EDITORIAL

# Observation of Moderately Dysplastic Nevi With Positive Margins
## Are We There Yet?

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**The management of dysplastic nevi** is a quotidian part of the clinical practice of dermatology, yet even directors of pigmented lesion clinics in the United States demonstrate significant practice variation with observation or therapeutic excision of dysplastic nevi.[1] This scenario is particularly true for biopsies of dysplastic nevi that have histologically positive margins. A 2015 consensus statement summarizing this practice gap included a call for further study of this common clinical question.[2] There are several important challenges in establishing evidence-based guidelines for the management of dysplastic nevi, and thus establishing practice consensus for the management of dysplastic nevi, including the lack of definitive evidence that dysplastic nevi are precursor lesions to melanoma, interobserver histopathologic variation in gradation of dysplasia, longitudinal risk of monitoring for clinical recurrence, and variation in diagnostic biopsy procedures (ie, risk of incisional or partial biopsies).

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The model of dysplastic precursors progressing to invasive carcinoma, as demonstrated with cervical dysplasia and cervical cancer, has not been established for dysplastic nevi and melanoma. Increasingly, evidence suggests that dysplastic nevi, as argued by many before, represent markers of increased risk of melanoma and not precursors preferentially destined to develop into invasive melanoma.[3] In fact, during the past 25 years there have been multiple appeals by many dermatologists and dermatopathologists to abandon the use of the term *dysplastic*, as it connotes precursor status.[4] To date, it has not been demonstrated that melanoma develops within dysplastic nevi at a frequency any higher than in normal skin or common nevi, with a recent meta-analysis estimating that more than 70% of melanomas arise de novo with no associated precursor nevus.[5]

Diversity of risk management strategies between dermatologists further challenges attempts to standardize the management of dysplastic nevi. The interobserver histopathologic variation in gradation of nevi atypia raises concern among clinicians that certain dysplastic nevi may demonstrate more aggressive biological behavior than is reflected in the histopathologic interpretation, prompting therapeutic excision of low-grade dysplastic nevi even with clear margins.[6,7] For young patients (and their clinicians), the risk of clinically monitoring specific biopsy sites for decades of anticipated life may prompt therapeutic excision to diminish the theoretical risk of recurrence, however small.

Another challenge for establishing evidence-based guidelines is diagnostic procedural variance between clinicians, some of whom routinely perform partial biopsy of concerning melanocytic lesions, whether by shave or punch technique, while others remove lesions in their clinical entirety. The partial biopsy approach raises the risk of sampling error and therefore the risk of misdiagnosis of a partially sampled lesion.[8-10]

In this issue of *JAMA Dermatology,* Kim et al[11] present the largest cohort to date examining melanoma-associated outcomes among patients with biopsy-proven moderately dysplastic nevi with complete clinical removal but positive histologic margins who undergo observation. Among the 467 dysplastic nevi with a mean (SD) follow-up time of 6.9 (3.4) years (range, 3.0-21.3 years), there were no cases of biopsy site-associated cutaneous melanoma; however, nearly one-fourth of the patients developed a cutaneous melanoma at a different site. Strengths of the study include its multisite design (9 sites), centralized dermatopathologic review, and duration of surveillance. These findings further add to the growing body of evidence that clinical observation is a reasonable strategy to managing dysplastic nevi, even those with moderate dysplasia and positive histologic margins.[12]

The data from Kim et al[11] are a welcome addition to the relative paucity of evidence-based literature to guide the management of dysplastic nevi. However, clinicians must interpret these results in the context of the study design. As in nearly all previous studies addressing melanoma-associated outcomes for clinical observation of dysplastic nevi, this study was retrospective, introducing possible risk of confounding by indication, as patients at lower risk of developing melanoma could have preferentially received observation. Evidence of this confounding may have resulted in fewer dysplastic nevi with positive deep margins (compared with positive peripheral margins) being observed in this cohort; therefore, risk of observation in this specific clinical scenario may be more uncertain.

Kim et al[11] present 2 key observations to guide practice: no biopsy site melanomas developed from sites of biopsied nevi with moderate dysplasia with complete clinical removal and positive histologic margins, and in multivariable analysis, patients with 2 dysplastic nevi or more were at increased risk of subsequent melanoma. Both observations should be considered in the context of the study design and population, which included highly specialized clinics from which these high-risk patients were drawn and the inclusion of patients with histologically transected dysplastic nevi, specifically when con-

sidering the recommendation that patients with 2 dysplastic nevi or more undergo routine surveillance for melanoma. Given that the study population originated from academic centers delivering quaternary care, the presence of no biopsy site melanomas perhaps suggests that the theoretical risk in the general practice population is even lower.

Despite dermatologists performing millions of biopsies per year, of which a significant fraction are melanocytic lesions, little is known about melanoma-specific associated outcomes.[13] Inclusion by Kim et al[11] of a central histopathologic review minimized variation in dysplastic grading of lesions. This study thus provides more evidence that dysplastic nevi are markers of melanoma risk but are not themselves melanoma precursors.

Moving forward, the ideal study design would be a prospective randomized trial that would eliminate many of the biases and confounding inherent in retrospective analyses. However, given the likely low (but unknown) transformation rate of dysplastic nevi to melanoma, for a randomized trial to be sufficiently powered to detect melanoma transformation at sites of previous biopsies of dysplastic nevi would likely require tens of thousands of individuals followed up for many years. Such a study would carry significant logistical challenges but could possibly quantify the risks (surgical site infection, pain, scarring, quality of life, and fiscal burdens) and benefits (precise quantification of the occurrence of dysplastic nevi to melanoma transformation) of structured monitoring vs therapeutic excision in the management of dysplastic nevi.

A more feasible study could be structured as a large administrative database retrospective analysis. One of the major issues hampering administrative database analysis is that dysplastic nevi do not have a separate *International Classification of Diseases, Ninth Revision*, or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, code, but rather are included with other cutaneous neoplasms. Intensifying the challenge is that both histopathologic reports and pathologic descriptors are not typically standardized or structured; thus, data extraction requires manual review and coding. However, the development of tools to standardize pathology reports of melanocytic proliferations and a recent study using natural language processing may diminish these hurdles in administrative database analysis of melanocytic proliferations.[13,14]

It remains remarkable that in the 40 years since the term *dysplastic nevus* was first coined, we continue to have only few, small, observational studies available to inform such a common clinical problem in dermatology.[15] However, in the absence of larger retrospective studies or a randomized trial, important observational studies such as the one by Kim et al[11] provide additional guidance. The evidence continues to mount that observation of moderately dysplastic nevi is a reasonable option, even for dysplastic nevi with focal positive histologic margins after complete clinical removal. The gap in the evidence for this recommendation continues to close.

## ARTICLE INFORMATION

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