Objective: To assess the frequency of occurrence and risk factors for multiple primary melanoma.

Design: Population-based, case-control study.

Setting: New Hampshire.

Participants: Three-hundred fifty-four New Hampshire residents with a confirmed first diagnosis of cutaneous melanoma.

Main Outcome Measure: Diagnosis of a subsequent primary cutaneous melanoma.

Results: An additional melanoma occurred in 27 individuals (8%) within 2 years of their initial diagnosis, including 20 (6%) within the first postdiagnosis year. In 9 (33%) of these 27 cases, at least 1 subsequent melanoma was deeper than the first tumor. The 27 individuals with a subsequent melanoma diagnosis were classified as “cases” and were compared on the basis of risk factors to the 327 “controls” with a single melanoma diagnosis. The data indicate an inverse relation of risk of multiple primary melanomas with multiple blistering sunburns ($P = .01$ for the trend); the odds ratio (OR) was 0.32 (95% confidence interval [CI], 0.11-0.93) for 2 or more sunburns compared with none. The number of atypical moles was significantly related to increased risk ($P = .004$ for the trend). The presence of 3 or more atypical moles compared with none was associated with more than a 4-fold risk of multiple primary melanomas (OR, 4.29; 95% CI, 1.51-12.16).

Conclusions: Additional melanomas occur more frequently than previously shown. Our study confirms that atypical moles are strongly associated with risk of multiple primary melanomas but provides little evidence that risk is influenced by pigmentary characteristics, hours of sun exposure, or benign moles. The inverse association with blistering sunburn may reflect the influence of an unmeasured covariate.

Arch Dermatol. 2006;142:433-438

Numerous studies have evaluated the occurrence of additional primary melanoma tumors among those with a previous melanoma diagnosis. Only 1 study, however, was population based, and with few exceptions, previous efforts were based on tumor registries or clinical-based records, approaches that rely on the stability of the target or patient population, respectively. Such studies do not actively ascertain subsequent melanomas in the target population initially at risk and are likely to underestimate the frequency of second tumors. Only a few clinic-based studies have attempted to identify factors that influence risk of multiple primary melanomas and all but 2 studies were limited to demographic and/or clinical characteristics.

METHODS

All activities associated with the New Hampshire Skin Study, on which the present analyses are based, were approved by the committee for the protection of human subjects at Dartmouth Medical School. All participants gave verbal consent for the interview, and signed consent was obtained for skin examination and release of medical records.

The goal of the present study was to determine the frequency of subsequent melanoma occurrence and to identify risk factors for multiple primary melanomas. Participants for the present study were identified through a parent case-control study of melanoma risk. As part of that study, individuals with a first incident diagnosis of cutaneous melanoma were ascertained over a 3-year period through the New Hampshire State Cancer Registry. Potentially eligible cases were New Hampshire residents, aged 20 to 69 years, with a working telephone number who were able to participate in an English-speaking interview. Prior to attempted recruitment, we sent a letter to the physician of record requesting permission to contact the patient. If an objection was not received within a month, a letter introducing the study was mailed to the potential participant, followed within 2 to 3 weeks by a telephone call.
from the interviewer. Through these methods, we enrolled 444 (77%) of 579 potentially eligible cases; 15 (3%) were excluded at their physician's request, 26 (4%) could not be reached, 30 (5%) had died, and 64 (11%) declined to participate. Of the 444 enrolled subjects, 21 were found to be ineligible for various reasons (eg, a prior melanoma diagnosis, ocular primary, unknown primary, or the acral lentiginous histologic subtype) and were excluded from further study.

To ensure a comparable opportunity for verifying subsequent primary tumors in all study participants, the analyses are confined to the 354 eligible participants (84%) for whom pathology records were available. A review of these records identified 27 individuals who developed at least 1 subsequent melanoma following their initial diagnosis and prior to participating in the parent study (cases) and 327 individuals who had not developed a subsequent melanoma in the same time frame (controls).

