Nevi, Family History, and Fair Skin Increase the Risk of Second Primary Melanoma

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Although risk factors for primary cutaneous melanoma are well defined, relatively little is known about predictors for second primary melanoma. Given the rising incidence of this cancer, coupled with improvements in survival, there is a prevalent and growing pool of patients at risk of second primary melanomas. To identify the predictors of second primary melanoma, we followed a cohort of 1,083 Queensland patients diagnosed with incident melanoma between 1982 and 1990 and who completed a baseline questionnaire. During a median follow-up of 16.5 years, 221 patients were diagnosed with at least one additional primary melanoma. In multivariate analyses, second primary melanomas were associated with high nevus count (hazard ratio (HR), 2.91; 95% confidence interval (CI) 1.94–4.35), high familial melanoma risk (HR, 2.12; 95% CI 1.34–3.36), fair skin (HR, 1.51; 95% CI 1.06–2.16), inability to tan (HR, 1.66; 95% CI 1.13–2.43), an *in situ* first primary melanoma (HR, 1.36; 95% CI 0.99–1.87), and male sex (HR, 1.49; 95% CI 1.12–2.00). Patients whose first primary was lentigo maligna melanoma (HR, 1.80; 95% CI 1.05–3.07) or nodular melanoma (HR, 2.13; 95% CI 1.21–3.74) had higher risks of subsequent primaries than patients whose first primary tumor was superficial spreading melanoma. These characteristics could be assessed in patients presenting with first primary melanoma to evaluate risk of developing a second primary.

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INTRODUCTION

During the past several decades, there have been marked increases in the incidence of cutaneous melanoma in fair-skinned populations around the world, particularly for thin melanomas (Garbe *et al.*, 2000; Jemal *et al.*, 2001; de Vries *et al.*, 2003; Coory *et al.*, 2006; MacKie *et al.*, 2007). Whereas for previous generations, a diagnosis of melanoma carried a grim prognosis, the majority of melanoma patients diagnosed today can expect to survive their disease. However, the improved survival rates coupled with population-wide increases in life expectancy mean that the risk of developing a subsequent melanoma will inevitably rise. This poses clinical challenges, for while guidelines exist to treat cutaneous melanoma and to manage recurrence, little attention has been paid to manage the risk of subsequent invasive melanoma.

Registry-based linkage studies suggest that the cumulative incidence of second primary melanomas varies across populations, estimated at 1.5% at 10 years in Switzerland (Levi *et al.*, 2005), 5.3% in the United States; (Goggins and Tsao, 2003), and 6.4% in Queensland, Australia (McCaul *et al.*, 2008). More detailed analyses of registry and clinical case series show that the risk of subsequent melanoma is highest in the first year following initial diagnosis (Goggins and Tsao, 2003; Ferrone *et al.*, 2005; McCaul *et al.*, 2008), and that the annual rate of new diagnoses of primary melanoma appears to be relatively constant thereafter (McCaul *et al.*, 2008). Most studies, but not all, indicate that the risk of subsequent melanoma increases with the age at which the first melanoma was diagnosed, but that sex and anatomic site do not appear to influence the risk of subsequent lesions (Goggins and Tsao, 2003; McCaul *et al.*, 2008).

Phenotypic or other host factors that could be ascertained in the clinic and which might predict future risk of subsequent melanomas have been examined only in two prospective studies (Ferrone *et al.*, 2005; Titus-Ernstoff *et al.*, 2006) from which some consistent features have emerged. A verified family history of melanoma and the presence of either very large numbers of banal nevi or at least one atypical nevus have been associated with increased risks of subsequent melanomas in both studies. Evidence for a role of pigmentary characteristics (such as freckling, hair color, and skin type) that are strongly associated with the risk of developing primary melanoma is inconsistent owing to the paucity of data.

In this study, we document the distribution of second and subsequent melanomas in a large prospective cohort of Queensland patients diagnosed with primary cutaneous

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Abbreviations: QCR, the Queensland Cancer Registry; QFMP, the Queensland Familial Melanoma Project

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melanoma, and identify the factors associated with their development.

RESULTS

The age and sex distribution of the 1,083 probands in the Queensland Familial Melanoma Project (QFMP) follow-up study are given in Table 1. There were 27% more women than men, and the latter were on average almost 4 years older (47.8 years among men, 43.9 among women). Only two probands were related to one another. The mean interval from index diagnosis to follow-up contact was 16.8 years (median 16.5 years) with a range of 12.3–23.0 years. There was little variation in this respect between men and women or by age.

