On the clinical significance of cutaneous melanoma's precursors

Giuseppe Noto

U. O. Dermatology, Oncological Department, La Maddalena, Palermo, Italy

ABSTRACT

We can identify three main groups of cutaneous pigmented lesions that could be represented as melanoma precursors: (a) congenital melanocytic nevi, (b) dysplastic or atypical nevi, and (c) acquired melanocytic nevi. The occurrence of melanoma in small and intermediate congenital melanocytic nevi is very uncommon, but there is a high risk in large congenital melanocytic nevi, in particular those arising in the so-called "bathing trunk" distribution. It is very important to distinguish the familial dysplastic nevus syndrome, which is a strong risk factor for cutaneous melanoma, from not familial (sporadic) dysplastic nevus, in which the risk for melanoma would depend on the total number of melanocytic nevi, phototype, and on the relationship to environmental factors.

Key words: Congenital nevus, dysplastic nevus, melanoma

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.96690

Quick Response Code:

Address for correspondence:
Dr. Giuseppe Noto,
Via Villareale, 54,
IT-90141 Palermo, Italy.
E-mail:
notoderm@libero.it

INTRODUCTION

About 75%–80% of cutaneous melanomas originate on healthy skin, therefore only 20%–25% of melanomas are thought to develop on a cutaneous lesion that we can identify as a clinical precursor. It remains to be established whether or not the so-called precursors are to be considered as precancerous lesions or, rather, melanoma insurgence on a pre-existing lesion could occur due to a merely statistic percentage. This can be substained when nevi are considered as simply melanocytic aggregates, the risk of developing a melanoma being genetically determined, enhanced by some environmental factors, and theoretically present on the whole skin.

Of course, different biological conditions can arise in those rare instances in which a cutaneous melanoma develops on skin where the ability to repair the photo-induced damage is altered genetically as xeroderma pigmentosum, with a reported incidence of melanoma approximately 2000 times greater,[1] or in case of genetic or acquired immunodeficiency, that is, cases of immune impairment in organ transplant recipients[2] or in patients affected by Hodgkin's lymphoma.[3]

We can identify three main groups of cutaneous pigmented lesions that could be represented as melanoma precursors: (a) congenital melanocytic nevi, (b) dysplastic or atypical nevi, and (c) acquired melanocytic nevi. The main aim of this paper should be to clarify the clinical impact of the so-called melanoma precursor and, above all, an attempt to understand which clinical behavior could be more appropriate for each group.

CONGENITAL MELANOCYTIC NEVI

The most simple and obvious definition for congenital melanocytic nevus could be "melanocytic nevus present at birth"; however, some lesions showing the clinicopathologic features of congenital nevus can develop also during early childhood. The clinicopathologic diagnosis of congenital nevus is usually made when observing a cutaneous pigmented plaque, with well-defined borders, light to dark brown in color, often with follicular activation, conventionally distinguished in small (<1.5 cm), medium (1.5–20 cm), and large (>20 cm), characterized by the presence of melanocytes in the two lower thirds of the dermis, with occasional extension to the subcutaneous tissue. Nevus cells, appearing isolated or in regular rows and aggregates, can be found among collagen fibers in the reticular dermis, with tendency to periadnexal, perineurial, and perivascular disposition.

However, some congenital nevi do not show such histopathologic features; that happens in particular for small congenital nevi and in a not defined percentage of congenital nevi of medium size. This clinicopathologic disagreement could determine some discrepancies in the case of studies trying to establish the degree of melanoma risk of congenital nevi based exclusively on histopathologic grounds. The correct quantification of the incidence of melanoma associated with a congenital nevus seems to be a problem yet unsolved. In 1982[4] a study found a risk of melanoma as 21 times higher in patients whose congenital nevi were diagnosed clinically and anamnestically, while the risk was "only" 3–10 times higher when the nevi were diagnosed on the basis of histologic parameters. Others[5] had previously demonstrated that the reliability of the questionnaire compiled by the parents was not so high, and only a third of the lesions described as congenital nevus were shown as such on the basis of the histologic parameters. Moreover, in this study[4] an 8.1% incidence of melanoma associated to nevi with histological characteristics of congenital nevus was reported, an association 8 times higher when compared to other studies.[6] An investigation on 48 congenital nevi with diameter less than 10 cm[7] revealed only two cases showing nevus cells in the lower third of the dermis or in the subcutaneous tissue. Melanomas arising in congenital nevus were of junctional origin and all of them developed after 18 years of age. None of these melanomas showed the neuromesenchymal features frequently observed in melanomas associated to giant congenital nevi. Indeed, the "nonepidermic" insurgence of a melanoma on small congenital nevi is considered exceptional,[8,9] unlike giant congenital nevi.

