Are Atypical Nevi a Risk Factor for Uveal Melanoma? A Case-Control Study

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Atypical nevi and other potential risk factors for uveal melanoma were studied in 109 uveal melanoma patients and 149 controls. Information concerning employment, medical history, drug use, family history of cancer, excess sun exposure, and blistering sunburn before and after the age of 15 was obtained. A total skin examination was performed and skin type, hair color, eye color, freckles, actinic damage, the total number of common acquired nevi, and the number of clinically atypical nevi were noted.

More atypical nevi were found in uveal melanoma patients than in controls (age- and sex-adjusted odds ratio of 2.9 [95% confidence interval 1.2–6.3] for one or two atypical nevi versus none; odds ratio of 5.1 [95% CI 1.3–20.0] for three or more atypical nevi versus none). Light skin types and freckling also prevailed in uveal melanoma cases.

In our study, atypical nevi are more common in uveal melanoma patients than in controls. Further studies will have to indicate whether risk factors comparable to those for cutaneous melanoma really exist for uveal melanoma. *Key words: dysplastic nevi/ocular melanoma/FAMMM syndrome. J Invest Dermatol 103:202–205, 1994*

Atypical nevi (synonyme dysplastic nevi, atypical moles) are well-known precursors of familial and sporadic cutaneous melanoma. Members of Familial Atypical Multiple Mole Melanoma (FAMMM) families harbor an extremely high melanoma risk. Apart from atypical nevi, risk factors for cutaneous melanoma are fair skin and hair color, blue eyes, a tendency to freckle, a tendency to burn rather than tan, a history of sunburn, especially in childhood, and indoor occupations with outdoor recreational lifestyles [1,2].

Risk factors for uveal melanoma are less well defined, although ultraviolet (UV)-light exposure and host factors such as eye color have been implicated [3–5]. The relationship between uveal melanoma and atypical nevi has yet to be clarified. Uveal melanoma, which comprises 80% of all malignant intraocular tumors in adults, is a potentially lethal tumor with a 5-year mortality of 14–51%. Its prognosis depends in part on tumor size, extrascleral invasion, and intravascular invasion, factors that may be influenced positively by early detection [6]. Apart from having a better prognosis, tumors that are detected early are smaller and may be treated conservatively such as with radiation therapy, thus saving the globe and part of the visual field.

The aim of this study was to determine the role of atypical nevi and other potential risk factors (such as those known for cutaneous melanoma) as risk indicators for uveal melanoma.

The incidence of atypical nevi and other potential risk factors was studied in 109 uveal melanoma patients and 149 controls between March, 1990 and March, 1992.

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MATERIALS AND METHODS

The cases were 109 patients with melanoma of the uveal tract (choroid, ciliary body, and iris) who consecutively visited the ophthalmology department of Leiden University Hospital. The diagnosis of uveal melanoma was confirmed either histopathologically (in 41 enucleated cases) or was based on standard diagnostic methods: funduscopy, fluorescence-angiography, echography, and visual field studies.

Sixty-six cases, a relatively large number, were treated with radiation therapy. Leiden is the referral center for this treatment in the Netherlands. To be selected for radiation therapy tumors must have a diameter smaller than 15 mm, prominate less than 5 mm, and they must not be situated at the optic nerve, preferably not at the fovea. Patients were asked by their ophthalmologist to participate in the study. All but two agreed.

The control group was drawn from three sources: patients attending the ophthalmology out- or inpatient department for reasons other than melanoma, patients attending several general practitioner clinics in the area, and patients attending our dermatology clinic for reasons other than pigmented lesions. Controls were asked by CvH or MBC to participate as they waited for their consultation. Of the 218 people approached, 201 agreed. Some reasons given for refusal were: "I do not participate in surveys", "Don't have time", or "The skin examination is too much bother" (especially among the elderly). Originally, 17 controls who had been admitted to have cataract surgery were also included. These were excluded from the study later to prevent selection bias, as UV exposure is a possible risk factor for cataract [7]. Cases were significantly older than controls, which creates difficulties in interpreting odds ratios for a strongly age-dependent risk factor such as atypical nevi. Two steps were taken to deal with this problem: 1) all cases (2) and controls (35) under age 30 were eliminated, and 2) adjustment for age was performed by decade in the final analysis. Of the remaining 149 controls, 45 were recruited from the ophthalmologic department, 36 from the dermatologic department, and 68 from general practice. All cases and controls were recruited between March, 1990 and March, 1992.

