Increased Cancer Risk in Families with Pediatric Cancer Is Associated with Gender, Age, Diagnosis, and Degree of Relation to the Child AC

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ABSTRACT

Background: Studies of cancer risk among relatives of children with cancer beyond parents and siblings are limited. We have investigated the cancer risk up to the third degree of relation in families with pediatric cancer to reveal patterns of inheritance.

Methods: A single-center cohort of 757 patients with pediatric cancer was linked to the Swedish National Population Register, resulting in 16,137 relatives up to the third degree of relation. All relatives were matched to the Swedish Cancer Register, and standard incidence ratios (SIR) were calculated to define relatives at risk.

Results: Children and adults up to the third degree of relation had increased cancer risk, with SIRs of 1.48 ($P = 0.01$) and 1.07 ($P < 0.01$), respectively. The SIRs for first- and third-degree adult relatives were 1.22 and 1.10, respectively, but no increased risk was observed in second-degree relatives. Male relatives had a higher risk than females, especially when related to a girl and when the child had leukemia. The risk was mainly increased for lung, prostate, and gastrointestinal cancer. When excluding 29 families of children with known pathogenic germline variants, the increased risk remained.

Conclusions: Relatives to children with cancer up to third degree of relation have an increased cancer risk. Known pathogenic germline variants do not explain this increased risk.

Impact: The overall increased cancer risk among relatives of children with cancer in this population-based cohort strengthens the importance of surveillance programs for families with pediatric cancer.

Introduction

Previous studies have reported an increased risk of cancer among relatives of patients with pediatric cancer (1–12). However, studies including family members up to the third degree of relation are rare. Curtin and colleagues showed an approximate two-fold increased risk of pediatric cancer when including second-degree relatives, but they did not study adult cancer risk beyond first-degree relations (9). A previous study by our research group showed an increased risk of cancer among adult and pediatric relatives up to the third degree (8); however, the size of the cohort was limited.

A family history of cancer is considered a risk factor for most types of adult cancer (9, 13–16). Inherited pathogenic alterations causing cancer have been suggested to have a higher impact on pediatric cancer than on cancer in adults, which is partially attributed to children having a shorter period of environmental exposure (15). Younger age at onset of pediatric cancer correlates with a higher cancer risk among adult relatives (17, 18), indicating that cancer at a young age is related to heredity and genetic irregularities.

The gender of relatives of children with cancer influences cancer risk. Female relatives have been reported to have a higher cancer risk than male relatives (10–12). However, no study has yet investigated whether the gender of the patient with pediatric cancer affects the cancer risk of relatives. In a study by Scheuner and colleagues of the prevalence of familial adult cancer, 14.6% of the study population had a two-fold increased risk of cancer, whereas 7.7% had a five- to seven-fold increased risk (19), indicating separate heredity patterns in family subsets. Similarly, a risk assessment by Knapke and colleagues revealed that 29% of families with cases of pediatric cancer were eligible for genetic counseling due to the increased risk of cancer among relatives (14), and the authors suggested that a high proportion of hereditary pathogenic variants remain unknown, and that novel hereditary syndromes have yet to be discovered. An estimated 10% of pediatric cancers are caused by inherited or sporadic germline pathogenic variants (20–26). The majority of highly penetrant clinically pathogenic variants have probably already been described, and novel approaches are therefore needed to detect other clinical syndromes with less obvious patterns.

The Lund Childhood Cancer Genetic (LCCG) study prospectively includes patients with a pediatric cancer diagnosis, and retrieves cancer diagnoses of relatives, in addition to blood samples of the child and parents. In an earlier study of the cohort, we observed that patients with pediatric cancer from the same family often had matching cancer diagnoses (27). Furthermore, we observed that families with more than one pediatric cancer case showed a higher prevalence of female patients with pediatric cancer than families with only one pediatric cancer case. We here investigated the cohort of 757 patients with pediatric cancer, and linked them to the comprehensive National Population and Cancer Registers to study the patterns of familial cancer up to third degree of relation.

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Materials and Methods

The ongoing LCCG study enrolls pediatric patients diagnosed with cancer below 18 years of age and treated at the Department of Pediatric Oncology, Skåne University Hospital in Lund, Sweden, covering a population of 1.9 million inhabitants. Blood samples from patients and parents are collected for germline analysis. Patients and parents complete a standardized self-reported questionnaire, providing a history of cancer among first-, second-, and third-degree relatives. Data on cancer type, date of/age at diagnosis, and outcome (if fatal, date of death) are obtained and recorded in pedigrees. All information from the questionnaires is verified and supplemented with data from national registers and medical records. Pathology reports for all patients with pediatric cancer included in the study were reviewed.

The Swedish National Population Register enables the identification of individuals through a unique personal number, as well as the degree of relation and vital status of relatives of patients with pediatric cancer. All relatives were subsequently matched to the Swedish Cancer Register to identify/confirm cancer diagnoses among relatives. As the national identification number was introduced in 1947, and the National Cancer Register was started in 1958, we decided not to include great-grandparents in the cohort as the identities and cancer diagnoses of these individuals could not be reliably confirmed.

Statistical methods

SPSS 22.0 was used for statistical analyses within the cohort. For comparison of continuous variables, such as age at diagnosis and time since diagnosis, Student t test was applied. For cohort comparison regarding diagnosis distribution, Fisher exact test was used. Results were adjusted for gender, date of birth, age, and degree of relation. P values were two-sided, and a significance level of $P < 0.05$ was used.