In another study the risk of melanoma was evaluated in 265 cases of congenital nevi[10]: no melanomas were observed in the 232 individuals with a congenital nevus involving less than 5% of the body area; in the 33 cases presenting nevi involving more than 5% of the body surface two melanomas were diagnosed. In a further clinical investigation,[11] on 230 medium-sized congenital nevi followed until 26 years of age, no melanoma was observed. On the contrary, in giant congenital nevi, the melanoma's risk has been estimated between 5% and 20%.[12] In another evaluation,[13] 46 cases of giant congenital nevus were followed and it was established that the cumulative risk of melanoma was 5.7%. The melanocytic tumor that develops on giant congenital nevus frequently shows a heterogenous morphology determined by transformation of neural crest cells in a heterotopic site probably for an altered migration in the embryogenetic phase.[14] There is also a risk of extracutaneous melanoma, in particular involving the leptomeninx, in patients with neurocutaneous melanosis. Moreover, it should be emphasized that approximately 60% of melanomas developing in giant congenital nevi arise during the first decade of life, in particular within the first 5 years.[15] A further problem is due to the fact that, as about two thirds of melanomas in giant congenital nevi are of "nonepidermic" origin,[16] clinical and dermoscopic observations, which should allow early detection of a "junctional" melanoma, are not helpful in this cases.

On the contrary, in small congenital nevi melanoma can develop, as happens in acquired melanocytic nevi, at the dermoepidermal junction presenting a risk that seems to be extremely low, therefore the prophylactic excision would not be immediately indicated. If surgical intervention is planned, this can be performed during the pubertal age because the malignant transformation in prepubertal age is an exceptional event. On the contrary, in giant congenital nevi, due to the high risk of developing a melanocytic tumor with neuro-mesenchymal features, surgical exeresis (often not easy) are advised in young age. In these cases the deepening of the surgical toilette up to the fascia does not guarantee to reach complete excision, since primordial neuromesenchimal cells can remain in deep tissues.[17] In medium-sized congenital nevi the precancerous risk could depend more on the histopathologic pattern of the lesion than on the size of the nevus. A good part of these "intermediate" nevi, as usually observed in small congenital nevi, can lack melanocytes in deeper layers of the dermis. Therefore a small incisional punch biopsy on medium-sized congenital nevi could sometimes allow a better prognostic evaluation.

DYSPLASTIC NEVI OR ATYPICAL NEVI [FIGURES 1-4]

Dysplastic nevus was first observed and described in 1978 in 6 families with an increased incidence of melanoma.[18] Such pigmented lesions showed heterogeneous features regarding shape, color and size, they appeared mainly localized in the upper portion of the trunk and on limbs, they were detected in a great number in each individual, and those families in which these nevi were observed showed a higher incidence of melanoma. This condition has been subsequently described under various denominations, that is, dysplastic nevus syndrome, atypical familial nevus syndrome, and melanoma syndrome.[19-21]

Dysplastic nevi can be observed in patients with or without melanoma; an important clinical feature seems to be its familial or sporadic presentation. Usually, dysplastic nevi show a diameter greater than 5 mm appearing as a macular lesion or a small plaque with or without a central relief, the color appearing light to dark brown often distributed irregularly. They are quite common in clinical practice, representing approximately 5% of cutaneous histopathologic reports.[22] Clinically, dysplastic nevi differ from common acquired nevi for appearing during pubertal age or even childhood, showing a dynamic behavior during the adult life, and also for continuing to develop during life, also beyond the fourth decade.