All participants were seen initially by one of us (CvH). Information was obtained about employment, medical history, drug use, family history (with specific reference to the occurrence of cancer in first-degree relatives), excess sun exposure before and after the age of 15 (having spent holidays or lived in subtropical or tropical countries), and blistering sunburn before and after the age of 15. A total skin examination was performed and skin type, hair color,

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Table I. Age and Gender Distribution of Patients with Uveal Melanoma and Control Patients

	Cases (n = 109)	Controls (n = 149)
Age		
30–39	5 (5%)	56 (38%)
40–49	9 (8%)	22 (15%)
50–59	26 (24%)	18 (12%)
60–69	37 (34%)	27 (18%)
70–79	26 (24%)	21 (3%)
80–89	6 (5%)	5 (3%)
Gender		
Male	47 (43%)	57 (38%)
Female	62 (57%)	92 (62%)

eye color, freckles, actinic damage, the total number of common acquired nevi, and the number of clinically atypical nevi were noted.

Atypical nevi were defined as nevi that showed three or more of the following criteria: size of 5 mm or larger, variegated pigmentation, hazy border, vascular hue (erythema), and asymmetry of shape. Patients with atypical nevi were seen immediately by a second investigator (MBC or WB) or the lesions were photographed and judged by a second investigator later (on slide, twice the actual size). In 11 cases and 10 controls excision was performed. A dermatopathologist evaluated the histology. The histologic diagnosis included features of architectural atypia, cellular atypia, and a stromal reaction [8]. All excised specimens fullfilled these criteria.

Skin types were defined as follows: skin type I did not tan at all but burned and freckled instead; skin type II tanned only after repeated sun exposures, often after mild or moderate sunburn and freckling; skin type III tanned easily and did not burn. Freckles were either "present" or "absent." Actinic damage (pigmentary changes, lentigines, actinic keratosis, and atrophy) was judged as being "normal for age" or "more than expected."

For further analysis several categories were created. For hair color 2 categories, dark brown and brown were classified as "dark," blond and red as "light." As a substantial number of participants had grey, white, or no hair, we inquired about hair color at age 20. Eye color (brown, green, grey, or blue) was also divided into two groups: "brown" versus "others" (the same calculations were made for "blue" versus "others" and the outcome was similar). The total number of common acquired nevi 2 mm or larger in diameter were counted and categorized as follows: 0–24 nevi, 25–49 nevi, and 50 or more nevi.

Crude odds ratios and 95% confidence intervals (CI) were obtained for each variable by cross-tabulation according to Woolf [9]. Analyses simultaneously controlling for several confounders were performed by logistic regression (Egret Statistics and Epidemiology Research Corporation, Seattle, WA).

RESULTS

Table I shows the age and sex distribution of cases and controls, and the age categories used in the analysis when controlling confounding. Although there was no significant gender difference between cases and controls, women outnumbered men in both groups. Table II shows the mean age and number of atypical nevi found in cases and controls per source (see *Materials and Methods*).

