Dysplastic nevus: Fact and fiction

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The term "dysplastic nevus" (DN) implies that this nevus exists as a distinct and defined entity of potential detriment to its host. We examine the current data, which suggest that this entity exists as histologically and possibly genetically different from common nevus, with some overlapping features. Studies show that a melanoma associated with a nevus is just as likely to arise in a common nevus as in DN. Furthermore, there is no evidence that a histologically defined DN evolves into a melanoma or that the presence of 1 or more DN on an individual patient confers any increased melanoma risk. We suggest that the term "dysplastic nevus" be abandoned so that the focus can shift to confirmed and relevant indicators of melanoma risk, including high nevus counts and large nevus size. (J Am Acad Dermatol 2015;73:507-12.)

Key words: B-K mole syndrome; *BRAF*; common nevus; congenital melanocytic nevus; cyclin-dependent kinase inhibitor 2A *(CDKN2A)*; dysplastic nevus; familial atypical multiple-mole melanoma; melanoma; *p16, p53*.

The term "dysplastic nevus" (DN) is derived from Greek "dys-" (bad or malfunction) and "-plasia" (growth development or change).[1] The name implies that this nevus exists as a distinct and defined entity of potential detriment to its host. In 1992 a National Institutes of Health (NIH) Consensus Conference recommended that the term "dysplastic nevus" be replaced with "nevus with architectural disorder" with or without cytologic atypia[2] but the appellation "dysplastic nevus" continues to be widely used. Not only is the term used but the implication persists that the DN per se is dangerous, as evidenced by a survey of Fellows of the American Academy of Dermatology where "most respondents, in agreement with the literature, accept the concept that patients with dysplastic nevi are at increased risk for melanoma."[3] The status of DN, whether it exists and whether it is potentially harmful or a marker of potential harm to its host, is worthy of clarification. Almost a quarter of a century after the NIH Consensus Conference recommended the term "dysplastic nevus" be abandoned, we believe enough evidence exists for this matter to be clarified.

Abbreviations used:

CMN:	congenital melanocytic nevus
CN:	common nevus
DN:	dysplastic nevus
DNS:	dysplastic nevus syndrome
NIH:	National Institutes of Health
WHO:	World Health Organization

HISTORY OF THE TERM "DYSPLASTIC NEVUS"

DN was originally described as a clinically and dermatopathologically defined lesion in melanoma-prone families, with the implication that it was premalignant.[1]

In 1952 Cawley et al[4] were the first to describe familial melanoma in a case with a father and 2 of his 3 children.

In 1978, Wallace Clark et al[5] described distinctive nevi in 6 melanoma-prone families that included 69 members over 4 generations, 25 (36%) of whom had melanoma. According to this study, 15 of these patients with melanoma were said to have the so-called B-K mole syndrome. The authors stated that this syndrome was characterized by the

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Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication April 16, 2015.

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Published online May 30, 2015.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.04.029

presence of less than 10 to more than 100 nevi, 5 to 15 mm in diameter (the ranges presented making these criteria arguably meaningless), and with variability in border and color. The authors excised some of these nevi and described the histologic findings.

It was in the same year that Lynch et al[6] reported what they regarded as a similar nevus phenotype in 1 melanoma-prone family over 5 generations. Three of the 4 individuals given a diagnosis of melanoma had "atypical and numerous (>200) nevi." They called this syndrome "familial atypical multiple-mole melanoma syndrome."

Not only were nevus counts very different between the familial atypical multiple-mole melanoma and B-K mole syndromes but the familial atypical multiple-mole melanoma syndrome, with 4 individuals developing melanoma over 5 generations, seems far removed from the B-K mole syndrome in which 36% of family members had melanoma, suggesting that the widely accepted belief that these 2 syndromes are synonymous is fundamentally flawed.

