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The Queensland Familial Melanoma Project: study design and characteristics of participants

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Family history of melanoma is associated with an increased risk for the disease. Neither the relative contributions of genetic and shared environmental factors to familial risk nor how genetic susceptibility is mediated are known. The Queensland Familial Melanoma Project was undertaken to investigate (a) the role of genetic susceptibility as indicated by skin type, pigmentation and the prevalence of naevi and (b) exposure to solar ultraviolet radiation, and their interaction in the aetiology of familial melanoma. After obtaining doctor's consent, a brief family history questionnaire was mailed to all Queensland residents with a first primary cutaneous melanoma diagnosed between 1982 and 1990. Detailed information on melanoma history and standard melanoma risk factors was sought from all responding twins and familial cases, from a sample of non-familial cases and from cases' relatives. Medical confirmation was sought for all relatives reported to have had melanoma. The final sample comprises 15,907 persons in the 1,912 families of 2,118 melanoma cases, including 509 families in which there are two or more individuals with confirmed melanoma. Melanoma history and risk factors were obtained for 9,746 relatives, including 94 twins of cases. This is the largest family and twin study of cutaneous melanoma yet conducted in an unselected, geographically-defined population. We describe the design of the study and the characteristics of the total study population.

Key words: family characteristics, genetics, melanoma, naevus, risk factors.

Introduction

Melanoma rates are increasing among white-skinned populations throughout the world. In Australia the incidence of cutaneous melanoma is rising more rapidly than that of any other recorded cancer, and melanoma incidence rates have now overtaken those of lung, bowel and breast cancers. In Queensland in 1987 the age-adjusted incidence of invasive melanoma was 48.9 per 100,000 for men and 39.7 per 100,000 for women.[1] These are the highest rates in the world, and represent a doubling of incidences among men and an increase of more than 50% among women since 1979–80.[1]

The aetiology and pathogenesis of cutaneous melanoma are not well understood. Exposure to solar ultraviolet (UV) radiation is considered the major environmental risk factor,[2] while host factors, including skin pigmentation, sensitivity of the skin to the sun, and the presence of naevi have even stronger associations.[3,4] It has been recognized for some years that a family history of melanoma is associated with an increased risk for this disease,[3,5,6] although neither the relative contributions of genetic and shared environmental factors to familial risk nor how genetic susceptibility is mediated are known. Melanoma susceptibility in some families has been linked to markers on chromosome 9p21[7] and 1p,[8] and recently a candidate for a melanoma susceptibility gene (CDKN2) was identified at the 9p21 locus.[9,10] The proportion of familial melanoma which can be attributed to mutations in CDKN2 and the prevalence of such mutations in the general population are unknown.[11,12]

Large, family studies, in which families are sampled from a defined population and information about individual risk factors is obtained from all family members, provide a powerful methodology for assessing the contributions from, and interactions between, genotype and environment in disease aetiology.[13] Queensland is an opportune setting for a population-based family study of melanoma as the high incidence of the disease guarantees the recruitment of a large number of incident melanoma cases over a reasonably short period of time. Here we describe the objectives and design of a family and twin study of melanoma in Queensland (the Queensland Familial Melanoma Project), as well as the methods of data collection and the characteristics of the total study population.

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Subjects and methods

Study objectives

The principal objective of the study is to investigate the roles of genetic and environmental factors, and their interaction, in the aetiology of familial melanoma. Gene–environment interaction occurs when the effect of environmental exposures on melanoma risk varies according to an individual's genetic make-up. Genetic influences on malignant melanoma may arise in a number of ways, most notably through major genes with a direct effect on the development of the disease, but also through genetic influences on risk factors such as skin colour, ability to tan or propensity to develop melanocytic naevi, as well as through genetic influences on behaviour leading to greater or lesser sun exposure.[14] We aim to determine the relative importance of these factors, and their interaction with solar UV exposure, in the familial aggregation of melanoma.

In general it is difficult to determine genetic susceptibility on the basis of family history alone: some family clusters are likely to occur by chance, while a melanoma susceptibility gene, for example, will not necessarily result in familial aggregation unless the family is reasonably large, and the gene produces melanoma in most who inherit it.[15] Thus, a proportion of multiplex pedigrees is likely to include only sporadic cases, while some families of apparently sporadic cases will have an underlying genetic susceptibility to melanoma. At present, such cases are misleadingly classified as familial and non-familial. We aim to develop criteria to differentiate such families.

