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MELANOMA IN ADOLESCENTS: A CASE-CONTROL STUDY OF RISK FACTORS IN QUEENSLAND, AUSTRALIA

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The incidence of melanoma increases markedly in the second decade of life but almost nothing is known of the causes of melanoma in this age group. We report on the first population-based case-control study of risk factors for melanoma in adolescents (15–19 years). Data were collected through personal interviews with cases, controls and parents. A single examiner conducted full-body nevus counts and blood samples were collected from cases for analysis of the *CDKN2A* melanoma predisposition gene. A total of 201 (80%) of the 250 adolescents with melanoma diagnosed between 1987 and 1994 and registered with the Queensland Cancer Registry and 205 (79%) of 258 age-, gender- and location-matched controls who were contacted agreed to participate. The strongest risk factor associated with melanoma in adolescents in a multivariate model was the presence of more than 100 nevi 2 mm or more in diameter (odds ratio [OR] = 46.5, 95% confidence interval [CI] = 11.4–190.8). Other risk factors were red hair (OR = 5.4, 95%CI = 1.0–28.4); blue eyes (OR = 4.5, 95%CI = 1.5-13.6); inability to tan after prolonged sun exposure (OR = 4.7, 95%CI = 0.9–24.6); heavy facial freckling (OR = 3.2, 95% CI = 0.9–12.3); and family history of melanoma (OR = 4.0, 95%CI = 0.8–18.9). Only 2 of 147 cases tested had germline variants or mutations in *CDKN2A*. There was no association with sunscreen use overall, however, never/rare use of sunscreen at home under the age of 5 years was associated with increased risk (OR = 2.2, 95%CI = 0.7–7.1). There was no difference between cases and controls in cumulative sun exposure in this high-exposure environment. Factors indicating genetic susceptibility to melanoma, in particular, the propensity to develop nevi and freckles, red hair, blue eyes, inability to tan and a family history of the disease are the primary determinants of melanoma among adolescents in this high solar radiation environment. Lack of association with reported sun exposure is consistent with the high genetic susceptibility in this group.

Key words: *melanoma; etiology; ultra-violet radiation; risk factors; adolescents; case-control study*

The incidence of melanoma in all ages has increased in white-skinned populations around the world in recent decades.[1–4] Although melanoma in children remains rare, accounting for only approximately 1–3% of all malignancies in children,[5] incidence increases markedly from the teenage years and in Australia, melanoma is now the most common cancer in those between 15–44 years of age.[6] Most studies of melanoma in adolescents have been descriptive case series[7–10] and little is known of the causes of melanoma in this age group. Recent data from a case-control study of melanoma in children in Queensland[11] suggest that constitutional factors, in particular, nevi, freckling and inability to tan and family history of melanoma play the largest role in development of melanoma in people under the age of 14 years. In that study, Whiteman *et al.*[11] found no apparent association between childhood melanoma and exposure to ultraviolet (UV) radiation from the sun, suggesting that in an environment of high ambient solar radiation, genetically-determined susceptibility is a more important predictor of risk than individual variation in sun exposure. It is not known if the same situation pertains for adolescents.

The *CDKN2A* gene encodes the cyclin-dependent kinase 4 (CDK4) inhibitor $p16^{INK4A}$ and plays a key role in cell cycle regulation. Germline mutations in *CDKN2A* confer susceptibility to melanoma.[12] Although germline *CDKN2A* mutations are rare in the population overall and are estimated to be carried by only approximately 0.2% of all melanoma cases in Queensland, their frequency is over 10% among cases with a strong family history of the disease, where melanoma also tends to occur at an earlier age than in the population at large.[13,14] The role of *CDKN2A* mutations in the occurrence of melanoma in adolescents has not been investigated. This Queensland study is the first population-based case-control study of the causes, both genetic and environmental, of melanoma in adolescents, aged 15–19 years.

