Malignant melanoma in families of children with osteosarcoma, chondrosarcoma, and adrenal cortical carcinoma

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SUMMARY Seven cases of malignant melanoma in the close relatives of children with osteosarcoma and chondrosarcoma are described. The association between certain childhood malignancies (adrenal cortical carcinoma, osteosarcoma, chondrosarcoma, retinoblastoma) and malignant melanoma is discussed and it is proposed that in certain families malignant melanoma may be another manifestation of the same gene defect which results in susceptibility to tumours characteristic of the SBLA cancer family syndrome.

Malignant melanoma constitutes about 1% of all malignancies and most cases are thought to be sporadic. Certain heritable forms of melanoma have, however, been described. Inherited site specific cutaneous melanoma in a father and two of his children was first reported by Cawley¹ and attention was drawn to the occurrence of melanoma with other malignancies by Lynch *et al*,² who described three families where malignant melanoma appeared to be associated with carcinoma of the breast and gastrointestinal tract. Malignant melanoma of the choroid has also been observed in association with neurofibromatosis.³

In the families exhibiting the SBLA (sarcoma, breast and brain tumours, leukaemia, laryngeal and lung cancer, and adrenal cortical carcinoma) syndrome,⁴⁻⁷ melanoma was not a feature. There have, however, been occasional reports of malignant melanoma occurring as a second primary tumour in children who have had malignancies related to this syndrome, or in their close relatives: amelanotic melanoma of the cheek has developed after adrenal cortical carcinoma⁸ and the mother of a child with osteosarcoma herself developed a malignant melanoma.⁹ The fact that retinoblastoma survivors are at subsequent high risk of osteosarcoma is now well recognised, but there have also been instances where malignant melanoma has been diagnosed after retinoblastoma.¹⁰⁻¹²

This report is concerned with the occurrence of malignant melanoma in the families of seven children with osteosarcoma, chondrosarcoma, or adrenal cortical carcinoma ascertained in the context of pedigree studies being carried out to determine overall cancer risks to close relatives of these children.

Methods

All children aged under 15 years in the Manchester Children's Tumour Registry (MCTR) with histologically confirmed diagnoses of osteosarcoma, chondrosarcoma, or adrenal cortical carcinoma, who were diagnosed between 1 January 1954 and 31 December 1983 have been included in a study carried out to estimate cancer risks in close relatives of these children. The MCTR is described in detail by Birch *et al*¹³ and ascertainment of cases has been estimated to be 95 to 98% complete.¹⁴

For each child included in the study the case records were abstracted with respect to the following: sex, age at diagnosis, site of tumour, congenital abnormalities, and, where available, family history of cancer.

The current general practitioners (GPs) of both parents of each child in the study were then identified and were asked for permission to approach the family for interview. Interviews were carried out in the parents' own homes and information was sought on past medical history, including congenital abnormalities, serious illnesses, long

term conditions, and operations in the child and all first degree relatives. Reports of neoplastic disease in second degree relatives and, where possible, third degree and more distant relatives were also recorded. An attempt was made to confirm reports of all neoplastic conditions in relatives by reference to hospital notes, the appropriate Regional Cancer Registry, questionnaires to GPs, or by obtaining copies of death notifications. Where possible the histology of neoplasms was reviewed.

The cumulative risk with age of malignant melanoma was estimated using population data for the North West Region.¹⁵ This was used to calculate the expected number of melanomas among the first degree relatives of the children, taking into account their age at last follow up or age at death as appropriate. Observed and expected numbers of melanomas among the relatives were compared and significance tests carried out using the method described by Rothman and Boice¹⁶ for exact testing and estimation for a Poisson variate.

Results

A total of 95 tumours occurring in 94 children was included in the study: 76 osteosarcomas, 10 chondrosarcomas, and nine adrenal cortical carcinomas. Two children were adopted and so no further information was available and one child had a double primary tumour. Hence, there were 92 families eligible for interview. A total of 64 inter-

views has been obtained and a further two families have completed a postal questionnaire. Among these interviews there were seven families where reports of malignancy in relatives were confirmed as malignant melanoma. The features of melanoma in the relatives in relation to neoplastic disease in the child are shown in the table and details of the individual families are given below.

FAMILY A
Chondrosarcoma of the right humerus was diagnosed at the age of 14 years. The mother had a mole on the right thigh present from birth, which at the age of 31 started to enlarge and bleed. Wide excision was performed and the lesion was reported as a malignant melanoma.
The mother's father developed a right upper mediastinal mass at the age of 63 and died shortly afterwards. There was no biopsy or necropsy. This patient also had a number of superficial lesions on the head, possibly basal cell carcinomas, although again there was no histological confirmation. There was apparently no evidence of Gorlin's syndrome. Both the mother, her father, her sister, and the index child's two cousins had polydactyly. The mother's paternal grandfather died of lung cancer aged 75 (unconfirmed) and from family history reports must have carried the polydactyly gene. The mother's maternal grandfather's death certificate showed that he died of a brain tumour aged 60 (fig 1).

