EDITORIAL

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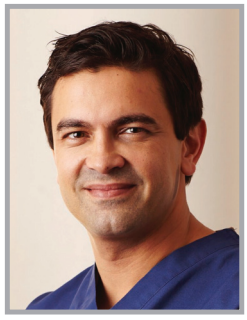
Melanoma Management

Does an increased number of moles correlate to a higher risk of melanoma?



"...determining nevus counts at a certain anatomic location that correlates to total body nevus count may be an effective screening tool in order to risk stratify and quickly examine those at an increased risk for melanoma."

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Melanoma is undoubtedly an important public health issue accounting for a bulk of skin cancer deaths despite accounting for <5% of all skin cancers [1]. Melanomas originate from melanin-producing cells called melanocytes. During embryological development, melanocytes originate in the neural crest cells eventually migrating to the epidermis [2]. While benign proliferations of melanocytes lead to formation of melanocytic nevi, or moles, malignant transformation of melanocytes leads to melanoma [3].

The interplay of a variety of factors seems to account for the formation and eventual total number of melanocytic nevi. Age, skin type and sun exposure are few of the common factors that are associated with increased nevi [4]. In general, the number of nevi tends to increase with age and then decrease during the third decade of life [5]. Delay of this process of senescence, possibly due to genetic mutations, has been associated with an increased risk of melanoma [6].

Melanoma is a deadly malignancy, which continues to increase in incidence worldwide. Fortunately, mortality rates have started to stabilize in many countries [7]. This could be attributed to new melanoma therapies that are continuously being researched and developed. More likely though, it is due to early detection via screening, which is vitally important for not only detecting melanomas at earlier stages but also for preventing melanomas [1]. A genetic etiology is clearly evident as a risk factor for melanoma, especially the role of mutations such as in *BRAF* and *CDKN2A* [3]. However, the total body number of melanocytic nevi remains one of the strongest risk factors for the development of melanoma [8].

Given that benign melanocytic nevi and melanomas arise from the same cell type, it may be easy to conclude that all melanomas initially arise from such nevi. However, that is not the case as only 20–40% of all melanomas arise from

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"The total number of common nevi also portends an increased risk of melanoma."

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"The counts of nevi on arms seem to be the most predictive location for estimating total body nevus counts."

pre-existing nevi, with the remaining majority arising *de novo* [9].

Melanocytic nevi are often thought of as being common or atypical. Atypical melanocytic nevi, often referred to as dysplastic nevi, are a controversial entity that denotes melanocytic nevi with either atypical features clinically or histologically. While the exact definition of what constitutes an atypical nevus continues to be unclear, in the setting of a family history of melanoma, some patients are referred to as having dysplastic nevus syndrome or familial atypical mole melanoma syndrome. This syndrome refers to patients with a family history of melanoma, a large number of nevi, usually >50, some of which appear atypical clinically, and nevi with certain histological features [10].

Patients with this syndrome have been found to have an increased relative risk of 500-fold for the development of melanoma [11]. Although not as robust, outside the context of familial melanoma, atypical nevi have also been associated with an increased melanoma risk. In one meta-analysis, those with five atypical nevi were found to have sixfold increase in relative risk in developing melanoma compared with those with no atypical nevi [8].

The total number of common nevi also portends an increased risk of melanoma. However, unlike in atypical nevi where risk seems to increase until a threshold of five atypical nevi, but not above this number [12], the risk with the number of common melanocytic nevi seems to increase linearly. This area has been extensively studied and the data are quite consistent showing that the increased number of melanocytic nevi increases the risk of melanoma [8,12–14].

Gandini *et al.* conducted a meta-analysis of 46 studies on this topic and found that in patients with >100 common nevi on their body, the relative risk of developing cutaneous melanoma was almost sevenfold higher compared with those with only 15 nevi or less. In this meta-analysis, a linear relationship was present indicating an increased relative risk of cutaneous melanoma as the number of total body common melanocytic nevi increased [8].

In darker-skinned populations, although the total body melanocytic nevi counts are generally less compared with lighter-skinned populations, the linear relationship between increasing melanocytic counts and increasing risk of cutaneous melanoma continues to be present [14]. Given such a linear relationship, melanoma risk is thought to increase by 2–4% per every additional nevi on the body. Moreover, the presence of this linear relationship at all latitudes indicates that the role of sun exposure may not be as important as nevus counts [15].

The type of melanomas associated with nevus counts has also been examined. In one case–control study done, superficial spreading and nodular melanomas had the strongest association with increasing nevus counts [16]. However, in general, superficial spreading melanoma and nodular melanoma are two of the most common types of melanomas.

An association between the number of melanocytic nevi and melanoma risk seems to be evident based on such extensive data. Clearly, the number of melanocytic nevi represents a possible risk factor in the development of melanoma. Given this relationship, there has been an effort to discern if certain anatomic locations are more predictive of total body nevus counts.

Body surface area seems to be an important factor. Between the sexes, females tend to have less number of total melanocytic nevi compared with males. However, the etiology of this difference is likely due to the larger body surface area of males compared with females. When nevi density, a term used to denote number of melanocytic nevi per body surface area, is taken into account then there is no difference in density between males and females [17].

While total body screenings are routinely done in dermatological practices, such screenings can be time-consuming, and thus, not often done in the general medicine setting [18]. Therefore, determining nevus counts at a certain anatomic location that correlates to total body nevus count may be an effective screening tool in order to risk stratify and quickly examine those at an increased risk for melanoma.

The counts of nevi on arms seem to be the most predictive location for estimating total body nevus counts. Ribero *et al.* in a recent study, examined 17 body sites of 3694 twins in the UK counting for number of melanocytic nevi at each of these sites. This study examined otherwise healthy patients and those not selected for any skin cancer screening. The authors noted that the arm seemed to correlate most closely to total body nevus counts. The right and left arms both had similar correlation coefficients. Moreover, nevus counts of 11 or more on an arm predicated an increased risk of having >100 total body nevi [19].

An increased number of moles do correlate to a high risk of melanoma. This is possibly due to the increased melanocyte burden posed by an increased number of melanocytic nevi. However, maybe those with an increased number of melanocytic nevi have genetic changes that predispose them to an increased risk of forming nevi and eventually melanoma. That has yet to be determined. Moreover, as a majority of melanoma arise *de novo* this indicates there is no prerequisite for the presence of a melanocytic nevus in order for melanoma to develop.

Thus, the etiology of melanoma is multifactorial with phenotypic risk factors such as melanocytic nevi that highlight the gene–environment interaction. Further studies are needed to elucidate such a relationship. However, it is quite clear that melanocytic nevi do pose an increased risk in melanoma, and as such, patients with increased melanocytic nevi need to be screened and monitored for melanoma.

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