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Melanoma risk in congenital melanocytic naevi: a systematic review

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Summary

Background The risk of malignant melanoma in congenital melanocytic naevi (CMN) is a matter of controversial and ongoing debate.
Objectives The purpose of this systematic review is to provide a careful and detailed summary of the published data, including several recently published studies.
Methods Articles on CMN (n = 1424) were retrieved from Medline, 1966–October 2005. Case reports and studies lacking relevant clinical information were excluded. Only systematic collections of cases were taken into consideration. Series with fewer than 20 patients or studies with a mean follow-up of <3 years were regarded as epidemiologically less significant.
Results Fourteen articles were finally chosen for further analysis. The studies varied significantly with respect to study design (source of cases; retrospective vs. prospective analysis), age of patients, follow-up time, and naevus characteristics. The frequency of melanomas ranged between 0·05% and 10·7% and was significantly higher in smaller studies ($P < 0·0001$). In a total of 6571 patients with CMN who were followed for a mean of 3·4–23·7 years, 46 patients (0·7%) developed 49 melanomas. The mean age at diagnosis of melanoma was 15·5 years (median 7). By comparison with age-adjusted data from the Surveillance, Epidemiology and End Results database, we calculated that patients with CMN carry an approximately 465-fold increased relative risk of developing melanoma during childhood and adolescence. Primary melanomas arose inside the naevi in 33 of 49 cases (67%). In seven cases (14%), metastatic melanoma with unknown primary was encountered; in four cases (8%) the melanoma developed at an extracutaneous site. The risk of developing melanoma and the rate of fatal courses were by far highest in CMN ≥40 cm in diameter.
Conclusions The overall risk of melanoma of 0·7% in all 14 studies was lower than expected. The higher incidence of melanomas in smaller studies indicates selection bias. The melanoma risk strongly depends on the size of CMN and is highest in those naevi traditionally designated as garment naevi. The median age of 7 years at diagnosis of melanoma points to a risk maximum in childhood and adolescence. Future studies on CMN should report: (i) diameter, percentage of body surface, and localization of the CMN; (ii) percentage of naevus area removed by excision or subject to dermabrasion or other superficial treatments; (iii) mean and median age at entry into the study; (iv) mean and median follow-up time; (v) details on each melanoma case; (vi) standardized morbidity ratio of melanoma; and (vii) percentage of neurocutaneous melanosis.

Congenital melanocytic naevi (CMN) represent pigment cell malformations that have formed during ontogenesis and are visible at or shortly after birth. Pathogenetically, CMN are mostly considered neural crest-derived hamartomas, i.e. defects of cell migration and/or differentiation due to postzygotic mutational events.[1] Larger CMN tend to be arranged in

specific shapes or patterns, probably reflecting genetic mosaicism.[2] The size of CMN varies from diameters of <1 cm to lesions covering large parts of the skin surface. The definitions of 'large' and 'giant' CMN in the literature are variable.[3] The most widely used definition of 'large' CMN subsumes all CMN with a largest diameter of ≥20 cm in adulthood[4] and, in the following, will be referred to as LCMN. However, with respect to their clinical behaviour, CMN that cover much larger body areas were regarded as a separate group by some authors.[5–7] In this article, we therefore refer to the traditional term 'garment naevus' (GN) which we define as a naevus situated on the trunk which measures >40 cm in largest diameter or is expected to reach this size in adulthood.

The incidence of CMN in newborn infants has been reported by numerous studies as being between 0·2%[8] and 2·1%.[9] Several studies observed a slightly higher incidence of CMN in women (male/female ratio between 1 : 1·17 and 1 : 1·4[6,7,10,11]). The incidence of CMN in South American newborns was 15 : 100 000 for naevi ≥4 cm and 5 : 100 000 for naevi ≥10 cm.[12] The incidence of GN has not been specified in any study. Up to the early 1960s, about 90 cases of this phenotype had been described, reporting a considerable degree of malignant transformation.[13] Pers, in 1963, published the first retrospective follow-up study of 110 patients with 'giant' CMN, including 11 cases of GN.[14] In his series, Pers found three cases of melanoma during 23 years of follow-up.

