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Magnusson, Susanne; Wiebe, Thomas; Kristoffersson, Ulf; Jernström, Helena; Olsson, Håkan

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Increased incidence of childhood, prostate and breast cancers in relatives of childhood cancer patients.

Susanne Magnusson, MSc[1], Thomas Wiebe, MD, PhD[3], Ulf Kristoffersson, MD, PhD[4], Helena Jernström, PhD[1] and Håkan Olsson, MD, PhD[1,2].

Departments of [1]Oncology, [2]Cancer Epidemiology and [3]Pediatrics, Clinical Sciences, Lund University, Lund, Sweden, Department of [4]Clinical Genetics, University and Regional Laboratories and Department of Laboratory Medicine, Lund, Lund University, Lund, Sweden.

*Correspondence: Susanne Magnusson, Department of Oncology, Clinical Sciences, Lund University, Barngatan 2B, 221 85 Lund, Sweden.

Fax: 46-46-147327

E-mail: susanne.magnusson@med.lu.se

Abstract

Background: Whether cancer predisposing familial factors are associated with childhood tumors is unclear. The purpose was to study the incidence of childhood and adult tumors in extended families of children with cancer.

Methods: Family history of cancer was obtained through questionnaires, and the Swedish Population-, and Cancer Registries for 194 childhood cancer patients aged ≤18 years, diagnosed 1972–2009. Standardized cancer incidence ratios (SIR), and 95% confidence intervals (CI) were estimated and compared with expected rates.

Results: Overall, 21 of the 194 patients had any relative with a childhood tumor. When restricted to first- to third degree relatives, increased incidences of childhood (SIR: 2.5; 95% CI: 1.3–4.4) and adult tumors (SIR: 1.5; 95% CI: 1.3-1.7), especially in the prostate (SIR: 2.7; 95% CI: 1.9-3.8) and breast (SIR: 1.7; 95% CI: 1.2-2.4) were observed. Prostate and breast cancers were observed at earlier than average ages. No *TP53* mutations or known cancer predisposing syndromes were found in families with multiple childhood tumors.

*Conclusions***:** Familial factors may increase the risk for childhood cancer and modify the age of onset of common adult tumors. Studying extended families with multiple childhood tumors may be a valuable approach to understanding the etiology of childhood tumors.

Key words: Pediatric cancer, familial cancer, heredity, breast cancer, prostate cancer

Introduction

The etiology of childhood cancer is unclear. Only a small proportion, 1-10%, is associated with known genetic predisposition syndromes [1]. A number of single-gene disorders are known to be associated with increased risk for childhood tumors [2, 3]. However, for most cases of childhood tumors there is no family history of cancer or known underlying genetic disorder.

The risk for childhood and adult tumors in first degree relatives to childhood cancer patients has previously been studied in several studies [4-13] Overall, most of the elevated risks could be attributed to known hereditary cancer syndromes. However, a small increased risk for childhood cancer in siblings remains even when families with known cancer predisposing disorders are excluded [4-9]. Therefore, the occurrence of a remaining genetic predisposition could not be excluded.

Occurrence of childhood tumors in more distant relatives has been investigated to a less frequent extent. The aims of this study were to study occurrence of childhood and adult tumors among relatives of children with cancer in extended families. Secondly to perform screening for germline *TP53* gene mutations in families with multiple childhood cases to exclude Li-Fraumeni syndrome (LFS), a hereditary syndrome with high risk for childhood tumors, at a molecular level [14, 15].

Patients and Methods

Patients and data collection

All children aged ≤18 years with a malignant disease in the Southern Swedish Health Care Region (approximately 1.8 million inhabitants) are referred for care to the Department of Pediatrics at the Skåne University Hospital, Lund. After completed medical therapy, patients are followed until 18 years of age at the Pediatric Clinic and then at the Late Effect Clinic at the Department of Oncology at Skåne University Hospital, Lund. Patients with a newly diagnosed malignancy and patients visiting the clinics for follow-up after completed treatment are invited to take part in an ongoing study regarding genetic factors and childhood cancer. Eligibility criteria include **a)** a diagnosis before 19 years of age with a malignancy following

codes 140-209 according to International Classification of diseases 7th edition (ICD-7) and **b)** a diagnosis after January, 1970. Written informed consent is obtained from parents if the patient is younger than 18 years of age and also from the patients themselves from 15 years of age. Blood samples are collected and patients and parents are requested to complete a standardized self-reported questionnaire, assessing name, date of birth, date of death, and history of cancer among first- second-, and third degree relatives. In addition, a question about cancer in more distant relatives is included. Information regarding specific type of cancer and date of, or age at, diagnosis for each relative with a history of cancer is obtained. The questionnaire is returned by mail. The study has been approved by the Regional Ethical Review Board in Lund (no. 2008/233, 2010/231 and 2011/33)

The study design and process of inclusion of patients and relatives are summarized in Fig. 1. Since the start of the study in September 2008 until August 2009, blood samples were collected from a total number of 267 patients. By October 2009, 196 of these patients had returned the questionnaires and 194 were included in this particular study. Pedigrees were constructed for each family with the childhood case as the index person. Using the Population Registry in Sweden, confirmation and identification of the unique national personal identification number was done for relatives living in Sweden. In case of incompletely answered questionnaires, pedigree expansion was done by collecting supplementary information using the Population Registry. Using the personal identification number, index cases and all relatives were linked to the Total Population Registry (Statistics Sweden) for data on vital status, and to the Swedish Cancer Registry (The National Board of Health and Welfare) either to confirm cancer diagnoses reported in the questionnaires, identify non-reported tumors in reported relatives or to identify cancer diagnosis among relatives identified through expansion. The Swedish Cancer Registry was established in 1958 and is estimated to

contain 96% of all cancer diagnosis because of mandatory registration [16]. For immigrated patients with relatives abroad, only questionnaire based information has been available and the information has not been confirmed through registry data. Therefore, relatives without a Swedish personal identification number have been included in the descriptive part of the study but not in the risk analyses.

Pathology reports and patient charts' were reviewed for index cases with any relative with a childhood cancer in order to evaluate the possibility of occurrence of hereditary syndromes and other cancer predisposing factors (e.g. Down's syndrome, neurofibromatosis). Records were also reviewed for relatives with a childhood tumor diagnosed and treated at Skåne University Hospital.

