Cancer Causes and Control (2005) 16:193–199
DOI 10.1007/s10552-004-4325-5

An analysis of risk factors for cutaneous melanoma by anatomical site (Australia)

Victor Siskind[1], David C. Whiteman[1,*], Joanne F. Aitken[2], Nicholas G. Martin[1] & Adèle C. Green[1]
[1]*Division of Population Studies and Human Genetics, Queensland Institute of Medical Research, Brisbane, QLD, Australia;* [2]*Queensland Cancer Fund, Brisbane, QLD, Australia*

Received 2 March 2004; accepted in revised form 5 May 2004

Key words: melanoma, nevus, risk factors, sunburn.

Abstract

Objective: Emerging evidence suggests that melanomas arising on the head and neck that are not lentigo maligna melanomas have different associations with phenotypic and environmental risk factors than those on the trunk and other sites. We sought to test this hypothesis in a population-based study in Queensland, Australia.
Methods: Risk factor data were collected from 2360 participants with incident cutaneous melanoma diagnosed 1982–1990, including 167 participants with lentigo maligna melanoma. For each risk factor, polytomous logistic regression analysis, using the trunk as a reference category, was used to estimate the odds ratio and 95% confidence interval for cutaneous melanomas by anatomical site.
Results: Participants with melanomas of the head and neck were significantly older than those with melanomas of the trunk (males 52.7 versus 49.7 years; females 47.8 versus 40.5 years). Compared with patients with truncal melanomas, those of the head and neck were less likely to have many nevi (OR 0.41, 95% CI 0.13–1.31), although this did not reach statistical significance. Among females, melanomas of the lower limb were negatively associated with a past history of non-melanoma skin cancer (OR 0.41, 95% CI 0.23–0.74).
Conclusions: We have observed heterogeneity for melanoma risk by anatomical site, lending weight to the hypothesis that cutaneous melanomas may develop through multiple causal pathways.

Introduction

Increasing epidemiologic and experimental evidence supports the theory that melanocytes, the pigment cells of the skin that give rise to melanoma, have different propensities to undergo malignant change depending upon their anatomical location [1].

We have previously proposed the 'divergent pathway' hypothesis for the development of cutaneous melanomas [2]. Our hypothesis posits that people with an inherently low propensity for melanocyte proliferation ('low nevus count' people) will tend to develop cutaneous melanomas only after chronic exposure to the sun, and that melanomas arising in this group of people will occur predominantly on habitually sun-exposed body sites such as the face. We predict that sun exposure initiates carcinogenesis among those with a high propensity for melanocyte proliferation (as characterized by high nevus counts), but thereafter, melanoma development is driven by other factors relating to the host. If our hypothesis were correct, this latter group would be more likely to develop melanoma at sites with unstable melanocyte populations (such as the trunk) than the 'low nevus count' group, and would be expected to have less solar damage.

We recently tested our hypothesis in a case–case comparison study, and found that patients with head and neck melanomas were significantly less likely to have many nevi than patients with truncal melanomas, but were more likely to have many solar keratoses and a past history of non-melanoma skin cancer [3]. Further support for the hypothesis comes from a recent reanalysis of an Italian case–control study [4], which reported similar findings. Here we use data from a large case–control study to explore associations between age, sex, phenotype and family history and risk of melanoma at different body sites.

*Address correspondence to: David C. Whiteman, Division of Population Studies and Human Genetics, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Brisbane, QLD 4029, Australia. Fax: +61-7-3845-3502; E-mail: daveW@qimr.edu.au

Methods

Subjects

Subjects were a population-based sample of melanoma patients and their relatives selected for the Queensland Familial Melanoma Project, as described fully elsewhere [5, 6]. Briefly, a one-page questionnaire about family history of melanoma was sent to 10,407 Queensland residents with a histologically confirmed first primary cutaneous melanoma (either *in situ* or invasive) diagnosed in Queensland between January 1, 1982 and December 31, 1990 and registered with the Queensland Cancer Registry. Only patients for whom the treating doctor's permission had been obtained were approached. Patients with acral lentiginous melanoma were not included. Of 7784 (75%) respondents who agreed to be approached again, all who reported a parent, sibling or child with a history of melanoma (n = 1529) and a 20% sample of those who reported no such family history (n = 1391), were selected for the study, a total of 2920 participants. Relatives were ascertained according to a sequential sampling procedure [7]. All reported first-degree relatives of the selected patients were included in the study, and if any of their relatives had a confirmed cutaneous melanoma then their first-degree relatives were also included, and so on [5].

