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CLINICAL REPORT

Factors Associated with Atypical Moles in New Hampshire, USA

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Only a few studies, conducted in Sweden, assessed factors associated with the presence of atypical moles in the general population. We conducted a population-based, case-control study in New Hampshire, USA, to identify factors associated with atypical moles. In our study, atypical moles affected 14% of the study population. The adjusted odds ratio (OR) was 0.34 (95% confidence interval (CI)=0.14–0.80) for those with the highest adulthood recreational sun exposure, relative to the lowest. The OR for any freckles, compared to none, was 2.24 (95% CI=1.18–4.25). We found a linear relationship between the number of benign moles and the presence of atypical moles (*p* for trend=0.0001). The OR was 7.34 (95% CI=3.03–17.80) for >15 benign moles, relative to 0–4. Our data indicate that freckles and benign moles, which may reflect melanocytic inducibility, are strongly associated with atypical moles. The inverse association with sun exposure should be considered with caution. ***Key words: moles; atypical moles; pigmentary characteristics; sun exposure.***

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Numerous epidemiological studies (1–9), including 2 population-based case-control studies, one in Sweden (10), and another in the USA (11), have shown that 34–56% of melanoma patients have clinically atypical moles, or evidence of histologically atypical moles. In addition to the epidemiological evidence, pathology studies indicate that about half of melanomas arise in histological contiguity with an atypical mole (12–14). Considered collectively, the evidence to date suggests that atypical moles are strong risk factors and potential precursors of melanoma (reviewed in 15).

Because atypical moles are strongly associated with risk of melanoma (1–11), and risk of second primary melanoma (16–19), prevention of the precursor offers a strategy for reducing melanoma incidence and burden. To date, several studies have attempted to identify risk factors for atypical moles (20–32), but most were limited to the assessment of host characteristics. Several studies used indirect measures of sun exposure (22, 24, 29, 31, 32) including a study of children (27); only a few directly assessed sun exposure histories (23–26, 30), and only one of these studies, conducted in Sweden, was population-based (26).

We conducted a population-based study of risk factors for atypical moles. Host characteristics and complete histories of sunburn and sun exposure were obtained by a telephone interview. Benign and clinically atypical moles were assessed in a physician-conducted skin examination.

METHODS

This study was approved by the Committee for the Protection of Human Subjects at Dartmouth College. All study participants gave verbal consent (for interview) and signed consent (for skin examination).

The study population consists of controls who participated in a population-based, case-control study of melanoma (11). The parent study was designed to over-sample controls to allow an embedded study of atypical moles within the control series. Controls of ages 20–69 years were ascertained through the New Hampshire Department of Motor Vehicles using drivers' license lists available between January 1995 and December 1998. Eligibility required current residence in New Hampshire, a working telephone number, and ability to participate in an English-speaking interview. A letter introducing the study was sent to potential participants, followed by a telephone call from the interviewer. We enrolled 684 of 1121 (61%) potentially eligible control subjects; 87 (8%) could not be reached, 13 (1%) had died, and 337 (30%) declined to participate. Of the 684 control participants, 6 were deemed ineligible due to a prior diagnosis of melanoma, leaving 678 eligible controls for the present analysis.

The 40-min telephone interview queried participants for demographic factors, family history of melanoma, pigmentary characteristics, sun sensitivity, episodes of sunburn, hours of sunbathing, and hours of recreational and occupational sun exposure. Pigmentary characteristics included hair color (black/dark brown, brown, light brown/red-brown, blond/red) eye color (brown, gray/green/hazel, blue), and the presence of freckles (none, any). Sun sensitivity was assessed by asking subjects how their skin would react if exposed for 1 h to strong summer sunlight; answer options included sunburn with peeling followed by no tan or a light tan; sunburn with peeling followed by freckles; sunburn followed by tan, and immediate tanning.