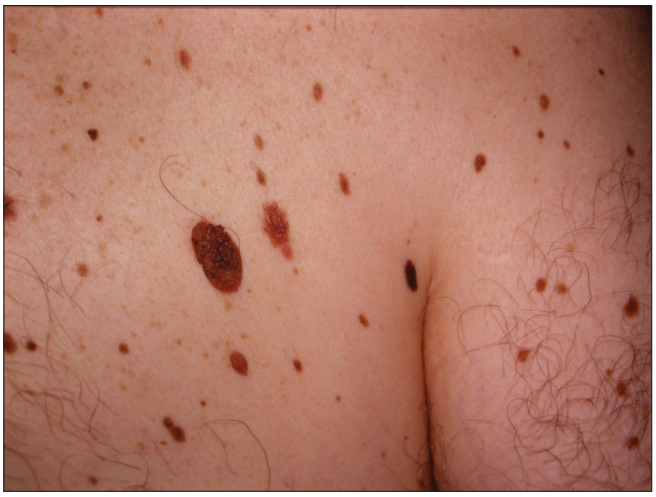

Figure 1: Dysplastic nevus syndrome

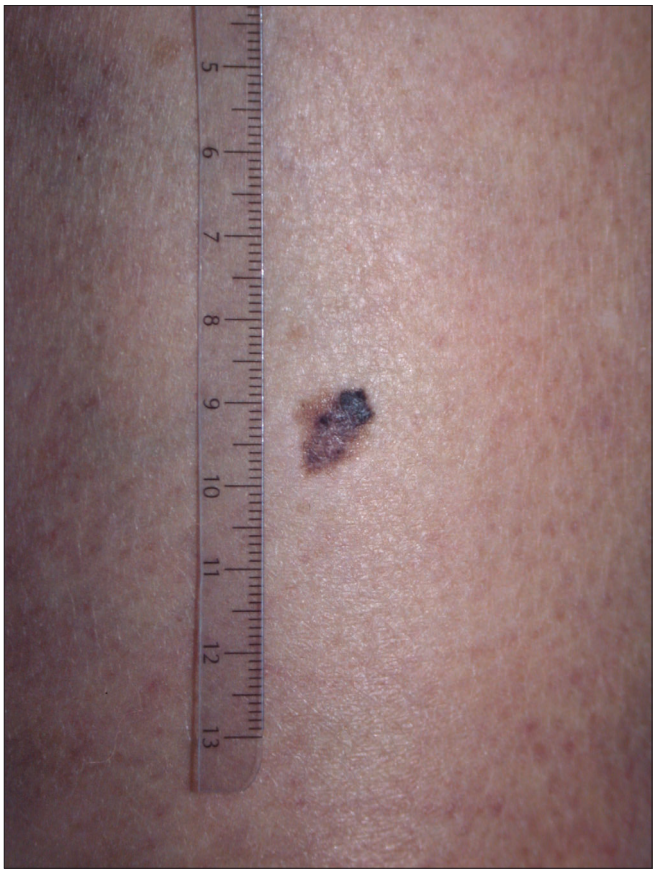

Figure 2: Early melanoma

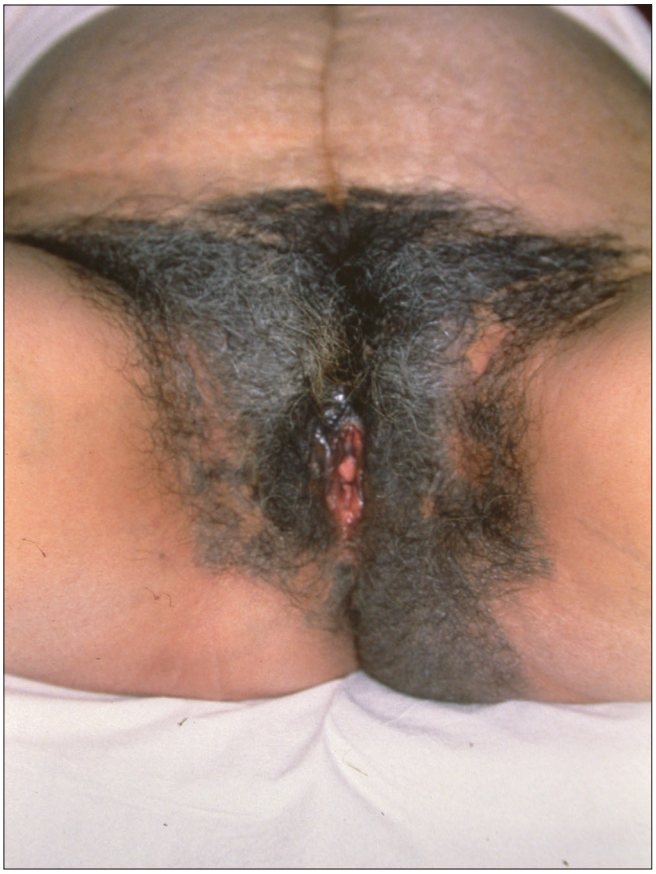

Figure 3: Giant congenital nevus

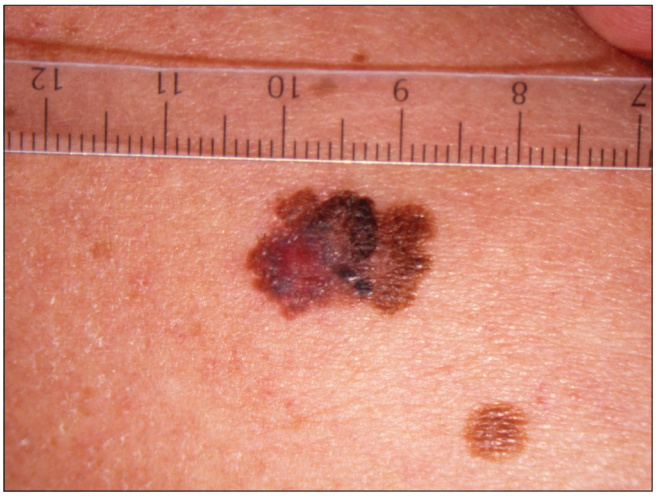

Figure 4: Superficial spreading melanoma

Histopathologic features for the diagnosis of dysplastic nevus are less clear than clinical ones. A consensus conference[20] defined some criteria, that is, the presence of architectural disorder with asymmetry, subepidermal fibroplasia (concentric or lamellar), atypical melanocytic hyperplasia with fusiform or epithelioid cells isolated or arranged in nests appearing irregular in shape and size with the formation of bridges between epidermal rete ridges. Cytological atypia of melanocytes can appear in variable degree, as well as a lymphomonocytic inflammatory infiltrate in the superficial dermis. The condition was defined as "atypical nevus and familial melanoma syndrome" with the presence of melanoma in one or more blood relatives of first or second degree, a great number of melanocytic nevi with atypical clinical aspect, often more than

50, and histopathologic features of dysplastic nevus.

Nowadays, the clinical evidence of familial dysplastic nevus syndrome is not called into question. The risk of developing a melanoma would be 184 times greater in patients with familial dysplastic nevus without familial melanoma, whereas it would be 500 times greater in patients with familial dysplastic nevus and familial history of melanoma[21] Subjects presenting sporadic dysplastic nevus are considered by some authors as patients having an increased risk of melanoma, however, in lower extent than subjects with familial dysplastic nevus.[23] With increasing of the number of dysplastic nevi in the same patient, the risk of correlated melanoma would also increase.[24,25] A remarkable nosologic problem on the concept of nonfamilial dysplastic nevus is represented by the clinicohistologic correlation that, often, is not coherent, as it is possible to observe a nevus clinically dysplastic that histologically reveals itself as normal and vice-versa. Therefore, the possibility to predict histologic dysplasia on clinical grounds is quite limited.[26] In a study on 91 clinically dysplastic nevi only 23 showed histologic dysplasia.[27] A further critical evaluation, using only objective histologic criteria for diagnosis of dysplastic nevus, paradoxically established an incidence of 53% dysplastic nevi in caucasian individuals.[28]