'Cases' were defined as the selected patients and all relatives of those patients with confirmed cutaneous melanoma, selected according to the above procedure, who returned useable questionnaires. In earlier analyses, cases were compared to a reference group comprising all of the cases' first-degree relatives with no history of melanoma who returned useable questionnaires. In this study all comparisons are between cases with lesions diagnosed at various anatomic sites.

Data collection

A self-administered questionnaire was mailed to the 2920 selected patients assessing standard melanoma risk factors, demographic and medical details, lifetime residence and sun exposure history to date and family history of melanoma [5]. The same questionnaire was mailed to all living first-degree relatives with a confirmed history of melanoma. Data collection was carried out between 1990 and 1994.

Variables for analysis

Age in the analysis was defined as age at diagnosis of melanoma. Skin color, self- assessed on unexposed sites such as the inner upper arm, was recorded in three categories (olive, medium, fair), eye color in three categories (blue/gray, green/hazel, brown), and early adult hair color in five categories (dark brown/black, fair/blonde, light brown, light red/ginger, dark red/auburn). Propensity to burn in the sun was categorized as 'always burn' or other, and tanning ability after prolonged sun exposure as 'slight or no tan' or other. Nevus density was recorded in four categories by comparison with diagrammatic representations (none, few, moderate or many) and density of freckling in summer was categorized as none, ≤100 freckles or >100. Number of sunburns during life was grouped as ≤5 or >5.

Cumulative lifetime UV exposure

A lifetime residence calendar asked in which town and state or country subjects had resided when aged 0–4 years (preschool), 5–12 years (primary school), 13–19 years (adolescence), 20–29 years and during each subsequent decade of life, and what proportion of the day during that period was spent in the sun. For Australian places of residence an average annual UV flux was assigned from tables prepared by Paltridge and Barton [8]. Localities outside Australia were assigned UV values calculated by Whiteman and Green [9]. For periods spent in the armed forces an average value was calculated from the experience of Australian ex-serviceman [9]. Missing UV values due to gaps in the residential record or unreported proportions of time outdoors were filled by inspection of the original questionnaire, by interpolation or by imputation, as described in an earlier paper (6). Cumulative age-specific UV doses from age 20 years were computed by multiplying the average annual UV flux in each life period by the reported proportion of time spent outdoors during that period, and summing to index age, taking the different period lengths into account and interpolating where necessary. In these analyses an average adult UV dose, that is the cumulative total dose since age 20 years divided by index age minus 20 years, was used.

Childhood and adolescent UV exposure

Separate questions asked about hours spent in the sun in summer on weekdays, weekend days and annual holidays between 9 a.m. and 3 p.m. from ages 5 to 12 years, and 13 to 19 years. Solar radiation during these 6 h accounts for about 75% of the total daily UV dose [10]. Each subject's annual total hours of exposure was calculated assuming a six-week summer holiday and taking the responses to apply to the entire year. (Although the question referred only to summer, over much of Australia and especially in Queensland, winters

are mild and the UV flux is substantial [10], thus to neglect winter exposure would introduce greater inaccuracy than confining the calculation to summer.) The cumulative UV doses for these two periods were again computed by multiplying the average annual UV flux for the place of residence by the total hours of exposure in each period. In calculating exposure, these values, termed 'childhood exposure' and 'adolescent exposure', were used in place of the exposures calculated from the residence calendar for the same periods as they were more specific and the questions were more completely answered. From analyses reported earlier [6] it transpired that adolescent exposure had no influence on melanoma risk in models including also childhood exposure, and thus it was not further considered.

The adult and childhood UV exposure variables were included as quantitative variables in all data-analytic models as in an earlier paper [6]. Substitution of three indicator variates for each, formed by division of the respective total distributions at the quartiles, made no discernible difference to any result.