Atypical nevi were related to uveal melanoma in our data. Crude odds ratios did not yield a statistically significant result, nor did stratum-specific odds ratios with 95% CIs for three age categories. Logistic regression analysis with adjustments made for age by decade and sex yielded increased and statistically significant odds ratios

Table II. The Mean Age and Number of Atypical Nevi (AN) Found in Controls from Three Sources and in Cases

	Mean Age (years)	AN 0	AN 1+2	AN 3+	Number of Patients
Ophthalmologic	61.6	41	4	0	45
Dermatologic	55.3	31	4	1	36
General practice	41.3	50	12	6	68
Cases	62.5	79	21	8	109

Table III. Atypical Nevi (AN) in Patients with Uveal Melanoma and Control Patients

	Cases (%)	Controls (%)	Odds Ratio	95% Confidence Interval
Crude Odds Ratio				
AN 0	79 (73)	122 (82)	1	
AN 1+2	21 (19)	20 (13)	1.62	0.8–3.2
AN 3+	8 (7)	7 (5)	1.72	0.6–5.0
Odds Ratio Specified for Age[a]				
Age 30–49				
AN 0	9 (69)	55 (70)	1	
AN 1+2	2 (15)	16 (20)	0.76	0.2–3.9
AN 3+	2 (15)	7 (9)	1.75	0.3–9.8
Age 50–69				
AN 0	47 (75)	41 (91)	1	
AN 1+2	13 (21)	4 (10)	2.8	0.9–9.4
AN 3+	3 (5)	0[b]	5.2	0.3–107.6
Age 70+				
AN 0	23 (72)	26 (100)	1	
AN 1+2	6 (19)	0	13.6	0.7–256.4
AN 3+	3 (9)	0	6.8	0.3–142.7
Logistic Regression[c]				
AN 0			1	
AN 1+2			2.9	1.2–6.7
AN 3+			5.3	1.3–20

[a] Age categories were obtained by adding two subsequent categories of the original six categories shown in Table I.

[b] To enable calculation of OR and CI despite zero numbers in some groups, 0.5 was added to each zero number.

[c] OR adjusted for age (using the 6 age categories shown in Table I) and sex.

Table IV. The Number of Atypical Nevi (AN) in Uveal Melanoma Patients Compared to Controls

Regression Terms (Always Including Age and Sex)	Odds Ratio	95% Confidence Interval
Sun < 15	AN 1+2 3.2	1.3–7.5
	AN 3+ 5.7	1.5–22.5
Sun > 15	AN 1+2 3.1	1.3–7.3
	AN 3+ 5.7	1.5–22.4
Burn < 15	AN 1+2 3.0	1.3–7.0
	AN 3+ 5.7	1.4–23.6
Burn > 15	AN 1+2 3.2	1.3–7.5
	AN 3+ 5.9	1.5–23.1
Skin type	AN 1+2 3.2	1.3–7.8
	AN 3+ 6.2	1.5–24.7
Eye color	AN 1+2 3.0	1.3–7.1
	AN 3+ 5.4	1.4–21.2
Common nevi	AN 1+2 4.0	1.6–10.1
	AN 3+ 10.3	2.0–52.3
Freckles	AN 1+2 2.3	1.2–6.8
	AN 3+ 5.1	1.3–19.9
Actinic damage	AN 1+2 3.0	1.3–7.1
	AN 3+ 5.5	1.4–21.3
Family history of malignancies	AN 1+2 3.0	1.3–7.1
	AN 3+ 5.3	1.3–20.8
Sun < 15, sun > 15, burn < 15, burn > 15	AN 1+2 3.4	1.4–8.3
	AN 3+ 6.8	1.6–28.8
Sun < 15, sun > 15, burn < 15, burn > 15, skin type, hair color, eye color, common nevi, freckles, actinic damage, familial malignancies	AN 1+2 5.3	1.8–15.0
	AN 3+ 13.9	2.3–84.8
Sun < 15, sun > 15, burn < 15, burn > 15, skin type, hair color, eye color, common nevi, freckles, actinic damage	AN 1+2 5.1	1.8–14.2
	AN 3+ 15.1	2.5–91.2

(Table III). Analyses adjusting for different combinations of potential risk factors did not change this finding; they resulted in similar or higher odds ratios, which had large CIs and remained statistically significant (Table IV). They did not influence the final outcome concerning atypical nevi.

Skin type and freckles were related to uveal melanoma in these data. Skin type II just reached statistical significance; skin type I did not. The found association of the disease with freckles correlates with the finding for skin type (Table V).

