

Melanocytic Naevi in Sun-exposed and Protected Skin in Melanoma Patients and Controls

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The possible link between exposure to ultraviolet light and naevus development was studied in 121 melanoma patients and 310 controls by comparing the number of naevi in a sun-exposed area on the back with that in a sun-protected area on the buttocks. Both patients and controls had a four-fold increase in the number of naevi in the exposed compared with the protected area, $p < 0.001$. The difference in naevus count between the exposed and the protected area was larger in patients than in controls, $p < 0.001$.

Subjects with dysplastic naevi, melanoma patients as well as controls, had a larger difference in the number of naevi between the two areas than subjects without dysplastic naevi, $p < 0.001$. These results support the idea that sunlight plays an important role in naevus development and may explain why a high naevus count is a risk marker for malignant melanoma.

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Repeated exposure to ultraviolet (UV) light stimulates melanocytes in the epidermis to proliferate and to produce more melanin (1,2,3). The obvious function of this melanocyte response is to provide protection against the harmful effects of UV irradiation. Certain melanocyte clones may, however, proliferate beyond a functional level to form lentigo and common as well as dysplastic naevi.

Epidemiological data have shown that a large number of common naevi (CN) and the presence of dysplastic naevi (DN) are markers for an increased melanoma risk (4,5,6). This association may occur because CN as well as DN are potential precursors of cutaneous malignant melanoma (CMM) (7,8). Furthermore, naevi and CMM may covary due to common etiological factors, for instance UV irradiation.

To differentiate between these possibilities, it seems important to elucidate the link between sun-

light, naevus induction and melanoma development. We have therefore studied the frequency of naevi in sun-exposed and sun-protected skin in a well-characterised population of melanoma patients and controls (6).

METHODS

Cases

All Caucasian patients, 30-50 years of age, with a history of CMM and living in Göteborg were selected from the Regional Cancer Register, $n=197$. Of these, 78% ($n=154$) were still alive. The participation rate was 90% ($n=137$). After histological re-examination of the tumour tissue, the diagnosis CMM was confirmed in 121 cases (52 men, 69 women, mean age 43.5 years). For details regarding the histological re-evaluation and exclusions see ref. 6.

Controls

Five-hundred Caucasian subjects in the same age-range were randomly selected from the census file in Göteborg. Thirty-one subjects had moved from the area, were severely ill or were deceased. Three-hundred and eighty-three of the remaining 469 (82%) were examined. Five of the subjects examined were excluded from analysis, four due to a non-Caucasian origin and one because a malignant melanoma *in situ* was diagnosed in this study. This part of the investigation started when 68 subjects were already examined. Thus, 310 consecutive subjects (152 men, 158 women, mean age 41.4 years) were included in the actual study.

Method

The subjects were examined by a dermatologist and an oncologist. Age, sex and skin type were registered and the use of sunbeds was noted. The number of melanocytic naevi ≥ 2 mm was counted in two 14×28 cm large areas, one sun-protected on the buttocks and one adjacent sun-exposed on the lower back (Fig. 1A). The area was defined on a transparent sheet and the median line was placed in the natal cleft. The sheet was then moved upwards so that the two studied areas were 14 cm apart. The upper area was situated just above the waist. These areas were selected to avoid traumatised skin and to minimise counting errors due to freckling. In addition, all subjects had a general skin examination and all brown macular or raised lesions ≥ 2 mm considered to be pigmented melanocytic naevi were counted. This total body naevus count included naevi in skin folds, palms, soles, scalp and genital area. Precautions were taken not to misdiagnose other pigmented lesions as naevi. If in doubt, the lesion was not counted.