Since then, numerous prospective and retrospective studies have been performed. Nowadays, CMN are commonly mentioned in dermatological textbooks as a risk factor for malignant melanoma. Nevertheless, there is an ongoing debate about the magnitude of this risk and as to whether it applies to all CMN or only to larger CMN. The attempt to establish a histopathological definition of 'congenital' naevi – irrespective of clinical information – has led to additional confusion (reviewed by Krengel[1]).

In several articles, the published data have been summarized in the form of short tabular presentations, without taking into account the special features of each study.[3,15,16] Watt *et al.*[17] confined their systematic review to CMN >2% total body surface. Consistently, the authors did not consider several studies that include CMN of smaller sizes.[18–20] Moreover, three new studies with data from more than 1500 patients have been published only recently.[7,10,11] In this article we present the first systematic review of all studies providing data on the melanoma risk in CMN. The results of this analysis should provide a reliable basis for the counselling of patients with CMN.

Materials and methods

We searched for the combination of the terms 'congenital', 'naevus' and ['melanoma' OR 'malignant' OR 'malignancy' OR 'risk'] in Medline (1966–October 2005), without restriction for language. The titles and abstracts (if available) were studied and all articles containing original clinical data, with the exception of case reports, were retrieved as full texts. Additionally, we checked the bibliographic data of the full-text publications and of other review articles about CMN for further studies. The decision was made whether an article represented a selection of individual cases or a systematic case collection in the sense of a retrospective or prospective study. Only the systematic collections of cases were taken into consideration for further analysis. Several studies, mainly focusing on histological findings or aspects of treatment, represented smaller case series or series with a relatively short follow-up. To avoid the increased potential of selection bias in these studies, we decided that studies with fewer than 20 patients or with a mean follow-up of <3 years should be regarded as epidemiologically less significant.

Results

Our literature search yielded a total of 1424 references (Fig. 1), of which 18 publications met the inclusion criteria.[6–8,10,11,14,18–29] To avoid overlap, only the publications containing the latest data of each group were considered (the data from Pers[14] were included by Lorentzen *et al.*;[18] the data from Gari *et al.*,[23] Marghoob *et al.*[26] and Bittencourt *et al.*[6] were included by Hale *et al.*[11]). The resultant 14 articles are shortly characterized as follows:

Greeley *et al.* (1965).[21] This is a retrospective analysis of 56 cases of CMN from a clinic of plastic surgery in Chicago between 1939 and 1964. The authors defined a giant pigmented naevus as covering an area of ≥900 cm^2 on the trunk or extremities or involving an entire orbit or the major portion of a face or hand, respectively (mean size 540 cm^2).

Lorentzen *et al.* (1977).[18] This study analysed 151 cases of CMN from the archives of two dermatological clinics and two radium centres in Denmark from 1915 to 1975. The patients were followed by questionnaire, hospital records or clinical examination. The authors defined a giant pigmented naevus as a lesion that exceeds the size of the palm of the patient's hand in the face or neck and twice this size elsewhere on the body.

Arons and Hurwitz (1983).[19] The authors collected 46 cases of CMN from the departments of surgery, paediatrics and dermatology at New Haven from 1965 to 1981. The naevi ranged from 2·0 × 0·6 to 24 × 18 cm (mean 33 cm^2) and were thus smaller than the naevi from most of the other studies.

Quaba and Wallace (1986).[22] Thirty-nine cases of CMN were retrospectively identified by questionnaires sent to British consultant plastic surgeons. All the patients had been seen at the reporting surgery units during the first year of life. The definition of a large congenital naevus was coverage of ≥2% of the total body surface area (mean 17%).

Ruiz-Maldonado *et al.* (1992).[24] This is a prospective analysis of 80 cases of CMN that presented to a country-wide paediatric reference centre in Mexico City between 1971 and 1990. All naevi were >20 cm in diameter.