Table 1. Distribution by sex of characteristics of participants (probands) in the QFMP follow-up study

	Males (*N*=477)	Females (*N*=606)	Total (*N*=1,083)
	N (%)	*N* (%)	*N* (%)
Age (years)			
<40	135 (28.3)	245 (40.4)	380 (35.1)
40–49	122 (25.6)	154 (25.4)	276 (25.5)
50–59	123 (25.8)	122 (20.1)	245 (22.6)
⩾60	97 (20.3	85 (14.0)	182 (16.8)
Site[1]			
Head/neck	66 (13.8)	56 (9.2)	122 (11.3)
Trunk	217 (45.5)	133 (22.0)	350 (32.3)
Upper limbs	92 (19.3)	157 (25.9)	249 (23.0)
Lower limbs	72 (15.1)	237 (39.1)	309 (28.5)
Unspecified	30 (6.3)	23 (3.8)	53 (4.9)
Clark level[1]			
1	110 (23.1)	136 (22.4)	246 (22.7)
2	191 (40.0)	256 (42.2)	447 (41.3)
3	85 (17.8)	110 (18.2)	195 (18.0)
4/5	52 (10.9)	64 (10.6)	116 (10.7)
Missing	39 (8.2)	40 (6.6)	79 (7.3)
Familial risk group			
High	30 (6.3)	33 (5.4)	63 (5.8)
Intermediate	109 (22.8)	170 (28.1	279 (25.8)
Low	338 (70.9)	403 (66.5)	741 (68.4)
Morphology[1]			
Nodular	29 (6.1)	30 (5.0)	59 (5.4)
SSM	318 (66.7)	435 (71.8)	753 (69.5)
LMM	26 (5.4)	28 (4.6)	54 (5.0)
NOS	104 (21.8)	113 (18.6)	217 (20.0)

Abbreviations: LMM, lentigo maligna melanoma; NOS, not otherwise specified; SSM, superficial spreading melanoma.
[1]Tumor-specific characteristics relate to the first primary melanoma.

Occurrence and characteristics of second primary melanomas

There were 221 persons in the subcohort with at least one primary melanoma other than the index lesion and a total of 375 such lesions (118 *in situ* and 257 invasive). Among these, the index melanoma was *in situ* or invasive in 63 and 158 persons, respectively. Excluding those with only synchronous melanomas reduced these numbers to 208 individuals (61 with *in situ* and 147 with invasive index melanomas) with at least one subsequent metachronous primary melanoma and 362 lesions (116 *in situ* and 246 invasive). The 158 individuals with invasive index lesions had 152 invasive and 105 *in situ* additional melanomas. In total, more than 20% of the overall sample had more than one primary melanoma, and one individual had nine (Table 2).

Compared with those with *in situ* index lesions, participants whose first primary melanoma was invasive (Clark level 2 or greater) were somewhat more likely to have invasive second melanomas but the difference was not statistically significant (Table 3). There was little difference in mean and median thickness from index to second metachronous melanoma (index melanoma: mean 0.82 ± 0.03 mm, median 0.55 mm; second metachronous melanoma: mean 0.85 ± 0.09 mm, median 0.55 mm). There was only weak evidence of specific anatomical concordance between the body site of the index and second metachronous primary melanomas (unweighted κ 0.21) although the association was highly significant (Table 3).

Table 2. Number of persons with at least one synchronous melanoma and by number of metachronous melanomas by behavior of index melanoma

	In situ	Invasive	Total
	N (%)	*N* (%)	*N* (%)
Number of additional melanomas			
0	199 (76.0)	663 (80.8)	862 (79.6)
Synchronous melanomas only			
	2 (0.8)	11 (1.3)	13 (1.2)
Metachronous melanomas			
1	33 (12.6)	93 (11.3)	126 (11.6)
2	14 (5.3)	28 (3.4)	42 (3.9)
3	8 (3.1)	13 (1.6)	21 (1.9)
4	3 (1.1)	7 (0.9)	10 (0.9)
5	2 (0.8)	6 (0.7)	8 (0.7)
⩾6	1 (0.4)	0 (0.0)	1 (0.1)
Total	262	821	1083

Table 3. Behavior and anatomic site of index melanomas versus metachronous second primary melanomas

Index melanoma	*In situ* (*N*)	*In situ* (%)	Invasive (*N*)	Invasive (%)	Total (*N*)	Total[1] (%)
In situ	34	55.7	27	44.3	61	29.3
Invasive	64	43.5	83	56.5	147	70.7
Total	98	47.1	110	52.9	208	100