MATERIAL AND METHODS

Case subjects

Eligible cases comprised all Queensland residents with a histologically confirmed first primary cutaneous melanoma, in situ or invasive, diagnosed between January 1, 1987 and December 31, 1994 and notified to the Queensland Cancer Registry and aged 15–19 years at the time of diagnosis, a total of 250 eligible cases. Notification of cancer to a central registry has been compulsory in Queensland since 1982 and it has been estimated that ascertainment is approximately 95% complete.[15] Missing histologic information was obtained from pathology laboratories. Letters explaining the study and seeking permission to contact the patient were sent to all treating doctors whose names were obtained from the Registry. Non-responding doctors were telephoned after 2 weeks. After permission was obtained, cases (or their parent or guardian if the case was still under the age of 18 years) were invited by letter to participate. Doctor's permission was refused for 20 patients, 8 patients were deceased, 17 could not be traced and 4 patients themselves refused to participate, leaving a total of 201 (80%) eligible patients who participated.

Of the total 250 eligible cases, 124 (49.6%) were males. The mean age at diagnosis was 17.4 years (similar for both genders). A

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total of 51 (20%) cases were *in situ*, either superficial spreading melanoma (60% of *in situ* cases) or type unspecified. Of the 198 invasive cases, 110 (44%) were superficial spreading melanoma, 14 (6%) were nodular melanoma and 74 (30%) were described as type unspecified. The remaining case had metastatic melanoma of unknown primary origin. Thickness was recorded for 191 invasive lesions and for these, overall mean thickness was 0.82 mm (range 0.11–9.0 mm), 0.88 mm and 0.75 mm for males and females respectively. The back (47% of all cases in males) was the most common site for melanoma in males and the lower limb (29%) in females.

Participating cases were similar to the eligible group in terms of their distributions of age, gender, histologic subtype and site of melanoma. Participating cases had thinner tumors on average, with mean thickness of 0.75 mm and 0.67 mm for males and females respectively.

Control subjects

Controls were matched to cases by age (within 1 year), gender and residence (South-East, South-West, North-East or North-West Queensland) according to the case's address at the time of diagnosis. Matched controls were selected from 2 sources according to the age of the cases at the time of the study. The majority of cases (192) were aged 18 years and over at the time of the study and were therefore required by law to be registered to vote. For these cases, controls were selected at random from the Queensland State Electoral Roll and invited by letter to participate. Non-responding controls were telephoned 2 weeks later. A total of 261 eligible controls were selected in this way, 13 were unable to be traced and of the remainder, 196 (79%) agreed to participate.

For the 9 cases less than 18 years of age at the time of the study and therefore not eligible for voter registration, controls were selected at random using an electronic listing of telephone numbers from the same postal area as the case. A trained interviewer telephoned each number selected, introduced the study and asked if there was a person living in the house who met the age and gender requirements. Eligible subjects were then asked if they would agree to participate. Of a total 423 households contacted, 411 contained no subject of the required age and gender and 2 refused before eligibility could be assessed. Of the 10 eligible contacts, all but 1 agreed to take part in the study. Thus, overall, of the 258 eligible controls contacted, 205 (79%) agreed to participate.

Consent and approval

Approval for our study was obtained from the appropriate local ethics review board and written informed consent was obtained from each subject (or, if under 18 years, from their guardian).

Interviews with cases, controls and their parents

Subjects were interviewed face-to-face in their homes, except for 17 cases (8%) who lived interstate or overseas and were interviewed by telephone. The structured interview elicited demographic information; residential history including the number of years in each location; and information on constitutional risk factors including density of nevi on the body (self-assessed as none, few, some and many by comparison with pictorial representations), hair and eye color, density of freckling on face, shoulders and arms (self-assessed by comparison with pictorial representations), tanning ability, propensity to burn with unprotected sun exposure and skin type (never, sometimes, usually or always burn).