All participants completed a 40-minute telephone interview that elicited demographic factors, medical history, including a family history of melanoma (in a first- or second-degree blood relative), and pigmentation characteristics (natural hair color at age 20 years, eye color, freckling before age 15 years, sun sensitivity defined using a 4-level scale reflecting skin reaction to 1 hour's exposure to strong summer sun, and tannability defined using a 4-level scale reflecting the degree of tan obtained after chronic sun exposure). A detailed account of the methods used to assess sunburn histories has been described previously.16 Briefly, we assessed the number of peeling and blistering sunburns occurring from age 10 years until the individual's reference date, which was 1 year prior to the date of the first melanoma diagnosis. Hours of sun exposure (capped at 10 h/d) were calculated separately for sunbathing, recreational exposure, and occupational exposure. Sunbathing (relaxing in the sun or trying to get a tan) and recreational exposure (11 standard activities and an unrestricted number of “other” activities) were assessed starting at age 10 years; occupational sun exposure (working outdoors at least 10 h/wk in the summer) was assessed starting at age 6 years (to accommodate farm work). For each of these measures, and for a variable representing the combined hours of sun exposure, the exposure hours were summed over the individual's lifetime, up to the reference date.

At the conclusion of the interview, subjects were asked to participate in a physician-conducted skin examination, which

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### Table 1. Risk Factors of Study Participants

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases (n = 27)</th>
<th>Controls (n = 327)</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (56)</td>
<td>175 (53.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>12 (44)</td>
<td>152 (46.5)</td>
<td>0.84 (0.38-1.87)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤39</td>
<td>8 (30)</td>
<td>60 (18.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>40-59</td>
<td>9 (33)</td>
<td>175 (53.5)</td>
<td>0.38 (0.14-1.02)</td>
</tr>
<tr>
<td>≥60</td>
<td>10 (37)</td>
<td>92 (28.1)</td>
<td>0.80 (0.30-2.15)</td>
</tr>
<tr>
<td>Family history of melanoma</td>
<td>24 (86)</td>
<td>243 (74.5)</td>
<td>0.32 (0.07-1.42)</td>
</tr>
<tr>
<td>Pigmentary characteristics</td>
<td>4 (14)</td>
<td>79 (24.2)</td>
<td>0.07 (1-4.12)</td>
</tr>
</tbody>
</table>

(continued)
was accomplished for 24 (89%) of the 27 multiple primary cases and 294 (90%) of the 327 single primary controls. During the skin examination, the presence and number of benign and atypical moles was assessed using a standardized protocol and data collection form. To reduce the likelihood of misclassifying a freckle or solar lentigo as a mole, benign moles were defined as palpable lesions, at least 3 mm in diameter, with a well-defined border and uniform coloration.17 We defined atypical moles as having at least 3 of the following features: diameter of 5 mm or more, flat (macular) component, erythema, irregular border, ill-defined border, and variegated color.

In our statistical analysis, eye color was categorized as brown, gray/green/hazel, or blue; because of the small number of cases with brown eye color, blue eye color was used as the reference category. Hair color was classified as black/dark brown (the reference category), brown/red-brown, or blond/red. Sunburn occurrence was evaluated using the cut points shown in Table 1 and Table 2; we attempted to use 0 sunburns as the reference category, but this was not possible for the variable representing peeling sunburn because virtually all cases had experienced a peeling sunburn. In general, the cut points for hours of sun exposure were based on approximate terciles in the control group, although this was not practical for lifetime hours of sunbathing.

Preliminary analyses included frequency distributions and descriptive statistics. Differences in mean counts of atypical moles, among those affected by at least 1, were assessed using t tests. The Fisher exact test was used to evaluate the differences in the proportion of individuals affected by moles according to age or sex. We used logistic models to generate odds ratios (ORs) and 95% confidence intervals (CIs) to assess factors of interest in relation to risk of an additional melanoma.18 Initially, risk factors were evaluated singly in preliminary models, to be significantly associated (P < .05) with risk of multiple primary melanoma. The analyses of pigmentary and solar risk factors were based on all 27 cases and 327 controls; models that included terms for benign or atypical mole counts were based on the 24 cases and 294 controls for whom skin examination data were available.