A detailed description of the sun-related variables has been published previously (11). Briefly, we asked participants about episodes of sunburn with peeling, and separately about sunburn with blistering, in 10-year age periods, starting at age 10 years. Questions regarding sun exposure included hours of sunbathing (asked in 10-year age intervals starting at age 10 years), hours of outdoor recreational sun exposure (starting at

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age 10 years), and hours of occupational exposure during the summer (starting at age 6 years to accommodate farm work). For the 3 sun exposure variables (sunbathing, recreational, and occupational sun exposure), daily exposure was capped at 10 h. Each of these variables was evaluated separately as the number of hours of sun exposure occurring prior to age 20 years, at age 20 years or more, and in total over the lifetime. Sun exposure was assessed prior to a reference date, which had been assigned to the controls at random to correspond to one year prior to the melanoma diagnosis date of cases participating in the parent study.

At the conclusion of the interview, participants were invited to undergo a dermatologist-conducted study-related skin examination during which the number and site of benign and atypical moles were recorded using a standardized form. The skin examination covered all skin areas other than the anogenital area. To help distinguish benign moles from lentigines, diagnostic criteria included palpability and a diameter of at least 3 mm (1). Additional diagnostic criteria for benign moles included a symmetrical shape, well-defined border, and uniform coloration (1). A mole was considered atypical if it met at least 3 of the following criteria: diameter of 5 mm or more, flat (macular) component, erythema, irregular border, ill-defined border, and variegated color (18).

Of the 678 eligible controls, 424 (63%) participated in the skin examination, which identified 59 participants with clinical evidence of at least one atypical mole and 365 participants without atypical moles. For the purposes of the present analyses, we classified those with clinical evidence of at least one atypical mole as "cases," and those without an atypical mole as "controls."

Preliminary analyses included frequency distributions and descriptive statistics. When possible, sun-related variables were assessed using zero as the reference level; when this was impractical (due to small numbers), the data were assessed in approximate tertiles, based on the distribution in the controls. Odds ratios (OR) and 95% confidence intervals (CI) were computed using multivariable logistic regression models (33) to assess the association between risk factors and atypical moles. Initially, factors were evaluated singly in models that included terms for age and gender. Multivariable models were used to assess variables that were significantly ($p < 0.05$; two-sided) associated with atypical moles in the age and gender adjusted analyses.

RESULTS

In our study population, 59 (14%) individuals had at least one atypical mole; 24 (40.7%) affected individuals had only one atypical mole, 18 (30.5%) had 2–3, and 17 (28.8%) had ≥ 4. Among those with any atypical moles, the mean count was 4.2 (median=2). Fifty-two (88.1%) affected individuals had at least one atypical mole on the trunk, and most of the trunk lesions (84.6%) were located on the back or shoulders.

The initial age-and-gender adjusted models indicated that the odds of having at least one clinically atypical mole were significantly decreased in the older age groups, compared to the youngest (Table I). Atypical moles were also observed significantly less often in women, compared to men. The data suggested possible slight associations with level of education and a family history of melanoma, but the findings were compatible with chance (data not shown). Freckles were associated with a near doubling of the odds of having atypical moles.

Table I. *Number (%) of cases and controls according to select characteristics and odds ratios (OR) and 95% confidence intervals (CI) for having at least one clinically atypical mole*

