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Incidence of Atypical Nevi in Olmsted County: An Epidemiological Study

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Abstract

Background—The association of atypical nevi with melanoma and other forms of skin cancer has not been clearly defined.

Methods—We studied 631 patients with first lifetime diagnosis of mild, moderate, or severely atypical nevus from 2000 through 2005, identified through a population-based approach.

Results—Age at first diagnosis differed significantly between men and women ($P<.001$). Incidence rates peaked in the second through fourth decades in women and in the third, sixth, and seventh decades in men. From 2000 through 2005, the overall age- and sex-adjusted incidence rate of all degrees of atypical nevi was 76.0 per 100,000 person-years. There were no statistically significant associations identified between the degree of atypia and the future development of basal cell carcinoma, squamous cell carcinoma, or MM ($P=.51$, $P=.28$, and $P=.19$, respectively).

Conclusion—There is no association between atypical nevi and the subsequent development of nonmelanoma skin cancer and MM. Incidence rates of atypical nevi are higher among younger women and older men. The association between degree of atypia and malignant melanoma warrants further study.

Keywords

basal cell carcinoma; dysplastic nevi; malignant melanoma; Rochester Epidemiology Project; squamous cell carcinoma

Introduction

About 5% to 10% of the US population has atypical moles (1), with the prevalence of atypical moles largely reported at between 2% and 53%, according to a literature review. However, a more accurate prevalence estimate is between 2% and 8% in young, fair-skinned adults (2). Patients with atypical nevi had an 85-fold risk of melanoma, a deadly form of

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skin cancer, according to a study of dysplastic nevi in families (3). The risk of melanoma also increased as the number of dysplastic nevi increased (3). The American Cancer Society has projected 76,100 new melanoma cases with 9,710 related deaths in 2014 (4).

Interest is growing in the study of the degree by which atypical moles affect the risk of melanoma. In a study of 80 patients with newly diagnosed melanoma whose spouses served as controls, investigators described an increased risk of another melanoma with occurrence of moles with moderate or severe atypia (5). Current data are sparse regarding the degree of atypia in moles and the risk of other, nonmelanoma skin cancers.

The Rochester Epidemiology Project was created in 1966 to allow accurate description of natural disease history in the defined population of Olmsted County, Minnesota, from linked medical records of all sources of health care available to the community (6). The Olmsted County population is mostly white, with age- and sex-specific mortality rates similar to those in the United States (7). This medical record linkage system allows population-based research while minimizing the risk of biases such as referral bias.

This study aimed to describe the incidence of mild, moderate, and severe atypical nevi in Olmsted County residents from 2000 through 2005, in addition to determining any potential association with the development of melanoma and nonmelanoma skin cancers in patients who receive a diagnosis of an atypical nevus.

Patients and Methods

Patient Selection and Data Collection

Institutional review board approval was received from the Olmsted Medical Center and Mayo Clinic, after which 631 patients with a first lifetime diagnosis of mild, moderate, or severe atypical nevus from 2000 through 2005 were identified using Rochester Epidemiology Project resources. Patients with other types of nevi or other biopsies were excluded, as were patients with an index development of atypical nevi outside the study period. Figure 1 shows the flow chart of patient selection for the study.

Atypical nevi were classified as mild, moderate, or severe per the available pathology report. We recognize that grading atypia is somewhat subjective. However, in general, the criteria used at this institution to grade atypia include, but are not limited, to architectural changes, such as circumscription, symmetry as opposed to asymmetry, confluence and cohesiveness of melanocyte nests, and maturation—including single-cell proliferation—in addition to cytologic changes, such as prominent nucleoli; cell or nuclear enlargement, or both; and monochromatic nuclei. Of the 631 patients identified within Olmsted County with an atypical nevus between 2000 and 2005, 57 had 2 atypical nevi diagnosed on the same date and 9 patients had 3 atypical nevi diagnosed on the same date. For these patients, the nevus with the highest degree of atypia was selected for analysis; if multiple nevi had the same degree of atypia, the nevus located on the trunk was analyzed.