Index melanoma	Head/neck, *N* (%)	Trunk, *N* (%)	Upper limb, *N* (%)	Lower limb, *N* (%)	Total (*N*)	Total[2] (%)
Head/neck	15 (50.0)	5 (16.7)	6 (20.0)	5 (16.7)	31	14.9
Trunk	10 (15.4)	28 (44.6)	14 (21.5)	12 (18.5)	64	32.2
Upper limb	15 (30.0)	13 (26.0)	15 (30.0)	7 (14.0)	50	24.8
Lower limb	7 (12.3)	10 (17.5)	15 (26.3)	25 (43.9)	57	28.2
Total	47 (23.3)	56 (27.7)	50 (24.7)	49 (24.3)	202	100

[1]Six index melanomas and second metachronous melanomas did not have anatomical site recorded.
[2]Totals do not sum to 100% due to rounding.

Predictors of multiple primary melanomas: univariate analyses
Mean numbers of subsequent melanomas increased by age overall and in women, whereas in men the only major difference was between those under 40 years of age and those in older age groups (Table 4). Sex, age, morphology, familial risk, numbers of nevi, red phenotype, skin color, skin type, tanning ability, and a history of solar keratoses or non-melanoma skin cancers were all significantly related to numbers of subsequent primary melanomas, some highly significantly; invasive behavior showed a marginal association (Table 4). Associations were generally weaker in women. We found no overall association between numbers of subsequent primary melanomas and any of anatomic site, freckling, Clark level, history of sunburns, and hair or eye color. Findings from failure-time analyses of time to first metachronous primary melanoma were broadly similar, except that the association with invasive behavior was stronger.

Of 40 individuals with at least four primary melanomas, 11 were from the high-risk group, almost five times expectation assuming no association between familial history and risk of multiple primaries, whereas 18 were from the low-risk group, 30% less than expectation.

We observed no association between time to second metachronous primary and either the thickness of index melanoma or with continuous measures of UV exposure in childhood, adolescence, or adulthood (data not shown). All nonparametric correlations were small, between −0.05 and 0.04, and nonsignificant (data not shown).

Table 4. Nonparametric (Kruskal–Wallis) analysis of variance of numbers of melanomas (excluding index primary)

		Males		Females		All	
Factor	d.f.	χ^2	*P*	χ^2	*P*	χ^2	*P*
Sex	1					8.67	0.003
Age category	3	23.9	<0.001	1.69	0.64	20.8	<0.001
Morphology	3	5.82	0.12	4.95	0.18	8.77	0.03
Familial risk category	2	18.9	<0.001	4.78	0.09	20.2	<0.001
Nevus category	3	24.6	<0.001	7.78	0.05	28.1	<0.001
Red phenotype	1	7.57	0.006	0.29	0.59	4.15	0.04
Skin color	2	8.10	0.017	3.10	0.22	8.92	0.012
Skin type	3	11.9	0.008	4.72	0.19	11.5	0.009
Tanning ability	3	9.79	0.020	7.09	0.07	10.5	0.015
Solar keratoses	1	10.9	0.002	0.01	0.97	6.15	0.013
Skin cancers	1	7.69	0.006	3.34	0.07	12.9	<0.001
Behavior							
(*in situ* vs invasive)	1	3.76	0.053	0.32	0.57	3.36	0.070
Freckling category	2	13.7	0.001	0.41	0.81	4.12	0.13
Anatomic site	5	5.80	0.33	1.09	0.95	5.29	0.38
Clark level	4	3.76	0.44	1.69	0.80	1.25	0.87
Sunburns	3	0.77	0.86	0.85	0.84	1.82	0.61
Hair color	5	2.46	0.79	2.07	0.84	1.91	0.86
Eye color	2	1.25	0.53	0.51	0.78	0.18	0.91

Predictors of second primary melanomas: multivariate analyses
Probands with a large number of nevi, those in the familial high-risk group or whose index melanoma was nodular had significant 2-fold and greater increased risks for subsequent primary melanomas. Men, individuals with a moderate number of nevi, whose index melanoma was an lentigo maligna melanoma or *in situ* or who had fair skin or an inability to tan were also at elevated risk of acquiring a second primary lesion (Table 5). We repeated the analysis by

Table 5. Hazard ratios and 95% CIs of time to first subsequent primary melanoma, *in toto* and within strata of familial risk group