Characteristics	Cases *n* = 59 *n* (%)	Control *n* = 365 *n* (%)	OR[a]	95% CI
Age group (years)				
≤ 39	17 (28.8)	47 (12.9)	1.00	–
40–59	33 (55.9)	182 (49.9)	0.46	0.23–0.91
≥ 60	9 (15.3)	136 (37.3)	0.16	0.07–0.40
Gender				
Male	38 (64.4)	216 (59.2)	1.00	–
Female	21 (35.6)	149 (40.8)	0.43	0.22–0.86
Freckles				
No	19 (32.8)	171 (48.3)	1.00	–
Yes	39 (67.2)	183 (51.7)	1.87	1.03–3.41
Benign nevi				
0–4	15 (25.4)	227 (62.2)	1.00	–
5–14	29 (49.2)	110 (30.1)	3.51	1.79–6.87
≥ 15	15 (25.4)	28 (7.7)	7.44	3.25–17.06
Sun sensitivity				
Burn, peel	20 (33.9)	164 (44.9)	1.00	–
Burn, freckle	3 (5.1)	24 (6.6)	1.02	0.28–3.76
Burn followed by tan	34 (57.6)	141 (38.6)	1.93	1.05–3.54
Tan only	2 (3.4)	36 (9.9)	0.45	0.10–2.05
Recreational hours age ≥ 20 years				
0–3300	24 (41.4)	115 (32.1)	1.00	–
3301–9000	24 (41.4)	114 (31.8)	0.96	0.51–1.81
9001+	10 (17.2)	129 (36.0)	0.40	0.18–0.90

[a]OR for age adjusted for gender, OR for gender adjusted for age. All other ORs adjusted for age and gender. Variations in column totals are due to missing valves.

Based on the cut-points shown, the odds of an atypical mole increased markedly with the number of benign moles. The elevated ORs corresponding to hair and eye color were not statistically significant, and did not increase consistently with lighter eye or hair color (data not shown). The ORs also did not appear to increase with greater sun sensitivity, but the data indicated an association with the tendency to tan following sunburn, compared to those who burned and peeled (Table I). The age-and-gender adjusted models provided little evidence of a positive association with any of the sun exposure variables (data not shown). If anything, the results suggested inverse associations with most measures of sunburn or sun exposure, whether before age 20 years, age 20 years or older, or in total over the lifetime. A significant inverse association was noted for the highest level of hours of adulthood recreational sun exposure, compared to the lowest (Table I).

In a multivariable model, the variables age, gender, freckles, recreational sun exposure at age 20 years or more, and number of benign moles were significantly associated with the presence of at least one atypical mole. Sun sensitivity did not retain a significant association, and was omitted from the final multivariable model. As age increased, the tendency to have atypical moles decreased, an inverse association that was statistically

Table II. *Factors associated with having at least one clinically atypical mole*

Risk factor	OR (95% CI)[a]
Age[b] (years)	
≤ 39	1.00
40–59	0.52 (0.24–1.13)
≥ 60	0.26 (0.10–0.69)
Gender	
Male	1.00
Female	0.44 (0.22–0.87)
Freckles	
None	1.00
Any	2.24 (1.18–4.25)
Recreation hours, age ≥ 20 years	
0–3300	1.00
3301–9000	1.01 (0.50–2.03)
≥ 9001	0.34 (0.14–0.80)
Benign moles[c]	
0–4	1.00
5–14	3.74 (1.86–7.51)
≥ 15	7.34 (3.03–17.80)

[a]OR for age was adjusted for gender; OR for gender was adjusted for age. Other ORs adjusted for all variables in the table.
[b]p for trend (continuous form of the variable) = 0.001.
[c]p for trend (continuous form of the variable) < 0.0001.

significant (p for trend=0.001) (Table II). Relative to those of age 39 years or less, the odds of having an atypical mole were reduced by nearly half for those of ages 40 to 59 years (OR=0.52; 95% CI=0.24–1.13), and by more than 70% in those of age 60 years or more (OR=0.26; 95% CI=0.10–0.69). Gender remained strongly associated with having an atypical mole, and the odds of having an atypical mole were more than halved for women, relative to men (OR=0.44; 95% CI=0.22–0.87). The presence of freckles more than doubled the odds of having an atypical mole (OR=2.24; 95% CI=1.18–4.25). We found no evidence that exposure to intermediate recreational sun exposure in adulthood was associated with an atypical mole, but the OR was 0.34 (95% CI=0.14–0.80) for those with the highest amount of exposure, relative to the least. The data indicated a positive association between the number of benign moles and having an atypical mole (p for trend <0.0001). The fully adjusted ORs were 3.74 (95% CI =1.86–7.51) for those with 5–14 moles, and 7.34 (95% CI=3.03–17.80) for those with at least 15 moles, relative to 0–4 benign moles.