History of non-melanoma skin cancer (NMSC)

Subjects reported their histories of treated NMSC, either basal cell (BCC) or squamous cell carcinoma (SCC), and the year in which they were first diagnosed. A single variable was derived indicating the presence/absence of a history of BCC or SCC upto the age of first diagnosis of melanoma. NMSC with unreported dates of diagnosis (15% of cases) were disregarded, since lesions with unknown dates could have occurred after the diagnosis of melanoma. Subjects were also asked whether they had had solar keratoses removed, but this information was not judged reliable enough for use.

Melanoma histology was categorized as nodular, superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM) and other and unspecified. LMM is believed to have a rather different etiology to other histological types [11]; as reported below, persons with the former were on average several years older than the latter and this lesion occurred preferentially on the head and neck. Subjects whose lesion had been classified as LMM were excluded from the main analyses.

Sites considered were head and neck, trunk, upper limbs and lower limbs. A small 'other site' class (including 'unspecified') was disregarded in all analyses except those concerning age at diagnosis.

Data analysis

For the analysis of risk factors, polytomous logistic regression analysis was used, controlling as tightly as possible for age by including age (in years) and age squared as continuous variables. In these analyses the reference category was the trunk, and the Wald 'effect' chi-square for each factor included (with three degrees of freedom) served as a test of heterogeneity. We present these effect chi-squares for each of the four exposure factors (childhood and adult UV exposure, sunburns and NMSC history), for nevus density as a quantitative variable and for those personal factors showing significant heterogeneity; overall and by gender. Site-specific odds ratios and their standard errors are presented for factors where significant heterogeneity was present. The factors examined were childhood and adult (≥20 years of age) UV exposures as defined above, history of NMSC, sunburn history (<6, ≥ 6), sex, tanning ability (deep/moderate tan, slight/no tan), skin type (always or usually burn, sometimes or never burn), skin color, eye color (brown, other), hair color (blonde/light brown, red/auburn, dark), nevus density (both as a quantitative variable, scored 1 for 'few', 2 for 'moderate' and 3 for 'many' and as three indicator variables) and freckles (<100, ≥ 100).

In previous work the familial melanoma risk of each participant had been categorized as low, intermediate and high by the degree to which the number of melanoma cases in the proband's family exceeded or fell short of the number expected on the basis of population incidence rates and the family members' sexes, ages and birth cohorts [12]. Subgroups defined by both high or intermediate risk level and site were too small for analysis of risk factors. However a table of risk level by site is presented. Age at diagnosis was analyzed by conventional normal theory models, in particular, analysis of variance.

Results

The sample comprised 2360 persons with melanoma, 167 of whom were diagnosed with LMM. The latter subjects had a mean age at diagnosis of 63.1 years compared with 48.1 years among subjects with other melanoma diagnoses ($p < 0.001$). Almost a quarter of lesions on the head and neck were classified as LMM, compared to only 4.4% on other sites ($p < 0.001$). As explained above, subjects with LMM were excluded from further analysis. Subjects with other and unreported sites, 7.5% of the remainder, were excluded from all site-specific analyses, although we report their mean age at diagnosis.

After the above exclusions, and exclusions due to missing values, 1039 subjects, 495 males and 544 females, formed the final sample for multivariate analysis. Of these, 231 (22%) were in family clusters of two

(89%), three (9%) or four (2%) first-degree relatives. However, there was no evidence of intra-family concordance by site (average κ, 0.09), and all intra-family correlations for risk factors were at most modest (range: 0.08–0.26), and negligible (−0.03) for age at diagnosis. Family clustering has therefore been ignored.

Age at diagnosis

Males were on average 4.6 years older at diagnosis than females (50.6 *versus* 46.0 years). The same pattern was observed at all subsites, the difference reaching statistical significance for melanomas on the head and neck (52.7 *versus* 47.8 years), upper limb (52.4 versus 47.8 years) and, in particular, on the trunk (49.7 *versus* 40.5 years). At diagnosis, males with lesions on the ears were over four years older on average than females with similarly sited melanomas, but there were only four cases of the latter (Table 1). Ears were not considered separately from head and neck in the remaining analyses.

After excluding the 'other and unspecified' class, there was significant heterogeneity within sexes among the sites with respect to age at diagnosis (males: $F_{3,931} = 2.95$, $p = 0.032$; females: $F_{3,1090} = 13.5$, $p < 0.001$). In males, lesions on the lower limbs and trunk were diagnosed on average at similar ages, whereas those on the upper limbs and head and neck were diagnosed about three years later. On the other hand, females with melanomas on the head and neck and on the limbs presented on average at approximately the same age, but those with lesions on the trunk some seven years earlier (Table 1).