Study population

Information on melanoma occurrence and melanoma risk factors was gathered in a cohort of families of melanoma cases recently diagnosed in Queensland. Index cases, through whom families were ascertained, were sampled from all Queensland residents with a histologically confirmed first primary cutaneous melanoma diagnosed in Queensland between 1 January 1982 and 31 December 1990. Patients with *in situ* as well as invasive disease were eligible; those with lentigo maligna (Hutchinson's melanotic freckle) were ineligible.

Sampling of index cases

Cancer has been legally notifiable in Queensland since 1982. The names and addresses of all eligible cases, and the names of their doctors, were obtained from the Queensland Cancer Registry, and written permission to approach patients was sought from the doctor of each case after ethical approval for the study was obtained from all appropriate hospital and institutional ethics committees. A 1-page questionnaire asking whether the case's parents, siblings or children had a history of melanoma, whether the case was a twin and whether they would agree to be contacted again, was mailed to all eligible cases (or their next-of-kin if the case was dead) for whom doctor's permission was obtained, followed by reminder telephone calls after 2 weeks.

Index cases were sampled from all respondents who indicated they were willing to be approached again, and included all twins, all patients who reported at least one first-degree relative with melanoma and a 20% random sample of remaining patients who reported no first-degree relatives with melanoma. As we anticipated that only about 10% of eligible cases would have a positive family history, this stratified sampling design was chosen to ensure as many positive history families in the sample as possible, thus maximizing study power.

Sampling of relatives

To avoid bias in evaluating the family history, relatives of index cases were sampled according to a predetermined sequential sampling scheme.[16] All first-degree relatives (parents, siblings and children) of the index cases were included in the study. If any of these relatives were confirmed to have had cutaneous melanoma (*in situ* or invasive), their first-degree relatives were also included, and if any of these had confirmed cutaneous melanoma, their first-degree relatives were included, and so on.

Twins

Twin pairs were eligible for the twin study if both members of the pair had lived to at least 20 years of age. As one of the aims of the study is to examine melanoma concordance between members of twin pairs, both members must have survived long enough to have had a reasonable chance of developing melanoma. In addition to the risk-factor questionnaire described below, detailed clinical information [including height, weight, full body naevus count, details of the five largest naevi, degree of actinic damage on the back of the hand graded from silicon moulds, the colour of exposed (back of hand) and unexposed (inner upper arm) skin (by reflectance photometry)] and venous blood samples were obtained from eligible sets of twins during home visits by a research nurse. Zygosity of same-sex twin pairs was established by DNA fingerprinting.

Data collection

A self-administered questionnaire was mailed to the index cases (or their next-of-kin), assessing standard melanoma risk factors including counts of naevi on the arm and back, demographic and medical details, lifetime residence and sun exposure history and family history of melanoma and other cancer (see Appendix). Initially, index cases were also asked about their relatives' melanoma risk factors, but these questions were later omitted to make the questionnaire shorter and easier to complete. A similar questionnaire, including all of the above items except family history, was mailed to the index cases' living first-degree relatives aged between 18 and 75 years for whom the case provided name and contact address. Non-respondents were telephoned after 2 weeks and given the option of answering the questionnaire over the telephone.

Medical confirmation, including histologic diagnosis, date of diagnosis, site and tumour thickness, was sought from pathology records (or if these were unavailable, from the relative's doctor, hospital notes or death certificate) for all relatives who were self-reported or reported by the index case to have had melanoma. Relatives with a history of confirmed cutaneous melanoma received a second questionnaire asking about their family history, and in particular whether any of *their* first-degree relatives had had melanoma. Risk-factor questionnaires were subsequently mailed to all additional living relatives aged 18 to 75 years ascertained through this sequential sampling procedure.[16]

Data analysis

Families will first be ranked according to the strength of their melanoma family history, defined as the number of cases in the family in excess of those predicted given the size of the family, and the age, sex and birth cohort of family members.[17] An interim analysis of the first 1,116 families sampled has shown significant heterogeneity of familial melanoma risk, with 53 families having a significantly higher melanoma incidence than expected.[18] This categorization used an arbitrary statistical cutpoint based on the conventional 5% significance level, and almost certainly has underestimated the number of families with increased familial melanoma risk. In future analyses, we will categorize families more broadly as low, intermediate and high risk, based on their familial risk ranking. All analyses will first include both invasive and *in situ* melanomas in index cases and relatives, and will then be repeated for invasive melanomas only.

