

A Natural History of Melanomas and Dysplastic Nevi

An Atlas of Lesions in Melanoma-Prone Families

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BACKGROUND. Few long-term clinical and histologic data for melanocytic lesions have been available based on the mutation status of families at an increased risk of melanoma. In the current study, the authors describe the clinical and histologic features of dysplastic nevi and melanoma over time in families at an increased risk of melanoma with differing germline mutations in *CDKN2A*, *CDK4*, or not yet identified genes.

METHODS. Thirty-three families with > 2 living members with invasive melanoma were evaluated clinically and followed prospectively for up to 25 years. All the participants were evaluated by the same study team at the Clinical Center of the National Institutes of Health or in local clinics. After informed consent was obtained, family members ($n = 844$) were examined and photographed. Blood was obtained for genetic studies; genotyping for *CDKN2A* and *CDK4* was performed. Sequential photographs of melanocytic lesions were taken as part of the clinical evaluations. When melanocytic lesions were removed, the histology was reviewed. Representative photographs and photomicrographs were selected for six classes of lesions and three mutation groups.

RESULTS. All the families were found to have members with dysplastic nevi and melanoma; 17 had mutations in *CDKN2A*, 2 had mutations in *CDK4*, and 14 had no mutations in either gene identified. The majority of dysplastic nevi either remain stable or regress; few change in a manner that should cause concern for melanoma. With careful surveillance, melanomas can be found early.

CONCLUSIONS. The melanomas and dysplastic nevi that were found to occur in the study families did not appear to vary by the type of mutation identified in the families. *Cancer* 2002;94:3192–209. © 2002 American Cancer Society.
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KEYWORDS: melanoma, dysplastic nevi, genetics, familial melanoma.

Dysplastic nevi first were described over 20 years ago among members of melanoma-prone families.^{1–4} In many melanoma-prone families, dysplastic nevi are important risk factors^{5–8} and nonobligate precursor lesions for melanoma.^{9–14} Since these relations were established, the presence of dysplastic nevi has been used clinically to identify the individuals in these melanoma-prone families who are at the highest risk of developing melanoma.^{5,6,8} Based on the presence of dysplastic nevi, clinical guidelines for members of high-risk families were developed. The guidelines include surveillance of pigmented lesions, routine clinical examinations, and the use of sun protective measures. Adherence to these guidelines appears to decrease the risk of new melanoma and changing nevi and aids in the detection of melanoma at an earlier stage.¹⁵

It now is well established that the etiology of familial melanoma is heterogeneous and complex.¹⁶ Two genes have been identified: *CDKN2A*, a tumor suppressor, and *CDK4*, a protooncogene. Muta-

TABLE 1
Average Thickness and Number of Melanomas Diagnosed in the Families by T Classification, Mutation Status, and Study Period

Period	T classification	Mutation status		
		<i>CDKN2A</i> (n)	<i>CDK4</i> (n)	Unknown (n)
Previous to study	T1a	0.46 (68)	0.34 (15)	0.49 (17)
	T1b	0.61 (3)	0.51 (1)	0.86 (3)
	T2a	1.48 (13)	1.46 (1)	1.36 (11)
	T2b	1.67 (1)		1.83 (1)
	T3a	2.68 (8)	2.10 (1)	2.40 (2)
	T4a	5.85 (3)		6.00 (1)
	T4b	7.00 (1)		10.00 (1)
Prevalent	Unknown	(30)		(13)
	T1a	0.42 (11)	0.32 (8)	0.47 (1)
	T1b	0.77 (1)		
Prospectively identified	T3a			2.85 (1)
	T1a	0.34 (52)	0.24 (13)	0.36 (7)
	T1b	0.59 (4)		0.68 (2)
	T2a	1.45 (4)	1.13 (1)	
	T3a	2.10 (1)		
	Unknown	(2)		

tions in *CDKN2A* have been found in approximately 20% of families evaluated worldwide, whereas mutations in *CDK4* have been reported in 3 families.^{17–19} Both these genes play an important role in cell cycle control in the retinoblastoma pathway. Despite one gene being a tumor suppressor and the other a protooncogene, there are no apparently significant differences in phenotype between families with *CDKN2A* mutations and families with *CDK4* mutations.¹ The estimated penetrances of these genes remain imprecise. Therefore, to make use of mutation status for melanoma risk assessment is problematic.²⁰ Additional genes that are significant in the development of melanoma currently are being sought.

As genes associated with melanoma susceptibility have been identified, the role of dysplastic nevi in the clinical management of family members has been questioned.²¹ Although dysplastic nevi and melanoma early on were hypothesized to be pleiotropic effects of a single gene,²² dysplastic nevi recently have been shown to be a risk factor for melanoma independent of mutation status in these families.²³ These nevi also are a substantial risk factor for melanoma outside of melanoma-prone families^{24–33} and are estimated to occur in 5–10% of the general population.^{34,35} The natural history of dysplastic nevi in individuals who are not from melanoma-prone families has been described previously.^{26–30}

Although some reports have found a correlation between the clinical and histologic characteristics of

dysplastic nevi, the genetic status of the affected individuals has not been included. The current atlas demonstrates the natural history of dysplastic nevi and primary melanomas within melanoma-prone families with differing germline mutations. We prospectively observed and photographically documented these lesions for > 20 years.

MATERIALS AND METHODS

Thirty-three families with ≥ 2 living members with invasive melanoma were referred by health care professionals (or were self-referred) to the National Cancer Institute (NCI). The families are geographically dispersed within the U.S., but the majority come from the mid-Atlantic region. Diagnoses of melanoma were verified by histologic review of the primary tumor ($n = 258$) or metastatic lesions ($n = 17$), local pathology report ($n = 19$), or medical record or death certificate ($n = 7$).

After providing written informed consent for participation in the NCI institutional review board-approved protocol, all willing family members ($n = 844$) underwent a medical history review, full skin examination, photography, and phlebotomy. Information recorded from the skin examination included degree of solar damage, extent of freckling, total number of nevi, pattern of nevi, and presence of dysplastic nevi. Individuals were classified as clinically affected with dysplastic nevi if they had multiple lesions which were at least 5 mm in dimension with a flat component and at least 2 of the following 3 characteristics: variable pigmentation, irregular asymmetric outline, and indistinct borders. Routine initial photography included overviews of all skin surfaces and close-up 1:1 photographs of the most atypical nevi. During and after the skin examination, family members also were instructed in sun protective measures, conduct of self-examinations, characteristics of dysplastic nevi, and recognition of the warning signs of melanoma. Recommended routine care in these families included monthly self-examination for those with dysplastic nevi (less frequent for those without); regular (3 month–1 year) health care worker examinations, depending on the activity of nevi; and the excision of nevi observed to be changing in a manner worrisome for melanoma or of new lesions suspicious for melanoma.

After initial evaluation at the NCI, routine care was provided by local physicians for the majority of family members. Follow-up information, including new diagnoses or excision of pigmented lesions, was obtained regularly. When pigmented lesions were excised, every effort was made to obtain slides for histologic review. The criteria used for diagnoses of invasive melanoma, radial and vertical growth phase

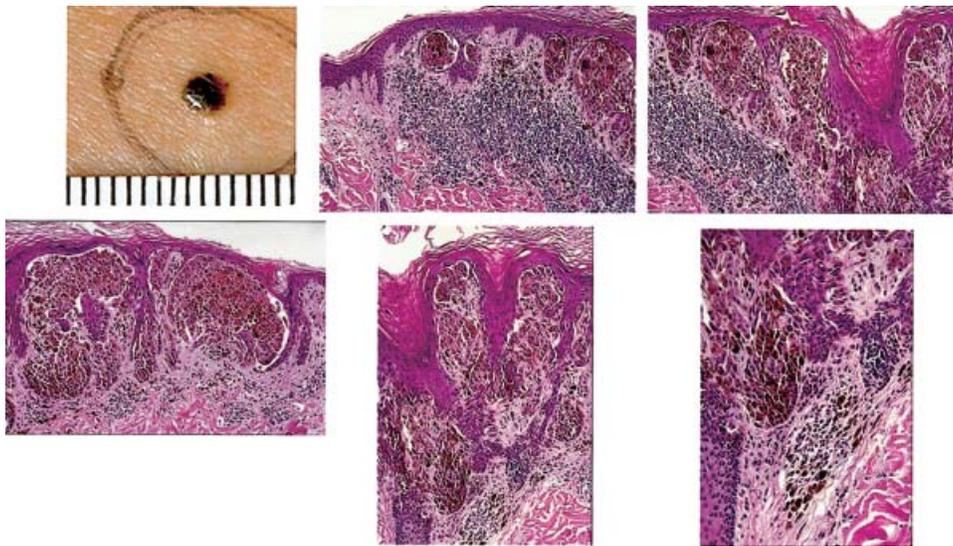


FIGURE 1. Radial growth phase melanoma arising from a dermal nevus (*CDKN2A* mutation). This lesion, which measured < 4 mm, was present at the time of initial examination on the center back of a 35-year-old patient (A). Based on history, there had been a nevus present at this site for an extended period. Neither the patient nor the spouse was concerned about the lesion. After specific questioning regarding changes in the lesion, the spouse believed that it had darkened. There were small “islands” of pigment at the periphery of the lesion. This clearly was the darkest lesion on the skin at the time of examination and was highly suspicious for melanoma. The patient had approximately 50 nevi measuring > 2 mm, many of which were atypical but did not meet all the clinical criteria of dysplastic nevi. The lesion was excised because of its intense pigmentation and loss of normal skin markings. The left portion of the photomicrograph in Panel B shows uninvolved reference skin. The lesion began abruptly with a prominent nest of deeply pigmented cells. These nests were large and possibly correlated with the small islands of pigment that were observed clinically at the periphery of this lesion. Proceeding into the lesion, the large nests became confluent, bulged well down into the dermis (C), and were associated with a well developed lymphocytic response. Centrally, the lesion was dominated by these nests, which virtually traversed the entire thickness of the epidermis. The cells had an abundance of dark brown pigment. The summation of all this pigment was responsible for the intensely black clinical color. At the far edge of the lesion, there again were large nests of cells (D). There was some pleomorphism and abundance of dark brown pigment. At the base of the central portion of the lesion (E), there was evidence of a precursor small dermal nevus. At the very base of the picture, just to the right of a part of a pilar unit, clusters of dermal nevic cells extended upward and to the right for a short distance. The last of the photomicrographs (F) shows the precursor dermal nevus at the base of the lesion at a higher power. This was a melanoma entirely in the radial growth phase. The lesion was largely intraepidermal, but showed extension into the papillary dermis and measured 0.71 mm in thickness. Much of this thickness was due to epidermal hyperplasia and large nests within the epidermis. The lesion arose from a small dermal nevus.