Swerdlow *et al.* (1995).[25] The authors retrospectively identified 265 cases of CMN through diagnostic indexes held

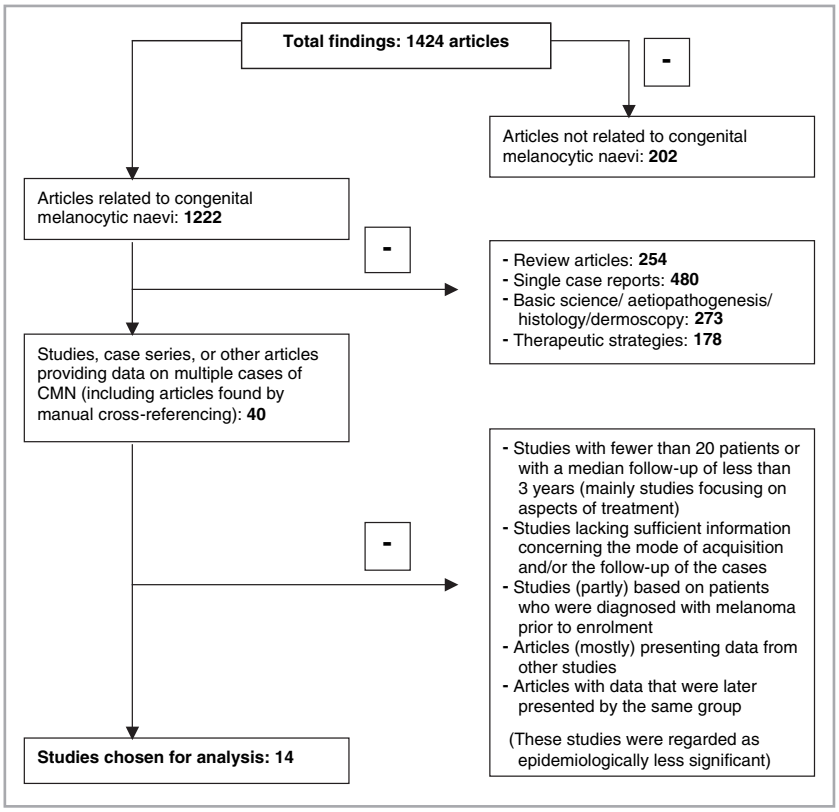

Fig 1. Algorithm of study selection criteria. CMN, congenital melanocytic naevi. Search terms: 'congenital' AND 'naevus' AND ['melanoma' OR 'malignant' OR 'malignancy' OR 'risk'], Medline (1966–October 2005).

between 1950 and 1984 at one dermatological and one paediatric hospital in London. The patients were traced at the National Health Service Central Register. The study included all CMN irrespective of their size, 10% of which were >20 cm in diameter.

Dawson *et al.* (1996).[20] This prospective study included 133 children with CMN presenting between 1987 and 1993. One half came from a dermatological clinic in London, the other half from dermatologists, paediatricians and plastic surgeons throughout the U.K. who had been personally informed or invited in journals. The parents filled in one initial and subsequent annual questionnaires. All sizes of CMN were accepted; the mean size was 6·7% of the body surface (median 2·3%).

Sahin *et al.* (1998).[27] This retrospective study analysed 230 CMN from a dermatology practice in New York that presented between 1955 and 1996. The patients were followed by clinical examination or by telephone. The naevi measured between 1·5 and 20 cm in their largest diameter ('medium-sized CMN').

Egan *et al.* (1998).[28] Between 1973 and 1996, the authors prospectively included 46 patients from two dermatology clinics in Philadelphia and New York. The patients were followed by medical records or by telephone. The size of the naevi was ≥5% of the body surface or ≥20 cm diameter. One of 46 patients (2·2%) had symptomatic neurocutaneous melanosis (NCM).

Foster *et al.* (2001).[29] The study retrospectively reviews 46 patients with CMN who presented at the paediatric dermatology service at the University of California at San Francisco between 1990 and 1997. All patients had LCMN or multiple CMN. All naevi involved the head and neck or overlaid the dorsal spine. The authors found a high incidence of asymptomatic, magnetic resonance (MR)-positive NCM (11% of 42 patients who underwent MR imaging).

Berg and Lindelöf (2003).[8] In this population-based study, the authors retrospectively analysed the Swedish Medical Birth Register and the Swedish Cancer Register between 1973 and 1993. They identified 3922 cases registered as CMN (0·2% of all newborns). A quality test in 150 patients showed that this diagnosis was correct in about 85%. The cases from 1973 to 1986 were classified as large ($n = 146$) and small CMN; however, this distinction was at the discretion of the reporting physicians and lacked a clear-cut definition.

Ka *et al.* (2005).[10] The authors evaluated an internet registry of LCMN (Nevus Outreach Inc.) which contains information from a detailed questionnaire. The registry opened in 1998 and, up to 2002, yielded 379 cases from 26 countries. Twenty-six patients (6·9%) had a diagnosis of NCM, 22 (5·8%) symptomatic and four (1·1%) asymptomatic.