		All participants	High+intermediate familial risk strata	Low familial risk stratum
Factor	**Category**	**Hazard ratio[1] (95% CI)**	**Hazard ratio[1] (95% CI)**	**Hazard ratio[1] (95% CI)**
Sex	Female	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Male	1.49 (1.12–2.00)	2.49 (1.47–4.23)	1.17 (0.81–1.68)
Histological type	SSM, unspecified	1.00 (ref)	1.00 (ref)	1.00 (ref)
	LMM	1.80 (1.05–3.07)	1.81 (0.74–4.43)	1.47 (0.70–3.10)
	Nodular	2.13 (1.21–3.74)	1.10 (0.38–3.17)	2.63 (1.35–5.15)
Behavior	Invasive	1.00 (ref)	1.00 (ref)	1.00 (ref)
	In situ	1.36 (0.99–1.87)	1.38 (0.77–2.44)	1.30 (0.87–1.95)
Nevus count	None or few	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Moderate	1.92 (1.40–2.65)	2.46 (1.41–4.29)	1.63 (1.08–2.47)
	High	2.91 (1.94–4.35)	2.81 (1.35–5.85)	2.98 (1.82–4.89)
Tanning ability	Able to tan	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Unable to tan	1.66 (1.13–2.43)	1.79 (0.88–3.61)	1.77 (1.11–2.83)
Skin color	Dark/medium	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Fair or pale	1.51 (1.06–2.16)	2.22 (1.09–4.53)	1.33 (0.87–2.04)
Familial risk	Low/intermediate	1.00 (ref)	NA	NA
	High	2.12 (1.34 – 3.36)		

Abbreviations: CI, confidence interval; LMM, lentigo maligna melanoma; NA, not applicable; SSM, superficial spreading melanoma.
[1]Hazard ratio and 95% CI derived by Cox's proportional hazards regression in four strata of age, adjusted for all factors in the table.
Synchronous melanomas excluded.

strata of familial risk group (high + intermediate; low); there was some suggestion that risk group membership may be a modifying factor, but the differences are likely to be due to chance.

DISCUSSION

We have identified a number of characteristics that are associated with significantly elevated risk of developing a second primary melanoma. The strongest predictor was the number of melanocytic nevi self-reported at baseline; patients reporting large numbers of nevi had 3-fold higher risks of developing a subsequent melanoma than those reporting only small numbers of nevi. Other factors associated with significantly elevated risks of second primary melanomas included having a high familial risk of melanoma, a sun-sensitive skin type, and a melanoma of nodular or lentigo maligna subtypes. Of note, about half of participants with four or more primary melanomas were from the low familial risk group, the clinical implication being that patients with no or weak family history of melanoma may still be at risk of multiple primary melanomas.

There are few studies with which to compare our findings. Although some earlier studies have explored the incidence and determinants of second primary melanoma in large populations using record linkage techniques (Giles *et al.*, 1995; Goggins and Tsao, 2003; Levi *et al.*, 2005; McCaul *et al.*, 2008), such investigations have been limited to using routinely collected data and thus have been constrained by the absence of data relating to the phenotype of the patient. A larger number of studies have reported the occurrence of multiple primary melanomas arising in historical cohorts of patients treated at single institutions (Ariyan *et al.*, 1995; Johnson *et al.*, 1998; Savoia *et al.*, 1998; DiFronzo *et al.*, 1999; Ferrone *et al.*, 2005). Such studies typically have rich information describing histopathological characteristics of the tumors, but phenotypic data relating to the patient have seldom been collected in a systematic manner. Three epidemiological studies of multiple primary melanomas have been reported, and each gathered systematic data on phenotype and family history of melanoma (Burden *et al.*, 1999; Begg *et al.*, 2006; Titus-Ernstoff *et al.*, 2006). The Scottish Melanoma Group compared the characteristics of patients with multiple versus single primary melanomas, and found strong associations with high nevus counts, family history of melanoma, and ''nonuse of sunscreen'' (Burden *et al.*, 1999). The study also reported a high prevalence of germ-line *CDKN2A* mutations among patients with multiple primary melanomas. The GEM study used a to our knowledge, previously unreported design comparing 1,210 patients with incident multiple primaries to 2,470 patients with a single primary melanoma (Begg *et al.*, 2006). That study also reported similar findings to ours; in particular, that patients with high nevus counts were almost 3-fold more likely than those with low nevus counts to

develop multiple primaries. The investigators also reported positive associations with family history of melanoma, freckling in childhood, and light hair color. Similar to the Scottish group, the GEM investigators found a strong and statistically significant 4-fold increased relative risk of multiple primary melanoma associated with the mutations in *CDKN2A* (Berwick *et al.*, 2006). The New Hampshire epidemiological study followed-up 354 cases from a case–control study, 27 of whom developed a subsequent primary within 2 years (Titus-Ernstoff *et al.*, 2006). Although limited in statistical power, this study reported a strong positive association with atypical nevi, and observed an inverse association between lifetime sunburns and risk of second primary melanoma.