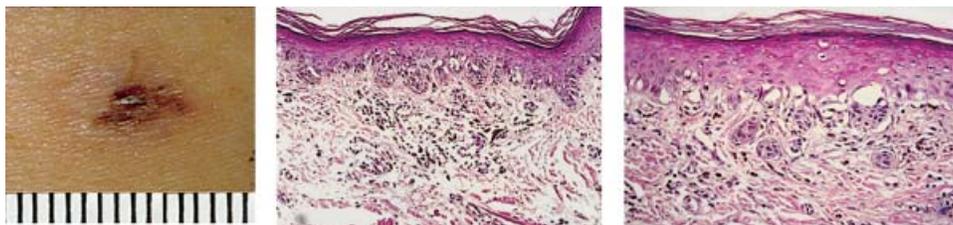


FIGURE 2. De novo severe epithelioid melanocytic dysplasia (*CDKN2A* mutation). Panel A shows a lesion on the posterior thigh several centimeters below the gluteal fold. This lesion was present at the time of the initial evaluation of a 41-year-old patient with a history of 3 previous in situ melanomas. At the time of examination, > 175 nevi measuring > 2 mm were noted, many of which were clinically dysplastic. The patient had undergone multiple nevus biopsies in the past, some of which were dysplastic. The pigmented lesion measured 6 mm in dimension and was characterized by asymmetry, very indistinct irregular borders, a deeply pigmented papule with apparent infiltration of the epidermis, and some loss of skin markings in the area of the papule. There was slight hypopigmentation surrounding the lesion. In the area of hypopigmentation there were normal skin markings. The lesion had been itching slightly for a few months. The lesion was excised because of its atypical appearance, dark pigmentation in the area of the papule, focal loss of the normal skin markings, and history of change over several months. Centrally (B), nests of melanocytes protruded as small blunt peninsulas into the subjacent dermis. Below this, there were lymphocytes and melanophages associated with somewhat prominent blood vessels. A few cells were visible at the upper levels of the epidermis. At higher magnification (C), these cells at the upper levels of the epidermis were easily noted. Nests of atypical melanocytes protruded downward into the dermis with perhaps one or two being free in the dermis. This lesion demonstrated epithelioid melanocytic dysplasia that was severe and apparently de novo (i.e., it did not have a precursor common nevus). The dark pigmentation was accounted for in the lower power photomicrograph, in which melanophages were visible in the dermis. Above this, nests of melanocytes were noted at the dermal-epidermal interface. Above this, melanocytes were noted at the upper levels of the epidermis. All this pigment summated into the relatively dark lesion evident in the clinical photograph.

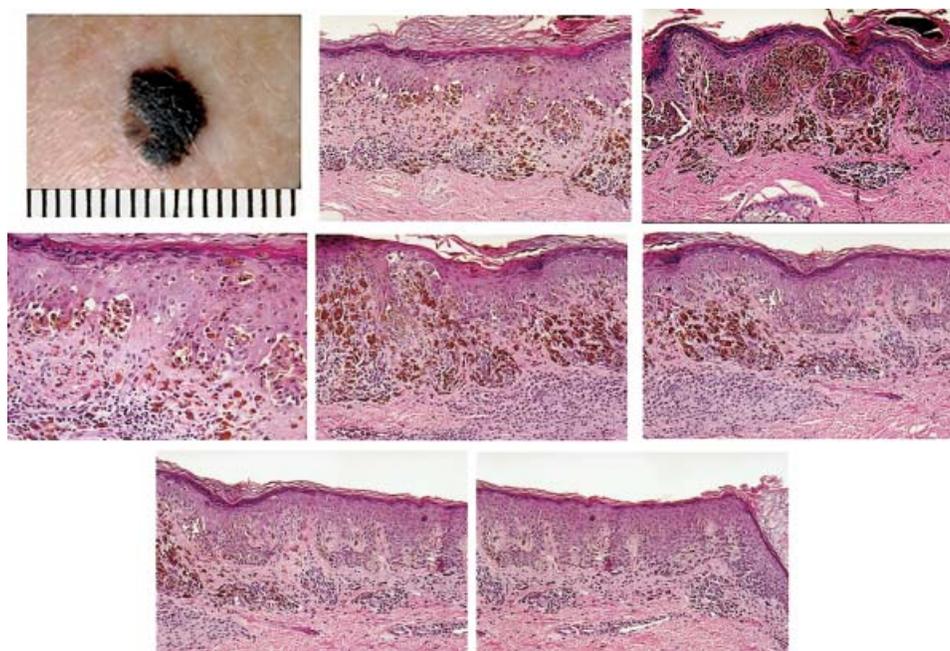


FIGURE 3. Superficial spreading melanoma arising from dysplastic nevus (*CDK4* mutation). This lesion (A) was on the shoulder of a 30-year-old patient at the time of initial evaluation. The lesion had been enlarging and darkening for > 1 year and measured 7 mm in maximum dimension at the time of examination. There was some erythema at the base and mild scaling over the entirety of the black portion of the lesion, with loss of normal skin markings. There was diffusion of the pigment into the surrounding normal skin at the superior border of the lesion. There was an apparent remnant of a precursor nevus at the left border area from approximately the 7 o'clock to 9 o'clock position. The rest of the lesion was a homogeneously black infiltrative lesion with mildly irregular borders. The patient had approximately 100 nevi measuring > 2 mm, many of which were clinically dysplastic. The lesion was excised because of the clinical suspicion of melanoma. The first photomicrograph (B) demonstrates atypical melanocytes at all levels of the epidermis. In the outer two-thirds of the epidermis, the cells were, for the most part, arrayed individually. At the dermal-epidermal interface the cells were in nests. The subjacent dermis demonstrated lymphocytes and prominent blood vessels. Further into the lesion (C) and correlated with the clinical picture of an elevated rough black surface, hyperkeratosis and prominent nests of deeply pigmented cells were evident. The lesion still was largely in the dermal-epidermal interface, although at higher magnification of the periphery (D), atypical melanocytes were identified easily at all levels of the epidermis. Still further into the lesion, just to the left of the center (E), there was a questionable area of microinvasion. The lower portion of this panel demonstrated the precursor dermal nevus. In the far right, corresponding to the pale area in the left border of the clinical picture, one can note relatively few cells in the epidermis but a confluence of atypical cells at the dermal-epidermal interface. As the far edge of the lesion was approached (F), bridging of the nests from one rete to the next was apparent, forming an area of dysplasia that was associated with the tip of the dermal nevus at the periphery. Panel G shows the precursor dermal nevus associated with melanocytic dysplasia. The bulk of the lesion demonstrated extensive melanocytic growth that is nearly entirely within the epidermis correlated with epidermal hyperplasia that caused the rough surface visible in the clinical photograph. The last photomicrograph (H) shows a relatively classic dysplastic nevus with bridging from one rete to the next, a rather sparse lymphocytic infiltrate, and some connective tissue changes around the rete. The lesion was a malignant melanoma of the superficial spreading type that was found to be largely in situ. It was associated with epidermal hyperplasia and deep pigmentation, which were responsible for the black rough surface. The very periphery of the lesion, the flat blackish rim, was that of melanoma in situ. In the left portion of the lesion, evidence of a precursor lesion was visible. This precursor lesion was confirmed histologically by a deep dermal nevus and an overlying area of dysplasia.

melanoma, in situ melanoma, and dysplastic nevi have been published previously.⁹⁻¹⁴ For this article, *melanocytic lesions* is an inclusive term for benign and malignant tumors of the melanocyte, including banal nevi. *Dysplastic nevi* are clinically or histologically diagnosed; *melanomas* are histologically diagnosed. For staging, we used the proposed American Joint Committee on Cancer (AJCC) staging system.³⁶

Families also were reevaluated intermittently at the NCI. During these clinical examinations, if nevi were found to have changed in the interval since the

last photographs, new close-up and overview photos were taken. Prospective follow-up of these families ranged from 2–25 years. The frequency of examinations at NCI varied from 3 months–10 years.

Mutation analyses were conducted as previously described.¹ Mutations in *CDKN2A* were described in 17 families, *CDK4* mutations were described in 2 families, and no mutations were found in 14 families. Although mutations in *CDKN2A* or *CDK4* were not identified, these 14 families appeared to have quite similar inheritance patterns of melanoma compared

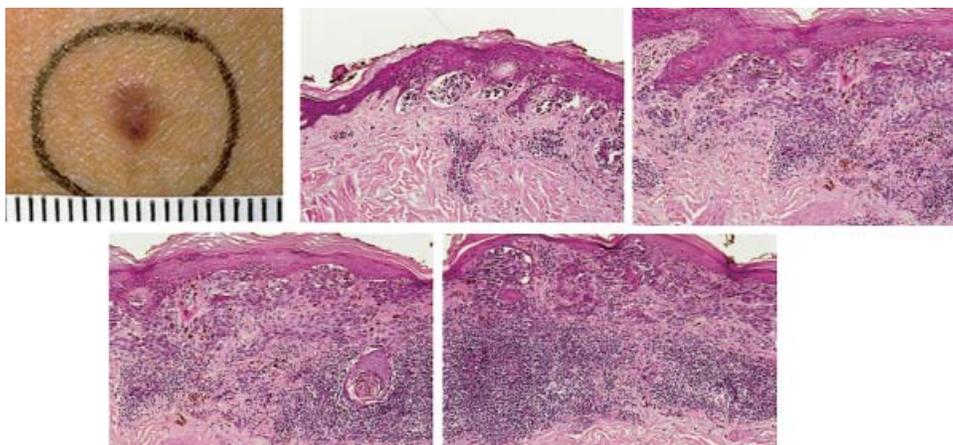


FIGURE 4. Superficial spreading melanoma without precursor lesion (unknown mutation). The photograph (A) shows a 5-mm lesion on the upper arm of a 35-year-old patient. This lesion had increased somewhat in diameter over several months. At the time of the initial evaluation it was the most atypical lesion on the patient. It measured 5 mm in dimension and had dusky pigmentation, indistinct borders, and prominent erythema throughout. This lesion demonstrated the difficulty in clinicopathologic correlation because of its rather innocuous appearance and lack of dark pigmentation. The patient was found to have multiple clinical dysplastic nevi on examination. The lesion was biopsied because of the history of some change over the previous months and its appearance with prominent erythema and dusky pigmentation. The left portion of the photomicrograph (B) shows uninvolved skin. The tumor began abruptly with prominent nests of quite atypical melanocytes, and melanocytes in individual cell arrays at all levels of the epidermis. Further into the lesion (C), the cells extended downward into the dermis. Even in a lesion this small, melanoma cells have established a vertical growth phase and impinge on the reticular dermis (a Level 3 lesion). The invasive cells were quite pleomorphic and arrayed in elongated islands. Further into the lesion (D), the cells were even more prominent, were associated with a prominent lymphocytic infiltrate, and extended around a pilar unit. Near the far edge of the lesion (E), the cells formed a nearly continuous plaque below the surface of the epidermis, separated, in this area, from the reticular dermis by a prominent lymphocytic infiltrate. The lesion was a malignant melanoma of the superficial spreading type without an identifiable precursor histologic lesion. This small lesion had both radial and vertical growth phases. It measured 0.47 mm in thickness.

