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Dysplastic Nevi in Association with Multiple Primary Melanoma

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ABSTRACT

Risk factors for multiple primary cutaneous melanoma were evaluated in a case-control study. Eight cases of multiple primary melanoma were matched on sex, age, and education to 24 first primary melanoma controls. Risk factors examined in the analysis included pigmentary characteristics, history of sun exposure, and nevi. The importance of histologically dysplastic nevi (DN) and clinically atypical nevi was of particular interest. Single-factor conditional logistic regression analysis showed that first primary melanoma patients with histological DN are at increased risk for a second primary (odds ratio, 6.2; 95% confidence interval, 1.2–33.4). Patients with two or more clinically atypical nevi also have elevated risk for a second primary (odds ratio, 8.8; 95% confidence interval, 1.0–80.7). Two-factor logistic models were used to evaluate the effect of histological DN while controlling singly for all other variables as potential confounders. Odds ratios for the association of histological DN varied from 6.1 to 10.4 when adjusting singly for pigmentary and sun exposure variables. In the two-factor model that included histological and clinical DN, both variables retained marginally significant statistical association with multiple primary melanoma. These results suggest that DN is a marker of increased risk for multiple primary melanoma and suggest that melanoma patients with evidence of DN should be followed closely for the development of additional primaries.

INTRODUCTION

An inherited syndrome characterized by atypical moles and high risk for melanoma was simultaneously described 9 years ago by independent investigators (1, 2). Subsequent study of this syndrome, now widely known as the FDNS[2], suggests that family members who develop atypical moles have an approximately 100% cumulative lifetime risk for melanoma (3).

A form of DNS has also been identified in individuals who are not members of melanoma kindreds (4). There is strong evidence to suggest that DN are markers of increased risk for melanoma outside the familial setting (4). Considered together, patient reports of a prior nevus at the site of tumor and histological evidence of DN in contiguity with melanoma suggest that a nevus is associated with the primary tumor in as many as 85% of melanoma patients (5). A recent study restricted to nonfamilial melanoma patients found DN in histological contiguity with melanoma in 46% of cases (6). In addition to nevi, sunlight exposure and pigmentary characteristics have been frequently studied and identified as risk factors for cutaneous melanoma (7–13).

In melanoma kindreds, 30% of those who develop one primary melanoma will subsequently develop a second primary melanoma (3). For FDNS patients, increased surveillance has resulted in the early identification and removal of shallow tumors (3). Among patients with nonfamilial melanoma, approximately 5% will develop an additional primary (14). Risk for a second primary is particularly high among newly diagnosed patients under the age of 40 (15). The ability to identify nonfamilial melanoma patients who are at elevated risk for additional primaries will result in improved surveillance and early detection of tumors for these patients. The following case-control study will focus on the importance of (*a*) the presence of DN, (*b*) exposure to sunlight, and (*c*) pigmentary characteristics, as risk factors for multiple primary melanoma.

METHODS

Eligibility Criteria

Study subjects were drawn from patients with first primary incident cutaneous melanoma diagnosed between January 1, 1983, and July 1, 1986, and seen at the Yale Melanoma Clinic. Patients were eligible if they had at least two follow-up visits at the clinic, were Caucasian, English speaking, and less than 70 years of age at diagnosis. Patients who were members of familial dysplastic nevus syndrome kindreds were excluded from the study. FDNS was defined as a kindred with evidence of DNS and at least two blood relatives with melanoma (1). The exclusion of cases of melanoma that could be attributed to FDNS was accomplished on the basis of direct specific query of patients for a history of melanoma or unspecified skin cancer among blood relatives, and by examination of family members for clinically atypical nevi when FDNS was suspected. A total of 164 patients were eligible for participation in the study. Of these eligible patients, 28 refused to participate, 13 patients died prior to enrollment, and two patients were lost to follow-up. The response rate for participation was 74%. Of the 121 melanoma patients who participated in the study, 8 developed a second primary melanoma.

Procedures. Each of the 121 subjects participated in an in-person interview adapted from Holman and Armstrong (9) and received a thorough skin examination excluding the anogenital area. The interview evaluated pigmentary characteristics, medical history, and environmental exposures, including an extensive section on sun exposure. Skin examination was independently conducted by three or more examiners, at least two of whom were physicians trained and experienced in the identification of pigmented lesions. For each patient, this skin examination included a total body count of all nevi greater than 3 mm and all clinically atypical nevi. In addition, as many as six clinically atypical nevi were characterized for location and physical appearance using a standardized descriptive form. The presence of each of the following criteria were evaluated in the identification of atypical nevi: size > 5 mm, macular component, irregular border, ill-defined border, erythema, and variegate color (1, 4, 16). For each patient, the examining physicians independently identified the most clinically atypical nevus for excision and histological evaluation. In the absence of agreement on the selection of the most clinically atypical nevus, the decision for excision was made by consensus. In the event that a clinically atypical nevus was not identified, the most atypical nevus or pigmented lesion was selected for biopsy.

