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Childhood melanoma in Europe since 1978: a population-based survival study

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Abstract

The existence of the EUROCARE database now makes it possible to compare population-based survival for childhood melanoma in different European populations. The database contains verified information, including histological data, from cancer registries in 17 European countries, and as such it represents a particularly important source of survival information on a very rare cancer like childhood melanoma. The aim of the present paper was to describe survival in children with melanoma (MM), by sex, age and subsite, diagnosed during the period 1978–1989, using analysis of the data of the European pool of cases. Five year-survival for childhood MM diagnosed in 1978–1989 in Europe, is relatively good (80%; 95% confidence interval (CI) 47–95 for boys and 78%; 95% CI 58–91 for girls). Analysis by subsite, revealed the survival for MM on the head and neck, legs and arms was generally higher than survival for MM on other cutaneous sites (trunk, neck and scalp). For skin melanomas outcome for girls was better than boys, adjusting for age and sub-site. We suggest that the good survival observed in childhood MM seems to be related to early diagnosis.

Keywords: Childhood cancer; Population-based cancer registries; survival; Melanoma; Europe

1. Introduction

Malignant melanoma (MM) is a very rare tumour in children. The incidence before the age of 15 years is approximately 1/1 000 000 [1]. In Europe, age-standardised incidence rates for boys (age 0–14 years) range from 0.2 new cases per million in Germany to 2.3 in Norway. For girls of the same age, the range is 0.2 in Bulgaria to 3.8 in Norway [1]. There is no clear correlation between the incidence of MM and geographical area, although it tends to be lower in Mediterranean countries [1].

Until about 30 years ago, MM was also rare in European adults, but its incidence has increased rapidly over the past two decades so that it now constitutes around 3% of all malignancies [2].

MM is divided histologically into three types: superficial spreading, nodular and lentigo maligna. In addition, childhood MM is divided into five categories based on the mode of occurrence [3]:

I. Transplacental melanoma, transmitted from the mother to the fetus.
II. Transformation from giant congenital melanocytic nevus.
III. In association with congenital predisposing conditions (*xeroderma pigmentosum*, dysplastic nevus syndrome, and rarely, albinism).
IV. Development from healthy skin.
V. Development from pre-existing nevus.

In most cases, childhood MM arises on healthy skin and about a third of cases develop from giant congenital nevi. These nevi give rise to melanoma in 6 to 31% of cases [4,5]. The diagnosis of small congenital nevi as precursors of melanoma is more difficult to make, and it is this uncertainty that often leads to the indication for their removal in children.

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Table 1
Quality of data for melanoma among European children by country (EUROCARE, period of diagnosis 1978–1989)[a]

Country	Cases	Gender *n* (%)		Microscopically verified cases	Cases lost to follow-up
	n (%)	Male	Female	*n* (%)	*n* (%)
Denmark	16 (8)	8 (8)	8 (7)	16 (100)	
Holland	4 (2)	1 (1)	3 (3)	4 (100)	
England and Wales	121 (57)	58 (57)	63 (57)	90 (74)	1 (1)
Estonia	3 (1)	2 (2)	1 (1)	3 (100)	
Finland	12 (6)	6 (6)	6 (5)	12 (100)	
France	8 (4)	2 (2)	6 (5)	8 (100)	
Germany (West)	13 (6)	6 (6)	7 (6)	13 (100)	4 (31)
Iceland	1 (0.5)	0 (0)	1 (1)	1 (100)	
Italy	5 (2)	2 (2)	3 (3)	5 (100)	
Scotland	9 (4)	4 (4)	5 (5)	9 (100)	
Slovakia	5 (2)	3 (31)	2 (2)	5 (100)	
Slovenia	1 (0.5)	0 (0)	1 (1)	1 (100)	
Spain	4 (2)	2 (2)	2 (2)	4 (100)	
Sweden	7 (3)	6 (6)	1 (1)	7 (100)	
Switzerland	3 (1)	1 (1)	2 (2)	3 (100)	1 (33)
All	212 (100)	101 (100)	111 (100)	181 (85)	6 (3)

The national registries are in bold.
[a] Source of data: EUROCARE II.