Information was collected of a history and the subsequent development of chronic lymphocytic leukemia or non-Hodgkin lymphoma, basal cell carcinoma (BCC), squamous

cell carcinoma (SCC), and malignant melanoma (MM). Survival free of each disease was estimated with the Kaplan-Meier method for the subset of patients without a disease history. Duration of follow-up was calculated from the date of atypical nevus diagnosis to the date when the disease of interest was diagnosed or when the patient was last evaluated by a dermatologist. For example, 14 patients had a diagnosis of MM before their diagnosis of atypical nevus. Survival free of the development of MM was estimated for the 617 other patients.

Statistical Methods

Continuous features were summarized with median, interquartile range, and overall range; categorical features were summarized with frequency count and percentage. Comparisons of features with the degree of atypia (mild, moderate, and severe) were evaluated with Spearman rank correlation coefficients and Kruskal-Wallis tests. Associations of the degree of atypia with time to development of BCC, SCC, or MM were evaluated through Cox proportional hazards regression models.

Incidence rates per 100,000 person-years were calculated with incident cases of atypical nevi as the numerator and age- and sex-specific counts of the population of Olmsted County as the denominator. The denominators were obtained from a complete enumeration of the Olmsted County population provided by the Rochester Epidemiology Project (7). The population of Olmsted County is nearly all white; hence, incidence rates were directly age- and sex-adjusted to the structure of the 2010 US white population. Incident cases were grouped for years of age at diagnosis: 0-19, 20-29, 30-39, 40-49, 50-59, 60-69, and 70 and older. The relations of age-group, sex, and year of diagnosis with incidence rates were assessed by fitting Poisson regression models through the SAS procedure GENMOD (SAS Institute Inc).

Statistical analyses were performed using the SAS software package (SAS Institute Inc). All tests were 2-sided, and P values less than .05 were considered statistically significant.

Results

Characteristics collected for the 631 patients with an incident case of atypical nevi are summarized in Table 1. A comparison of selected characteristics with degree of atypia is shown in Table 2. Characteristics that showed little or no variability, such as race and ethnicity, were not compared. Survivals free of BCC, SCC, and MM with degree of atypia are summarized in Table 3. For example, 4 patients who had MM during follow-up had a severely atypical nevus at the time of their incident diagnosis. Patients with severely atypical nevi were more likely to have MM during follow-up than patients with mild and moderately atypical nevi, although this difference did not achieve statistical significance ($P=.19$).

Overall age- and sex-adjusted incidence of atypical nevi was 76.0 per 100,000 person-years. Incidence rates of age at diagnosis are summarized in Table 4 and illustrated in Figure 2; incidence rates by year of diagnosis are summarized in Table 5 and illustrated in Figure 3. There was no statistically significant change in incidence rates over time ($P=.29$). Interaction between age at diagnosis and sex was statistically significant ($P<.001$), indicating that

differences in incidence rates across age at diagnosis differed among women and men. For women, incidence rates peaked in the second, third, and fourth decades of life and then decreased with older age. For men, incidence rates peaked in the third decade of life, dropped somewhat, and then increased again in the sixth and seventh decades.

Discussion

The present study describes the overall incidence rate adjusted for age and sex for atypical nevi as 76 per 100,000 person-years. A difference in the pattern of occurrence of atypical nevi among men and women was identified (Figure 2 and Table 4). Development of atypical nevi in women was more pronounced in the second through fourth decades as opposed to men, whose rates peaked in the third decade and showed a second peak in sixth and seventh decades. Experts have suggested that painful sunburns increase the risk of melanoma and atypical nevi, as described in a cohort study of women aged 30 to 50 years who had ongoing solar and artificial ultraviolet exposure (8). It was found that melanoma risk increased with increasing sunburn severity and number of sun bathing vacations (8). The risk of developing melanoma has been examined through the lens of numbers of dysplastic nevi (9). It was shown that the risk of melanoma was increased 12-fold when there were 10 or more dysplastic nevi. However, the level of risk of developing a melanoma was not assessed with respect to varying degrees of atypia (9). Another study examined the risk of melanoma in people with nevi more than 2 mm in diameter (10). The study described higher risks of melanoma with increasing numbers, with the highest risk of 9.8 ascribed to people with more than 100 atypical nevi.

