IMPORTANCE  Nevi are among the strongest risk factors for melanoma. However, little is known about the association of many total nevi (TN) or atypical nevi (AN) with tumor thickness.

OBJECTIVES  To examine the association between age and the number of TN and AN and to explore whether there was a relationship between TN or AN and tumor thickness, controlling for multiple variables.

DESIGN, SETTING, AND PARTICIPANTS  Survey of patients with melanoma at 2 academic sites and an affiliated Veteran Affairs medical center. Participants included 566 patients surveyed within 3 months of diagnosis. Patients were surveyed in the melanoma clinics from May 17, 2006, through March 31, 2009, within 3 months of diagnostic biopsy. The dates of the analysis were April 1, 2015, to August 1, 2015.

MAIN OUTCOMES AND MEASURES  Counts of TN and AN were performed at the first visit after diagnosis and were categorized as 0 to 20, 20 to 50, or more than 50 for TN and as 0, 1 to 5, or more than 5 for AN. Tumor thickness was categorized as 2.00 mm or less or as 2.01 mm or greater. All analyses were stratified by patient age (<60 or ≥60 years). Logistic regression was used to test associations, controlling for age, sex, anatomic location of melanoma, institution, histologic subtype, marital status, performance of skin self-examination, number of health care visits in the past year, mode of melanoma discovery, and receipt of skin examination by a physician.

RESULTS  The study population included 566 patients. Their mean (SD) age was 56.7 (15.9) years, and 39.0% (n = 221) were female. Of 566 patients, the number of TN was classified as 0 to 20 (66.4% [n = 376]), 20 to 50 (20.5% [n = 116]), or more than 50 (13.1% [n = 74]). Atypical nevus counts were 0 (73.3% [n = 415]), 1 to 5 (14.5% [n = 82]), or more than 5 (12.2% [n = 69]). For those younger than 60 years, the presence of more than 50 TN was associated with a sharply reduced risk of thick melanoma (odds ratio, 0.32; 95% CI, 0.12-0.81), and the presence of more than 5 AN compared with no AN was associated with thicker melanoma (odds ratio, 2.43; 95% CI, 1.02-5.75).

CONCLUSIONS AND RELEVANCE  Most patients with melanoma had few nevi and no AN. In younger patients (<60 years), thick melanomas were commonly found in those with fewer TN but more AN, suggesting that physicians and patients should not rely on the total nevus count as a sole reason to perform skin examinations or to determine a patient’s at-risk status. Younger patients should be educated on the increased risk of thicker melanomas that is associated with having more AN.
Studies have provided evidence that the number of total nevi (TN) and atypical nevi (AN) is strongly associated with risk of melanoma. Yet, the relationship of these distinctive mole patterns with tumor thickness and cancer prognosis is unclear and appears to be complex. The presence and number of TN and AN are known to vary by age and sex, but it is unknown how this finding relates to the severity and outcomes of melanoma. Furthermore, individuals with these mole patterns may be more likely to practice skin self-examination (SSE) and receive physician skin examination (PSE) for skin cancer, which may lead to earlier detection of melanoma and thinner tumors at diagnosis. These questions have received little attention in prior studies.

Our group conducted a survey of 566 patients with melanoma at 2 academic centers in California and Michigan within 3 months of diagnosis. Patients were asked at that time to recall events in the year before diagnosis. Our primary objectives were to examine the association between age and the number of TN and AN and to explore whether there was a relationship between TN or AN and tumor thickness at diagnosis, controlling for multiple variables.

### Methods

#### Study Participants

Approval for the study was obtained from the institutional review boards of Stanford University Medical Center (SUMC), the affiliated Veterans Affairs Palo Alto Health Care System (VAPAHCS), and the University of Michigan (UM). Written informed consent was obtained for all study participants. Eligible, consecutive patients 18 years or older with a recent diagnosis of invasive cutaneous melanoma were surveyed at SUMC/VAPAHCS, as previously described. Because of the high proportion of thin melanoma at UM, a random sample of 33% of individuals with melanoma thickness of 2.00 mm or less and all eligible patients with melanoma thickness of 2.01 mm or greater were surveyed. Patients were surveyed in the melanoma clinics from May 17, 2006, through March 31, 2009, within 3 months of diagnostic biopsy. The dates of the analysis were April 1, 2015, to August 1, 2015. Respondents were instructed in person to answer all questions for the 12 months before diagnosis, and there were reminders in multiple locations on the survey to reinforce this point. All surveys were reviewed to ensure that all questions were completed.