The existence of the EUROCARE database now makes it possible to compare population-based survival for childhood melanoma in different European populations. The database contains verified information, including histological data, from cancer registries in 17 European countries, and as such represents a particularly important source of information on a very rare cancer like childhood melanoma, since hospital series necessarily provide very limited and unrepresentative information. The aim of this present paper was to describe survival in children with melanoma, by sex, age and subsite, diagnosed during the period 1978–1989, analysing the data from the European cases.

2. Patients and methods

We considered all cases of primary childhood malignant melanoma (MM) with a follow-up of at least five years diagnosed between 1978 and 1989. Data from 17 European countries participating in EUROCARE were analysed; registries in Austria and Poland did not record any cases of childhood melanoma during the study period. Nine registries (those of Finland, Denmark, Iceland, Scotland, England and Wales, West Germany, Estonia, Slovakia and Slovenia) cover the entire populations of their respective countries. Most other participating countries are represented by one or more local or regional registries that cover a large fraction of the whole population. Table 1 shows the principal characteristics of the 212 childhood melanoma cases by country. Over half of the cases came from the National Registry of Childhood of England and Wales; no other single country provided more than 8% of the total. It is also evident that MM, in the EUROCARE database, is more common in females than males, and this reflects, to a lesser extent, the situation in adults. The high proportions of microscopically verified cases and the low proportions of cases lost to follow-up, in almost all countries, indicate the high quality of the data.

Table 2 shows the distribution of cases by site and gender. There were no major site differences between gender. The head and neck site (24% versus 17%) was slightly more common in boys than girls, whereas the opposite was the case for the trunk (19% versus 25%) and lower limb (20% versus 28%). A survival analysis of the entire series of cases was performed, as the rarity

Table 2
Distribution of melanoma sub-sites among European children by gender[a]

Subsite	Males *n* (%)	Females *n* (%)	All *n* (%)
Melanoma of the head and neck	24 (24)	18 (17)	42 (21)
Trunk	19 (19)	27 (25)	46 (23)
Upper limb	17 (17)	15 (14)	32 (16)
Lower limb	20 (20)	30 (28)	50 (25)
Other skin melanomas	6 (6)	3 (3)	9 (4)
Eye	8 (8)	10 (9)	18 (9)
Other non-skin not including the eye	4 (4)	3 (3)	7 (3)
All	98 (100)	106 (100)	204 (100)

[a] Source of data: EUROCARE.

Table 3
5-year survival (%) in European children with malignant melanoma diagnosed between 1978 and 1989, according to age and gender[a]

Gender	Age at diagnosis (years)				
	<1	1–4	5–9	10–14	0–14
Boys					
5-year survival	100	42	96	64	80
95% Cl	34–100	25–62	34–100	43–81	47–95
(*n* of cases)	(2)	(15)	(29)	(52)	(98)
Girls					
5-year survival	86	89	81	77	78
95% Cl	20–99	25–100	39–97	47–92	58–91
(*n* of cases)	(6)	(16)	(25)	(59)	(106)
All					
5-year survival	93	66	88	70	79
95% Cl	21–100	40–85	48–98	53–84	60–91
(*n* of cases)	(8)	(31)	(54)	(111)	(204)

95% Cl, 95% confidence limits.
[a] Source of data: EUROCARE.

of this malignancy limits subset analysis due to small numbers involved.

Observed survival rates were calculated by the actuarial method [6]. Overall European survival was estimated as the weighted average of the survival in each country. Weights were proportional to the childhood population (0–14 years) in each country (Magnani and colleagues, this issue). Survival rates were calculated for each sex, either for four age classes: <1, 1–4, 5–9 and 10–14 years or for subsite according to three age groups 0–4, 5–9 and 10–14 years and sex.

