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Micro-nevi in peri-tumoral skin of cutaneous melanoma and basal cell carcinoma

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ABSTRACT

Background: Harboring many melanocytic nevi is a risk factor for melanoma. The prevalence of micro-nevi, melanocytic nevi that can only be detected microscopically, has been studied scarcely and the significance is unknown.

Objectives: To systematically analyze the presence of micro-nevi in cutaneous excisions from cutaneous melanoma and basal cell carcinoma to achieve an insight in the density of micro-nevi per mm peri-tumoral skin. Also to speculate in the relevance and significance of micro-nevi for evolving melanoma at the same anatomical site.

Methods: We re-examined histologically peri-tumoral skin of primary and re-excised melanomas and primary excisions of basal cell carcinomas for comparison. The size of a micro-nevus was defined to a diameter < 2 mm, of either a junctional, compound or intradermal nevus.

Results: 104 melanoma and 208 basal cell carcinoma cases were microscopically re-examined. In the melanoma group 6 micro-nevi were found. The sum of the peri-tumoral skin was 1768 mm, giving a density of 1 nevus per 295 mm. In the basal cell carcinoma group 5 micro-nevi were found. The sum of the peri-tumoral skin was 1370 mm, giving a density of 1 nevus per 274 mm. No difference in the density of micro-nevi in the two groups of skin cancer was found.

Conclusions: The significance of these micro-nevi remains unclear. The aim with this study is to draw attention to the existence of micro-nevi and further studies are needed to determine the significance of the presence of micro-nevi.

Keywords: Basal cell carcinoma, histopathology, malignant melanoma, melanocytic nevus

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INTRODUCTION

It is well known that the incidence of cutaneous melanoma (MM) is directly correlated to UV exposure and that the number of melanocytic nevi correlates to UV exposure, especially during childhood[1,2]. It is also acknowledged that a high number of melanocytic nevi are a risk factor for developing cutaneous MM[1, 2]. In histological slides from cutaneous excision specimen, small foci of benign nevic aggregates, so called micro-nevi, can occasionally be detected. Commonly, these foci are separate from the main lesion. Histologically these micro-nevi are junctional, compound, or intradermal. Clinically these micro-nevi are unapparent but dermoscopically they can be detected when searched for, according to our clinical experience.

This phenomenon of subclinical, so-called micro-nevi has barely been described in the literature. A study by Dadzie et al.[3] describes nevic aggregates in cutaneous excisions. In their study, the most frequent skin tumor associated with a micro-nevus was basal cell carcinoma (BCC) and the most frequent anatomical location was the head and neck region, followed by the trunk. The most frequent nevus subtype was intradermal.

BCC, MM and melanocytic nevi affect similar body sites and UV exposure is the most common predisposing factor for them all[1,2,4-7]. Sometimes collision tumors are detected; this is when two neoplasms are either adjacent to each other or admixed with one another[3,8].

The primary aim of this retrospective study is to systematically analyze the presence of micro-nevi in cutaneous excisions from MM and BCC, in order to achieve an insight in the density of micro-nevi per mm peri-tumoral skin. The secondary aim is to speculate in the relevance and significance of micro-nevi for evolving MM at the same anatomical site.

MATERIAL AND METHODS

We define a micro-nevus as follows: a small group of aggregates of nevus cells in nests with or without lentiginous hyperplasia, separated from the scar, the MM or BCC by normal appearing stroma. Junction, compound, and intradermal nevi were included (Fig1-3). In this study, we defined the size of a micro-nevus to <2 mm, in accordance with the protocol of The International Agency for Research on Cancer (IARC), which defines the size of a melanocytic nevus to ≥ 2 mm[2,9]. In all detected micro-nevi the maximum horizontal diameter was measured in millimeters.

The Study-population is shown in Table 1.

MM cases were searched for systematically in the database at the Karolinska university laboratory, department of clinical pathology based on the SNOMED code M80703 including codes for subtypes. All cases from 2013, a total of 209 excision specimen were microscopically re-examined, 104 cases primary MM with 104 re-excisions, one patient underwent two re-excisions: approximately 1000 slides/fractions.