ACQUIRED MELANOCYTIC NEVI

Common melanocytic nevi are constituted by aggregates of nevus cells (or melanocytes) which in the great majority of caucasian population clinically appear as small cutaneous macular or maculopapular lesions, colored from brown to dark brown, measuring a few millimeters in diameter. Apart from this common melanocytic flat nevus, the rest of the acquired melanocytic nevi with peculiar features observed in caucasian individuals can be defined, following a well-known eponymic classification, as Clark's, Unna's, Miescher's, Spitz's, and Reed's nevus.[29]

Histologically, melanocytic nevi are classified as junctional (regular aggregates of melanocytes located at the tips of epidermal rete ridges), intradermal (regular cords of nevus cells in the dermis with progressive maturation in depth), compound (with both the components), and lentiginous (with a regular epidermal hyperplasia).

Apart from the small flat pigmented common nevus, Clark's nevi constitute the great majority of acquired melanocytic nevi; they appear as macular, maculopapular or small plaque lesions, light to dark brown in color, with a round or ovoid shape, with a variable diameter from a few millimeters up to one centimeter, sometimes with irregular borders and/or slight asymmetry, a smooth surface or a slightly raised palpable area found in the center of the lesion. In Clark's nevi one can occasionally observe a small regular regressive area appearing very limited when compared to the total area of the nevus. Unna's nevi appear as exophytic, pedunculated or sessile lesions, dark brown in color, measuring a few millimeters, with soft texture and smooth surface. Miescher's nevi present as papular lesions, a few millimeters in diameter, light brown or of skin colored, with a dome-shaped smooth surface and regular borders, generally localized on the face.

Spitz's nevi usually develop during childhood, they are frequently localized on the face, appearing as red/pink to light brown papular lesions, with smooth surface and regular borders; histologically, they show epithelioid or fusiform melanocytes, usually hypopigmented, forming within the epidermis a number of vertically arranged ovoid nests, with epidermal hyperplasia and typical clefts; small eosinophilic globules (Kamino's bodies), residual of basal membrane, can be observed. Melanocytes can penetrate deeper in the dermis with some cell maturation and occasional slight lymphomonocytic inflammatory infiltrate. Reed's nevi, considered as a variant of Spitz's nevi formed by pigmented spindle cells, clinically appear as round to ovoid papules or plaques, heavily pigmented, dark brown to black in color, symmetrical, with onset in the young adult, mainly on the limbs, slightly palpable, with a typical dermoscopic pattern characterized by radial streaks all around the perimeter (starburst pattern); it is a current opinion, we do not know if absolutely right, to remove surgically Reed's nevi after the pubertal age. Blue nevus appears like a small papule or plaque lesion, frequently localized on the dorsal aspect of hands and feet, with a homogeneous bluish color, smooth surface, histologically formed by the presence of dendritic melanocytes localized in the dermis, accompanied by occasional melanophages and fibrous stroma. The so-called malignant blue nevus is a rare melanoma developing within a blue nevus or differentiating towards it. Other less frequent nevi must not be forgotten, like Sutton nevus or halo nevus (a round, regular vitiligo-like halo around the nevus), Meyerson's nevus (with spongiotic inflammatory reaction) and Barr's nevus (with desmoplastic histologic pattern).