This study differs from the aforementioned studies in that it explores the data with respect to degrees of atypia and how that affects the risk of developing melanoma and nonmelanoma cancers. This study also describes the incidence of atypical nevi and explores the relations between degrees of atypia and the development of MM, BCC, and SCC. Table 3 outlines the degrees of atypia and survival-free years to development of MM, BCC, and SCC. The associations between degree of atypia and development of BCC ($P=.51$) and SCC ($P=.28$) were not significant. No association was found between having a severely atypical nevus and also having a diagnosis of MM at last follow-up ($P=.19$). The association between degree of atypia and a preexisting diagnosis of BCC did not approach significance ($P=.41$). However, patients with severely atypical nevi were significantly more likely to have preexisting diagnoses of SCC ($P=.02$) and MM ($P=.01$) than patients with mild or moderately atypical nevi. We do acknowledge, however, the possibility that having knowledge that a patient has had a previous MM could influence a pathologist in calling a nevus atypical.

One strength of the present study is the population-based approach using a cohort of patients chosen from the Rochester Epidemiology Project who had no prior history of atypical nevi. Another strength is the inclusion of all age-groups, making for a more robust study, as well as describing the actual incidence of atypia; prior studies mentioned herein have mainly gathered prevalence data. In addition, the association between all degrees of atypia and development of BCC, SCC, and MM has not been examined, to our knowledge.

This retrospective study is useful in clarifying the research questions at hand and was able to explore and describe the burden and degree of atypical nevi and their association with development of MM, BCC, and SCC (11). A weakness of this study is its retrospective design. In addition, although the total number of patients studied is robust compared with existing data, the relative number of patients with severely atypical nevi was somewhat small. This study, despite these weaknesses, accurately depicts a true incidence of atypical nevi and lays the groundwork for additional study to draw further conclusions regarding the association between the degrees of atypical nevi and the development of MM, BCC, and SCC.

Conclusion

This study has described the incidence of atypical nevi in Olmsted County. An important pattern was identified in the occurrence of atypical nevi between the sexes of all age-groups in Olmsted County—with younger women having a higher incidence of atypical nevi than men in the same age-group. This result could be due to tanning bed use during previous years of life. Currently, legislation prohibits minors from using tanning beds in Minnesota, which went into effect August 1, 2014. Older men also had a higher incidence of atypical nevi than younger men and older women. This study also describes the occurrence of MM, BCC, and SCC after a first diagnosis of atypical nevi; although the associations observed in this study were not statistically significant, this is an area of study that will benefit from further research.

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Abbreviations

BCC	basal cell carcinoma
MM	malignant melanoma
SCC	squamous cell carcinoma

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Figure 1.
Flowchart of Patient Selection.

Figure 2.
Incidence of Atypical Nevi in Men and Women.

Figure 3.
Incidence of Atypical Nevi From 2001 Through 2005.

Table 1**Demographic Information Among 631 Cases of Atypical Nevus**

Characteristic	Patients, No (%)
Year of diagnosis	
2000	88 (14)
2001	115 (18)
2002	102 (16)
2003	96 (15)
2004	112 (18)
2005	118 (19)
Age at diagnosis, median (IQR; range), y	38 (28-47; 2-88)
Age at diagnosis, y	
0-19	39 (6)
20-29	141 (22)
30-39	172 (27)
40-49	147 (23)
50-59	57 (9)
60-69	35 (6)
70	40 (6)
Sex	
Female	344 (55)
Male	287 (45)
Race (n=630)	
White	629 (>99)
Asian	1 (<1)
Ethnicity (n=630)	
Non-Hispanic	629 (>99)
Hispanic	1 (<1)
Family history of MM (n=397)	
No	308 (78)
Yes, first-degree relative	58 (15)
Yes, not first-degree relative	29 (7)
Adopted into family	2 (1)
Fitzpatrick type (n=179)	
1	37 (21)
2	95 (53)
3	39 (22)
4	8 (4)
Degree of atypical nevus	
Mild	408 (65)
Moderate	162 (26)
Severe	61 (10)