BCC cases were searched for by SNOMED code M80903 including all subtypes. They were matched with the MM group according to age (+/- 5 years) and anatomical location. Two BCC cases for every MM were chosen to compensate for the larger amount of peri-tumoral skin in MM since cutaneous excisions of MM are generally wider. These controls were searched for 2013 - 2017. A total of 208 cases were systematically microscopically re-examined, of primary excision specimen or re-excisions (not biopsies); approximately 1000 slides/fractions.

Dimensions of peri-tumoral skin were measured in mm and only once in each case. In the primary excisions or re-excisions of MM, this was done, either in the level of the largest tumor diameter, or, if no tumor residual was present, one representative level was chosen for measurement. In the BCC group the peri-tumoral skin was measured in the level of the largest tumor diameter. The sum of the peri-tumoral skin in each group was divided with the number of micro-nevi found to obtain the density within each group.

TABLE 1 A summary of the characteristics of the MM and BCC groups.

Characteristics of the study group	MM	BCC
Mean age (range), yr	61(31-94)	62 (32-96)
Gender		
Male	48	103
Female	56	105
Location		
Face	7	14
Head and neck	4	8
Trunk	44	88
Lower extremities	23	46
Upper extremities	26	52
Number of cases	104	208

TABLE 2 A summary of the characteristics of micro-nevi found in the MM and the BCC groups.

Patient No	**Primary diagnosis**	**Subtypes Nevi**	**Site of micro-nevi**	**Age**	**Gender**	**Anatomical location**
1	MM	Intradermal	1,0	44	M	Trunk
2	MM	Intradermal	1,9	66	F	Trunk
3	MM	Intradermal	1,8	88	M	Face
4	MM	Intradermal	0,9	44	M	Upper extremities
5	MM	Compound	1,8	73	M	Upper extremities
6	MM	Junction	0,8	64	F	Upper extremities
7	BCC	Intradermal	1,3	69	M	Face
8	BCC	Junction	0,9	71	F	Upper extremities
9	BCC	Compound	1,1	71	F	Upper extremities
10	BCC	Compound	1,0	50	F	Trunk
11	BCC	Compound	1,9	61	F	Trunk

