Factors Associated with Atypical Nevi: A Population-based Study

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Abstract
We conducted a case-control study to identify factors associated with the presence of clinically atypical nevi. Potential participants were selected, using a two-staged sampling scheme, from a population-based cohort of 50,000 Swedish women who had responded to a previous health survey questionnaire. Of 500 women sampled for study recruitment, 400 (80%) agreed to participate. Study participants underwent a physician-conducted skin examination, which identified 130 women who had at least one clinically atypical nevus (cases) and 270 women without these lesions (controls). The physician-conducted skin examination also assessed women for benign nevus counts; other risk factor information was based upon responses to a health survey questionnaire. We found a strong and highly statistically significant relationship between number of benign nevi and the presence of at least one clinically atypical nevus ($P < 0.0001$). Women with 100 or more benign nevi had a 26-fold increased likelihood of having an atypical nevus. We noted statistically significant interactions between number of benign nevi and other factors of interest; thus, the results are reported separately for women with low (<50) or high ($\geq50$) counts of benign nevi. Among women with low counts of benign nevi, the likelihood of having an atypical nevus increased with degree of freckling; there was also a suggested role for early sun exposure. Among women with high counts of benign nevi, difficulty tanning and lack of peeling sunburns between ages 10 and 19 appeared to increase the likelihood of case status; our data also suggested an inverse relationship between parity and atypical nevi in this subgroup.

Introduction
Numerous epidemiological studies indicate that sun exposure and sun sensitivity traits are associated with increased melanoma risk (1). However, odds ratios for these factors are generally modest and vary considerably among study populations. In contrast, most studies have shown strong associations between high counts of benign nevi, or the presence of atypical nevi, and melanoma risk (1).

In an effort to clarify the etiology of melanoma, several investigators have evaluated risk factors for atypical nevi, the nonobligate melanoma precursors. Most of these studies have shown a relation between atypical nevi and sun sensitivity factors (skin type, ability to tan, freckling, hair color, and eye color; Refs. 2–5), but none have examined the role of benign nevi.

We conducted a case-control study to identify factors associated with atypical nevi. Case and control classification was determined by a physician-conducted skin examination. Study participants with at least one clinically atypical nevus were classified as cases; those with no evidence of these lesions were classified as controls. Study participants were also assessed for benign nevus counts; other exposure data were obtained from a health survey questionnaire completed previously.

Subjects and Methods
Subjects. In 1991–1992, a health survey was sent to an age-stratified cohort of 96,000 women aged 30–49 who lived in seven counties of central Sweden and who were sampled from a population registry at Statistics Sweden. Nearly 50,000 women responded to the survey, which included inquiries regarding pigmented characteristics, sun exposures, and sun sensitivity. Respondents were also asked to examine their legs for “irregular moles,” guided by three color photographic examples in the questionnaire.

The sampling strategy used to select potential case-control participants from the health survey cohort has been described earlier (6, 7). Briefly, we randomly selected (from the cohort of 50,000) 2,500 women who were residents of an area proximal to the University Hospital of Uppsala. We classified these women according to their responses on the health survey, identifying 407 women who had reported an irregular mole and 196 who had not (97 women with ambiguous responses were excluded). From this sampling frame, we randomly selected 160 women who had reported an irregular mole and 340 women who had not; these 500 women were recruited by mail and telephone for study participation.

Skin Examinations. All participants were examined by an oncologist (E. M. B.) with expertise in the diagnosis of melanoma and atypical nevi. The skin examinations took place at the University Hospital of Uppsala over a 3-month period (March–May, 1994). A standardized form was used to record the physician’s assessment of number and body site of benign and atypical nevi. The examination covered the entire skin surface.