Descriptive data analyses

The statistical software SPSS 19.0 was used for descriptive statistical analyses. Mann Whitney U test was used to compare continuous variables, such as age at diagnosis and time since diagnosis between families with single and multiple cases of childhood tumors. Fisher's exact test was used to compare the frequency of dichotomous variables. The McNemar's test was used to compare the concordance of cancer events in relatives based on questionnaire data reported by the patient and data from the Swedish Cancer Registry. Further, Fisher's exact test was used to compare the proportion of cancer events in relatives reported by the patient to that in the subgroup of relatives found by expansion. Logistic regression was used to calculate an odds ratio (OR) with 95% confidence interval (CI). All *P*-values are two-sided and a significance level at 5% was used.

Cohort for risk analyses

Relatives with a Swedish personal identification number, still alive in 1958 or onwards, were included in the cohort used for risk analyses. Cancer diagnoses were coded according to ICD-7. Person-years at risk were determined from January 1st, 1958 or date of birth to the earliest time of development of cancer, emigration, death or December 31st, 2008, the last date of follow up. Person years at risk were stratified by age, sex and calendar year and multiplied by year-, age-, and sex-specific rates of cancer types of interest from Swedish National data (South Health Care Region) to yield expected rates of each cancer type. Standardized incidence ratios (SIR), observed/expected ratios, 95% confidence intervals (CI) and *P*-values were computed. All *P*-values were two-sided and a significance level at 5% was used. Analyses were performed for first-, second-, third- and first- to third degree relatives, respectively. To estimate the incidence of childhood and adult cancer all malignancies (ICD-7: 140-209) diagnosed between 0-19 years and all malignancies (ICD-7:140-209) except cervical tumors (ICD-7: 171) between 20-79 years of age were included, respectively. Since this study was a hypothesis generating study Bonferroni correction has not been performed to adjust for multiple testing.

TP53 mutation screening

Genomic DNA from peripheral blood lymphocytes from the index cases was isolated and amplified by polymerase chain reaction (PCR) using standard protocols. Mutation screening of *TP53* was performed using direct sequencing. All coding exons (2-11) and splice junctions were analyzed in both directions. Primer sequences are available upon request. Screening for larger genomic alteration, genomic DNA was analyzed by multiplex ligation-dependent probe amplification (MLPA®) using SALSA MLPA kit P056-A2 TP53 (MRC Holland) according to manufactures protocol. Mutation screening with direct sequencing was successfully

performed for all index cases, while MLPA was successfully performed for all except for two index cases (family 36 and 150).

Results

Patient characteristics by family history of childhood tumors are provided in Table 1. A significant difference in the sex distribution was observed (P= 0.04), with a higher frequency of females among index cases having a relative with a childhood tumor. No other significant difference in patient characteristics was found. Number of relatives reported by patients, identified by pedigree expansion and included in the descriptive and analytic part of the study is summarized in Supplementary table 1.

Reliability of patient-reported family information

A significant difference in concordance of cancer events in relatives reported by the patients and by data from the Swedish Cancer Registry was found (5.9%; 177/3022 relatives *vs*. 6.7%; 202/3022 relatives, P=0.005), suggesting that patients did not report or were aware of all cancers in relatives. Further, 5.9% (177/3022) of the relatives reported by the patient had a cancer diagnosis, while 3.1% (8/259) of the relatives found by pedigree expansion, had a cancer diagnosis (P=0.07; OR: 2.0; 95% CI: 1.0-4.0), suggesting that patients were more prone to report relatives with than without cancers.

Occurrence of childhood tumors in relatives

Of 194 patients, 18 (9.3%) patients reported a relative with a childhood tumor. Further, linkage with the Swedish Cancer Registry identified three additional relatives diagnosed with a tumor in late adolescence. In total 21 (10.8%) of the 194 patients have a relative with a childhood tumor diagnosed between 0-19 years of age. In two cases the affected relative was

of first degree, in five cases of second degree and in seven cases of third degree. Further, seven patients reported occurrence of a childhood tumor in a more distant relative. One of these patients reported two affected relatives, one in childhood and one in late adolescence. Clinical data for the index cases and their relatives are summarized in Table 2. Three of the 21 index cases with an affected relative was included at diagnosis (3/27; 11%) while 18 were included at follow up (18/167; 11%), suggesting there is no difference in the prevalence of relatives with childhood tumors between incidental and prevalent cases.

Cancer predisposing syndromes in families with multiple childhood tumors

A documented cancer predisposing syndrome was found in two of the index cases. One girl with acute lymphatic leukemia had Down's syndrome. One boy with optic glioma had neurofibromatosis type 1 (NF1). Absence of reported neurofibroma or other NF1 associated tumors in relatives suggested that the NF1 was caused by a *de novo* mutation. None of the relatives with a childhood tumor, for which medical records were reviewed, were found to be affected with any documented cancer predisposing syndrome. Pedigree evaluation revealed two families with a family history corresponding to Chompret criteria for Li-Fraumeni-like syndrome [17, 18]. None of the other families showed a family history of cancer corresponding to a known cancer predisposing syndrome.

Incidence of childhood tumors in relatives

The incidence of childhood tumors in relatives is summarized in Table 3. Overall, the incidence of childhood tumors among first-to third degree relatives were higher than expected (SIR: 2.5; 95% CI: 1.3-4.4). The highest incidence was found in second (SIR: 2.9; 95% CI: 0.8-7.3) and third (SIR: 2.7; 95% CI: 1.0-5.9) degree relatives. First degree relatives had no significantly increased risk for childhood tumors (SIR: 1.7; 95% CI: 0.2-6.1). We then

excluded five index cases with Langerhans cell histiocytosis, one index case with pituitary adenoma, and a relative with a cervical tumor. This resulted in fewer cases of childhood tumors in second- and third degree relatives, but the trend towards a two-fold increased incidence for first- to third degree relatives remained (SIR: 2.0; 95% CI: 0.9-3.7).

