Cutaneous Melanomas Associated With Nevi

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Objective: To determine the frequency of and the histologic and clinical factors associated with melanoma existing in histologic contiguity with a nevus.

Design: Pathology reports from melanomas collected from January 1, 1993, to December 31, 1997, were retrospectively reviewed.

Setting: Independent, community-based dermatopathology laboratory.

Patients: A total of 1606 patients with a histologic diagnosis of melanoma.

Intervention: None.

Main Outcome Measures: Differences in histologic (subtype, Breslow thickness, and Clark level) and clinical (age, sex, and anatomic location) features between melanomas that are associated and unassociated with a nevus.

Results: Twenty-six percent of the melanomas reviewed were histologically associated with nevi (dysplastic nevi, 43.0%; and other nevi, 57.0%). Factors that were significantly associated with an increased likelihood of a melanoma being histologically contiguous with a nevus included younger age, superficial spreading subtype, truncal location, Breslow thickness, and Clark level. However, after multivariate analysis, only younger age (odds ratio, 1.27; 95% confidence interval, 1.19-1.37), superficial spreading subtype (odds ratio, 2.96; 95% confidence interval, 2.17-4.02), and truncal location (odds ratio, 3.26; 95% confidence interval, 2.55-4.19) remained significant.

Conclusions: Most melanomas were not histologically contiguous with a nevus. Younger age, superficial spreading subtype, and truncal location are independent significant predictors of a melanoma being histologically associated with a nevus.

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THE NOTION that a melanocytic nevus can serve as a precursor lesion from which melanoma may develop is supported by clinical and histologic evidence. Clinically, melanomas have been observed to arise in previously photographed nevi and, as such, may present as a focal color change in a previously stable lesion.1 By patient history, the percentage of melanomas believed to have arisen from preexisting nevi ranges from 18% to 85%.2 Histologically, evidence of an associated nevus can be seen in melanomas that demonstrate portions of nevi lateral to or below the tumor.3 In an attempt to estimate the frequency with which melanomas are associated with nevi, studies4-12 have examined series of melanomas for histologic evidence of nevic remnants. Although a percentage of melanomas is found in contiguity with nevi, most studies demonstrate that the majority of melanomas appear to arise de novo. Furthermore, the actual risk of any given nevus transforming into a melanoma has been estimated to be exceedingly low.13

Although virtually any type of nevus can be found in association with melanoma, much attention has been given to the dysplastic nevus (DN) as a precursor and risk factor for melanoma. An estimated 2% to 8% of the population have DN.1,20 Such patients comprise a genetically and phenotypically heterogeneous group, with the actual risk of melanoma being dependent on factors such as the number of DN the patient has and the presence or absence of a family history of DN and melanoma.21-23 Although the presence of DN confers an elevated risk for developing melanoma, increased numbers of common acquired nevi are also associated with an increased risk.1,24

Our study examines the frequency with which melanomas are histologically...
associated with nevi and factors that are associated with an increased likelihood of a melanoma being found in histologic contiguity with a nevus.

**METHODS**

All pathology reports from invasive cutaneous melanomas diagnosed between January 1, 1993, and December 31, 1997, at Pathology Services, Inc, were obtained using a computer-assisted natural language search. Pathology Services, Inc, is an independent community-based dermatopathology laboratory that receives biopsy and excision specimens chiefly from local dermatologists and plastic surgeons. Pathology Services, Inc, also functions as a regional and national reference laboratory for pigmented lesions, which comprise less than 5% of the reported melanomas. Pathology Services, Inc, uses standard methods in the evaluation of elliptical excision specimens whereby each specimen is serially sectioned and entirely submitted for histologic examination. In specimens for which the primary dermatopathologist generates a diagnosis of melanoma, the slides are reviewed independently by a second staff dermatopathologist before the final diagnosis is released. During the study period, if the first 2 observers did not reach concordance, then the medical director of the laboratory or the senior dermatopathologist in residence would be consulted for an additional tiebreaking opinion. A test set of 346 randomly selected melanoma cases that were reviewed by pathologists at Pathology Services, Inc, revealed 5 disagreements (1.4%) over the diagnosis. A standard protocol is followed at Pathology Services, Inc, whereby the reviewing pathologist comments on melanoma subtype, growth phase, mitotic count, regression, tumor infiltrating lymphocytes, Breslow thickness, Clark level, site, sex, and presence or absence of a precursor lesion.

