Dispelling a common myth: Most melanomas do not arise from moles

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It is not uncommon to hear patients and occasionally physicians describe moles (nevi) as "precancerous." At time of skin exam, some may report they had "precancerous moles" removed in the past and may request that other nevi be excised in the hopes of "preventing melanoma." In fact, prophylactic excision of nevi has not been shown to reduce melanoma risk. The confusion is understandable as even among dermatologists the description and management of nevi is a topic that has been under much scrutiny.

Nevi, benign melanocytic proliferations, are found on most patients. Here are a few important points that may be helpful to all physicians, regardless of specialty:

The majority of melanomas do not arise from pre-existing moles. Studies show that over 70% of melanomas arise "de novo" and have no associated nevus. In other words, most melanomas appear as a new growth that did not arise from a prior nevus. The lifetime risk of a nevus transforming into a melanoma is 0.03% for men and 0.009% for women.[1]

Dysplastic nevi can look clinically similar to melanoma, but do not have a higher chance of becoming melanoma as compared to benign nevi. Dysplastic (or atypical) nevi are defined clinically as moles with 2 of the 3 following characteristics: variable pigmentation, irregular asymmetric outline and indistinct borders. These are features that can also be seen in melanoma and distinguishing a dysplastic nevus (DN) from a melanoma can be challenging clinically.[2] Therefore, if a lesion is suspicious, biopsy is warranted to exclude melanoma.

Histopathologically, all melanocytic lesions are evaluated at low magnification for breadth (overall size) and the presence or absence of symmetry and circumscription. This is why it is recommended that the entire lesion be submitted for histologic evaluation. Benign melanocytic nevi are typically smaller in size, and they are relatively symmetric and well circumscribed. DNs also demonstrate architectural disorder and cytologic atypia that is graded mild, moderate, or severe. Architectural disorder refers to features such as bridging of adjacent nests of melanocytes along the dermoepidermal junction, extension of the junctional component beyond the dermal component at the periphery of the lesion (shoulder sign), and lentiginous melanocytic hyperplasia along the dermoepidermal junction. Cytologic atypia is characterized by variable nuclear enlargement and nucleoli. There is also associated lamellar and concentric fibroplasia within the dermis, and there is often an associated inflammatory cell infiltrate.

In most cases, the diagnosis can be reached following review of the routine hematoxylin and eosin stain slide. However, in some cases DNs can display overlapping features with malignant melanoma. For example, DNs that have been previously excoriated or partially sampled can display architectural disorder that resembles changes that are also seen in malignant melanoma (i.e. contiguous growth of melanoctyes along the dermoepidermal junction and upward spread of melanocytes into the epidermis). These histologic changes are referred to as recurrent nevus phenomenon.

When a definitive diagnosis cannot be reached following review of the routine hematoxylin and eosin stain slide, additional studies can be performed to further evaluate the lesion. Immunohistochemical stains (i.e. Melan A, SOX10, HMB-45, PRAME, Ki67) are routinely employed in these circumstances, and other studies can also be utilized when findings are still equivocal following the review of the immunohistochemical stains (i.e. gene expression profiling, SNP array, next generation sequencing).

Patients with higher numbers of nevi and/or atypical nevi are at higher risk of melanoma. As overall number of nevi (benign or dysplastic) increases, so does melanoma risk. Patients with 41-60 nevi have a 2.2X increased risk of melanoma, and patients with 101-120 nevi have an almost 7-fold increased risk. For most of these patients, if they develop a melanoma, it will be a "de novo" lesion (not associated with one of their moles). However, the number and atypia of their nevi can be phenotypic markers of melanoma risk.[3] If you have patients with numerous nevi and/or large (>5 mm), multicolored, asymmetric nevi, they should be seen by dermatology for an annual exam. A retrospective, cross-sectional study at the University of Pittsburgh showed that patients who had an established dermatologist were more likely to have a diagnosis of in situ melanoma or thinner invasive melanoma than patients without an established dermatologist. They hypothesize that the education received during dermatology exam and the ability to obtain an appointment more easily, may allow for earlier diagnosis.[4]

Nevus associated melanoma does not occur more frequently with dysplastic nevi. When a melanoma does arise from a prior mole (nevus associated melanoma), it is more often in an acquired vs. congenital nevus (nevus that appears within the first year of life). Among the acquired nevi, dysplastic nevi do not have a higher risk of turning into melanoma than benign nevi.[3]

Guidelines state that only dysplastic nevi with severe atypia need to be fully excised. Grading of dysplastic nevi is a nuanced skill with some inherent subjectivity that requires an overall assessment of the degree of cytologic atypia and architectural disorder within a given lesion. If you are performing skin biopsies in your office, be certain that (1) you sample the entire lesion (do not perform a partial biopsy of a pigmented lesion) and (2) that you send the biopsy to a laboratory with an experienced dermatopathologist to review the case. Good data supports that mildly and moderately atypical DNs do not need to be re-excised, even if biopsy margins are positive. According to findings from a multicenter retrospective study performed by the Pigmented Lesion Subcommittee, moderately atypical DNs did not evolve into melanoma. However, 20% of patients who had a moderately atypical DN went on to develop a melanoma at another site during the study – supporting the recommendation that these higher risk patients be followed by regular skin exams.[5] Severely atypical DNs are likely not precursor lesions either. However, because severely atypical DNs and melanoma can display overlapping histopathologic findings, it is recommended that these lesions be fully excised to prevent misdiagnosis.[6] Importantly, negative margins on punch or shave biopsies do not confirm complete lesion removal. Studies show 30% of punch excised melanocytic lesions with negative margins in the initial sections, had positive margins when additional sections were reviewed.[6]

BRAFV600E mutation is the most common mutation in melanoma. Eighty percent of benign nevi also harbor this mutation. Genetic studies suggest that secondary and tertiary proliferation mutations (mainly TERT and CDKN2A) are needed to produce melanoma. Despite some genetic similarities, most nevi, even most atypical nevi, do not progress to melanoma. Patients and clinicians should not consider nevi "precancerous." Instead, they should understand that patients with a higher number of nevi and clinically atypical nevi are at overall higher lifetime risk of developing melanoma and require dermatologic monitoring. In addition, UV exposure is the main cause of genetic mutations leading to melanoma. Encouraging sun protection can help reduce melanoma risk.

References

1. *Tsao H, Bevona C, Goggins W, Quinn T. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma: a population-based estimate. Arch Dermatol 2003; 139: 282–288.*
2. *Drozdowski R, Spaccarelli N, Peters, MS, et al. Dysplastic nevus part I: Historical perspective, classification and epidemiology. J Am Acad Dermatol 2023 Jan;8(1):1-10.*
3. *Dessinioti C, Geller AC, Stratigos AJ. A review of nevus-associated melanoma: What is the evidence? J Eur Acad Dermatol Venereol 2022 Nov;36(11):1927-1936.*
4. *Cheng MY, Moreau JF, McGuire ST, Ho, J, Ferris LK. Melanoma depth in patients with an established dermatologist. J Am Acad Dermatol. 2014 May; 70(5):841-6.*
5. *Kim CC, Berry EG, Marchetti MA, et al. Risk of subsequent cutaneous melanoma in moderately dysplastic nevi excionally biopsied but with positive histologic margins. JAMA Dermatol. 2018:154(12):1401-1408.*
6. *Spaccarelli N, Drozdowski R, Peters MS, et al. Dysplastic nevus part II: Molecular/genetic profiles and management. J Am Acad Dermatol 2023 Jan;8(1):1-10.*

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