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The number of peeling sunburns was assessed over the same exposure, sunblock use, eye and hair color, freckling, and case status within subgroups of high evaluated, using single-factor logistic models, in relation to test indicated a significant overall interaction between benign nevi cutpoints used in previous studies (3, 5). The likelihood ratio atypical nevus case status (≤50) and other risk factors in relation to benign nevus counts. Variables associated with case status (P ≤ 0.10) in the single-factor models or related to hypotheses regarding early sun exposure were evaluated in multiple logistic regression models. Odd ratios (OR) and 95% confidence intervals (95% CI) from the logistic models were used to assess the adjusted effects of potential risk factors on atypical nevus case status (11). A p-value of < 0.05 (two-sided) was considered statistically significant.

Results

Of the 500 women recruited for participation in the case-control study, 400 (80%) agreed, including 134 (84%) women who had self-reported an irregular mole, and 266 (78%) women who had not. The mean age of women participating in this study was nearly identical to that of the 2,403 women in the sampling frame (39.3 and 39.1 respectively); the age distribution (by five year age groups) was also similar. Mean years of education were 13.1 in our study sample and 13.0 in the sampling frame; the distribution of subjects by educational level showed only minor variations. Thus, study participants appeared to be representative of the sampling frame with regard to these basic characteristics (7).

The physician-conducted skin examination identified 130 cases and 270 controls. Case women had, on average, 3.7 clinically atypical nevus (range of 1–37). Atypical nevi were most frequently found on the trunk (affecting 79% of all cases), followed by the legs (42%), head or neck (9%), and arms (9%). The likelihood of having an atypical nevus decreased with age (P = 0.04); relative to women below age 35, women who were 45 or older were 46% less likely to have atypical nevi (data not shown).

The mean number of benign nevi was 98.4 among case women (counts ranged from 4 to 587) and 37.5 among control subjects (counts ranged from 2 to 181). We found a strong and consistent relationship between number of benign nevi and the likelihood of having a clinically atypical nevus (p trend < 0.0001). Compared to women with 1–24 benign nevi, those with ≥ 100 benign nevi had a 26-fold increased likelihood of having an atypical nevus (Table 1). This relationship was only minimally diminished by adjustment for age and other potential risk factors, and was not modified by excluding women who reported family histories of melanoma.

Adjusted OR and 95% CI for the relation between other risk factors and atypical nevi, according to benign nevus level, are shown in Table 2. Among women with fewer than 50 benign nevi, amount of freckling was significantly related to case status (P trend = 0.01); those with many freckles had more than a 4-fold increased likelihood of having an atypical nevus. Although the likelihood of case status appeared to increase with the number of weeks of beach vacation between ages 10 and 19, the relationship was not significant (P trend = 0.12). Light eye color appeared to be associated with atypical nevi in this subgroup, but only one case had brown eyes, and cell frequencies were too small to permit a meaningful evaluation of this factor.

Among women with at least 50 benign nevi, inability to tan or light tanning after chronic sun exposure appeared to be associated with case status, but the relationship did not reach statistical significance. We also found that cases, relative to controls, had fewer episodes of peeling sunburn between ages 10 and 19, but there was no indication of a dose-response

The abbreviations used are: OR, odds ratio; CI, confidence interval

Analyses. We used logistic regression models, with and without covariate adjustment, to assess the relation between number of benign nevi and atypical nevus case status in the entire sample (11). Other factors of interest were generally treated as categorical variables evaluated according to a priori plans based on earlier studies or by percentiles corresponding to their distribution among controls. A likelihood ratio test was used to formally evaluate potential interactions between number of benign nevi (<50 and ≥50) and other risk factors in relation to atypical nevus case status (11); the benign nevus cutpoint was selected to ensure an adequate number of subjects for analysis in the group with low benign nevus counts and to conform with cutoffs used in previous studies (3, 5). The likelihood ratio test indicated a significant overall interaction between benign nev i and other risk factors (P = 0.01); thus, factors were evaluated using single-factor logistic models, in relation to case status within subgroups of high (≥50) and low (<50)
relationship \((P = 0.43)\). Greater parity was associated with a statistically significant reduced likelihood of atypical nevi \((P\text{ trend} = 0.02)\), and women who reported two or more full-term pregnancies had a substantially reduced likelihood of having an atypical nevus.