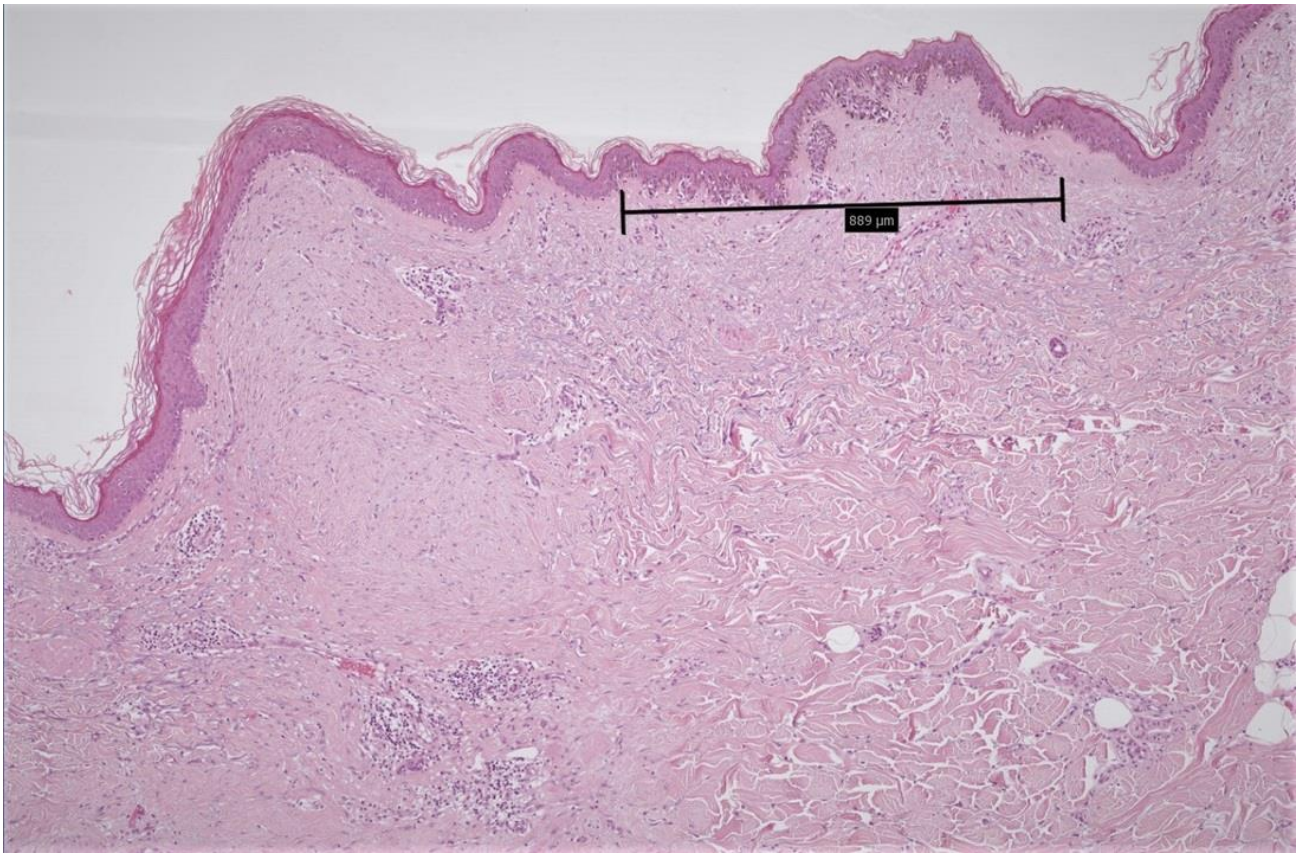

FIGURE 1 A micro-nevus of junction type in the periphery of a scar after previous excision of melanoma, separated by normal stroma. (Magnification 200x)