In 1980 Elder et al,[7] reporting on 79 patients with melanoma, but no family history of melanoma, coined yet another term: "dysplastic nevus syndrome" (DNS). It is significant that although 7 patients (9%) had 2 to 5 larger (0.5-1.5 cm) buttock lesions, the average total nevi was only 26, and 5 patients (6%) had no other identifiable nevi whereas 59 patients (74%) had normal-appearing nevi. On the basis of this study Elder et al[7] postulated the existence of sporadic and familial variants of DNS and claimed that DN was a precursor to melanoma, based on the microscopic dysplasia.

Clark et al[5] described a patient cohort with modest nevus numbers and 36% of family members having melanoma, calling it "B-K mole syndrome," whereas Lynch et al[6] presented a cohort with much higher average nevus counts and a much smaller number of melanoma-affected individuals and Elder et al[7] coined the term "dysplastic nevus syndrome" referring to a cohort with no family history of melanoma at all, most of whom had normal-appearing nevi. It does not appear credible that these 3 so-called syndromes are synonymous as has been accepted by so many for so long.

CAPSULE SUMMARY

- In 1992, the National Institutes of Health recommended that the term "dysplastic nevus" be abandoned.
- We reassess whether dysplastic nevus is a separate entity of potential harm to its host.
- A study of nomenclature, in light of historical context and scientific literature, will enable clinicians to make informed decisions about dysplastic nevus.

In 1992, the NIH Consensus Conference defined DNS/familial atypical mole melanoma syndrome with the following criteria: melanoma in 1 or more first- or second-degree relatives; the presence of more than 50 nevi with many having atypical clinical features; and nevi that have distinct histologic features.[2] The NIH also recommended that the term "dysplastic nevus" be abandoned and replaced with "nevus with architectural disorder, accompanied by a statement describing the presence and degree of melanocyte atypia" (mild, moderate, or severe).[2]

In spite of the fact that initial assumptions from studies on melanoma kindreds may be flawed, there have been many studies of melanoma-prone families and the following information has been verified: (1) members of these families who do not have DN phenotype can get melanoma[5]; (2) although up to 30% to 40% of these melanoma-prone families harbor cyclin-dependent kinase inhibitor 2A (*CDKN2A*) mutations, conversely, 60% to 70% do not[8]; and (3) most so-called atypical nevi in these family members remain stable or regress over 25 years and most melanomas in these families actually arise de novo or in clinically typical nevi.[9]

CAN DN BE DIAGNOSED CLINICALLY?

There is now compelling evidence that DN as a histologic entity cannot reliably be correlated with any clinical entity.[1]

In 1 study 58 clinically common nevi (CN) were prospectively analyzed (<5-mm diameter, uniformly pigmented, symmetric, with distinct margins and no erythema). Of these nevi, 88% had at least 1 histologic feature of DN, 69% had 2 features, and 29% had 3 features.[10]

In another study 940 acquired nevi were assessed clinically by 5 dermatologists and then blindly examined by a dermatopathologist.[11] Poor correlation between clinical atypia and histologic dysplasia was evidenced by a κ value of 0.17 (sensitivity 58.4%, specificity 66.6%). In particular, many small nevi (3-5 mm), not thought to be clinically atypical, were found to exhibit histologic dysplasia.

It is accepted, including by proponents of the term "dysplastic nevus," that this entity cannot be defined by clinical criteria and that it must therefore be defined histologically.[1] In fact although the NIH

Table I. Molecular and genetic characteristics of dysplastic nevi compared with common nevi

Molecular/genetic feature	DN compared with CN	References
Clonality	Present in both	16,17
RNA expression patterns		
Mitosis and apoptosis	Similar	16,18
Transcription regulation	Similar	16,19
BRAF mutation	Similar	20,21
p16 mutations	Rare in both	16,22
p53 protein expression	Increased in DN in 2 studies (similar in earlier studies)	16,23,24(16,25,26)
Microsatellite instability		
1p and *9p*	Present in 17/60 DN but in none of the CN	16,27
9p21 deletions	Present in 12/22 DN and 2/20 CN	16,28
Proliferation (*Ki-67*)	Higher in DN	16,18,29
Reactive oxygen species	Elevated in DN compared with CN	16,30
Senescence markers		
BRAF and *IGFBP7* Dissociation	Similar rates in DN and CN	16,31

CN, Common nevus; *DN*, dysplastic nevus; *IGFBP7*, insulin growth factor binding protein 7.