Incidence of adult tumors in relative

The overall incidence of adult tumors in childhood cancer families are summarized in Table 4. The cancer incidence was significantly higher than expected in first- to third degree relatives to the 194 index cases (SIR: 1.5; 95% CI: 1.3-1.7). The highest incidence was found among first degree relatives (SIR: 2.2; 95% CI: 1.2-3.5), while the incidence was somewhat lower for second degree relatives (SIR: 1.4; 95% CI: 1.2-1.7). No increased risk was observed for third degree relatives (SIR: 1.1; 95% CI: 0.1-3.9).

The incidence of breast (SIR:1.7; 95% CI: 1.2-2.4) and prostate cancer (SIR: 2.7; 95% CI: 1.9-3.8) was found to be significantly increased among first- to third degree relatives, with a median age at diagnosis of 58 (range 39-76) and 68 (range 52-88) years, respectively. Excess of breast cancer was especially found in first degree relatives, all observed cases were mothers (SIR: 4.6; 95% CI: 1.7-10.1) with a median age at diagnosis of 47.5 (range 39-65) years. In addition, an increased incidence of breast cancer was also observed in second degree relatives (SIR: 1.5; 95% CI: 1.0-2.2). The excess of prostate cancer was mainly due to increased incidence in second degree relatives (SIR: 2.7; 95% CI: 1.9-3.8). Moreover, an excess of lung cancer (SIR: 1.7; 95% CI: 0.9-2.7) and non-Hodgkin's lymphoma (SIR: 2.3; 95% CI: 1.0-4.3) were observed in first- to third degree relatives.

Further, to investigate whether there were any differences in cancer incidence between families with single and multiple cases, families were stratified according to the occurrence of multiple childhood tumors (Supplementary table 2 and 3, respectively). Increased cancer incidence was found in first- to third degree relatives, both in families with multiple cases (SIR: 1.5; 95% CI: 0.8-2.4) and with single cases (SIR: 1.5; 95% CI: 1.3-1.7) of childhood tumors. An excess of breast cancer was found in both subgroups. However, this was somewhat higher in families with multiple cases (SIR: 2.6; 95% CI: 0.9-6.2) compared with families with single cases (SIR: 1.6; 95% CI: 1.1-2.3). Moreover, families with single childhood cases also had an excess of lung cancer (SIR: 1.7; 95% CI: 0.9-2.8), prostate cancer (SIR: 2.8; 95% CI: 1.9-3.9), and Non-Hodgkin's lymphoma (SIR: 2.5; 95% CI: 1.2-4.8). There was no significantly increased incidence for these cancers in families with multiple tumors.

The occurrence of second primary tumors was assessed in first- to third degree relatives of the 194 index cases. A total number of 29 first- to third degree relatives developed a second primary tumor, most (26 of 29 diagnoses) occurred in second degree relatives. Following the cohort of first- to third degree relatives until a second primary tumor did not result in substantial changes in the estimate of cancer incidence, neither for total cancer (208 observed tumors *vs*. 128.8 expected; SIR: 1.6; 95% CI: 1.4-1.9) nor for specific cancer types (results not shown). Most of the second primary tumors (28 of 29 tumors) occurred in relatives of families with single childhood tumors.

Mutation screening of TP53

Mutation screening of *TP53* was performed for all 21 index cases in families with multiple childhood tumors. No pathogenic mutations were identified.

Discussion

The main finding in this study was a significant increased risk for especially childhood cancer but also for certain adult cancers in relatives of childhood cancer patients. A two-fold increased incidence of childhood tumors was found in first- to third degree relatives. Notably, most of the affected relatives were found in more distant relatives. No pathologic *TP53* mutations were found in any of the 21 tested index patients and in most of the families no other underlying genetic disorders or hereditary cancer predisposing syndromes appeared to occur. This suggests that the increased risk would probably neither be associated with LFS, nor other known cancer predisposing syndromes.

The second finding was an increased incidence of adult tumors in first- to third degree relatives. First degree relatives had a higher overall cancer risk than second degree relatives. No increased cancer risk was observed for third degree relatives. This may be due to the young age of the relatives, resulting in too few person-years at risk. However, a valid genetic association would compel higher ratios for closer relatives, which is in line with the findings of the present study. There was no substantial increase in second primary tumors in the cohort and including them in the analyses did not materially change the results. However, most of the secondary primary tumors occurred in second degree relatives. The second degree relatives included in this cohort were generally older with a median age of 56.5 years compared to the first degree relatives who had a median age of 37.0 years. This age difference may explain the difference of secondary primary tumors between first- and second degree relatives, suggesting that the cohort needs longer follow-up before any conclusions about occurrence of secondary primary tumors could be drawn.

A significantly increased risk for especially prostate and breast cancer was found. Prostate- and breast cancer are the two most common cancers in the general population with an average diagnosis age of 70-74 years and 60-64 years, (according to statistics from 2003 and 2001, which represent the median year of diagnosis for each tumor type, respectively) [19, 20]. However in present study a lower average age at onset was found for both prostate- and breast cancer, which may suggest a possible shared pathway that increase the risk for childhood cancer and modify the onset age of common adult tumors. An especially low median age at diagnosis was found for mothers with breast cancer. As all clinical screening for *BRAC1/BRCA2* mutations in Sweden is performed at our department we had the possibility to exclude that these mothers belonged to known families with hereditary breast and ovarian cancer that would explain the early onset. Moreover, an increased cancer incidence was found both for relatives in families with single childhood tumors and multiple cases. Most of the risk estimates were either similar or higher for families with multiple cases compared to families with single cases. However, due to smaller numbers the risks failed to reach statistical significance for families with multiple cases. Moreover, the incidence of breast cancer was considerably higher than expected in both groups, with the highest incidence in families with multiple childhood tumors.

Since this is a rather small study, the estimated incidence for tumors should be interpreted with caution. No separate analyses according to specific childhood tumor were possible because of the small sample size. However, the material is population based since all children with a malignancy in the south health care region are referred to one clinic, but so far we have only included a small part of the total number of possible available participants. The existence of a selection bias could not be excluded. The response rate at the time of compilation of the material, November 2009, was 73%. It cannot be excluded that patients who respond may

have a more pronounced history of familial cancer compared to those patients from whom we yet not have received the questionnaire. Further, when using self-reported questionnaires recall bias appear to exist, both in accurately reporting of all relatives and not only relatives with a positive cancer history and in correctly reporting of cancer diagnosis in relatives. However, to minimize this bias, we used the Swedish Population Registry to collect supplementary information about possible unreported relatives. In addition, only relatives with a Swedish identification number and tumors verified or identified by the Swedish Cancer Registry were included in the estimation of incidence ratios, both for childhood and adult tumors. Moreover, the comparison of cancer diagnoses in relatives reported by patients and Cancer Registry data showed that patients and their families failed to report all cancers in relatives. However, patients were almost twice more prone to report relatives with cancer than relatives without cancer. This strengthens the importance of expanding families through registries to obtain a more accurate estimate of cancer incidence in the families.