Sex

It is well known that the site distribution of melanoma differs markedly between males and females, and this is reflected in the large value of the homogeneity statistic for this factor (Table 2). As anticipated, females had more lesions on the lower limbs and males on the trunk. Females also had a significant excess of melanomas on the upper limbs.

Phenotypic characteristics

Table 2 lists the homogeneity statistics obtained from the polytomous logistic regression analysis of melanoma cases with the trunk as reference category. All models included four factors related to sun exposure and seven derived from personal characteristics. Age was controlled by including a linear and a quadratic term in all models [13].

No evidence of heterogeneity in childhood or adult UV exposure was noted, whereas the indirect measures, history of NMSC and sunburn history, did demonstrate significant heterogeneity, although not among males. For history of NMSC, the discrepant site is the lower limbs, (OR = 0.41 95% CI, 0.23–0.74 among females, OR = 0.55, 95% CI, 0.38–0.82 overall) while the discrepant site for sunburn history is the head and neck, with estimated odds ratios of 0.28 (95% CI, 0.12–0.67) among females and 0.48 (95% CI, 0.29–0.80) overall (Table 3). The corresponding odds ratios relating to melanomas on the upper and lower limbs are all close to unity for both factors (Table 3). The only other factor showing significant heterogeneity is light colored hair in males only; the odds ratio for the head and neck was significantly less than unity, being 0.44 (95% CI, 0.23–0.88).

Table 1. Mean age at diagnosis by sex and site (subjects with LMM excluded)

Site	Males			Females		
	n	Mean	SD	n	Mean	SD
All	1026	50.6	15.4	1167	46	15.8
Head and neck						
excluding ears	107	52.1	17.0	104	47.7	17.2
including ears	124	52.7	16.7	108	47.8	16.9
Ears	17	56.6	14.7	4	52.3	7.8
Trunk	434	49.7	15.5	252	40.5	14.4
Upper limbs	210	52.4	16.1	303	47.9	15.7
Lower limbs	167	48.8	13.8	431	47.3	15.6
Other and unspecified	91	50.5	14.4	73	46.4	16.62

Table 2. Homogeneity statistics for factors related to UV exposure and personal characteristics

Factor[a]	Males	Females	Overall
Childhood UV exposure	0.18	0.64	0.62
Adult UV exposure	1.20	0.61	2.15
History of NMSC	3.49	12.31*	8.81*
Sunburn history (< 6/≥6)	4.67	8.68*	10.44*
Nevus density	2.05	2.55	3.99
Skin color	1.01	3.29	2.26
Blond/light brown hair	7.84*	0.07	4.02
Red/auburn hair	3.22	2.68	1.24
Tanning ability (deep/moderate tan, slight/no tan)	2.52	2.77	0.96
Skin type (always or usually burn, sometimes or never burn)	5.95	7.01	2.22
Freckle density (< 100, ≥100)	0.84	4.50	5.33
Eye color (brown, other)	4.62	2.73	2.93
Sex			56.76**

[a] calculated from polytomous logistic regression and distributed as χ^2 with 3 degrees of freedom
* $p < 0.05$; ** $p < 0.01$.

Table 3. Odds of developing melanoma on the head and limbs compared with trunk associated with salient risk factors