The Cox proportional hazard model [7] was used to compare hazard rates over the time period of 1985–1989 between boys and girls taking into account the different distribution of age and the anatomical sub-site where the melanoma of the skin originated.

3. Results

Table 3 shows 5-year survival, by age and gender for the entire period 1978–1989. Overall survival for all was generally good (79%, 95% confidence interval (CI) 60–91), with no differences between gender. Some survival differences emerged when the age classes were considered separately: survival was lower in boys diagnosed in the age range 10–14 years (64%; 95% CI 43–81 at 5 years) and 1–4 years (42%; 95% CI 25–62 at 5 years).

Table 4 shows the observed 5-year survival by cutaneous site and age, and Table 5 shows survival for non-cutaneous sites by gender. Site is one of the main prognostic factors in adult melanoma. As in adults, for both genders, trunk was a cutaneous site associated with poor survival (69%; 95% CI 54–80). Survival was also low for the category of 'other skin melanomas' (67%; 95% CI 35–88). This pattern was present in all the three age groups considered. Furthermore, prognosis slightly increased from infants up to children aged 10–14 years (Table 4).

Survival was good for melanoma developing in the eye (88%; 95% CI 65–97), much better than for other non-cutaneous sites (57%; 95% CI 25–84) (intracranial, and lymph node from unknown primary).

Outcome for girls was better than for boys for melanoma of skin (Table 6). The relative risk (RR) of dying adjusted by age and sub-site was higher for boys than girls. The analysis for the time period of 1985–1989 confirmed the better prognosis associated with subsites of the limbs and head and neck and for children aged 5–14 years.

Table 4
5-year survival rates and 95% confidence limits for cutaneous melanoma by subsite and age among European children, diagnosed 1978–1989[a]

Site (total no. of cases)	All (95% Cl)	0–5 years (95% Cl)	5–9 years (95% Cl)	10–14 years (95% CI)
Melanoma of head and neck (42)	90 (78–96)	75 (41–93)	91 (62–98)	96 (79–99)
Trunk (46)	69 (54–80)	50 (22–78)	65 (37–86)	76 (57–89)
Upper limb (32)	94 (79–98)	100 (65–100)	100 (65–100)	88 (66–97)
Lower limb (50)	92 (81–97)	91 (62–98)	93 (69–99)	92 (74–98)
Other skin melanomas (9)	67 (35–88)	50 (9–91)	67 (21–94)	75 (30–95)
All sites (179)	85 (60–91)	76 (58–91)	85 (47–92)	87 (59–92)

[a] Source of data: EUROCARE.

Table 5
5-year crude survival rates and 95% confidence limits (CI) for non-cutaneous melanoma by subsite and gender among European children, diagnosed 1978–1989[a]

Site (total no. of cases)	Boys (95% CI)	Girls (95% CI)	All (95% CI)
Eye (18)	86 (49–97)	90 (60–98)	88 (65–97)
Other non-skin melanomas not including the eye (7)	75 (30–95)	33 (6–79)	57 (25–84)

[a] Source of data: EUROCARE

Table 6
Cox proportional regression analysis of survival of European children with melanoma of skin diagnosed in 1985–1989

	RR, adjusted for gender, age and sub-site	S.E.
Gender		
Girls versus boys	0.65	*0.34*
Age (years)		
10–14	1 (ref.)	
5–9	0.99	*0.41*
0–4	1.58	*0.42*
Sub-sites		
Limbs (ICD-IX 172.6–172.7)	1 (ref.)	
Head and Neck (ICD-IX 172.0–172.4)	0.88	*0.55*
Trunk (ICD-IX 172.5)	4.15	*0.40*
Other skin sites (ICD-IX 172.9, 187.1)	2.64	*0.66*

S.E., standard error; ref. reference; RR, relative risk.

4. Discussion

Five-year survival for childhood MM diagnosed in 1978–1989 in Europe, is relatively good (80%; 95% CI 47–95 for boys, 78%; 95% CI 58–91 per girls and 79%; 95% CI 60–91 for all).