Acquired melanocytic nevi usually appear after the first year of life and can increase in number and diameter during (and also after) the somatic growth, normally not exceeding 5 millimeters in diameter.[23] Only 20% of adults would not show common flat nevi or Clark's nevi larger than 2 millimeters.[30] In any case, the presence of acquired melanocytic nevi in each population is determined by genetic, environmental and probably immunologic factors.[31] Nevi are mainly located in the photoexposed areas or in sunburn areas.[32] It has been established that patients with more than 50 melanocytic nevi should have an increased relative risk for melanoma, quantified in 12.1 in the absence of clinical criteria for dysplastic or atypical nevi, whereas in individuals with clinically atypical nevi, that is, diameter greater than 7 mm, irregular borders and not

homogeneous color, the relative risk for melanoma should grow to 54.[30] In another study, subjects with a total number of nevi between 50 and 100 had a relative risk for melanoma of 3.2, compared to a control group composed of individuals with a total number of nevi between 0 and 4. Patients with more than 100 nevi should have a risk of 7.7.[33] In a further investigation, the relative risk for melanoma in central Europe, in subjects with more than 50 nevi, was quantified in 14.9.[34]

According to another study,[35] the relative risk for melanoma does not depend on the presence of clinically atypical nevi but only on the total number of Clark's nevi; patients with more than 120 nevi had a 19.6 risk and patients with nevi in sun unexposed areas should be looked upon as a subgroup with a major risk. Screening for melanoma seems to be more important when performed in mature and old age.[36]

Some methods, such as (fluorescence) in situ hybridization and mutation analysis can detect cytogenetic alterations in melanocytic tumors. Some mutations, early events in melanocytic tumors, in BRAF (melanocytic nevi), NRAS (congenital nevi), HRAS (Spitz nevi), and GNAQ (blue nevi) can all cause activation of the mitogen-activated protein kinase (MAPK) signaling pathway in the initiation of melanocytic tumors. However, other molecular alterations are implicated in tumor progression. This genetic heterogeneity in distinct types of nevi and melanomas could be used in the future for the development of molecular tests for diagnostic purposes.[37] Dysplastic nevi, clinically atypical with histologic architectural disorder and cytologic atypia, are significant only in relation to melanoma, as mimickers of melanoma, as markers of individuals at increased risk of developing melanoma, and maybe as potential and occasional actual precursors of melanoma. Individuals with dysplastic nevi may have deficient DNA repair, and dysplastic nevi lesions are associated with overexpression of pheomelanin, which may lead to increased oxidative damage and increased potential for DNA damage and tumor progression.[38] A recent, very impressive study on oncogenic BRAF-positive dysplastic nevi and the tumor suppressor IGFBP7 challenged the concept of dysplastic nevus as precursor lesion of cutaneous melanoma.[39]

CONCLUSION

Although the occurrence of melanoma in small and intermediate congenital melanocytic nevi is very uncommon, there is a high risk in large congenital melanocytic nevi, in particular those arising in the so-called "bathing trunk" distribution, risk estimated to be from 2.5% to 5%, highest in the first 5–10 years of life, with significant mortality. Large congenital melanocytic nevi, mainly those overlying the posterior axis and occurring within multiple satellite melanocytic nevi, are also associated with the development of neurocutaneous melanosis, with neurologic and neurodevelopmental sequelae, associated with a high risk of primary central nervous system melanoma.[40,41]

It is very important to distinguish the familial dysplastic nevus syndrome, which is a strong risk factor for cutaneous melanoma, from not familial (sporadic) dysplastic nevus, in which the risk for melanoma would depend on the total number of melanocytic nevi, on the phototype and on the relationship to environmental factors, keeping in mind that a great number of Clark's nevi constitute a risk factor for cutaneous melanoma in caucasian patients.[42] A current possible explanation of this could be that the patient with many nevi, having a greater number of nevus cells, or melanocytes, has also a greater probability to develop a melanoma. But, in reality, the great majority of melanomas (75%–80%) develop on healthy skin, therefore the clinical expression of many Clark's nevi, or sporadic dysplastic nevi, could simply be one of the aspects of the patient phenotype, whose skin has a greater relative risk for melanoma, a genetically encoded risk jointly enhanced by environmental factors.