Factor	Head and neck		Upper limb		Lower limb	
	OR	95% CI	OR	95% CI	OR	95% CI
Males						
History of NMSC	0.84	0.43–1.64	0.61	0.35–1.04	0.97	0.55–1.70
Sunburn history	0.65	0.34–1.26	0.88	0.52–1.47	1.43	0.84–2.5
Nevus density						
Few	0.85	0.34–2.2	1.08	0.50–2.3	1.35	0.55–3.3
Moderate	0.67	0.24–1.83	0.99	0.44–2.3	0.97	0.38–2.5
Many	0.41	0.09–1.80	0.61	0.19–1.91	1.03	0.33–3.2
Quantitative	0.76	0.51–1.13	0.89	0.65–1.21	0.92	0.66–1.26
Light hair color	0.44	0.23–0.85	1.18	0.66–2.1	1.04	0.57–1.90
Females						
History of NMSC	0.88	0.38–2.0	0.99	0.55–1.77	0.41	0.23–0.74
Sunburn history	0.28	0.12–0.67	0.89	0.52–1.54	0.89	0.54–1.46
Nevus density						
Few	1.92	0.54–6.7	0.77	0.33–1.82	1.05	0.46–2.4
Moderate	1.17	0.32–4.3	0.63	0.26–1.51	0.92	0.40–2.1
Many	0.42	0.06–2.8	0.97	0.36–2.6	0.80	0.29–2.2
Quantitative	0.72	0.47–1.10	0.94	0.69–1.29	0.88	0.66–1.18
Overall						
History of NMSC	0.83	0.50–1.37	0.80	0.54–1.17	0.55	0.38–0.82
Sunburn history	0.48	0.29–0.80	0.95	0.65–1.37	1.13	0.79–1.60
Nevus density						
Few	1.24	0.59–2.6	0.87	0.50–1.51	1.14	0.65–2.0
Moderate	0.85	0.39–1.85	0.75	0.42–1.33	0.93	0.52–1.67
Many	0.41	0.13–1.31	0.85	0.42–1.71	0.87	0.42–1.77
Quantitative	0.75	0.57–1.00	0.92	0.74–1.14	0.90	0.73–1.10
Female sex	1.26	0.77–2.05	2.4	1.61–3.5	3.9	2.7–5.6

For the factor of *a priori* interest, nevus density on the body, the heterogeneity statistic was not significant, although the odds ratios arising from the quantitative formulation of nevus density were all below unity relative to the trunk for the head and neck, with little difference between males and females (Table 3). The odds ratios associated with the nevus density indicator variables are consistent with the existence of a gradient.

The site distribution by level of familial risk as estimated by the method described above is given in Table 4, unadjusted for age or sex. Adjustment for these factors causes only minor changes to the distribution, which shows little association between site and familial melanoma risk ($\chi^2_6 = 11.4$, $p = 0.08$ unadjusted for age and sex, $= 9.4$, $p = 0.15$ after adjustment).

Discussion

We have found that cutaneous melanomas grouped according to their site of occurrence differ in the magnitude of associations with some established risk factors. Importantly, our analyses excluded patients with LMM (which typically occur on the face) and acral lentiginous melanoma (which typically occur on the distal extremities), for which risk factor differences have already been described [11, 14]. The most notable effects observed here were the different age and sex distributions of patients with melanomas at different anatomical sites. Patients with cutaneous melanomas on the head and neck (not including LMM) were diagnosed at significantly older ages than patients with melanomas at other body sites, whereas patients with melanomas of the trunk were younger at diagnosis than other melanoma patients. Other risk factors were also differently associated with melanoma by anatomical site. A history of more than six sunburns was significantly less likely among people with melanomas of the face, and the risk of melanoma associated with large numbers of melanocytic nevi was weakest for melanomas of the head and neck and strongest for melanomas of the trunk.

We considered the possibility that our findings might be explained by various sources of error. Random error may account for some findings as many statistical tests were performed. All measures of exposure or phenotype in this study were self-reported by participants, consequently some misclassification cannot be excluded. But since the analysis was confined to subjects who had had

Table 4. Site distribution by familial risk level

Site	Head and neck N (%)	Trunk N (%)	Upper limb N (%)	Lower limb N (%)	Total N (%)
Familial risk level					
High	17 (8.7)	58 (29.7)	57 (29.2)	63 (32.3)	195 (100)
Intermediate	67 (11.2)	190 (31.9)	138 (23.2)	201 (33.7)	596 (100)
Low	136 (11.6)	409 (35.0)	304 (26.0)	321 (27.4)	1170 (100)

melanoma, any misclassification will almost certainly be non-differential, and would, on average, tend to reduce the magnitude of observed associations. Confounding by recognized or unrecognized factors other than age is unlikely. Introducing a quadratic age term results in tighter control of this factor.

We have ignored the fact that a proportion of our subjects formed clusters of two or more first-degree relatives. The absence of intra-family concordance for site implies that relatives were as likely to be in a different site categories as in the same category. It can be shown that under these circumstances the effect on first or second moment functions is small, especially since there are no strong correlations between family members in any risk factor.