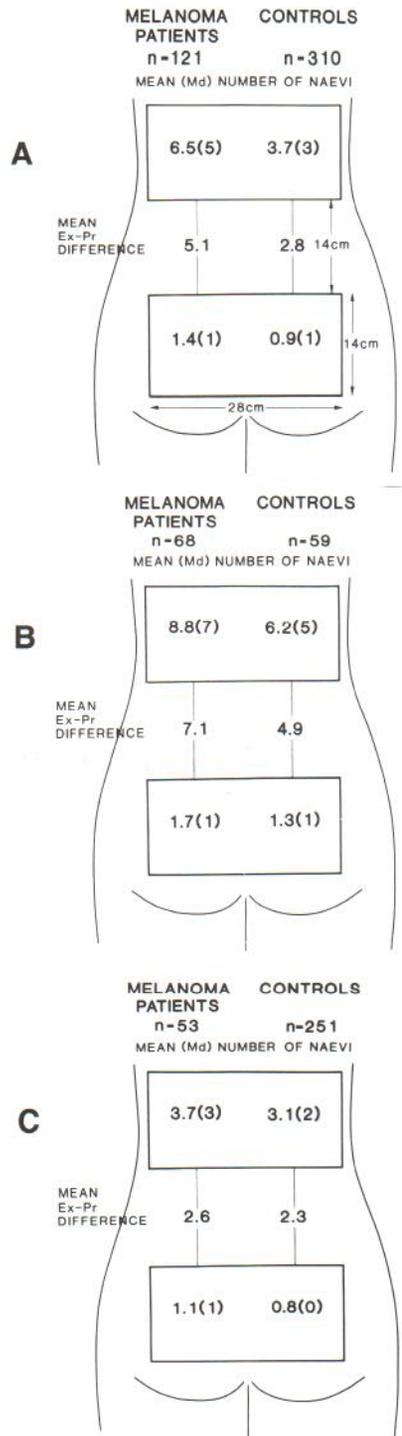


Fig. 1. Mean (median) number of melanocytic naevi and the difference in number of naevi between the sun-exposed and the sun-protected area.
 A. All melanoma patients and controls.
 B. Subjects with dysplastic naevi.
 C. Subjects without dysplastic naevi.

Table I. Total body naevus count

Category	Cases			Controls			P-value ¹
	n	mean (SE)	median	n	mean (SE)	median	
All	121	115(7)	89	310	66(3)	53	p<0.001
Without DN	53	78(7)	59	251	57(3)	45	}2 p<0.01
With DN	68	144(10)	117	59	102(7)	95	

¹Wilcoxon's two-sample test²p<0.001

Dysplastic naevi were registered separately. We have earlier shown that the clinically diagnosed DN is as good a marker for melanoma risk as the histologically diagnosed DN (6). Therefore, in this study the diagnosis DN was

based on clinical characteristics only. The major clinical criterion for a dysplastic naevus was a diameter ≥ 5 mm. In addition, at least two of the following criteria were required: an ill-defined or irregular border, speckled pigmentation, erythema or a pebbled surface (9).

Statistical methods

Spearman's rank test was used for the correlation analyses. For comparisons between groups, Wilcoxon's two-sample test was used. For comparisons of proportions between groups, Fisher's exact test was used. Trends in contingency tables were analysed using the Mantel-Haenzel chi-square test (10). For comparisons between the sun-exposed and the protected area Wilcoxon's test for paired observations was used. Two-sided tests were used.

RESULTS

Total body naevus count and the prevalence of DN

A total of 121 melanoma patients and 310 controls were examined. The sex ratio did not differ between the two groups. The phenotypic characteristics of these individuals and a detailed evaluation of the pigmented naevus as a risk factor for CMM have been given in a previous paper (6). The melanoma patients had almost twice as many naevi as the controls. The mean total body naevus count was 115 for the cases (median 89, range 13–355) versus 66 for the controls (median 53, range 1–305), $p < 0.001$. The number of naevi was not influenced by age, sex or skin type in either of the groups. One or more clinical DN were found in 56% (68/121) of the patients and in 19% (59/310) of the controls. The presence of DN was not influenced by age or sex. In controls, subjects with DN had a more sun-sensitive skin type than those without DN, $p < 0.001$. Such a correlation could not be seen in the melanoma group. Subjects with DN, patients as well as controls, had a significantly higher mean total body count of naevi than those without DN (Table I).