The average number of benign moles was 7 overall, 13 in cases with atypical moles, and 6 in controls. Table III shows the number of benign moles (0–14; ≥15), and the mean number of benign moles, by age group (<50, ≥50) and by gender in cases and controls. Based on the cut-points shown, a larger proportion of cases than controls had high (≥15) benign mole counts, but within the case and control groups, the proportion affected by high mole counts was similar for the younger and older individuals. Similarly, the mean number of benign moles (in those with at least one) was about doubled in cases compared to controls, but within the case and control groups, the mean number of benign moles was similar by age group.

In the case group, a larger proportion of women than men had high counts of benign moles, but the proportions were more similar for men and women in the control group. For both men and women, the mean number of benign moles was roughly doubled in cases, compared to controls, but within the case and control groups, the mean counts were similar for men and women.

DISCUSSION

To our knowledge, this is the first report of sun exposures and host characteristics, including benign moles, in relation to atypical moles in a geographically defined population in the USA. Our data indicate that about 14% of individuals in the non-melanoma study population were affected by at least one clinically atypical mole, an estimate within the bounds suggested by previous studies. Estimates of atypical mole prevalence based on previous studies vary as much as 9-fold, perhaps reflecting differences in the ages of study participants, population differences in susceptibility, and/or participation bias associated with referral patterns. Clinic-based studies in the USA indicate that 7–17% of controls have at least one atypical mole (2, 3, 8), those in Europe report a prevalence of 2–18% (4, 7, 32, 34, 35), and studies in Australia show a prevalence

Table III. *The number (%) of subjects with benign moles, and the mean number of benign moles[a], by age group and gender in cases and controls*

	No. of benign moles					
	Cases (n = 59)			Controls (n = 365)		
	0–14	≥ 15	Mean (SE)	0–14	≥ 15	Mean (SE)
Age (years)						
< 50	20 (74.1)	7 (25.9)	13.8 (2.2)	101 (90.9)	10 (9.1)	6.6 (0.8)
≥ 50	24 (75.0)	8 (25.0)	11.7 (1.7)	236 (92.9)	18 (7.1)	5.7 (0.4)
Gender						
Male	30 (78.9)	8 (21.1)	12.3 (1.8)	201 (93.1)	15 (6.9)	6.1 (0.5)
Female	14 (66.7)	7 (33.3)	13.2 (2.2)	136 (91.3)	13 (8.7)	5.8 (0.5)

[a]Mean counts are based on those with at least one benign mole.

of 6–22% (6, 32). Variation also exists in reports from population-based studies; a study in Israel indicated that only 2.5% of men had atypical moles (36), whereas 2 studies in Sweden reported a prevalence of 11% (30) and 18% (28), respectively.

Our finding of a strong association between having atypical moles and counts of benign moles is consistent with a clinic-based investigation (35) and the population-based studies in Sweden (26, 28, 30). Consistent with previous reports, women were less likely than men to be affected by atypical moles (23), as were older individuals (21, 23). The strong association observed here between age and atypical mole counts was not found in the Swedish study (28), perhaps because enrollment was limited to individuals of ages 30–50 years. In our data, benign mole counts were substantially lower than observed in the control series of clinic-based melanoma case-control studies (2–5, 7), consistent with the possibility that mole counts are higher in clinic populations than in the general population. To the extent that benign mole development is influenced by sunlight (20, 29), the low mole counts in our study may also reflect the relatively northern latitude of New Hampshire (42°–45°), although high counts have been noted in Sweden (28). We counted moles that were of at least 3 mm diameter, whereas most studies counted lesions of at least 2 mm diameter, but this probably would not account for the magnitude of difference observed.