For calculation of cancer risk over time, the Poisson distribution was applied. Cancer diagnoses were coded according to ICD-7. The number of person years at risk was calculated as the difference between date of birth, or January 1, 1958 (in cases when the individuals were born before January 1, 1958), and date of death/emigration or end of follow-up on December 31, 2015. Person years at risk was stratified by age, sex, and calendar year, and multiplied by year-, age-, and sex-specific rates of cancer types obtained from the Swedish Cancer Register to yield the expected rates of each cancer type. Standardized incidence ratios (SIR), observed/expected ratios, 95% confidence intervals (CI), and P values were computed. P values were one-sided (as solely increased cancer risk was studied), and $P < 0.05$ was considered significant. To test for heterogeneity by sex, expected and observed values for male and female was compared using χ^2. P values were two-sided, and $P < 0.05$ was considered significant.

Cancer diagnoses among relatives were divided into 30 different diagnostic groups. Several groups were too small for statistical analysis. Thus, the results for some diagnoses should be considered as hypothesis generating as they have not been subjected to correction for multiple testing. All other results were adjusted by correction for FDRs to account for multiple testing. When analyzing cancer in relatives of children with different cancer diagnoses, they were divided in five groups; relatives to children with either (i) leukemia, (ii) central nervous system (CNS) tumors, (iii) lymphoma, (iv) sarcoma, or (v) other diagnoses. All intracranial tumors were defined as CNS tumors.

Results

By December 31, 2015, 757 children with cancer had been enrolled in the LCCG study. A total of 16,430 relatives up to the third degree were identified through the National Population Register. A total of 250 relatives (1.5%) were excluded because of invalid personal numbers, the majority of which were due to emigration or death having occurred too long ago for records to be available. Finally, a further 43 relatives (0.3%) were excluded as they had died before 1958, when the

Table 1. Characteristics of adults up to the third degree of relation to 757 patients with pediatric cancer.

Distribution of childhood cancer diagnoses, % (*n*)	Men		Women		All relatives	
	n (%)	Average age at cutoff (years)	*n* (%)	Average age at cutoff (years)	*n* (%)	Average age at cutoff (years)
Leukemia, 33.7% (255)	2,748 (50.7)	47.5	2,676 (49.3)	49.6	5,424	48.5
CNS tumor, 20.7% (157)[a]	1,721 (49.3)	49.0	1,767 (50.7)	49.4	3,488	49.2
Lymphoma, 13.5% (102)	1,084 (51.0)	48.6	1,041 (49.0)	50.0	2,125	49.3
Wilms tumor, 6.7% (51)	570 (50.6)	47.0	557 (49.4)	49.8	1,127	48.4
Soft-tissue sarcoma, 6.6% (50)	566 (50.9)	47.6	547 (49.1)	48.4	1,113	48.0
Bone tumor, 7.1% (54)[b]	501 (48.7)	48.6	528 (51.3)	48.2	1,029	48.4
Neuroblastoma, 4.0% (30)	279 (51.6)	47.5	262 (48.4)	48.8	541	48.2
Histiocytosis, 2.2% (17)	220 (52.8)	45.5	197 (47.2)	48.2	417	46.8
Germ-cell tumors, 1.8% (14)[a]	145 (52.0)	49.9	134 (48.0)	51.8	279	50.8
Hepatic tumor, 1.2% (9)	120 (52.6)	51.5	108 (47.4)	54.4	228	52.9
Retinoblastoma, 0.7% (5)	62 (54.9)	55.8	51 (45.1)	58.7	113	57.1
Carcinomas, 0.9% (7)[a]	61 (45.9)	45.7	72 (54.1)	45.4	133	45.5
Others, 0.8% (6)	53 (44.9)	44.0	65 (55.1)	52.2	118	48.5
Total, 100% (757)	8,130 (50.4)	48.1	8,006 (49.6)	49.5	16,136	48.8
Age at first diagnosis, years	66.5		62.9		64.8	
Cancer diagnoses, *n*	1,246		1,162		2,408	
Years at risk, years	297,923.4		308,634.2		606,557.5	
Cancer/1,000 years at risk, *n*	4.18		3.76		3.97	

[a]Significantly lower than the Swedish Childhood Cancer Register.
[b]Significantly higher than the Swedish Childhood Cancer Register.

National Cancer Register was set up, and the reported cancer diagnosis could not be confirmed. This resulted in 16,137 relatives up to the third degree whose identity could be confirmed, totaling 606,558 person years at risk. The characteristics of all adult relatives, divided according to gender and cancer diagnosis of the related child, are given in **Table 1**.

The distribution of diagnoses of the children included in the LCCG cohort was largely in line with that of the Swedish Childhood Cancer Register (**Table 1**, first column). However, an underrepresentation of CNS tumors, germ-cell tumors, and carcinomas was observed in addition to an overrepresentation of bone tumors. Seventy-four families (9.8%) had more than one pediatric cancer case in relatives up to the fifth degree of relation. When restricting the study up to third-degree relatives, 39 families (5.2%) had more than one case of pediatric cancer.

Adult cancer incidence in the LCCG cohort compared with the general population

We observed a significant increase in the risk of adult cancer among relatives of patients with pediatric cancer up to the third degree of relation (SIR 1.07, 95% CI: 1.03–1.11, $P < 0.01$, FDR $P < 0.01$), compared with the general population. Incidence ratios of cancers in adult relatives of children with cancer are presented in **Table 2**. When separated by gender, male relatives showed a higher risk of adult cancer than the general population (SIR 1.11, 95% CI: 1.05–1.17, $P < 0.01$, FDR $P = 0.01$). In contrast, female relatives up to the third degree of relation showed no overall increased risk of cancer (SIR 1.03). The diagnoses associated with increased risk in adult relatives differed considerably between men and women, as can be seen from **Table 2**.