with those with identified mutations. It is likely that additional melanoma susceptibility genes will be identified in these families. The age at the time of first diagnosis of melanoma, the number of primary melanomas per individual, the thickness of the melanomas, and the presence of dysplastic nevi did not appear to vary among the three categories.^{1,37}

For this atlas, melanocytic lesions with available histology suitable for photomicrographs were reviewed. Representative photomicrographs of informative lesions were taken. Clinical photographs also were reviewed to identify two classes of lesions: those with photomicrographs that had photographs prior to excision and those not excised that had sequential photographs. Among the latter group of lesions, pigmented lesions that developed into dysplastic nevi, dysplastic nevi stable for long periods, or dysplastic nevi that regressed and disappeared were selected to illustrate representative phases in the natural history. Among the lesions in individuals with *CDKN2A*, *CDK4*, or unknown mutations, the following were selected: prevalent melanoma at the time of first examination, new melanoma during follow-up, dysplastic nevus changing in a manner worrisome for melanoma, new dysplastic nevus, stable dysplastic nevus, and involuting dysplastic nevus. For the last three groups, there was no histopathology.

RESULTS

Prior to the families' enrollment into the current study, 194 melanomas occurred among 140 individuals. Of the 151 primary lesions for which we were able to measure thickness on review, 100 were classified as T1a lesions and 7 were classified as T1b lesions (Table 1). The majority of the T1 lesions were superficial spreading melanomas; there were three nodular melanomas, two lentigo maligna melanomas, two unclassified lesions, and one acral lentiginous melanoma. Sixty-four lesions had an identified precursor lesion; 43 of these were histologically dysplastic nevi.

Prevalent Lesions Suspicious for Melanoma

At the time of the initial examination, 22 melanomas were identified on 14 people, 6 of whom had previous melanomas (Figs. 1–4). Eighteen had radial growth phase only; 4 had radial and vertical phase growth. There was 1 thick melanoma (measuring 2.85 mm, Clark Level 4). The average thickness of all other lesions was 0.45 mm among those with *CDKN2A* mutations, 0.32 mm among those with *CDK4* mutations, and 0.47 mm among those with unknown mutations (Table 1). All but 2 (1 of which was lentigo maligna melanoma) had an identified precursor lesion; 17 of the precursor lesions were dysplastic nevi. These four

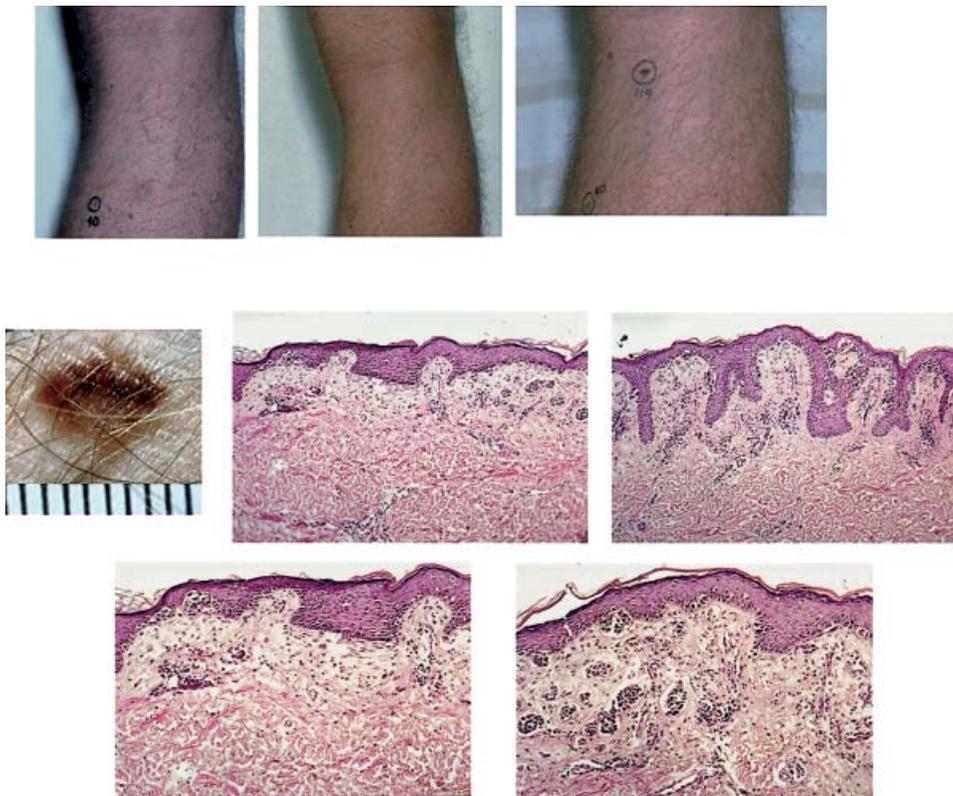


FIGURE 5. De novo superficial spreading melanoma (*CDKN2A* mutation). Panel A shows the right popliteal fossa of a 37-year-old patient on which there were two small nevi to the left, close to the medial aspect. It is interesting to note that the right center part of the popliteal fossa had no pigmented lesions. Two years later, when the patient was quite tan, repeat overviews (B) demonstrated the persistent medial nevi and no lesions in the central area. Two years later, on routine follow-up (C), there was a new lesion detected to the right of the previously noted nevi. Panel D shows a close-up of the lesion. The superior border was quite dark with obvious elevation of the epidermis fading into a flat, less pigmented area on the inferior of the lesion. There was fairly prominent erythema. The patient had > 650 nevi, a high proportion of which were clinically dysplastic, and had undergone many biopsies. The lesion was biopsied because of a high suspicion for melanoma. Panel E shows a great increase in the number of melanocytes in the epidermis at all levels. Small clusters of similar cells extended into the subjacent papillary dermis, and are observed best in the right portion of the photomicrograph. Centrally, deep to a broad rete ridge, was an area of lamellar fibroplasia characteristic of the stroma of severe dysplasia leading into melanoma. Panel F demonstrates a classic picture of malignant melanoma of the superficial spreading type occurring largely in the epidermis, in which all levels of the epidermis were involved with atypical melanocytes. These cells were disposed in individual cell array and in nests. In a higher magnification view of the first area (G), the lamellar fibroplasia was well illustrated as well as nests of cells at all levels of the epidermis. In the final view (H), the intraepidermal pattern of superficial spreading melanoma with clusters of cells in the papillary dermis was apparent. This nested pattern in the papillary dermis associated with extensive amounts of connective tissue is characteristic of malignant melanoma of the superficial spreading type in the radial growth phase. The lesion was a malignant melanoma of the superficial spreading type, radial growth phase only. No precursor lesion was observed, confirming the photographic evidence that the melanoma arose de novo. It measured 0.37 mm in thickness.

lesions are representative of prevalent lesions suspicious for melanoma. Three of these lesions were the first melanoma for each individual and, typical of these familial melanomas, occurred at an early age (35 years, 30 years, and 35 years, respectively); the fourth lesion was a severely dysplastic nevus.

Prospectively Identified Melanomas

A major part of the care for these melanoma-prone families is education regarding sun and ultraviolet protection. When queried, many of the family members report that their sun exposure patterns change

after enrollment in the study.¹⁵ Family members are urged repeatedly to minimize midday exposure, use protective clothing and sunscreens, and avoid burning. Clinical recommendations for these family members include regular self-examinations and routine health care provider examinations. Family members are provided with copies of their clinical photographs for their use in self-examinations, and for the use of the clinicians who examine them. The majority of family members receive their care from local physicians, and frequency of follow-up and rates of biopsies vary among providers. The clinical recommendations