### RESULTS

Within 2 years of the initial primary melanoma, 27 (8%) of 354 study participants developed a subsequent melanoma, and for 20 (6%) of these individuals, the second diagnosis occurred within the first postdiagnosis year (Table 3). Of those cases occurring during the first postdiagnosis year, 8 were either synchronous or detected within about a month of the initial diagnosis. Of the 27 individuals who developed an additional primary tumor, 23 had 2 tumors, and 4 developed a third melanoma.

Only 8 individuals (30%) had an initial tumor of at least 1 mm in thickness (Table 3). For 9 patients (33%), a subsequent tumor was deeper than the initial diagnosis, including 4 with melanoma in situ who subsequently developed an invasive lesion and 2 whose subsequent lesions were more than doubled in depth.

The average time elapsed between the first primary diagnosis and the date of study interview was 24 months for both the 27 cases of multiple primary melanoma and the 327 controls with a single primary melanoma. The male-female ratio in cases (1.3:1) was similar to that in the controls (1.2:1). Both cases and controls were, on average, 53 years old at the time of the first melanoma diagnosis. For 13 patients (48%), the first and second melanoma occurred at a similar body site (eg, upper back vs midback). For 4 patients (15%), the subsequent tumor appeared on a different area of the trunk (eg, front vs back or below vs above the waist). For the remaining 10 pa-
controls (294) with at least 1 mole of the type specified. The mean age at diagnosis of the first melanoma was lower for those controls had at least 1 clinically atypical mole. The mean age and sex suggested a possible association between higher counts of benign moles and risk, but the findings were compatible with chance (Table 3).

The mean number of benign moles, assessed in those with at least 1 benign mole, but most had fewer than 15. A higher proportion of cases than controls had at least 1 atypical mole, and the case-control disparity was particularly evident in the older group (Table 4). Within the case and control groups, a higher proportion of atypical moles than for those without in both cases (50.8 vs 57.7 years) and in controls (48.8 vs 55.4 years).

The mean number of atypical moles among those with at least 1 was 7.4 in cases and 7.7 in controls. Age- and sex-adjusted analyses indicated a strong association between the number of atypical moles and risk of an additional primary melanoma. The presence of at least 3 atypical moles, relative to none, conferred an approximately 4-fold increased risk of a subsequent primary melanoma: OR, 3.95 (95% CI, 1.44-10.86) (Table 1). Results of a test of linear trend, based on the categories shown, were highly significant (P = .004).

We used a multivariate model (Table 2) to assess the mutually adjusted effects of the 2 risk factors associated with multiple primary melanomas. These analyses upheld a strong and statistically significant inverse association with 2 or more blistering sunburns compared with none: OR, 0.32 (95% CI, 0.11-0.93). Risk was also reduced for those reporting 1 blistering sunburn, but the finding was compatible with chance. Atypical moles also remained strongly associated with risk. Compared with the absence of atypical moles, the presence of 3 or more atypical moles was associated with more than a 4-fold and significant increase in risk: OR, 4.29 (95% CI, 1.51-12.16).

Table 4 shows the distribution and mean counts of benign and atypical moles according to age (<50 or ≥50 years) and sex. Although high benign mole counts were more frequent in younger controls, findings of an overall Fisher exact test did not support an association between age and mole counts (P = .85), and t test results did not support a difference in mean counts by age (P = .90). Within the case and control groups, the distribution of benign mole counts was roughly similar for men and women (P > .99), as was the mean number of benign moles (P = .54).

A higher proportion of cases than controls had at least 1 atypical mole, and the case-control disparity was particularly evident in the older group (Table 4). Within the case and control groups, a higher proportion of younger

### Table 4. Distribution and Mean Counts of Benign and Atypical Moles in Study Participants

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases (n = 24)</th>
<th>Controls (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-14</td>
<td>≥15</td>
</tr>
<tr>
<td></td>
<td>Benign Moles</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>6 (75)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>≥50</td>
<td>12 (75)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (73)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (78)</td>
<td>2 (22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>≥1</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>2 (25)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>≥50</td>
<td>7 (44)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (47)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (22)</td>
<td>7 (78)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are reported as number (percentage) of study participants; percentages are calculated in rows; means are calculated in those with at least 1 mole of the type specified.

