# Dysplastic nevi: do they exist and what are they actually? [White Paper]

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## Abstract

The understanding of dysplastic (also known as atypical) nevi as a precursor lesion of malignant melanoma is hampered by incongruities on different levels. Neither epidemiological data nor clinical and histomorphological features nor biological aspects are suitable to prove a sequential tumor progression from nevi to melanoma. With respect to basic mechanisms of malignant transformation such as proliferation rate and telomerase activity, no significant differences between dysplastic and other nevi could be found. Thus, the dysplastic nevus represents a type of benign nevi and is to be distinguished from early forms of malignant melanoma in diagnostics. Their use as an easy to take "emergency exits" for pathologists must come to an end.

# The unfortunate invention of "dysplastic nevi"

When a certain Wallace Clark described a familial clustering of the incidence of malignant melanoma in patients with multiple nevi, he believed he had identified a pathogenetic model for melanoma development. Little did he know that his conclusions would lead to a rapidly growing controversy that persisted for decades and was further fueled by David Elder's extension of the concept to sporadic cases. In fact, the concept of the so called "dysplastic nevus" contains several difficulties that make objections against it well founded. In epithelial lesions, dysplasia is understood as an architectural and cytologic deviation from a normal configuration of the epithelium in question. However, such a definition is not applicable to melanocytic proliferations, since inevitably each nevus deviates in its cytologic aspect and arrangement from normal melanocytes of the skin. Therefore, the "common nevus" has been used as a reference. But how should such a "common" nevus be defined? A closer look reveals that this term probably represents a collective pot for all kinds of melanocytic tumors with quite different clinical and histological aspects. This is likely to include essentially papillomatous nevi of the Unna type, which occur predominantly on the trunk and are almost always purely dermal, polypoid nevi of the Miescher type, which are typically found on the face and head and may occasionally have a junctional component, and flat mostly distinctly pigmented nevi of the junctional or compound type, which may be localized virtually anywhere.[2,4,5,8]

# Macroscopic aspects

Congenital nevi are rarely considered, as the discussion of dysplastic nevus revolves around acquired nevi. Spitz nevi are also out of the question. It remains unclear on the basis of previous research from which type of nevus the dysplastic nevus might originate or from which it is to be differentiated. For the "common" nevus there is no uniform international definition, only the conclusion that it is characterized by an absence of atypia, whatever this may be. Sporadic melanocytic nevi characteristically appear as partly slightly raised, partly fibroma-mimicing tumors with varying intensity but largely uniform pigmentation. As a rule, they occur sporadically or at least in limited numbers. In contrast, members of the two families described by Clark were found to have multiple nevi, often far exceeding 120 in number. The aspect of the individual lesions was characterized by a high variability of the tumor diameter, which unusually often exceeded 5 mm and was characterized by a frequently strong, occasionally strikingly irregular pigmentation. Initially referred to as the "syndrome of dysplastic nevi", this phenotype was also named "familial atypical multiple mole melanoma syndrome", with the diagnostic focus on the clinical presentation. Prerequisites for the diagnosis of this syndrome are the presence of multiple nevi (usually >60) and a clinical picture in which a high proportion of nevi are in conflict with the so-called ABCD rule: an asymmetry of the lesion, blurred tumor margins, irregular pigmentation and a diameter of more than 5 mm. However, this immediately gives rise to serious problems: The ABCD criteria are identical for atypical nevi and malignant melanoma, so it would be more appropriate to refer to such lesions as "clinically suspicious melanocytic tumor." What is more, based on numerous studies, it can be considered certain

that the risk of melanoma increases approximately proportionally to the number of melanocytic nevi. However, it is by no means proven that there is a direct correlation to the presence of atypical (dysplastic) nevi, if one disregards the fact that with an increased total number of melanocytic nevi, atypical nevi are logically also observed in greater numbers. If we assume a normal linear correlation (there are no known studies contradicting this assumption) and a prevalence of about 10% of atypical nevi in patients with the syndrome, one atypical nevus would be expected in a patient with a total number of 10 nevi, which probably corresponds to the actual situation.

*There seems to be no increased risk of melanoma in atypical nevi,*
*unless additional risk factors are present.*

Accordingly, sporadic atypical/dysplastic nevi are unlikely to be significant as an indicator of melanoma risk. The risk increases with the number of all melanocytic nevi per person and not with the percentage of "dysplastic" or "atypical" ones.[8,9,14]