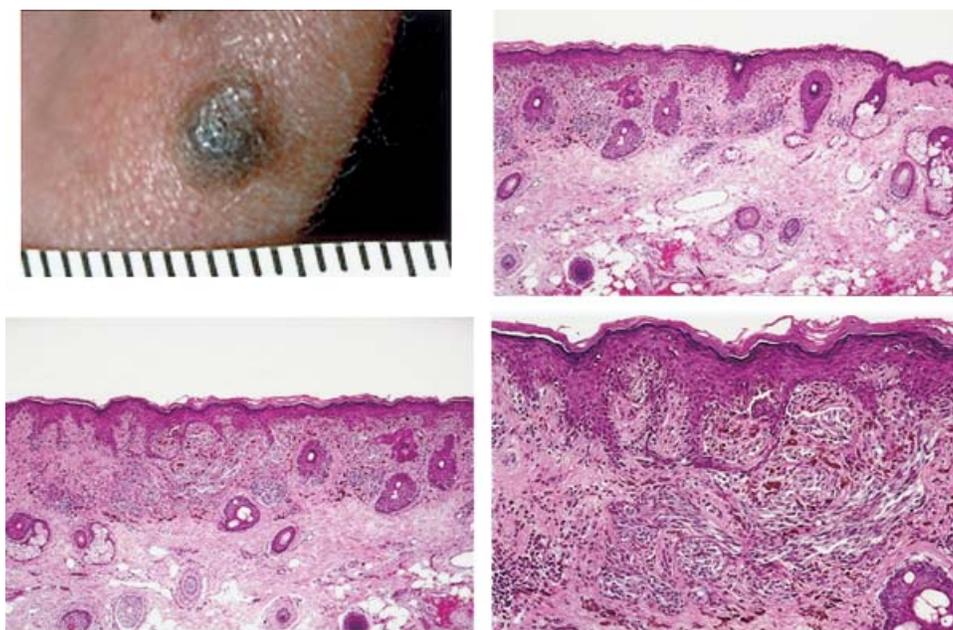


FIGURE 6. Superficial spreading melanoma without precursor lesion (unknown mutation). This 6-mm lesion (A) was present on the posterior helix of the ear when the 43-year-old patient returned for a follow-up visit after 10 years. At the time of the initial examination, the patient did not have nevi on the ears. The patient had received routine care from multiple physicians for several medical problems requiring frequent examinations. None of the physicians had noted the lesion, and it was unknown to the patient. It had very indistinct borders and was asymmetric, varying from tan brown, minimally elevated areas to a very dark brown to black papule in the center of the lesion. There was some scale and loss of skin markings in the central papule. The patient had approximately 150 nevi, many of which were clinically dysplastic nevi. The lesion was excised as highly suspicious for melanoma. The right portion of Panel B shows essentially normal skin of the ear. Moving into the lesion, the atypical cells were largely in the basilar region of the epidermis. This would account for a relatively flat tan periphery to the lesion. Further into the lesion, a significant number of cells were present at the dermal epidermal interface, and they extended into the subjacent dermis (C). Here, in the central most area of the lesion, the cells were well into the reticular dermis. At higher magnification (D), this central area demonstrated vertical growth phase melanoma. These pictures illustrate tumor progression from the radial growth phase into the vertical growth phase, and are correlated with a clinical lesion that is tan at the periphery but black or near black and elevated at the center. The lesion was a malignant melanoma of the superficial spreading type with both radial and vertical growth phases present. It measured 0.51 mm in thickness. No precursor lesion was identified.

for these family members include biopsy of lesions changing in a manner worrisome for melanoma or new lesions suspicious for melanoma. Some health care providers are more aggressive in removing lesions. Greater than 2000 lesions have been removed from over 300 family members and subsequently reviewed by W.H.C.

In a prospective follow-up of all the family members, 86 new melanomas were found to have occurred in 37 individuals, 16 of whom did not previously have melanoma. Seventy-two melanomas were classified as T1a³⁶ lesions (≤ 1.0 mm and \leq Clark Level 3, no ulceration) with an average thickness of 0.31 mm; 6 melanomas were classified as T1b (≤ 1.0 mm and $>$ Clark Level 3, no ulceration) with an average thickness of 0.62 mm; 5 melanomas were classified as T2a with an average thickness of 1.39 mm; 1 melanoma was classified as T3a, 2.10mm thick; and 2 melanomas were of unknown thickness (Table 1). The lesions that were at least T2a occurred in individuals who were not compliant with the care guidelines. Among the 16

individuals without previous melanoma, no one who followed the guidelines has developed metastatic disease to date. The average thickness among families with *CDKN2A* mutations was 0.44 mm, that among families with *CDK4* mutations was 0.27 mm, and the average thickness among those with no known mutations was 0.38 mm. Sixty-three melanomas had a radial growth phase only, 18 had a radial and a vertical growth phase, and 5 had a vertical growth phase only. Fifty-one were found to have identified precursor lesions on histologic review, 32 of which clearly were dysplastic nevi. The distribution of precursor lesions did not vary by mutation status. In addition, new lesions that were highly suspicious for melanoma occurred in areas without previous known nevi which had no identifiable precursor on histologic review.

New Lesions Suspicious for Melanoma

The two lesions shown in Figures 5 and 6 were new lesions that were highly suspicious for melanoma and

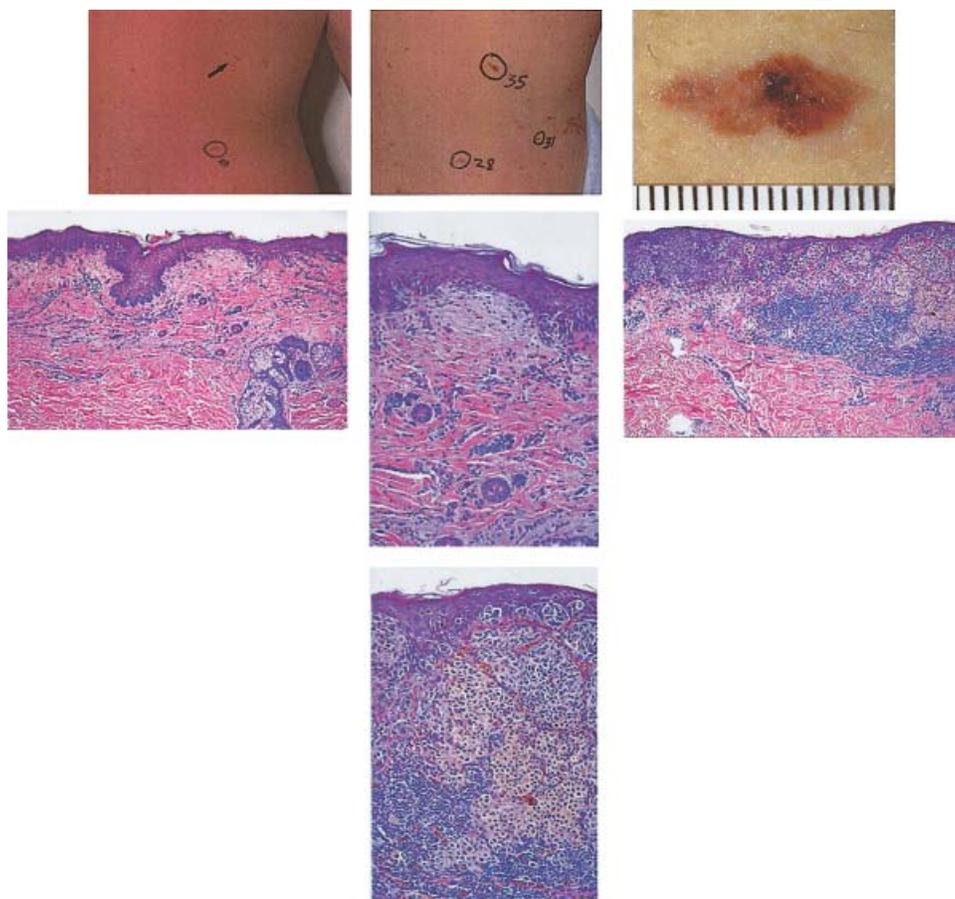


FIGURE 7. Superficial spreading melanoma arising from a dysplastic nevus (*CDKN2A* mutation). Panel A shows an area on the right lower back of a 52-year-old patient. The lesion of interest is indicated by an arrow directly above the circled lesion #28. There was a uniformly pigmented irregular nevus, which was not different from the other nevi in the local area. It was not particularly dark, and did not prompt a close-up photograph or removal at the time of this examination. The patient had > 100 nevi, many of which were clinically dysplastic, and had undergone many previous biopsies. The next photograph (B) shows an overview of the same area 3 years later. The previously mentioned lesion now is circled as #35. In comparison with the earlier photograph, the lesion was quite different. On the right side of the lesion, there was a new extension that was much darker than the other lesions in that area. Panel C shows a close up of the lesion. It measured 14 mm in diameter on the long axis. On the left side of the lesion were two areas of minimal elevation separated by a depressed depigmented central area. The depressed region extended to the dark area noted on the overview. The borders of the lesion were indistinct. The lesion was quite asymmetric and variably pigmented, with a black central papule. Because the lesion was clinically very suspicious for melanoma, an excisional biopsy was performed. The photomicrograph (D) is of a transverse section of the wider portion of the clinical lesion that was relatively flat. At the dermal-epidermal interface at either side of the picture, there was an increased number of melanocytes, some of which protruded into the subjacent dermis as small rete. Centrally, there was a circumscribed area of lamellar fibroplasia, shown at a higher magnification in the next picture. Below the dermal-epidermal interface, there was extensive deposition of collagen. Within some of the collagen bundles toward the lower part of the lesion there were clusters of mature nevic cells. The second photomicrograph (E) shows the area of lamellar fibroplasia at a higher magnification with atypical melanocytes in nests over this fibroplasia and at the sides of it. The mature dermal nevic cells entrapped in dense fibrous tissue were noted in the lower half of the photomicrograph. The photomicrograph is of a relatively flat but dark area of the lesion extending into one of the elevated papules. The flat dark area shows melanocytes at all levels of the epidermis on the left portion of the picture (F). The histology of the elevated black nodule is shown on the right. Here, nests of melanocytes extended into the papillary dermis, and filled and widened the papillary dermis. There was a prominent lymphocytic response. Panel G shows the histology of the black papule at higher magnification. The epidermis showed melanocytes at all levels, with those at the dermal-epidermal interface being predominantly nested. In the dermis, there were large numbers of melanocytes in discrete nests. The cytoplasm of these cells has an abundance of melanin and the nuclei are relatively dark. Tumor-infiltrating lymphocytes were visible in the lower and lower left portion of the photomicrograph. The lower right portion of the picture indicates that this area is at Level 3. The lesion was a malignant melanoma of the superficial spreading type arising from a dysplastic nevus. The lesion was in the radial and vertical growth phases and measured 0.84 mm in thickness.

