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Dysplastic naevi with moderate to severe histological dysplasia: a risk factor for melanoma

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Summary

Background The risk of malignant melanoma associated with histologically dysplastic naevi (HDN) has not been defined. While clinically atypical naevi appear to confer an independent risk of melanoma, no study has evaluated the extent to which HDN are predictive of melanoma.

Objectives To estimate the risk of melanoma associated with HDN. Secondarily, the risk associated with number of naevi and large naevi is estimated.

Methods We enrolled 80 patients with newly diagnosed melanoma along with 80 spousal controls. After obtaining information on melanoma risk factors and performing a complete cutaneous examination, the most clinically atypical naevus was biopsied in both cases and controls. Histological dysplasia was then assessed independently by 13 dermatopathologists (0, no dysplasia; 1, mild dysplasia; 2, moderate dysplasia; 3, severe dysplasia). The dermatopathologists were blinded as to whether the naevi were from melanoma subjects or controls. Multivariate analyses were performed to determine if there was an independent association between the degree of histological dysplasia in naevi and a personal history of melanoma.

Results In persons with naevi receiving an average score of > 1 (i.e. naevi considered to have greater than mild histological dysplasia), there was an increased risk of melanoma [odds ratio (OR) 2·60, 95% confidence interval (CI) 0·99–6·86] which persisted after adjustment for confounders (OR 3·99, 95% CI 1·02–15·71). Very few dermatopathologists reliably graded naevi of subjects with melanoma as being more dysplastic than naevi of control subjects. Among the entire group, the interobserver reliability associated with grading histological dysplasia in naevi was poor (weighted kappa 0·28).

Conclusions HDN do appear to confer an independent risk of melanoma. However, this result may add more to our biological understanding of melanoma risk than to clinical assessment of risk, because HDN assessed by a single pathologist generally cannot be used to assess risk of melanoma. Future studies should be directed at establishing reproducible, predictive criteria for grading naevi.

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Conflicts of interest
None declared.

The atypical or dysplastic melanocytic naevus accounts for 650 000 new patient visits annually to U.S. dermatologists.[1] It is a defining feature of melanoma high-risk groups such as the atypical mole syndrome, although it occurs much more commonly as a sporadic finding in otherwise healthy individuals. Despite their prevalence, sporadic dysplastic naevi remain a poorly defined entity. A recent survey of dermatologists suggests that there exists a substantial degree of variation in how the dysplastic naevus is defined and treated.[1] Others remain sceptical of its existence.[2] When defined clinically (pigmented lesions > 5 mm with any number of features including colour variegation, border irregularity and asymmetry) atypical naevi appear to confer an independent risk for malignant melanoma.[3–8] However, the histopathological correlates of clinical atypia are inconsistent,[9] and while some advocate defining the dysplastic naevus histologically,[10,11] no study has determined melanoma risk associated with histological dysplasia. Previous studies have found melanocytic dysplasia to be a common histological finding in the general white-skinned population, suggesting that it is not a strong predictor of melanoma.[12]

Given this controversy, we utilized a case–control design to evaluate the risk of invasive malignant melanoma associated with histologically dysplastic naevi (HDN). We further examined whether this relationship was independent of the effects of naevus count or the presence of large naevi, which are risk factors for melanoma[4,5,7,13] and correlate with dysplastic naevi.[14]

Patients and methods

Subject selection

Eighty cases of invasive malignant melanoma were enrolled between 1998 and 2001. Cases were patients with incident melanoma under evaluation in outpatient dermatology and oncology clinics at the University of Washington Medical Center. In addition, 80 unaffected spousal controls were accrued. In two cases, same-sex domestic partners were enrolled as controls. A matched design was chosen to minimize variation in other risk factors (thus increasing precision of the model), as spouses tend to be matched on a number of important melanoma risk factors such as race, residence and socioeconomic status. Spouses were also selected as the control group because they are typically motivated to participate in medical studies, and we asked controls to undergo a cutaneous examination and biopsy. The study was approved by the Institutional Review Board of the Human Subjects Division, University of Washington Medical Center.

