Dysplastic Nevi

Markers for Increased Risk for Melanoma

DARRELL S. RIGEL, MD, JASON K. RIVERS, MD, FRCP(C), ALFRED W. KOPF, MD, ROBERT J. FRIEDMAN, MD, ANNE F. VINOKUR, BA, EDWARD R. HEILMAN, MD,* AND MARCIA LEVENSTEIN, DSc

A total of 452 white patients, classified into four dysplastic nevi groups, were followed prospectively by repetitive, complete cutaneous examinations using total-body photographs taken on entry into the study. Sixteen patients (3.5%) developed 18 newly diagnosed malignant melanomas (MM) during an average follow-up period of 27 months. Twelve of the 18 MM were *in situ*, and all of the six primary invasive MM diagnosed prospectively in this follow-up were less than 0.89 mm in Breslow thickness, implying an excellent prognosis. Compared with reference populations, the number of MM detected significantly exceeded the number estimated to occur in the comparable age-matched control groups. These data support the concept of repetitive follow-ups of all groups of patients with dysplastic nevi.

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DYSPLASTIC NEVI (DN) are considered to be cutaneous markers, which identify individuals who are at increased risk for developing malignant melanoma (MM) compared to individuals in the general population.[1-7] Several studies have estimated the substantial relative risk for MM in those relatives who have DN in the familial MM setting.[2,8] However, controversy continues regarding the magnitude of this risk in patients along the spectrum of DN syndromes.[9] The results of our prospective study confirm that patients in all DN groups are prone to develop MM.

Materials and Methods

A series of 452 consecutive white patients with a clinical (Table 1) and histologic diagnosis[10] of DN are reported herein. The overall composition of the patients included in this study is summarized in Table 2. These patients were followed prospectively between January 1980 and October 1987. Prior to entry into the study, each patient had a biopsy performed of one or more atypical nevi, which had the clinical and histologic characteristics of DN. A family and personal history for MM in the modified nuclear pedigree was obtained. A standardized series of 23 color transparencies (35 mm) documenting the total body surface was taken.[11] Each patient was followed at 3- to 12-month intervals at which times a complete cutaneous examination was performed using the baseline photographs for comparison.

Any lesion that changed or arose *de novo* and was clinically suggestive of MM was surgically removed *in toto*. The surgical specimen was blocked by cutting parallel steps at 2-mm intervals throughout. Sections were stained with hematoxylin and eosin and reviewed independently by two dermatopathologists (R.J.F., E.R.H.). Each specimen was examined for the presence of the histologic features of MM[12] and any associated histologic precursor (*e.g.*, DN) using previously published histologic criteria.[10]

Each patient was categorized into one of four DN groups on the basis of the personal and/or family history of MM (Table 3).[13] Briefly, in this classification one point is given if the patient has had MM prior to entry into the study and two points are given per family member (modified nuclear pedigree) who has had MM. The modified nuclear pedigree includes parents, offspring, siblings, grandparents, aunts, and uncles. Based on the total points, each patient is classified into one of four groups as follows:

From the Departments of Dermatology, New York University School of Medicine and Downstate Medical Center; New York University Melanoma Cooperative Group; and the Oncology Section, Skin & Cancer Unit, New York University Medical Center, New York, New York.

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Address for reprints: Darrell S. Rigel, MD, Oncology Section, Skin and Cancer Unit, 562 First Avenue, New York, NY 10016.

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TABLE 1. Clinical Characteristics of Patients With Classic Dysplastic Nevi

Feature	Clinical finding
General clinical characteristics	
No. of nevocytic nevi	Often many (>75) including non-DN*
Uniformity of dysplastic nevi	Heterogeneous (neighbors differ)
Clinical characteristics of dysplastic nevi	
Size	Vary, but at least some over 7 mm diameter
Color	Variegate; multiple shades of tans, browns, black, red
Elevation	Usually raised centrally
Perimeter	Fades imperceptibly into surrounding skin
Shoulder	Peripheral macular tan zone
Surface	Often mammillated (pebbly), cobblestoned
Location	Usually trunk > limbs > face
Change	Relatively stable once fully developed
Sun-exposed sites	DN greater numbers on sun exposed *versus* non-sun-exposed sites
Non-sun-exposed sites	DN greater numbers than non-DN*
Hypertrichosis	Absent
Symptoms	None
Erosion/ulceration	Absent

*Non-DN (non-dysplastic nevi): all nevocytic nevi except dysplastic, Spitz, congenital, spilus, blue.