Childhood cancer incidence in relatives of patients with pediatric cancer

An increased risk of cancer was found in children up to third degree of relation to children with cancer (SIR 1.48, 95% CI: 1.05–2.02, $P = 0.01$, FDR $P = 0.03$), compared with the general population. The risk was significantly increased in girls, but not in boys: SIR 1.60 (95% CI: 0.98–2.48, $P = 0.03$) and SIR 1.37 (95% CI: 0.82–2.13, $P = 0.11$), respectively. However, the difference between the sexes was not significant ($P = 0.69$). As diagnoses of relatives were classified according to ICD-7, comparison between specific pediatric cancer diagnoses was not possible.

Adult cancer risk in first- to third-degree relatives of patients with pediatric cancer

Adult cancer types associated with increased risk according to degree of relation and gender are given in **Table 3**. First-degree adult relatives showed the highest risk of cancer (SIR 1.22, 95% CI: 1.04–1.43, $P = 0.01$, FDR $P = 0.02$). Second-degree relatives showed no increased risk (SIR 1.02), while third-degree relatives did (SIR 1.10, 95% CI: 1.03–1.16, $P < 0.01$, FDR $P < 0.01$; **Table 3**).

Female first-degree relatives showed an overall increased risk of cancer (SIR 1.27, $P = 0.02$, 95% CI: 1.01–1.57, $P = 0.02$, FDR $P = 0.05$), while male first-degree relatives did not (SIR 1.17). Again, no increased risk was observed among second-degree relatives when separated by gender (men: SIR 1.06 and women: SIR 0.97). Among third-degree relatives, men showed a significantly increased risk of cancer at any location (SIR 1.14, 95% CI: 1.05–1.23, $P < 0.01$, FDR $P < 0.01$), whereas female relatives did not (SIR 1.05; **Table 3**). No overlap was observed in the types of cancer with increased risk between adult male and female relatives.

Adult cancer risk in relatives according to gender of the patient with pediatric cancer

The increase in cancer risk in first- to third-degree relatives of girls and boys with cancer was similar (SIR 1.06, $P = 0.03$, FDR $P = 0.05$ and SIR 1.07, $P < 0.01$, FDR $P < 0.01$, respectively; **Table 4**). Female relatives of girls with cancer showed no increased cancer risk (SIR 0.99), while male relatives did, (SIR 1.14, $P < 0.01$, FDR $P < 0.01$); however, there was no statistical significance when comparing the increased risk for men and women ($P = 0.11$). In contrast, male relatives of boys with cancer showed a higher risk, whereas women did not (SIR 1.08, $P = 0.02$, FDR $P = 0.05$, compared with SIR 1.06 $P = 0.06$, FDR $P = 0.10$), as can be seen from **Table 4**.

Adult cancer risk in relatives according to diagnostic group of the patient with pediatric cancer

The highest cancer risk was observed among relatives of children with CNS tumors (SIR 1.11, $P < 0.01$, FDR $P = 0.02$), followed by

Table 2. Incidence ratio of cancers in adult relatives of patients with pediatric cancer.

		Men		Women		SH	All relatives	
	n	SIR	95% CI	SIR	95% CI	*P*	SIR	95% CI
Any cancer	2,360	1.11[a]	1.05–1.17	1.03	0.97–1.09	0.23	1.07[a]	1.03–1.11
Prostate	335	1.11[a]	0.99–1.23	—	—	—	1.11[a]	0.99–1.23
Breast	307	1.06	0.13–3.82	0.97	0.87–1.09	0.98	0.97	0.87–1.09
Lung	176	1.12	0.91–1.36	1.35[a]	1.07–1.69	0.41	1.21[a]	1.04–1.40
Pharynx	16	1.66[a]	0.91–2.78	0.61	0.07–2.20	—	1.36	0.78–2.22
Esophagus	28	1.56[a]	0.95–2.40	1.69	0.73–3.34	0.95	1.59[a]	1.06–2.30
Stomach	80	1.12	0.82–1.48	1.33[b]	0.91–1.88	0.60	1.19[b]	0.95–1.49
Colon	184	1.04	0.82–1.30	1.31[a]	1.07–1.59	0.29	1.18[a]	1.01–1.36
Bile duct/gallbladder	33	1.88[a]	1.08–3.06	1.14	0.66–1.83	0.41	1.41[a]	0.97–1.98
Pancreas	63	1.26	0.87–1.76	1.18	0.79–1.69	0.83	1.22[b]	0.94–1.56
Kidney	69	0.94	0.65–1.32	1.57[a]	1.10–2.17	0.16	1.19[b]	0.93–1.51
Urinary tract	111	1.18[b]	0.95–1.45	0.72	0.44–1.11	0.13	1.06	0.87–1.28
Hodgkin	18	1.73[a]	0.90–3.03	1.20	0.44–2.62	0.64	1.51[b]	0.90–2.39

Note: Prostate, breast, and lung cancer and cancer types with at least one *P* value <0.1 are presented.
Abbreviation: SH, sex heterogeneity.
[a]$P < 0.05$.
[b]$P < 0.1$.

Table 3. Incidence ratio of cancer in adult relatives of patients with pediatric cancer.