Data collection

Full cutaneous examinations were performed by a dermatology fellow (S.K.). The most clinically atypical macular naevus was biopsied in both cases and controls. Clinical atypia was subjectively assessed by a combination of size, macularity, colour variegation, asymmetry and border irregularity. Thirteen dermatopathologists separately reviewed all histological sections blinded to the status of the subject, and each assigned a dysplasia score of: 0, no dysplasia; 1, mild dysplasia; 2, moderate dysplasia; or 3, severe dysplasia. All dermatopathologists have a special interest in melanocytic lesions and interpret atypical (dysplastic) naevi on a daily basis. In order to re-create the current standard of practice, there was no discussion or consensus about criteria in grading histological dysplasia prior to the review of the study set. All the dermatopathologists graded dysplasia by the criteria they use in their daily practice, based on their understanding of the medical literature. The basic features of naevomelanocytic dysplasia have been published elsewhere.[10,15,16]

Naevus counts were performed on the back. An individual was considered to have large naevi if a single naevus on the back measured > 5 mm. Freckles on the shoulders (0–10, 11–50, > 50) were likewise tabulated, in addition to eye colour and Fitzpatrick skin type (I–VI). Hair colour was obtained by asking the participant their natural hair colour at 15 years. Enrolled subjects completed a questionnaire concerning demographic characteristics including age, education, income, current residence, birth residence and occupation. In addition, information on personal cancer history (all-site cancer history and specifically nonmelanoma and melanoma skin cancers) and family history of melanoma in first-degree relatives was obtained. Sunburn history was defined as the lifetime number of blistering sunburns. Sensitivity to intermittent and chronic sun exposure was estimated by asking participants their tendency to burn ('If your skin is exposed to strong sunlight for the first time in summer for 1 h, would you: get a severe sunburn with blistering; have a painful sunburn for a few days followed by peeling; get mildly burnt followed by some degree of tanning; tan without any sunburn?') and ability to tan ('After repeated and prolonged exposure to sunlight your skin becomes: deeply tanned; moderately tanned; only mildly tanned; only freckled or no suntan at all?'). Other estimates of ultraviolet (UV) exposure were obtained, including the number of weeks spent in sunny resorts, use of tanning beds or use of UV radiation for medical conditions.

Data analysis

The three main risk factors of interest were the dysplasia score of the most clinically atypical naevus (obtained as a group average of each dermatopathologist's score), number of naevi on the back and presence or absence of a large naevus. Risk of melanoma associated with dysplasia was calculated for individual pathologists as well as for the overall group-averaged dysplasia score. The average score is reported as a dichotomous variable (≤ 1 and > 1). Several cutoffs were considered. The strongest risk of melanoma was seen for naevi with an average dysplasia score of > 1. Because this group can also be interpreted as naevi with greater than mild dysplasia, it was chosen as the cutoff. A weighted kappa statistic was calculated to estimate the interobserver reliability between pathologists in grading mild, moderate, severe and no dysplasia. A weighted

kappa statistic accounts for the magnitude of disagreement when using ordinal data.[17]

Given the inherent matching with a spousal referent group, conditional logistic regression was performed in all analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) for the relation between the risk factors and melanoma risk were computed as age- and sex-adjusted ORs, as well as a fully adjusted OR, which included adjustment of all confounders. Inclusion of potential confounders in the fully adjusted model was determined by addition of the strongest predictors in a stepwise fashion into the logistic regression model. To establish the relative contribution of large naevi, naevus counts and histological dysplasia to melanoma risk, each of these variables was also reported with mutual adjustment of the other predictors. Data analysis was performed using Intercooled STATA 8.0 software (College Station, TX, U.S.A.).