Sun exposure throughout life will be estimated from the lifetime residence and sun exposure calendar in the self-administered questionnaire. Using standard epidemiologic analyses, we will examine differences in sun exposure during the whole of life and during different periods of life, between cases from high-, intermediate- and low-risk families, and between relatives with and without melanoma, stratified by host characteristics including ability to tan, pigmentation and naevus density. We will also estimate the distribution of age of onset of melanoma among relatives according to their relationship to the index case, birth cohort and familial melanoma risk, and examine the familial incidence of other cancers in high-, intermediate- and low-risk families. Maximum likelihood segregation analysis using the REGTL program in the computer package SAGE[19] will be used to test hypotheses about the mode of inheritance of susceptibility to melanoma, after adjusting for sun exposure and the host characteristics listed above.

Twin analyses will provide estimates of the relative importance to melanoma aetiology of genetic factors, environmental factors shared by co-twins and environmental factors specified to individuals.[20] Anlayses will include (a) comparison of melanoma concordance between monozygotic and dizygotic twins to estimate heritability of melanoma liability, (b) comparison of environmental exposures between pairs discordant for melanoma to estimate environmental associations with melanoma independent of genetic factors, and (c) genetic modelling incorporating measured host and environmental risk factors to investigate gene–environment interaction in melanoma risk.[21]

Results

Sample size and response rates

We ascertained 12,016 first incident cases of invasive and *in situ* cutaneous melanoma diagnosed among Queensland residents between 1 January 1982 and 31 December 1990 (Figure 1). This included 11,868 cases who were reported to the Queensland Cancer Registry and an additional 148 cases found by verifying cancer registrations for two selected years (1984 and 1987) against the records of pathology laboratories in Brisbane and in regional centres throughout Queensland. We estimate from this that registry ascertainment was approximately 95% complete.

Of 10,407 eligible cases for whom we obtained doctor's permission (87%), 8,412 (81%) completed and returned the brief family history questionnaire, including 7,784 cases (93%) who agreed to further participation (Figure 1). Of these, detailed family history and risk-factor questionnaires were posted to 2,920 selected index cases, comprising all twins ($n=145$), in all cases who reported one or more first-degree relatives with melanoma ($n=1,529$) and a 20% random sample of the remaining 6,110 cases ($n=1,246$) (Figure 1). After intensive tele-

phone follow-up, 2,118 index cases (73%) returned the detailed questionnaire, including 108 twins (74%), 1,112 (73%) self-reported positive family history cases and 898 (72%) self-reported negative family history cases. Positive family history was confirmed for only 509 (46%) of the total 1,112 index cases who reported it (59 index cases provided family history information only, and did not report their own melanoma risk factors).

In total, 15,907 relatives (441 with confirmed cutaneous melanoma), belonging to 1,912 separate families, were reported by the 2,118 index cases or other relatives, an average of 8.3 reported relatives per family (Figure 1). (The number of families is less than the number of index cases as 174 families contained two index cases, 10 families contained three index cases and four families contained four index cases.) Risk-factor questionnaires were posted to 7,619 living relatives aged between 18 and 75 years for whom the index case provided a name and contact address, of whom 5,158 (68%) responded after intensive telephone follow-up. Other relatives provided proxy reports for an additional 4,588 relatives. We have previously found variable agreement in this sample between proxy reports by index cases about their relatives and those relatives' self-reports of their melanoma risk factors, with correlation coefficients ranging from 0.26 for number of sunburns and 0.45 for naevus density to 0.60 for ability to tan.[22] For all variables except number of sunburns, proxy reports and self-reports were combined to give a total of 9,746 relatives for whom standard risk factor information was available.

Of the 108 index cases in the sample who were twins, 95 were eligible for the twin study, i.e. both members of the pair had reached at least 20 years of age. In total, the sample comprised 94 separate pairs of twins (two of the index cases formed a single pair), and included 71 dizygotic pairs and 23 monozygotic pairs. Two pairs are concordant for melanoma, both monozygotic. To date, risk-factor questionnaires have been obtained for both members of 74 pairs, and clinical visits and blood collection completed for 39 pairs. A companion twin study underway in New South Wales is expected to recruit a similar number of twins with melanoma. These two samples will be combined for the twin analysis, giving approximately 180 pairs in total.