The number of episodes during life of peeling sunburns and of blistering sunburns was asked overall and for the site of the melanoma (or referent site in controls). The number of hours of weekday and weekend sun exposure were elicited for all periods from age 5 up to the age of diagnosis for cases or referent age for controls (5–10th birthday , 10–15th birthday, 15–17th birthday, 17 to age of diagnosis [or referent age]). Participants were asked "how many hours between 9 am and 5 pm did you spend outside without any shade on a usual weekday/weekend day?" with possible responses being nil, less than 2, 2 up to 4, 4 up to 6, or 6 or more hours. For the same periods, subjects were asked about frequency of weekend or holiday sunbathing (never, rarely, sometimes, often) and frequency of using sunscreen at school, home and on holidays (never, rarely, sometimes, always). Subjects were asked whether they spent their lunchtime whilst at school (or the hours of 10 am to 2 pm on weekends) mostly indoors or in the shade, mostly outdoors in the sun, or both indoors and outdoors.

One parent of each subject was interviewed in their home or by telephone. Information was not obtained from parents of 10 cases who did not want their parents to be involved. Questions about the child's hours of weekday and weekend sun exposure, residential history and constitutional risk factors were asked of the parents to allow cross-checking of information obtained from the child. In addition, parents were asked about the child's ancestry; family history of melanoma; occupational history of parents at the time their child was diagnosed (or referent year for controls); medical history of the child including birth weight, presence of congenital nevi, childhood illnesses and use of medications including cytotoxics and immunosuppressants; and the child's history of exposures to X-rays, chemicals such as pesticides and fertilizers. Histological confirmation was sought for each first-degree relative reported by the parent to have been diagnosed with melanoma. The relative was contacted (or their next-of-kin if deceased) and asked for consent to contact their treating doctor. The treating doctor was then contacted for confirmation of melanoma history.

Clinical examinations

Whole body skin examinations and counts of nevi 2 mm or more in diameter (as measured by a transparent plastic stencil) were completed in the participants' homes by a trained examiner (PY) for 184 (92%) cases and all controls. All areas of the body were included in the examination except for the scalp and areas covered by underwear. Nevi were defined as brown to black discrete pigmented lesions that could be macular or papular. Nevi 5 mm or more were counted separately.

Blood collection, DNA extraction and molecular analysis

Blood samples (10 ml) were collected by venipuncture from 147 cases and frozen until ready for use. After thawing, 40 ml of a solution of 10 mM Tris/1 mM EDTA (TE) was added and the samples centrifuged at 1,800 rpm for 10 min. The supernatants were decanted and the white cell pellets resuspended in 50 ml TE before being repelleted. Cell pellets were washed again with TE and then each taken up in 3 ml lysis buffer (135 μg/ml proteinase K, 0.68% SDS, 1.87 mM EDTA, 324 mM NaCl, 8.1 mM Tris.HCl, pH 8). DNA was extracted according to the method of Miller *et al.*[16] *CDKN2A* exons 1α and 2, which encode the vast majority of p16 were amplified and sequenced as described previously.[17]

Statistical analysis

An estimate of total sun exposure for each period was obtained by summing the average daily ambient UV radiation for each place of residence, obtained from published figures,[18] weighted by the total number of hours spent in the sun on weekdays and weekends during the period. Cumulative lifetime sun exposure up to the age of diagnosis (or referent age for controls) was obtained by summing the estimated UV exposure for the periods 0–2nd birthday and 2–5th birthday (from parent questionnaire), 5–10th birthday, 10–15th birthday, 15–17th birthday and 17 to age of diagnosis (or referent age) (from the case's or control's questionnaire). For the 10 cases whose parents had not participated, missing values for sun exposure for ages under 5 years were replaced by median values obtained from the whole sample. Results were the same when these participants were excluded from the analyses. Quintiles were calculated on the basis of the UV exposure distribution in the controls and the lowest level of total cumulative sun exposure was used as the referent category in the analyses.

Average lifetime indices of sunscreen use and of sunbathing frequency were obtained by multiplying the coded response for

each period by the number of years for that period, summing across all periods and dividing by the participant's age at diagnosis (or referent age). For sunscreen use, parental reports were used from birth to the fifth birthday and combined with self-reports for 5 years and older.