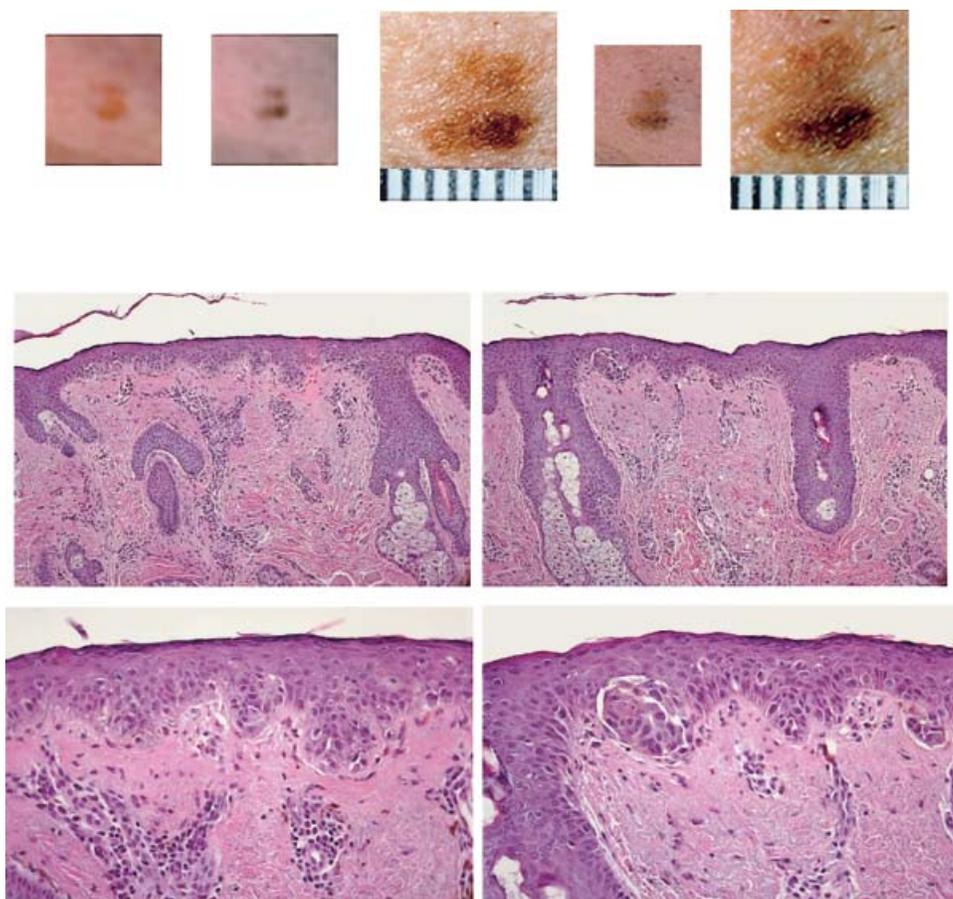


FIGURE 8. De novo severe epithelioid dysplasia (*CDK4* mutation). Panel A was taken as a follow-up photograph when a lesion detected in a 23-year-old patient approximately doubled in size in comparison with photographs taken 8 years earlier. The lesion also had become more irregular with a slightly darker area in the lower pole of the lesion. Despite the slight variability in pigmentation, the lesion still was not extremely dark and was not worrisome. Three years later (B), the lesion had become more irregular with a new dark focus on the right lower pole of the lesion. The lower half of the nevus was approximately 1.5 times as wide as the upper half of the nevus. Panel C shows the close-up photograph corresponding to Panel B with the new dark focus in the right lower pole. The lesion measured $< 5 \text{ mm} \times 5 \text{ mm}$ and was irregular in outline with indistinct borders. Panel D, taken 1 year later, shows an overview of the lesion in which the area between the upper and lower pole had filled in somewhat. The lower half of the lesion had become uniformly darkly pigmented except for the farthest left part of the lesion. Panel E corresponds to Panel D and demonstrates the indistinct borders, the asymmetric and irregular outline of the lesion, and the slightly pebbly appearance of the dark portion of the inferior half of the lesion. The patient had > 300 nevi, many of which were clinically dysplastic. The lesion was excised because of the increase in size to nearly $6 \text{ mm} \times 6 \text{ mm}$ and the increase in the dark area in the lower pole. The histology of the lesion (F) was characterized by an increased number of epithelioid melanocytes in the basilar region of the epidermis. These were present throughout the majority of the central part of this photomicrograph along with some disposition of cells in nests. There was a suggestion of some of these cells present in the mid-spinus layer, but this was not prominent. Panel G shows a somewhat less cellular histology. The majority of the cells of the lesion were gathered together in clusters. The nest on the left was large whereas others were smaller. This histology is associated with an area of the lesion that is somewhat lighter in color. At a higher magnification of Panel F (H), the large epithelioid melanocytes were evident in the basilar region of the epidermis associated with prolongation of plump rete and one or two cells present at the upper level. A closer view of the nested area in Panel G (I) shows prominent nests and a significant amount of pleomorphism of cells within the nests. Between the nests there was only a slight increase detected in the individual number of melanocytes. The lesion is severe epithelioid cell dysplasia de novo associated with solar change in the dermis. This lesion was photographically documented evolving over a 12-year period. It was comprised nearly entirely of epithelioid melanocytes, showing that this form of dysplasia may evolve exceedingly slowly over a period of many years.

occurred in areas previously examined without identified nevi.

Changing Lesions Suspicious for Melanoma

The lesions presented herein are typical of nevi changing in a manner worrisome for melanoma; the lesions

were biopsied soon after the photographs were taken (Figs. 7-10).

New Nevi to Dysplastic Nevi

When they first appear, nevi that eventually become dysplastic often are indistinguishable from nevi that

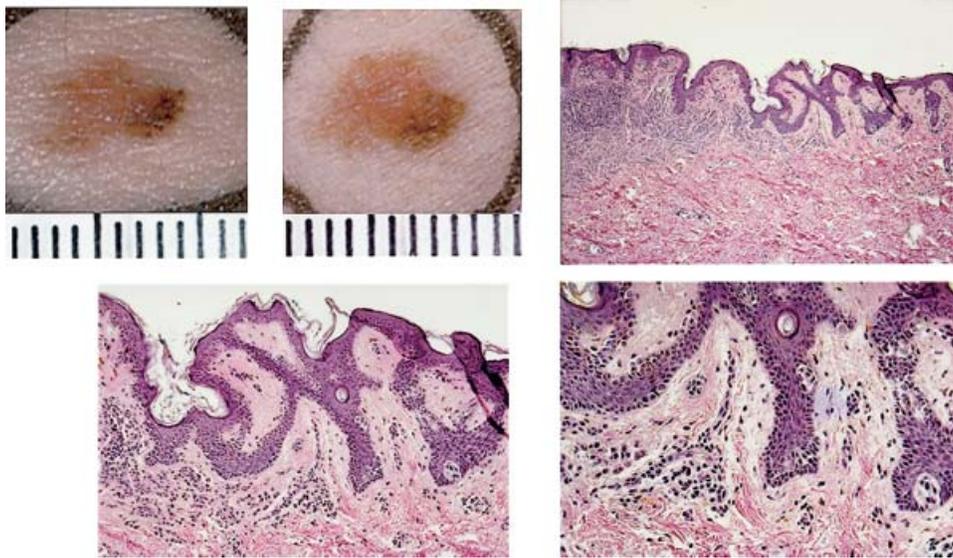


FIGURE 9. Compound nevus with moderate to severe epithelioid dysplasia (unknown mutation). Panel A shows a lesion on the upper left anterior axillary line that was typical of the > 500 nevi detected on the 22-year-old patient. The lesion was irregular, predominantly flat with an indistinct outline, variable pigmentation and asymmetric configuration. The lesion did not appear to differ significantly from multiple other dysplastic nevi at the time of the examination. Panel B was taken 6 years later. In the interval time period, the nevus had enlarged, changed in configuration, and developed a central papule. Because of the increasing area of the more deeply pigmented flat component and the change in size and outline, the lesion was biopsied. The sections show the elevated central area and the dark area at one edge of the specimen (C). The elevated central area to the left in the photomicrograph was dominated by strands of orderly nevic cells. The cells in the epidermis showed varying atypia. This atypia extended beyond the dermal component of the lesion forming the histology of the flat dark clinical component. At a higher magnification, clusters of epithelioid melanocytes were visible as well as individual melanocytes that were a portion of the dark shoulder of this lesion. There was bridging across the rete due to large epithelioid melanocytes. At a higher magnification the variable atypia of these cells was noted. This was a compound nevus with epithelioid melanocytic dysplasia that was moderate to severe. The histology was found to correlate well with the clinical picture of an elevated tan area and one peripheral area that is dark brown.

will become ordinary compound or dermal nevi (Figs. 11–13). When they reach a dimension of approximately 3 mm, the first abnormality in the morphology frequently is an irregular outline or indistinct borders. These lesions were first photographed when they appeared as new nevi in comparison with previous overview photographs. Over time, they developed the clinical characteristics of dysplastic nevi. Evaluating patterns of new nevus development over time was difficult in these families because they altered their sun exposure patterns. In general, although family members may develop new clinical dysplastic nevi at any age, it certainly is more common in the second, third, and fourth decades of life.

Minimally Changed Dysplastic Nevi

Removal of all nevi or all clinically dysplastic nevi in these family members was not recommended because many individuals were found to have several hundred nevi (some exceeding 500). The vast majority of clinically dysplastic or other nevi, similar to other precursor states, either remain relatively stable over time or regress. The clinically dysplastic nevi shown in Figures

14–16 changed minimally over many years, despite their clearly abnormal morphology.