REFERENCES

1. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum: Cutaneous, ocular and neurologic abnormalities in 830 published cases. Arch Dermatol 1987;123:241-50.
2. Greene MH, Young TL, Clark WH Jr. Malignant melanoma in renal-transplant recipients. Lancet 1981;1:1196-9.
3. Tucker MA, Misfeldt D, Coleman CN, Clark WH Jr, Rosenberg SA. Cutaneous malignant melanoma after Hodgkin's disease. Ann Intern Med 1985;102:37-41.
4. Rhodes AR, Melski JW. Small congenital nevocellular nevi and the risk of cutaneous melanoma. J Pediatr 1982;100:219-24.
5. Walton RG, Jacobs AH, Cox AJ. Pigmented lesions in newborn infants. Br J Dermatol 1976;95:389-96.
6. Kopf AW, Barb RS, Hennessey P. Congenital nevuscytic nevi in malignant melanoma. J Am Acad Dermatol 1979;1:123-4.
7. Illig L, Weidner F, Hundeiker M, Gartmann H, Biess B, Leyh F, *et al*. Congenital nevi ≤10 cm as precursors to melanoma. Arch Dermatol 1985;121:1274-81.
8. Sharpe RJ, Salasche SJ, Barnhill RL, Sober AJ. Non-epidermal origin of cutaneous melanoma in a small congenital nevus. Arch Dermatol 1990;126:1559-61.
9. Paull WH, Polley D, Fitzpatrick JE. Malignant melanoma arising intradermally in a small congenital nevus of an adult. J Dermatol Surg Oncol 1986;12:1176-8.
10. Swerdlow AJ, English JS, Qiao Z. The risk of melanoma in patients with congenital nevi: A cohort study. J Am Acad Dermatol 1995;32:595-9.
11. Sahin S, Levin L, Kopf AW, Rao BK, Triola M, Koenig K, *et al*. Risk of melanoma in medium-sized congenital melanocytic nevi: A follow-up study. J Am Acad Dermatol 1998;39:428-33.
12. Consensus conference on precursors of melanoma. JAMA 1984;251:1864-6.
13. Egan CL, Oliveria SA, Elenitsas R, Hanson J, Halpern AC. Cutaneous melanoma risk and phenotype changes in large congenital nevi: a follow-up study of 46 patients. J Am Acad Dermatol 1998;39:923-32.
14. Jerdan MS, Cohen BA, Smith RR, Hood AF. Neuroextradermal neoplasms tumors in congenital nevi. Am J Dermatopathol 1985;7 Suppl:S41-8.
15. Kaplan EN. The risk of malignancy in large congenital nevi. Plast