Multiple logistic regression analysis, both unmatched and matched, was used to obtain estimates of risk while controlling for confounding factors. Variables considered for inclusion in the model were those that were statistically significant in a univariate analysis. Where variables were found to be highly correlated during pair-wise analysis the variable with the highest odds ratio was chosen for inclusion in the model. All tests of significance were 2-sided. For the unmatched analysis, odds ratios and 95% confidence intervals were obtained using Proc Logistic procedure in the SAS statistical package.[19] Conditional logistic regression was performed using the Proc Phreg procedure in SAS.

RESULTS

On clinical examination all participants had at least 1 nevus. Cases had an average of 119.2 nevi 2 mm or larger compared to 52.5 for controls. A total of 99 (54%) cases had more than 100 such nevi compared to 27 (13%) controls. Cases had an average of 6.1 nevi 5 mm or larger compared to 2.1 for controls and 28 (15%) cases and 6 (3%) controls had more than 10 such nevi. In univariate analysis, the risk of melanoma was strongly and significantly associated with increasing numbers of total nevi and increasing numbers of large nevi, with a significant trend for both factors (Table I). There was a 34-fold increased risk of melanoma associated with having 100 or more nevi *vs*. 25 or less (OR = 34.1, 95%CI = 11.2–103.9) and a greater than 15-fold increased risk associated with 10 or more large nevi *vs*. none (OR = 15.4, 95%CI = 4.7–50.2). The parent's report of the degree of moliness of their child at age 15 years (assessed by comparison with pictorial representations) was also a strong risk factor, with a significant increase in risk for "many moles" *vs*. "none" (OR = 34.7, 95%CI = 3.8–315.2). As nevus counts were somewhat skewed log transformation was carried out and the analysis was repeated on the log transformed data with no change to the results. A history of a congenital nevus was not associated with risk of melanoma.

Propensity to sunburn, ability to tan, skin type, density of facial freckling, hair color and eye color were all significantly associated with risk of developing melanoma in univariate analysis (Table I). Significant trends were seen with all of these variables. There was

TABLE I – DISTRIBUTION OF CONSTITUTIONAL AND OTHER RISK FACTORS FOR MELANOMA AMONG CASES AND CONTROLS

	Cases[1] (n = 201)	Controls[1] (n = 205)	Unmatched OR[4] (95% CI)	Matched OR (95% CI)[2,4]	χ^2_{trend} (p-value)
Total nevi (≥2 mm)					
<26	9	73	1.0	1.0	
26–50	23	69	2.7 (1.2–6.3)	2.6 (0.9–7.3)	
51–100	53	36	11.9 (5.3–26.9)	15.8 (5.1–48.9)	
>100	99	27	29.7 (13.2–67.0)	34.1 (11.2–103.9)	99.2 (<0.001)
Nevi ≥ 5 mm					
Nil	35	95	1.0	1.0	
1–4	59	79	2.0 (1.2–3.4)	2.2 (1.3–4.0)	
5–10	62	25	6.7 (3.7–12.3)	8.3 (3.9–17.5)	
>10	28	6	12.7 (4.8–33.2)	15.4 (4.7–50.2)	56.9 (<0.001)
Tanning ability					
Dark tan	14	40	1.0	1.0	
Medium tan	54	89	1.7 (0.8–3.5)	2.3 (1.1–5.1)	
Mild tan	91	57	4.6 (2.3–9.1)	5.2 (2.4–11.6)	
No tan	40	19	6.0 (2.7–13.6)	8.0 (3.0–21.1)	33.8 (<0.001)
Propensity to burn					
Tan easily	14	44	1.0	1.0	
Tan slightly	62	85	2.3 (1.2–4.6)	2.5 (1.2–5.3)	
Burn/peel	125	76	5.2 (2.7–10.1)	6.1 (2.9–13.1)	29.2 (<0.001)
Skin type					
Never burn	7	17	1.0	1.0	
Sometimes burn	64	100	1.6 (0.6–4.0)	1.8 (0.7–4.7)	
Usually burn	82	67	3.0 (1.2–7.6)	3.1 (1.2–8.3)	
Always burn	48	21	5.6 (2.0–15.4)	6.2 (2.1–18.7)	24.5 (<0.001)
Facial freckling					
None	45	80	1.0	1.0	
Few	70	69	1.8 (1.1–3.0)	1.9 (1.1–3.3)	
Some	49	39	2.2 (1.3–3.9)	2.3 (1.3–4.1)	
Many	34	15	4.0 (2.0–8.2)	4.1 (2.0–8.6)	17.8 (<0.001)
Hair color					
Black/brown	68	105	1.0	1.0	
White/blonde	113	90	1.9 (1.3–2.9)	2.0 (1.3–3.0)	
Red	20	10	3.1 (1.4–7.0)	3.3 (1.4–7.6)	8.4 (0.004)
Eye color					
Brown	32	58	1.0	1.0	
Hazel	46	52	1.6 (0.9–2.9)	1.7 (0.9–3.2)	
Green	27	24	2.0 (1.0–4.1)	2.4 (1.1–5.1)	
Blue	96	71	2.5 (1.4–4.2)	2.7 (1.5–4.9)	11.4 (<0.001)
Family history[3]					
No	168	199	1.0	1.0	
Yes	23	6	4.5 (1.8–11.4)	3.8 (1.6–9.4)	12.8 (<0.001)
Lived on farm					
No	156	183	1.0	1.0	
Yes	35	22	1.9 (1.1–3.3)	1.8 (1.0–3.3)	4.6 (0.03)