Questionnaire reliability

Approximately 6 months after the detailed risk-factor questionnaires were returned, another copy of the same questionnaire was remailed to 600 relatives selected at random, of whom 412 (69%) responded. We assumed that this time interval was sufficient for relatives to have forgotten their original responses. Reports from relatives on the two occasions were compared using the κ statistic[23] for the categorical variables hair and eye colour, and the polychoric correlation coefficient[24] for the other variables, which were all ordinal. The polychoric correlation coefficient yields similar results to the weighted κ statistic calculated with quadratic weights, the intraclass correlation coefficient, and the Pearson correlation coefficient. A coefficient of 0 indicates no agreement, and 1 perfect agreement. Concordance between the first and second reports was high for all variables (0.91 for ability to tan, 0.92 for propensity to burn, 0.81 for number of sunburns, 0.85 for skin colour, 0.80 for hair colour, 0.88 for eye colour, 0.87 for tendency to freckle in summer and 0.81 for naevus density), indicating that the risk-factor questionnaire is a reliable instrument.

Characteristics of participants

The final sample consists of 1,912 separate families of 2,118 index melanoma cases. Including the index cases, 1,403 families each contain a single member with cutaneous melanoma, 415 families contain two, 67 contain three and 27 families contain four or more members with cutaneous melanoma (Table 1).

Index cases are similar to the total group of eligible cases with respect to sex, age at diagnosis, proportion of *in situ* and invasive melanomas, tumour site and tumour thickness (Table 2). There were no significant differences in any of these items between index cases from single-case and multiple-case families. Relatives with melanoma were diagnosed at slightly younger ages than index cases, and had a lower proportion of *in situ* tumours (15.0% *vs*

Table 1. Distribution of 1,912 families of cutaneous melanoma cases diagnosed in Queensland, Australia, 1982–90, according to family size and number of melanomas per family[a]

Cases per family[b]	No. of persons sequentially sampled per family[b]						Total no. of families
	2–4	5–9	10–11	15–19	20–29	30–39	
1	99	911	340	52	1	0	1,403
2		123	198	76	18	0	415
3		8	27	17	15	0	67
4			4	8	8	0	20
5			1	1	2	0	4
6					0	0	0
7					0	1	1
8					1	0	1
9						0	0
10						1	1
Total	99	1,042	570	154	45	2	1,912

[a] In total, 2,559 family members had confirmed cutaneous melanoma, including the 2,118 index cases and 441 of their relatives.
[b] Including index cases.