Following a routine pathology review, each excised nevus was independently histologically evaluated for dysplasia and, in the absence of consensus, reviewed by reference dermatopathologists who were blinded to the clinical diagnosis. The interrater reliability of histopathological diagnoses of DN has been described elsewhere (17). The diagnosis of a dysplastic nevus required architectural abnormalities and the presence of at least two of the following five criteria for cytological dysplasia: large nuclei, hyperchromatic nuclei or pleiomorphic nuclei, and pale, eosinophilic or dusty cytoplasm. The presence of nucleoli, giant melanosomes, and mitotic figures was also noted.

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[2] The abbreviations used are: FDNS, familial dysplastic nevus syndrome; DNS, dysplastic nevus syndrome; DN, dysplastic nevi; OR, odds ratio; CI, confidence interval.

Cases and Controls. For the present analysis, cases are patients diagnosed with a second primary melanoma during the 3.5-year study period. Eight cases of multiple primary melanoma were identified among 121 eligible participants. For two cases, the second primary was identified by routine pathological review of the most clinically atypical nevus removed for this study. In these two patients, the second primary was found in histological continuity with a dysplastic nevus. One of these patients was categorized both as a case of multiple primary melanoma and as an individual with DN, based on the histological finding of the single lesion. The second patient developed a third primary melanoma. For the other six cases, the second primary was diagnosed in a separate lesion identified simultaneously with or subsequent to the diagnosis of the first primary. Controls were selected from the 113 patients who did not develop a second primary melanoma during the study period. For each of the eight cases, three controls were randomly chosen from the pool of controls who were the same sex, age (within 10 years), and education (high school, college or graduate school) as the case. To control for survivorship, eligible matches were restricted to controls whose survival after the diagnosis of melanoma was at least as long as the interval between the diagnosis of a first and second primary in the corresponding case.

RESULTS

The analyses presented here are based on eight cases of multiple primary melanoma and 24 matched controls. Subjects ranged in age from 33 to 69 years at initial diagnosis, with a mean age of 52 years for cases and 51 years for controls.

Risk factors included in the analysis were selected *a priori* on the basis of reported associations with single primary melanoma. The specific variables included were: (*a*) histological presence of a dysplastic nevus, (*b*) number of clinically atypical nevi (clinical DN), (*c*) total number of nevi > 3 mm in diameter, (*d*) history of blistering due to acute sun exposure, (*e*) history of suntanning, (*f*) tannability (self-reported skin response to sun exposure), (*g*) natural hair color at age 20, and (*h*) self-assessed skin color (measured on a scale of 1 to 10, with 10 representing the lightest skin color).

In the preliminary statistical evaluation, unadjusted OR and corresponding CI were estimated by conditional regression analysis (18). This analysis examined single factor models while taking into account the matching variables (sex, age, and education).

In the single-factor logistic regression analysis, histological DN is associated with a 6-fold increase in the risk of multiple primary melanoma, (OR, 6.2; 95% CI, 1.2–33.4). The presence of two or more clinically atypical nevi is associated with an almost 9-fold increase in risk (OR, 8.8; 95% CI, 1.0–80.7). The distribution of cases and controls across levels of histological and clinical DN is shown in Table 1. Elevated relative risks were also observed for the presence of 20 or more nevi > 3 mm, a history of blistering due to sun exposure, red or light hair color, and light skin pigmentation. None of these effects, however, were statistically significant and the confidence intervals were wide, allowing for the exclusion of only large detrimental or protective effects. The point estimates and confidence intervals generated by the single-factor conditional logistical regression analysis are shown in Table 2.

Due to the small number of cases of multiple primary melanoma available for this analysis, it was not possible to simultaneously control all potential confounders in a multivariable model. Conditional logistic regression analysis was useful, however, for examining two-factor models while taking into account the matching variables. Using this technique, histological DN was evaluated while controlling singly for each potential confounder. In this analysis, the estimated relative risk for the presence of histological DN varied from 6.1 to 10.4 and remained statistically significant when controlling singly for each of the factors measuring sun exposure, and pigmentary characteristics. When the histological presence of DN and the clinical presence of two or more DN were included in a two-factor logistic model, the effects of both factors remained elevated with borderline statistical significance (OR, 5.5; 95% CI, 0.8–35.8; $P = 0.075$ for histological DN and OR, 6.9; 95% CI, 0.7–67.5; $P = 0.10$ for two or more clinical DN).