[1]Totals for each variable vary due to missing values.–[2]Matched for age, sex and geographical region of residence.–[3]Family history defined as histologically confirmed melanoma in first degree relative.–[4]OR, odds ratio; CI, confidence interval.

a greater than 6-fold increase in risk for participants who always burned (OR = 6.2, 95%CI = 2.1–18.7) and an 8-fold increased risk for those who did not tan after prolonged sun exposure (OR = 8.0, 95%CI = 3.0–21.1) (Table I). More than twice the proportion of cases (17%) reported "many" facial freckles as did controls (7%) and the presence of many facial freckles compared to none increased risk by a factor of four (OR = 4.1, 95%CI = 2.0–8.6). A total of 56% of cases had blonde/fair hair at the age of five years compared to 44% of controls and twice as many cases (10%) had red hair as controls (5%). Red hair was associated with a greater than 3-fold increased risk (OR = 3.3, 95%CI = 1.4–7.6) compared to those with brown/black hair.

As a means of checking the level of agreement between the case or control and their parent, the same phenotypic variables were recorded in both questionnaires. There was good agreement for the questions about propensity to sunburn, tanning ability, hair color and eye color (weighted kappa coefficients of 0.65, 0.67, 0.85 and 0.94 respectively). Levels of agreement were similar for cases and controls.

Risk of melanoma was significantly elevated in those with a first-degree relative with the disease (OR = 3.8, 95%CI = 1.6–9.4) (Table I). Of 36 relatives reported to have had melanoma, 7 proved to be false reports (3 basal cell carcinomas and 4 benign nevi). A total of 23 cases (11.7%) had a first-degree relative with confirmed melanoma (2 siblings and 21 parents) compared to 6 (2.9%) controls (1 sibling and 5 parents). No cases or controls had more than 1 first-degree relative with melanoma.

The mean cumulative lifetime exposure to ultraviolet radiation was similar for cases (1.83×10^6 units) and controls (1.79×10^6 units). There was no association with melanoma at any level of cumulative exposure (Table II), either overall or within each life period and no association with exposure accumulated in the middle of the day (10 am to 2 pm). Mean total ambient UV exposure was also similar for cases and controls (2.4×10^6 units 2.3×10^6 units respectively).