TABLE Malignant melanoma in relatives of children with osteosarcoma, chondrosarcoma, and adrenal cortical carcinoma.

Relative						Child			
Family	Histology	Site	Age at diagnosis (y)	Sex	Degree of relationship	Histology	Site	Sex	Age at diagnosis (y)
A	Invasive malignant melanoma with adjacent in situ component of superficial spreading type [†]	R thigh	31	F	1	Chondrosarcoma	R humerus	F	14
B	Nodular malignant melanoma [‡]	R cheek	36	F	1	Osteosarcoma	R femur	M	14
C	Invasive malignant melanoma	Choroid, R eye	58	M	2	Osteosarcoma	R tibia	F	13
D	Malignant melanoma [‡]	R forearm	70	F	2	Adrenal cortical carcinoma	R adrenal	F	9
E	Invasive malignant melanoma with adjacent component of superficial spreading type [‡]	Limbal conjunctiva, R eye	36	F	2	Osteosarcoma	R femur	M	14
F	Malignant melanoma [‡]	Face	32	M	2	Mesenchymal chondrosarcoma	L fibula	M	2
G	Malignant melanoma [‡]	Orbit	66	F	3	Osteosarcoma	R femur	F	10

[†]Special pathology review. [‡]Death certificate. [§]Clinical diagnosis.

FIG 1 Pedigree of family A.

FAMILY B

The index patient was diagnosed as having an osteosarcoma of the right femur at the age of 14 years. His sister developed a malignant melanoma of the right cheek at the age of 36, just above an intradermal naevus which had been present for many years. The mother of these sibs was diagnosed as having mucin producing adenocarcinoma of the stomach aged 61 and the father had a lipoma removed aged 62.

FAMILY C

The child was diagnosed as having osteosarcoma of the left tibia aged 13 years. The father's father had his right eye enucleated at the age of 58 for a large malignant melanoma of the choroid. There is no other family history of cancer.

FAMILY D

The child was diagnosed as having an adrenal cortical carcinoma at the age of nine years. Her maternal grandmother had died of a malignant melanoma of the right forearm aged 70. Other family cancers included a brain tumour in the child's

FIG 2 Pedigree of family D.

father at the age of 35, carcinoma of the prostate at the age of 70 in the paternal grandfather, and carcinoma of the stomach at the age of 76 in the maternal grandfather (fig 2).

FAMILY E

Osteogenic sarcoma of the right femur was diagnosed at the age of 14 years. The mother's sister presented at the age of 36 with a swelling of the right eye present from birth which, after repeated excisions, was finally reported as a malignant melanoma of the limbal conjunctiva. She is alive and well 10 years later, but has also developed multiple sebaceous keratoses on the left arm, breast, and on her back. Other malignancies in this family include carcinoma of the lung aged 61 in the mother's father, carcinoma of the pancreas aged 63 in the mother's father's brother, and a mesenteric lymphoma aged 43 in the mother's father's sister's son. The mother herself developed severe cerebral oedema aged 26 but there was no evidence of neoplasm.

FAMILY F

The child was diagnosed as having a mesenchymal chondrosarcoma of the left fibula aged two years. His paternal uncle presented at the age of 32 with a pigmented, bleeding, pedunculated lesion in front of the left ear which had grown over the previous 18 months at the site of a freckle which had been present for some time. The lesion was clinically diagnosed as a malignant melanoma and was excised. Unfortunately the specimen was mislaid so there was no histological confirmation of the diagnosis. Several years later, at the age of 37, the same patient developed a lump in the right breast. Simple mastectomy was performed and the tumour proved to be papillary intraduct carcinoma. Paget disease of the nipple was also present.

FAMILY G

The child was diagnosed as having an osteosarcoma of the right femur at the age of 10 years. The death certificate of the father's mother's mother showed that she died of malignant melanoma of the orbit aged 66. Interestingly, the father himself presented at the age of 54 with a warty, pedunculated lesion on the left side of the abdomen which had grown from a small mole present for about 10 years. The lesion was strongly suspected to be a malignant melanoma and wide excision was carried out. Histological examination, however, showed that the tumour was a large pigmented basal cell papilloma with no evidence of malignancy. The child's mother was diagnosed as having infiltrating duct carcinoma of the right breast aged 51 (fig 3).