Characteristic	Patients, No (%)
History of cancer	
CLL/non-Hodgkin lymphoma	1 (<1)
BCC	32 (5)
SCC	16 (3)
MM	14 (2)

Abbreviations: BCC, basal cell carcinoma; CLL, chronic lymphocytic leukemia; IQR, interquartile range; MM, malignant melanoma; SCC, squamous cell carcinoma.

Table 2

Characteristics of 631 Patients With Incident Cases of Atypical Nevi by Degree of Atypia

Characteristic	Degree of Typia ^a			P Value
	Mild (n=408)	Moderate (n=162)	Severe (n=61)	
Year of diagnosis				
2000	62 (15)	22 (14)	4 (7)	.04
2001	85 (21)	22 (14)	8 (13)	
2002	60 (15)	27 (17)	15 (25)	
2003	59 (14)	23 (14)	14 (23)	
2004	71 (17)	33 (20)	8 (13)	
2005	71 (17)	35 (22)	12 (20)	
Age at diagnosis, median (IQR; range) y	37 (28-47; 8-83)	38 (28-46; 12-83)	42 (28-54; 2-88)	.51
Sex				
Female	210 (51)	94 (58)	40 (66)	.03
Male	198 (49)	68 (42)	21 (34)	
Education (n=561)				
8th grade or less	0	0	3 (6)	.04
Some high school	4 (1)	3 (2)	0	
High school graduate	29 (8)	25 (16)	4 (8)	
Some college	106 (30)	34 (22)	17 (33)	
College graduate	98 (27)	45 (30)	17 (33)	
Postcollege graduate	121 (34)	45 (30)	10 (20)	
Family history of MM (n=397)				
No	194 (77)	84 (77)	30 (83)	.46
Yes, first-degree relative	35 (14)	18 (17)	5 (14)	
Yes, not first-degree relative	21 (8)	7 (6)	1 (3)	
Adopted into family	2 (1)	0	0	
Fitzpatrick type (n=179)				
1	20 (19)	12 (23)	5 (25)	.45
2	57 (53)	31 (60)	7 (35)	
3	23 (22)	8 (15)	8 (40)	
4	7 (7)	1 (2)	0	
Region of atypical nevus (n=630)				
Head and neck	15 (4)	6 (4)	3 (5)	.01
Upper extremities	40 (10)	16 (10)	11 (18)	
Lower extremities	49 (12)	24 (15)	18 (30)	
Trunk	303 (74)	116 (72)	29 (48)	
Side of atypical nevus (n=609)				.04 ^b
Right	138 (35)	57 (37)	23 (38)	
Left	156 (40)	74 (47)	28 (46)	
Bilateral	1 (<1)	0	0	

Characteristic	Degree of Typia ^a			P Value
	Mild (n=408)	Moderate (n=162)	Severe (n=61)	
Central	97 (25)	25 (16)	10 (16)	
Margin positivity postbiopsy				
No	332 (81)	83 (51)	27 (44)	<.001
Yes	66 (16)	55 (34)	27 (44)	
<1.0 mm	10 (2)	24 (15)	7 (11)	
Treatment (n=618)				
WLE	92 (23)	82 (53)	57 (98)	<.001
None	313 (77)	73 (47)	1 (2)	
Days to WLE, median (IQR; range) (n=231)	18 (11-26; 0-185)	20 (14-33; 0-1,432)	20 (12-31; 0-85)	.39
History of disease				
BCC	19 (5)	8 (5)	5 (8)	.41
SCC	7 (2)	3 (2)	6 (10)	.02
MM	5 (1)	5 (3)	4 (7)	.01

Abbreviations: BCC, basal cell carcinoma; IQR, interquartile range; MM, malignant melanoma; SCC, squamous cell carcinoma; WLE, wide local excision.