Hale *et al.* (2005).[11] This study represents an update on the largest clinic-based collection of LCMN, the New York University Registry (NYU-LCMN Registry). Since 1979, 205 cases have been collected. One hundred and seventy of the 205 patients were followed prospectively. Six additional patients had already been diagnosed with melanoma at the time they entered into the registry and were excluded from analysis. Seventeen of 205 patients (8·3%) had NCM, nine (4·4%) symptomatic and eight (3·9%) asymptomatic.

Bett (2005).[7] In this study, 1008 cases of CMN from the internet-based registry of a naevus support group (Nevus Network) were analysed. These cases included 599 with GN, representing the largest cohort of GN in the literature, and 17 patients with multiple (>3) congenital naevi but no individual naevus ≥20 cm. The remaining patients had non-garment LCMN. The patients were followed by mail, telephone or e-mail.

In all cases of melanoma, the diagnosis was confirmed by histology. The proportion of melanomas in the 14 studies ranged from 0·05% to 10·7% of the CMN cases. Taken together, 49 melanomas were reported in 46 of 6571 patients (0·7%).

The mean follow-up times in 11 of 14 studies ranged between 3·4 and 23·7 years (Table 1). In the remaining three studies, the mean follow-up was not specified, but the observation period clearly exceeded 3 years.[10,19,21] The mean age of the patients at entry into the study ranged between 0 and 19 years.

The data extracted from the studies are listed in the Tables. Table 1 shows the study design (retrospective vs. prospective), sample size, risk of melanoma and study duration. Other characteristics of the reported melanoma cases are summarized in Tables 2–4 (age at diagnosis; location of the primary melanoma; percentage of fatal cases).

Discussion

The studies varied significantly with respect to study design (source of cases; retrospective vs. prospective analysis), age of patients, follow-up time and naevus size. In the following, we make an attempt to analyse how this heterogeneity might have influenced the proportions of melanoma.

The sample size of the studies ranged between 39 and 3922 patients. Table 1 illustrates that smaller studies report higher incidences of malignant transformation ($P < 0{\cdot}0001$; χ^2 for linear trend). This indicates selection bias. Cases from referral centres and retrospective case collections are likely to result in highly selected cohorts of patients who are at an increased risk for melanoma.

In the 14 studies, longer follow-up times did not necessarily result in higher proportions of melanomas. This points to the influence of additional factors, among which the age of the patients and the size of the naevi are probably the most important. It has long been reported that, in patients with CMN, a significant percentage of melanomas arises in early childhood.[15,30] In the 46 melanoma cases, the mean age at diagnosis was 15·5 years (median 7) (Table 2). This seems to confirm a risk maximum for melanoma in childhood and adolescence. However, most studies only include information between childhood and early adulthood; therefore, younger cases might be relatively over-reported. The results of ongoing prospective studies with longer follow-up times should provide more reliable data.

The observed number of melanoma cases in the 14 studies was compared with age-matched data from the Surveillance, Epidemiology and End Results database to quantify the relative

Table 1 Selected studies on melanoma risk in congenital melanocytic naevi

Authors	Study type	Total number of patients	Proportion of melanomas/total (%)	Mean age at entry into the study	Mean follow-up time
Greeley *et al.* (1965)[21]	Retrospective	56	10·7% (6/56)	9 years	n.g.
Quaba and Wallace (1986)[22]	Retrospective	39	5·1% (2/39)	<1 year	8·6 years
Egan *et al.* (1998)[28]	Prospective	46	4·3% (3 melanomas in 2/46 patients)	8·4 years	7·3 years
Ruiz-Maldonado *et al.* (1992)[24]	Prospective	80	3·75% (3/80)[a]	1·75 years	4·7 years
Hale *et al.* (2005)[11]	Prospective	205 (170/205 patients prospectively followed)	2·4% (4/170)	n.g.	5·3 years (median)
Lorentzen *et al.* (1977)[18]	Retrospective	151	2% (3/151)	8·2 years	23 years
Bett (2005)[7]	n.g.	1008	1·7% (17/1008)	n.g.	5·6 years
Sahin *et al.* (1998)[27]	Retrospective	230	1·3% (5 melanomas in 3/230 patients)	3·1 years (median 1·8 years)	3·4 years (median 3·4 years)
Dawson *et al.* (1996)[20]	Prospective	133	1·5% (2/133)	19 years (median 12 years)	6·7 years (median 5·8 years)
Swerdlow *et al.* (1995)[25]	Retrospective	265	0·75% (2/265)	n.g. (<5 years: 30%; <15 years: 84%)	23·7 years (median 25 years)
Berg and Lindelöf (2003)[8]	Retrospective	3922	0·05% (2/3922)	0 years (at birth)	10 years (median)
Ka *et al.* (2005)[10]	Prospective	379	0	8 years (median 3 years)	n.g. (2–6 years)
Arons and Hurwitz (1983)[19]	Retrospective	46	0	n.g. (mean age at operation: 10·5 years)	n.g. (1–17 years)
Foster *et al.* (2001)[29]	Retrospective	46	0	0·4 years	5 years

