Frequency of Dermoscopic Nevus Subtypes by Age and Body Site

A Cross-sectional Study

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Objective: To subclassify acquired nevi by dermoscopic pattern.

Design: Cross-sectional study with consecutive enrollment.

Setting: Pigmented lesion clinics in referral academic medical centers.

Participants: Individuals older than 2 years undergoing total skin examination were consecutively recruited between October 1, 2008, and May 31, 2009, and, based on their age, assigned to 1 of 8 groups. For each patient, the location and dermoscopic pattern of all nevi on the torso were recorded. Nevi were dermoscopically subclassified as globular, reticular, mixed (reticular-globular) pattern with peripheral or central globules, or unspecified pattern.

Main Outcome Measure: Frequency of dermoscopic nevus subtypes stratified by patient age and location of the nevi.

Results: A total of 5481 nevi in 480 individuals were evaluated. The number of all nevus subgroups, except for unspecified pattern nevi, significantly increased before and decreased after the fourth decade of life. Globular nevi were most prevalent on the upper trunk in children and adolescents; the number decreased consistently after the second decade of life. The reticular pattern was the most common nevus pattern after the second decade of life and the most common nevus subgroup on the upper and middle back. Although uncommon, central globular nevi also showed an age-dependent trend, similar to that of reticular nevi. Nevi with the peripheral globular pattern declined rapidly after the third decade of life and were no longer observed after the sixth decade. The number of unspecified pattern nevi was stable across all age groups.

Conclusion: Age, dermoscopic pattern, and location of nevi should be jointly considered when evaluating melanocytic lesions.

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The number of acquired melanocytic nevi varies with age; nevus counts increase from youth to midlife and, thereafter, decrease.¹,² Recent dermoscopic studies³,⁴ suggest that the nevus patterns also are age dependent. The fact that most dermoscopic features correlate well with histopathologic criteria, which remains the criterion standard for the diagnosis of nevi, makes dermoscopy a useful technique for translational research.

See also pages 655 and 731

Dermoscopy has allowed for a more detailed classification of nevi into subgroups.⁵ With the use of this classification, it became obvious that nevi in a given individual tend to share the same dermoscopic pattern, an observation referred to as the predominant nevus pattern, moles breed true, or signature nevus.⁶-⁷ In addition, the dermoscopic patterns of nevi were found to be related to the location on the body,⁸,⁹ the patient’s pigmented phenotype,¹⁰-¹² a heightened melanoma risk,¹³ and age.¹¹,¹²,¹³,¹⁴,¹⁶ In particular, children often have nevi with a globular or structureless pattern (ie, compound and dermal nevi, often shown to have congenital-like features on histopathologic examination). In adults, most nevi show a reticular or reticular mixed pattern (corresponding histopathologically to lentiginous, junctional, or compound nevi).

Based on these observations, it was proposed that nevogenesis occurs via 2 pathways¹⁷,¹⁸: one pathway, the constitutional or endogenous pathway, gives rise to nevi with a globular or structureless dermoscopic pattern, an unspecified dermoscopic pattern, with onset during child-
hood. These nevi are thought to derive from predominantly dermal melanocytes and represent persisting proliferations that acquire, with time, the stereotypical appearance of an intradermal nevus. In contrast, the acquired or exogenous pathway of nevogenesis gives rise to nevi with a reticular dermoscopic pattern. The most likely exogenous factor resulting in nevogenesis is intermittent UV light exposure resulting in the proliferation of epidermal melanocytes, which have a propensity to involute over time. Thus, nevus pattern was predicted to be age dependent; reticular nevi would appear and involute during adult life, and globular structureless nevi would appear in youth and persist indefinitely.

This model is based primarily on cross-sectional studies11,14-16 of dermoscopic patterns of nevi in which only 1 or few nevi per individual were assessed; selection of these nevi was either random or based on the predominant nevus pattern. Thus, these studies were limited by selection bias.

To expand the findings from those investigations, we conducted a cross-sectional study comparing the prevalence of dermoscopic nevus subtypes across different age groups and between different anatomic sites. To avoid selection bias, we recorded the dermoscopic pattern and precise location of all nevi on the torsos of participants.

PATIENT SELECTION

Patients undergoing total skin examination were recruited from 7 pigmented skin lesion clinics in Austria (Graz), France (Lyon), Italy (Modena, Naples, and Rome), Spain (Barcelona), and the United States (New York City) between October 2008 and May 2009.