Results

Table 1 presents the distribution of demographic and melanoma risk factors in the study and gives the estimated risk of melanoma associated with these factors in this population. Cases were 56% male, with a mean age of 47 years (range 25–75), and controls were 41% male with a mean age of 48 years (range 23–77). Given that spouses are to some extent matched on age, CIs for the risk of melanoma with age were wide and nonsignificant, although cases tended to be older than controls. Both groups were generally college educated. More cases than controls attended college or obtained a graduate degree, and while this was not statistically significant, variance estimates were wide, consistent with some degree of matching. History of nonmelanoma skin cancer was strongly associated with melanoma risk, as to a lesser extent was family history of melanoma. Personal characteristics such as red or blond hair, blue or green eyes, and Fitzpatrick skin type I and II were all associated with melanoma risk. More than 50 freckles on the shoulder was a significant risk factor for melanoma (OR 3·72, 95% CI 1·23–11·24). A lifetime history of more than six blistering sunburns was also statistically significant (OR 4·58, 95% CI 1·23–17·00). More cases than controls had a strong tendency to burn and no or mild ability to tan.

Table 2 presents the estimated risk of melanoma associated with histological dysplasia in naevi, presence of a large naevus (> 5 mm) on the back, and naevus counts on the back. ORs and 95% CIs were calculated after adjustment for age and sex, as well as in a full model that included the dysplasia score, naevus counts on the back and large naevi, as well as eye colour, Fitzpatrick skin type, history of severe sunburns and family history of melanoma. The presence of at least one large naevus on clinical examination was not significantly associated with melanoma risk (age- and sex-adjusted OR 1·81, 95% CI 0·75–4·37, fully adjusted model OR 2·52, 95% CI 0·67–9·42). Naevus counts were associated with melanoma risk (for ≥ 10 naevi on back: age- and sex-adjusted OR 3·68, 95% CI 1·38–9·80, P for trend 0·01, fully adjusted model OR 4·25, 95% CI 0·99–18·3, P for trend 0·04). Average dysplasia scores were low, with only 17·5% of specimens receiving an average score > 1, and only one biopsy receiving an average score > 2. An average dysplasia score of > 1 was associated with a statistically significantly increased risk of melanoma in the age- and sex-adjusted model (OR 2·60, 95% CI 0·99–6·86), and remained an independent risk factor after adjustment for number of naevi and other risk factors (OR 3·99, 95% CI 1·02–15·71).

Table 3 presents each individual pathologist's dysplasia score. This reflects to what degree melanoma subjects' naevi

Table 1 Age- and sex-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for risk of melanoma

Risk factor	Cases	Controls	OR (95% CI)
Sex			
Female	35	47	1
Male	45	33	1·25 (0·78–2·02)
Age (years)			
< 41	27	28	1
41–51	26	29	1·47 (0·12–18·03)
> 51	27	23	3·37 (0·21–55·12)
Education			
High school	13	17	1
College	51	49	2·23 (0·75–6·64)
Graduate degree	15	14	2·56 (0·61–10·83)
History of NMSC			
No	65	77	1
Yes	14	3	11·89 (1·52–92·53)
Family history of melanoma			
No	61	73	1
Yes	17	7	2·91 (1·05–8·10)
Hair colour			
Brown/black	49	63	1
Red/blond	31	17	2·72 (1·23–6·03)
Eye colour			
Brown	8	24	1
Blue	42	37	5·4 (1·55–18·83)
Green	30	19	9·08 (2·27–36·29)
Fitzpatrick skin type			
III/IV	48	60	1
I/II	32	20	2·25 (1·10–4·60)
Freckles, shoulders			
0–10	17	31	1
11–50	22	18	2·62 (0·94–7·31)
> 50	41	31	3·72 (1·23–11·24)
Blistering burns (lifetime)			
None	10	18	1
1–3	37	39	2·12 (0·67–6·63)
4–6	12	12	2·54 (0·61–10·54)
> 6	20	11	4·58 (1·23–17·00)
Tendency to burn			
Mild or no burn	43	49	1
Severe or painful burn	36	31	1·37 (0·70–2·68)
Ability to tan			
Moderate to deep	50	56	1
None or mild	29	20	2·16 (0·99–4·72)

NMSC, nonmelanoma skin cancer.