n.g., not given. [a]One additional patient with a rapidly growing tumour in the area of the naevus diagnosed as a neuroblastoma.

Table 2 Age at diagnosis and additional characteristics of melanomas in patients with congenital melanocytic naevi (CMN)

	Age at diagnosis of melanoma	
Authors	Non-fatal cases (n = 23)	Fatal cases (n = 23)
Greeley *et al.* (1965)[21]	1 year,[a] 38 years	1 year, 10 years, 10 years,[b] 30 years[b]
Lorentzen *et al.* (1977)[18]		28 years,[c] 38 years, 40 years
Arons and Hurwitz (1983)[19]		
Quaba and Wallace (1986)[22]		7 years, 10 years
Ruiz-Maldonado *et al.* (1992)[24]	14 years[d]	8 months, 2 years
Swerdlow *et al.* (1995)[25]		18 years, 20 years
Dawson *et al.* (1996)[20]	0 years, 0 years[e]	
Sahin *et al.* (1998)[27]	26 years,[f] 42 years, 57 years	
Egan *et al.* (1998)[28]	2 years	3 years
Foster *et al.* (2001)[29]		
Berg and Lindelöf (2003)[8]	7 years[g]	1 year[h]
Ka *et al.* (2005)[10]		
Hale *et al.* (2005)[11]		1 year, 1 year, 1 year,[i] 3 years
Bett (2005)[7]	at birth, 3 months, 6 months, 7 months,[j] 9 months, 1 year, 3 years, 7 years, 8 years,[k] 20 years, 26 years,[l] 34 years, 39 years	4 years, 24 years, 39 years, 58 years
Mean age	14·1 years	15·8 years
Median age	7 years	10 years

Studies were considered only where both the mean follow-up time and the mean age at entry were specified. For all cases combined, the mean age was 15·5 years (median 7). [a]Histologically diagnosed as juvenile melanoma. [b]Leptomeningeal melanosis at post mortem examination. [c]CMN were treated with X-rays in very large doses 8 years prior to diagnosis of melanoma. [d]Histologically diagnosed as minimal deviation melanoma. [e]Both congenital melanomas were considered as a self-healing type of melanoma or a pseudomelanoma. [f]Patient developed further cutaneous melanomas at 33 and 36 years. [g]Later histologically re-evaluated as a benign proliferative nodule. [h]Considered by the authors as congenital melanoma. [i]Leukaemic melanoma. [j]Lymph node dissection, lost to follow-up. [k]Hepatic metastases at age 24 years, <1 year of follow-up. [l]Lymph node dissection, 1 year of follow-up.

Table 3 Primary site of melanomas in patients with congenital melanocytic naevi (CMN)

Authors	Cutaneous melanomas arising in CMN	Cutaneous melanomas outside CMN	Extracutaneous primary melanomas	Primary melanoma not identified
Greeley *et al.* (1965)[21]	2			4 (†)
Lorentzen *et al.* (1977)[18]	2 (†)			1 (†)
Arons and Hurwitz (1983)[19]				
Quaba and Wallace (1986)[22]	2 (†)			
Ruiz-Maldonado *et al.* (1992)[24]	3 (2†)			
Swerdlow *et al.* (1995)[25]	2 (†)			
Dawson *et al.* (1996)[20]	2			
Sahin *et al.* (1998)[27]		5 (3 patients)		
Egan *et al.* (1998)[28]	3 (2 patients)			
Foster *et al.* (2001)[29]				
Berg and Lindelöf (2003)[8]	2			
Ka *et al.* (2005)[10]				
Hale *et al.* (2005)[11]			3 (†)	1 (†)
Bett (2005)[7]	15 (3†)		1 (†)	1 (†)
Total	33 (11†)	5 (0†)	4 (†)	7 (†)

†Fatal.