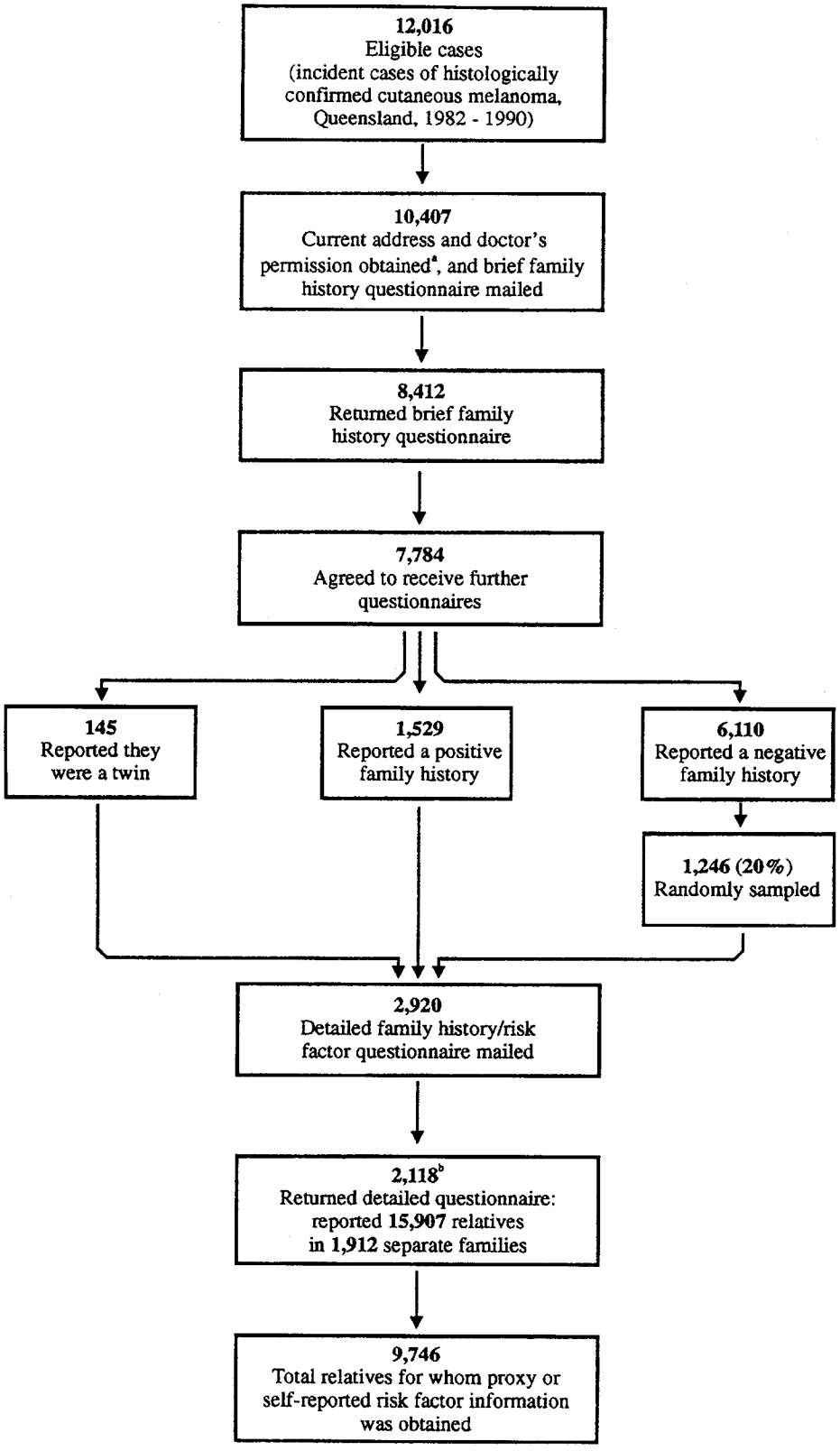

Figure 1. Flow chart for population-based ascertainment of families in the Queensland Familial Melanoma Project. [a] Permission to approach cases was obtained by writing to over 14,000 separate medical practitioners. Usually, the name of the case's family doctor was obtained from the Queensland Cancer Registry. In many instances, the family doctor provided the name of the case's surgeon or other treating doctors, whom we then also contacted for their permission to approach the case. [b] Includes 108 twins, 1,112 cases with self-reported positive family history (509 were confirmed to have positive family history) and 898 cases with self-reported negative family history.

Table 2. Patient and tumour characteristics for all eligible cases, index cases, and relatives of index cases. Eligible cases comprise all cases with histologically confirmed cutaneous melanoma diagnosed in Queensland, 1982–1990; index cases are a sample of these