#### Measures

Measures included age, sex, race/ethnicity, and marital or cohabitation status (married, widowed, single or never married, and divorced or separated). Age was first categorized by quartiles (<45, 46–57, 58–68, or ≥69 years). Subsequently, it was dichotomized as younger than 60 years vs 60 years or older given increasing rates of thicker tumors and increased mortality among older individuals. Performance of SSE was defined as carefully examining all of one's moles, including those on the back, at least once per year. Receipt of a PSE was defined as a health care professional examining a patient's skin, including the back and chest, for cancer in the year before diagnosis. The number of health care visits in the year before diagnosis was categorized as never, once, 2 to 3 times, or more than 3 times. Mode of discovery of melanoma was defined as self, other (family, friend, or partner), or health care professional (including physician or nurse). Anatomic location of the primary tumor was recorded on the pathology report according to the number of possible body sites and then classified as either anterior or posterior. Pathology reports included melanoma thickness, ulceration, and histologic subtype (superficial spreading, nodular, lentigo maligna melanoma, acral lentiginous, desmoplastic, or other).

At the first visit after diagnosis, 2 experienced pigmented lesion specialists (T.M.J. and S.M.S.) counted the number of TN and AN using established guidelines, based on size (generally >6 mm), color (variegation), topographical asymmetry, dermoscopic features, and overall nevus morphologic structure. All nevi were counted in the total nevus count, regardless of the size, and dermoscopic examination of AN was standard in these pigmented lesion practices to avoid misclassification of early or evolving melanoma in situ as AN. Subsequent analyses controlled for institution.

#### Outcome Measures

The primary study outcomes were the TN count and the presence of AN, which were assessed by the physician at the initial melanoma visit, with classification of TN as 0 to 20, 20 to 50, or more than 50 and AN as 0, 1 to 5, or more than 5. Tumor thickness was categorized as 2.00 mm or less or as 2.01 mm or greater.

#### Statistical Analysis

Among all case respondents with tumor thickness as an outcome, we used a multivariable logistic regression model that first adjusted for age alone and then in the second analysis included terms for age, sex, anatomic location of melanoma (anterior vs posterior), institution (UM vs SUMC/VAPAHCS), histologic subtype (superficial spreading melanoma vs non–superficial spreading melanoma), marital status (married vs unmarried), performance of SSE, number of health care visits in the past year, mode of melanoma discovery, and receipt of PSE. A term for TN was included in models of AN, and a term for AN was included in models of TN. Age was dichotomized as younger than 60 years vs 60 years or older, and tumor thickness was assessed as 1.00 mm or less vs 1.01 mm or greater and as 2.00 mm or less vs 2.01 mm or greater, with the latter being the primary analysis. Model results are presented as odds ratios (ORs) with 95% CIs.

#### Results

##### Total Nevi

This study included 566 patients with melanoma (Table 1). Most (66.4% [n = 376]) had 0 to 20 TN, with 20.5% (n = 116) having 20 to 50, and 13.1% (n = 74) having more than 50. Notably, 43.7% (n = 62) of the youngest patients (<45 years) had few TN (<45 years), and this rate almost doubled for the oldest patients. Twenty-eight percent (n = 40) of the youngest patients had more than 50 TN. This rate dropped to 14.1% (n = 19) for patients 46 to 57 years, 7.5% (n = 11) for patients 58 to 68 years, and 2.8% (n = 4)
for the oldest patients. There were no significant differences in TN by sex, race/ethnicity, marital status, institution, or anatomic location of melanoma. Patients with lentigo maligna melanoma were also more likely to have fewer TN.