A slightly higher proportion of cases (37%) than controls (31%) reported more than 10 episodes of peeling sunburns and there was a statistically significant trend to increasing risk of melanoma associated with increasing numbers of peeling or blistering sunburns ($p < 0.02$) (Table II). There was no increase in risk associated with repeated sunburn at the site of the melanoma. Both cases and controls used sunscreen quite frequently when on holidays but not at home (Table II). Overall, there was no association between sunscreen use and risk of melanoma at home or on holidays. The only period of life for which there was an association with sunscreen use was under 5 years of age, when risk of melanoma was doubled for those who never/rarely used sunscreen at home *vs*. often/always (OR = 2.1, 95%CI = 1.2–3.9). This association was not apparent for reported sunscreen use whilst on holidays within the same time period.

TABLE II – DISTRIBUTION OF SUN EXPOSURE VARIABLES AMONG CASES AND CONTROLS

	Cases[1] (n = 201)	Controls[1] (n = 205)	Unmatched OR (95% CI)[4]	Matched OR (95% CI)[2,4]	χ^2_{trend} (p-value)
Total cumulative UV					
<20th percentile	34	41	1.0	1.0	
20–40th percentile	49	41	1.4 (0.8–2.7)	1.4 (0.7–2.7)	
40–60th percentile	32	41	0.9 (0.5–1.8)	0.9 (0.5–1.9)	
60–80th percentile	36	41	1.1 (0.6–2.0)	1.1 (0.5–2.2)	
>80th percentile	50	41	1.5 (0.8–2.7)	1.5 (0.8–3.0)	0.5 (0.5)
Lifetime number of peeling sunburns					
Never	7	12	1.0	1.0	
Once	9	14	1.1 (0.3–3.9)	1.1 (0.3–4.5)	
2–5	56	74	1.3 (0.5–3.5)	1.4 (0.5–4.4)	
5–10	55	42	2.2 (0.8–6.2)	2.5 (0.8–8.2)	
>10	74	63	2.0 (0.7–5.4)	2.1 (0.7–6.6)	5.5 (0.02)
Lifetime number of blistering sunburns					
Never	88	113	1.0	1.0	
Once	50	47	1.4 (0.8–2.2)	1.4 (0.8–2.2)	
2–5	37	27	1.7 (1.0–3.1)	1.8 (1.0–3.4)	
5–10	14	10	1.8 (0.8–4.2)	1.6 (0.7–3.7)	
>10	12	8	1.9 (0.8–4.9)	1.9 (0.7–4.8)	5.6 (0.02)
Sunburns at site of melanoma					
Never	24	26	1.0	1.0	
Once	10	16	0.7 (0.3–1.8)	0.7 (0.3–1.9)	
2–5	58	73	0.9 (0.4–1.7)	0.9 (0.4–1.9)	
5–10	48	38	1.4 (0.7–2.8)	1.5 (0.6–3.4)	
>10	59	51	1.3 (0.6–2.5)	1.3 (0.6–2.8)	2.2 (0.14)
Average lifetime index of sunscreen use at home[3]					
Often/always	47	49	1.0	1.0	
Sometimes	53	56	1.0 (0.6–1.7)	0.9 (0.5–1.7)	
Never/rarely	89	94	1.0 (0.6–1.6)	0.9 (0.5–1.7)	0.1 (0.77)
Average lifetime index of sunscreen use on holidays[3]					
Often/always	115	127	1.0	1.0	
Sometimes	48	43	1.2 (0.8–2.0)	1.3 (0.8–2.0)	
Never/rarely	28	32	1.0 (0.6–1.7)	1.0 (0.5–1.8)	0.2 (0.70)
Sunscreen use at home ≤5 yrs					
Often/always	24	42	1.0	1.0	
Sometimes	75	88	1.5 (0.8–2.7)	1.4 (0.8–2.6)	
Never/rarely	92	71	2.3 (1.3–4.1)	2.1 (1.2–3.9)	7.2 (0.03)
Sunscreen use on holidays ≤5 yrs					
Often/always	127	147	1.0	1.0	
Sometimes	31	25	1.4 (0.8–2.6)	1.4 (0.7–2.5)	
Never/rarely	33	30	1.3 (0.7–2.2)	1.2 (0.7–2.1)	1.9 (0.38)

[1]Totals for each variable vary due to missing values.–[2]Matched for age, sex and geographical region of residence.–[3]See text.–[4]OR, odds ratio; CI, confidence interval.