Excess sun exposure and blistering sunburn, in the first 15 years of life and thereafter, did not relate to uveal melanoma in our study. Of these four factors only "sun exposure before age 15" had an odds ratio greater than unity, but with a very wide CI. More controls than cases had 25–49 common acquired nevi. This difference disappeared for more than 50 common acquired nevi. There was also no difference in actinic damage, hair color, and eye color (Table V).

Four cutaneous melanomas were found among our study participants, two in the case group and two in the control group. One superficial spreading melanoma (Breslow thickness 0.3 mm) was situated on the lateral lower leg of a 67-year-old female uveal melanoma patient and another superficial spreading melanoma (Breslow thickness 0.3 mm) on the calf of a 78-year-old female control patient. A melanoma *in situ* was removed from the lower leg of a 54-year-old female patient and another from the back of a 45-year-old male control.

The family history with regard to cancer yielded some interesting data. Five cases had a family history of cutaneous or ocular melanoma, compared to two controls. Different types of cancer were found in cases and controls, with a trend towards a positive association with uveal melanoma.

DISCUSSION

In our study, atypical nevi were associated with uveal melanoma. Light skin types and freckles showed a slight association. Excess sun exposure, blistering sunburn, and the total number of common acquired nevi were not related to uveal melanoma.

Before accepting these results some methodologic points must be considered. Controls were recruted from several medical centers and comprised people with different medical conditions, to avoid the risk of running into unknown associations. An example of such a potential problem is our original intention to incorporate cataract patients into our control group. These were eventually excluded because of the relationship between cataract and sun exposure [7]. The use of controls with several conditions is a well-known strategy to spread the risk of unknowingly introducing associations with the exposure under study [10].

Atypical nevi were always judged by two investigators, either directly upon physical examination or later on slide by a second investigator. A nevus needed to exhibit at least three of the previously described criteria to be judged clinically atypical. In 11 cases and 10 controls histologic examination of an excisional biopsy was performed and dysplasia confirmed.

In the analysis, age adjustment was necessary because controls were much younger than cases. We tackled this problem in two ways: first, all cases and controls under age 30 were eliminated; second, the final analysis was performed using six 10-year age cate-

Table V. Excess Sun Exposure, Blistering Sunburn, Skin Type, Hair Color, Eye Color, Common Acquired Nevi, Freckles, Actinic Damage, and Maligancies in 1st-Degree Relatives and Risk of Uveal Melanoma

	Cases (n = 109)	Controls (n = 149)	Crude Odds Ratio	95% CI	Adjusted Odds Ratio[a]	95% CI
Sun < 15						
No	98	133	1.0		1.0	
Yes	9	16	0.8	0.3–1.8	1.5	0.5–4.2
Sun > 15						
No	56	50	1.0		1.0	
Yes	51	99	0.5	0.3–0.8	0.6	0.4–4.3
Burn < 15						
No	91	99	1.0		1.0	
Yes	16	50	0.4	0.2–0.7	0.5	0.2–1.0
Burn > 15						
No	76	87	1.0		1.0	
Yes	31	62	0.6	0.3–1.0	0.6	0.4–1.2
Skin type						
III	18	55	1.0		1.0	
II	76	77	3.0	1.6–5.6	2.5	1.2–5.1
I	13	17	2.3	1.0–5.7	2.2	0.8–6.0
Hair color						
Dark	81	100	1.0		1.0	
Light	26	48	0.7	0.4–1.2	0.7	0.4–1.3
Eye color						
Dark	24	32	1.0		1.0	
Light	83	117	0.9	0.5–1.7	0.9	0.4–1.7
Nevi						
0–24	94	93	1.0		1.0	
25–49	7	31	0.2	0.1–0.5	0.3	0.1–0.8
50+	6	25	0.2	0.1–0.6	0.8	0.3–2.4
Freckles						
Absence	33	67	1.0		1.0	
Presence	75	82	1.9	1.1–3.1	1.9	1.1–3.4
Actinic damage						
Normal	87	125	1.0		1.0	
More	20	24	1.2	0.6–2.3	1.1	0.5–2.2
Familial malignancies						
0	45	88	1.0		1.0	
1	38	45	1.7	0.9–2.9	1.2	0.7–2.3
2+	24	16	2.9	1.4–6.1	1.6	0.7–3.4