Consensus Conference in 1992 defined DNS as a clinical entity, the World Health Organization (WHO) since 1991 has defined DN on histologic features alone with the diagnosis requiring both of 2 major criteria and at least 2 minor criteria[12]:

Major criteria

- Basilar proliferation of atypical melanocytes that must extend at least 3 rete ridges beyond the dermal component
- Organization of this proliferation in a lentiginous or epithelioid-cell pattern

Minor criteria

- Lamellar fibrosis or concentric eosinophilic fibrosis
- Neovascularization
- Inflammatory response
- Fusion of rete ridges

When using the WHO (histologic) criteria stated above, there is a reported 92% overall concordance in distinguishing among acquired melanocytic CN, DN, and melanoma.[12]

Although it is true that many epidemiologic studies that have cited an increased risk of melanoma have evaluated DN primarily or exclusively using clinical criteria,[13] it is evident that the weak correlation between clinical atypia and histologic dysplasia disqualifies such an approach.[14,15]

IS THERE ANY MOLECULAR AND GENETIC EVIDENCE FOR (HISTOLOGIC) DN AS AN ENTITY DISTINCT FROM CN?

Studies that have compared molecular and genetic characteristics of DN and CN are presented in Table I.

In sum, DN appears to differ from CN with respect to reactive oxygen species and some proliferation genes but not with respect to other RNA expression patterns, clonality, *BRAF* or *p16* mutations, apoptosis markers, or senescence markers. There is conflicting evidence regarding differences with respect to microsatellite instability and *p53* expression.

WHAT IS THE RELATIVE INCIDENCE OF (HISTOLOGIC) DN AND CN?

This is not known because the diagnosis of DN versus CN requires histology and the majority of nevi are not examined histologically.[1]

There is limited information about the prevalence of DN from autopsy studies and in 1 such study it was found to be 10%.[32] Another study estimated the prevalence of DN to be 50% in Caucasians.[33]

IS THERE EVIDENCE THAT LESIONS IDENTIFIED AS (HISTOLOGIC) DN INCLUDE CONGENITAL NEVI?

In 2005, Harada and Ackerman[34] were the first to point out that a significant entity had been overlooked: the congenital melanocytic nevus (CMN). CMN, identified as being present at birth, have distinctive histologic features.[35,36] These features are also found in nevi with no verified presence at birth and such nevi, including some with terminal hair as evidence of their hamartomatous nature, are known as congenital-like melanocytic nevi. In 2007, Ackerman and Kittler[37] published a series of clinical and histopathological images taken from textbooks and studies, which purported to show DN but that they argue actually displayed CMN.

IS THERE ANY SIGNIFICANCE OF (HISTOLOGIC) DN WITH RESPECT TO MELANOMA RISK?

There is no evidence that individual CN or DN will inevitably progress through sequentially higher grades of dysplasia to melanoma.[1] Unfortunately, there is no model to examine this because identification of any nevus results in its destruction and there are no suitable animal models.[1]

Using a model that examined the number of melanomas each year with associated nevi (any type) components and assuming that this approximated the minimal number of nevi transforming to melanomas, it has been estimated that the lifetime risk of any individual nevus transforming to a melanoma is 1 in 10,000.[38]

Again, considering the possibility of a genetic link between nevi (any type) and associated melanoma, studies indicate similar levels of *BRAF* mutation in CN and DN.[20,21] Another study selectively microdissected and genotyped cells from 46 melanomas, the nevus associated with these melanomas, and 25 control nevi from the same patients. No significant differences in the distribution of *BRAF* or *NRAS* mutations could be found between melanoma and associated nevi or between melanoma-associated nevi and control nevi.[39]