Table 4 Proportion of fatal cases in patients with large congenital melanocytic naevi (LCMN)

	Fatal cases/total melanoma cases	
Authors	Non-garment LCMN	Garment naevi
Greeley *et al.* (1965)[21]	0/2	3/3
Lorentzen *et al.* (1977)[18]	1/1	2/2
Arons and Hurwitz (1983)[19]		
Quaba and Wallace (1986)[22]		2/2
Ruiz-Maldonado *et al.* (1992)[24]	2/3 cases fatal; size of LCMN n.g.	
Swerdlow *et al.* (1995)[25]		2/2
Dawson *et al.* (1996)[20]	n.g.	n.g.
Sahin *et al.* (1998)[27]		
Egan *et al.* (1998)[28]		1/2
Foster *et al.* (2001)[29]		
Berg and Lindelöf (2003)[8]	0/1	
Ka *et al.* (2005)[10]		
Hale *et al.* (2005)[11]		4/4
Bett (2005)[7]	0/1	5/15
Total	1/5 (20%)	19/30 (63%)

n.g., not given.

risk of developing malignant melanoma, i.e. the ratio between observed and expected cases in a similar age group. In only seven of the 14 studies were both the mean follow-up time and the mean age at entry specified.[18,20,22,24,27–29] In these studies, comprising CMN of all sizes, 15 of 725 patients developed melanoma (2·1%). The mean age at entry was 7 years; the mean follow-up time was 8·9 years. The incidence of melanoma in the general population between the age of 10 and 14 years is 0·5 per 100 000 per year.[31] Comparing these data, we calculated that patients with CMN carry an approximately 465-fold increased risk of developing melanoma during childhood and adolescence. It is not possible to calculate an exact standardized morbidity ratio (SMR) without individual-based information on age and outcome. Therefore the figure only represents an estimate. Swerdlow *et al.*[25] calculated the SMR for melanoma development as 103 for all CMN ≥1 cm vs. 1224 for LCMN, suggesting highly size-dependent risk magnitudes. In studies focusing on LCMN, the SMR has been calculated as being between 101 and 324.[6,11,26,28] In their review, Watt *et al.*[17] considered four studies with a total of five melanomas in 120 patients with LCMN and calculated the SMR as 2599 (95% confidence interval 844–6064).

Kopf *et al.*, in 1979, proposed to divide CMN depending on their largest diameter in adulthood into small (<1·5 cm), medium (1·5–19·9 cm) and large (20 cm or more).[4] According to published nomograms, an infant's CMN of 12 cm (head) and 7 cm (torso), respectively, will finally reach 20 cm.[26] The classification of Kopf *et al.* has been followed by several authors. However, some studies demonstrated that the vast majority of melanomas in their samples arose in 'very large' CMN with an adult diameter of 50 cm or greater.[6,7] These naevi, in turn, are in most instances identical to those naevi traditionally designated as GN.

We analysed the numbers of LCMN and GN, respectively, in the selected studies. The number of LCMN was specified in six of 14 studies[7,10,11,24,25,28] and was reconstructed by description or drawings in three additional studies.[18,21,22] In these nine studies, a total of 39 melanomas occurred in 1539 LCMN (2·5%). This figure is close to the figure of 2·8% from the review by Watt *et al.*[17] The number of GN was stated in only three of 14 studies.[7,18,21] In these three studies, the proportion of melanomas was 3·1% (20 of 636). Compared with the overall incidence of 0·7% in all 14 studies, this clearly shows a higher incidence of melanoma in LCMN and in GN. Additionally, we analysed the size of the underlying CMN in the melanoma cases. Sufficient clinical information was available in 41 of 46 cases. In 30 of 41 cases (73%) the patients had a GN; in only five of 41 cases (12%) did the patients have a non-garment LCMN. These figures underscore that the risk of malignancy is markedly elevated in GN in comparison with non-garment LCMN.