Individuals older than 2 years were eligible for inclusion if they had at least 1 acquired melanocytic nevus on the trunk, defined as a nevus with a macular, papular, or nodular component with a diameter of more than 2 mm and less than 15 mm. In addition, the nevus could not have been present at birth or developed within the first 2 years of life. Individuals with a history of intentional or prolonged sun exposure in the 4 weeks before the examination or those with deeply tanned skin on the trunk compared with double-covered (eg, the buttock) were excluded because recent tanning has been shown19 to transiently affect the dermoscopic pattern. Lesions on the head and neck, including the face, and lesions on the extremities, genital region, and mucosal surfaces were not included; lesions with a clinical or dermoscopic pattern of Spitz nevus, agminated nevus, recurrent nevus, halo nevus, and congenital nevus (including blue nevus, combined nevus, and nevus spilus) were also excluded.

All participants or, in the case of individuals younger than 18 years, their parents or legal guardians were informed about the study’s goal and gave verbal consent. Because the study did not include any intervention or alter the established care of the patients, ethical committee approval was not required.

Consecutive patients who agreed to participate in the study were assigned to their appropriate age group until there were 60 participants per age group. Age groups were categorized as (1) childhood (>2-10 years), (2) adolescence (11-20 years), (3) early adulthood (21-30 years), (4) adulthood (31-40 years), (5) middle (41-50 years), (6) late middle (51-60 years), (7) late adulthood (61-75 years), and (8) elderly (>75 years).

For all participants, sex, age, skin type (ST) according to the Fitzpatrick scale, history of melanoma or nonmelanoma skin cancer (without further specification), and presence of freckles or actinic keratoses were recorded. The skin lesions of all patients received routine clinical and dermoscopic examination.

Patients with equivocal skin lesions or lesions with a suspected diagnosis of melanoma or nonmelanoma skin cancer were excluded from the study, with treatment given according to the standard of care at the clinical sites (eg, excision for histopathologic diagnosis). For all other melanocytic nevi meeting the aforementioned inclusion criteria, the dermoscopic patterns and location on the trunk were recorded on a designated patient documentation sheet (Figure 1). The location on the trunk was subdivided into upper, middle, and lower segments on the anterior and posterior torso.

Each nevus was dermoscopically classified according to 5 patterns: (1) uniform globular pattern (G), (2) uniform reticular pattern (R), (3) mixed pattern composed of central globular or structureless area surrounded by a network (MC), (4) mixed pattern composed of a central network or structureless brown-gray area surrounded by a peripheral rim of small brown globules (MP), and (5) unspecified pattern (U), which encompassed all patterns other than G, R, MC, or MP (Figure 2).

Before initiation of the study, each participating center was provided with a visual file (PowerPoint; Microsoft Corp, Redmond, Washington) containing representative examples of nevi showing the 5 dermoscopic pattern categories to ensure agreement among investigators on the classification of dermoscopic nevus patterns.

STUDY DESIGN

A total of 480 individuals (60 persons per 8 age groups) with 5481 nevi were enrolled. Of these, 259 (54.0%) were women. The mean (SD) age of participants was 42.0 (24.7) years (range, 2-101 years). Age of participants, with number and frequency of nevi, is summarized in Table 1.

Skin types of the participants were ST I, 38 (9.7%); ST II, 132 (33.8%); ST III, 178 (45.5%); and ST IV, 43 (11.0%). Information on ST was unavailable for 89
Figure 1. Example of the patient documentation sheet. During patient examination, nevi were identified and their dermoscopic pattern and location were recorded on the sheet. AK indicates actinic keratoses; HX, history of; and ST, skin type.

Figure 2. Representative examples of dermoscopic nevus types. A, Globular. B, Reticular. C, Mixed pattern with central structureless areas and peripheral rim of brown globules. D, Mixed pattern with central globules and peripheral reticulation.
participants. Among all participants, 206 (42.9%) had freckles and 172 (35.8%) had a history of skin cancer. Individuals with freckles and those with a history of skin cancer were significantly older (51.2 [21.8] vs 58.8 [20.8] years) compared with patients without freckles and those without a history of skin cancer (35.0 [24.5] vs 32.6 [21.6] years; P < .001 for both groups).