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) reporting the relative contribution of histological dysplasia in naevi,[a] naevus counts and presence of at least one large naevus (> 5 mm) towards melanoma risk

Risk factor	Cases	Controls	OR (95% CI)[b]	OR (95% CI)[c]
Average dysplasia score				
≤ 1	61	71	1	1
> 1	19	9	2·60 (0·99–6·86)	3·99 (1·02–15·71)
Naevi on back				
0–4	12	23	1	1
5–9	17	28	1·27 (0·48–3·34)	0·71 (0·19–2·69)
≥ 10	51	29	3·68 (1·38–9·80)	4·25 (0·99–18·3)
P for trend			0·01	0·04
Naevi > 5 mm				
None on back	57	65	1	1
At least 1 on back	23	15	1·81 (0·75–4·37)	2·52 (0·67–9·42)

[a]Most clinically atypical naevus biopsied, and average histological dysplasia scores determined by North American Dysplastic Nevus Panel. [b]Age- and sex-adjusted. [c]Mutual adjustment of other risk factors, in addition to adjustment for age, sex, eye colour, Fitzpatrick skin type, history of severe sunburns and family history of melanoma.

demonstrated more histological dysplasia than naevi from control subjects, as graded by individual pathologists blinded to the status of cases and controls. Of the 13 pathologists, only one had scores which significantly correlated with melanoma risk. This individual graded naevi more often as moderate or severe in melanoma subjects (OR 5·52, 95% CI 1·13–26·97), although the scores of several others had high but not statistically significant ORs. Interobserver reliability was poor, with a weighted kappa statistic of 0·28. However, when a group average was used, the histological grading was predictive of melanoma.

Discussion

We found HDN to be more common in patients with melanoma than in controls. This association was independent of naevus counts, as well as other well-known risk factors for melanoma. Our utilization of 13 pathologists provides stability to an entity which is variably defined and recognized. While there are numerous case–control studies examining the importance of clinically atypical naevi, this is the first study designed to evaluate an independent melanoma risk associated with HDN.

Several previous studies have suggested an association between HDN and melanoma. In a retrospective review of HDN, persons with a history of melanoma were more likely to have a severely (OR 4·08, 95% CI 2·91–5·7) or moderately (OR 1·45, 95% CI 1·13–1·87) dysplastic naevus vs. a mildly dysplastic naevus. This study depended on providers reporting a melanoma history in the pathology accession, and adjustment for other confounders such as naevus counts could not be performed.[18] A similar study of archived pathology data found that 57% of persons with HDN had a history of melanoma, while if the naevus was considered 'questionably dysplastic' or nondysplastic, only 25% and 18% had a history of melanoma, respectively.[19] Bergman *et al.*[20] similarly reported that markedly atypical naevi were more likely to arise in persons with a history of melanoma. Half of their cohort belonged to melanoma kindreds, a small subpopulation clearly at increased risk of melanoma, making the results difficult to interpret.

Other studies have not demonstrated a relationship between melanoma risk and histological dysplasia. Piepkorn *et al.*[12] found mild dysplasia in the naevi of 7–32% of a healthy population, suggesting that dysplasia is common and not a strong predictor of melanoma. Another study compared naevi from persons with dysplastic naevi with a control population, finding a nonsignificant trend towards more dysplasia among the group with dysplastic naevi. No adjustments for confounders could be performed.[15] Klein and Barr[21] examined clinically benign naevi in healthy individuals, and found that 88% had at least one feature of dysplasia, and 29% had three features. Our study does demonstrate an independent risk associated with HDN, although the interpretation of our cutoff is important. All naevi in the study (both cases and controls) were graded as at least mildly dysplastic by at least one pathologist. The excess risk was seen only in naevi in which the group average was > 1, or naevi in which the average group score was greater than mild. Most naevi graded as mild by an individual pathologist are not associated with an increased risk of melanoma. These results are also corroborated by a previous study showing that one begins to observe DNA aneuploidy in dysplastic naevi that are graded as moderately atypical.[22]

HDN appear to be an independent risk factor for melanoma, perhaps reflecting the pleiotropic effects of genetic and environmental aetiological factors that are common between the two entities. A population-based study evaluated biopsies of the two most clinically atypical naevi from a single individual, and demonstrated a significant correlation, suggesting that some persons have a predisposition to melanocytic dysplasia.[23] Some argue that a substantial proportion of melanomas arises from dysplastic naevi. Our study was not designed to examine any potential precursor role of the HDN. To date, no study has evaluated the prophylactic excision of dysplastic naevi as a modality of melanoma prevention.