Our sample of melanoma subjects has previously been shown to be similar in age and sex structure to the overall distribution of melanoma patients in the source population, hence biased selection of study participants is unlikely to explain our findings [6].

Our findings are in broad agreement with previous epidemiologic research, although most published papers dealing with the site distribution of cutaneous melanoma are essentially concerned with the etiological role of intermittent *versus* chronic UV exposure, a topic which our data cannot adequately address. At the descriptive level, it has long been recognized that melanomas are distributed across the body surface in patterns that defy simple explanations based on differences in sun exposure alone. For example, while melanomas typically occur most frequently on sun exposed body sites [13, 15], there are notable exceptions. The high incidence of cutaneous melanomas on some relatively unexposed body sites (such as the lower limbs in females) contrasts with the paucity of melanomas on some habitually exposed sites (such as the forearms and dorsum of the hand), indicating that site-specific differences in melanoma development are likely to exist [16]. Moreover, the incidence of melanomas of the trunk peaks before that of the head and neck, even after accounting for the underlying effects of birth cohort and time period on melanoma rates [13, 15, 17–20]. These descriptive observations suggest that melanomas develop through different pathways depending upon their anatomical location, for which there is some support from analytical epidemiological studies.

A case–control study [21] restricted to women with SSM found that sunburns in childhood and adolescence, nevus counts and blond hair were least associated with tumors on the legs. In contrast, at least three other case-control studies observed markedly increased risks for melanoma of the trunk and legs associated with having many nevi, but found weaker associations with melanomas of the head and neck or upper limbs [22–24]. Another case–control study [25] found that people with melanomas of the trunk, upper limb, and lower limb were almost six-fold more likely than disease-free controls to have many nevi, whereas people with melanoma of the head and neck were only 3-fold more likely than controls to have many nevi. These differences were not statistically significant however. Most recently, two studies conducted in Australian populations [3, 26] found that patients with melanomas of the head and neck had substantially fewer nevi and more solar keratoses than patients with melanoma of the trunk.

Several investigators have put forward the theory that the proliferative behavior of melanocytes, the cells of origin for melanoma, may vary according to anatomical site [1, 3, 27]. While differences in melanoma incidence and age-at-onset across anatomical regions may reflect site-specific differences in the density of epidermal melanocytes [28–30], there is now experimental evidence from studies in mice that the site of origin of a donor graft determines the frequency with which melanoma develops in transplanted skin [31]. We conclude that melanomas at different anatomical sites might arise through different causal pathways. Investigating this intriguing hypothesis should be the aim of future epidemiologic research.

Acknowledgements

This work was supported by grants from the National Health and Medical Research Council of Australia (961061, 981339, 199600), the Queensland Cancer Fund, the Cooperative Research Centre for Discovery of Genes for Common Diseases, and the US National Cancer Institute (CA88363). We thank the melanoma patients and their families for their cooperation. David

Whiteman is a Senior Research Fellow of the National Health and Medical Research Council of Australia.