DERMOSCOPIC NEVUS SUBTYPES, LOCATION, AND CLINICAL FEATURES

Dermoscopic analysis of the 5481 nevi revealed a total of 2933 R nevi (53.5%), 1512 G nevi (27.6%), 494 MC nevi (9.0%), 389 U nevi (7.1%), and 153 MP nevi (2.8%). There were no significant differences between STs with respect to frequency of dermoscopic nevus pattern.

Table 1. Age Groups, With Number and Frequency of Nevi

<table>
<thead>
<tr>
<th>Age Group No. (Age Range, y)</th>
<th>Total Nevi, No. (%)</th>
<th>Total Nevi, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (3-10)</td>
<td>7.2 (2.3)</td>
<td>363 (6.6)</td>
</tr>
<tr>
<td>2 (11-20)</td>
<td>15.8 (3.0)</td>
<td>902 (16.5)</td>
</tr>
<tr>
<td>3 (21-30)</td>
<td>22.2 (2.7)</td>
<td>1015 (18.6)</td>
</tr>
<tr>
<td>4 (31-40)</td>
<td>35.6 (3.1)</td>
<td>1057 (19.3)</td>
</tr>
<tr>
<td>5 (41-50)</td>
<td>45.1 (2.7)</td>
<td>832 (15.2)</td>
</tr>
<tr>
<td>6 (51-60)</td>
<td>55.4 (3.0)</td>
<td>677 (12.4)</td>
</tr>
<tr>
<td>7 (61-75)</td>
<td>68.8 (4.2)</td>
<td>446 (8.1)</td>
</tr>
<tr>
<td>8 (&gt;75)</td>
<td>82.8 (4.9)</td>
<td>185 (3.4)</td>
</tr>
<tr>
<td>Total No. of participants, 480</td>
<td>41.96 (24.7)</td>
<td>5481 (100)</td>
</tr>
</tbody>
</table>

Table 2. Number and Frequency of Nevus Dermoscopic Subtypes by Age

<table>
<thead>
<tr>
<th>Dermoscopy</th>
<th>Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
</tr>
<tr>
<td>G nevi</td>
<td>1512 (27.6)</td>
</tr>
<tr>
<td>frequency (%)</td>
<td>3.15 (4.50)</td>
</tr>
<tr>
<td>MP nevi</td>
<td>2933 (53.5)</td>
</tr>
<tr>
<td>frequency (%)</td>
<td>3.15 (4.50)</td>
</tr>
<tr>
<td>R nevi</td>
<td>1037 (19.3)</td>
</tr>
<tr>
<td>frequency (%)</td>
<td>3.58 (4.07)</td>
</tr>
<tr>
<td>MC nevi</td>
<td>389 (7.1)</td>
</tr>
<tr>
<td>frequency (%)</td>
<td>3.58 (4.07)</td>
</tr>
</tbody>
</table>

Abbreviations: G, uniform globular pattern; MC, mixed pattern composed of central globular or structureless area surrounded by a network; MP, mixed pattern composed of a central network or structureless brown-gray area surrounded by a peripheral rim of small brown globules; R, uniform reticular pattern; U, unspecified pattern.

Comparison of anatomic subsites by sex was not performed separately for dermoscopic nevus patterns because total nevus count on 6 six segments showed no substantial sex difference with respect to distribution.
FREQUENCY OF DERMOSCOPIC NEVUS SUBTYPES BY AGE GROUP AND LOCATION

Multivariate analysis of dermoscopic nevus subtype counts by age group revealed a significant overall effect \( (F_{26,1502} = 7.20, P < .001) \) and age-related differences with respect to the frequency of G \( (F_{7,472} = 15.26, P < .001) \), R \( (F_{7,472} = 11.66, P < .001) \), MC \( (F_{7,472} = 7.48, P < .001) \), and MP \( (F_{5,354} = 4.55, P < .001) \) nevi, but not for U nevi \( (F_{7,472} = 1.46, P = .18) \).

Comparison between the corresponding anterior and posterior segments indicated that R, MC, and U nevi were significantly more prevalent on the posterior compared with the anterior sites \( (P < .01) \). In contrast, no significant differences between the anterior and posterior sites were seen for G and MP nevi.

