# Naevi as a Risk Factor for Basal Cell Carcinoma in Caucasians: a Danish Case-control Study

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The number of melanocytic naevi in Caucasians is related to previous exposure to the sun and is a well-documented major risk factor for cutaneous malignant melanoma. Basal cell carcinoma, which is the most common form of skin cancer, has also been shown to be related to exposure to the sun. To investigate whether the number of common naevi is a risk factor for basal cell carcinoma in Caucasians we performed whole-body counting of naevi $\geq 2$ mm in a Danish case-control study with 145 cases of primary basal cell carcinoma and 119 controls matched on age, gender and place of residence. Naevi were recorded according to size and body region and the skin phototype was assessed. There was no correlation between self-reported skin type and the number of naevi. Females with basal cell carcinoma had more naevi than did female controls (median number of naevi: 65 and 32, respectively) while males with basal cell carcinoma did not differ from male controls (median number of naevi: 48 and 43, respectively). Female cases had more small size naevi (2 mm), intermediate size naevi (3–4 mm) and large size naevi ($\geq 5$ mm) than did female controls. Females with basal cell carcinoma had a substantially higher number of naevi on the arms and the legs than did female controls, but also had more naevi on the trunk. For females, the risk for basal cell carcinoma increased with increasing number of naevi. Naevi were not a risk factor for basal cell carcinoma in males. *Key words: epidemiology; skin cancer; skin type; ultraviolet radiation.*

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Basal cell carcinoma (BCC) of the skin is a common disease in white-skinned populations and is now reported to be the most common malignancy in Denmark (1, 2). The aetiology of BCC has been studied less intensely than that of cutaneous malignant melanoma, but recent case-control studies indicate that intermittent exposure to sunlight is also a major causative factor for BCC (3, 4) as demonstrated for melanoma (5, 6).

Melanocytic naevi (MN) are rare in newborn Caucasians (7). The number increases through childhood and youth (8–10) and with sun exposure (11–14). Melanoma patients have a higher number of MN than do age-matched controls (15, 16), and the number of MN has consistently been shown to be a strong risk factor for melanoma in white-skinned populations (6). Since BCC is also related to exposure to the sun, it is possible that an increased number of MN might be found in BCC patients. However, only 1 Australian case-control study has investigated this hypothesis in which only large size naevi

($\geq 5$ mm) on the back were counted by non-professionals (17). In this study, Kricker et al. found that the risk of BCC increased with the number of large naevi on the back, but their findings were not statistically significant.

We therefore decided to perform a Danish case-control study on the significance of MN for BCC. To investigate whether MN is a risk factor for BCC in lightly pigmented Caucasians the study should assess the number and size of MN by whole-body examination in cases with primary BCC and matched controls without skin cancer.

## MATERIALS AND METHODS

### Study design

Whole-body naevus counting was performed by 2 trained observers in 145 cases with primary BCC and in 119 age-, gender- and residency-matched controls. The study was approved by the local Ethics Committee and was part of a larger study on risk factors for BCC and cutaneous melanoma (18, 19). Subjects younger than 18 years or older than 75 years of age were excluded. All subjects were invited by a standard letter and gave informed consent. Whole-body naevus counting were performed in exactly the same manner in cases and controls and the number of MN were recorded according to size and body region. Furthermore, the skin phototype of the subjects was assessed. All physical examinations were performed at the National University Hospital in Copenhagen during the period February to May 1996.

### Selection of cases and controls

In Denmark the majority of patients with primary BCC are treated in private dermatology clinics. As cases we selected patients treated consecutively for primary BCC in the period January 1995 to March 1996 from 4 dermatology clinics in eastern Denmark (Hørsholm, Hundige, Roskilde and Køge). Details of the selection of cases and controls have been published previously (18, 19). The diagnosis of BCC was verified histopathologically in all cases. A total of 145 cases (75 females and 70 males) accepted to participate, resulting in a response rate of 73%. The median time from BCC treatment to naevus counting was 8 months (range 1–16 months). At the time of investigation the females had a median age of 58 years (range 41–75 years) and the males had a median age of 60 years (range 29–73 years). Controls with the same sex and age (within ± 5 years) and place of residence (county) as the included cases were selected randomly from the Danish Central Population Registry. A previous history of skin cancer was an exclusion criterion. Of the invited 225 controls, 119 persons accepted, giving a response rate of 53%. Non-responders did not differ from responders with regard to age, gender or place of residence. The included 52 female controls had a median age of 59 years (range 29–70 years) and the 67 male controls had a median age of 60 years (range 29–70 years).