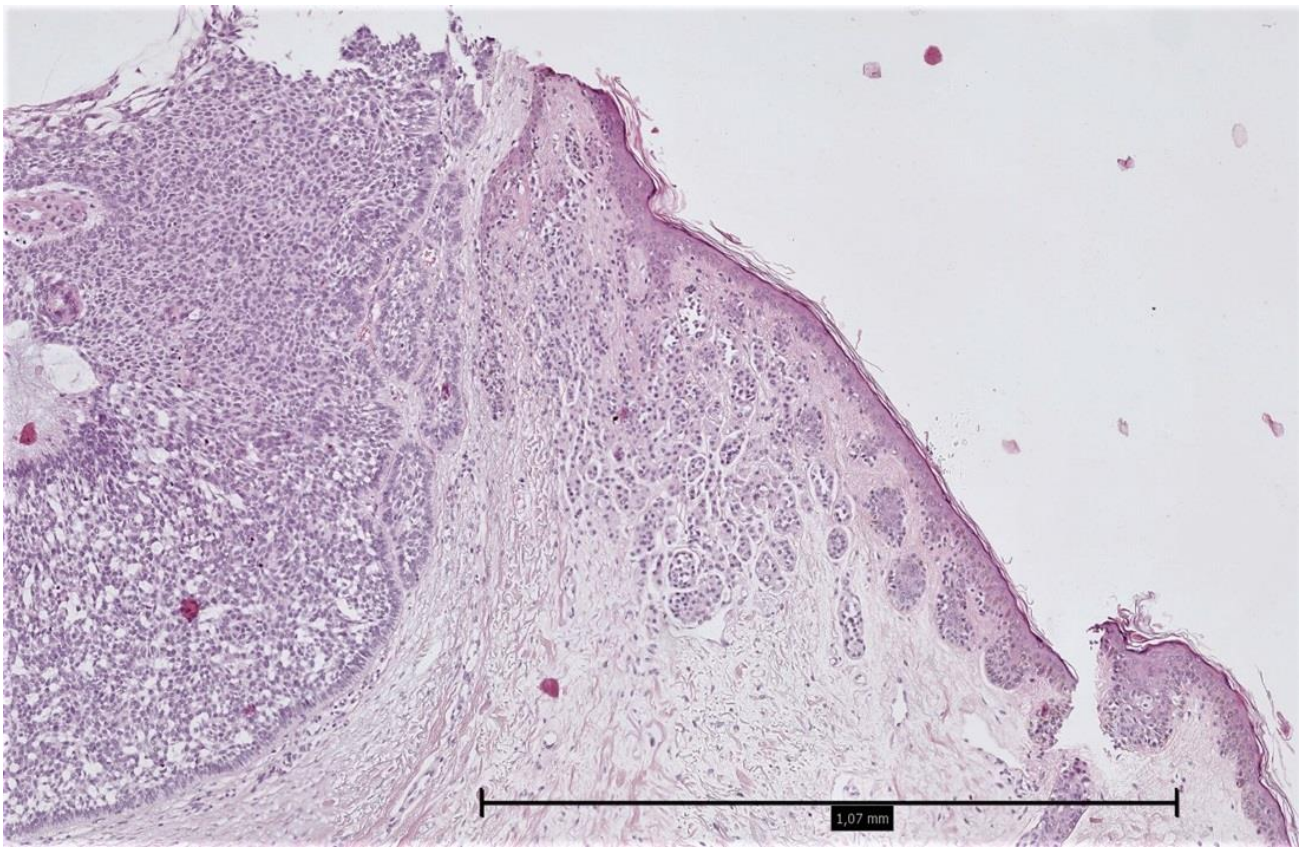

FIGURE 2 Micro nevus of compound type next to BCC. (Magnification 200x)