Several studies have attempted to correlate the degree of melanocyte dysplasia with melanoma risk. Retrospectively reviewed nevi with mild, moderate, and severe dysplasia on histology revealed that 19.7% of patients with severely DN had a history of melanoma, a higher percentage than patients with mild (5.7%) or moderately (8.1%) DN.[14] It was concluded that melanoma risk is higher for individuals with severely DN. Although this appears to show a relation between histologic dysplasia and melanoma risk these findings depend fundamentally on the integrity of the grading of dysplasia and although a 92% overall concordance in the diagnosis of DN using WHO histologic criteria has been demonstrated,[12] the grading of dysplasia does not appear to be as reliable. In 1 study that assessed correlation between DN and melanoma risk, 80 patients with melanoma and 80 spousal control subjects had the most clinically atypical nevus on each person biopsied. Thirteen dermatopathologists independently graded dysplasia. Among the entire group interobserver reliability associated with grading was poor with a κ value of 0.28.[15] Only 2 of the 13 pathologists had individual scores that correlated with melanoma risk.

With respect to the relative proportion of nevi-associated melanomas that arise in association with a DN, the evidence is conflicting, but the majority of melanomas associated with nevi are found with CN.[40-42]

Accepting that histologic grading of dysplasia in melanocytic nevi is unreliable, there is no evidence that the presence of DN as opposed to CN confers increased melanoma risk.

IS THERE ANY USE IN RE-EXCISING (HISTOLOGIC) DN?

The current literature suggests that re-excision of mildly to moderately DN is not warranted. In most cases, when a DN with positive biopsy margins is re-excised, the pathology shows only a scar.[43,44] More importantly, long-term follow-up shows no development of melanoma at the biopsy site of DN incompletely or narrowly removed.[45] Caution lies in the diagnosis of a severely DN, because it may represent misdiagnosed melanoma in situ.[46] In fact this recommendation to re-excise DN graded as severely dysplastic highlights the likelihood that the grading may reflect dermatopathological uncertainty.

WHAT FEATURES OF NEVI DO RELATE TO MELANOMA RISK?

There are 2 objective criteria that have been shown to correlate with melanoma risk:

1. It is known that a high nevus count correlates with a higher risk of melanoma.[47] In 1 meta-analysis, people with a nevus count over 100 had a 7 times higher risk of melanoma compared with those with a count of less than 15.[13]

2. The presence of large nevi on an individual increases the relative risk of melanoma. One study that histologically examined the nevus deemed to be most clinically atypical on an individual found that if such nevi less than 2.4-mm diameter have a relative risk of 1.0, the relative risk increases progressively to 5.08 at a diameter of greater than 4.4 mm with respect to that individual's risk of having had a melanoma.[48]

Conclusion

Based on current data, there is evidence that there is a histologic entity, currently named "dysplastic nevus," that is histologically and possibly genetically different from CN, with some overlapping features.

With respect to the implication that DN is in some way harmful to its host, over 20 years of research since the first recommendation to abandon the term

has produced no convincing evidence. To the contrary, there is strong evidence that a melanoma associated with a nevus is just as likely to arise in a CN as in a DN, even without considering the likelihood that some designated DN are CMN. Furthermore, there is no evidence that a DN evolves into a melanoma or that the presence of 1 or more DN on an individual patient confers any increased melanoma risk.

What does confer increased melanoma risk are high nevus counts and large nevus size.

The entity named "dysplastic nevus" is as harmless, as dangerous, and as common as any other nevus. Why does such a misnomer continue to be propagated? Maybe, as Kittler and Tschandl[49] suggested, it is because the concept of stepwise tumor progression is appealing and plausible, the diagnosis of DN can conveniently cover uncertainty of a pathologist, and, in some cases, it can sanctify an unnecessary excision by a clinician.

Continued use of the appellation "dysplastic nevus" has a clear potential to encourage inappropriate practice and we suggest this name should be abandoned so that the focus can shift to confirmed and relevant indicators of melanoma risk.

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