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Risk of Cancer Among Children of Cancer Patients - A Nationwide Study in Finland

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Abstract

Cancer treatments have the potential to cause germline mutations that might increase the risk of cancer in the offspring of former cancer patients. This risk was evaluated in a population-based study of early onset cancer patients in Finland.

Using nationwide registry data, 26,331 children of pediatric and early onset cancer patients (diagnosed under age 35 between 1953 and 2004) were compared to 58,155 children of siblings. Cancer occurrence among the children was determined by linkage with the cancer registry, and standardized incidence ratios (SIRs) were calculated comparing the observed number of cancers with that expected, based on rates in the general population of Finland.

Among the 9877 children born after their parent's diagnosis, cancer risk was increased (SIR 1.67; 95% CI 1.29–2.12). However, after removing those with hereditary cancer syndromes, this increase disappeared (SIR 1.03; 95% CI 0.74–1.40). The overall risk of cancer among the offspring of siblings (SIR 1.07; 95% CI 0.94–1.21) was the same as among the offspring of the patients with non-hereditary cancer. Risk of cancer in offspring born prior to their parents cancer diagnosis was elevated (SIR 1.37, 95% CI 1.20–1.54), but removing hereditary syndromes resulted in a diminished and non-significant association (SIR 1.08, 95% CI 0.93–1.25).

This study shows that offspring of cancer patients are not at an increased risk of cancer except when the patient has a cancer-predisposing syndrome. These findings are directly relevant to counseling cancer survivors with regard to family planning.

Keywords

Offspring; cancer survivors; genetic effects

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Using registry linkage, we studied the risk of cancer in the offspring of early onset cancer patients. The results will provide cancer survivors with guidance for family planning and thus contribute meaningfully to their quality of life.

Introduction

With improvements in cancer diagnostics and treatment in the last few decades, the overall 5-year survival after cancer has reached 81% for children and 87% for adolescents and young adults1. This growing population of long-term cancer survivors highlights the need to search for deleterious effects of treatment on adult health, including the reproductive system. Many cancer types and their treatment do not affect fertility, while others cause reduced fertility or infertility. For the latter group, fertility sparing techniques such as protecting the gonads (oophoropexy and testicular shielding) during radiotherapy and modification of gonadotoxic adjuvant therapies, have been developed. These techniques together with current assisted reproductive technologies, have made parenthood possible for cancer survivors2. Consequently, there is increased interest in the potential trans-generational effects of treatments. To date, however, there are no indications of increased risk of cancer among children of cancer survivors when hereditary cancer syndromes are excluded3, 4.

Although radiation and chemotherapeutic agents have been found to cause germ cell mutations in animal models, cancer treatments have not to date been found to cause germ cell mutations or genetic disease in the offspring of cancer survivors5. Radiation-induced genetic diseases have not so far been demonstrated in humans and estimates of population risk are based largely on mouse experiments6. Japanese atomic bomb survivors have no significantly increased risk of indicators of germ cell mutagenesis7–9. Failure to detect human germ cell mutagenic effects may be a consequence of inadequate study sizes10 or perhaps ‘biological filtration’, a phenomenon where the mammalian organism can eliminate serious chromosome abnormalities or lethal mutations early in pregnancy and, therefore, result in surviving offspring that have a normal or background incidence of birth defects or genetic disease11.

Cancer survivors offer the largest group of people of reproductive age exposed to a relatively wide range of ionizing radiation doses to the gonads as well as to genotoxic chemotherapeutic agents12. High doses of ionizing radiation and chemotherapy used for childhood and young adult cancers cause somatic cell mutations that elevate the risk of second malignant neoplasms among survivors13–15. However, there is little understanding of the genetic consequences of these treatments or whether treatment induced germ cell mutations will affect the health of the offspring. Few studies exist on the possible mutagenic effects of cancer therapy16, 17. Previous studies focused on small subgroups of patients, with a short follow-up. Sex ratio18, 19, congenital malformations20, 21, stillbirths8, 22, and neonatal deaths23 have been used as measures of genetic damage in the next generation. Cancer is one of the possible indicators of genetic effects in offspring3, 4, 24–26.

