

## Dysplastic Nevi in Relation to Superficial Spreading Melanoma

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### Abstract

**The aim of the present study was to evaluate the frequency with which histologically confirmed dysplastic nevi are observed among patients with superficial spreading melanoma compared to patients with nodular melanoma. A pathology review of 117 new cases of first primary nonfamilial cutaneous melanoma identified 61 patients with superficial spreading melanoma and 19 with nodular melanoma. Study participants received a physician-conducted skin examination which included enumeration of clinically benign and atypical nevi and the surgical excision of the clinically most atypical nevus. Patients' dysplastic nevus status was established by histological review of the clinically most atypical nevus. A comparison based on the tumor subtypes showed that dysplastic nevi occur nearly four times more frequently among patients with a prior diagnosis of superficial spreading melanoma relative to nodular melanoma (odds ratio = 3.6;  $P = 0.03$ ).**

### Introduction

Clinical observation and pathology studies suggest that a large fraction of melanomas arise within a precursor dysplastic nevus (1-7). Pathology studies have also shown that superficial spreading (radial) melanomas are more likely than nodular (vertical) melanomas to be found in histological contiguity with a dysplastic nevus (4, 6, 7), suggesting divergent histological origins for the two tumor subtypes. It has been argued, however, that the apparent relationship between precursor nevi and superficial spreading melanoma may be an artifact of the greater tumor thickness (4) or more aggressive properties of nodular melanomas, resulting in obscuration or obliteration of preexisting lesions (8). Indeed, many investi-

gators contend that superficial spreading and nodular melanomas have common histological origins. Holman *et al.* (8) have suggested that nodular melanoma may be the end stage of superficial spreading melanomas and other histological subtypes. Clark *et al.* (6) and McGovern (9) have proposed that superficial spreading melanoma and nodular melanoma are histologically similar but are distinguished by different rates and modes of progression to invasive growth phase.

The aim of the following study was to evaluate the relative frequency with which dysplastic nevi are observed among patients with a prior diagnosis of superficial spreading melanoma versus those with nodular melanoma, using an epidemiological approach. We established dysplastic nevus status through skin examination, with excision and histological assessment of each patient's clinically most atypical nevus. The histological type (nodular or superficial spreading melanoma) of each study participant's primary tumor was established by an independent pathology review. While this approach cannot identify patients whose tumor arose within a precursor lesion, it allows an evaluation of the relationship between dysplastic nevi and superficial spreading melanoma and averts the potential bias introduced to studies of histological contiguity by differential tumor growth rates.

### Subjects and Methods

Potential study participants were 117 patients with a diagnosis of first primary cutaneous melanoma between January 1, 1983 and July 1, 1986 and followed at the Yale Melanoma Clinic. Patients with familial dysplastic nevus syndrome, defined as a kindred with evidence of dysplastic nevus syndrome and at least two blood relatives with melanoma (10), were ineligible for participation.

A pathology review of original primary tumors identified 80 eligible patients: 61 patients with superficial spreading melanoma and 19 patients with nodular melanoma. Superficial spreading melanoma was diagnosed by the characteristic intraepidermal pagetoid distribution of malignant melanocytes (11). Nodular melanoma was distinguished from superficial spreading melanoma by the presence of an expansile nodule in the papillary dermis and the absence of adjacent intraepidermal melanocytic proliferation (radial growth phase), or limitation of such a radial growth component to within three rete ridges of the nodule (11). Patients with melanoma *in situ* or invasive melanoma of the acral lentiginous, unclassified, or lentigo maligna type were excluded from this study.

Study participation included a physician-conducted skin examination (including the scalp but excluding the anogenital area) during which all nevi  $\geq 3$  mm were counted, and clinically atypical nevi were counted and described on a standardized form. Clinically atypical nevi

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**Table 1** Relationships between superficial spreading melanoma and number of benign nevi, number of atypical nevi, and histologically confirmed dysplastic nevi

| Factor                          | Histologic type of tumor |                  |                  | 95% CI                 |
|---------------------------------|--------------------------|------------------|------------------|------------------------|
|                                 | Nodular                  | SSM <sup>a</sup> | OR               |                        |
| No. of benign nevi              |                          |                  |                  |                        |
| 0-9                             | 8                        | 22               | 1.0              | Reference <sup>b</sup> |
| 10-19                           | 5                        | 21               | 1.5              | (0.43-5.42)            |
| ≥20                             | 4                        | 13               | 1.2              | (0.31-4.71)            |
| No. of clinically atypical nevi |                          |                  |                  |                        |
| 0                               | 7                        | 17               | 1.0              | Reference              |
| 1-2                             | 6                        | 16               | 1.1              | (0.30-3.98)            |
| ≥3                              | 4                        | 23               | 2.4              | (0.60-9.41)            |
| Dysplastic nevus                |                          |                  |                  |                        |
| Absent                          | 15                       | 31               | 1.0              | Reference              |
| Present                         | 4                        | 30               | 3.6 <sup>c</sup> | (1.08-12.21)           |

<sup>a</sup> Superficial spreading melanoma.