Degree of relation	Relatives (*n*)			Men		Women		SH	All relatives	
			n	SIR	95% CI	SIR	95% CI	*P*	SIR	95% CI
1st degree	2,138	Any cancer	154	1.17	0.91–1.48	1.27[a]	1.01–1.57	0.71	1.22[a]	1.04–1.43
2nd degree	4,990	Any cancer	1,019	1.06[b]	0.98–1.16	0.97	0.89–1.07	0.32	1.02	0.96–1.08
3rd degree	6,525	Any cancer	1,187	1.14[a]	1.05–1.23	1.05	0.97–1.14	0.36	1.10[a]	1.03–1.16
1st degree										
Median age 37 years		Prostate	16	1.00	0.57–1.63	—	—		1.00	0.57–1.63
		Breast	28	0.00	0.00–36.0	1.18	0.79–1.71		1.18	0.78–1.70
		Lung	9	0.57	0.07–2.06	2.32[a]	0.93–4.77		1.38	0.63–2.62
		Mouth	4	4.18[a]	0.86–12.22	2.48	0.06–13.82		3.57[a]	0.97–9.14
		Pharynx	4	5.58[a]	1.52–14.28	0.00	0.00–15.06		4.16[a]	1.13–10.64
		Pancreas	3	0.00	0.00–3.41	3.82[a]	0.79–11.17		1.61	0.33–4.70
		Cervix	8	—	—	2.54[a]	1.10–5.01		2.54[a]	1.10–5.01
		Testis	6	2.12[b]	0.78–4.62	—	—		2.12[b]	0.78–4.62
		Melanoma	15	1.14	0.37–2.66	1.91[a]	0.92–3.52		1.56[b]	0.87–2.57
		CNS tumor	9	0.99	0.21–2.91	1.96[b]	0.72–4.27		1.48	0.68–2.81
2nd degree										
Median age 57 years		Prostate	164	1.13[b]	0.96–1.31	—	—		1.13[b]	0.96–1.31
		Breast	143	0.00	0.00–4.60	0.97	0.82–1.15		0.97	0.82–1.14
		Lung	77	1.14	0.84–1.52	1.08	0.73–1.53		1.12	0.88–1.39
		Esophagus	11	1.68[b]	0.81–3.09	0.52	0.01–2.90		1.40	0.70–2.50
3rd degree										
Median age 47 years		Prostate	155	1.1	0.93–1.29	—	—		1.1	0.93–1.29
		Breast	136	0.99	0.25–7.33	0.94	0.79–1.11		0.95	0.79–1.12
		Lung	90	1.15	0.86–1.50	1.55[a]	1.10–2.13		1.29[a]	1.04–1.58
		Mouth	12	1.38	0.51–3.01	1.78	0.65–3.87		1.56[b]	0.80–2.72
		Esophagus	15	1.44	0.66–2.72	2.27[b]	0.83–4.95		1.68[a]	0.94–2.78
		Stomach	50	1.11	0.74–1.59	1.39[b]	0.86–2.13		1.21	0.90–1.60
		Colon	111	0.97	0.68–1.34	1.70[a]	1.33–2.13		1.36[a]	1.12–1.64
		Bile duct/gallbladder	20	2.56[a]	1.32–4.47	0.88	0.38–1.74		1.45[b]	0.89–2.25
		Pancreas	37	1.52[a]	0.95–2.30	1.08	0.61–1.78		1.31[b]	0.92–1.80
		Kidney	37	0.86	0.48–1.41	1.76[a]	1.10–2.67		1.23	0.87–1.70
		Urinary tract	65	1.40[a]	1.05–1.83	0.80	0.41–1.40		1.23[b]	0.95–1.56
		Thyroid	13	2.37[a]	0.87–5.17	1.06	0.43–2.18		1.42	0.76–2.43
		Non-Hodgkin	38	1.53[a]	0.99–2.26	0.89	0.48–1.53		1.23	0.87–1.69
		Hodgkin	12	2.77[a]	1.27–5.25	1.24	0.25–3.61		2.11[a]	1.09–3.69

Note: Prostate, breast, and lung cancer and other cancer with at least one *P* value <0.1 are presented.
Abbreviation: SH, sex heterogeneity.
[a]$P < 0.05$.
[b]$P < 0.1$.

lymphoma (SIR 1.10, $P = 0.05$, FDR $P = 0.09$), leukemia (SIR 1.06, $P = 0.06$, FDR $P = 0.10$), "other" diagnoses, mainly Wilms tumor and neuroblastoma (SIR 1.05, $P = 0.15$, FDR $P = 0.19$), and finally sarcomas (SIR 1.01, $P = 0.43$, FDR $P = 0.43$). Only relatives of children with CNS tumors showed a significantly increased risk of cancer of any type (for details, see **Table 5**). Male relatives of patients with pediatric leukemia showed a significantly higher cancer risk than female relatives (SIR 1.15 and SIR 0.96, respectively, $P = 0.01$). Relatives to children with sarcoma showed a higher risk for men than women, although this was not statistically significant (SIR 1.10 and SIR 0.92, respectively, $P = 0.10$). A gender-dependent pattern was not seen among relatives of children with CNS tumors or lymphoma

Adult cancer risk of first-degree relatives according to age at diagnosis of pediatric cancer

First-degree relatives of children diagnosed before 5 years of age showed a higher risk of adult cancer than the general population (SIR 1.42, $P < 0.01$, FDR $P = 0.02$; **Table 6**). Male relatives exhibited an increased risk of adult cancer (cancer in the mouth/pharynx), whereas females did not. Relatives of children diagnosed after 5 years of age did not show any overall increased risk compared with the general population. No significant difference was found in the cancer risk of relatives of children diagnosed with cancer before or after 5 years of age, when the two groups were compared with each other, instead of with the general population (SIR 1.18, $P = 0.31$).

Adult cancer risk in families with one or more than one pediatric cancer

Seventy-four children in the LCCG cohort (9.8%) had a relative up to the fifth-degree with pediatric cancer. When comparing the cancer incidence in relatives up to third degree in families with one (FAM1) or more than one pediatric cancer (FAM>1), no significant difference was seen in the diagnosis distribution or age at onset of adult cancer (Supplementary Table S1). Adult relatives in FAM>1 showed no overall increase in cancer risk compared with the general population (SIR 1.00, $P = 0.49$). Adult relatives in FAM>1 showed no increase in risk when compared with relatives in FAM1.