We found no relation between case status and age, education, reaction to acute sun exposure, hair color, sunblock use, solarium visits, or oral contraceptive use, factors sometimes noted in relation to melanoma \((1)\).

### Discussion

Previous studies have shown that roughly 39–56% of melanoma cases and 7–18% of the general population are affected by clinically atypical nevi \((3, 8, 12–15)\). In this study, we increased the number of case women by oversampling the stratum of survey respondents who had reported an atypical nevus on the legs; thus, our data are not useful for estimating the prevalence of atypical nevi. However, an earlier population-based study indicates that about 18% of Swedish women are affected by clinically atypical nevi \((3)\).

We found that the likelihood of having atypical nevi decreased with age, a relationship that has been noted by others \((2, 4, 5)\). Declining risk associated with age reflects the natural history of these lesions, which tend to appear during the second decade of life, and to fade during later decades \((8)\).

In our study, and in one other Swedish study \((3)\), benign nevus counts among control subjects were substantially higher than those typically observed in control populations \((8, 12, 13, 16, 17)\). However, both Swedish studies were restricted to middle-aged persons, who, relative to younger and older age groups, tend to have higher numbers of benign nevi; thus, the elevated counts noted in these studies may have been a function of the age groups evaluated \((3)\). Nevertheless, given the strong relation between high counts of benign nevi and melanoma risk \((1)\), the possibility of elevated nevus counts among Swedes, who have relatively high age-adjusted melanoma incidence rates \((18\text{ per 100,000})\), warrants further exploration.

Previous case-control studies of atypical nevi \((2–5)\) have not considered the role of benign nevi. In this study, we observed a strong and consistent association between number of benign nevi and case status, indicating that high counts of benign nevi may be useful for identifying persons with atypical nevi. Although it is well known that high counts of benign nevi and atypical nevi are related to melanoma \((1)\), the biological relationship between benign and atypical nevi is unclear. High counts of benign nevi occurring with atypical nevi may represent a syndrome that includes elevated risk of melanoma \((18)\); it is also possible that high counts of benign nevi increase risk of atypical nevi in a probabilistic fashion. Alternatively, high counts of benign nevi may be a marker of sun sensitivity but may not be in the causal pathway for melanoma.

#### Table 1

Number of benign nevi in relation to atypical nevus case status: unadjusted ORs, 95% CIs, and \(P\) of trend test

<table>
<thead>
<tr>
<th>No. of benign nevi</th>
<th>Controls n (%)</th>
<th>Cases n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–24</td>
<td>122 (45)</td>
<td>12 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>25–49</td>
<td>76 (28)</td>
<td>18 (14)</td>
<td>2.41 (1.10–5.28)</td>
</tr>
<tr>
<td>50–74</td>
<td>43 (16)</td>
<td>34 (26)</td>
<td>8.04 (4.82–16.92)</td>
</tr>
<tr>
<td>75–99</td>
<td>13 (5)</td>
<td>25 (19)</td>
<td>19.55 (7.99–47.84)</td>
</tr>
<tr>
<td>≥100</td>
<td>16 (6)</td>
<td>41 (32)</td>
<td>26.05 (11.38–59.62)</td>
</tr>
<tr>
<td>(P) trend &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Table 2

Distribution of case and control women, grouped by number of benign nevi and select factors, adjusted ORs, 95% CIs, and \(P\) of trend test for the relation with atypical nevus case status