Parental reports of childhood immunizations, history of childhood illnesses or therapeutic radiation exposures showed no association with melanoma. Those who indicated that they had lived or currently live on a farm had a significantly increased risk of melanoma (OR = 1.9, 95%CI = 1.1–3.3) (Table I), although reported exposures to pesticides, fertilizers or aerial spraying showed no significant associations.

In the multivariate model, the total number of nevi (≥2 mm) remained by far the strongest predictor of melanoma risk after adjusting for other constitutional factors, with an adjusted odds ratio of 46.5 (95%CI = 11.4–190.8). Hair color, eye color, inability to tan, heavy facial freckling, family history of melanoma and never/rarely using sunscreen at home under the age of 5 years also showed strong and significant trends to increased melanoma risk (Table III). Frequency of peeling sunburns was not associated with melanoma after adjustment for other factors. The inclusion of total cumulative UV exposure in the multivariate model did not alter any of these associations.

Of the 147 adolescent melanoma cases analyzed for germline mutations in *CDKN2A* only 2 cases (neither with a family history of melanoma) had variants known to abrogate the function of p16. One individual carried the common G101W variant[20] and another possessed the nucleotide −34G > T change in the 5′ untranslated region of *CDKN2A*, which leads to the generation of an alternative start codon out of frame with wild-type p16.[17]

DISCUSSION

In our study, the factors most strongly associated with risk of melanoma in adolescence are constitutional factors including the presence of large numbers of nevi (either ≥2 mm in diameter or ≥5 mm), red hair and blue eyes, inability to tan and a propensity to freckle, factors known from studies in children and adults to indicate increased susceptibility to the disease.[11,21–28] The extremely high risk for melanoma associated with large numbers of nevi in adolescents is consistent with a 30-fold increased risk for adults associated with the presence of any nevi on the arms *vs.* none.[21]

A confirmed history of melanoma in a first-degree relative was a strong risk factor for melanoma, again consistent with studies in adults[21,26,29] and children.[11] The proportion of germline *CDKN2A* mutation carriers in our sample (2/147, 1.4%) is extremely low and indicates that this gene accounts for very little early-onset melanoma in the population of Queensland. This result builds on our previous observation that *CDKN2A* mutations were found in approximately 10% of 87 high-risk melanoma families (predominantly families with 3 or more cases of melanoma and accounting for fewer than 1% of melanoma cases in the population) and none of 395 intermediate- or low-risk families analyzed from the same population, unselected for age of the proband.[13] None of the adolescent cases with a positive family history reported here had more than one relative with confirmed melanoma and none would fit into the high familial risk group of our previous study.

Although UV exposure is the strongest known environmental risk factor for melanoma[30] there was a complete lack of any association in our study between melanoma during adolescence and cumulative sun exposure, consistent with the results of a study of melanoma in children in Queensland.[11] After adjustment for other risk factors, neither was there a significant association with the number of peeling or blistering sunburns, nor was there an association with sunscreen use overall. Using sunscreen never or rarely at home under the age of 5 years (as reported by the parent)