### Skin phototype

The skin's sensitivity to sunlight was assessed according to the Fitzpatrick classification as the self-reported burning tendency and tanning ability to first sunlight exposure in the summer (20). Four skin types were defined. I: always burn, never tan; II: usually burn,

tan less than average; III: sometimes mild burn, tan about average; IV: rarely burn, tan more than average.

*Defining and counting naevi*

Criteria to differentiate between naevi and other pigmented lesions were determined before the study. Performing the study in the winter and spring season helped to differentiate freckles from solar lentigines because freckles often disappear in the winter months while solar lentigines are permanent. Furthermore, skin pigmentation is low during this period (21), making identification of naevi easier. Freckles were defined as small, well-demarcated macular elements varying in colour from light brown to dark brown and mainly present in sun-exposed areas (22). A macular lesion was considered a solar lentigo if well circumscribed and of yellow, brown or tan colour and with a diameter from 5 to 30 mm and positioned in a sun-exposed area (22). Seborrhoeic keratosis was defined as well-demarcated, slightly elevated lesions with a greasy appearance and often verrucous. Naevi less than 2 mm in diameter were not included. If the examiner was in doubt if a pigmented element was a naevi, that lesion was excluded. The size (diameter) of a lesion was measured with a standard ruler and recorded in 1 of 3 different categories: small MN (2 mm); intermediate MN (3–4 mm) and large MN ($\geq$5 mm).

After the initial interview, naevi were identified and counted by 1 of 2 trained professional observers according to size and body region. The body regions defined were: the head and neck (defined as superior to the clavicles and a horizontal line through the seventh cervical vertebra and excluding the scalp region), the trunk (defined caudally by the inguinal folds and the infragluteal folds), the arms (separated from the trunk by a line through top of the axilla and the acromion) and the legs. Separate recordings were made for the anterior and posterior part of each region. The scalp region was not examined because this was considered to be too time consuming and unacceptable to some subjects. Whole-body naevus counting took on average 15–30 min per subject.

*Training and consistency of naevi counting*

To enhance the quality and consistency of naevi identification and counting, only 2 professional examiners performed all the examinations. Before the actual study, 70 skin cancer cases and 70 controls were used for training. Simultaneous recordings were performed in the first 20 subjects, then separately in 110 subjects and again simultaneously in the last 10 subjects. Also, during the study period the 2 examiners performed simultaneous counting at regular intervals. Furthermore, cases and controls were randomly assigned to the 2 examiners in order to minimize systematic bias in counting.

*Statistics*

Naevus distribution in cases and controls did not follow a Gaussian distribution, but was right skewed (Fig. 1). Therefore, the median numbers of naevi are indicated in the tables and non-parametric statistics were utilized. Mann-Whitney's test was used to analyse differences in naevus counts between cases and controls and between females and males. Spearman correlation were utilized for analysis of association between self-reported skin type and number of MN. Risk factor calculations were performed by contingency table analysis and chi-squared test for linear trend. *p*-values less than 0.05 were considered significant.

## RESULTS

*Number of MN by whole-body examination (see Fig. 1 and Table I)*

In controls, the median number of MN $\geq$2 mm by whole-body examinations was 42 (25th quartile to 75th quartile: 14–75; mean number: 53) with no significant difference between the number found in females and in males. In BCC cases, the
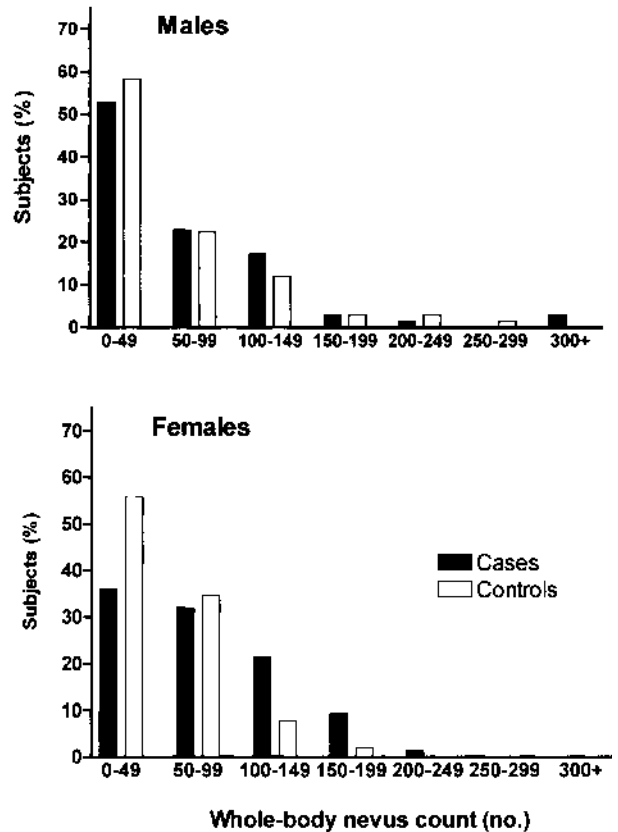


