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Familial risk for histology-specific bone cancers: An updated study in Sweden

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ABSTRACT

We used the nation-wide Swedish Family-Cancer Database to examine the familial risks of histology-specific bone cancers in offspring by parental or sibling probands. Adjusted standardised incidence ratios (SIRs) were used to measure the risk. Among the 1327 offspring bone cancers, only two parent–offspring pairs and one sibling pair were noted with concordant bone cancer but the SIRs were not significant. Significant associations were observed in specific histological types or specific age groups, some of which may be chance findings arising from multiple comparisons. However, the risk of early-onset (<25 years) osteosarcoma in offspring was significantly increased when mothers presented with breast cancer (1.7) and melanoma (2.9), suggesting that Li–Fraumeni syndrome could partly explain this familial aggregation. Other associations, such as childhood osteosarcoma with parental liver cancer, Ewing's sarcoma with kidney cancer and giant cell sarcoma with maternal breast cancer, were novel findings and may be related to other familial diseases.

1. Introduction

Primary bone cancer is rare and it accounts for 0.2% of all malignancies in Sweden.[1] However, bone cancer occurs often in children and adolescents and it accounts for about 5% of all childhood cancers in developed countries, particularly in North America and Europe.[2] Osteosarcoma is the most common malignant tumour of the bone, with a peak incidence during the adolescent growth spurt; it generally involves the long bones, particularly the distal femur or proximal tibia.[3] Ionising radiation may contribute to the development of some osteosarcomas.[4] Patients with hereditary retinoblastoma have a high risk of second cancer, 50% of which are osteosarcoma.[5] Osteosarcoma can arise in patients with Li–Fraumeni syndrome or Paget's disease of the bone.[3,6,7] Ewing's sarcoma is the second most common cancer of the bone in children and adolescents, beginning in the immature nerve tissue of the bone marrow.[8] Chondrosarcoma usually afflicts people over 40 years of age, arising from central portions of the skeleton, such as pelvis and proximal femur. Other types of bone cancer, such as giant cell sarcoma, chordoma and teratoma, are rare.

A multi-centre study conducted in the United States and Canada showed that about 3% of osteosarcoma patients exhibited germ-line p53 mutations.[9] Somatic mutations of p53,[6,10] RB[11] and EXTS genes[12] were also reported in osteosarcoma and chondrosarcoma. For Ewing's sarcoma, most cases are characterised by a re-arrangement of chromosome 22, generally t(11;22) (q24;q12) translocation, resulting in the fusion of the EWS and FLI1 genes.[13,14] The frequency of certain types of cancer, such as stomach and brain tumours, was high among the first-degree relatives of Ewing's sarcoma

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patients.[15] In consideration of the frequent genetic mutations of bone cancer and the involvement of osteosarcoma on some familial cancer syndromes, reliable data on familial bone cancer are required for clinical counselling and cancer genetics. However, population-based studies on familial bone cancer are limited,[16] prompting us to examine the familial risks of histology-specific bone cancers using the 2004 update of the nation-wide Swedish Family-Cancer Database, which covered offspring between birth and age 70 years. The Association of Bone Cancers with other cancer sites was also studied. The special properties of the Database are the registered sources of family relationships and medically verified cancer cases with a practically complete national coverage, which offer unique possibilities for a reliable estimation of familial risks. To our knowledge, this is the largest study published on familial bone cancer.