Cancer survivors have concerns that their children may be at an elevated risk of cancer27, 28. According to one survey, nine percent of cancer survivors reported this fear as the reason for not having children29. Young women who have survived cancer appear to be overly concerned about the possible risk of birth defects and cancer in their children27. Thus, the health of offspring is an important factor influencing family planning and reproductive choices of cancer survivors.

In this nationwide population-based cohort study, using the comprehensive population and health registries in Finland, we asked whether or not treatments received by childhood and early adulthood cancer patients had an effect on the risk of cancer among their offspring. Methodological strengths of our approach are the exclusion of hereditary cancer syndromes from the risk estimates, the inclusion of young adulthood cancer patients under age 35 at diagnosis and the evaluation of children born before and after cancer treatment.

Material and Methods

Each individual living in Finland since 1 January 1967 has a unique personal identification number (PIN), which enables merging of data from different registries. In this study, data from two databases provided information on patients, siblings, and their offspring.

Finnish Cancer Registry

The Finnish Cancer Registry (FCR), founded in 1952, started systematical registration in 1953. The FCR is population-based, nationwide and almost complete (100% for solid tumors, over 90% for hematological malignancies, and 100% for childhood cancers)30. Linkage to other registries can be conducted using the PIN for persons who were alive in 1967 or born after that.

Central Population Register

The Population Register Centre hosts a nationwide central population register (CPR) which includes the name and former names, PIN, municipality of birth and residence, date of emigration, or date of death of each individual living in Finland and alive in 1967 or born thereafter. Within the CPR, individuals can be linked to their parents and to their offspring. Linking an individual to his/her parents allows the identification of his/her siblings. Links to siblings are reliably available for persons born after 1955 and alive in 1967. Links to offspring, including legal children of males, are randomly available for children born after 1940 and systematically for children born after 1955 and alive in 1967.

Patients and Their Offspring

The cohort of 25,784 patients diagnosed with cancer between 1953 and 2004 and aged 0 to 34 years at diagnosis, was identified from records of the FCR. Of childhood cancer patients (aged 0–14 years at diagnosis, N = 6070), 2801 attained age of fertility (16 years). Among those who did not reach the age of fertility, 1991 died before the age of 16 and 1278 had insufficient length of follow-up. Including pediatric and early onset patients (aged 15–34 years at diagnosis), a total of 22,465 (87%) patients were followed up for live-born offspring. Of this cohort, 12,735 patients parented a child either before diagnosis, after diagnosis or within 9 months of diagnosis (in order to include those women exposed to cancer treatments during pregnancy). Of the survivors who parented offspring, 825 were former childhood cancer survivors.

The proportion of patients parenting children at any time in relation to their cancer diagnosis is shown in Table 1. A cohort of 26,331 offspring of pediatric and early onset cancer patients was identified using data from the CPR.

Siblings and Their Offspring

By further linkage to the CPR, siblings of cancer patients and the siblings' offspring were identified. In total, 44,611 siblings (99%) attained reproductive age (16 years). Of them, 386 siblings with early onset cancer were only included in the patient cohort. During the study period, 25,827 siblings (58%) (12,454 brothers and 13,373 sisters) had children. A cohort of 58,155 offspring of siblings free of cancer was identified as the comparison cohort.

Follow-up for Death, Emigration and Cancer

After identification of both offspring cohorts from the CPR, the vital status was checked for every cohort member, and the cohorts were followed up through the FCR for cancer incidence during 1972–2006. The follow-up ended on the date of death or emigration or the closing date of the study, December 31, 2006. Person-years were counted accordingly. Due

to the identification process of the sibling cohort, the age distribution of offspring of siblings is different from that of the offspring of patients. This, however, does not influence the age- and sex-specific cancer risk estimates.