Although the above data suggest a correlation between naevus size and magnitude of risk, the risk in small CMN remains to be systematically evaluated. Additionally, it remains to be investigated whether this risk exceeds that of acquired naevi of the same size. Our literature search did not identify studies focusing on the melanoma risk in smaller CMN. In the population-based study by Berg and Lindelöf,[8] in which 3922 (probably mostly small) CMN were followed for a median of 10 years, no melanoma developed in small CMN.

The recommendation of prophylactic surgical excision depends on the assumption that melanoma will arise directly inside the CMN. In the 14 studies, 33 of 49 (67%) melanomas developed inside the CMN, whereas four of 49 (8%) originated at an extracutaneous primary site; in seven of 49 (14%) the primary tumour was not identifiable (Table 3). In only one study,[27] cutaneous primary melanomas developed outside the CMN (five melanomas in three patients). In one case, the formation of melanoma underneath a previously excised area was reported.[7] Therefore, removal of the CMN is no guarantee to protect the patients against melanoma. Moreover, GN (i.e. the CMN at greatest risk of melanoma) may be too large to be excised completely. The impact of prophylactic surgical or other therapeutic measures on the risk of melanoma is difficult to assess. Certainly, the removal of melanocytic cells reduces this risk. However, a quantitative analysis is hampered by the heterogeneity of the studies concerning mode and extent of prophylactic therapy. The (mostly incomplete) information on these subjects is not suitable for an inter-study comparison of treated cases vs. controls.

In our analysis, one-third (11 of 33) of the melanomas arising inside the CMN proved fatal. It is well established that benign melanocytic tumours in childhood may mimic melanoma.[32] Therefore, metastasis represents the only definite proof of malignancy. We analysed the fatal (n = 23) vs. non-fatal cases (n = 23) in the 14 studies. Both groups had a comparable mean and median age at diagnosis (Table 2). However, the proportion of fatal cases was 20% (one of five) in patients with non-garment LCMN, and 63% (19 of 30) in patients with

GN (Table 4). This difference indicates a better prognosis of melanomas in patients with non-garment LCMN than with GN.

Certain clinical features of CMN have been considered to influence the individual melanoma risk. Bett[7] reported that all 15 patients with GN and melanoma had a naevus involving the posterior axis. In their review of 289 cases, DeDavid *et al.*[30] found that all patients with LCMN in whom melanoma developed had naevi in axial locations. Although most GN and a significant proportion of LCMN involve this location, this point is of interest as the involvement of the posterior axis is also a prerequisite for NCM.[5] Possibly, pathophysiological events reflected by this morphological pattern lead to a higher risk of leptomeningeal involvement and malignant degeneration. It has been recommended to perform MR imaging – or at least a careful neurological and developmental assessment with a close follow-up – in all infants with CMN >2 cm in diameter on the head or over the spine.[33] Likewise, the presence of more than 20 satellite naevi has been reported to represent a risk factor for NCM.[34] DeDavid *et al.*[30] found no case of melanoma originating from a satellite naevus. Recently, Bett[7] reported the first case of cutaneous melanoma in a satellite naevus.

In conclusion, the rarity of (large) CMN and the heterogeneity of the studies only allow a preliminary assessment of the risk of melanoma. Regarding the range of follow-up times between 3·4 and 23·7 years in the selected studies, conclusions on the lifetime risk of melanoma should be drawn with caution. As a main result of our review, we would like to emphasize that nearly three in four melanomas appeared in GN. We agree with Ruiz-Maldonado,[35] who recommended to classify CMN according to their largest diameter as follows (patients with giant naevi and with more than 50 small or medium-size satellite naevi should be classified one group above their corresponding size classification): small, <1·5 cm; medium, 1·5–10 cm; large, 11–20 cm; giant G, >20 cm; G1, 21–30 cm; G2, 31–40 cm; G3, >40 cm.

Minimum information required for epidemiological studies on the risk of melanoma in CMN includes: (i) diameter, percentage of body surface, and localization of the CMN; (ii) percentage of naevus area removed by excision or subject to dermabrasion or other superficial treatments; (iii) mean and median age at entry into the study; (iv) mean and median follow-up time; (v) clinical and histopathological details on each melanoma case; (vi) relative risk of melanoma; and (vii) percentage of patients with symptomatic and asymptomatic NCM.

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