2. Materials and methods

Statistics Sweden maintains a 'Multigeneration Register' where children, offspring, born in Sweden in 1932 (maximally 70 years old) and later are registered with their parents and they are organised as families.[17] Information on the Database is also available at the Nature Genetic website as 'Supplementary information' to Ref. [18] and the current update (2004) of the Database has recently been described.[19] The data on families and cancers have a complete coverage, baring some groups of deceased offspring, which affected those born in the 1930s and those who died before 1991. Although this small group of offspring with missing links to parents has a negligible effect on the estimate of familial risk,[20] we limited the present study to offspring whose parents were known to eliminate the possibility of bias. This Register was linked by the individually unique national registration number to the Cancer Registry from 1958 to 2002. Cancer registration is currently considered to be close to 100%.[1] A 4-digit diagnosis code according to the 7th revision of the *International Classification of Diseases* (ICD-7) has been used. The following ICD-7 codes were grouped: 'upper aerodigestive tract' cancer codes 161 (larynx) and 140–148 (lip, mouth, pharynx), except for code 142 (salivary glands), 'non-Hodgkin lymphoma' code 200 and 202, and 'leukemia' codes 204–207 (leukemias), 208 (polycytemia vera) and 209 (myelofibrosis). Rectal cancer, ICD-7 code 154, was subdivided into the anus (squamous cell carcinoma, 154.1) and mucosal rectum (154.0). Basal cell carcinoma of the skin is not registered in the Cancer Registry. Only the first primary bone cancer was considered in the present study. The histological classification of bone cancer was used to define osteosarcoma (PAD codes 766), Ewing's sarcoma (756), chondrosarcoma (736), giant cell sarcoma (746), chordoma (886) and teratoma (826).

Standardised incidence ratios (SIRs) were used to measure the risks for offspring according to the occurrence of cancers in their families. SIRs were calculated for offspring bone cancer when the parent or sibling had any cancer, i.e. using parents or siblings as probands. The follow-up was started for each offspring at birth, immigration or on 1 January 1961, whichever came latest. Follow-up was terminated at the diagnosis of first cancer, death, emigration, the closing date of the study on 31 December 2002 or the age of diagnosis as specified in the study. When more than two affected offspring were found in any family, they were counted as independent events.

Parents' ages were not limited, but offspring were 0–70 years of age. SIRs were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, gender-, tumour type-, period-, socioeconomic status- (six groups) and residential area- (three groups) specific standard incidence rates for all offspring lacking a family history.[21] Confidence intervals (95% CI) were calculated assuming a Poisson distribution, and they were rounded to the nearest one decimal.[21] Risks for siblings were calculated using the cohort method, as described elsewhere.[22]

3. Results

The Swedish Family-Cancer Database, which covered years 1958–2002 from the Swedish Cancer Registry, included 1327 offspring (0–70 years) and 1657 parents with primary bone cancer (Table 1). Because of the truncated age structure among offspring, the proportion of early onset tumours, such as osteosarcoma and Ewing's sarcoma, was higher among the offspring generation (38.1% for osteosarcoma and 22.0% for Ewing's sarcoma) than the parental generation (22.1% for osteosarcoma and 5.6% for Ewing's sarcoma). The opposite was true for chondrosarcoma, with a relatively old age of onset. The distributions of giant cell sarcoma and teratoma did

Table 1 – Numbers of cases among parents/offspring by histology and age of onset

Histological types	Parents						Offspring					
	<15		> = 15		All ages		< 15		> = 15		All ages	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Osteosarcoma	33	45.8	333	21.0	366	22.1	185	48.8	320	33.8	505	38.1
Ewing's sarcoma	20	27.8	72	4.5	92	5.6	123	32.5	169	17.8	292	22.0
Chondrosarcoma	6	8.3	609	38.4	615	37.1	12	3.2	262	27.6	274	20.7
Giant cell sarcoma	2	2.8	74	4.7	76	4.6	2	0.5	49	5.2	51	3.8
Chordoma	0	0.0	182	11.5	182	11.0	7	1.9	55	5.8	62	4.7
Teratoma	4	5.6	3	0.2	7	0.4	22	5.8	1	0.1	23	1.7
Others	7	9.7	312	19.7	319	19.3	28	7.4	92	9.7	120	9.1
All	72	100.0	1585	100.0	1657	100.0	379	100.0	948	100.0	1327	100.0