**Atypical Nevi**
Atypical nevus counts were 0 (73.3% [n = 415]), 1 to 5 (14.5% [n = 82]), or more than 5 (12.2% [n = 69]) (Table 1). A total of 51.4% (n = 73) of patients 45 years or younger had no AN, and this proportion rose considerably by age up to 93.0% (n = 133) for the oldest patients. A total of 26.8% (n = 38) of patients 45 years or younger had more than 5 AN as opposed to 14.1% (n = 19) in those 46 to 57 years old and 6.8% (n = 10) in those 58 to 68 years old. Only 1.4% (n = 2) of patients 69 years or older had more than 5 AN. No significant differences were found in AN by sex, race/ethnicity, marital status, or anatomic location of melanoma. Patients with lentigo maligna melanoma were also more likely to have no AN, and AN were more common in patients from UM.

**TN by AN**
The number of AN rose as the number of TN increased, and AN were uncommon among those with few TN. For example, 90.7% (341 of 376) with 0 to 20 TN had no AN. Conversely, 13.1% (74 of 566) of patients had more than 50 TN, and, of these, 58.1% (43 of 74) had more than 5 AN.

**TN or AN and Tumor Thickness**
In the crude analysis (ignoring cells with <10 cases), a strong direct relationship between TN or AN and tumor thickness was found (Table 2). The mean tumor thickness decreased from 2.33 mm for 0 to 20 TN and 0 AN to 1.12 mm for more than 50 TN or AN.
TN and 0 AN. Thickest melanomas were found for individuals with 20 to 50 TN and at least 1 AN.

**Associations of Nevi With Tumor Thickness**

We conducted multivariable logistic regression analyses to test the relationship between the number of TN or AN and tumor thickness (≤2.00 mm vs >2.01 mm), with separate models for patients younger than 60 years and 60 years or older (Table 3). The results were similar between the 2 models, and these data confirmed the findings from the crude analysis. For those younger than 60 years, the presence of more than 50 TN was associated with a sharply reduced risk of thick melanoma, with age-adjusted and fully adjusted ORs of 0.32 (95% CI, 0.12-0.81) and 0.35 (95% CI, 0.11-1.12), respectively. Compared with no AN, the presence of more than 5 AN was associated with thicker melanoma, with age-adjusted and fully adjusted ORs of 2.43 (95% CI, 1.02-5.75) and 2.89 (95% CI, 0.96-8.72), respectively. These associations were not found in the older patients; however, the numbers with many TN or AN were small, and the 95% CIs were wide.

**Discussion**

Three notable findings emerged from this case study of 566 patients from 2 states newly diagnosed as having melanoma in 2 states. First, overall, most patients had 0 to 20 TN and no AN, and this finding was most pronounced among older patients, for whom both TN and AN were uncommon. Second, after controlling for potential confounders, a higher mole count (>50 TN) was associated with thinner melanoma (≤2.00 mm) for those younger than 60 years. Third, paradoxically, the presence of more than 5 AN was associated with thicker melanoma for patients younger than 60 years.

**TN and AN**

Having many TN or any AN is often reported to be a major risk factor for melanoma by public advocacy organizations. However, it appears from the present large case series that many patients with melanoma do not routinely have an increased mole count or AN. Herein, among 566 patients, we found that 66.4% (n = 376) of patients had few TN (0-20), and 73.3% (n = 415) had no AN. Among those 60 years or older, only 19.0% (47 of 247) had 20 or more TN, and 10.5% (26 of 247) had at least 1 AN. Public awareness efforts encourage at-risk individuals (including the elderly) with many nevi to examine their skin and request medical skin examinations, but it may be that the focus of such efforts discourages those with few nevi from these practices. Likewise, the degree to which physicians are less concerned about patients 60 years or older who have few TN or AN is also unknown but deserves further scrutiny. Our findings raise the question as to whether major public health messages overstate the emphasis on many TN or AN and suggest that at-risk patients and their health care professionals should be equally concerned about melanoma risk in those with few nevi.