[a] Odds ratio adjusted for age and sex.

gories to reduce confounding. One may still wonder whether the strata are fine enough, but should keep in mind that in these age ranges, atypical nevi are more common at younger ages. Therefore if the age adjustment is inadequate, it should artificially lower the odds ratio, not raise it.

No association was found between excess sun exposure or blistering sunburn and uveal melanoma (although blistering sunburn before age 15 showed a trend towards being protective). UV exposure as a risk factor for uveal melanoma has been studied before, in telephone interview and retrospective studies. Seddon *et al* [3], Holly *et al* [4], and Tucker *et al* [5] found an association of uveal melanoma with some UV-related factors, but not with others. Schwartz *et al* [11] dispute a relationship between sun exposure and ocular melanoma. The issue remains controversial.

There was no difference in the presence of large numbers of common acquired nevi (more than 50). Controls more frequently belonged to the middle category of people with 24–49 nevi. It was quite remarkable that very few common acquired nevi were found in older age groups. Atypical nevi are generally related to larger numbers of nevi so both nevi categories would be expected to be associated with uveal melanoma. An explanation for this finding may be that common nevi tend to regress with age [12,13]. Perhaps it is so that whereas common nevi regress with age, atypical nevi persist.

Skin types I and II prevailed in the case group, which is consistent with the findings of Seddon *et al* [3], Holly *et al* [4], and Gallagher *et al* [14]. As lighter skin types have more freckles, the finding of more freckles in the case group complies with this.

Eye color did not relate to uveal melanoma in these data. This was also found in an earlier study [3] but is not supported by the findings from other studies [4,5,14], in which people with brown eyes had a somewhat lower uveal melanoma risk than those with green, grey, or blue eyes. Hair color showed no association with the disease. A relationship with red or blond hair was found by one other author [14].

The association between uveal melanoma and atypical nevi appeared after correction for age, as can be seen in Table III. Logistic regression analysis was also performed adjusting for different combinations of the other potential risk factors. The results of these analyses are shown in Table IV. They invariably yielded statistically significant odds ratios.

In a recent study by Bataille *et al* [15] findings similar to ours are reported. The finding of more atypical nevi in patients with uveal melanoma suggests a common (genetic?) predisposition for their development, which perhaps needs an external variable to come to expression. UV radiation has been suggested to be such a factor. Our data do not support this hypothesis. The finding of several cutaneous melanomas in uveal melanoma patients and their first-degree relatives in this study supports the idea of a genetic predisposition for pigmented lesions, whether they be melanoma or atypical nevi. A number of authors have described cases and families in which uveal melanoma, cutaneous melanoma, or atypical nevi concur [15–26], thus presenting case-report evidence that the relationship exists. Uveal melanocytes share a common embryology with melanocytes of the conjunctiva and skin; they all originate in the neural crest, migrate to their respective sites during embryologic development, and may all give rise to nevi or melanomas [27].

The family history finding of a higher prevalence of several kinds of cancer in uveal melanoma patients and their first-degree relatives implies that there may be an even broader predisposition for the development of malignancies. Interpretation of these data is difficult, however, because the family histories were not verified and also in view of the age differences between cases and controls. A complete systemic cancer spectrum, in particular cancer of the gastrointestinal tract and pancreas, has been published in studies on the FAMMM Syndrome [28,29].

At present, our results are a first confirmation of anecdotal case reports and clinical impression. The question of whether there is already enough ground for clinical action cannot be answered yet on the basis of these data. Further confirmation of the strength of the association between uveal melanoma and atypical nevi will be needed.

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