The effects of the pigmentary and sun exposure covariates remained statistically nonsignificant when controlling for histological DN. Due to the joint distribution of history of suntanning and histological DN, the effects of these variables were not estimable using conditional logistic regression analysis.

Table 1 *Distribution of cases and controls across levels of histological and clinical DN*

	Cases	Controls
Histological		
DN+	5	4
DN−	3	20
Clinical DN		
0	0	8
1	2	8
2–9	4	6
10+	2	2

DISCUSSION

The results of this study indicate that the presence of a histologically confirmed DN is associated with increased risk for multiple primary cutaneous melanoma. In addition, the clinical presence of two or more nevi assessed as DN may be a good marker of risk for multiple primary melanoma. When presence of nevi fulfilling criteria for histological DN and clinical DN are included in the model predicting multiple primaries, both variables retain marginal significance as predictors. The magnitude of the overall increased risk associated with histological DN is approximately 6-fold in the present study, consistent with an estimated 6-fold risk for single pri-

Table 2 *OR and CI estimated by single-factor conditional logistic regression analysis*

	OR	95% CI	
Histological DN	6.2	1.2–33.4	$P = 0.03$
History of blistering	2.3	0.2–21.3	
Number of clinical DN			
2+ *vs.* 0,1	8.8	1.0–80.7	$P = 0.05$
Number of nevi			
10 nevus difference	1.1	0.8– 1.4	
>20 *vs.* <19	2.9	0.5–16.5	
History of tanning			
Suntan	3.4	0.4–31.0	
Skin color[a]			
8+ *vs.* <7	1.7	0.2–11.5	
9+ *vs.* <8	3.0	0.5–19.0	
10 *vs.* <9	4.4	0.4–51.2	
Tannability[b]			
Tan *vs.* no tan (3,4) (1,2)	1.2	0.2– 6.5	
Hair color	1.7	0.3–10.2	

[a] Skin color self-assessed using a color chart from 1 to 10, with 1 representing the darkest skin color and 10 the lightest skin color.

[b] Tannability: 1, very brown and deeply tanned; 2, moderately tanned; 3, mildly tanned due to tendency to peel; 4, freckles and no tan.

mary melanoma among Australians with clinically atypical nevi (19). This similarity in risk suggests that the effect of DN in the etiologies of first primary and multiple primary melanoma may be similar (20).

The pigmentary and sun exposure variables examined in the present study have been repeatedly identified as risk factors for single primary melanoma. In this study, lack of statistical evidence for an association between these variables and multiple primary melanoma may be attributed at least in part to the small number of multiple primary cases available for analysis. A larger sample of multiple primary melanoma cases will be needed to evaluate similarities in the etiologies of first and multiple primary melanoma. In this analysis, the confidence limits for the associations between pigmentary and sun exposure factors and risk for multiple primary melanoma do not exclude the "average" effect of these factors on risk for a first primary melanoma. Consequently, it is not possible to determine from these data whether the etiologies of first primary and multiple primary melanoma are similar with regard to the influence of pigmentary and sun exposure factors (20).

It is interesting to note that two of the cases of multiple primary melanoma were identified as a result of the removal of a "most" clinically atypical nevus during the course of this study. In each of these two cases, the nevus that was biopsied was not considered by multiple observers to be clinically suggestive of melanoma. The histological identification of malignancy in these nevi suggests that an increased index of suspicion should prevail when evaluating clinically atypical lesions occurring among melanoma patients.

Because of the small number of multiple primary cases evaluated here, these results require confirmation from additional studies using larger case groups. However, the inadequacy of the sample size to detect minor effects and the *a priori* nature of the statistical evaluation suggest that DN is a useful marker of risk for additional primaries.

The results of this study have important implications for patient management. In the clinical setting, melanoma patients with two or more nevi judged clinically to be DN may be considered at increased risk for a second primary. These patients may benefit from the removal of nevi that are suspicious for DN. The finding of histological dysplasia is particularly suggestive of risk for additional primaries. Overall, these data suggest that melanoma patients with clinical or histological evidence of DN should be carefully followed to minimize risk of developing undetected additional primaries.

Evidence from a variety of histological, epidemiological, and clinical studies suggests that up to 85% of first primary melanomas may arise from a preexisting nevus (5). In this small series of multiple primary melanoma patients, it is interesting to note that the histological presence of DN was found in five of eight cases. Because a suspicious lesion must be excised to determine its histological identity, it is not possible to provide direct evidence that a particular dysplastic nevus will fulfill its malignant potential. In addition, it is apparent that a fraction of first primary melanomas arise without evidence of a preexisting nevus, and that many individuals with sporadic DN will never develop a melanoma (16). However, the importance of dysplastic nevi as markers of risk for first primary melanoma is well established. The results of this study provide evidence that DN are also important markers of risk for additional primaries among patients already diagnosed with melanoma.

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