**Age and Nevi**

Prior studies have examined the relationship between age and the presence of nevi in the general population. In a study of 432 residents of white race in the United Kingdom, it was found

**Table 2. Mole Patterns by Thickness**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) Thickness, mm</th>
<th>OR (95% CI) for Thickness &gt;2.01 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 AN</td>
<td>2.33 (2.68) (n = 341)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1-5 AN</td>
<td>1.66 (1.62) (n = 33)</td>
<td>0.89 (0.44-1.79)</td>
</tr>
<tr>
<td>&gt;5 AN</td>
<td>0.40 (0.03) (n = 2)</td>
<td>0.81 (0.03-1.81)</td>
</tr>
<tr>
<td>Mean</td>
<td>2.26 (2.61) (n = 376)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

**Table 3. Multivariable Logistic Regression of Mole Profiles and Thickness, Stratified by Age and Controlling for Other Variables Among 319 Patients Younger Than 60 Years and 247 Patients 60 Years or Older**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total No. of Patients</th>
<th>OR (95% CI) for Thickness &gt;2.01 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20 TN</td>
<td>376</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>20-50 TN</td>
<td>116</td>
<td>0.74 (0.38-1.45)</td>
</tr>
<tr>
<td>&gt;50 TN</td>
<td>74</td>
<td>0.32 (0.12-0.81)</td>
</tr>
<tr>
<td>0 AN</td>
<td>415</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1-5 AN</td>
<td>82</td>
<td>0.89 (0.44-1.79)</td>
</tr>
<tr>
<td>&gt;5 AN</td>
<td>69</td>
<td>2.43 (1.02-5.75)</td>
</tr>
</tbody>
</table>

Abbreviations: AN, atypical nevi; OR, odds ratio; SSM, superficial spreading melanoma; TN, total nevi.

* Estimated from a multivariable logistic model that controlled for age. Total nevi count was controlled for when analyzing AN and vice versa. An OR higher than unity suggests an association between the specific level of that variable and an increased thickness at diagnosis.

* Estimated from a multivariable logistic model that controlled for age, sex, anatomic location of melanoma (anterior vs posterior), institution, histologic subtype (SSM vs non-SSM), marital status, performance of skin self-examination, receipt of skin examination by a physician, number of health care visits in the past year (<2 vs ≥2), and mode of melanoma discovery (health care professional vs other). Total nevi count was controlled for when analyzing AN and vice versa. An OR higher than unity suggests an association between the specific level of that variable and an increased thickness at diagnosis.
that the total nevus count rose rapidly in the second decade of life and was highest in the third decade, with a mean of 33 nevi for women and 22 nevi for men. Thereafter, the nevus count slowly dropped until the eighth decade, when one typically has a nevus count similar to that of a prepubertal child. Similarly, in a study7 of 600 control participants from Japan, the total nevus count reached a peak of 6.7 nevi in those 20 to 39 years old before declining. A study8 of 379 patients in Sweden 30 to 50 years old found that mole counts were not affected by age within this group. A study9 of 59 Australians frequently than the acquired type. 12 The first is the congenital type, which follows the junctional to dermal evolution and persists throughout life, and the second is the acquired type, usually reticular via dermoscopy, which is positively influenced by sun exposure, grows superficially within the skin, and usually disappears over time. 

While the number of nevi after midlife decreases, the risk for melanoma continues to increase. It has been estimated that the risk of any individual nevus becoming melanoma is low, especialy in younger individuals, while the remaining nevi that persist into old age may have an increased risk of malignant transformation, although this concept remains unproven.13 It has been suggested that there are 2 subsets of nevi development. The first is the congenital type, which follows the junctional to dermal evolution and persists throughout life, and the second is the acquired type, usually reticular via dermoscopy, which is positively influenced by sun exposure, grows superficially within the skin, and usually disappears over time. These 2 types have been found to be molecularly different, with the congenital type having BRAF mutations much more frequently than the acquired type.12

TN, AN, and Tumor Thickness
We explored the relationship between TN or AN and tumor thickness, testing 2 different hypotheses. First, we hypothesized that patients with more TN and AN would have thicker melanoma because of the difficulty of self-monitoring and physician monitoring. Second, we alternatively hypothesized that patients with more TN and AN would have thinner melanoma because of more vigilant care, as determined by the reported number of patient visits in the year before diagnosis.