Group 0 = 0 points; Group I = 1 point; Group II = 2 points; Group III = 3 or more points.

The estimated occurrence of invasive MM, based on age-specific incidence rates from both the 1980 to 1986 Connecticut Tumor Registry and the 1980 to 1985 Surveillance Epidemiology and End Results (SEER) data bases,[14,15] was calculated for a cohort of the general white population of the same size and age distribution as each of the four DN groups.

An MM diagnosed at the initial visit to the physician was not considered as a newly diagnosed MM in this study. Only those MM that were newly diagnosed after the first examination were included in the results.

The significance of these findings was assessed by a binomial distribution calculation[16] using the Statistical Analysis System (SAS Institute Inc., Cary, NC).

Results

A total of 16 (3.5%) of the 452 DN patients followed for an average of 27 months (range, 1 to 83 months) developed newly diagnosed cutaneous MM. Two patients in Group II developed a second newly diagnosed primary MM at 8 and 20 months of follow-up, respectively. Of these 18 MM, 14 were diagnosed during the first half of the study (at average follow-up of 13 months) and the remainder (four lesions) in the second half of the study. Details concerning these 16 patients are shown in Table 4. Twelve of the 18 MM were Level I (MM *in situ*) lesions, whereas the remaining lesions ranged between 0.1 and 0.88 mm in Breslow thickness. No patient has developed recurrence or metastasis during subsequent follow-up (range, 6 to 47 months; average, 25 months).

TABLE 2. Distribution of Dysplastic Nevi Patients

No. of patients	452
Males	206 (46%)
Females	246 (54%)
Average age (yr)	36.1
Total patient-months of follow-up	12,227
Average months of follow-up per patient	27

Using the classification of Rigel *et al.*,[13] Table 5 illustrates the number of invasive MM developing according to DN group, and the number of invasive MM estimated to occur in a population of the same size and age distribution derived from the age-specific incidence rates for invasive MM of the Connecticut Tumor Registry and SEER data bases.

Histologically, 12 of the MM diagnosed prospectively were *in situ* lesions. The six remaining MM were 0.1, 0.26, 0.4, 0.5, 0.7, and 0.88 mm in Breslow thickness, respectively. Also of note was that eight of the 18 MM had contiguous DN associated with them on histologic examination of the step-sectioned specimens.

The binomial distribution calculations[16] showed that in each DN group and in the aggregate there were significantly ($P < 0.003$) more invasive MM observed than expected.

Discussion

Patients with DN have been reported to be at increased risk for developing MM when compared with the general white population of the United States.[2,5] Kraemer *et al.*[8] followed DN patients with familial MM (Type D2-2 or more family members with history of MM) and estimated them to be 395 times more likely to develop MM than individuals in the general population. These investigators

TABLE 3. Classification of Dysplastic Nevi Patients According to Relative Risk for Developing Malignant Melanoma

Dysplastic nevi group	Score*
0	0
I	1
II	2
III	3 or more

* Scores are based on a point system as per by Rigel *et al.*[13] as follows: personal history of malignant melanoma = 1 point; family history of malignant melanoma = 2 points per family member with MM.

TABLE 4. Data on Dysplastic Nevi Patients in Whom Malignant Melanoma was Detected During Study

Age (yr)	Sex	Personal history of prior malignant melanoma	Family history of malignant melanoma	Dysplastic nevi group	Thickness of malignant melanoma (mm)
48	M	No	No	0	IS*
23	M	No	No	0	IS
24	F	No	No	0	IS*
39	F	No	No	0	0.88*
33	F	Yes	No	I	IS*
58	M	Yes	No	I	IS
45	M	Yes	No	I	0.26*
25	F	No	Yes (1)	II	IS, IS*
34	F	No	Yes (1)	II	IS, IS
30	F	No	Yes (1)	II	IS*
35	M	No	Yes (1)	II	0.7*
29	F	No	Yes (2)	III	IS
70	M	Yes	Yes (2)	III	IS
37	F	No	Yes (2)	III	0.1
51	M	No	Yes (2)	III	0.4
64	M	Yes	Yes (2)	III	0.5