The malignant neoplasms of the offspring were classified according to the International Classification of Childhood Cancer31. Multiple primary neoplasms present in one child were considered separate cancers. Clinical details of the cancers of the survivor parents and of the offspring were based on FCR data including histology of tumors.

Statistical Analyses

The numbers of observed cases and person-years at risk were counted, by five-year age groups and gender, separately for 5 calendar periods: I) 1972–1978, II) 1979–1985, III) 1986–1992, IV) 1993–1999 and V) 2000–2006. The expected numbers of cases for total cancer and for specific cancer types were calculated by multiplying the number of person-years in each age group and gender by the corresponding average cancer incidence in all of Finland during the period of observation. The standardized incidence ratio (SIR) was calculated by dividing the observed number of cases of cancer (specific for sex, age and calendar year) in the cohort by the expected number. The 95% confidence intervals (CI) for the SIR were based on the assumption that the number of observed cases followed a Poisson distribution. SIRs were calculated for all cancer cases as well as for sporadic cancers only. SIRs for sporadic cancer were calculated by removing the identified hereditary cases.

The offspring of cancer patients were classified according to their date of birth relative to their parent's diagnosis as follows: I) born before; II) born within 9 months and III) born over 9 months after diagnosis. SIRs were calculated for each group separately as well as for all offspring of patients together. For the group of offspring born after their parent's diagnosis, separate analyses were conducted by primary site and gender of the patient parent as well as by radiotherapy treatment (Yes/No).

Identification of Hereditary Cancer Cases

According to a recent comprehensive review, fifty-four hereditary cancer syndromes have been established32. Most of these cancer susceptibility syndromes are autosomal dominant, such as neurofibromatosis 1 and 2, von Hippel-Lindau disease, hereditary breast and ovarian cancer, Li-Fraumeni syndrome and retinoblastoma32. As our aim was to evaluate the risk of sporadic cancer in the offspring of sporadic cancer patients, we first identified all known cancer syndromes among the offspring and their parents. For all parent-offspring pairs in which both the parent and the child had cancer, histology was checked from pathology reports and pedigrees were constructed to identify possible familial cancer susceptibility syndromes. For parent-offspring pairs suggestive of Li-Fraumeni-like syndrome, pedigrees were constructed and the grandparents were checked for neoplasms confirmatory of Li-Fraumeni syndrome. In the case of pairs in which the offspring of a patient was diagnosed with cancer, also the offspring of siblings were identified to spot possible syndromes of incomplete penetrance. However, we did not identify any affected offspring among the children of these siblings and therefore, no hereditary cases were identified among the siblings' offspring. Thus, the analysis of sibling offspring was restricted to non-hereditary cancer risk.

Appendix A shows clinical details of parent-offspring pairs for offspring born >9months after diagnosis and grounds for exclusion of hereditary cases. Similar criteria were used to identify hereditary cases among offspring born before and within 9 months of their parent's diagnosis.

Results

There were at total of 26,331 patients' and 58,155 siblings' offspring under follow-up. The numbers of person-years were 560,611 and 998,517 for offspring of patients and siblings, respectively. The incidence rates for all sites combined was not elevated among the offspring of siblings, SIR 1.07 (95% CI 0.94–1.21), whereas the overall risk of cancer among patients' offspring was elevated, SIR 1.43 (1.27–1.59) (Table 2). After excluding hereditary cases, the risk dropped to SIR 1.08 (0.94–1.22).

Offspring Born Post-Diagnosis

In the cohort of offspring of former cancer patients born >9 months after diagnosis, there were 5113 males and 4764 females under follow-up. The numbers of person-years were 76,541 and 70,253, respectively and the mean length of follow-up of an offspring was 14.9 years.