Patients (37%), the subsequent tumor(s) occurred at an entirely different site (eg, trunk vs arm).

Analysis of potential risk factors (Table 1), adjusted for age and sex, suggested that women and older individuals had a lower risk of an additional primary melanoma, but these possible associations did not reach statistical significance. Our data suggested an unexpected inverse association between family history of melanoma and risk of an additional primary melanoma, although the association did not reach statistical significance.

Risk seemed elevated for those with lighter hair color and reduced for those with freckling by age 15 years or with dark eye color, but these findings were unreliable. Similarly, suggested associations with reaction to short-term sun exposure (sun sensitivity) and long-term sun exposure (tannability) were nonsignificant.

Both variables representing sunburn histories were inversely related to risk of multiple primary melanoma, although the association with peeling sunburn was not statistically significant. A lifetime history of 2 or more blistering sunburns compared with none was associated with a nearly 80% and significant reduction in risk: OR, 0.22 (95% CI, 0.07-0.70). A test of trend, based on the categories shown, was also statistically significant (P = .01). Our data did not indicate an influence of lifetime hours of sun exposure, and the ORs corresponding to the 3 sun exposure variables were inconsistent with regard to the direction of possible effects.

Virtually all cases (96%; n = 23) and controls (94%) had at least 1 benign mole, but most had fewer than 15. The mean number of benign moles, assessed in those with at least 1, was 12.0 in cases and 13.1 in controls. Analy- ses adjusted for age and sex suggested a possible association between higher counts of benign moles and risk, but the findings were compatible with chance (Table 3).

Sixty three percent of cases (n = 15) and 37% of controls had at least 1 clinically atypical mole. The mean age at diagnosis of the first melanoma was lower for those
than older participants was affected by atypical moles, but the overall association between age and atypical moles was not statistically significant (P = .46). The mean number of atypical moles was comparable for cases and controls. Although mean counts of atypical moles were higher in the younger age group, the difference was not significant (P = .54). Regardless of sex, cases were more likely than controls to be affected by atypical moles, and the case-control disparity was greater in women than in men. There was no overall association, however, between sex and the presence of atypical moles (P = .22). The mean number of atypical moles was also roughly comparable for men and women (P = .85).

**COMMENT**

The importance of studying risk for additional primary tumors within a defined population-based study group is underscored by our findings, which indicate that 8% of patients with melanoma developed a second primary melanoma within 2 years of their initial diagnosis, including 20 (6%) who developed a second primary melanoma within the first postdiagnosis year. These findings, which indicate a higher frequency of second primary melanomas than suggested by previous studies, also underscore the importance of close surveillance of patients with melanoma.

When we take a conservative approach, use as a denominator the underlying group of 579 patients with melanoma who were potential study participants, and assume that no second primary melanomas occurred in the nonparticipants, the estimated occurrence in the first postdiagnosis year decreases to 4% (27/579), an estimate that still exceeds the frequencies observed in most clinic-based studies, a population-based study in Australia, most institution-based record reviews, and registry-based efforts. In part, the high frequency of additional tumors reported herein reflects our inclusion of in situ melanomas; however, given that most cases had at least 1 invasive tumor, it seems unlikely that in situ disease, in this context, represents pseudodisease. If we consider only the 14 cases who had at least 2 invasive tumors, 4% of patients developed a second melanoma during the first postdiagnosis year, an estimate that also exceeds that of most previous studies.

We were unable, due to our study design, to identify additional melanomas occurring, on average, more than 2 years after the initial diagnosis. Some institution-based studies have shown that most second primary melanomas occur within 2 to 3 years of the initial diagnosis, but others suggest that a sizeable fraction of second primary melanomas occur more than 5 years after the initial diagnosis. The tendency of second tumors to diminish in frequency over time after the initial diagnosis may reflect increasing losses to follow-up, as patients relocate or change health care providers.