In our study, freckles were moderately associated with atypical moles. Our analyses were based on self-reported freckling, so we cannot rule out the possibility that study participants confused atypical moles or solar lentigines for freckles. However, the association was also observed in a previous study in which both freckles and atypical moles were assessed by a physician (26). Freckles and benign moles may be lesions that signal individuals with increased melanocytic reactivity to sun exposure.

Our data suggested a possible inverse association between sunburns and atypical moles, consistent with the lower sun exposure in the case group, but our findings were not statistically significant. A previous study, conducted in Sweden showed a significant inverse association between the number of sunburns and atypical moles (26), while other studies, including 2 suggesting positive effects (23, 25), produced findings consistent with chance (23–25, 30).

The role of sun exposure in relation to atypical moles is also uncertain. Some studies using indirect measures of sun exposure supported an association between sun exposure and atypical moles (24, 29, 31, 32), but others did not (20, 35). Similarly, of the studies using direct measures of sun exposure, 2 reported null results (23, 30), one suggested positive effects (26), and 2 more suggested inverse associations (24, 25), but all findings were consistent with chance (23–26, 30). The paucity of evidence supporting a positive association between sun exposure and atypical moles poses an interesting contrast with the established association between sun exposure and melanoma. Our study suggested inverse relationships between atypical moles and most measures of sun exposure. Individuals with a susceptibility or tendency to develop moles or atypical moles might not require extensive sun exposure to develop these lesions (37).

Although highly speculative, it is also conceivable that sun exposure is avoided by individuals whose experience indicates a tendency to develop atypical moles. To explore this possibility, we informally inspected shifts in hours of recreational sun exposure (which accounted for the majority of sun exposure) from childhood to adulthood. In cases with atypical moles, the proportion with the highest level of recreational sun exposure hours decreased from 33.9% in childhood to 17.2% in adulthood. In contrast, in controls, the proportion with the highest level of recreational sun hours increased slightly from 31.9% in childhood to 36.0% in adulthood. Thus, it is conceivable that individuals who develop melanocytic lesions reduce their sun exposure over time, a behavior that could account for the inverse association observed here between adult recreational sun exposure and atypical moles. In any case, due to the preliminary nature of this finding, and the uncertainty concerning biological mechanisms, our data should not be interpreted as suggesting that more extensive sun exposure will prevent the development of atypical moles.

Because of the small size of our study, we were unable to detect modest associations, or to assess factors according to the number or site of atypical moles. Most cases had at least 2 atypical moles, offering some assurance that they were correctly classified as cases, and that our findings are relevant to individuals with multiple atypical moles. Nearly all cases had at least one atypical mole on the trunk, so our results would almost certainly apply to this lesion site. Also, we designed a population-based study, but enrollment of non-melanoma participants, on which this report is based, was suboptimal, and those who self-selected for participation may not represent the underlying population. It is conceivable, for example, that those with multiple or worrisome moles are over-represented in our study, which offered a no-cost, physician-conducted skin examination. If the factors influencing participation were also associated with measured exposures, our results may be biased. However, our findings are generally consistent with those of clinic-based studies, and with the few existing population-based studies, arguing against bias. For example, the prevalence of atypical moles observed here (14%) is similar to that seen in 2 previous population-based studies (11% and 18%), in which participation was high (28, 30). Also, our findings with regard to the association

between benign and atypical moles are consistent with the small number of previous population-based studies, which were conducted in Sweden (26, 28, 30).

In summary, our data indicate a strong association between atypical moles and benign moles, and a moderately strong relationship with freckling, characteristics that may reflect melanocytic inducibility. Consistent with most previous studies, we found no evidence that sun exposure increases the odds of atypical moles. Although we noted an inverse association between atypical moles and the highest amount of total recreational sun exposure, further studies are needed to assess this relationship.

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