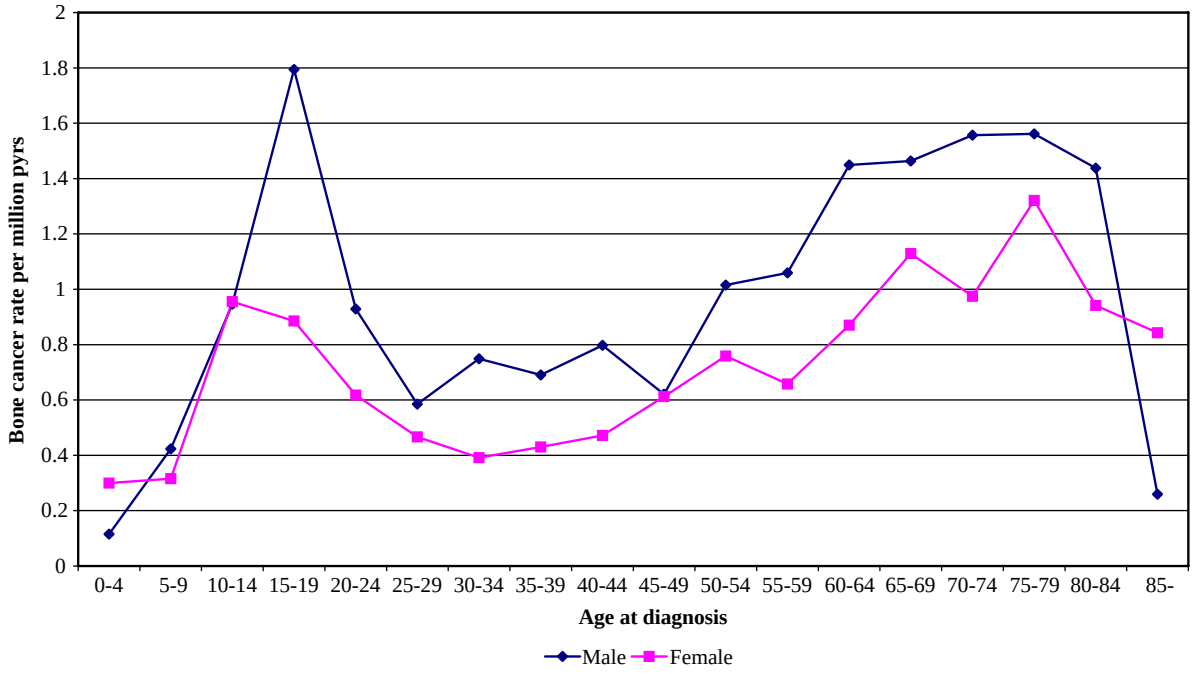

Fig. 1 – Age-specific incidence rate for bone cancer in the Swedish Family-Cancer Database.