Pathology reports from the study period were reviewed, and melanomas representing a local recurrence or a cutaneous metastasis were omitted from analysis. Biopsies from specimens that were not adequate to accurately assess the lesion (ie, small shave biopsies) were also omitted (<2.0% of reports reviewed). In situ melanomas (n=392) were also omitted from analysis because of the morphologic overlap between dysplastic nevi and melanoma in situ, which can sometimes make classification difficult. After excluding the aforementioned cases, pathology reports from 1606 melanomas remained. When available, information from the pathology report of a reexcised melanoma was combined with that of the initial biopsy. The pathology reports were reviewed, and data were collected on sex, age at diagnosis, histologic subtype, Breslow thickness, Clark level, anatomic location, whether a nevus was associated with the melanoma, and, if so, the nevus type. The histologic subtypes were categorized as superficial spreading melanoma (SSM), nodular melanoma, lentigo maligna melanoma, acral lentiginous melanoma, desmoplastic melanoma, or unclassified.

Location was divided into head and neck, trunk, upper extremities, and lower extremities. Melanomas that were anatomically located on the shoulder were designated truncal. Nevus type was classified as DN or other nevus. Histologic criteria used to determine melanoma subtype, diagnose dysplastic nevi, and distinguish nevus cells from small melanoma cells were as outlined by Elder and Murphy.31 Nevic remnants categorized as other included junctional, dermal, compound, intradermal, and congenital nevi or nevi with congenital features. Congenital nevi or nevi with congenital features were not analyzed as a separate category, as no clinical history was available to confirm whether these nevi were present at birth.

The collected data were analyzed using SAS version 8.0 statistical software (SAS Institute, Cary, NC). Odds ratios and corresponding 95% confidence intervals and P values were calculated using logistic regression. Adjusted odds ratios and their associated 95% confidence intervals and P values were calculated using multivariate logistic regression. The final multivariate model was determined using a backward stepwise procedure. Variables with P<.20 were considered significant and were retained in the final model. Indicator variables were created for sex (with men as baseline), location, and subtype. Clark level of 1 through V was entered as an ordinal categorical variable, and age and depth were entered as continuous variables.

**RESULTS**

The study population was composed of 841 men and 739 women, with a mean age of 60 years (range, 11-95 years). The mean tumor thickness was 0.87 mm (range, 0.05-17.4 mm). The number of melanomas measuring 1.0 mm or less, 1.01 to 4.0 mm, and greater than 4.0 mm in depth was 1221, 347, and 26, respectively. Most melanomas were classified as SSM (n=1013), followed by lentigo maligna (n=257), unclassified (n=231), nodular (n=80), desmoplastic (n=13), and acral lentiginous (n=12) melanomas. The distribution of melanomas by age is shown in Figure 1. Information on sex, Breslow thickness, anatomic location, and age was not available for 26, 12, 5, and 2 patients, respectively.

Overall, 26.2% of the melanomas in our series were histologically associated with nevi (M-N). Of these, 43.0% were associated with DN and 57.0% with other nevi. The percentage of M-N was found to steadily decrease with increasing age and ranged from 63.6% in patients younger than 20 years to 11.1% in those 90 and older (Figure 2). Because we identified only 11 cases of melanoma in patients younger than 20, estimates in this age group may be somewhat unreliable. However, the overall trend of a continuous drop in the percentage of M-N by age is retained.

When examined by subtype, a higher percentage of SSMs (35.4%) showed evidence of an associated nevus compared with unclassified (19.0%), nodular (11.3%), and lentigo maligna (3.9%) melanomas (Figure 3). No nevi were found in association with acral lentiginous or desmoplastic melanomas. None of the lentigo maligna melanomas were associated with DN, and most of the nodular melanomas that were associated with nevi were with other nevi. A higher percentage of truncal melanomas had associated nevi, compared with those on the head and neck or the upper and lower extremities (Figure 4).
Dysplastic nevi comprised a higher percentage of truncal M-N compared with those on the head and neck or extremities. Although men had a higher percentage of melanomas located on the trunk than did women (Figure 5), there was no significant difference in the percentage of M-N on the trunk between men and women (P = .23) (Figure 6).