Table 3 Risk of melanoma for individual pathologists' interpretation of dysplasia

Pathologist	Cases	Controls	OR (95% CI)[a]
1			
No dysplasia	34	37	1
Mild dysplasia	34	27	1·35 (0·64–2·82)
Moderate or severe dysplasia	12	16	0·64 (0·24–1·65)
2			
No dysplasia	29	29	1
Mild dysplasia	40	44	0·75 (0·35–1·59)
Moderate or severe dysplasia	11	7	1·32 (0·41–4·18)
3			
No dysplasia	37	36	1
Mild dysplasia	20	26	0·67 (0·29–1·59)
Moderate or severe dysplasia	23	18	1·07 (0·47–2·47)
4			
No dysplasia	48	51	1
Mild dysplasia	26	26	1·00 (0·49–1·99)
Moderate or severe dysplasia	6	3	2·01 (0·44–9·29)
5			
No dysplasia	58	66	1
Mild dysplasia	19	12	1·61 (0·72–3·61)
Moderate or severe dysplasia	3	2	1·50 (0·24–9·51)
6			
No dysplasia	49	53	1
Mild dysplasia	22	25	0·86 (0·41–1·81)
Moderate or severe dysplasia	9	2	7·05 (0·85–58·33)
7			
No dysplasia	44	44	1
Mild dysplasia	29	35	0·84 (0·44–1·61)
Moderate or severe dysplasia	7	1	6·20 (0·72–52·63)
8			
No dysplasia	37	46	1
Mild dysplasia	25	19	1·52 (0·72–3·22)
Moderate or severe dysplasia	18	15	1·30 (0·54–3·12)
9			
No dysplasia	40	52	1
Mild dysplasia	30	24	1·65 (0·80–3·44)
Moderate or severe dysplasia	10	4	5·02 (0·96–26·39)
10			
No dysplasia	27	32	1
Mild dysplasia	32	35	0·98 (0·49–1·98)
Moderate or severe dysplasia	21	13	2·00 (0·76–5·23)
11			
No dysplasia	37	37	1
Mild dysplasia	24	31	0·65 (0·30–1·39)
Moderate or severe dysplasia	19	12	1·50 (0·53–4·25)
12			
No dysplasia	44	49	1
Mild dysplasia	23	26	0·85 (0·43–1·70)
Moderate or severe dysplasia	13	5	5·52 (1·13–26·97)
13			
No dysplasia	67	72	1
Mild dysplasia	12	8	2·13 (0·75–6·01)
Moderate or severe dysplasia	1	0	2·3E+14 (0–∞)

OR, odds ratio; CI, confidence interval. [a]Age- and sex-adjusted odds ratios. Interobserver reliability for no, mild, moderate or severe dysplasia was estimated as poor (weighted kappa statistic 0·28).

Several limitations should be mentioned. The potential for recall bias exists for many of our covariates such as personal or family history of cancer, number of sunburns and sun sensitivity. Assessment of pigmentary characteristics by a single clinical dermatologist unblinded to the status of subjects is a possible source of bias. In addition, having a single

dermatologist choose the most clinically atypical naevi may not be generalizable. However, it is difficult to imagine how this might have systematically contributed to a bias. Importantly, no biopsied specimen was considered to be an entity other than a melanocytic naevus by the majority of pathologists. If melanomas removed in the cases arose from HDN, our estimates of risk associated with HDN may be conservative. Lastly, the cumulative dysplasia scores were low, which accounts for the variance in our estimates of the risk associated with moderate to severe dysplasia.

The variability in grading of dysplasia is troubling. Our kappa statistic of 0·28 reflects agreement on a group of naevi which were on average mildly dysplastic and cannot be compared directly with previous studies that have examined samples more representative of the spectrum of atypia. None the less, most other studies demonstrate similar poor to fair interobserver reliability.[12,24] When predefined criteria are used, interobserver agreement generally improves somewhat.[25–27] Future studies should determine which histological features are most useful in predicting melanoma risk so that universal criteria can be developed.

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