Reconstr Surg 1974;53:421-8.
16. Rhodes AR, Wood WC, Sober AJ, Mihm MC Jr. Nonepidermal origin of malignant melanoma associated with a giant congenital nevocellular nevus. Plast Reconstr Surg 1981;67:782-90.
17. Ruiz-Maldonado R, Orozco-Covarrubias ML. Malignant melanoma in children: A review. Arch Dermatol 1997;133:363-71.
18. Clark WH Jr, Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ. Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K mole syndrome'. Arch Dermatol 1978;114:732-8.
19. Greene MH, Clark WH Jr, Tucker MA, Elder DE, Kraemer KH, Fraser MC, *et al*. Precursor naevi in cutaneous malignant melanoma: a proposed nomenclature. Lancet 1980;2:1024.
20. NIH Consensus conference. Diagnosis and treatment of early melanoma. JAMA 1992;268:1314-9.
21. Greene MH, Clark WH Jr, Tucker MA, Kraemer KH, Elder DE, Fraser MC. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. Ann Intern Med 1985;102:458-65.
22. Crutcher WA, Sagebiel RW. Prevalence of dysplastic naevi in a community practice. Lancet 1984;1:729.
23. Rhodes AR, Weinstock MA, Fitzpatrick TB, Mihm MC Jr, Sober AJ. Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals. JAMA 1987;258:3146-54.
24. Bataille V, Bishop JA, Sasieni P, Swerdlow AJ, Pinney E, Griffiths K, *et al*. Risks of cutaneous melanoma in relation to the numbers, types, and sites of naevi: A case-control study. Br J Cancer 1996;73:1605-11.
25. Tucker MA, Halpern A, Holly EA, Hartge P, Elder DE, Sagebiel RW, *et al*. Clinically recognized dysplastic nevi: A central risk factor for cutaneous melanoma. JAMA 1997;277:1439-44.
26. Annessi G, Cattaruzza MS, Abeni D, Baliva G, Laurenza M, Macchini V, *et al*. Correlation between clinical atypia and histologic dysplasia in acquired melanocytic nevi. J Am Acad Dermatol 2001;45:77-85.
27. Roush GC, Dubin N, Barnhill RL. Prediction of histologic melanocytic dysplasia from clinical observation. J Am Acad Dermatol 1993;4:555-62.
28. Piepkorn M, Meyer LJ, Goldgar D, Seuchter SA, Cannon-Albright LA, Skolnick MH, *et al*. The dysplastic melanocytic nevus: A prevalent lesion that correlates poorly with clinical phenotype. J Am Acad Dermatol 1989;20:407-15.
29. Ackerman AB, Magana-Garcia M, di Leonardo M. Naming acquired melanocytic nevi - Unna's, Miescher's, Spitz's, Clark's. Am J Dermatopathol 1990;12:193-209.
30. Swerdlow AJ, English J, MacKie RM, O'Doherty CJ, Hunter JA, Clark J, *et al*. Benign melanocytic naevi as a risk factor for malignant melanoma. Br Med J (Clin Res Ed) 1986;292:1555-9.
31. Williams ML, Pennella R. Melanoma, melanocytic nevi, and other melanoma risk factors in children. J Pediatr 1994;124:833-45.
32. Gallagher RP, McLean DI, Yang CP, Coldman AJ, Silver HK, Spinelli JJ, *et al*. Anatomic distribution of acquired melanocytic nevi in white children. A comparison with melanoma: the Vancouver Mole Study. Arch Dermatol 1990;126:466-71.
33. Bataille V, Bishop JA, Sasieni P, Swerdlow AJ, Pinney E, Griffiths K, *et al*. Risk of cutaneous melanoma in relation to the numbers, types, and sites of naevi: a case-control study. Br J Cancer 1996;73:1605-11.
34. Weiss J, Bertz J, Jing EG. Malignant melanoma in southern Germany: different predictive value of risk factors for melanoma subtypes. Dermatologica 1991;183:109-13.
35. Grob JJ, Gouvernet J, Aymar D, Mostaque A, Romano MH, Collet AM, *et al*. Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. Cancer 1990;66:387-95.
36. Geller AG, Gilchrest B, Miller D. Should mass screening for skin cancer be targeted to middle-aged and older men? Findings from the United States. Melanoma Res 2001;11 Suppl 1:150-1.
37. Blokx WA, van Dijk MC, Ruiter DJ. Molecular cytogenetics of cutaneous melanocytic lesions - diagnostic, prognostic and therapeutic aspects. Histopathology 2010;56:121-32.
38. Elder DE. Dysplastic naevi: An update. Histopathology 2010;56:112-20.
39. Decarlo K, Yang S, Emley A, Wajapeyee N, Green M, Mahalingam M. Oncogenic BRAF-positive dysplastic nevi and the tumor suppressor IGFBP7--challenging the concept of dysplastic nevi as precursor lesions? Hum Pathol 2010;41:886-94.
40. Shah KN. The risk of melanoma and neurocutaneous melanosis associated with congenital melanocytic nevi. Semin Cutan Med Surg 2010;29:159-64.
41. Price HN, Schaffer JV. Congenital melanocytic nevi-when to worry and how to treat: Facts and controversies. Clin Dermatol 2010;28:293-302.
42. Psaty EL, Scope A, Halpern AC, Marghoob AA. Defining the patient at high risk for melanoma. Int J Dermatol 2010;49:362-76.

Cite this article as: Noto G. On the clinical significance of cutaneous melanoma's precursors. Indian Dermatol Online J 2012;3:83-8.

Source of Support: Nil, **Conflict of Interest:** None declared.