Regressing Dysplastic Nevi

The nevi shown in Figures 17–19 regressed. Often, when a clinically dysplastic nevus begins to differentiate, a central papule appears, and the flat surrounding area becomes less pigmented and less prominent over time. In contrast to lesions suspicious for melanoma, the skin markings remain normal, and there is no visual evidence of stretched or thinned epidermis or telangiectasia in the papule. The papule is soft, similar to a compound or dermal nevus. When the lesion becomes less pigmented, it becomes the color of the baseline skin, similar to a dermal nevus. It does not lose pigment like a regressing melanoma or halo nevus. When the papule flattens, it usually does so proportionally and gradually. An asymmetric involution or change should prompt biopsy. The majority of dysplastic nevi differentiate to dermal nevi or regress and completely disappear over time. Although regression of lesions can occur at any age, it is more common in individuals age > 50 years. In these families,

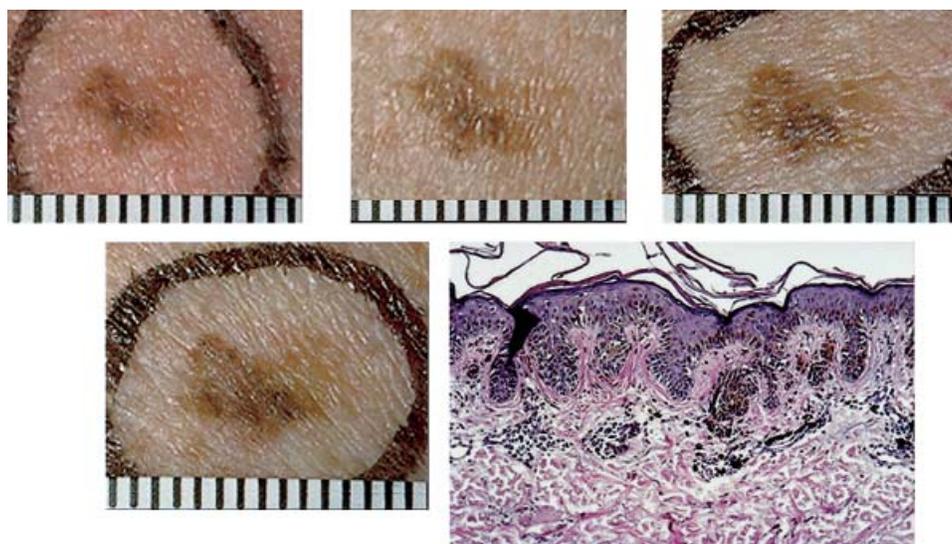


FIGURE 10. Dermal nevus with overlying dysplasia (unknown mutation). Panel A shows a typical lesion on the back of a 44-year-old patient at the time of the initial evaluation. The patient had > 500 nevi, many of which were clinically dysplastic. The lesion measured 6 mm in greatest diameter and was irregular in outline with indistinct borders, variable pigmentation, and a predominantly flat configuration. It was not worrisome for melanoma. Panel B shows the lesion 1.5 years later. In the interim, the area to the left of the lesion had become more uniformly pigmented and had changed in outline. The central area, which was the darkest area of the nevus in the previous photograph, is essentially unchanged, but the area to the right was minimally darker. The whole nevus still was predominantly flat, but there were two areas in which there was beginning papule formation. Panel C shows the lesion 2 years later, when the 2 areas at the lower pole that were dark before were nearly coalescent. The area to the left of the lesion was somewhat darker with a pebbly surface. There was beginning small papule formation both on the left and the right sides of the lesion. In addition, the superior right area was becoming more deeply pigmented with some suggestion of papule formation as well. Panel D was taken 1.5 years later when the superior area on the right was uniformly elevated in a plaque-like fashion and light tan. The dark areas at the inferior and left had become coalescent. There were two papules in the dark area in what had become the center of the lesion, and there was a new area of pigmentation inferior to those two papules which was not found to be prominent previously. The area to the far left of the lesion had become a more discreet dark area than in previous photographs. The skin markings were relatively intact throughout the entire lesion, but because of the gradual change over time and the increasing pigmentation, the nevus was removed. The light areas in Panel D were on the left of the lesion shown in Panel E in which there is a moderate amount of pigment and slight hyperkeratosis. The rete were abnormal and demonstrated an increased number of melanocytes. There was prominent concentric eosinophilic fibroplasia, a marker of melanocytic dysplasia. Centrally, there were the pigmented cells in the dermis of a pigmented dermal nevus. To the right the lesion had much more pigment. It also demonstrated features of melanocytic dysplasia. The lesion was a small dermal nevus with overlying dysplasia and variable amounts of pigment.

regression also appears to be related to sun protection over time. In contrast to a regressed melanoma (Fig. 7) or halo nevus, the site of a regressed dysplastic nevus, like a regressed dermal nevus, appears similar to the surrounding skin.

DISCUSSION

The original atlas of dysplastic nevi was, of necessity, cross-sectional,⁴ and could not provide sequential documentation of the natural history of these important risk markers and potential precursor lesions. The current atlas provides photographic documentation of representative lesions followed for up to 24 years. Clinically, many of these lesions are relatively stable or regress over time. The photomicrographs correlate well with the clinical photographs. These photographs and clinical notes also demonstrate that the history of change, as well as the individual morphology (including the skin markings) of the lesion, are critical in the

decision to perform excisional biopsy. As shown in Figures 1-4, even small lesions can be recognized as early melanoma. Similar to other initial melanomas in these high-risk families, the lesions in Figures 1, 3, and 4 occurred in relatively young individuals. Other figures demonstrated the evolution of changes worrisome for melanoma that should prompt biopsy (Figs. 8-10). Lesions that are changing in a manner suggestive of melanoma out of proportion to other nevi are particularly worrisome. However, some lesions, such as that shown in Figure 18, stabilize and then regress. Melanocytic lesions vary in activity over time. One trigger for increased activity appears to be sun exposure;¹⁵ after acute sun exposure, multiple nevi may change and new nevi develop.

Although the majority of melanomas in these families arise from nevi, particularly dysplastic nevi, some melanomas arise de novo in previously normal skin (Figs. 5 and 6). These de novo melanomas usually



FIGURE 11. Development of clinically dysplastic nevus (*CDKN2A* mutation). Panel A shows an overview of the left posterior shoulder of a 50-year-old patient with > 100 nevi, many of which were clinically dysplastic. The skin was freckled with actinic damage, some acneiform lesions, and several nevi. Panel B shows a newly prominent nevus arising from previously unremarkable skin 5 years later, which is circled and labeled as #13. Panel C is the first close-up photo of #13. The lesion measured 6 mm and was predominantly circular and flat with indistinct borders, an irregular outline, and minimally variable pigmentation. Panel D depicts the lesion 2 years later, when it was somewhat darker, especially centrally. The pigment had extended at the lower pole in which there also was minimal papule formation. Panel E shows a similar overview to Panel B an additional 5 years later. The emerging papule is observed more clearly in Panel F. At that time, the lesion measured 8 mm × 7 mm and predominantly was flat, with an irregular outline, indistinct borders, and minimally variable pigmentation.

occur in individuals who have dysplastic nevi. The progression is consistent with other tumor progression systems such as colon carcinoma, which may arise from villous adenomas, adenomatous polyps, or adjacent clinically normal colonic epithelium. However, the majority of nevi, including clinically dysplastic nevi, evolve to a relatively stable state or regress (Figs. 11-19); only a very small percentage progress to melanoma. Because progression to melanoma is unpredictable and rare, removal of all nevi is not warranted. Even if all nevi were removed, the frequency of clinical follow-up in these individuals would not change because they still would develop new nevi or could develop *de novo* melanoma. Individuals still would have to check their own skin frequently and undergo routine healthcare worker examinations. Clinically dysplastic nevi are not only potential direct precursor lesions, but also phenotypic markers of individuals with skin that is at particularly increased risk of both familial and sporadic melanoma.^{6-8,15,20,23-33}

This information is descriptive, and inferences therefore are limited. To quantify the rate of change in nevi for a sufficient number of individuals to achieve statistical significance over a 25-year period obviously would be prohibitive. Despite the inevitable limitations of the information, clinical characterizations of different phases of the natural history of melanocytic

lesions that are useful for health care providers can be demonstrated.

Clinical overview photographs are very helpful in identifying either new lesions in previously uninvolved skin or changing lesions, such those seen in several of the figures in the current atlas. In addition, close-up photographs are useful for identifying subtle variations over time, which may indicate that a particular nevus is changing in a manner worrisome for melanoma.^{4,30,31,38} Prevention and early diagnosis are the keys to reducing the mortality from melanoma. As shown in these figures, changing nevi can be removed before they become melanomas, or melanomas can be recognized while they still are very early lesions (e.g., *in situ* or invasive radial growth phase melanoma without apparent capacity for metastasis). Unfortunately, many facilities are unable to provide the type of photographic documentation that is an important part of the clinical care for these families, and photography often is not covered by medical insurance. However, for members of high-risk families, clinical photography is an essential diagnostic and screening tool and should be available routinely.

The etiology of familial melanoma is complex. Important risk factors include not only mutations in *CDKN2A*, *CDK4*,^{1,17-21} and most likely other genes, but also dysplastic nevi²³ and sun exposure.³⁹ Although it