^aValues are presented as number and percentage of patients unless specified otherwise.

^bPvalue calculated after excluding the 1 patient with bilateral atypical nevus.

Table 3

Survival Free of Other Diseases of Interest by Degree of Atypia

Disease and Degree of Atypia	Patients, No.	Years to Disease of Interest, Median (IQR; Range)	Survival Rate, % (95% CI; No. at risk)		P Value
			At 5 y	At 10 y	
BCC					
Mild	38	5.6 (2.6-7.7; 0.2-12.1)	93 (90-96; 194)	82 (77-88; 68)	.51
Moderate	14	6.0 (4.2-10.0; 3.8-12.2)	93 (88-99; 80)	87 (80-95; 28)	
Severe	8	7.8 (3.9-9.6; 1.0-12.2)	91 (82-100; 28)	79 (65-96; 9)	
SCC					
Mild	20	4.9 (2.7-7.5; 0.6-11.6)	96 (94-99; 209)	90 (86-95; 83)	.28
Moderate	7	5.0 (3.7-12.2; 2.1-13.3)	97 (94-100; 87)	94 (89-99; 34)	
Severe	5	3.3 (0.3-6.8; 0.1-6.9)	93 (85-100; 26)	84 (72-99; 8)	
MM					
Mild	12	7.6 (2.8-9.6; 1.7-11.7)	98 (96-100; 214)	94 (90-98; 87)	.19
Moderate	5	5.6 (3.5-8.2; 2.5-9.1)	98 (95-100; 86)	93 (87-99; 36)	
Severe	4	2.3 (1.2-3.4; 0.6-3.9)	90 (80-100; 28)	90 (80-100; 10)	

Abbreviations: BCC, basal cell carcinoma; IQR, interquartile range; MM, malignant melanoma; SCC, squamous cell carcinoma.

Table 4

Incidence Rate of Atypical Nevus in Olmsted County, Minnesota, by Age at Diagnosis, 2000-2005

Age at Diagnosis, y	Female Patients		Male Patients		Total	
	No.	Rate ^a	No.	Rate ^a	No.	Rate ^a
0-19	20	17.0	19	15.5	39	16.2
20-29	95	140.1	46	78.9	141	111.8
30-39	95	155.5	77	130.4	172	143.1
40-49	90	135.5	57	92.5	147	114.8
50-59	25	54.1	32	76.7	57	64.9
60-69	8	28.0	27	103.6	35	64.1
70	11	31.6	29	121.5	40	68.1
Total	344	75.4 ^b	287	78.4 ^b	631	76.0 ^c

^aIncidence per 100,000 person-years.^bIncidence per 100,000 person-years, age-adjusted to 2010 US white population.^cIncidence per 100,000 person-years, age- and sex-adjusted to 2010 US white population.

Table 5

Incidence Rate of Atypical Nevi by Year of Diagnosis in Olmsted County, Minnesota, 2000-2005

Year of Diagnosis	Female Patients		Male Patients		Total	
	No.	Rate ^a	No.	Rate ^a	No.	Rate ^b
2000	45	57.9	43	74.5	88	65.1
2001	70	94.6	45	78.1	115	85.0
2002	53	72.0	49	80.1	102	75.6
2003	52	70.4	44	68.7	96	69.3
2004	59	75.5	53	81.4	112	77.8
2005	65	82.3	53	87.8	118	83.3

^aIncidence per 100,000 person-years, age-adjusted to 2010 US white population.^bIncidence per 100,000 person-years, age- and sex-adjusted to 2010 US white population.