Among the variables univariately associated with an increased likelihood of M-N were younger age, SSM subtype, and truncal location (Table). Clark level and Breslow thickness were also significant predictors in univariate models, with lower level and thinner melanomas more likely to be associated with a nevus. After adjusting for the possibility of confounding using a multivariate model,
only younger age, SSM, and truncal location were still significant predictors of an increased likelihood of M-N. Among these, location was the most strongly associated. Melanomas on the trunk were more than 3 times as likely to be associated with a nevus compared with those in other locations.

COMMENT

Twenty-six percent of the melanomas in our series were histologically associated with nevi. This rate falls within the range of results from similar studies,1-18 which have found remnants of nevi in 9% to 58% of melanomas. There have been several clinical and pathologic variables that differ between studies and may contribute to the broad range of estimated M-N. These include the histologic subtype, Clark level, and Breslow thickness of the melanomas included in the analysis, differences between patient populations, and variation among the histologic criteria used to diagnose nevic remnants. The latter is particularly true in the case of dysplastic nevi, which is a topic that is surrounded by much controversy.11

In our series, SSMs were more frequently associated with nevi compared with other melanoma subtypes. This finding confirms previous reports7,14,16,17 and supports the idea that different melanoma subtypes may evolve through different histogenic pathways.7 By stratifying our series into 10-year age groups, we observed an inverse relationship between age and percentage of melanomas associated with nevi. Our study is one of the largest analyses to date documenting this effect, although smaller series have noted similar trends.11,14,16,26 This age effect is likely due to the smaller numbers of nevi noted in older individuals, which might result from a time-related involution of nevi and fewer nevic precursors available from which melanomas may develop. Alternatively, melanomas in older individuals may result from cumulative solar damage to epidermal melanocytes, while melanomas in younger patients may be more prone to arise from an altered precursor substrate, such as a nevus.

Although younger age, male sex, truncal location, SSM subtype, and thinner tumors were associated with an increased likelihood of M-N, only subtype, truncal location, and age remained significant predictors by multivariate analysis. Interestingly, truncal location appears to be the leading predictor for M-N (odds ratio, 3.26). Two smaller studies have addressed the effect of confounding factors in their statistical analyses. Skender-Kalnenas et al14 found SSM, truncal location, and younger age to be associated more frequently with M-N. In addition, they found increasing Clark levels (but not Breslow thickness) to be associated with fewer M-N. However, this relationship was only found among invasive melanomas (ie, in situ melanomas did not show evidence of nevi more frequently than level II melanomas). In a study by Gruber et al,7 variables that were associated with an increased likelihood of M-N included SSM and truncal location. By multivariate analysis, however, only subtype remained significant. Unlike our study, they found no association between M-N and age.

Some of the limitations of our study are inherent in the retrospective analysis. First, some melanomas were diagnosed with incisional punch or shave biopsies; therefore, complete examination of the lesion was not always possible even when the reexcision was analyzed. In cases for which the reexcised specimen was not available for review, it was possible that the reexcised melanoma might have shown an associated nevus that was not detected on initial biopsy, thus underestimating the percentage of M-N. Another limitation is the difficulty sometimes encountered when trying to differentiate nevus cells from melanoma. Two cases in which this distinction is particularly problematic are nevoid melanomas, in which deep melanoma cells may show differentiation and be mistaken for an associated nevus, and melanomas arising from DN, because there is overlap between the histologic features of DN and melanoma.4,10

In conclusion, we performed one of the largest retrospective analyses to date and found that 26.2% of melanomas in our series were histologically contiguous with nevi. Our findings are in agreement with other similar studies and support the idea that most melanomas arise de novo from previously normal skin. Patients should be educated to pay as much attention to suspicious new pigmented lesions as they would to changing moles. We also demonstrated that SSM, truncal location, and younger age were more likely to be associated with M-N. Our findings support the idea that there is variation in the histogenesis of melanoma, with nevi tending to give rise to SSM more often than to other subtypes. Although we found a decrease in the likelihood of M-N to occur with increasing age, clinicians should not assume that any given nevus on an older patient has a lower risk of malignant transformation. Increasing age should not alter the level of clinical suspicion or the decision to perform a biopsy of a changing nevus that may otherwise be indicated.

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