			Index cases ($n=2118$)					
	All eligible cases		From single-case families[a]		From multiple-case families[b]		Relatives with melanoma	
Patient and tumour characteristics	*n*	%	*n*	%	*n*	%	*n*	%
Total	12,016	–	1,403	–	715	–	441	–
Sex								
Male	6,183	51.5	688	49.0	331	46.3	195	44.2
Female	5,833	48.5	715	51.0	384	53.7	246	55.8
Age at diagnosis (years)								
<20	294	2.4	33	2.4	20	2.8	14	3.2
20–39	2.971	24.7	360	25.7	188	26.3	142	32.2
40–59	3,976	33.1	552	39.3	271	37.9	166	37.6
≥60	4,597	38.3	458	32.6	236	33.0	119	27.0
Unknown	178	1.5	–	–	–	–	–	–
Site of tumour								
Face	1,057	8.8	111	7.9	43	6.0	28	6.3
Ear	201	1.7	17	1.2	12	1.7	3	0.7
Neck, scalp	611	5.1	65	4.6	35	4.9	22	5.0
Trunk	3.644	30.3	445	31.7	212	29.7	93	21.1
Upper limb, including shoulder	2,809	23.4	330	23.5	170	23.8	92	20.9
Lower limb, including hip	2,614	21.8	337	24.0	193	27.0	115	26.1
Unspecified	1,080	9.0	98	7.0	50	7.0	88	20.0
Histology								
Preinvasive	2,334	19.4	321	22.9	141	19.7	66	15.0
Melanoma *in situ*, arising in lentigo maligna	395	3.3	47	3.4	13	1.8	3	0.7
Superficial spreading melanoma *in situ*	1,388	11.6	195	13.9	88	12.3	34	7.7
In situ melanoma, other types or unspecified	551	4.6	79	5.6	40	5.6	29	6.6
Invasive	9,682	80.6	1,082	77.1	574	80.3	375	85.0
Melanoma, invasive, arising in lentigo maligna	731	6.1	61	4.4	39	5.5	13	2.9
Superficial spreading melanoma,	5,853	48.7	722	51.5	375	52.5	105	23.8
invasive Nodular melanoma	1,002	8.3	97	6.9	43	6.0	27	6.1
Invasive, other types or unspecified	1,758	14.6	185	13.2	106	14.8	209	47.4
Cutaneous metastases from unknown primary	338	2.8	17	1.2	11	1.5	8	1.8
Metastatic melanoma, primary unspecified	–	–	–		–	–	13	2.9
Tumour thickness (mm)[c]								
<0.75	5,065	52.3	623	57.6	352	61.3	70	18.7
0.75–1.49	1,937	20.0	228	21.1	109	19.0	29	7.7
1.50–2.24	691	7.1	77	7.1	29	5.1	13	3.5
2.25–2.99	328	3.4	30	2.8	13	2.3	5	1.3
≥3.00	747	7.7	50	4.6	29	5.1	13	3.5
Unspecified	914	9.4	74	6.8	42	7.3	245	65.3

[a] Containing one case of melanoma only.
[b] Containing two or more cases of melanoma.
[c] Invasive tumours only; all *in situ* tumours were <0.75 mm, except for three with thicknesses of 0.75, 0.76 and 0.87 mm.

Table 3. Demographic characteristics and melanoma risk factors for pooled index cases and relatives from 1,912 families of 2,118 histologically confirmed cutaneous melanoma cases, diagnosed in Queensland, 1982–1990, according to the total number of cutaneous melanoma cases in the family

Melanoma risk factors	Members of 1,403 single-case families[a]		Members of 509 multiple-case families[b]		*P*-value; χ^2 test[c]
	n	%	*n*	%	
Sex					
Male	5,766	50.2	3,235	49.4	
Female	5,713	49.8	3,311	50.6	0.30[d]
Age when recruited into the study (years)					
<20	994	9.3	619	9.9	
20–39	2,834	26.4	1,561	24.9	
40–59	3,129	29.1	1,746	27.8	
≥60	3,775	35.2	2,354	37.5	0.09
Unknown	747		266		
Place of birth					
Australia, New Zealand	4,379	95.3	2,482	97.0	
England, Northern Europe	133	2.9	53	2.1	
Ireland, Scotland, Wales	28	0.6	6	0.2	
Southern Europe	10	0.2	1	0.0	
Other country	46	1.0	18	0.7	<0.01[d,e]
Unknown	6,883		3,986		
Ability to tan					
Very brown	1,220	17.3	509	14.4	
Moderate tan	3,104	43.9	1,506	42.6	
Slight tan	2,011	28.4	1,054	29.8	
No tan/freckle only	737	10.4	468	13.2	<0.001
Unknown	4,407		3,009		
Propensity to burn					
Never burn, always tan	472	6.7	173	4.9	
Sometimes burn, usually tan	3,581	50.8	1,661	47.3	
Usually burn, sometimes tan	2,065	29.3	1,122	31.9	
Always burn, never tan	938	13.3	558	15.9	<0.001
Unknown	4,423		3,032		
No. of sunburns					
0	1,260	20.7	641	20.5	
1	790	13.0	375	12.0	
2–5	2,564	42.0	1,279	41.0	
≥6	1,487	24.4	827	26.5	0.16
Unknown	5,378		3,424		
Skin colour					
Olive/dark	609	8.1	210	5.6	
Medium	2,400	31.9	1,083	29.1	
Fair/pale	4,525	60.1	2,428	65.3	<0.00
Unknown	3,945		2,825		
Hair colour at age 21					
Black	671	8.9	264	7.2	
Light/dark brown	4,600	60.9	2,229	60.6	
Fair/blonde	1,625	21.5	773	21.0	
Light/dark red	664	8.8	415	11.3	<0.00
Unknown	3,919		2,865		
Eye colour					
Brown	1,641	23.6	739	21.3	
Green/hazel	2,385	34.2	1,193	34.3	
Blue/grey	2,940	42.2	1,543	44.4	<0.01
Unknown	4,513		3,071		

Continued...