Although we found some evidence of an association between the anatomical sites of the first and second melanomas, the concordance within specific sites was modest, with a κ value of only 0.21. A large, registry-based study in Australia reported κ statistics for body site concordance 0.41 for synchronous melanomas and 0.29 for metachronous lesions (Giles *et al.*, 1995). Other studies have also reported that anatomical concordance between first and second primary melanomas exceeds that expected by chance, but falls far short of a strong relationship (Johnson *et al.*, 1998).

Strengths of this study include the large sample, prospective design, and the systematic collection of phenotypic and family history data at baseline. In addition, study participants were followed-up through self-report and linkage to population registers; the latter ensuring close to complete ascertainment of subsequent melanomas. Thus our study is likely to have high internal validity. We used standard measures for assessing phenotype, which we have previously demonstrated to possess moderate to high levels of repeatability (Baxter *et al.*, 2008). Moreover, as all such measures were collected before outcomes, misclassification of these exposures must have been nondifferential regarding outcome and any resulting bias would likely be toward the null.

A potential limitation of this study was the fact that the study sample was not representative of the population of people having a first primary melanoma. This occurred for two reasons. First, the parent study (QFMP) was designed to identify genetic factors associated with melanoma development and thus intentionally oversampled patients from families with higher than average risk of developing a primary cutaneous melanoma (Aitken *et al.*, 1996). Second, we were required to obtain new consent from study participants in 2003–2005 to enable linkage to the cancer registry that necessarily restricted the cohort to those who were alive and contactable at that time. Supplementary analyses showed significant differences in age and tumor characteristics between those QFMP participants who were followed up with those who were not, and thus the cumulative risk of developing a second melanoma in this cohort was higher (13% at 10 years) than has been reported previously in the Queensland population (6.4%) (McCaul *et al.*, 2008). For these reasons, our findings about the incidence of second primary melanoma may not be generalizable to other populations. However, we have no reason to believe that the associations we observed between patient characteristics and the risk of developing a second primary melanoma would be biased.

In conclusion, patients diagnosed with a first primary melanoma have a high risk of developing a second primary tumor, and the risks are highest for those with large numbers of nevi or who have a higher than average family history of melanoma. Other factors, including red hair phenotype and fair skin, appear to modestly increase the risk of subsequent melanoma. These factors can be assessed in all patients at the time of diagnosis with a first primary melanoma; those at highest risk for developing second melanomas can be counseled appropriately.

MATERIALS AND METHODS

The analyses presented here were embedded within the QFMP, a family-based study of melanoma patients for which the full details have been described elsewhere (Aitken *et al.*, 1996; Siskind *et al.*, 2002; Baxter *et al.*, 2008). Briefly, the QFMP comprised a sample of melanoma patients diagnosed with first primary cutaneous melanoma in Queensland between 1 January 1982 and 31 December 1990 and registered with the Queensland Cancer Registry (QCR; notification of cancers became mandatory in Queensland in 1982). Diagnoses had to be confirmed by histology, and could be *in situ* or invasive. Patients with acral lentiginous melanoma were not eligible for the QFMP. The QFMP intentionally oversampled patients with a known family history of melanoma to facilitate future genetic research; the algorithm used to stratify patients by family history is described below. In total, 1,897 probands (i.e., patients meeting the eligibility criteria above) completed a detailed, self-administered questionnaire in 1991–1993 requesting information on family history, risk factors, and medical and residential history.

A subsample of 1,083 QFMP probands was re-contacted between 2002 and 2005 to elicit further diagnoses of melanoma and authorize a confirmatory search in the QCR (Baxter *et al.*, 2008). All participants gave their informed written consent to take part, and the study was conducted according to the Declaration of Helsinki Principles. The human research ethics committee of the Queensland Institute of Medical Research approved all described studies.

Records were sought for all consenting respondents who reported melanoma diagnosed in Queensland since 1982 (the first year of mandatory cancer registration in that state). Where a respondent was known by a name other than their legal name, or changed their names, a record for each known alias was submitted to the QCR to attempt to capture all possible records for an individual. For completeness of records, information pertaining to all reported cancers (not only melanomas) was requested.

