SHORT COMMUNICATION

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Sex Differences in Axial and Limb Distribution of Melanocytic Naevi

Calogero PAGLIARELLO[1], Ignazio STANGANELLI[2], Fabio ZAMBITO-SPADARO[1], Claudio FELICIANI[1] and Sergio DI NUZZO[1]
[1]Section of Dermatology, Department of Clinical and Experimental Medicine, University of Parma, Via Gramsci 14, IT-43100 Parma, and [2]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy. E-mail: calogero.pagliarello@libero.it
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Melanomas are more frequent on the trunk in males and the legs in females (1). Moreover, a predominance of melanomas on the left side of the body has been described (2). Although naevus counts represent the strongest risk factor for developing melanomas, data about the distribution and side predominance of melanocytic naevi (MN) in adults are lacking. Recently, a study involving twins has suggested that the upper and lower limbs have different responses to ultraviolet (UV) radiation for genetic expression of MN compared with the head, neck and chest (3). We consider this issue to be of interest.

MATERIALS AND METHODS

Consecutive outpatients attending the Parma Dermatology Outpatient Clinic between October 2013 and January 2014 were asked to participate in this study. After signing informed consent, demographic data, such as sex, age, body mass index (BMI), smoking, and having parents with numerous moles, were recorded. A questionnaire eliciting sun exposure in infancy and adult life was also administered. The questionnaire consisted of 21 questions about lifetime history of sun exposure for recreational and occupational reasons, clothing while in the sun, exposure to non-solar sources of UV radiation, and use of sunscreens (Appendix S1[1]). The questionnaire has not been validated in terms of comprehension and reproducibility. It required approximately 10 min to complete. All the information was merged into a semi-quantitative score, arbitrarily ranging from 1 to 9 for childhood sun exposure and from 1 to 33 for adulthood sun exposure. The Skin Fitzpatrick Phototype (ranging from 1 to 6) and skin photodamage (evaluated on a physician global assessment scale based on evaluation of characteristic features, such as wrinkling and pigmentary change, ranging from 1 (mild pigment changes, no keratosis) to 10 (obvious sunburn freckles, visible capillaries, visible keratosis) were also assessed by a dermatologist. The number of MN for each of 36 anatomical sites and side (left vs. right) was recorded. Lesions with diameters >2 mm for each anatomical site were considered, according to a previous study (4). A simple instrument (nevometer) was used to assess the diameter. For analysis purposes, continuous variables were dichotomized at a median value (age 44 years; body mass index (BMI) 25 kg/m²; childhood sun exposure 5; adulthood sun exposure 19, phototype 3; and photodamage 3). The ratio between head and trunk and total MN (the nevotype (a high value suggests an axial naevus predominance, whereas a low value indicates limb naevus predominance)) as well as the ratio between right hemisoma naevus count over total naevus count were calculated and compared among the considered variables. Multivariate analysis was used to assess each variable contribution in predicting nevotype values. Data were analysed with IBM SPSS Statistics 21 (IBM SPSS Statistics for Windows, version 21.0 [released in 2012]; IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 111 patients agreed to participate in the study. No patients declined enrolment. Patient's mean ± standard deviation (SD) age was 44.14 ± 16.3 years, whereas median age was 40 years (15–81 years). There were no statistical differences among age values between sex (males age mean ± SD: 44.58 ± 18.1, females age mean ± SD: 43.75 ± 14.7, $p = 0.8$). Values for the following variables are shown in Table SI[1]: total MN count, ratio between trunk and head naevus count over total naevus count, and ratio between MN on the right hemisoma over total naevus count. Median ± standard error of mean value for the total MN count was 31 ± 3.8. The total MN count was higher in patients <44 years of age ($p < 0.01$), among patients with parents who had numerous moles ($p < 0.01$), and in patients with a dark skin phototype ($p < 0.05$) (Table SI[1]). Considering MN distribution, male patients and those with a dark skin phototype had more frequent axial localization of MN (trunk and head naevus count over total naevus count ratio ± SD, 0.62 ± 0.1; female sex, 0.52 ± 0.3; $p < 0.01$; fair phototype, 0.54 ± 0.2; dark phototype, 0.60 ± 0.3; $p < 0.05$). However, no significant differences were noted about MN distribution for age, BMI, smoking, having parents with numerous moles, sun exposure in infancy, or sun exposure in adulthood as noted by questionnaire and skin photodamage. Considering the distribution among left and right hemisomas, we found that patients with a dark phototype presented with a left dominance of MN (ratio between MN on the right hemisoma over total naevus count (mean ± SD): fair phototype, 0.55 ± 0.1; dark skin phototype, 0.51 ± 0.1; $p < 0.05$), but when adjusting for confounders, this association was not confirmed. In a model considering sex, age, sun exposure in infancy, sun exposure in adulthood, skin phototype, and photodamage, a high trunk/limb MN ratio was significantly linked to male sex (odds ratio (OR) 2.9, 95% confidence interval (95% CI) 1.1–7.6, $p < 0.05$), and to a darker phototype (OR 2.2, 95% CI 1.0–4.6, $p < 0.05$), whereas there was an inverse relationship with high age (OR 0.6, 95% CI 0.2–1.6, $p > 0.05$) and skin photodamage (OR 0.8, 95% CI 0.6–1.2, $p > 0.05$), all other factors being equal (Table SII[1]).

DISCUSSION

This study revealed sex differences in axial and limb distribution of MN, which seems similar to melanomas, presenting more commonly on the trunk in males and

on the legs in females. A left-side predominance of MN distribution, as previously described for melanomas (2), was not noted.

We found that MN counts in the elderly decreased and that the number of parental moles was linked to patient naevus counts, as previously reported (5); we found a lack of influence of sun exposure in infancy on total number of MN (5). Although the questionnaire for sun exposure we used is similar to others used in the literature, it has never been validated, thus possibly underestimating sun exposure in children. Recall bias should be also considered. Furthermore, the patient sample was not perfectly random.

Previous studies suggest that male children and adolescents have more MN than their female counterparts on the head, neck and trunk, while prevalence in females is higher on the limbs (6–9). Some authors have also suggested that naevi on the legs in girls might develop later than naevi elsewhere on the body (7). Since our study was cross-sectional, it cannot clarify whether the higher number of naevi on women's limbs can be explained by an increase from adolescence to adulthood and whether it varies in different populations.

The development of MN is a multi-factorial process that involves pre- and post-natal steps. To explain age-related variations in MN count, Zalaudek et al. (10) proposed that congenital, compounded, and dermal naevi could originate early in childhood and persist throughout life and are influenced by genetic factors. Junctional naevi are believed to be induced from exogenous factors, such as UV radiation, and, in the course of time, disappear due to involution (10). It has been postulated that, in addition to neural crest cells migrating in the dorsolateral pathway, melanocytes could also be derived from Schwann cell precursors present in nerves as part of post-natal tissue maintenance (11), corroborating the Cramer hypothesis of naevogenesis (12). It could be speculated that endogenous nevogenesis accounts for axial naevi and exogenous factor-driven naevogenesis would preferentially act for limb naevi. According to this hypothesis, the protective role of a darker phototype toward UV exposure could thus prevent the formation of nerve-derived naevi after UV injury, resulting in a trunk predominance of naevi compared with patients with a fair phototype.

It is also possible that regional differences in the sensitivity of melanocyte precursors to sexual hormones could exist (13), probably unrelated to UV exposure, as suggested by a study on Hutterite children, in whom traditional clothing covers all areas of the body (14).

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