*Fig. 1.* Whole body counts of naevi $\geq$2mm in patients with primary basal cell carcinoma and matched controls. Females with basal cell carcinoma had more naevi than female controls (median number of naevi 65 and 32, respectively; $p < 0.01$). Males with basal cell carcinoma did not differ from male controls (median number of naevi 48 and 43, respectively; $p = 0.55$).

median number of MN was 54 (25th quartile to 75th quartile: 25–106; mean number: 73) with females cases having more MN than male cases. Females with BCC had more MN than matched female controls (median number of MN: 65 and 32; mean number: 80 and 46, respectively), whereas males with BCC did not have more MN than matched male controls (median number of MN: 48 and 43; mean number: 66 and 59, respectively). The higher number of MN in female cases than in female controls was observed both for small size, intermediate size and large size naevi while male cases did not have higher numbers than male controls for any size of MN. The higher number of MN in female cases than in male cases were due to a higher number of intermediate size MN.

*Number of MN by body region*

Except for the front of the trunk, control males and females did not differ in the number of MN according to body region (Table II). Females with BCC had a higher number of MN in all body regions compared with female controls, except for the head and neck. Males with BCC did not differ from male controls in the number of MN in any body region. The increased number of MN found in female cases compared with male cases were due to a substantially higher number of MN on the arms and the legs.

Table I. *Number of naevi by whole-body examination according to naevi size and gender of subjects*

| Naevi | Cases | | Controls | | |
|---|---|---|---|---|---|
| | Median | (25th – 75th quartile) | Median | (25th – 75th quartile) | p |
| **2mm naevi** | | | | | |
| females | 21 | (11 – 38) | 15 | (6 – 24) | <0.01 |
| males | 18 | (8 – 36) | 13 | (3 – 32) | 0.30 |
| | | p = 0.18 | | p = 0.97 | |
| **3 – 4mm naevi** | | | | | |
| females | 42 | (17 – 71) | 19 | (6 – 34) | <0.01 |
| males | 25 | (12 – 53) | 25 | (8 – 47) | 0.81 |
| | | p = 0.03 | | p = 0.20 | |
| **≥5mm naevi** | | | | | |
| females | 2 | (0 – 5) | 1 | (0 – 2) | 0.04 |
| males | 2 | (0 – 3) | 1 | (0 – 3) | 0.60 |
| | | p = 0.65 | | p = 0.22 | |
| **all naevi ≥2mm** | | | | | |
| females | 65 | (37 – 116) | 32 | (13 – 71) | <0.01 |
| males | 48 | (22 – 94) | 43 | (15 – 84) | 0.55 |
| | | p = 0.04 | | p = 0.42 | |

## Naevi and self-reported skin type

There was no relationship between self-assessed sensitivity to sunlight and the number of MN by whole-body counting, either for cases or controls or for females or males (Table III). Females with basal cell carcinoma had more MN than female controls for skin type I through skin type IV (Table III).

## Naevi and risk of basal cell carcinoma

The risk for BCC according to the number of MN by whole-body counting is shown in Table IV. In males, the number of MN was not found to be a risk factor for BCC, whereas in females an increasing number of MN at the trunk, the arms and the legs were associated with increasing risk of BCC

(Table IV). The higher number of large size MN ($\geq 5$ mm) in females with BCC than in female controls did only translate into moderately increased risk estimates in females: odds ratio (OR) of 1.5 (95% CI: 0.7 – 3.4) for 1 – 4 large MN and OR = 3.0 (95% CI: 1.1 – 8.1) for more than 4 large MN compared with no large size MN.