Data were received from QCR in the form of a de-identified electronic data file. Where a record could not be located at the QCR, or diagnosis was reported in another state, a request was submitted to a doctor nominated by the respondent (generally the diagnosing doctor) for a copy of the histopathology reports. If the doctor did not reply within 2 weeks, a telephone interviewer called the practice to request a copy of information. Where the practice advised that the doctor had died, moved, or sold the practice, the interviewer then contacted the family of the doctor, the new practice owner, or associated record management company in an attempt to locate the

missing records. Where this was unsuccessful, an attempt was made to locate the information through subsequent treating doctors nominated by the respondent. Once received, the histopathology reports were then coded by a QCR-trained medical coder using *International Classification of Diseases for Oncology* (third edition) and double-entered into a database.

Pathology reports were reexamined and corrected, and the file correspondingly updated, in 2009. For each primary melanoma diagnosed, trained study nurses abstracted salient details from the pathology report including the date of diagnosis, anatomic site, behavior (*in situ* or invasive), and Clark level or Breslow thickness.

Variables for analysis

All variables used in analyses were derived from the original baseline questionnaire. Age was defined as age at diagnosis of the first primary melanoma. Skin color, self-assessed on unexposed sites such as the inner upper arm, was recorded in two categories (dark/medium, fair), eye color in three categories (blue/gray, green/hazel, and brown), and early adult hair color in six categories (fair/blonde, light brown, light red/ginger, dark red/auburn, dark brown, and black). Propensity to burn in the sun was categorized as never, sometimes or always burn, and tanning ability after prolonged sun exposure as none, slight, moderate, or deep tan. Self-reported 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, $\leqslant 100$ freckles or >100. Number of sunburns during life was recorded as none, 1, 2–5, or >5. Self-reported history of solar keratoses or keratinocyte skin cancers (squamous cell carcinomas and basal cell carcinomas) was also obtained.

We derived a ''red phenotype'' variable, defined as individuals with red hair and/or more than 100 freckles. Participants were further classified as belonging to high-, intermediate-, or low-risk families according to a previously derived measure of familial melanoma risk described in detail elsewhere (Aitken *et al.*, 1994). Briefly, this index was based on the number of cases of melanoma among all relatives in the family in excess of those predicted from the age-, sex- and birth cohort-specific cumulative incidences of melanoma among all relatives in the sample. Participants in the top 2.5% of the cohort were placed in the high-risk category, those between the median and the 97.5 percentile were assigned to the intermediate category, and those below to the low-risk category. Familial risk categories were determined at entry to the cohort. High-risk individuals were oversampled for re-contact.

UV radiation exposure—total in childhood (5–12 years), adolescence (13–19 years), and average per year from 20 years of age on—was estimated from the lifetime residence and sun exposure calendars were completed by the participants at baseline (Siskind *et al.*, 2002).

Data analysis

Our primary aim was to identify predictors of second primary melanomas within the cohort. Our secondary aim was to describe the distribution of second and subsequent melanomas, but generalization of the latter findings to other populations should be pursued with caution given the selected nature of our cohort.

Second melanomas were deemed to be synchronous with the index lesion if they were diagnosed within 30 days of the latter. These were included in analyses of total numbers of lesions, but not when time from first to the second histological diagnosis of primary melanoma was the outcome measure. In comparisons of characteristics of first (index) with second melanomas, persons with only synchronous lesions have been excluded. In those with both synchronous and metachronous lesions, the first melanoma occurring more than 30 days after the index melanoma served as the ''second'' lesion in the above analyses.

Univariate analysis of numbers of subsequent melanomas was performed using Kruskal–Wallis nonparametric tests for categorical or ordinal factors. As a check failure-time analysis of time to first subsequent metachronous melanoma, with log-rank tests, was also used. For continuous factors (thickness, UV exposure) Kendall's nonparametric correlation coefficient (τ) was used.

Multivariate analysis was by means of Cox proportional hazard regression on time to first subsequent melanoma across four age strata (<40, 40–49, 50–59, and $\geqslant 60$ years). On the basis of the results of the univariate analyses, levels in several of the phenotypic variables were combined before inclusion in the proportional hazards models. Phenotypic variables are highly intercorrelated; the minimal included subset of this group of variables was established by sequential elimination.

Apart from the entire file, men, and women were also analyzed separately by univariate methods. In the multivariate analysis, sex is included as a predictor.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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