References

1. Green A (1992) A theory of site distribution of melanomas: Queensland, Australia. *Cancer Causes Control* **3:** 513–56.
2. Whiteman DC, Green A, Parson PG (1998) p53 expression and risk factors for cutaneous melanoma: a case-control study. *Int J Cancer* **77:** 843–848.
3. Whiteman DC, Watt P, Purdie DM, *et al.* (2003) Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* **95:** 806–812.
4. Carli P, Palli D (2003) Re: melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* **95:** 1801.
5. Aitken JF, Green AC, MacLennan R, Youl P, Martin NG (1996) The Queensland Familial Melanoma Project: study design and characteristics of participants. *Melanoma Res* **6:** 155–165.
6. Siskind V, Aitken J, Green A, Martin N (2002) Sun exposure and interaction with family history in risk of melanoma, Queensland, Australia. *Int J Cancer* **97:** 90–95.
7. Cannings C, Thompson EA (1977) Ascertainment in the sequential sampling of pedigrees. *Clin Genet* **12:** 208–212.
8. Paltridge GW, Barton IJ (1978) Erythemal ultraviolet radiation over Australia.
9. Whiteman D, Green A (1998) History of tropical military service and risk of primary cutaneous melanoma in Queensland men. *Melanoma Res* **8:** 60–63.
10. Barton IJ, Paltridge GW (1979) The Australian climatology of biologically effective ultraviolet radiation. *Australas J Dermatol* **20:** 68–74.
11. Cohen LM (1995) Lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol* **33:** 923–936.
12. Aitken JF, Duffy DL, Green A, *et al.* (1994) Heterogeneity of melanoma risk in families of melanoma patients. *Am J Epidemiol* **140:** 961–973.
13. Green A, MacLennan R, Youl P, Martin N (1993) Site distribution of cutaneous melanoma in Queensland. *Int J Cancer* **53:** 232–236.
14. Green A, McCredie M, MacKie R, *et al.* (1999) A case-control study of melanomas of the soles and palms (Australia and Scotland). *Cancer Causes Control* **10:** 21–25.
15. Osterlind A, Hou-Jensen K, Moller-Jensen O (1988) Incidence of cutaneous malignant melanoma in Denmark 1978–1982. Anatomic site distribution, histologic types and comparison with non-melanoma skin cancer. *Br J Cancer* **58:** 385–391.
16. Green A, McCredie M, Giles G, Jackman L (1996) Occurrence of melanomas on the upper and lower limbs in eastern Australia. *Melanoma Res* **6:** 387–394.
17. Magnus K (1973) Incidence of malignant melanoma of the skin in Norway, 1955–1970: variations in time and space and solar radiation. *Cancer* **32:** 1275–1286.
18. Teppo L, Pakkanen M, Hakulinsen T (1978) Sunlight as a risk factor of malignant melanoma of the skin. *Cancer* **41:** 2018–2027.
19. Thorn M, Bergstrom R, Adami H-O, Ringborg U (1990) Trends in the incidence of malignant melanoma in Sweden, by anatomic site, 1960–1984. *Am J Epidemiol* **132:** 1066–1077.
20. Bulliard JL, Cox B, Elwood JM (1997) Comparison of the site distribution of melanoma in New Zealand and Canada. *Int J Cancer* **72:** 231–235.
21. Cress RD, Holly EA, Ahn DK, LeBoit PE, Sagebiel RW (1995) Cutaneous melanoma in women: anatomic distribution in relation to sun exposure and phenotype. *Cancer Epidemiol Biomarkers Prev* **4:** 831–836.
22. Weinstock MA, Colditz GA, Willett WC, *et al.* (1989) Moles and site-specific cutaneous malignant melanoma in women. *J Natl Cancer Inst* **81:** 948–952.
23. Kruger S, Garbe C, Buttner P, *et al.* (1992) Epidemiologic evidence for the role of melanocytic nevi as risk markers and direct precursors of cutaneous malignant melanoma. *J Am Acad Dermatol* **26:** 920–926.
24. Rieger E, Soyer HP, Garbe C, *et al.* (1995) Overall and site-specific risk of malignant melanoma associated with nevus counts at different body sites: a multicenter case-control study of the German central malignant-melanoma registry. *Int J Cancer* **62:** 393–397.
25. Chen YT, Dubrow R, Holford TR, *et al.* (1996) Malignant melanoma risk factors by anatomic site: a case-control study and polychotomous logistic regression analysis. *Int J Cancer* **67:** 636–643.
26. Bataille V, Sasieni P, Grulich A, *et al.* (1998) Solar keratoses: a risk factor for melanoma but negative association with melanocytic naevi. *Int J Cancer* **78:** 8–12.
27. Autier P, Boniol M, Severi G, *et al.* (2001) The body site distribution of melanocytic naevi in 6–7 year old European children. *Melanoma Res* **11:** 123–131.
28. Quevedo WC, Szabo G, Virks J, Sinesi SJ (1965) Melanocyte populations in UV-irradiated human skin. *J Invest Dermatol* **45:** 295–298.
29. Whiteman DC, Parson PG, Green AC (1999) Determinants of melanocyte density in adult human skin. *Arch Dermatol Res* **291:** 511–516.
30. Szabo G (1954) The number of melanocytes in human epidermis. *Br Med J* **1:** 1016–1017.
31. Silvers WK, Mintz B (1998) Differences in latency and inducibility of mouse skin melanomas depending on the age and anatomic site of the skin. *Cancer Res* **58:** 630–632.