Table 4. Incidence ratio of cancer in relatives of patients with pediatric cancer according to gender.

Gender of child		*n*	Men		Women		SH	All relatives	
			SIR	95% CI	SIR	95% CI	*P*	SIR	95% CI
Girl	Any cancer	1,018	1.14[a]	1.05–1.24	0.99	0.90–1.08	0.11	1.06[a]	1.00–1.13
Boy	Any cancer	1,342	1.08[a]	1.00–1.17	1.06[b]	0.98–1.15	0.83	1.07[a]	1.02–1.13
Girl									
	Prostate	156	1.18[a]	1.00–1.38	—	—		1.18[a]	1.00–1.38
	Breast	122	1.21	0.03–6.77	0.89	0.74–1.06		0.89	0.74–1.07
	Lung	75	1.16	0.85–1.56	1.22	0.83–1.75		1.19[b]	0.93–1.49
	Mouth	9	0.72	0.15–2.09	2.07[b]	0.76–4.50		1.27	0.58–2.41
	Stomach	39	1.24	0.78–1.85	1.59[b]	0.91–2.59		1.36[a]	0.97–1.86
	Colon	84	1.03	0.71–1.43	1.47[a]	1.09–1.94		1.25[a]	1.00–1.55
	Bile duct/gallbladder	17	1.90[b]	0.76–3.92	1.59	0.76–2.93		1.71[a]	0.99–2.73
	Pancreas	26	1.54[b]	0.91–2.44	0.76	0.33–1.50		1.17	0.77–1.72
	Pharynx	7	1.86[b]	0.75–3.83	0.00	0.00–6.15		1.60	0.64–3.30
	Urinary tract	49	1.25[b]	0.90–1.69	0.59	0.24–1.22		1.08	0.80–1.43
	Leukemia	11	0.95	0.26–2.44	1.91	0.77–3.94		1.40	0.70–2.51
	CLL	15	1.69[b]	0.77–3.22	1.91	0.70–4.15		1.77[a]	0.99–2.93
Boy									
	Prostate	179	1.05	0.90–1.22	—	—		1.05	0.90–1.22
	Breast	185	0.94	0.02–5.22	1.04	0.89–1.20		1.03	0.89–1.20
	Lung	101	1.09	0.82–1.42	1.45[a]	1.06–1.94		1.23[a]	1.00–1.49
	Mouth	13	2.03[a]	1.01–3.64	0.51	0.06–1.85		1.40	0.74–2.39
	Esophagus	17	1.79[a]	0.95–3.06	1.47	0.40–3.76		1.70[a]	0.99–2.73
	Bile duct/gallbladder	16	1.87[b]	0.85–3.55	0.81	0.33–1.67		1.19	0.68–1.93
	Pancreas	37	1.05	0.60–1.70	1.49[b]	0.92–2.28		1.26[b]	0.89–1.74
	Testis	13	1.65[b]	0.88–2.82	—	—		1.65[b]	0.88–2.82
	Kidney	46	1.11	0.69–1.68	1.83[a]	1.17–2.73		1.40[a]	1.02–1.86
	CNS tumor	42	0.86	0.48–1.41	1.36[b]	0.89–1.97		1.12	0.81–1.52
	Hodgkin	10	1.80[b]	0.72–3.71	1.06	0.22–3.11		1.49	0.71–2.74

Note: Prostate, breast, and lung cancer and other with at least one *P* value <0.1 are presented.
Abbreviations: CLL, chronic lymphocytic leukemia; SH, sex heterogeneity.
[a]$P < 0.05$.
[b]$P < 0.10$.

Adult cancer risk in families with known pathogenic germline mutations

Twenty-nine of 728 patients with pediatric cancer from the LCCG cohort (4%) tested positive for a pathogenic germline variant in a parallel ongoing study. Targeted sequencing (Illumina HiSeq 2500) of 22 autosomal dominant predisposition genes analyzed in a study by Zhang and colleagues (25) revealed 29 carriers in 10 of these genes (*NF1, TP53, BRCA2, RB1, BRCA1, PMS2, SDHA, APC, PALB2*, and *PTCH1*, while none for *ALK, ATM, CDH1, KRAS, MSH2, MSH2, MSH6, NF2, NRAS, RET, RUNX1, SDHAB*, and *VHL*). Upon exclusion of these patients, and 29 patients in which no germline analysis had been performed ($n = 58$), no difference in the increased risk of cancer in adult relatives was observed, thus SIR 1.07 ($P < 0.01$) remained unchanged.

Discussion

We have shown that first-degree adult relatives of children with cancer had a 22% increased risk of cancer, and third-degree adult relatives had a 10% increased risk, compared with the general population. There was no increase in cancer risk among second-degree adult relatives. The increased risk in first-degree adult relatives is in line with reports from previous studies (6, 7, 9, 12). Heath and colleagues reported a decreased risk in second-degree relatives (10), which is confirmed in this study but difficult to explain in combination with increased risk for third-degree relatives. Winther and colleagues reported that adult relatives had an increased cancer risk at younger age (6). In this study, second-degree relatives had a higher median age than first- and third-degree relatives (**Table 3**), which could partly explain why second-degree relatives had no increased risk of cancer when compared with the general population. Nevertheless, after correcting for age, second-degree relatives still showed no overall increased risk of adult cancer in this study. To further speculate, environmental factors might affect epigenetics and penetrance of inherited germline variants (28–30), and it may be that second-degree relatives were exposed to different lifestyle factors in their generation of time. The increased cancer risk in third-degree adult relatives is novel and intriguing. We attribute this finding mainly to the increased cancer risk among male relatives.