Table 3. Continued

Melanoma risk factors	Members of 1,403 single-case families[a]		Members of 509 multiple-case families[b]		P-value; χ^2 test[c]
	n	%	*n*	%	
Total freckling in summer					
0	2,774	41.5	1,116	33.3	
1–100	2,904	43.4	1,579	47.1	
>100	1,008	15.1	658	19.6	<0.001
Unknown	4,793		3,193		
No. of naevi					
None	1,128	17.8	458	14.1	
Few	3,490	55.2	1,672	51.4	
Moderate number	1,390	22.0	891	27.4	
Very many	318	5.0	232	7.1	<0.001
Unknown	5,153		3,293		

[a] Containing one case of melanoma only ($n=11,479$).
[b] Containing two or more cases of melanoma ($n=6,546$).
[c] Compares the distribution of melanoma risk factors between single- and multiple-case families.
[d] χ^2 test for association.
[e] Because of the small number of individuals born outside Australia and New Zealand, all other countries were combined into a single category for this comparison.

21.8%) and apparently fewer invasive tumours under 0.75 mm thick, although tumour thickness was not routinely recorded until recently and was unknown for over half of the tumours in relatives.

The vast majority of participants (96%) were born in Australia or New Zealand, with most of the remainder (3%) coming from England, Northern Europe or the Celtic countries (Ireland, Scotland, Wales) (Table 3). Most participants reported they had fair skin (62%), at least some degree of freckling in summer (61%), and few naevi (54%). Half said they sometimes burnt but usually tanned in the sun, and a similar proportion (43%) reported they would develop a moderate tan after prolonged exposure to sunlight.

Compared with members of single-case families, a significantly higher proportion of members of multiple-case families were born in Australia ($P<0.01$), were unable to tan ($P<0.001$), developed more than 100 freckles in summer ($P<0.001$) and had skin which always burnt in the sun ($P<0.001$), fair skin colour ($P<0.001$), red hair ($P<0.001$), blue/grey eyes ($P<0.01$) and very many moles ($P<0.001$) (Table 3). These differences remained when the comparison was repeated among family members with melanoma and then among family members without melanoma, and suggest that a predisposition to melanoma in some families may be partly explained by familial correlation for genetically determined melanoma risk factors, including inability to tan, tendency to sunburn, fair pigmentation and a propensity to develop freckles and naevi.

Discussion

Families in this Queensland Familial Melanoma Project were ascertained through incident cutaneous melanoma cases using a two-stage sampling procedure, namely first contacting all melanomas cases diagnosed in Queensland during the study period, and then sampling families conditional on the cases' self-reported family melanoma history. It is possible that individuals who believe they have a positive family history may be more motivated to participate in such research, and thus that the sample may be biased towards positive history families. However, this seems unlikely as the number of melanoma cases with a self-reported positive family history (19%) agrees reasonably closely with estimates of 15–18% obtained in previous studies in Queensland[3] and Western Australia,[6] and rates of response to the self-administered risk-factor questionnaire were the same for cases with and without a self-reported positive family history.

Accurate measurement of past sun exposure is extremely difficult. The lifetime residence and sun exposure calendar which we have used in this study can, of course, provide only an approximation to the actual cumulative UV dose received by an individual, which depends not only on ambient solar radiation and time spent outdoors, but also on the fraction of ambient radiation received, the fraction received at times of the day that UV radiation is most intense, the fraction received on different body sites and individual sun protection habits.[25] Nevertheless, we will be able to group participants into broad categories of potential exposure for comparative analyses. The mea-

surement of host factors such as ability to tan, propensity to sunburn and pigmentation is probably less prone to error. We have shown here that self-reports of these items are reliable, and that there is reasonable agreement between proxy and self-reports for most items.[22]

The Queensland Familial Melanoma Project is the largest family study of melanoma of which we are aware, and the only one in which families of melanoma cases have been sampled from a population base using a fully defined sampling scheme with close to complete ascertainment of eligible cases. The results of this work will be generalizable to the population of Queensland, and to other white-skinned populations living in areas of high solar radiation. Analyses are now underway which we anticipate will provide new insights into the interaction of host characteristics and solar UV exposure in melanoma aetiology and in the familial aggregation of melanoma. We are currently collecting DNA from relatives in the sample, so that we can investigate for the first time the importance in the population of melanoma susceptibility genes such as CDKN2,[9–12] and their interaction with known melanoma risk factors both genetic and environmental.

