLETT, W.C., STAMPFER, M.J., BRONSTEIN, B.R., MIHM, M.C., JR. and SPEIZER, F.E., Nonfamilial cutaneous melanoma incidence in women associated with sun exposure before 20 years of age. *Pediatrics*, **84,** 199–204 (1989).

WEINSTOCK, M.A., COLDITZ, G.A., WILLETT, W.C., STAMPFER, M.J., ROSNER, B. and SPEIZER, F.E., Recall (report) bias and reliability in the retrospective assessment of melanoma risk. *Amer. J. Epidemiol.*, **133,** 240–245 (1991).

WESTERDAHL, J., ANDERSON, H., OLSSON, H. and INGVAR, C., Reproducibility of a self-administered questionnaire for assessment of melanoma risk. *Int. J. Epidemiol.*, **25,** 245–251 (1996).

WESTERDAHL, J., OLSSON, H. and INGVAR, C., At what age do sunburn episodes play a crucial role for the development of malignant melanoma? *Europ. J. Cancer,* **30A,** 1647–1654 (1994).

WHITE, E., KIRKPATRICK, C.S. and LEE, J.A.H., Case-control study of malignant melanoma in Washington State. 1. Constitutional factors and sun exposure. *Amer. J. Epidemiol.*, **139,** 857–868 (1994).

WHITEMAN, D. and GREEN, A., Melanoma and sunburn. *Cancer Causes Control*, **5,** 564–572 (1994).

ZANETTI, R., FRANCESCHI, S., ROSSO, S., COLONNA, S. and BIDOLI, E., Cutaneous melanoma and sunburns in childhood in a southern European population. *Europ. J. Cancer,* **28A,** 1172–1176 (1992).

ZANETTI, R., ROSSO, S., FAGGIANO, F., ROFFINO, R., COLONNA, S. and MARTINA, G. Etude cas-témoins sur le mélanome de la peau dans la province de Torino, Italie. *Rev. Epidemiol. Santé Publ.*, **36,** 309–317 (1988).

ZARIDZE, D., MUKERIA, A. and DUFFY, S.W., Risk factors for skin melanoma in Moscow. *Int. J. Cancer,* **52,** 159–161 (1992).