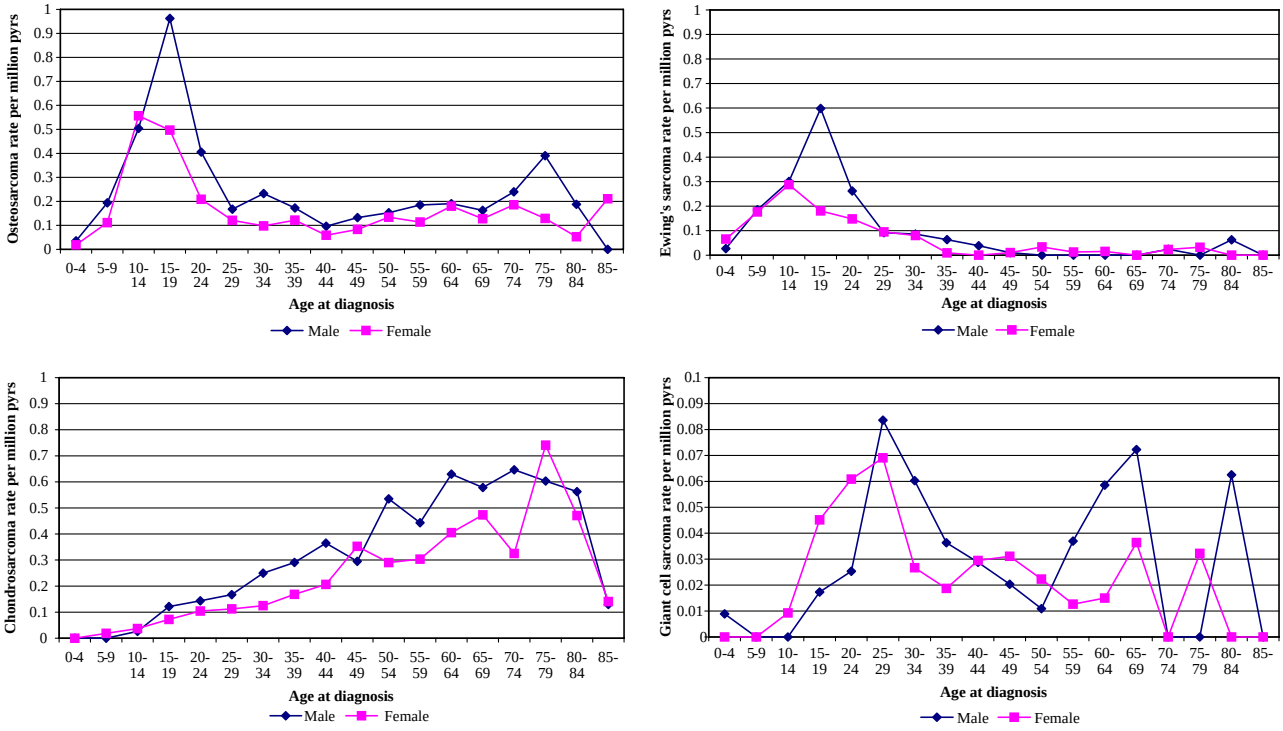

Fig. 2 – Age-specific incidence rate for histology-specific bone cancer in the Swedish Family-Cancer Database.

not differ much between the two generations. Bone cancer was more common in males than in females, with a peak incidence in the second decade of life and another peak rate in the 75–79 year age group (Fig. 1). Fig. 2 shows age–incidence relationships for specific histological types. Osteosarcoma and Ewing's sarcoma presented at an early age, with a peak incidence in the 15–19 year age group. The incidence of chondrosarcoma increased with age. The age–incidence curve for the rare giant cell sarcoma was irregular (note the 10-fold difference in y-scale for giant cell sarcoma). Later, we inspected the familial risks at ages <25 years and 25–70 years for osteosarcoma and Ewing's sarcoma, at ages <50 years for chondrosarcoma and ages <35 years for giant cell sarcoma, divided according to their different age-specific incidence rates.

Additional analysis covered childhood cancers diagnosed before age 15 years.

Familial risks for bone cancer in offspring were calculated when parents or siblings were used as probands. Only two parent–offspring pairs and one sibling pair with concordant bone cancer were noted in the present study and the SIRs were not significant (data not shown). Except for maternal melanoma with a significant SIR of 2.2 (N = 15, 95%CI 1.2–3.6), no significant association was found for other discordant cancer sites.

SIRs for histology-specific bone cancers were analysed by parental cancer (Table 2). Significant SIRs were shown by bold font; other significant associations found in a specific age group were listed in the footnotes. Osteosarcoma was associated with parental rectal cancer (2.0), paternal colon cancer (2.1) and maternal endocrine gland cancers (3.6). Adrenal cortical carcinoma was not observed in these mothers with endocrine gland tumours. Maternal melanoma (2.9) and breast cancer (1.7) were associated with an increased risk of early onset osteosarcoma (age < 25). Giant cell sarcoma was associated with maternal breast cancer (2.8); none of these mothers were diagnosed before age 50 years, and the SIR was increased to 3.3 when mothers were diagnosed at ages older than 50. No significant associations were observed for Ewing's sarcoma and chondrosarcoma. However, an increased risk for Ewing's sarcoma, with a SIR of 16.5 (2, 1.6–60.8), was noted when a sibling was diagnosed with concordant Ewing's sarcoma (data not shown).