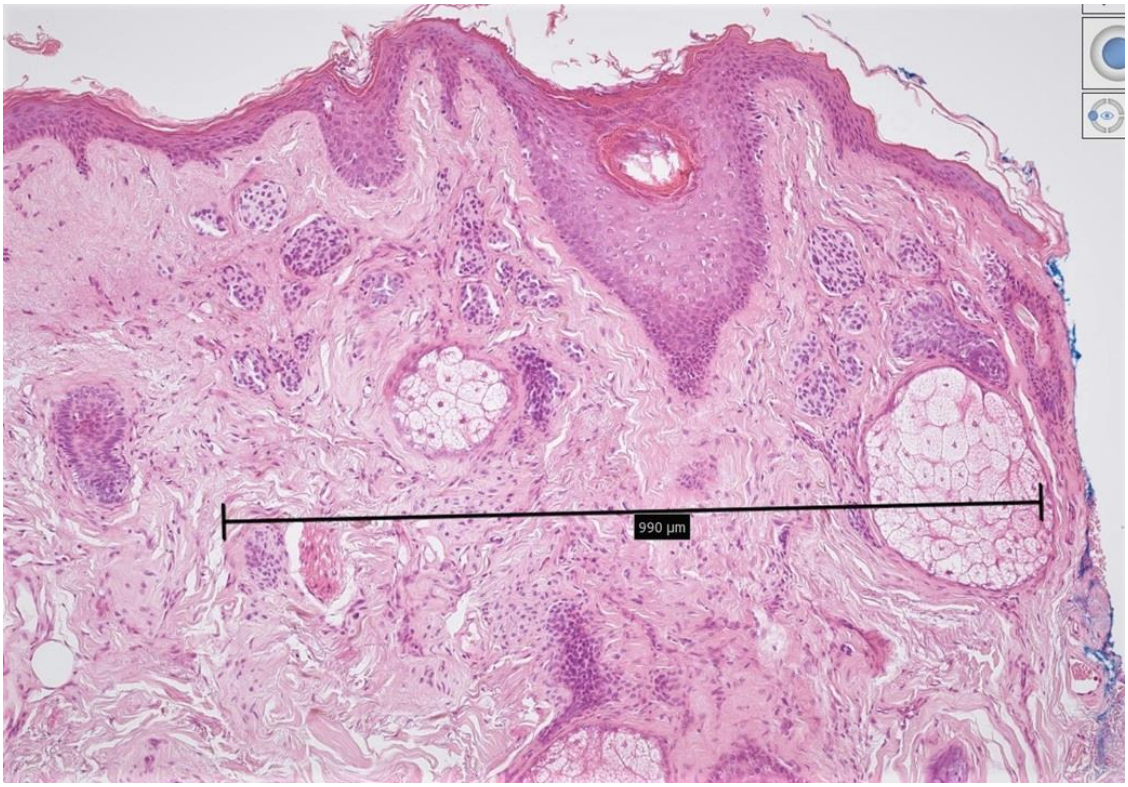

FIGURE 3 An incidental found micro-nevus of intradermal type in an excision of BCC. (Magnification 200x)

RESULTS

Localization of micro-nevi and subtypes as well as demography is shown in Table 2.

In the MM group, all micro-nevi were found in the re-excisions. A total of 12 nevic aggregates were detected but only 6 fulfilled the criteria of micro-nevi, due to size. 3 of 6 micro-nevi were pigmented. In 5 of these 6 cases the pathologist had initially reported the micro-nevus, but neither the clinician nor the laboratory technician had reported the presence of these small lesions.

66,7% of the micro-nevi were of intradermal subtype. 16,7% were junctional and 16,7% were compound. The mean horizontal diameter of the micro-nevi was 1,37 mm (range 0,8-1,9 mm). The mean age was 63,2 years (range 44-88) and 2 out of 6 cases were in females (Table 2). The sum of the peri-tumoral skin was 1768 mm and the density was 1 nevus / 295 mm.

In the BCC group, a total of 8 nevic aggregates were found but only 5 fulfilled the size criteria of micro-nevi. 2 of 5 micro-nevi were pigmented. In 4 of 5 cases the pathologist had initially reported the micro-nevus, but neither the clinician nor the laboratory technician had reported the presence of them.

60% of these micro-nevi were of compound type. 20% were junctional and 20% intradermal. The mean horizontal diameter of these micro-nevi was 1,24 mm (range 0,9-1,9 mm). The mean age was 64,4 years and 4 out of 5 cases were in females (Table 2). The sum of the peri-tumoral skin was 1370 mm giving a density of 1 nevus / 274 mm.

DISCUSSION

In this retrospective study, we have demonstrated the presence of micro-nevi in excisions of cutaneous MM matched with twice the number of BCC excisions. Our results show that micro-nevi are seldom appearances with an equal density in association to MM compared with BCC. Further, micro-nevi were more often detected on the trunk and upper extremities and the intradermal subtype was most common followed by the compound type.

There are only few studies of micro-nevi and to our knowledge, Dadzie et al. [3] are the only to

have reported this phenomenon in association to a broader range of both benign and malignant skin tumors. Dadzie's group defined the horizontal dimension of a micro-nevus to ≤ 1,5 mm, while in this study, the horizontal diameter was set to < 2 mm, which is in accordance with the protocol of The International Agency for Research on Cancer (IARC) that defines a melanocytic nevus to ≥ 2mm [2,9]. Possibly, a few more micro-nevi were according to this definition included in our study but the fact that neither the clinician nor the technician reported these very small lesions support their subclinical nature which was the purpose of this study. Dadzie's group analyzed all received pathology reports of cutaneous excisions in their laboratory in 2005 while in this study the focus lied on MM and BCC. These two tumor types were chosen in order to enable comparison of a similar amount of peri-lesional tissue, from similar body sites and age groups. Because MM excisions are generally wider and include more peri-tumoral skin the number of BCCs was doubled. All histological slides were systematically chosen and microscopically re-assessed. Re-examination of slides is important since not all pathologists mentioned micro-nevi in their reports. To only rely on the written pathology reports presents a risk of incompleteness when performing a retrospective study.