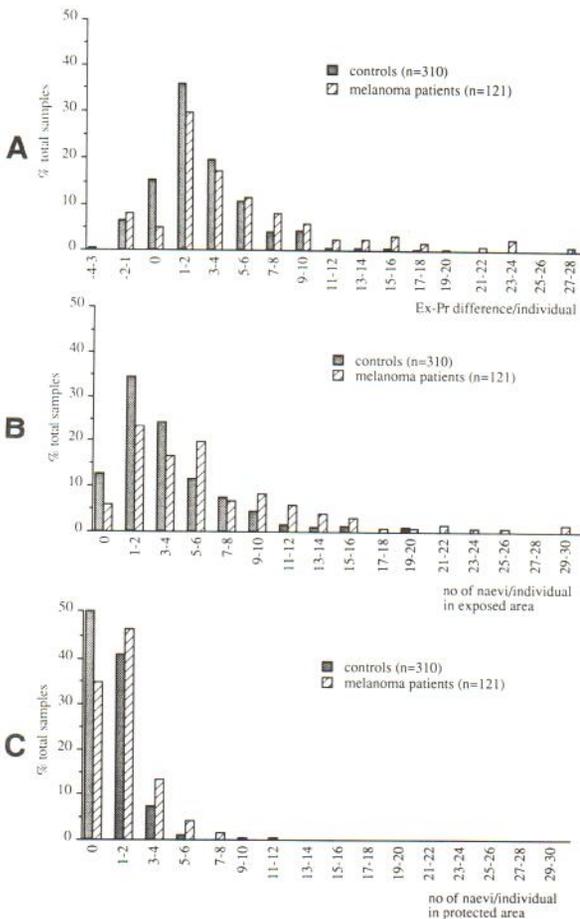


Fig. 2. The numerical distribution of melanocytic naevi/individual in melanoma patients and controls. A. Difference in number of naevi between the sun-exposed and the sun-protected area. B. Sun-exposed area. C. Sun-protected area.

Naevus counts in sun-exposed and sun-protected areas

Both patients and controls had more naevi in the sun-exposed area just above the waist than in the protected area on the buttocks, $p < 0.001$. The mean naevus count in the exposed area was in patients 6.5 (range 0–29) and in controls 3.7 (range 0–20) (Fig. 1A). The corresponding figures for the protected area were in patients 1.4 (range 0–8) and in controls 0.9 (range 0–12). Sporadic use of UVA sunbeds was reported by 11% of the patients and 14% of the controls. These subjects showed the same naevus pattern, with significantly higher counts in exposed than in protected areas. However, the controls with previous use of sunbeds had a significantly higher naevus count in the protected area, mean 1.4, than the rest of the controls, mean 0.8, $p < 0.05$. Excluding this subgroup ($n=42$) from the analysis did not influence our results. As there are other unknown factors concerning occasional sun-exposure of the buttock area, for example during childhood, we have decided to include these subjects. The difference in naevus count between the exposed and the protected area in each individual will be referred to as the Ex-Pr difference (Exposed-Protected). The mean Ex-Pr difference was larger in patients, 5.1, than in controls, 2.8, $p < 0.001$ (Fig. 1A + 2A) and it corresponded to a more than four-fold increase in mean naevus count in exposed skin.

Melanoma patients had more naevi than controls both in the protected $p < 0.01$, and in the exposed skin area, $p < 0.001$. The difference was more pronounced in the exposed area (Fig. 1A). For both groups, the interindividual variation in naevus count was greater in the exposed than in the protected area (Fig. 2B + C). Men had a larger mean number of naevi in the exposed area on the back than women, both among patients, $p < 0.05$ and among controls, $p < 0.001$. Age or skin type did not influence the number of naevi in the defined areas studied.

For further analysis, patients and controls were divided into subgroups with and without clinically diagnosed DN. Melanoma patients with DN had more naevi in protected skin than those without DN, $p < 0.05$. The same tendency was seen in controls with and without DN. The difference in naevus counts between the subgroups with and without DN was even more pronounced in the exposed area, $p < 0.001$ in both patients and controls (Fig. 1B + C). Still melanoma patients with DN had more naevi

than controls with DN in both areas studied, $p < 0.05$. No significant difference in naevus counts was found between patients without DN and controls without DN (Fig. 1C). For all subgroups, the exposed area had more naevi than the protected area, $p < 0.001$. There was a weak but significant correlation between counts in the exposed and the protected area in both patients and controls, corr. coeff. 0.28, $p < 0.01$. Both patients and controls with DN had a significantly larger mean Ex-Pr difference than patients and controls without DN, $p < 0.001$. Melanoma patients with DN had a mean Ex-Pr difference of 7.1, and the corresponding figure for controls with DN was 4.9. Melanoma patients without DN had a mean Ex-Pr difference of 2.6, and the corresponding figure for controls without DN was 2.3. The mean Ex-Pr difference did not differ significantly between patients and controls with DN, or between patients and controls without DN.