<sup>b</sup> Baseline category for the comparisons.

<sup>c</sup>  $P = 0.03$ .

were identified using the following criteria, adapted from others: size  $\geq 5$  mm in diameter; haphazard color; irregularity of border; ill-defined border; macular component; and presence of erythema (2, 12-14).

Each patient's clinically most atypical nevus was removed by simple surgical excision and was histologically reviewed for dysplasia. A patient was considered positive for dysplastic nevus if the clinically most atypical nevus was found to have readily evident architectural abnormality and unequivocal cytologic atypia (1, 2). More detailed discussions of study methods (15) and the sensitivity and specificity of clinical diagnosis of dysplastic nevi are available elsewhere (16).

The OR<sup>2</sup> was used as a measure of association between variables; 95% confidence intervals were constructed for each OR. Statistical significance was evaluated by Mantel-Haenszel  $\chi^2$  and tests for linear trend (17).

## Results

Table 1 shows the cross-classification of the two tumor subtypes with number of benign nevi, number of clinically atypical nevi, and the presence of at least one histologically dysplastic nevus. Nevus counts were available for 73 participants. There was no evidence of a linear relationship between tumor subtype and number of benign nevi or number of clinically atypical nevi. Although patients with superficial spreading melanoma, relative to nodular melanoma, were more likely to have  $\geq 3$  clinically atypical nevi (OR = 2.4), the relationship was not statistically significant. Histologically confirmed dysplastic nevi were observed significantly more frequently among patients with superficial spreading melanomas than among patients with nodular tumors (OR = 3.6;  $P = 0.03$ ).

## Discussion

In this study, the number of benign nevi was not related

to tumor subtype. Numerous melanocytic lesions may serve as markers of heightened melanocytic proliferation and increased risk of melanoma (13, 18-23) without being related to a specific melanoma histological subtype. While the data suggested that the presence of  $\geq 3$  clinically atypical nevi is associated with superficial spreading melanoma, the relationship was not statistically significant, perhaps due to small sample size. The results of this study show that histologically confirmed dysplastic nevi occur more frequently among patients with superficial spreading melanoma than among those with nodular melanoma. Because patients were unaware of their dysplastic nevus status prior to the diagnosis of a melanoma, it is unlikely that the observed relationship is an artifact of closer surveillance of patients with dysplastic nevi and consequent early detection of radial growth tumors.

The histological progression of dysplastic nevi to superficial spreading melanoma is supported by a recent electron microscopy study showing that melanocytic ultrastructures of dysplastic nevi are similar to those of radial growth tumors (24); unfortunately, the melanocytic ultrastructures of nodular melanomas were not included in this comparison. It is difficult, if not impossible, to provide direct evidence to support or refute the notion of common histological origins for nodular and superficial spreading melanomas. A prospective investigation of histological origins of the tumor subtypes would obviously interrupt the natural progression of histological events. Pathology studies showing a greater relative frequency of dysplastic nevi in histological contiguity with superficial spreading melanoma, compared to nodular melanoma, support the notion of histologically diverse origins for the two tumor subtypes but have been challenged on the basis that nodular tumors are more likely than superficial spreading melanomas to obliterate evidence of preexisting lesions.

Because patients with dysplastic nevi typically have multiple lesions and tend to develop new lesions over time (2, 25), we were able to establish patients' dysplastic nevus status by identifying lesions occurring apart from the primary tumor site. Our method of evaluating the relationship between dysplastic nevi and melanoma subtypes averts the potential bias introduced to studies of histological contiguity by differential tumor growth rates. While this approach clearly does not determine whether a given tumor arose within a precursor nevus, it identifies persons with a tendency to develop dysplastic nevi and allows an epidemiological evaluation of the relative frequency with which these patients have a prior diagnosis of superficial spreading melanoma versus nodular melanoma. The results of this study, which show that patients with dysplastic nevi are nearly four times more likely to have a superficial spreading melanoma than a nodular melanoma, are consistent with the results of histological contiguity studies and support the notion of divergent histological origins for the two tumor subtypes.

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<sup>2</sup> The abbreviation used is: OR, odds ratio.

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