The trunk and upper extremities are anatomical locations which are frequent sites of melanocytic nevi, as well as MM and BCC[4,6,7], indicating a biological correlation maybe even beyond UV-exposure.

It has been reported that the number of melanocytic nevi correlates with the risk of developing MM, that increased sun exposure has an impact on the number of nevi as well as on the incidence of MM[1,2]. BCC was used as a control group because they develop at similar anatomical sites as MM, and also because their incidence correlates with increased sun exposure[5-7]. Richmond-Sinclair et al. showed that high individual nevus prevalence, in this case they included only nevi >2 mm on the arms, was associated with an increased risk of developing BCC in the future. [5] Interestingly BCC has been associated with benign and/or malign neoplasm at the same skin site[8]. The etiology is not established yet, but different theories have been suggested, e.g. that the first tumor induces epithelial or stromal changes that facilitate the growth of the second tumor by inducing growth factors and cytokines in the same region of the skin. Another theory mentioned, is the phenomenon of field cancerization caused by UV radiation or other environmental carcinogens, or both. Also, the incidence of two neoplasms at the same skin region could be simply caused by chance[8].

Unlike micro-nevi in skin, incidental benign nevic aggregates are frequently observed in lymph nodes, especially in the context of sentinel node biopsy analysis. Both normal and pathologic lymph nodes have been well described in literature. [3,10,11] There are two main theories regarding their incident in lymph nodes: the "migration arrest" theory and the "benign metastasis" theory. The "migration arrest" theory refers to melanocytic precursors that during embryologic development prematurely end their migration in the neural crest in the lymph node instead of the skin[3,10]. The "benign metastasis" theory refers to cutaneous nevus cells that migrate via dermal lymphatics to lymph nodes[3,10]. Even though these incidental nevic aggregates are benign, they still can be a challenge for pathologists when diagnosing sentinel nodes in patients with melanoma[11]. Dadzie et al[3] hypothesize in the so-called "Hochsteigerung" theory of nevogenesis, meaning derivation from dermal melanocytes, as opposed to the "Abtropfung" theory, e.g., derivation from junctional melanocytes. To explain the finding of micro-nevi of junction type by the "Hochsteigerung" theory would imply "epidermotropism" of dermal melanocytes, while in fact junctional nevi are most probably UV induced. Also, the compound type and the intradermal type of micro-nevi are possibly due to UV radiation and as such a risk marker for

increased sun exposure. Micro-nevi could also be a risk marker for future development of new MM, BCC and other non-melanoma skin cancers. Or due to to their scarceness they could be seen, simply as totally benign and inert nevic aggregates that are stable with no impact.

The intention of this study is to draw the existence of micro-nevi to the attention of both pathologist and dermatologist, with the encouragement to report them. Based on our results, a rough estimate of how many micro-nevi could be present in the skin of a medium-sized human is; approximately 5 micro-nevi were found in perilesional skin with the measurement of about 1,5 meters (1500 millimeters). With a section thickness of approximately 2 mm and an average skin area of 2 square meters, a number of 2500 micro-nevi in a single person could be speculated (individual variations such as age, sex, different body areas, skin type and sun-exposed/nonexposed skin have not been taken into account in this approximation).

Although the number of nevus cells at risk for malignification is small in these micro-nevi compared to visible ordinary benign nevi, they might have special properties? There are many questions that seek answers: Are they formed gradually or are micro-nevi present early in life? If so, are the micro-nevus cells structurally different compared to ordinary nevus cells because they do not appear to have the same growth potential. Do they carry genetic alterations?

In summary, we note that micro-nevi could be more common than we expected and that there was no difference in the incidence in association to MM compared to BCC. The significance of these small nevi is unclear, but more studies are needed to determine if micro-nevi may play a role in the carcinogenesis of MM or could at least be an indicator of risk for MM and/ or other non-melanoma skin cancers.

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Conflict of Interest and Source of Founding: Non declared.

The Ethics Committee at the Karolinska Institute, Stockholm, Sweden, approved this study; DNR 2017/573-13 and DNR 2018/687-32.

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