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Appendix

Summary of questions in the mailed self-administered melanoma risk-factor and family-history questionnaire.

1.0 Melanoma risk factors

1.1 Sun tan after repeated and prolonged exposure to sunlight:

A Very brown and deeply tanned
B Moderately tanned
C Slightly tanned due to a tendency to peel
D Not suntanned at all or only freckled
X Don't know

1.2 Propensity to sunburn:

A Always burns, never tans
B Usually burns, sometimes tans
C Sometimes burns, never tans
D Never burns, always tans
X Don't know

1.3 History of sunburns: how many times in your life were you sunburnt so as to cause pain for 2 or more days?

A Never
B Once
C 2–5 times
D 6 times or more
X Don't know

1.4 Skin colour before tanning or on areas never exposed:

A Fair/pale
B Medium
C Olive/dark
X Don't know

1.5 Natural hair colour at age 21 (if not yet 21 give hair colour now):

A Fair/blonde
B Light brown
C Light red/ginger
D Dark red/auburn
E Dark brown
F Black
X Don't know

1.6 Eye colour:

A Blue or grey
B Green or hazel
C Brown

1.7 Total freckling in summer:

A None
B 1–100
C More than 100

1.8 Moles: (i) first, read about moles opposite. We would then like you to estimate how 'moley' you th\xiink you are. Which diagram is closest to your number of moles? (This question was accompanied by descriptions and colour photographs of moles and freckles, and graphical illustrations representing individuals in each of the response categories.[26])

A No moles
B Few moles
C Moderate number
D Very many moles

(ii) Please ask a family member to mark, on the diagrams below, the moles you have on your back and right upper arm. (On diagrams of the back and right upper arm, participants were asked to mark moles 2 mm or larger with a dot and moles 5 mm or larger with an X. Participants were supplied with a transparent plastic strip with 2 and 5 mm circles which they placed over their pigmented lesions to estimate size. The question was accompanied by descriptions and lifesize colour photographs of moles, freckles and solar lentigines.)

1.9 Ancestry: where were you born? If not born in Australia, how old were you when you arrived in this country? Please write the country of birth and ancestry of your father's parents and your mother's parents.

2.0 History of sun exposure

2.1 Lifetime residence and sun exposure calendar: please list the town where you were living, whether your main job or activity was outdoors, indoors, or a mixture of indoors and outdoors, and the average number of daylight hours you spent outdoors each day on weekdays and weekend days, for each of the following periods of life: <5 years; 5–12 years; 13–19 years; 20–29 years; and then for each decade to the present. (This question was set out as a grid which respondents were asked to complete, with a separate line for each age group.)

2.2 Sun exposure during childhood and adolescence: on average, between the ages of 5 and 12 years; and then between the ages of 13 and 19 years, how many hours per day did you spend in strong sun in summer: on weekdays?; on weekends?; on summer holidays?

A Nil
B Up to 1
C 1–3
D More than 3

3.0 Personal history of skin diseases

Has a doctor ever treated you for: sun spots (solar keratoses); cancer other than skin cancer; skin cancer—BCC (basal cell carcinoma); skin cancer—SCC (squamous cell carcinoma); melanoma; or Hutchinson's melanotic freckle?

4.0 Family history of melanoma and other cancer

4.1 Please list the first name, sex, date of birth and date of death of your parents, each of your siblings and each of your children. Have any of these family members ever had melanoma, Hutchinson's melanotic freckle, or other cancer? (Specify type.) (This question was set out as a grid which respondents were asked to complete, with a separate line for each relative.)

4.2 Have any of your grandparents, uncles/aunts, first cousins, nephews/nieces, or other relatives ever had melanoma or Hutchinson's melanotic freckle or other cancer? (Please specify.)

5.0 Contact information for relatives

Please list the full name, address and telephone number of your parents, and each of your siblings and children.