In addition other factors exist that may have influenced our results. Firstly, we had to use different ages for index cases and relatives to define childhood tumors. Index cases were eligible until 18 years of age while relatives were eligible until 19 years of age. It would had been preferable to also use 18 years of age as eligibility criteria for relatives, but this was not possible since the population based incidence matrix used to calculate expected ratios has a stratification interval of five years. However, it is unlikely that this have had a major impact on the results. Secondly, we cannot exclude that our results are influenced of a survival effect, since the majority of index cases are included at follow up. However, there is no difference in the prevalence of relatives with childhood tumors between incidental and prevalent index cases. Further, except for sex distribution, there were no significant difference in patient characteristics between index cases in families with single and multiple cases of childhood

tumors. There is no reason to believe that the sex ratio are related to having multiple cases of childhood tumors and consider the finding to be due to chance.

The cancer incidence in first degree relatives to childhood cancer patients is well studied. The occurrence of childhood tumors among siblings to childhood cancer patients has previously been examined in four systematic population-based studies [4-7] and in two hospital-based series [8, 9]. These studies showed similar results, with an overall two-fold increased risk for childhood and adolescent cancer in sibling. Although, most of the risk could be attributed to known hereditary cancer syndromes, a small increased risk seemed to remain even when families with known cancer predisposing disorders were excluded [5]. Further, cancer incidence in parents has also been well studied in several larger studies [10-13]. Generally, parents do not seem to have increased cancer risk except when known familial cancer syndromes are recognized. However, increased risk for breast cancer in mothers and sisters has been reported in previous studies. [7, 10, 11]. The increased breast cancer risk in mothers and sisters in these studies could in part but not fully be explained by known syndromes. Although, cancer incidence in close relatives are well studied there is a paucity of data on cancer incidence among the wider families of children with cancers.

Our results may suggest that every tenth childhood cancer patient had a relative affected by tumor disease in childhood or adolescence. Single families with multiple childhood tumors may be due to chance. However, since childhood tumors are uncommon, the high incidence of childhood tumors among relatives to childhood patients in present study seems unlikely to be caused only by chance. Notably, most of the affected relatives were of more distant degree. This may suggest that it is less likely that highly penetrant genes account for the phenotype. Instead, as previous suggested by Birch, it is more likely that recessive genes or common

allelic variants of susceptibility genes with low to moderate penetrance, possibly modifying the response to environmental factors, may account for the development of childhood tumors in these families [21].

In the clinic, it may be of value to obtain information regarding childhood tumors also for more distant relatives. Notably, after that patient inclusion for present study was closed, another third child with an ependymoma was brought to our attention in family 241. The affected patient was found to be a cousin to the previously reported affected relative. Occurrence of three childhood brain tumors in a family with no other conspicuous family history of cancer may suggest common risk factors. Studying families with multiple childhood tumors may be a valuable approach to understanding the etiology of childhood tumors, such as shared genetic predispositions in combination with certain environmental factors that have not been captured in previous studies. In the future, it would be of interest to study the genomic profile of patients with childhood tumors that occur within the same family to evaluate any genetic similarities. This could be accomplished by using whole genome sequencing of normal and tumor tissue to identify common genetic alterations. This approach could be one step further to evaluate the genetic heterogeneity of childhood tumors and identifying candidate genes or pathways that confer increased risk of tumors in childhood within these families. Such pathways may also reveal novel potential treatment targets for primary and secondary prevention.

Moreover, these pathways may play a role for earlier than average age of onset of breast and prostate cancer. For example, high insulin-like growth factor 1 (IGF-1) levels have been associated with increased risks for both breast and prostate cancer [22] as well as childhood ALL [23] and Ewing sarcoma [24]. Both high and low birth weights may influence childhood

cancer risk [25, 26], possibly through the IGF-system [27]. A previous study reported that birth weight was significantly lower in *BRCA1* mutation carriers compared to relatives without *BRCA1* mutations [28], indicating an effect *in utero*. However, no increased risk of childhood tumors in families with *BRCA1* mutations was observed in a recent study from the southern Swedish health care region [29]. Conversely, an increased risk was found in families with *BRCA2* mutations. As birth weight was not routinely registered in our database, we were unable to address the effect of birth weight as a risk factor in the present study. Currently, there are multiple clinical trials investigating the effect of IGF-1 receptor inhibitors for several cancer types including childhood tumors [24, 30].

In conclusion we found an increased risk for childhood and adult tumors among relatives of childhood cancer patients. An especially increased risk was found for breast and prostate cancer, with an earlier than average age of onset. At present, this study has little clinical importance as the findings need to be validated in an independent cohort before offering genetic counseling to families with multiple childhood tumors, unless there are indications for known hereditary syndromes. However, the increased risk of both childhood and adult tumors in relatives of childhood cancer patients found in the present study lends additional support to the hypothesis that familial factors may play a role in the etiology of childhood tumors. To assess the possible interplay between genetic susceptibility and environmental factors in the etiology of tumors further molecular epidemiological studies are needed.

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Conflict of Interest

We have no conflict of interest.