IS: *in situ*. Values in parentheses are the no. of relatives with malignant melanoma.
* With contiguous dysplastic nevi.

also estimated the relative risk for MM in all other types of DN combined to be approximately 7 to 26 times that of the general population by extrapolation of their data.[5,8] The present study provides data, which indicate that individuals with DN of groups other than Group III (Type D2) are prone to develop MM.

As noted in Table 5, the number of invasive MM detected in each DN group is greater than the corresponding estimate for a population of the same size and age distribution using both the Connecticut Tumor Registry and SEER data bases as reference populations. Although we believe that the majority of *in situ* MM will evolve into invasive MM over a period of time, in Table 5 we have excluded the *in situ* lesions from the number of MM detected in each DN group. As Schmoeckel[18] pointed out, there are interobserver problems in differentiating *in situ* MM from other melanocytic neoplasms.

TABLE 5. Number of Invasive Malignant Melanoma Detected in Dysplastic Nevi Patients and the Number of Invasive Malignant Melanoma Estimated in Reference Populations of Same Size, Age Distribution, and Observation Period*

Group	N	Total months of follow-up	Malignant melanoma detected	No. of malignant melanoma estimated in reference populations	
				SEER	Connecticut
0	281	6988	1	0.062	0.064
I	66	2523	1	0.028	0.030
II	69	1872	1	0.015	0.016
III	36	1014	3	0.009	0.010
Total	452	12,227	6	0.113	0.118

* The chance of finding the number of malignant melanoma detected (or a greater number) in early dysplastic nevi group as determined by a binomial distribution[16], given the estimated values in the SEER or Connecticut reference populations, is $P < 0.003$ for each group and the aggregate.

There are several factors that might affect the magnitude of the results of this study. First, one must assume that the reference population has qualities that mirror those of the study group. Connecticut is contiguous to New York state; consequently, geographic and socioeconomic differences are minimized. However, SEER data are collected from several geographic locations across the United States, include people from all walks of life, and are based on a population of approximately 22 million people.[19] The strong concordance between these two minimally overlapping populations supports their validity as reference populations.

Another important difference between our study group and the two reference populations was the manner in which surveillance was performed. Our patients had full cutaneous examinations every 3 to 12 months using total-body photographs as an aid to detect any lesions suspicious for MM. The general population is not followed as closely. This may explain why two-thirds of the prospectively diagnosed MM in our study population were *in situ* lesions compared with only 10% in both the Connecticut Tumor Registry and SEER data bases.[14,15]

The manner in which patients are recruited into the study population may also affect these calculations. Some of the study patients were specifically referred to physicians with a special interest in this syndrome. This is not the referral route in which patients entered the reference populations.

It has been shown that early diagnosis and complete surgical excision of MM less than 0.86 mm in thickness (Breslow) is associated with excellent prognosis. Because there is no effective treatment for systemic metastases of MM, early intervention is clearly important. Because all of the 18 MM detected were well within a thickness range that is virtually 100% curable,[20–23] close surveillance of this group was successful in alleviating potential mortality rates.

In conclusion, based on our observations in a series of 452 consecutive white patients who had nevocytic nevi that were both clinically and histologically diagnosed as DN, all subsets (groups) of such patients were shown to develop MM more frequently than expected when compared to the reference populations. Some of this increased risk might be attributed to telescoped surveillance. However, during an average follow-up of 27 months six (1.3%)

of these patients prospectively developed invasive MM. Thus, in approximately 2 years the study patients have already exceeded the lifetime risk for MM in the general United States population, which is approximately 1% for whites.[24] Although the absolute numbers of detected lesions were relatively small, there was a progressive increase in the proportion of patients that developed MM in those who had a personal and/or family history of MM. Given the importance of early detection and treatment in persons with MM, these results suggest that increased regular surveillance of DN patients may be helpful in their management.

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