Familial risks for childhood bone cancers, diagnosed before age 15 years, were shown in Table 3 using parents as probands. Only osteosarcoma, Ewing's sarcoma and all types were listed because of the lack of significant associations in other subtypes. Childhood bone cancer was associated with parental liver cancer (3.3). Childhood osteosarcoma was associated with parental liver cancer (4.2) and maternal breast cancers (2.0). Two gallbladder and two primary liver cancers were noted in these parents with liver cancer, and the SIR was 6.8 and 6.2, respectively. Half of the mothers with breast

Table 2 – SIR for offspring histology-specific bone cancers when parents were probands

Cancer site	Osteosarcoma				Ewing's sarcoma				Chondrosarcoma				Giant cell sarcoma			
	O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Upper aerodigestive tract	0				0				2	0.7	0.1	2.7	0			
Salivary gland	1	2.5	0.0	14.6	0				1	3.3	0.0	19.2	0			
Esophagus	0				0				3	3.1	0.6	9.0	0			
Stomach	6	1.1	0.4	2.4	3	1.2	0.2	3.7	10	1.8	0.9	3.3	3	2.8	0.5	8.2
Small intestine	0				1	3.0	0.0	17.0	0				1	9.8	0.0	56.1
Colon	14[A]	1.4	0.8	2.4	4	0.8	0.2	2.2	7	0.8	0.3	1.6	1	0.6	0.0	3.4
Rectum	12	**2.0**	1.1	3.6	0				4	0.8	0.2	2.0	2	2.0	0.2	7.4
Liver	5	1.3	0.4	3.1	1	0.6	0.0	3.3	5	1.4	0.4	3.2	0			
Pancreas	2	0.5	0.1	1.9	2	1.1	0.1	4.1	4	1.1	0.3	2.9	2	2.9	0.3	10.7
Nose	1	4.0	0.0	22.7	0				0				0			
Lung	11	1.0	0.5	1.8	5	0.9	0.3	2.2	8	0.9	0.4	1.8	2	1.3	0.1	4.6
Breast in mother	27[B]	1.4	0.9	2.0	8	0.8	0.3	1.5	13	1.0	0.5	1.7	7[C]	**2.8**	1.1	5.7
Cervix	4	1.1	0.3	2.9	2	1.1	0.1	4.0	2	0.8	0.1	2.9	0			
Endometrium	2	0.5	0.1	1.9	0				3	0.9	0.2	2.7	0			
Ovary	3	0.8	0.2	2.4	0				2	0.7	0.1	2.5	0			
Prostate	20	1.0	0.6	1.6	6	0.6	0.2	1.4	20	1.2	0.7	1.8	4	1.2	0.3	3.1
Testis	1	1.6	0.0	9.0	0				0				0			
Kidney	5	1.1	0.3	2.6	5	2.2	0.7	5.2	5	1.3	0.4	3.0	2	2.6	0.2	9.4
Urinary bladder	7	1.0	0.4	2.1	3	0.9	0.2	2.7	5	0.9	0.3	2.0	1	0.9	0.0	5.3
Melanoma	9[D]	1.7	0.8	3.2	4	1.3	0.3	3.4	3	1.0	0.2	2.9	1	1.8	0.0	10.4
Skin	4	0.9	0.2	2.3	1	0.5	0.0	2.7	4	0.9	0.2	2.4	1	1.3	0.0	7.6
Eye	0				1	4.3	0.0	24.6	0				0			
Nervous system	2	0.4	0.0	1.5	3	1.1	0.2	3.2	0				0			
Thyroid gland	2	1.4	0.1	5.2	1	1.3	0.0	7.2	0				0			
Endocrine glands	7[E]	2.4	1.0	5.0	2	1.3	0.1	4.8	1	0.5	0.0	2.9	0			
Bone	2	7.2	0.7	26.6	0				0				0			
Connective tissue	1	1.0	0.0	5.6	0				2	2.6	0.3	9.7	0			
Lymphoma	6	1.3	0.5	2.9	0				2	0.6	0.1	2.2	1	1.5	0.0	8.6
Hodgkin's disease	2	2.4	0.2	8.9	0				0				0			
Myeloma	1	0.5	0.0	2.8	1	1.0	0.0	5.9	1	0.6	0.0	3.2	0			
Leukemia	3	0.8	0.1	2.2	3	1.5	0.3	4.4	0				0			
All	145	**1.2**	1.0	1.4	53	0.9	0.7	1.1	94	1.0	0.8	1.2	22	1.2	0.8	1.9