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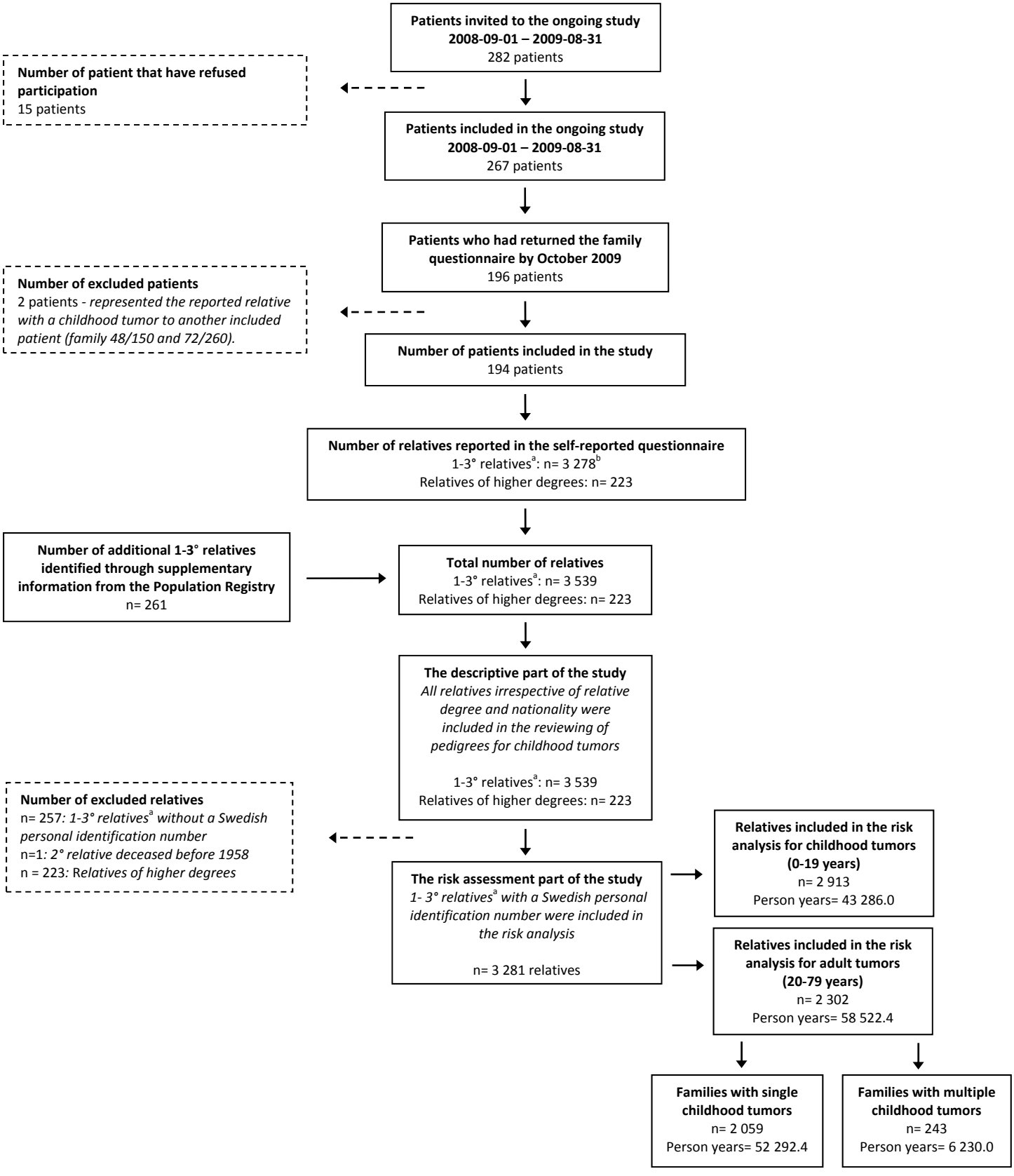

Fig. 1 Flowchart over childhood cancer patients included in the study and number of relatives included in the analyses.

[a] Relatives of 1-3° includes; parents, siblings, offspring, half-siblings, nephews/nieces, grandparents, uncles/aunts nephews/nieces of half-siblings and cousins.
[b] Of whom 3 022 had a Swedish personal identification number

Table 1. Patient characteristics in relation to occurrences of childhood tumors in relatives.

	All	Patients with a relative with childhood tumor	Patients without a relative with a childhood tumor
Primary diagnosis, *n (%)*			
Total	194	21	173
Leukemia	70 (36.1)	8 (38.1)	62 (35.8)
Central nervous system neoplasms	37 (19.1)	3 (14.3)	34 (19.7)
Lymphomas	26 (13.4)	3 (14.3)	23 (13.3)
Soft tissue sarcomas	18 (9.3)	2 (9.5)	16 (9.2)
Malignant bone tumors	8 (4.1)	-	8 (4.6)
Renal tumors	13 (6.7)	1 (4.8)	12 (6.9)
Neuroblastomas	10 (5.2)	1 (4.8)	9 (5.2)
Others	12 (6.2)	3 (14.3)	9 (5.2)
Sex, *n (%)*			
Male	116 (59.8)	8 (38.1)	108 (62.4)
Female	78 (40.2)	13 (61.9)	65 (37.6)
Age at diagnosis, yrs, *median (min-max)*	4.4 (0.0-18.2)	4.0 (0.3-17.0)	4.5 (0.0-18.2)
Time since diagnosis, yrs, *median (min-max)*	6.3 (0.0-35.9)	4.2 (0.0-27.6)	6.6 (0.0-35.9)
Year of diagnosis, *median (min-max)*	2002 (1972-2009)	2004 (1980-2009)	2002 (1972-2009)
Time of inclusion, *n (%)*			
Primary diagnosis	27 (13.9)	3 (14.3)	24 (13.9)
Follow-up	167 (86.1)	18 (85.7)	149 (86.1)

Table 2. Overview of childhood tumor diagnoses in index cases and their childhood relatives.