G Nevi

Globular nevi were significantly more prevalent in participants aged 2 to 20 years compared with all older age groups \( (P < .05) \) for all significant pairs. The number increased from the youngest age group and peaked in age group 2, in which 25.1% of all G nevi were documented. After the age of 20 years, the number decreased almost linearly among all older age groups and reached the lowest frequency \( (0.9\%) \) in the oldest age group. The G nevi were significantly more frequent on the upper compared with the middle segments \( (F_{16,1771} = 70.79, P < .001, \varepsilon = 0.73) \), although this difference reached significance only in age groups 1 and 2 \( (P < .006) \).

R Nevi

Reticular nevi were the most prevalent nevus pattern in all groups older than 20 years \( (P < .05) \) for all pairs. Their number increased from the youngest up to age group 4 \( (22.0\%) \) of all R nevi). Although the numbers decreased thereafter, the R pattern remained the prevalent nevus type in all older age groups compared with all other nevus subtypes. The R nevi were significantly more prevalent on the posterior middle segment of the torso \( (F_{16,1771} = 74.20, P < .001, \varepsilon = 0.68) \), with the exception of age group 4, in which they were more commonly located on the posterior upper segment \( (P < .006) \).

MC Nevi

Similar to R nevi, total counts and frequencies of MC nevi increased from age group 1 to age group 4, in which 23.9% of all MC nevi were identified \( (P < .05) \) for all pairs. However, differences in the frequency of MC nevus counts across different age groups were less evident than among R nevi. The MC nevi were most frequent on the anterior middle and posterior upper sites \( (F_{5,354} = 27.47, P < .001, \varepsilon = 0.75) \). In age group 4, MC nevi were also significantly more common on the posterior middle segment compared with the posterior upper segment \( (P < .006) \).

MP Nevi

The MP nevi were generally rare. Because exploratory data inspection indicated that there were no cases of MP nevi in participants older than 60 years, these nevi were compared separately by 1-way analysis of variance between age groups 1 through 6.

Their frequency peaked in age groups 2 and 3, in which 29.4% and 28.8%, respectively, of all MP nevi were seen. After the third decade of life, their number decreased rapidly, and no patients older than 60 had this nevus type \( (P < .05) \) for all pairs. Similar to MC nevi, MP nevi were most frequently located on the anterior and posterior middle segments \( (F_{16,1771} = 7.51, P < .001, \varepsilon = 0.81) \). Only in the youngest age group were MP nevi significantly more frequent on the posterior upper compared with the posterior middle segment \( (P < .006) \).

U Nevi

Comparison of U nevus counts between the different age groups failed to reach significance. However, there was a trend toward a lower frequency in the youngest age group and in persons older than 50 years \( (P = .18) \). For U nevi, only 1 significant main effect for location \( (F_{16,1771} = 19.31, P < .001, \varepsilon = 0.75) \) was found, indicating more nevi on posterior upper and middle segments compared with the corresponding anterior segments \( (P < .008) \).

CLUSTERING OF DERMOSCOPIC NEVUS SUBTYPES BY AGE

Clustering of nevus types within age groups indicated a significantly higher number of G nevi compared with all other nevus patterns within age group 1 \( (P < .01) \) for all. In age group 2, G nevi remained the predominant nevus pattern, although R nevi were also common. For all older age groups, R nevi were predominant compared with all other nevus subtypes, which were substantially lower in frequency.

Figure 3. Mean number of nevi with globular pattern, reticular pattern, mixed pattern with peripheral globules, mixed pattern with peripheral network, and unspecified pattern across the 8 age groups. The age groups are described in Table 1.
A small subset of nevi in children and adolescents exhibit a peripheral rim of small brown globules (defined herein as MP nevi); this dermoscopic pattern has been shown to be a sign of nevus growth. For example, these peripheral globules were shown, using reflectance confocal microscopy, to correlate with junctional and dermal melanocytes that grow centrifugally. In our study, the number of MP nevi increased from childhood, reached the peak prevalence in individuals between 11 and 20 years, and decreased rapidly thereafter, until this pattern was no longer present in persons older than 60 years. This observation has practical implications because the management of lesions with peripheral globules becomes age dependent. In adolescents, MP nevi are an expected finding and, as such, do not require interventions. In patients older than 30 years, we recommend close digital dermoscopic monitoring of lesions with a peripheral rim of brown globules in the absence of other melanoma-specific criteria to monitor the symmetry of enlargement. Lesions with a peripheral rim of brown globules in persons older than 50 are infrequent and should be viewed with great caution. The presence of peripheral globules in such older individuals can be the clue to diagnosis of an otherwise elusive melanoma (Figure 5). Management options include excision or close observation.