Boldface shows that 95% CIs do not overlap with 1.00.
A Paternal probands, SIR 2.1 (N = 11, 95%CI 1.0–3.8).
B Offspring <25, SIR 1.7 (N = 25, 95%CI 1.1–2.5).
C Mother > =50, SIR 3.3 (N = 7, 95%CI 1.3–6.7).
D Offspring <25 for maternal probands, SIR 2.9 (N = 6, 95%CI 1.0–6.3).
E Maternal probands, SIR 3.6 (N = 7, 95%CI 1.4–7.4).

Table 3 – SIR for childhood bone cancers (age < 15) when parents were probands

Cancer site	Osteosarcoma				Ewing's sarcoma				All types			
	O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Stomach	3	2.4	0.5	7.1	1	1.4	0.0	8.2	5	2.0	0.6	4.8
Colon	4	1.5	0.4	4.0	0				4	0.8	0.2	2.0
Rectum	2	1.3	0.1	4.7	0				3	1.0	0.2	2.9
Liver	4	**4.2**	1.1	11.0	1	1.9	0.0	11.1	6	**3.3**	1.2	7.2
Pancreas	1	1.0	0.0	6.0	1	1.9	0.0	10.7	2	1.1	0.1	3.9
Lung	4	1.3	0.3	3.4	0				4	0.7	0.2	1.7
Breast in mother	12[A]	**2.0**	1.0	3.6	3	0.8	0.2	2.4	19	1.6	1.0	2.5
Cervix	3	2.8	0.5	8.3	2	3.0	0.3	11.1	5	2.4	0.7	5.5
Ovary	1	1.0	0.0	5.5	0				3	1.5	0.3	4.3
Prostate	6	1.2	0.4	2.6	3	1.0	0.2	3.1	11	1.1	0.5	2.0
Kidney	1	0.8	0.0	4.7	4	**5.6**	1.5	14.6	6	2.5	0.9	5.4
Urinary bladder	1	0.5	0.0	3.1	1	0.9	0.0	5.4	3	0.8	0.2	2.4
Melanoma	3	1.7	0.3	5.1	0				5	1.4	0.4	3.3
Skin	1	0.9	0.0	5.1	0				1	0.5	0.0	2.6
Eye	0				1	12.3	0.0	70.3	1	3.7	0.0	21.2
Thyroid gland	0				0				1	1.1	0.0	6.1
Endocrine glands	0				2	3.7	0.4	13.5	2	1.1	0.1	4.2
Non-Hodgkin's lymphoma	2	1.5	0.2	5.7	0				3	1.2	0.2	3.4
Hodgkin's disease	1	3.9	0.0	22.1	0				1	1.9	0.0	10.9
Myeloma	1	1.9	0.0	11.1	1	3.4	0.0	19.4	2	2.0	0.2	7.2
Leukemia	0				2	3.0	0.3	11.1	2	0.9	0.1	3.4
All	43	1.3	0.9	1.7	20	1.0	0.6	1.5	78	1.1	0.9	1.4

Boldface shows that 95% CIs do not overlap with 1.00.
A Mother < 45, SIR 4.9 ($N = 6$, 95% CI 1.8–10.7).

cancers (6/12) were diagnosed at an early age; the SIR was 4.9 if mothers were diagnosed before age 45 years. Parental kidney cancer was associated with an increased risk of Ewing's sarcoma (5.6).