Five-year relative survival for skin melanomas (ICD-9 172) in adults was slightly lower: for young adults (aged 15–44 years), recorded in the period 1985–1989 it was 81%, and for the entire adult age group (15–99 years) it was 77% [8]. The corresponding figure in this study for children was 85%; 95% CI 60–91 (Table 4). In addition, for choroid melanoma survival was better in children than young adults (88% versus 68%) [8].

Data available from the USA Surveillance, Epidemiology and End Results (SEER) shows, for the age group of 10–14 years, a five year survival of 86% (period 1985–1994), that points to a better prognosis in comparison with our results (70%; 95% CI 53–84) [9]. In this database, when analysing the total population aged under 20 years, females had slightly better survival probabilities than males, as reported in our data. Applying the Cox proportional hazard model adjusting for age and sub-site, we found a better survival for females, despite the unfavourable distribution of subsites. The hypothesis that the female survival advantage, in many cancers, is dependent on sexual maturity, was tested in a population-based cohort of 6262 individuals, aged under 20 years, affected by a malignant disease [10]. When examining epithelial cancers, males and females have similar hazard ratios, before the age of 11 years, otherwise between 11 and 18 years, the rates were 55–65% lower in females than in males [10]. These findings fit the hypothesis that high levels of endogenous oestrogen and/or progestogen or cyclic ovarian function prevent the establishment of distant metastasis, probably involving immunological response [10].

Analysis by subsite, revealed that survival for MM on the head and neck, legs and arms was generally higher than survival for MM on other cutaneous sites (trunk, neck and scalp). Location is known to be an independent prognostic factor for adults with primary cutaneous MM and survival data by subsite, available in literature, are mostly in agreement with our findings [11].

In this case, however, the small number of cases means the data must be interpreted with caution. It is now generally accepted that childhood melanoma does not differ in biological behaviour from adult onset melanoma [2]. However, it is difficult to determine whether the prognosis in children correlates with Breslow thickness and Clark levels as is the case in adults [2].

Parents are more aware than in the past of the danger of melanoma, and tend to consult a dermatologist or paediatrician for pigmented lesions much more readily. The visibility of skin lesions and unattractiveness of pigmented lesions (particularly in light-skinned children) also induces parents to ask for their removal [12]. Dermatologists and other physicians tend to excise pigmented lesions in children, when there is any doubt about their nature. In most cases, clinical observation is able to differentiate benign pigmented nevi from potentially malignant lesions such as mixed, junctional or dermal nevi. However, clinical doubt is sustained by the fact that multiple lesions are often found, some of which presenting characteristic pigmentations, that are not easy to interpret, having indefinite margins and reported as having increased in size or changed form.

Furthermore, although histological diagnosis is the only way of confirming malignancy, differential diagnosis against other pigmented lesions, particularly Spitz nevus (SN), is often very difficult. SN, described for the first time in 1948, is histologically similar to melanoma, but its course is generally benign. There is no single criterion for reliably distinguishing the two entities, and the diagnosis generally depends on a combination of features; pathologists may disagree on cases [3]. Histopathological review resulted in the reclassification of between 30 and 95% of MM cases as Spitz nevus or other benign lesions [12–16].

Finally, considering that European children are exposed much more than in the past to the sun's rays and that acquired melanocytic nevi are the most important risk factor for the development of cutaneous MM, the frequency of excision biopsies for these lesions is increased. This policy results in the diagnosis of more melanocytic tumours in their early stages and represent, till now, the main strategy to improve survival in children.

5. Conclusions

In children, survival for MM is slightly different to that of adults. Since the natural history of the disease is

not influenced by age, a better prognosis in children is probably due to the early radical removal of pigmented skin lesions, a situation favoured by the greater awareness of parents and physician of the dangers of melanoma and also because of the antiaesthetic features of skin lesions. If such an attitude becomes even more widespread, one may hope that the diagnosis of early stage MM will increase in children, with a consequent improvement in survival and cure rates.

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