The risk of pediatric cancer in families with cases of pediatric cancer was increased by 48% in first-degree relatives, compared with the general population. This is lower than the two-fold increase reported previously (4, 9), but families with pediatric leukemia, the most frequent pediatric cancer diagnosis, showed an increased risk of 86% in this study. We observed an increased risk of cancer in the gastrointestinal (GI) tract, prostate, and lungs in adult relatives of

Table 5. Incidence of cancer in adult relatives of patients with pediatric cancer.

Diagnosis of child		*n*	Men		Women		SH	All relatives	
			SIR	95% CI	SIR	95% CI	*P*	SIR	95% CI
Leukemia	Any cancer	779	1.15[a]	1.05–1.27	0.96	0.86–1.07	0.01[a]	1.06[b]	0.98–1.13
CNS	Any cancer	542	1.10[b]	0.97–1.24	1.12[a]	1.00–1.27	0.84	1.11[a]	1.02–1.21
Lymphoma	Any cancer	319	1.13[b]	0.96–1.31	1.07	0.91–1.26	0.75	1.10[a]	0.98–1.23
Sarcoma	Any cancer	290	1.10	0.94–1.28	0.92	0.77–1.09	0.10	1.01	0.90–1.13
Other	Any cancer	429	1.02	0.88–1.16	1.09	0.95–1.24	0.61	1.05	0.95–1.16
Leukemia	Prostate	124	1.24[a]	1.03–1.48	—	—		1.24[a]	1.03–1.48
	Breast	98	0.00	0.00–5.89	0.93	0.76–1.14		0.93	0.75–1.13
	Lung	60	1.25	0.88–1.72	1.23	0.78–1.84		1.24[b]	0.95–1.59
	Mouth	11	2.20[a]	0.88–4.52	1.74	0.48–4.46		2.01[a]	1.00–3.59
	Stomach	31	1.27	0.75–2.01	1.61[b]	0.86–2.76		1.40[a]	0.95–1.98
	Bile duct/gallbladder	11	2.14[b]	0.79–4.66	1.00	0.32–2.33		1.41	0.70–2.52
	Pleura	4	3.12[a]	0.85–8.00	0.00	0.00–13.2		2.57[b]	0.70–6.57
	Melanoma	39	1.24	0.73–1.95	1.34	0.83–2.04		1.29[b]	0.92–1.76
	Leukemia	8	1.57	0.51–3.66	1.05	0.22–3.06		1.32[b]	0.57–2.60
CNS tumor	Prostate	61	0.93	0.71–1.19	—	—		0.93	0.71–1.19
	Breast	89	2.40	0.06–13.4	1.26[a]	1.01–1.55		1.27[a]	1.02–1.56
	Lung	34	0.98	0.59–1.53	1.20	0.67–1.97		1.06	0.74–1.49
	Pharynx	6	2.73[a]	0.89–6.37	1.38	0.03–7.68		2.35[a]	0.86–5.11
	Esophagus	8	2.14[b]	0.79–4.66	1.89	0.23–6.84		2.07[a]	0.89–4.08
	Colon	49	0.78	0.42–1.34	2.01[a]	1.41–2.78		1.42[a]	1.05–1.87
	Pancreas	18	2.04[a]	1.05–3.56	1.08	0.40–2.35		1.57[a]	0.93–2.49
	Kidney	19	1.18	0.54–2.24	1.94[a]	0.93–3.57		1.49[b]	0.89–2.32
	Hodgkin	5	3.34[a]	1.08–7.78	0.00	0.00–3.38		1.93	0.63–4.50
	Leukemia	8	1.43	0.29–4.17	2.61[a]	0.85–6.09		1.99[b]	0.86–3.92
Lymphoma	Prostate	49	1.19	0.88–1.58	—	—		1.19	0.88–1.58
	Breast	32	4.01	0.10–22.3	0.76	0.52–1.08		0.78	0.54–1.11
	Lung	19	0.76	0.35–1.44	1.38	0.66–2.53		0.99	0.60–1.55
	Colon	30	1.47[b]	0.83–2.43	1.48[b]	0.83–2.45		1.48[a]	1.00–2.11
	Bile duct/gallbladder	7	4.39[a]	1.43–10.3	1.05	0.13–3.79		2.30[a]	0.92–4.74
	Ovary	12	—	—	1.86[a]	0.96–3.24		1.86[a]	0.96–3.24
	Testis	6	3.10[a]	1.14–6.74	—	—		3.10[a]	1.14–6.74
	Kidney	13	1.29	0.47–2.81	2.39[a]	0.96–4.92		1.71[a]	0.91–2.93
	CNS	17	1.67	0.67–3.45	2.17[a]	1.04–4.00		1.94[a]	1.13–3.10
	Myeloma	6	2.47[b]	0.80–5.77	0.66	0.02–3.66		1.69	0.62–3.68
Sarcoma	Prostate	42	1.07	0.77–1.44	—	—		1.07	0.77–1.44
	Breast	40	0.00	0.00–14.9	1.00	0.71–1.36		0.99	0.71–1.35
	Lung	24	1.36	0.78–2.21	1.12	0.49–2.21		1.27	0.81–1.89
	Skin	16	1.51[b]	0.83–2.54	0.29	0.04–1.06		0.99	0.57–1.61
Other	Prostate	59	1.05	0.80–1.36	—	—		1.05	0.80–1.36
	Breast	48	0.00	0.00–10.6	0.83	0.61–1.10		0.82	0.61–1.09
	Lung	39	1.15	0.69–1.8	1.9[a]	1.16–2.94		1.44[a]	1.03–1.98
	Colon	39	0.99	0.54–1.66	1.72[a]	1.11–2.53		1.36[a]	0.96–1.85
	Skin	2	1.26	0.75–2.00	1.38	0.73–2.36		1.31[b]	0.89–1.86
	Urinary tract	26	1.53[a]	0.96–2.32	0.79	0.21–2.02		1.34[b]	0.87–1.96
	Non-Hodgkin	17	1.19	0.52–2.35	1.7[b]	0.78–3.22		1.42	0.82–2.27
	Hodgkin	5	3.15[a]	0.86–8.07	1.1	0.03–6.14		2.3[b]	0.75–5.36