FIG 3 Pedigree of family G.

In one further family, the sib of a girl with an osteosarcoma was born with a black, warty, cauliflower-like lesion on the occipitoparietal region of the scalp, described as a melanoma. The mother is well but the maternal grandmother was diagnosed as having a papillomatous cystadenoma of the ovary aged 44 and died of carcinomatosis aged 57.

Information of all first degree relatives was available from the interviews and hence it was possible to estimate the relative risk to these persons of developing malignant melanoma. A total of 196 female and 195 male first degree relatives was reported. No melanomas occurred in the male relatives (expected number = 0.08), but there were two cases of malignant melanoma in the female relatives (expected number = 0.15). Overall this represents a significant excess (relative risk 8.7, $p=0.023$). While discrepancy between population based incidence data for malignant melanoma and information gained at interview is probably minimal for first degree relatives, this is less likely to be the case for second and higher degree relatives. Hence, no accurate estimation of risk for the latter is possible.

Discussion

Mothers of children with soft tissue sarcoma and osteosarcoma and chondrosarcoma have been shown to have a significant three-fold excess risk of developing breast cancer.^{17 18} The association between breast cancer in mothers, soft tissue sarcomas in children, and other neoplastic disease in close relatives was first described as a possible familial syndrome by Li and Fraumeni in 1969.⁴ They considered that in the four families studied in detail it was likely that there was an inherited predisposition for the development of these tumours and that the pattern of cancers seen was compatible with the transmission of an autosomal dominant gene with

pleiotropic effects. It seems likely that a similar genetic susceptibility mechanism may be operating in at least some of the families where the child develops an osteosarcoma or chondrosarcoma. The occurrence of malignant melanoma in seven of such families raises two possibilities. Firstly, malignant melanoma may be an additional manifestation of the same gene defect but with a low level of penetrance. Alternatively, there may be a separate genetic mechanism leading to the development of malignant melanoma coincidentally present in these families, which is acting to enhance the effects of the major susceptibility gene leading to tumours characteristic of the SBLA syndrome.

None of these families appears to suffer from any other syndrome known to predispose to the development of cancer. The only notable congenital abnormality was the occurrence of polydactyly in family A, which appeared to be transmitted alongside the cancer susceptibility. Polydactyly has been reported in association with retinoblastoma,¹⁹ and a small accessory thumb was also present in a patient included in the MCTR who developed Hodgkin's disease at the age of nine, followed by a leiomyosarcoma of the iris aged 13.

The occurrence of carcinoma of the breast at the early age of 37 following malignant melanoma at the age of 32 in the paternal uncle of the child with the mesenchymal chondrosarcoma (family F) is of particular interest in view of the reported association between breast cancer and malignant melanoma.² In family E the development of multiple seborrhoeic keratosis in the malignant melanoma sufferer may be an example of the Leser-Trelat sign which has been described by Lynch *et al*²⁰ in a mother and daughter who both had carcinoma of the breast. It is possible that this condition affected the maternal grandfather in family A.

Some evidence for the second proposed mechanism of inheritance could be put forward from families D and G where melanoma occurred in one branch of the family and a brain tumour and breast cancer were present in a first degree relative from another side of the family. However, the multiple associations which have so far been reported between adrenal cortical carcinoma, breast cancer, osteosarcoma, chondrosarcoma, soft tissue sarcoma, retinoblastoma, and malignant melanoma do indicate that, in certain families at least, these tumours might all be related to the same gene defect.

The association with malignant melanoma also appears to be stronger in relation to childhood adrenal cortical carcinoma, osteosarcoma, chondrosarcoma, and retinoblastoma than in relation to childhood soft tissue sarcoma. Malignant melanoma

has not been described in families with childhood soft tissue sarcoma and has not so far been confirmed in any close relative of more than a hundred soft tissue sarcoma children in the MCTR for whom family data are available. In addition, although soft tissue sarcomas do occur after retinoblastoma, osteosarcoma is by far the commonest second neoplasm in retinoblastoma survivors.¹² Hence, there are indications that the SBLA syndrome may be related to more than one gene defect leading to similar constellations of tumours in family members. In some families, childhood soft tissue sarcomas and early onset breast cancers in the mothers may be the predominant features. In other families, such as those described here, childhood bone sarcomas may have a stronger association with adrenal cortical tumour, retinoblastoma, breast cancer, and malignant melanoma. These differences in the families may, however, be explained by different degrees of penetrance of the same gene in different genetic backgrounds or by a greater degree of genetic heterogeneity which may exist in families with soft tissue sarcomas.

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