Younger patients with more than 50 TN had 3 times the likelihood of being diagnosed as having thinner melanomas than those patients with few (0-20) or some (20-50) TN. Virtually no differences were found whether one controlled only for age or for age and multiple confounders. For older patients, a relationship was not apparent in the multivariable analysis, although this lack of a finding may be explained by the fact that there were only 10 patients 60 years or older with more than 50 nevi.

Few prior investigations have explored the relationship between nevus count or type and tumor thickness. Cadby et al13 found that individuals who reported having no nevi had an increased Breslow thickness compared with individuals who reported having nevi, when adjusted for age at diagnosis. Liu et al14 found a significant association between the rate of growth of melanoma and the number of nevi. Specifically, individuals with fewer nevi had a faster melanoma growth rate. However, the association between the presence of nevi and Breslow thickness may have been confounded by melanoma type because thicker melanomas tend to be of the nodular variety, which are known to be associated with fewer nevi.14

Most recently, Ribero et al15 found that high nevus counts conferred a favorable prognosis, with markedly improved 5-year and 10-year survival rates for those with more than 50 moles exceeding 2 mm in diameter. The number of AN was not reported. Rather than being behaviorally driven, the authors suggested a different biological behavior of melanomas in patients with high nevus counts.

One can only speculate as to the key results of our analysis, namely, that younger individuals have an increased likelihood of thinner melanomas in the setting of a higher total nevus count but a decreased likelihood of a thinner tumor if they have a higher atypical nevus count. Thinner melanomas in patients with more TN might be due to a less aggressive biological behavior of melanoma and a tendency of these patients to have their moles checked more frequently, whereas having more AN may make discovery by either the patient or his or her physician more difficult because the true “outlier” melanoma may be less easily recognized. This latter explanation may relate to pattern recognition, such that it is easier for a person with many common nevi to see the “ugly duckling” outlier nevus compared with an individual with many AN, which share clinical features with melanoma but are rarely true melanoma precursors. Regardless of the method of detection (by self, other, or physician), the relationship between tumor thickness and nevi persisted for younger cases. The relationship was stronger with the cutoff of 2.00 mm relative to 1.00 mm, suggesting that the biological behavior of intermediate-thickness melanoma (1.01-2.00 mm) best reflects this phenomenon of tumor thickness and TN or AN.

Strengths and Limitations
This study has several strengths. All patients were surveyed within 3 months of diagnosis to reduce potential recall bias (most case surveys were conducted within 6 weeks of diagnosis), although patients were asked to describe their SSE and PSE practices in the 12 months before survey administration. Also, using established clinical guidelines, an experienced pigmented lesion specialist at each institution performed counts of TN and AN at the first visit after diagnosis. Pathology reports, including anatomic location of melanoma, histologic subtype, and tumor thickness, were available for all 566 cases. The study is limited by small numbers in certain subgroups and by the use of broad categories (eg, the lowest single threshold for TN included individuals who had as few as 0 nevi and as many as 20 nevi). It also is limited by studying patients at academic centers rather than a more population-based sample, although patients were referred from the surrounding regions at both sites. There is also the possibility of biological factors related to age, presence of nevi, and tumor thickness that were not examined in this study that could be the focus of future research. Finally, other risk factors, such as family history of melanoma or personal history of skin cancer, and their relationship to these findings should be explored in larger databases.

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Conclusions

Several novel public health messages emerge from our study, including that melanomas are more commonly diagnosed in individuals with fewer nevi compared with those with a high mole count. Therefore, physicians and patients should not rely on the total nevus count as a sole reason to perform skin examinations or to determine a patient’s at-risk status. Younger and middle-aged patients with an increased total nevus count have a lower risk of thick melanoma, but this age group has higher rates of thick melanoma if they have more than 5 AN. These younger patients should be educated on the increased risk of thicker melanomas that is associated with having more AN, the clinical features of which should be taught in the practice setting.

REFERENCES