Note: Prostate, breast, and lung cancer and cancer types with at least one *P* value <0.1 are presented.
Abbreviation: SH, sex heterogeneity.
[a]$P < 0.05$.
[b]$P < 0.1$.

children with cancer (**Table 2**). The cancer risk in the GI tract was independent of the degree of relation, gender, or diagnosis of the child with cancer, but relatives of children with CNS tumors and leukemia were particularly at risk. Pathogenic germline variants in the *APC* gene has been associated with an increased risk for medulloblastoma in children as well as for colorectal cancer in adults (31), and future sequencing studies might reveal additional pathogenic variants behind these associations.

Pediatric rhabdomyosarcoma, CNS tumors, and skin cancer are associated with increased risk of breast cancer in adult relatives (8, 11, 12). We indeed observed an increase in the risk of breast cancer among female relatives of children with CNS tumors (SIR 1.27, $P = 0.02$; **Table 5**). Compared with relatives of children with any other cancer diagnosis, we observed a SIR of 1.49 and a three-fold higher risk in first-degree relatives to children with CNS tumors (SIR 3.34). The relatively low number of children with CNS tumors in the current

Table 6. Adult cancers in first-degree relatives of patients with pediatric cancer.

Age at diagnosis of child		*n*	Men		Women		SH	All relatives	
			SIR	95% CI	SIR	95% CI	*P*	SIR	95% CI
0–5 years of age	Any cancer	65	1.59[a]	1.10–2.22	1.27	0.86–1.80	0.56	1.42[a]	1.10–1.81
>5 years of age	Any cancer	89	0.94	0.66–1.30	1.27[b]	0.95–1.66	0.35	1.11	0.89–1.36
0–5 years of age									
	Prostate	6	1.14	0.42–2.48	—	—		1.14	0.42–2.48
	Breast	11	0.00	0.00–98.5	1.26	0.63–2.26		1.26	0.63–2.25
	Lung	5	0.86	0.02–4.77	3.76[a]	1.02–9.62		2.24[b]	0.73–5.23
	Mouth	3	7.82[a]	0.95–28.27	6.66	0.17–37.1		7.39[a]	1.52–21.6
	Pharynx	3	11.8[a]	2.43–34.50	0.00	0.00–40.2		8.68[a]	1.79–25.4
	Liver	2	3.91	0.10–21.81	9.27	0.23–51.7		5.50[b]	0.67–19.9
	Urinary tract	3	2.79[b]	0.58–8.16	0.00	0.00–11.0		2.13	0.44–6.22
	Melanoma	7	1.82	0.38–5.33	1.97	0.54–5.04		1.90[b]	0.77–3.92
	Non-Hodgkin	4	2.19	0.27–7.93	3.50	0.42–12.6		2.70[b]	0.73–6.91
>5 years of age									
	Prostate	10	0.94	0.45–1.73	—	—		0.94	0.45–1.73
	Breast	17	0.00	0.00–56.7	1.14	0.66–1.82		1.13	0.66–1.81
	Lung	4	0.43	0.01–2.38	1.53	0.32–4.48		0.93	0.25–2.38
	Esophagus	1	0.00	0.00–8.80	9.88[b]	0.25–55.1		1.92	0.05–10.7
	Pancreas	2	0.00	0.00–5.19	3.95[b]	0.48–14.3		1.64	0.20–5.93
	Cervix	7	—	—	3.71[a]	1.49–7.64		3.71[a]	1.49–7.64
	Testis	4	2.50[b]	0.68–6.41	—	—		2.50[b]	0.68–6.41
	CNS	7	1.08	0.13–3.91	2.66[a]	0.86–6.21		1.88[b]	0.75–3.87
	Hodgkin	3	2.14	0.05–11.92	5.48[b]	0.66–19.8		3.61[b]	0.74–10.5
	CLL	2	5.46[b]	0.66–19.72	0.00	0.00–22.3		3.76	0.46–13.6

Note: Prostate, breast, and lung cancer and cancer types with at least one *P* value <0.1 are presented.
Abbreviations: CLL, chronic lymphocytic leukemia; SH, sex heterogeneity.
[a]$P < 0.05$.
[b]$P < 0.1$.

cohort could explain the lack of overall increased breast cancer risk among first-degree relatives. Specific pathogenic germline variants are associated with increased risk for both pediatric CNS tumors and breast cancer, such as variants in *TP53, BRCA2, BRCA1*, and *APC* (31, 32). However, in the present cohort, these variants were identified in a minority of the patients with childhood cancer ($n = 12$). Hence, the increased risk of breast cancer in relatives of children with CNS tumors is more complex than current knowledge can explain.

When dividing the relatives according to gender, we found that first-degree female relatives had an increased risk of cancer of any kind, but this was not seen in second- or third-degree female relatives. An increased risk of cancer in first-degree female relatives has been reported previously (10–12), often related to the increased risk of breast cancer (11, 12). Studies reporting no increased risk still indicated a higher risk of cancer in women than in men (18, 33). A total of 55% of first-degree female relatives in the study cohort were mothers to pediatric cancer patients. Parous women have lower risk for cancer, especially for breast cancer (34, 35), which might affect the reported results in this study.