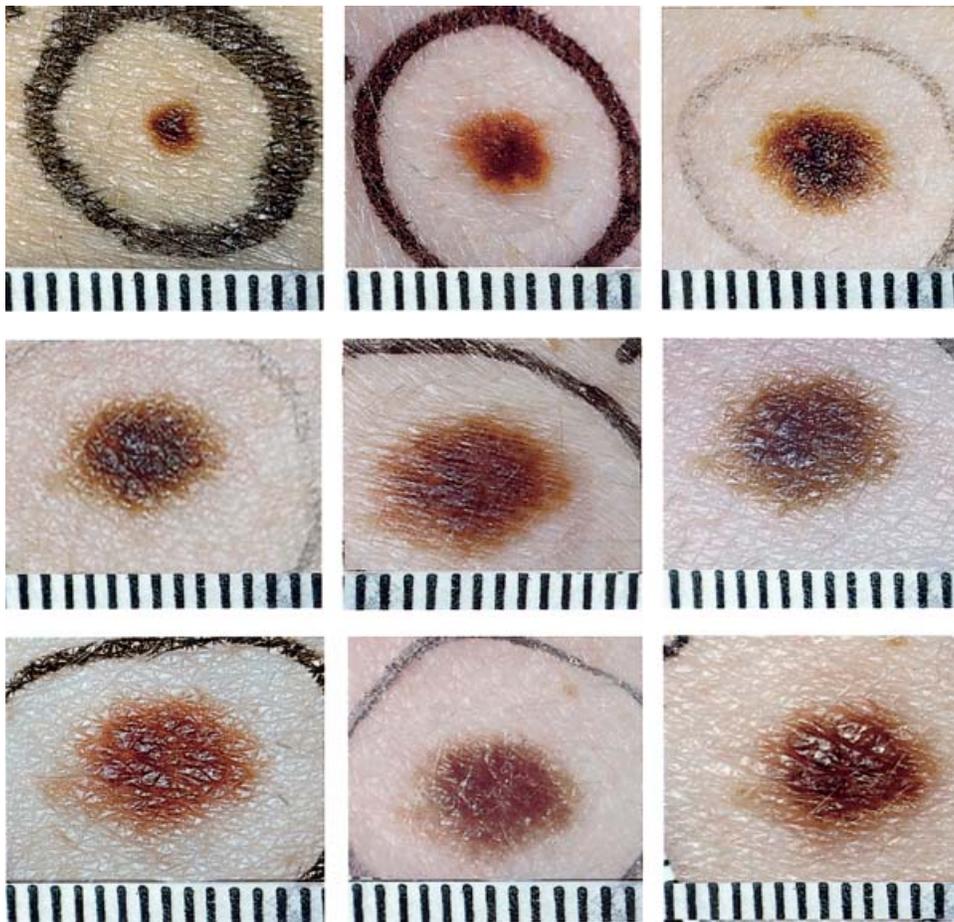


FIGURE 12. Development of a clinically dysplastic nevus (*CDK4* mutation). Panel A is a close-up of a new nevus that appeared in the interval since the 26-year-old patient's previous examination. The patient had > 200 nevi, many of which were clinically dysplastic. At the time this lesion appeared, the patient was developing several new lesions. The new lesion was a 2-mm flat lesion with minimal pigment variation. It was minimally asymmetric, with a small irregular extension at the 1 o'clock position, and minimally indistinct borders. Panel B is the same lesion 6 months later. At that time it measured 5 mm in greatest diameter and was more asymmetric, with increasingly indistinct borders. Panel C was taken 1 year later, when the nevus had increased by 1 mm but remained relatively uniformly dark, with little asymmetry. Six months later (D), a new lightly pigmented extrusion was visible at the 8 o'clock position, which became more prominent 6 months later (E). The lesion remained stable in configuration and size for 6 months (F), but there were the beginnings of central papule formation in the darkly pigmented areas. Skin markings remained normal. One year later (G), the lesion was stable but was decreasing in pigmentation. Six months later (H), the papule formation was more prominent and the extrusion at the 8 o'clock position had regressed. Six months later (I), this area was less prominent and the papule formation was more obvious.

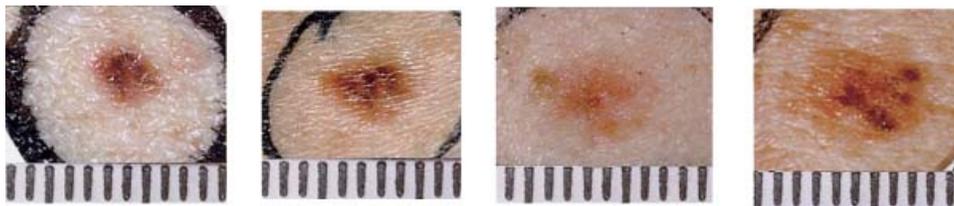


FIGURE 13. Development of a clinically dysplastic nevus (unknown mutation). Panel A shows a new 3-mm lesion on the upper back of a 34-year-old patient with > 600 nevi, many of which were clinically dysplastic. The borders were indistinct, the pigment varied from erythematous tan at the 10 o'clock position to dark brown to less pigmented at the 4–5 o'clock position, and the lesion was flat. Panel B is the same lesion 1 year later. The lesion at that time measured 5 mm and demonstrated all the clinical criteria of a dysplastic nevus. It was a flat, asymmetric lesion with quite variable pigmentation and irregular, indistinct borders. Panel C is the same lesion 5 years later. At that time the lesion was found to be < 1 mm larger in greatest diameter and had become much less pigmented. It still was predominantly flat, but had developed some papular areas. Panel D shows the same lesion 3 years later. It measured 2 mm larger. The area at the 10 o'clock position, which previously was dark tan, had lightened. The central dark area had increased in size and substantially darkened. There were new dark areas at the 3 o'clock and 4 o'clock positions. Using epiluminescence microscopy, the pigment pattern was found to be normal. This lesion was typical of the other clinical dysplastic nevi noted on this patient.

is difficult to alter mutation status or an individual's propensity to develop dysplastic nevi, sun exposure is the major environmental risk factor for melanoma⁴⁰ and is potentially modifiable. Sun exposure does appear to impact on the progression of dysplastic nevi to melanoma and melanoma development. There is some evidence that minimizing sun exposure at any age, even in high-risk families, decreases the risk of melanoma.¹⁵

The clinical and histologic morphologies of dysplastic nevi and melanomas occurring in these families do not appear to vary by the melanoma suscepti-

bility gene that is altered in the family. This is consistent with the finding of independent effects of dysplastic nevi and *CDKN2A* mutations, both functional and nonfunctional, in the risk of melanoma.^{23,41} The prospective risks of developing melanoma also do not appear to vary by mutation status in families from

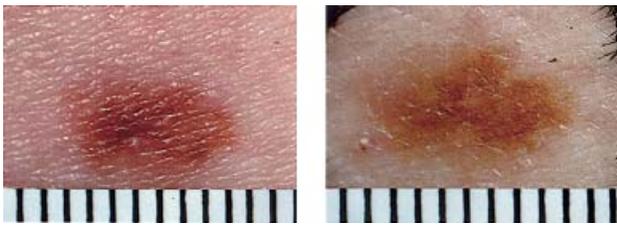


FIGURE 14. Minimal change in a clinically dysplastic nevus (*CDKN2A* mutation). Panel A shows a 7 mm × 4 mm flat, irregularly shaped, indistinctly bordered lesion with variable pigmentation in nonsun exposed skin. The 34-year-old patient had > 200 nevi, many of which were clinically dysplastic. Fourteen years later (B), the lesion measured 8 mm × 5 mm and had changed only minimally. In the upper mid lesion, the pigment extended upward in a peninsula. In general, the lesion was lighter and the borders were less distinct.

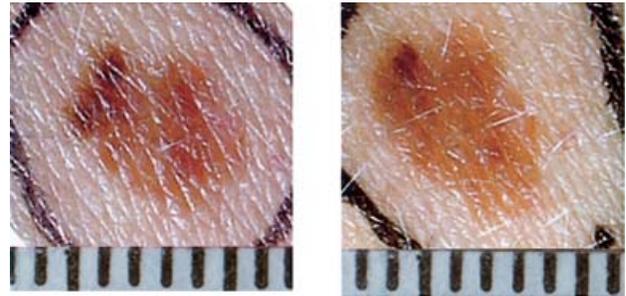


FIGURE 15. Minimal change in a clinically dysplastic nevus (*CDK4* mutation). The lesion on a 28-year-old patient was photographed from a low sun exposure site because of its 6-mm diameter, predominantly flat morphology, area of increased pigmentation from the 10 o'clock to 11 o'clock positions, and irregular outline with indistinct borders from the 2–4 o'clock position. Over a 4-year period, minimal change occurred. The lesion increased in diameter by 1 mm (toward the 5 o'clock position). The previously hyperpigmented area on the upper left side decreased in size, and the pigmentation became less varied. However, overall, the lesion remained predominantly stable over time. The patient had approximately 500 nevi measuring > 2 mm, many of which were clinically dysplastic.

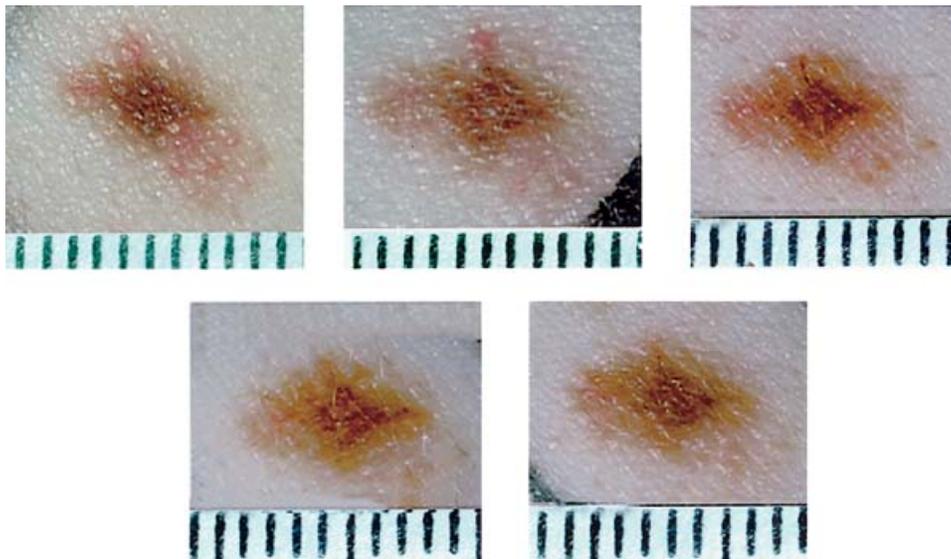


FIGURE 16. Minimal change in a clinically dysplastic nevus (unknown mutation). Panel A shows an irregular flat nevus occurring in a 17-year-old patient with an eccentric brown, diamond-shaped area on the left and an indistinct pink, flat extension to the lower right. Panel B is the same lesion 2 years later. The superior portion of the brown diamond had become more distinct with a pink peninsula. The left point of the diamond had enlarged and become lighter and more diffuse. The right lower pink area had receded back toward the diamond. Panel C was taken 4 years later. The smudge at the lower right had become even less distinct with three small tan macules. The left portion of the lesion also had regressed somewhat. Three years later (D), the lesion essentially was unchanged. Five years later (E), the right side smudged border had receded back to the brown diamond. Over a 14-year period, there was minimal variation in a mostly stable lesion. The patient had > 450 nevi measuring > 2 mm, many of which were clinically dysplastic.