Family ID	Index case *(Sex; age at diagnosis, yrs)*	Childhood relative *(Sex; age at diagnosis, yrs[a])*	Relative degree	Type of relative
89	Astrocytoma (m; 1)	Neuroblastoma, adrenal (f; 0)[b]	1	Sister
430	ALL (f; 2)	Ganglioglioma (m; 7)[b]	1	Son
132	ALL, Down's Syndrome (f; 2)	AML (m; 17)[b]	2	Half-brother
72	Hepatoblastoma (f; 2)	Hodgkin's lymphoma (m; 11)[b]	2	Uncle
84	Wilms' tumor (m; 3)	ALL (m; 5)[c]	2	Uncle
53	ALL (f; 3)	Leukemia UNS (f; 13)[d]	2	Aunt
33	Langerhans cell histiocytosis (m; 4)	Colon cancer (m; 18)[c,e]	2	Uncle
60	Large cell B-cell non-Hodgkin lymphoma (m; 16)	AML (m; 8)[b]	3	Cousin
230	ALL (f; 6)	ALL (f; 14)[c]	3	Cousin
281	AML (f; 2)	AML (m; 0)[b]	3	Cousin
12	Pituitary adenoma (f; 12)	Neuroblastoma, extra-adrenal (m; 2)[b]	3	Cousin
265	Hodgkin's lymphoma (f; 17)	Congenital brain tumor (m; infant)[d]	3	Cousin
172	ALL (f; 3)	Cervical cancer *in situ* (f; 15)[c,e]	3	Cousin
239	Embryonal rhabdomyosarcoma (f; 4)	Malignant melanoma (f; 19)[c,e]	3	Cousin
241	Ependymoma (m; 6)	Malignant astrocytic glioma (f; 5)[b]	4	Mother's cousin
142	Acute monocytic leukemia (f; 12)	Acute leukemia UNS (f; 4)[c]	4	Mother's cousin
150	Anaplastic large-cell lymphoma (m; 12)	Hepatoblastoma (m; 0)[b]	5	Second cousin
216	Optic glioma, NF1 (m; 2)	Wilms' tumor (f; 1)[c]	5	Grandmother's cousin
36	ALL (f; 8)	Ewing's sarcoma (f; 8)[b]	5	Second cousin
90	Embryonal rhabdomyosarcoma (m; 2)	Brain tumor (f; d. 6)[d]	5	Second cousin
		Malignant melanoma (m; d. 18)[d]	4	Mother's cousin
25	Neuroblastoma, extra-adrenal (f; 0)	Brain tumor (f; 9)[c]	6	Great-grandmother's cousin

ALL acute lymphatic leukemia, *AML* acute myeloid leukemia, *NF1* neurofibromatosis type 1

[a] When age is preceded by d. only age at death is known

[b] Diagnosis verified by pathology reports

[c] Diagnosis verified by Cancer Registry

[d] Diagnosis not verified

[e] Identified by the Cancer Registry but not reported by the patient

Table 3. Standardized incidence ratios for childhood tumors in relatives of childhood cancer patients

	Relative degree	O	E	SIR	95% CI		*P*
All tumors							
	1° [b]	2	1.2	1.7	0.2	6.1	0.7
	2° [c]	4	1.4	2.9	0.8	7.3	0.1
	3° [d]	6	2.2	2.7	1.0	5.9	0.05
	1-3° [e]	12	4.8	2.5	1.3	4.4	0.008
Excluding LCH, pituitary adenoma and cervical tumor [a]							
	1° [f]	2	1.2	1.7	0.2	6.3	0.6
	2° [g]	3	1.4	2.2	0.5	6.5	0.3
	3° [h]	4	2.1	1.9	0.5	4.9	0.3
	1-3° [i]	9	4.6	2.0	0.9	3.7	0.09

Childhood tumors diagnosed 0-19 years of age

CI Confidence interval, *LCH* Langerhans cell histiocytosis, *SIR* Standardized incidence ratios

[a] Index cases with Langerhans cell histiocytosis and pituitary adenoma and cervical tumors in relatives were excluded from the analyses

[b] n= 665; Total sum of person-years= 10 726.2

[c] n= 1 078; Total sum of person-years= 15 221.2

[d] n=1 170; Total sum of person-years=17 338.6

[e] n= 2 913; Total sum of person-years= 43 286.0

[f] n= 641; Total sum of person-years= 10 355.6

[g] n= 1 039; Total sum of person-years= 15 221.2

[h] n= 1 117; Total sum of person-years= 15 883.4

[i] n= 2 797; Total sum of person-years= 41 460.2

Table 4. Standardized incidence ratios for adult tumors in relatives of childhood cancer patients

		1° relatives					2° relatives					3° relatives					1-3° relatives				
Tumor type	**ICD-7**	**O**	**E**	**SIR**	**95% CI**		**O**	**E**	**SIR**	**95% CI**		**O**	**E**	**SIR**	**95% CI**		**O**	**E**	**SIR**	**95% CI**	
Total	140-209	16	7.4	2.2[c]	1.2	3.5	161	112.0	1.4[d]	1.2	1.7	2	1.9	1.1	0.1	3.9	179	121.3	1.5[d]	1.3	1.7
Head and neck	[a]	1	0.4	2.3	0.1	12.7	4	4.7	0.9	0.2	2.2	0	0.1				5	5.2	1.0	0.3	2.2
Esophagus	150	0	0.0				0	1.1				0	0.0				0	1.1			
Stomach	151	1	0.1	7.7	0.2	42.9	3	3.1	1.0	0.2	2.8	0	0.0				4	3.2	1.2	0.3	3.2
Colorectal	153-154	1	0.5	1.9	0.0	10.5	14	12.0	1.2	0.6	2.0	0	0.1				15	12.6	1.2	0.7	2.0
Liver	1550	0	0.0				1	0.8	1.2	0.0	6.7	0	0.0				1	0.9	1.1	0.0	6.4
Gall bladder	1551-1559	0	0.0				1	1.0	1.0	0.0	5.4	0	0.0				1	1.1	0.9	0.0	5.2
Pancreas	157	0	0.1				4	2.4	1.7	0.5	4.3	0	0.0				4	2.5	1.6	0.4	4.1
Lung	1620-1621	0	0.3				15	8.7	1.7	1.0	2.8	0	0.0				15	9.1	1.7	0.9	2.7
Pleura	1622	0	0.0				0	0.4				0	0.0				0	0.4			
Breast	170	6	1.3	4.6[c]	1.7	10.1	26	17.7	1.5	1.0	2.2	1	0.3	3.7	0.1	20.6	33	19.3	1.7[c]	1.2	2.4
Corpus uteri	172,174	0	0.1				2	3.3	0.6	0.1	2.2	0	0.0				2	3.5	0.6	0.1	2.1
Ovarian	175	0	0.2				5	3.2	1.6	0.5	3.6	0	0.1				5	3.5	1.4	0.5	3.4
Vulva and vagina	176	0	0.0				0	0.4				0	0.0				0	0.4			
Prostate	177	1	0.3	3.2	0.1	18.0	34	12.5	2.7[d]	1.9	3.8	0	0.0				35	12.9	2.7[d]	1.9	3.8
Testis	178	0	0.4				2	1.1	1.8	0.2	6.5	0	0.2				2	1.8	1.1	0.1	4.1
Kidney	180	0	0.1				3	3.0	1.0	0.2	2.9	0	0.0				3	3.2	0.9	0.2	2.8
Urinary tract	1801, 181	0	0.2				3	5.8	0.5	0.1	1.5	0	0.0				3	6.1	0.5	0.1	1.4
Melanoma	190	1	0.8	1.2	0.0	6.8	8	5.9	1.4	0.6	2.7	0	0.3				9	7.0	1.3	0.6	2.5
Non-melanoma skin cancer	191	0	0.2				7	4.0	1.8	0.7	3.7	0	0.0				7	4.2	1.7	0.7	3.5
Brain and central nerve system	193	1	0.6	1.7	0.0	9.6	4	4.5	0.9	0.2	2.3	0	0.2				5	5.2	1.0	0.3	2.2
Bone and soft tissue	196,197	0	0.1				2	1.1	1.9	0.2	6.8	0	0.0				2	1.2	1.6	0.2	5.8
Non-Hodgkin's lymphoma	200,202	2	0.3	6.7	0.8	24.1	6	3.6	1.7	0.6	3.7	1	0.1	12.5	0.3	69.7	9	3.9	2.3[b]	1.0	4.3
Hodgkin's lymphoma	201	0	0.2				0	0.7				0	0.1				0	1.0			
Myeloma	203	0	0.1				4	1.3	3.1	0.8	7.8	0	0.0				4	1.4	2.9	0.8	7.5
Acute leukemia	2040, 2050, 2060	0	0.1				1	1.1	1.0	0.0	5.3	0	0.0				1	1.2	0.8	0.0	4.6
Chronic leukemia	2041, 2051	0	0.1				1	1.2	0.8	0.0	4.5	0	0.0				1	1.4	0.7	0.0	4.1
Polycythemia Vera	208	0	0.0				1	0.3	3.7	0.1	20.6	0	0.0				1	0.3	3.6	0.1	19.9
N		459					1 331					512					2 302				
Total sum of person-years		10 148.1					42 946.2					5 428.1					58 522.4				