4. Discussion

Primary bone cancers are overall rare but they are fairly common forms of cancer in children and adolescents. The age-specific incidence of bone tumours varies by histological types. The incidence of osteosarcoma, the most common childhood bone cancer, varies little by gender and race,[23,24] but it varies greatly by age with the majority occurring in adolescence and another peak in the seventh and eighth decades of life.[25] Because of the truncated age structure for the offspring generation in our Database, only one peak incidence during the second decade of life was noted in Fig. 2. Ewing's sarcoma frequently affects individuals between ages 10 and 20. Chondrosarcoma is largely a disease of old age, with a peak incidence at ages 70–80. The incidence of giant cell sarcoma is low. The different age-specific incidence curves in Fig. 2 suggest an underlying etiological heterogeneity for the four histology specific bone cancers.

Even though all bone cancer cases reported to the Swedish Cancer Registry are histologically verified and our study was nation-wide, the number of bone cancer cases was still small, especially for specific histological types. Another cautionary aspect is that of multiple comparisons, 35 cancer sites, 4 histology types and different age groups, which may lead to spurious associations. Biological plausibility and consistency with earlier findings may be useful to sort our chance findings. However, the options are limited because of a lack of independent data in the literature on familial bone cancer.

In the present study familial risks were not significant when parents or sibling presented with bone cancer. Histology specific bone cancers were associated with specific discordant cancer sites and the degree of association varied among histologies. Some significant associations, such as offspring osteosarcoma with maternal breast cancer and endocrine gland tumours, were reported in an earlier study.[16] Additional associations, such as offspring osteosarcoma with parental liver cancer and maternal melanoma, were novel findings. Germ-line mutations in tumour-suppressor genes, P53 and RB, are linked to the development of osteosarcoma in families with Li–Fraumeni syndrome and hereditary retinoblastoma.[3,26,27] In RB mutation carriers, osteosarcoma usually occurs as a second tumour after retinoblastoma; second primary cancers were not studied here. A recent study showed that breast cancer, soft tissue sarcomas, osteosarcoma, brain carcinoma and adrenocortical carcinoma were strongly associated with germ-line p53 mutations.[28] In the present study, early-onset osteosarcoma (ages < 25 years) was increased when mothers presented with breast cancer and melanoma, the former being a feature of Li–Fraumeni syndrome and the latter of the extended Li–Fraumeni syndrome.[29] The increased risk of childhood osteosarcoma (4.86) in mothers with early-onset breast cancer (age younger than 45 years) further strengthened the involvement of Li–Fraumeni syndrome. The association of childhood osteosarcoma with parental liver cancer was largely ascribed to gallbladder and primary liver cancers. The SIRs were far from significant, although they were high. For other associated cancer sites, such as colon

and rectum, the moderately increased risks may be chance findings or related to other familial diseases. An increased risk of giant cell sarcoma (SIR 2.8) was observed in offspring of maternal breast cancer patients. This association was reported earlier,[16] and its possible relation to Li–Fraumeni syndrome was also discussed. Although we cannot solve this issue, we noted here that the risk was much higher than that for osteosarcoma (1.4), suggesting perhaps the existence of an unrelated familial association. Also noteworthy was that the maternal probands were preferentially old, with a SIR of 3.3 when probands were over 50 years. Classical Ewing's sarcoma and primitive neuroectodermal tumours are known to be the same tumour with variable differentiation.[3,30] An increased risk of stomach cancer, melanoma and breast tumour has been observed in first-degree relatives of patients with Ewing's sarcoma.[15] However, none of these tumour sites were associated with Ewing's sarcoma in our study, in which an increased risk of Ewing's sarcoma by parental kidney cancer was a novel observation.

In summary, the present analysis showed that familial clustering of bone cancer differed by subtypes. Histology specific bone cancers were associated with specific cancer sites and the degree of association varied among histologies. The association of offspring osteosarcoma with maternal breast cancer and melanoma suggested that Li–Fraumeni syndrome could partly explain this familial aggregation. Parental liver cancer was associated with childhood osteosarcoma. The increased risk of offspring giant cell sarcoma in mother with late onset breast cancer may be a distinct familial disease. The association of childhood Ewing's sarcoma with parental kidney cancer was a novel finding.

Conflict of interest statement

None declared.

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