In this study, we found that the overall relative risk in first- to third-degree relatives was higher in men than in women (SIR 1.14 and 1.05, respectively); however, the difference was not significant. Moreover, we found that third-degree male relatives had a higher overall cancer risk than women (**Table 3**), although not statistically significant. This tendency could be due to the protective effect of female sex hormones, as discussed in the case of colorectal cancer (36). Another explanation could be that men and women are exposed to environmental factors to different degrees, or that one gender is more susceptible to them than the other.

We observed a difference between women and men regarding cancer types associated with increased risk. Women showed increased risks of colon, lung, and kidney cancer, while in men the risks of pharynx, esophagus, and biliary tract/gallbladder cancer and Hodgkin disease were increased (**Table 2**). Differences between the genders were also seen when subcategorizing according to degree of relation, gender of the child with cancer, and pediatric cancer diagnosis (**Tables 3–5**). These findings are intriguing, and indicate that there may be gender differences in cancer vulnerability in families with pediatric cancer.

The current data suggest that the risks of cancer in male and female relatives of patients with pediatric cancer differ depending on the characteristics of the child. Male relatives were found to have a higher risk of cancer if the patient with pediatric cancer was female and/or the child had leukemia, while female relatives did not. In a previous study, we showed that children with leukemia in families with more than one case of pediatric cancer were likely to be related to another child with leukemia (69%) and that 77% of all leukemia cases were girls (27). In this larger cohort, we confirm that 56% of patients with leukemia in FAM>1 had a relative with leukemia and that 69% of the patients with leukemia were girls. However, no general increase in cancer risk was found in adult women in these families compared with the general population. The observation that the gender of a child with cancer affects the risk of cancer in relatives has not been described previously, and these results will have to be independently validated.

The diagnostic group of the child did not affect the overall adult cancer risk among relatives. However, there was a clear gender difference in risk between relatives of children with leukemia; women showed no increased risk whereas men did (SIR 0.96 and 1.15, respectively, $P = 0.01$; **Table 5**). Relatives of children with sarcoma

indicated a similar increased risk for men, while relatives of children with CNS tumors or lymphoma did not (**Table 5**). Families with cases of pediatric leukemia were the only ones to show an increased risk of prostate and lung cancer. Families with cases of pediatric CNS tumors were the only ones to show an increased risk of acute leukemia, breast cancer and pancreatic cancer. Furthermore, families with cases of pediatric lymphoma were the only ones to show an increased risk of ovarian or testicular cancer and CNS tumors. Relatives of children with sarcoma showed unexpectedly the lowest overall cancer risk, currently we cannot explain this observation.

No significant difference was observed in the cancer risk between first-degree relatives of children diagnosed with cancer before or after 5 years of age. Thus, we could not confirm the observations of Goldgar and colleagues or Friedman and colleagues (17, 18). However, first-degree relatives of children diagnosed before 5 years of age did show an increased risk of adult cancer when compared with the general population (**Table 6**), while relatives of children diagnosed later did not. The smaller cohort in our study could explain why we did not observe a significant difference when comparing the two groups.

We have previously observed differences in pediatric cancer characteristics in families with one (FAM1) or more (FAM>1) pediatric cancers (27), and used this here as a variable to study adult cancer in relatives of children with cancer. In the current cohort, 9.8% of the families were FAM>1, which is in accordance with our previous study, where we found a value of 8.8% (27). There was no differences between FAM>1 and FAM1 in the distribution of cancer diagnoses or age at onset for adult relatives (Supplementary Table S1). Adult relatives in FAM>1 showed no increased risk of adult cancer of any type up to the third degree of relation (SIR 1.00), compared with the general population, however, the FAM>1 group of 74 families might be too small to detect significant differences in cancer incidence.

In a parallel study, most of the children in this LCCG cohort were tested for 22 of the most common autosomal dominant germline mutations among pediatric cancers. When families to children with positive germline mutations and those not tested were excluded, an increased cancer risk remained, (SIR 1.07, 95% CI: 1.02–1.11, $P < 0.01$). Thus, known cancer predisposition germline mutations do not explain the increased risk of cancer among adult relatives of children with cancer. Future extended analysis with "Trio-Sequencing," i.e., germline sequencing of parents and child might identify combinational effect of inherited risk variants in the same signalling pathway in children with cancer (37).

In conclusion, relatives of children with cancer have an increased cancer risk when compared with the general population of Sweden, which cannot be explained by currently known cancer predisposition germline variants. Moreover, this risk extends to adults up to the third degree of relation, where mainly male relatives are at risk. The risk in adults was primarily increased for cancer of the GI tract, lungs, and prostate. Men and women showed distinct differences in the cancer types with increased risk. Furthermore, the gender of the child with cancer affected the cancer risk of male relatives, but not female relatives. The study strengthens the importance of surveillance programs for families with pediatric cancer.

Disclosure of Potential Conflicts of Interest

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Authors' Contributions

K.-J. Stjernfelt: Data curation, formal analysis, funding acquisition, investigation, visualization, methodology, writing–original draft, project administration. **K. von Stedingk:** Resources, data curation, formal analysis, supervision, investigation, writing–review and editing. **T. Wiebe:** Conceptualization, supervision, validation, writing–review and editing. **L. Hjorth:** Conceptualization, resources, validation, writing–review and editing. **U. Kristoffersson:** Resources, validation, writing–review and editing. **M. Stenmark-Askmalm:** Validation, writing–review and editing. **H. Olsson:** Conceptualization, resources, supervision, funding acquisition, investigation, project administration, writing–review and editing. **I. Øra:** Conceptualization, resources, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

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