TABLE III – ADJUSTED ODDS RATIOS FOR CONSTITUTIONAL AND SUN EXPOSURE VARIABLES FOR MELANOMA IN ADOLESCENTS

	Adjusted OR[1] (95% CI)	χ^2_{trend} (*p*-value)
Total nevi (≥2 mm)		
<26	1.0	
26–50	2.9 (0.8–10.2)	
51–100	17.3 (4.2–69.7)	
>100	46.5 (11.4–190.8)	73.5 (<0.001)
Hair color		
Black/brown	1.0	
White/blonde	1.7 (0.8–3.7)	
Red	5.4 (1.0–28.4)	2.8 (0.09)
Eye color		
Brown	1.0	
Hazel	3.7 (1.0–13.5)	
Green	3.8 (0.9–16.5)	
Blue	4.5 (1.5–13.6)	4.3 (0.04)
Tanning ability		
Dark tan	1.0	
Medium tan	3.4 (0.7–16.5)	
Mild tan	3.9 (1.0–16.0)	
No tan	4.7 (0.9–24.6)	9.4 (0.002)
Facial freckling		
None	1.0	
Few	0.6 (0.2–1.7)	
Some	1.0 (0.4–2.9)	
Many	3.2 (0.9–12.3)	5.2 (0.02)
Family history		
No	1.0	
Yes	4.0 (0.8–18.9)	4.7 (0.03)
Sunscreen use at home ≤5 yrs		
Often/always	1.0	
Sometimes	1.6 (0.5–5.3)	
Never/rarely	2.2 (0.7–7.1)	6.2 (0.01)
Lifetime number of peeling sunburns		
0–5	1.0	
>5	1.8 (0.8–4.0)	1.3 (0.25)

[1]Conditional logistic regression matched on age, sex and geographical region of residence adjusted for all variables listed above. OR, odds ratio; CI, confidence interval.

was associated with a doubling of risk, however, the association was not apparent when sunscreen use was assessed during holidays during the same time period. Although 1 case-control study of melanoma in young females[31] has reported a more than 2-fold increased risk for infrequent or no use of sunscreen, others have reported increased risk associated with sunscreen use[11,32–35] including use in childhood[11,32] and this issue remains contentious. In the present study, it is not possible to check a parent's response against the child's response for the youngest time periods. Biased reporting of sunscreen use by parents of cases, due to a belief that infrequent sunscreen use may have contributed to their child's melanoma, is a possible explanation for our result.

A strength of this population-based study is the similarly high level of participation of eligible cases and controls (80% and 79% respectively). Cases were ascertained from a state-wide population cancer register and most controls from the state electoral roll. The 29 cases (15%) eligible to vote but not registered on the electoral roll were examined in terms of demographics and melanoma risk factors and were not systematically different from the remaining sample. A single experienced nurse interviewer/examiner, trained by a dermatologist, completed all interviews and skin examinations. The examiner was aware of which subjects were cases, but potential interviewer bias was minimized by using a consistent and structured protocol for mole counting and a highly structured interview protocol. Histopathologic confirmation of all reported histories of melanoma in first degree relatives was sought and misclassification of family history of melanoma is unlikely. Biased recall of sun exposure is possible, given that the relationship between skin cancer and the sun is well known to the Queensland population. Overestimation of sun exposure by cases or their parents, however, would tend to bias the results in the positive direction and is unlikely to explain our null result. Constitutional factors, which did show strong positive associations, such as coloring and the presence of nevi, are less likely to be associated with biased reporting. Self- and parental reports of degree of moliness were recorded before clinical examination and elevated risk was found for those reporting "many" moles *vs*. "none" for both reports.

In conclusion, predictors of melanoma in adolescents in Queensland are related to an inborn susceptibility to the disease, including the presence of large numbers of nevi, propensity to freckle, inability to tan, red hair, blue eyes and having a close relative with melanoma. A uniformly high level of sun exposure during the early childhood and school years in Queensland's subtropical climate means that most people born in this part of Australia achieve consistently high levels of sun exposure early in life. Although this high exposure to UV radiation is the main reason for the high incidence of melanoma and large numbers of nevi in all age groups in Queensland compared to populations with a similar genetic background living further from the Equator, it is not what discriminates cases from controls among young Queenslanders. In this environment, with uniformly high levels of solar radiation, genetic susceptibility to melanoma, in part mediated through susceptibility to the effects of sun exposure, is a primary determinant of who will get the disease at an early age.

These results are consistent with a recent analysis of melanoma risk and sun exposure among adults in Queensland that found a strong association with sun exposure amongst families at low genetic risk, but no association amongst families at high genetic risk,[36] whose members also tend to develop the disease at a younger age on average than the population at large.[14] Our results suggest that adolescent cases, who on the basis of their family histories would not be regarded as members of familial melanoma kindreds, nevertheless have an unusually high genetic susceptibility for the disease.

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