## DISCUSSION

Ultraviolet (UV) radiation is a powerful stimulus of melanocyte proliferation and melanogenesis (23, 24) and there is evidence from different types of investigations that sunlight plays an important role in initiation or promotion of MN. The anatomic distribution of MN is compatible with a

Table II. *Number of naevi ( ≥2 mm) according to body region and gender of subjects*

| Body region | Cases | | Controls | | |
|---|---|---|---|---|---|
| | Median | (25th – 75th quartile) | Median | (25th – 75th quartile) | p |
| **Face and neck** | | | | | |
| females | 2 | (1 – 4) | 1 | (0 – 3) | 0.11 |
| males | 1 | (0 – 3) | 1 | (0 – 2) | 0.77 |
| | | p = 0.04 | | p = 0.65 | |
| **Trunk, front** | | | | | |
| females | 6 | (2 – 12) | 3 | (1 – 8) | <0.01 |
| males | 9 | (2 – 17) | 7 | (1 – 18) | 0.55 |
| | | p = 0.21 | | p = 0.01 | |
| **Trunk, back** | | | | | |
| females | 12 | (4 – 21) | 8 | (2 – 21) | 0.04 |
| males | 14 | (6 – 26) | 12 | (4 – 24) | 0.42 |
| | | p = 0.44 | | p = 0.13 | |
| **Arms** | | | | | |
| females | 20 | (8 – 31) | 8 | (4 – 16) | <0.01 |
| males | 13 | (4 – 21) | 10 | (4 – 22) | 0.58 |
| | | p < 0.01 | | p = 0.70 | |
| **Legs** | | | | | |
| females | 23 | (6 – 41) | 10 | (3 – 21) | <0.01 |
| males | 9 | (4 – 18) | 9 | (1 – 18) | 0.48 |
| | | p < 0.01 | | p = 0.45 | |

Table III. *Number of naevi (≥2 mm) by whole-body examination according to self-reported sensitivity to sunlight*

| | Cases | | | Controls | | |
|---|---|---|---|---|---|---|
| | Subject no. | Naevi Median | (25th–75th quart.) | Subject no. | Naevi Median | (25th–75th quart.) |
| Skin type I | | | | | | |
| females | 10 | 70 | (23–121) | 10 | 14 | (7–62) |
| males | 7 | 39 | (6–81) | 17 | 34 | (14–62) |
| Skin type II | | | | | | |
| females | 37 | 73 | (41–114) | 22 | 52 | (15–89) |
| males | 33 | 29 | (21–59) | 15 | 9 | (3–62) |
| Skin type III | | | | | | |
| females | 15 | 83 | (45–140) | 7 | 44 | (12–83) |
| males | 20 | 85 | (26–120) | 19 | 58 | (38–98) |
| Skin type IV | | | | | | |
| females | 13 | 50 | (23–68) | 11 | 22 | (10–59) |
| males | 10 | 49 | (41–63) | 15 | 47 | (37–86) |

There was no relationship between self-reported skin type and number of naevi by correlation analysis: female cases: $r = -0.01$ and $p = 0.93$; male cases: $r = 0.17$ and $p = 0.17$; female controls: $r = -0.01$ and $p = 0.95$, and male controls: $r = 0.24$ and $p = 0.05$. r: Spearman correlation coefficient.

UV influence showing more MN in areas exposed to sunlight than in non-exposed or protected areas (11, 13, 14, 25, 26). This has been interpreted as consistent with the theory that intermittent sun exposure is more "nevogenic" than chronic exposure (11, 14, 25, 26). Furthermore, it has been suggested that there is only a narrow dose range wherein UV exposure can effectively promote melanocyte proliferation and thereby stimulate naevus formation (14). Genetic factors are also important and a study in twins found a strong correlation for the number of naevi in monozygotic twins but not in dizygotic twins (27).

To perform whole-body MN counting consistently in a larger number of subjects is a demanding task (10). In our study we used only 2 examiners, who were medical professionals and trained together. We used well-defined criteria to distinguish between MN and other pigmented lesions and all examinations were performed in the winter and spring period in order to minimize the effect of freckling and tanning. Furthermore, any doubt that a lesion was a MN resulted in the exclusion of the lesion. This may rather have the effect that we under-estimated than over-estimated the true number of MN.