An interesting observation is that MP nevi are not only most prevalent in young adolescence but that this type of nevus is more prevalent during pregnancy. One explanation for the increased frequency of growing nevi could be related to the growth hormone–rich environment in both periods (adolescence and pregnancy). An increase in the level of stimulating hormones, such as α-melanocyte stimulating hormone, could affect nevus growth; indeed, there are recent reports of eruptive nevi during α-melanocyte stimulating hormone treatment, with most of these nevi showing the MP pattern on dermoscopy. Another explanation for the higher prevalence of MP nevi in youth is that this is a temporal finding and, at older ages, these nevi simply develop R or MC patterns. The finding of a similar anatomic site–related distribution for MP nevi and for MC nevi and R nevi is in line with this hypothesis. The significant age-related differences in the predominance of G and R nevi support the hypothesis that they...
represent distinct pathways to nevogenesis. Previous cross-sectional and longitudinal studies have shown that most G nevi maintained their baseline dermoscopic pattern despite showing a symmetric enlargement during growth.4,11,16,21 The early onset of G nevi, as opposed to the later predominance of R nevi, is also in line with the notion that G nevi are more likely to be congenitally determined and that R nevi may be more driven by exogenous influences such as UV light. This is further supported by a recent study27 showing significant age- and anatomic site–related differences between clinically flat (ie, nevi with a presumably R pattern by dermoscopy) and nodular (ie, nevi with a presumably G or unspecified U pattern by dermoscopy) nevi.

However, contrary to our supposition that G nevi will prove to be persistent throughout life,17 we found a decline in the number of G nevi in adulthood. The cross-sectional design of our study did not permit us to determine the outcome of G nevi. One possibility, as we originally proposed, is that the G nevi persist but lose their pigmentation as they “age” (acquiring features of a dermal nevus), with the G dermoscopic pattern becoming more homogeneous with time. In our study, these were classified as U nevi. We did not see an increase in U nevi in later decades because the numbers of G nevi declined; rather, the prevalence of U nevi remained stable across all age groups. Another possibility is that G nevi completely involute as the individual progresses into late adulthood. Finally, it is possible that a certain portion of evolving nevi initially showing a G pattern will develop into a nevus with a peripheral rim of globules, as also recently suggested,4 and another proportion will persist, acquiring a more structureless pattern (U pattern) in older individuals (Figure 6). Longitudinal study design will allow elucidation of the outcome of G nevi in adulthood.

Our study has limitations. First, we cannot exclude interobserver variability regarding the assessment of dermoscopic patterns, which has been reported28-31 to vary from excellent to poor across different studies; we tried to minimize this variability by providing investigators with several examples of nevus dermoscopic patterns before study initiation. Second, the study was designed as a cross-sectional observation. Drawing inferences on longitudinal evolution of nevi is limited by this design (eg, age cohort effect); more definitive observations await a longitudinal study design. Third, the prevailing color and pigment distribution of nevi are influenced by the individuals’ skin phototype.10 In the present study, we did not evaluate these 2 criteria, which likely explains the lack of association between dermoscopic pattern and skin phototype in our sample. Fourth, we excluded obvious congenital nevi based on history (eg, nevi not present at birth or shortly thereafter) and physical examination (eg, absence of hairy nevi larger than 15 mm). We are aware of the limitation of these criteria in excluding small congenital nevi among adults, who may not recall their presence in infancy; however, because truly congenital nevi are relatively rare (1% of the population),15 such misclassification is not likely to affect our results.

Finally, some of the participants had a relatively low nevus count; the fact that persons with high nevus counts compose a small percentage in a general population and considering that our study was designed to enroll only 10 persons per age group and center could explain this finding. On the other hand, individuals attending pigmented lesion clinics are not representative of the general population (eg, patients in these clinics tend to have higher nevus counts); therefore, our findings may apply only to the population referred to pigmented lesion clinics.

In conclusion, our study demonstrates significant age- and anatomic site–related differences in the prevalence of various nevus dermoscopic subgroups. These findings should be integrated into the management of nevi in patients. In particular, any melanocytic lesion showing peripheral globules or signs of growth in a patient older than 50 years should be considered highly unusual.

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REFERENCES