Adult tumors diagnosed 20-79 age of years. Cervical tumors (ICD-7: 171) are excluded

CI Confidence interval, *SIR* Standardized incidence ratios

[a] 140-148,160-161, 194

[b] $P < 0.05$

[c] $P < 0.01$

[d] $P < 0.001$

Supplementary table 1. Number of relatives identified by respective source and included in the descriptive and analytic part of the study

	Reported in self-reported questionnaire	Identified by National Population Registry	Included in pedigree review	Included in risk analyses
Mother	190	4	194	194
Father	188	3	191	189
Children	22	-	22	22
Siblings	259	8	267	266
Half-siblings	69	4	73	72
Nephews/Nieces	49	6	55	52
Grandparents	693	20[b]	713	656
Uncles/aunts	694	46	740	660
nephews/nieces of half-siblings	33	6	39	39
Cousins	1 081	164	1 245	1 131
Relatives of higher degrees	223	-	223	-
Total number of 1-3° relatives	3 278[a]	261[b]	3 539	3 281
Total number of relatives	3 501	-	3 762	-

[a] Of whom 3 022 have a Swedish identification number
[b] Of whom one has no Swedish identification number and one was deceased before 1958

Supplementary table 2. Standardized incidence ratios for adult tumors in relatives of families with single childhood tumors[a]

		1° relatives					2° relatives					3° relatives					1-3° relatives				
Tumor type	**ICD-7**	**O**	**E**	**SIR**	**95% CI**		**O**	**E**	**SIR**	**95% CI**		**O**	**E**	**SIR**	**95% CI**		**O**	**E**	**SIR**	**95% CI**	
Total	140-209	15	6.8	2.2[d]	1.2	3.6	146	101.8	1.4[e]	1.2	1.7	2	1.8	1.1	0.1	4.1	163	110.4	1.5[e]	1.3	1.7
Head and neck	[b]	1	0.4	2.6	0.1	14.3	4	4.2	0.9	0.3	2.4	0	0.1				5	4.7	1.1	0.3	2.5
Esophagus	150	0	0.0				0	1.0				0	0.0				0	1.0			
Stomach	151	1	0.1	8.3	0.2	46.4	3	2.8	1.1	0.2	3.1	0	0.0				4	3.0	1.3	0.4	3.4
Colorectal	153-154	1	0.5	2.0	0.1	11.4	13	10.9	1.2	0.6	2.0	0	0.1				14	11.5	1.2	0.7	2.0
Liver	1550	0	0.0				1	0.8	1.3	0.0	7.3	0	0.0				1	0.8	1.3	0.0	7.0
Gall bladder	1551-1559	0	0.0				1	1.0	1.1	0.0	5.9	0	0.0				1	1.0	1.0	0.0	5.6
Pancreas	157	0	0.1				4	2.2	1.9	0.5	4.7	0	0.0				4	2.3	1.8	0.5	4.5
Lung	1620-1621	0	0.3				14	7.9	1.8	1.0	3.0	0	0.0				14	8.3	1.7	0.9	2.8
Pleura	1622	0	0.0				0	0.3				0	0.0				0	0.4			
Breast	170	5	1.2	4.2[c]	1.4	9.8	22	15.9	1.4	0.9	2.1	1	0.3	3.8	0.1	21.4	28	17.4	1.6[c]	1.1	2.3
Corpus uteri	172,174	0	0.1				1	3.0	0.3	0.0	1.8	0	0.0				1	3.2	0.3	0.0	1.8
Ovarian	175	0	0.2				5	2.9	1.7	0.6	4.0	0	0.1				5	3.2	1.6	0.5	3.7
Vulva and vagina	176	0	0.0				0	0.3				0	0.0				0	0.4			
Prostate	177	1	0.3	3.4	0.1	19.2	32	11.6	2.8[e]	1.9	3.9	0	0.0				33	11.9	2.8[e]	1.9	3.9
Testis	178	0	0.4				2	1.0	2.0	0.2	7.4	0	0.2				2	1.6	1.3	0.2	4.6
Kidney	180	0	0.1				3	2.7	1.1	0.2	3.2	0	0.0				3	2.9	1.0	0.2	3.0
Urinary tract	1801, 181	0	0.2				3	5.3	0.6	0.1	1.6	0	0.0				3	5.6	0.5	0.1	1.6
Melanoma	190	1	0.7	1.4	0.0	7.5	7	5.3	1.3	0.5	2.7	0	0.2				8	6.3	1.3	0.6	2.5
Non-melanoma skin cancer	191	0	0.2				5	3.6	1.4	0.4	3.2	0	0.0				5	3.8	1.3	0.4	3.1
Brain and central nerve system	193	1	0.5	1.9	0.0	10.7	4	4.0	1.0	0.3	2.6	0	0.2				5	4.7	1.1	0.3	2.5
Bone and soft tissue	196,197	0	0.1				1	0.9	1.1	0.0	5.9	0	0.1				1	1.1	0.9	0.0	5.0
Non-Hodgkin's lymphoma	200,202	2	0.3	7.4	0.9	26.8	6	3.2	1.9	0.7	4.0	1	0.1	12.5	0.3	69.7	9	3.6	2.5[c]	1.2	4.8
Hodgkin's lymphoma	201	0	0.2				0	0.6				0	0.1				0	0.9			
Myeloma	203	0	0.1				3	1.2	2.5	0.5	7.3	0	0.0				3	1.3	2.4	0.5	7.0
Acute leukemia	2040, 2050, 2060	0	0.1				1	1.0	1.1	0.0	5.9	0	0.0				1	1.1	0.9	0.0	5.1
Chronic leukemia	2041, 2051	0	0.1				1	1.1	0.9	0.0	4.9	0	0.0				1	1.2	0.8	0.0	4.5
Polycythemia Vera	208	0	0.0				1	0.3	4	0.1	22.3	0	0.0				1	0.3	3.8	0.1	21.4
N		408					1 180					471					2 059				
Total sum of person-years		9 065.9					38 125.5					5 101.0					52 292.4				