Overall, 65 cases of cancer were diagnosed in the offspring of former cancer patients born >9 months after their parents' diagnosis (SIR 1.67, 95% CI 1.29–2.12) (Table 3). The incidence for cancers of the brain and central nervous system (SIR 2.27, 95% CI 1.37–3.55) and retinoblastoma (SIR 8.98, 95% CI 2.91–20.94) were significantly elevated.

After excluding 25 cases of cancer with a probable hereditary cancer component (Appendix A), there were 40 sporadic cancers left, resulting in an SIR of 1.03 (95% CI 0.74–1.40) (Table 3).

Even after excluding the hereditary cases, a slightly elevated, though non-significant risk was visible for leukemia (SIR 1.68, 95% CI 0.84–3.01) and brain and central nervous system tumors (SIR 1.20, 95% CI 0.58–2.21) (Table 3). Among the 15 parental cancer categories evaluated (Table 3), elevated cancer risks in offspring were seen for 6 and decreased risks for 9, a distribution consistent with the play of chance.

Gender, Diagnostic Age of Parent, Radiotherapy and Primary Site

Gender of the parent (female SIR 1.09 95% CI 0.69–1.65 and male SIR 0.97 95% CI 0.57–1.52) did not influence the risk of cancer in the offspring cohort (data not shown). Age of parent at diagnosis did not affect the risk of cancer after the exclusion of the hereditary syndromes (data not shown). Radiotherapy did not affect the risk (SIR 0.91 95% CI 0.51–1.49). Considering all sites, sporadic cancer risk in offspring was not affected by the primary site of the parent. Although diagnosis of Hodgkin lymphoma in the parent did not significantly increase the overall risk of all cancers in offspring (n=6, SIR 1.42, 95% CI 0.52–3.09), the risk of thyroid cancer was significantly elevated in their offspring (n= 2, SIR 9.65, 95% CI 1.17–34.84).

Offspring born within 9 months

Among the 746 offspring born within 9 months of their parent's diagnosis, there were 8 malignant neoplasms diagnosed, of which 6 were sporadic. One woman diagnosed at the age of 37 years with both an endometrial adenocarcinoma and an adenocarcinoma of the transverse colon was removed as a hereditary case due to hereditary non-polyposis colorectal cancer syndrome, as the father had also been diagnosed with adenocarcinoma of the transverse colon at 32 years of age. The overall risk of sporadic cancer in this subgroup was not significantly elevated (SIR 1.23, 95% CI 0.45–2.67).

Offspring born before diagnosis

Among the 15,708 children born before their parent's diagnosis, there were a total of 232 malignant neoplasms, of which 183 were identified as sporadic. The overall risk of cancer was significantly elevated (SIR 1.37, 95% CI 1.20–1.54) (Table 4). However, removing the 49 hereditary cases, greatly diminished the elevation in the risk (SIR 1.08, 95% CI 0.93–1.25). Among sporadic cases, it appeared that only the risk of thyroid cancer was significantly elevated (SIR 1.80, 95% CI 1.05–2.88) among offspring born before their parent's diagnosis. All 17 sporadic cases of thyroid cancer among the offspring were either papillary (n=15), follicular (n=1) or medullary (n=1) adenocarcinomas. The distribution of malignancies in their parents was heterogeneous.

Offspring of siblings

Among the offspring of siblings, there was no significant increased risk of overall cancer (SIR 1.07, 95% CI 0.94–1.21). In the primary site-specific analyses, no statistically significantly increased risk of cancer was observed (data not shown).

Discussion

In this population-based study, we found no increase in the risk of sporadic cancer among the children of survivors of non-hereditary cancer. The risk among the offspring of survivors was also similar to that of the offspring of their healthy siblings. Cancer risk in the offspring born after their parent's diagnosis was similar to that in offspring born prior to the diagnosis. Among offspring born after their parent's cancer diagnosis, neither radiotherapy treatment of the parent nor the primary site could be shown to elevate the risk of cancer in offspring. In addition, offspring born within 9 months of the parent's cancer diagnosis, (for female survivors, thus, possibly exposed to cancer treatments in-utero; and for males possible exposure during sperm maturation), the risk of cancer in offspring was not found to be elevated compared to that of the general population.