DISCUSSION

This case-control study focuses on the possible link between sun exposure, naevus induction and melanoma development. Kopf et al. reported more naevi in sun-exposed than in sun-protected skin in both volunteers (11) and subjects with dysplastic naevi (12,13) and proposed that UV-light stimulates naevus development. Their approach, comparing the number of naevi in exposed and protected skin, most likely gives a more objective estimation of the UV effects than anamnestic data on lifetime UV exposure. To avoid interference from solar lentigines and freckles, we selected areas on the buttocks and the lower back. Furthermore, the study was performed during the winter season. The areas were chosen so as to avoid traumatised skin. All subjects were also examined directly by trained doctors. Altogether, these measures should give reliable naevus counts. Our subjects were part of a larger investigation where many pigmented lesions were excised. All excised lesions diagnosed clinically as naevi were confirmed to be naevi histologically (6).

In agreement with Kopf et al., we found significantly more naevi in the sun-exposed than in the protected skin. This was true for both melanoma patients and controls. It may be argued that this difference does not reflect differences in UV dose but is secondary to a variation in original melanocyte population density. An uneven melanocyte distribution could have occurred during the embryonic mi-

gration of melanocytes in dorsoventral and cephalocaudal fashion. This interpretation seems less likely in view of the finding by Szabó that in the newborn child the melanocyte number is similar in the skin from the buttocks and the back (14). Furthermore, Szabó reported that the distribution of naevi is not directly related to the melanocyte population density (14). Other possible naevus-inducing factors, for example hormones or medications, may contribute to the interindividual variability (15) but it is far-fetched to assume that they should influence the two areas differently. It seems therefore reasonable to conclude that the observed difference in naevus counts is UV-dependent. Comparing the mean total body counts (Table I) with mean counts from the protected area extrapolated to the total body surface may give a rough estimate of at least 40% of the naevi being UV-dependent. We are convinced that this is an underestimate of the »naevogenic« effect of UV-light since the protected skin area most probably has been exposed to some sunlight during a subject's lifetime. First, a small amount of direct UV exposure of this area may have occurred due to UV-transparent clothing or occasional sun exposure. Second, an indirect UV effect mediated by »a solar circulating factor« may exist as for normal melanocytes (16,3). The fact that there was a significant correlation between naevus counts from the exposed and the protected area certainly suggests that at least one common factor influences naevus formation in both areas. Whatever the exact proportion, there can be little doubt that the total body naevus count is strongly influenced by UV exposure.

The mean number of naevi was significantly larger in melanoma patients than in controls in both areas studied. In addition, the Ex-Pr difference was larger in melanoma patients. The subgroups with the highest naevus counts and the largest Ex-Pr differences were melanoma patients with DN and controls with DN. This is in line with our finding that subjects with DN have the highest total body naevus counts (Table I). In fact, there was a larger difference between melanoma patients with and without DN than between patients with DN and controls with DN. In subjects without DN, all naevus counts were low and similar and there were no significant differences between the two groups. Melanoma patients with DN had a naevus profile similar to controls with DN and patients without DN to controls without DN. The fact that the melanoma group as a whole has higher naevus counts and a larger Ex-Pr difference than

controls may mainly be due to the greater proportion of subjects with DN in the melanoma group.

The high total body naevus count in subjects with DN is partly explained by a more pronounced UV response. The stronger response may reflect different habits of sun exposure and/or an increased sensitivity to the »naevogenic« effects of UV-light. It will be an important objective for future studies to differentiate between these alternatives. At present, the mechanism for naevus induction by UV-light is unknown. Repeated UV exposure stimulates epidermal melanocytes to proliferate (2). This mitogenic effect and the change in spatial relation between neighbouring melanocytes and keratinocytes (17) might for some melanocytes be the first step towards naevus development.

Sun exposure is one etiological factor for malignant melanoma. A large number of melanocytic naevi is a marker for an increased melanoma risk. Our findings suggest that UV exposure is the common etiological factor responsible for this covariation. In this perspective, the value of a high naevus count as a risk marker may be that it represents a cumulative record of the UV response whether caused by high dose or high sensitivity.

The finding that men have more naevi on the back than women, as also observed by Nicholls and Kopf et al. (18,12), might reflect different clothing habits. This is of interest in view of the fact that melanoma on the back is far more common in men than in women. We are currently analysing data from our case-control study correlating naevus distribution with melanoma location. This will hopefully add some further knowledge to our understanding of the link between sun-exposure, melanocytic naevi and melanoma development.

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