<table>
<thead>
<tr>
<th>Controls n (%)</th>
<th>Cases n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;50\text{ benign nevi})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freckles on arms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>108 (55)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>A few</td>
<td>71 (36)</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Many</td>
<td>19 (10)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>(P) trend</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Weeks of beach vacation (ages 10–19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>63 (33)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>1</td>
<td>49 (26)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>≥2</td>
<td>77 (41)</td>
<td>16 (53)</td>
</tr>
<tr>
<td>(P) trend</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Eye color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>32 (16)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Blue/green/gray</td>
<td>165 (84)</td>
<td>29 (97)</td>
</tr>
<tr>
<td>≤50 benign nevi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin reaction to chronic sun</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark brown</td>
<td>12 (17)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Brown</td>
<td>53 (74)</td>
<td>56 (57)</td>
</tr>
<tr>
<td>Light/no tanning</td>
<td>7 (10)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Sunburns with peeling (ages 10–19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3 (4)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>1</td>
<td>38 (56)</td>
<td>45 (47)</td>
</tr>
<tr>
<td>≥2</td>
<td>27 (40)</td>
<td>38 (40)</td>
</tr>
<tr>
<td>(P) trend</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (6)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>1</td>
<td>8 (11)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>≥2</td>
<td>58 (83)</td>
<td>64 (66)</td>
</tr>
</tbody>
</table>

\(\text{Note: Variations in column totals are due to missing values.}\)

\(\text{Note: Among women with }<50\text{ benign nevi, the model was adjusted for age, freckling, and number of weeks of beach vacation between ages 10 and 19. Among women with }≥50\text{ benign nevi, the model was adjusted for age, skin reaction to chronic sun exposure, number of peeling sunburns between ages 10 and 19, and parity.}\)

Our data indicate that, among women with low benign nevus counts, the likelihood of having an atypical nevus increases with degree of freckling, a characteristic that reflects both sun sensitivity and sun exposure. Freckling has been reported in relation to atypical nevi in a previous study \((5)\) and has been frequently found in relation to melanoma \((1)\). Our data also suggest a role for early sun exposure in this subgroup, but the association did not reach statistical significance. Atypical nevi first appear during late childhood and are most frequently found on sun-exposed skin areas \((19–21)\); thus, a role of early sun exposure is plausible. However, only one study, based entirely on melanoma cases, found a relationship between sun exposure and atypical nevi \((15)\); a case-control study has found no association \((4)\), and a study of atypical nevi among high schoolers found no relation with sun exposure \((22)\). Although two studies (including the study confined to melanoma cases) have found an association with sunburn \((5, 15)\), this event, like freckling, reflects both sun sensitivity and sun exposure.

We found that women with relatively high benign nevus counts are less likely to have atypical nevi if they report a history of peeling sunburn between ages 10 and 19. The inverse relationship observed here, which contradicts earlier studies \((5, 15)\), was unexpected, and is probably a chance finding. Our data also suggest that women who have difficulty tanning are at increased likelihood of atypical nevi. Although this finding was not statistically significant, it is consistent with earlier studies.
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noting skin type or tanning ability in relation to atypical nevi
(2–4). Finally, we found an inverse relationship between parity
and atypical nevi among women who have high benign nevus
counts. We are unaware of studies evaluating parity in relation
atypical nevi. Although some previous studies of melanoma
have noted an inverse relationship with parity (23–25), most
have found no association after adjustment for sun exposure
(1).

In summary, we found a strong relationship between high
counts of benign nevi and the presence of atypical nevi, a new
finding that has potential clinical usefulness. In addition, we
found evidence suggesting that sun sensitivity is related to
atypical nevi. We observed a possible role for early sun expo-
sure among women with few benign nevi. Because of the
importance of sun exposure in relation to melanoma (1) and the
biological plausibility of an association with atypical nevi, this
potentially modifiable factor merits consideration in future
studies. We also observed an inverse relationship with parity
among women with high counts of benign nevi, a provocative
finding given longstanding interest in the role of female hor-
mones in melanoma etiology. Although most of our findings
were consistent with earlier studies of atypical nevi or mel-
noma, our sample size was small, and some of our results must
be considered preliminary.

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