CI, Confidence interval; SIR, Standardized incidence ratios

[a] Adult tumors diagnosed 20-79 age of years. Cervical tumors (ICD-7: 171) are excluded

[b] 140-148,160-161, 194

[c] $P < 0.05$

[d] $P < 0.01$

[e] $P < 0.001$

Supplementary table 3. Standardized incidence ratios for adult tumors in relatives of families with multiple childhood tumors[a]

		1° relatives					2° relatives					3° relatives				1-3° relatives				
Tumor type	**ICD-7**	**O**	**E**	**SIR**	**95% CI**		**O**	**E**	**SIR**	**95% CI**		**O**	**E**	**SIR**	**95% CI**	**O**	**E**	**SIR**	**95% CI**	
Total	140-209	1	0.6	1.6	0.0	9.0	15	10.2	1.5	0.8	2.4	0	0.1			16	10.9	1.5	0.8	2.4
Head and neck	[b]	0	0.0				0	0.5				0	0.0			0	0.5			
Esophagus	150	0	0.0				0	0.1				0	0.0			0	0.1			
Stomach	151	0	0.0				0	0.3				0	0.0			0	0.3			
Colorectal	153-154	0	0.0				1	1.0	1.0	0.0	5.4	0	0.0			1	1.1	0.9	0.0	5.3
Liver	1550	0	0.0				0	0.1				0	0.0			0	0.1			
Gall bladder	1551-1559	0	0.0				0	0.1				0	0.0			0	0.1			
Pancreas	157	0	0.0				0	0.2				0	0.0			0	0.2			
Lung	1620-1621	0	0.0				1	0.8	1.3	0.0	7.3	0	0.0			1	0.8	1.3	0.0	7.1
Pleura	1622	0	0.0				0	0.0				0	0.0			0	0.0			
Breast	170	1	0.1	9.1	0.2	50.7	4	1.8	2.3	0.6	5.8	0	0.0			5	1.9	2.6	0.9	6.2
Corpus uteri	172,174	0	0.0				1	0.3	3.2	0.1	18.0	0	0.0			1	0.3	3.1	0.1	17.4
Ovarian	175	0	0.0				0	0.3				0	0.0			0	0.3			
Vulva and vagina	176	0	0.0				0	0.0				0	0.0			0	0.0			
Prostate	177	0	0.0				2	1.0	2.1	0.3	7.5	0	0.0			2	1.0	2.1	0.2	7.4
Testis	178	0	0.1				0	0.1				0	0.0			0	0.2			
Kidney	180	0	0.0				0	0.3				0	0.0			0	0.3			
Urinary tract	1801, 181	0	0.0				0	0.5				0	0.0			0	0.5			
Melanoma	190	0	0.1				1	0.6	1.6	0.0	9.0	0	0.0			1	0.7	1.4	0.0	7.8
Non-melanoma skin cancer	191	0	0.0				2	0.3	6.1	0.7	21.9	0	0.0			2	0.3	5.9	0.7	21.3
Brain and central nerve system	193	0	0.1				0	0.5				0	0.0			0	0.5			
Bone and soft tissue	196,197	0	0.0				1	0.1	9.1	0.2	50.7	0	0.0			1	0.1	8.3	0.2	46.4
Non-Hodgkin's lymphoma	200,202	0	0.0				0	0.3				0	0.0			0	0.4			
Hodgkin's lymphoma	201	0	0.0				0	0.1				0	0.0			0	0.1			
Myeloma	203	0	0.0				1	0.1	8.3	0.2	46.4	0	0.0			1	0.1	8.3	0.2	46.4
Acute leukemia	2040, 2050, 2060	0	0.0				0	0.1				0	0.0			0	0.1			
Chronic leukemia	2041, 2051	0	0.0				0	0.1				0	0.0			0	0.1			
Polycythemia Vera	208	0	0.0				0	0.0				0	0.0			0	0.0			
n		51					151					41				243				
Total sum of person-years		1 082.3					4 820.6					327.1				6 230.0				

CI, Confidence interval; SIR, Standardized incidence ratios

[a] Adult tumors diagnosed 20-79 age of years. Cervical tumors (ICD-7: 171) are excluded

[b] 140-148,160-161, 194

[c] $P < 0.05$

[d] $P < 0.01$

[e] $P < 0.001$