## Microscopic aspects

In congruence with the clinically atypical aspect, histopathologic features characteristic of dysplastic/atypical nevi have been described. They are typically junctional or compound nevi with lentiginous melanocyte hyperplasia (widespread confluence of melanocytic cells in the junctional zone), occasionally irregularly contoured and slightly blurred horizontally oriented cell nests with a tendency to bridging between adjacent reticula and a variably pronounced nuclear atypia of isolated melanocytic cells. In addition, there is a reaction of the dermal tissue in the form of a so called "concentric eosinophilic or lamellar fibroplasia" as well as a perivascular lymphohistiocytic infiltrate in the papillary dermis. Problems arise on the one hand from the lack of precision in the formulation of these criteria and their almost impossible reproducibility, and on the other hand from the evolution in the diagnosis of melanocitic tumors that has taken place in the meantime. In fact, Clark's description is based on the diagnostic standard of the 1970s, whereas today the criteria of Ackerman are generally applied. When based on these, microscopy leads to the conclusion that some of the lesions described as dysplastic nevi were not nevi but in melanomas in situ or early invasive melanomas. The histopathologic criteria have not been precisely formulated to date, as they appear to include both benign and malignant lesions. This is a scandal, considering the impact on both the patients and the costs to the health care system, if it is financed by taxes or insurances. As if this were not enough ambiguity, it is still not undisputed on the basis of which characteristics a differentiation from a non-dysplastic nevus of the junctional or compound type to a nevus with "atypia" is possible. In plain language, this means that the classification into "dysplastic/atypical" or "normal" is largely a matter of the pathologist's subjective judgment. Ackerman therefore suggested replacing the term "dysplastic nevus" with the term "Clark's nevus" in analogy to the Spitz nevus. In fact, studies of large numbers of cases have shown that in an overwhelming percentage of nevi there are single to a considerable number of features that meet Elder's criteria for dysplastic nevi. Clark's model of melanoma development suggests an evolution in stages, starting from

benign melanocyte proliferation via different degrees of dysplasia to malignant melanoma, comparable to the genesis of squamous cell carcinoma or the adenoma-carcinomas of the colon. At first sight, this idea may seem quite plausible. However, quite apart from the fact that such a sequence has not been proven for all carcinomas, it seems to be ignored that melanocytic cells as migratory cells of neuroectodermal origin are in no way comparable to epithelial cells, already due to their physiological properties. A carcinogenesis model based on the latter therefore does not seem to be justified in the first place. Much more obvious would be a comparison with neural tumors, which, however, would show the significance of the architectural, but especially the cytological changes in a completely different light. It is well known that in tumors of neural origin regressive changes can lead to considerable cytological atypia without this being an indication for a premalignant or malignant transformation. It is highly probable that the atypia of isolated cells in melanocytic nevi are due to regression phenomena and are not an expression of tumor progression. The detection of residual dysplastic nevi in malignant melanomas has been used as an argument in favor of the melanocytic tumor progression model. However, publications in this field present very different results which do not yet allow a definitive conclusion. It can be considered certain that a large number of malignant melanomas develop de novo. However, co-localization with melanocytic nevi does occur. In a not yet completed study we have examined 137 malignant melanomas with nevus components. In >50% residual parts of a small congenital dermal nevus were found, in about 12% residual parts of common compound nevi and in another 10% residual parts of dysplastic nevi. The remaining cases showed portions of various other nevus types. This distribution clearly contradicts the hypothesis that dysplastic nevi represent typical precursor lesions of malignant melanoma and also makes their significance as risk markers (apart from clearly defined syndromes) appear questionable.[1,2,6,8,10,12,14]

## Conclusions

From the preceding considerations it follows that the dysplastic or atypical nevus is a lesion with high prevalence in the fair-skinned population irrespective of the definition used. Since a specific transition to malignancy and also a premalignant biological behavior can apparently not be proven, a dysplastic nevus should be considered a variant of benign nevus. In the first instance, an experienced dermatologist should remove a macroscopically conspicuous or suspicious melanocytic lesion surgically without any hesitation, as this is a minimal procedure that does not require a particularly substantial diagnosis. That can be conveniently left to the pathologist. Under no circumstances, however, should the dysplastic nevus be a compromise solution in the event of diagnostic difficulties: a skin tumor is either benign or malignant. Verbal emergency exits for pathologists are harmful to the patient and the dermatologist who is treating him/her. However, it is undisputed that the dignity of melanocytic lesions cannot always be assessed with certainty. In case of doubt, which cannot be resolved by all additional examination methods, the formulation: "melanocytic tumor of uncertain malignant potential" is recommended, which should then be handled analogously to a malignant melanoma. However, even this entity must not become just another emergency exit for pathologists who are feeble in their decision-making. It is

therefore imperative to comment in detail on such a finding and to recommend complete excision if this was not done on the initial biopsy. Thus, the dysplastic nevus is not a biological entity but a concept on shaky ground. As long as clear biological criteria for initialization of malignant melanoma cannot be defined, dysplastic nevi (apart from rare syndromes) should be considered a nevus as any other benign nevus. It remains to be seen attentively whether future investigative methods will be able to elucidate the exact mechanisms of melanoma development. Until then, dermatologists should directly remove any new, relevant lesion and any changing or otherwise macroscopically abnormal nevus. The pathologist will then need to come up with a diagnosis anyway; and he/she must then diagnose so clearly that basically three findings are sufficient: "benign", "malignant" or, if there is absolutely no other option, "of uncertain malignant potential".

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## Ethical standards, data safety compliance and patient's rights

This article is about scientific facts. It is not reporting on a clinical trial (or anything similar) in its legal definition, especially not a prospective one. Our work was conducted in accordance with the Declaration of Helsinki.

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