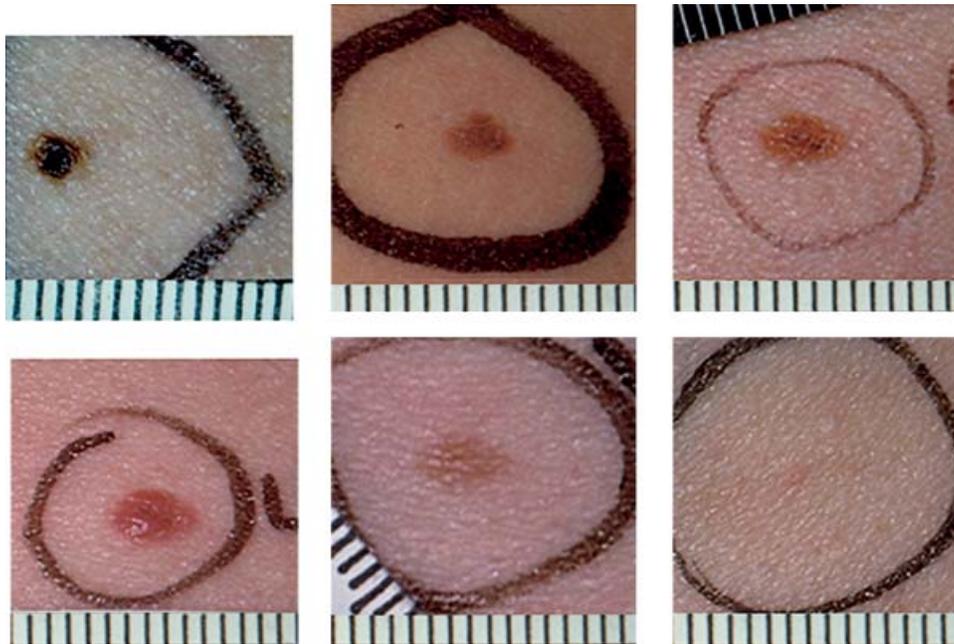


FIGURE 17. Evolving and regressing clinical dysplastic nevus (*CDKN2A* mutation). This lesion, which measured > 3 mm (A), was photographed at the time of the initial evaluation because of its deep, variable pigmentation in a non-sun exposed area, irregular shape, and indistinct borders. At that time, the 27-year-old patient was noted to have floridly expressed clinical dysplastic nevi. Nineteen months later (B), the lesion had lightened substantially, enlarged slightly, and developed more distinct borders. Three years later (C), after an intervening pregnancy, the lesion was flat, barely measured 5 mm, and had minimally variable pigmentation and indistinct borders. One year later (D), after a second pregnancy, the lesion was predominantly papular and more erythematous with minimally indistinct borders and a flat component at the 3 o'clock position. Three months later (E), the lesion had faded substantially, flattened, decreased in size, and developed more indistinct borders. Nineteen months later (F), there was a remnant flesh-colored, flat papule measuring < 1 mm.

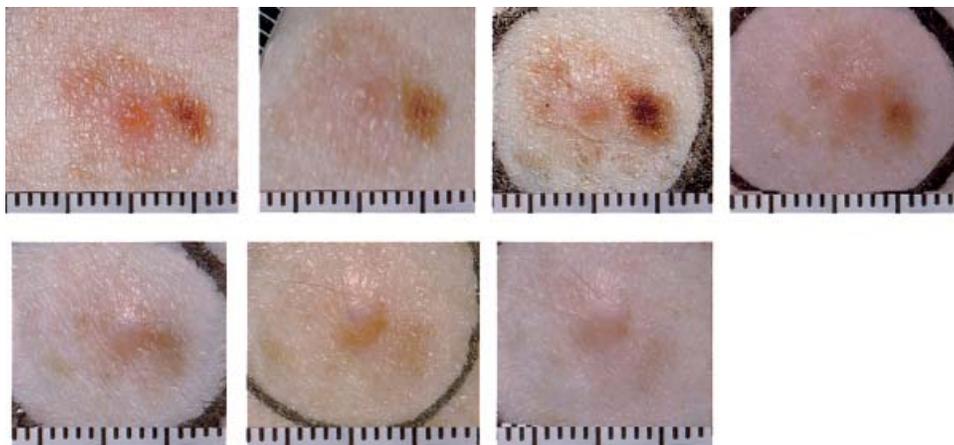


FIGURE 18. Evolving and regressing clinical dysplastic nevus (*CDK4* mutation). A close-up was taken of this lesion (A) because of its large size (13 mm \times 10 mm), irregular outline, indistinct border, variable pigmentation, and predominant flat component in a 25-year-old patient with multiple other clinical dysplastic nevi and > 300 total nevi. There was a complex central papule (2 mm) arising from a raised shoulder (4 mm) with normal skin markings. The more deeply pigmented area measured 6 mm \times 3 mm in diameter at the 3 o'clock position and had irregular indistinct borders. Two years later (B), the more deeply pigmented area had changed slightly in conformation, measuring 6 mm \times 4 mm, but was more uniformly and lightly pigmented. The central papule still measured 2 mm, but the 4-mm elevation surrounding it was no longer apparent. Two years later, at a time when other nevi were actively changing and biopsy was required (C), the central papule appeared to be more deeply pigmented with the color extending inferiorly. A second, less pigmented papule was noted arising superior to the central papule. The darker area was more deeply and irregularly pigmented, but had not changed in size or configuration. Three years later (D), the light pigmentation from the 9 o'clock to 11:30 position had faded. The central papule measured 3 mm and was more dome-shaped with normal skin markings and lighter color. The previously deeply pigmented area had faded. Two years later (E), the central papule was flesh colored with normal skin markings and the previously deeply pigmented area was light tan. Three years later (F), the central papule measured approximately 5 mm \times 4 mm, with a small rim of tan on the inferior border and a pale tan remnant of the previously dark area between the 3 o'clock and 4 o'clock positions. One year later, the lesion appeared to be a 7 mm \times 5 mm dermal nevus. Thus, over the course of 14 years, the lesion evolved from a classic clinical dysplastic nevus to a dermal nevus.

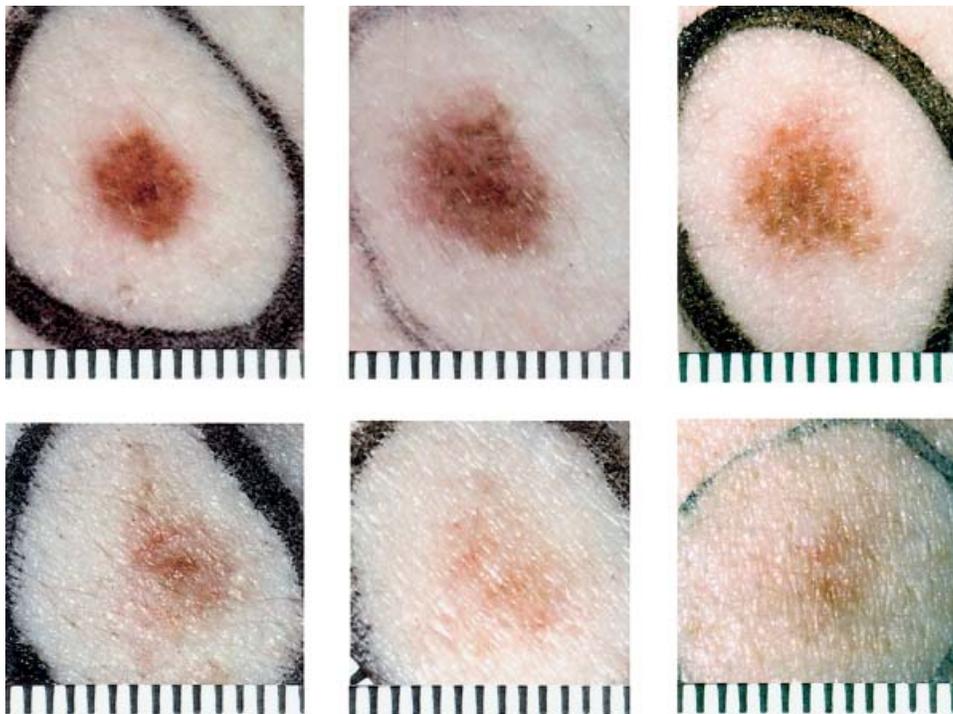


FIGURE 19. Evolving and regressing clinical dysplastic nevus (unknown mutation). A close-up photograph was taken of this 5-mm lesion because of the central darker area, indistinct borders, and erythematous base (A). The 15-year-old patient had > 200 nevi, many of which were clinical dysplastic nevi. This lesion was less atypical than many others found at the time of this examination. Panel B was taken 15 months later, when the lesion was 2-mm larger. The lesion had grown more in the area from the 9 o'clock to the 1 o'clock position with a more irregular, indistinct border. The pigment appeared less uniform, with the base pigmentation somewhat lighter, making the contrast between the darker and lighter areas more pronounced. The same linear dark plaque can be noted at the upper pole of the lesion. Two years later, the lesion had faded somewhat (C) at a time when other lesions were lightening. The linear dark plaque at the upper pole was much lighter, and the lower pole had changed from convex to concave. The erythematous base was less prominent, except at the upper pole. Four years later (D), the central dark area measured approximately 1 mm in greatest dimension and the entire lesion had faded dramatically. At the upper pole, there were some vestiges of pigment, which appeared to be outside the lesion. Three years later, the nevus has continued to fade, with some suggestion of beginning papule formation in the center (E). Five years later (F), the lesion was difficult to see, with only minimal darkened areas. Thus, over a 16-year period, the lesion progressed from a small to a larger dysplastic nevus, then regressed to a barely visible lesion.

similar geographic areas.^{1,37} In families without *CDKN2A* mutations, dysplastic nevi also are associated with an increased risk of melanoma.²³ It is impossible to predict mutation status on clinical examination, but the presence of dysplastic nevi is an important predictor of risk, regardless of mutation status. Nearly all melanomas in these American families occur in individuals with dysplastic nevi, similar to other melanoma-prone families in the mid-Atlantic region of the U.S.,⁴² in Sweden,⁴¹ and perhaps in the Netherlands.⁴³ A somewhat lower percentage of individuals with familial melanomas have been found to have dysplastic nevi in northeast Italy⁴⁴ and Australia.⁴⁵

The role of genetic testing in melanoma-prone families remains controversial. Members of an international melanoma consortium recently published guidelines for considering genetic testing in mela-

noma-prone families²⁰ and recommended that, although genetic testing is an important research tool for understanding the biology and the etiology of melanoma, it is not as useful for clinical decision-making. At the current time, knowledge of the mutation status of individuals does not change the clinical management of high-risk family members. As we have demonstrated in these photographs, there are no clinical or histologic differences in the nevi or melanomas that occur in these families regardless of whether mutations are found in *CDKN2A*, *CDK4*, or in neither. Even if an individual is found to have dysplastic nevi without a mutation in a family having a known mutation, that individual is at increased risk of melanoma and should follow clinical guidelines for skin care. The risk of melanoma in an individual without dysplastic nevi, but who has a mutation in *CDKN2A* or *CDK4*, is not well quantified. If these individuals follow clinical

guidelines for members of high-risk families (i.e., minimizing sun exposure, intermittent self-examination, and at least annual health care worker examination), it is likely that any suspicious lesions they may have also will be detected early.

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