Consistent with previous institution-based reports, our data indicate that, for most patients, subsequent melanomas are shallower than the initial diagnosis. However, consistent with a previous study, we found a large minority (33%) of patients whose subsequent tumors were deeper than their initial melanoma, and for many of these patients, the subsequent diagnosis might potentially affect prognosis. These findings emphasize the importance of surveillance and biopsy in patients with a personal history of melanoma. We also found that about half of second melanomas occur on a site different from the initial tumor, underscoring the importance of complete skin examinations during follow-up. Finally, although our findings in this regard were not statistically significant, our data also suggest that atypical moles may have particular importance in women and in older patients.

Although previous studies have noted a positive association between family history of melanoma and risk of a second primary melanoma and a high percentage of cases (24%-65%) with a family history of melanoma, our data suggested the surprising possibility of an inverse association. We speculate that patients with melanoma and a family history of the disease may be more inclined to undergo mole biopsy, thereby reducing their risk of a second primary melanoma. Exploratory analyses, although based on small numbers, were consistent with this possibility, showing an inverse association between family history and multiple primary melanomas in those who had undergone mole biopsy (OR, 0.26 [95% CI, 0.06-1.20]) but not in those who had not undergone mole biopsy (OR, 1.71 [95% CI, 0.31-9.53]).

The inverse relationship between blistering sunburn and risk of multiple primary melanomas must be viewed cautiously. Recently, an inverse association between sun-related variables and melanoma mortality was interpreted as evidence that sun exposure confers a survival benefit. While this is possible, effect distortion by an unmeasured variable is also conceivable. Such distortion can be profound; in a familiar example, clinical trial results reversed prior findings that postmenopausal hormones improve cardiovascular and cognitive health. In the present setting, we compared individuals with multiple primary melanomas to those with a single melanoma. Consequently, the inverse association with sunburn indicates that persons with a single melanoma have more extensive sunburn histories than those with multiple melanomas. Although speculative, a predisposition for multiple primary melanomas may involve a decreased susceptibility for severe sunburn or an increased susceptibility offset by avoidance. In any case, the association should not be construed as suggesting that sunburn protects patients with melanoma from developing additional tumors.

Similar to a previous study, we found that the number of benign moles was not significantly associated with risk of a second primary melanoma. Benign moles are powerful markers of melanoma risk, but arguably atypical moles, as potential precursors, may play a greater role in the setting of multiple primary melanoma. Our data indicate that 63% of second primary melanoma cases had clinical evidence of at least 1 atypical mole, an estimate comparable to that of a clinic-based study of histologically confirmed atypical moles. Others have reported a higher percentage (67%-82%) of affected cases, while at least 2 studies suggest a lower frequency (38%-46%). As expected, we found a strong association between elevated counts of atypical moles and multiple primary melanomas, which has
been shown previously in clinic-based and registry studies, although the association noted herein was somewhat weaker than in most previous reports. With continued follow-up, some controls in our study may develop additional melanomas (ie, convert to case status), perhaps shifting the importance of risk factors.

In conclusion, we found limited evidence that pigmented characteristics or sun exposure are related to increased risk of additional primary melanomas, but our study population was limited in size, and statistical power was inadequate to detect modest associations. Unexpectedly, we noted an inverse association with a history of blistering sunburn, which may reflect the influence of an unmeasured covariate. We also found little evidence that the number of benign moles influenced risk of a second primary melanoma; however, risk increased with the number of atypical moles.

Accepted for publication: October 26, 2005.
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Financial Disclosure: None.

Funding/Support: This project was supported by grant RO1 CA66032 from the National Cancer Institute, Bethesda, Md (Dr Titus-Ernstoff).

Acknowledgment: We thank Jane Barrett, MS, Judith Harjes, Lee Mott, MS, Shafika Abrahams-Gessel, MS, Cheryl Robie, and Elaine Campbell for their contributions to the study. We are indebted to the physicians in our state, who kindly cooperated with the implementation of this study. We are particularly grateful to the people of New Hampshire, whose generosity made this research possible.

REFERENCES