Some studies have reported an association between sensitivity to sunlight (skin phototype) and the number of MN, which were increased in persons with a high sensitivity to sunlight compared with persons with a low sensitivity (10,

Table IV. *Risk of basal cell carcinoma according to number of naevi ≥2 mm*

| Factor | Category | Females | | | | Males | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cases | Controls | OR | 95% CI | Cases | Controls | OR | 95% CI |
| Trunk | | | | | | | | | |
| | 0–10 | 24 | 26 | 1.0[a] | | 21 | 23 | 1.0[a] | |
| | 11–20 | 13 | 7 | 2.0 | (0.7–5.9) | 11 | 13 | 0.9 | (0.3–2.5) |
| | >20 | 38 | 19 | 2.2 | (1.0–4.7) $p = 0.05$[b] | 38 | 31 | 1.3 | (0.6–2.9) $p = 0.42$[b] |
| Arms | | | | | | | | | |
| | 0–15 | 30 | 39 | 1.0[a] | | 39 | 43 | 1.0[a] | |
| | 16–30 | 26 | 9 | 3.8 | (1.5–9.2) | 21 | 16 | 1.5 | (0.7–3.2) |
| | >30 | 19 | 4 | 6.2 | (1.9–20.1) $p < 0.01$[b] | 10 | 8 | 1.4 | (0.5–3.8) $p = 0.38$[b] |
| Legs | | | | | | | | | |
| | 0–15 | 28 | 34 | 1.0[a] | | 47 | 46 | 1.0[a] | |
| | 16–30 | 19 | 10 | 2.3 | (0.9–5.8) | 13 | 12 | 1.1 | (0.4–2.6) |
| | >30 | 28 | 8 | 4.3 | (1.7–10.8) $p < 0.01$[b] | 10 | 9 | 1.1 | (0.4–2.9) $p = 0.85$[b] |
| Whole-body | | | | | | | | | |
| | 0–25 | 16 | 23 | 1.0[a] | | 22 | 22 | 1.0[a] | |
| | 26–75 | 25 | 18 | 2.0 | (0.8–4.8) | 27 | 27 | 1.0 | (0.5–2.2) |
| | 76–150 | 25 | 10 | 3.6 | (1.4–9.5) | 16 | 15 | 1.1 | (0.4–2.7) |
| | >150 | 9 | 1 | 12.9 | (1.5–112.5) $p < 0.01$[b] | 5 | 3 | 1.7 | (0.4–7.8) $p = 0.63$[b] |

[a]Reference category. [b]p-value for trend by chi-squared test. OR: odds ratio = a calculation of risk based on the observed occurrence of the risk factor in the cases relative to the occurrence in the controls.

28, 29). However, we did not find any relationship between the number of MN and self-reported skin type, either for persons with BCC or for controls (Table III).

The Swedish population is generally assumed to be similar to the Danish population with regard to phenotypic traits and age- and sex-distribution. Augustsson et al. performed whole-body MN counting of MN $\geq 2$ mm in 379 Swedes aged 34–52 years without skin cancer (30). They found a median number of 53 MN (range 4–300) with no difference in the numbers found in males and females. This compares quite well to the median number of 42 MN (range: 1–290) found in our control group, who were somewhat older. In our controls we found a tendency to males having more MN than did females, due to more MN on the trunk in males, but there was no gender difference in MN at the extremities (Table II).

We found that females with BCC had significantly more MN than did female controls, whereas males with BCC did not differ from male controls (Fig. 1). The distribution of MN in BCC females were considerably different from that in males with females having substantially more MN at the arms and legs (Table II). It is not likely that the increased number of MN in females with BCC is due to hormonal factors because control females did not have more MN than control males. The study presented is an observational one and explanations of this gender difference must be sought in an analytical study properly designed to address this issue. We can therefore only speculate on possible reasons for our observations, but they may indicate a different sun exposure pattern for females with BCC which could be related to differences in clothing as well as to differences in type and extent of recreational and occupational exposure to sunlight and artificial UV. However, the observed distribution of BCC tumours was not different in females and males, with 13% of the females having tumours at the extremities compared with 10% in the males (19).

The only previous study reporting the number of MN in persons with BCC is the Australia study by Kricker et al. (17). Whole-body mole counting had been considered in this study but was not performed due to lack of resources. A total of 222 cases of BCC and 999 controls (age 40–64 years) were asked to have a relative or a friend count the moles $\geq 5$ mm on their back. Kricker at al. found that 4–9 large moles and 10–48 large moles on the back increased the risk 1.4 and 2.0 times for BCC compared with 1–3 moles, but the findings were not statistically significant and no gender analysis is mentioned in the paper.

In conclusion, our study showed the number of MN to be a significant risk factor for BCC in females, but not in males. Considerably higher risk estimates were found for increased numbers of MN in females (Table IV). Large size naevi $\geq 5$ mm were also shown to be a risk factor in females, but only with moderate risk estimates. Compared with whole-body examinations, the arms and legs were found to be readily accessible and useful sites for BCC risk estimations according to number of MN. Further research has to be done to investigate why females with BCC have a different number and distribution of MN than males with BCC.

## ACKNOWLEDGEMENTS

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