Our study cohort consisted of all offspring of pediatric and young adult cancer patients diagnosed between 1953 and 2004. The offspring of cancer-free siblings were also used as one comparison group. The follow-up for cancers in offspring began from January 1, 1972. After that, the identification of cohort members and follow-up for deaths and emigration are complete for the period of this study, up to the end of 2006. The cancer registration system in Finland is also virtually complete30 and the computerized record linkage procedure is exceptionally precise. Therefore, methodological deficiencies in the registration or linkage procedures are unlikely to have biased study results.

One population based study on the risk of cancer in offspring of cancer survivors is cited in the literature3. This Nordic study included 5847 offspring of 14,652 pediatric and adolescent cancer survivors, who were followed up to 1994. In this Nordic study, hereditary cancer syndromes were removed, however full pedigrees were not constructed. For this reason, all hereditary syndromes could not be identified and removed from sporadic risk calculations. The authors found the risk of cancer in offspring to be slightly elevated (SIR 1.3, 95% CI 0.8–2.0), however non-significant. The results of our study are in agreement with this study.

The large sample size and long follow-up, enabled by population-based registry linkage, are further strengths of our study. Young adults diagnosed with cancer at ages 20–34 are often overlooked in studies of late effects and their inclusion provides new knowledge on an understudied group of patients. In principal, their gonadal doses can approach the maximum tolerated without infertility12. Thus, we have been able to evaluate a wide and severe range of potentially mutagenic exposures.

Limitations include our likely inability to identify all hereditary cancer syndromes, both known and unknown, which may have contributed to the slight, though nonsignificant, elevation in offspring cancer risk. Further, actual gonadal doses from radiotherapy or cumulative doses of chemotherapy were not known for individual patients which tempers somewhat our conclusions regarding the absence of an effect from these mutagenic exposures. Nonetheless, it is clear that in a study of cancer in the children of patients that spanned over 50 years in an entire nation, there was little evidence for increased risks and greater than 1.2-fold risks could be excluded with 95% confidence.

Siblings of cancer patients offered an additional comparison group to that of the general population of Finland and results are in agreement in providing little evidence for an increase in cancer risk among the children of cancer survivors. The elevated risk of thyroid cancer among the offspring could be due to increased surveillance activity leading to overdiagnosis of microcarcinomas of the thyroid.

In conclusion, offspring of childhood and early onset sporadic cancer survivors had similar cancer patterns as the general population and their siblings. This result is reassuring in that it implies that cancer treatments per se had little if any effect on risk of cancer in the children of cancer survivors. The results of this study can be used in counseling of cancer survivors in the setting of family planning.

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Table 1

Numbers of parents and offspring (born before, within 9 months and more than 9 months after their parents' diagnosis) according to the primary site of cancer of the parent.

				Offspring born		
Primary Site of Parent	**Patients**	**Parents**	**Offspring**	**before**	**within 9 months***	**after**
Leukemia	3028	581	1064	609	37	418
Lymphomas						
Hodgkin lymphoma	2151	1101	2164	997	82	1085
Non-Hodgkin lymphoma	1542	686	1393	765	48	580
Central nervous system	3811	1411	2762	1592	85	1085
Sympathetic nervous system	435	60	127	35	2	90
Retinoblastoma	187	48	92	0	0	92
Renal tumours	582	208	432	211	3	218
Hepatic tumours	166	54	112	100	2	10
Malignant bone tumours	815	332	724	272	18	434
Soft-tissue sarcomas	1874	979	2063	1021	55	987
Germ cell, trophoblastic and other gonadal neoplasms						
Testes	1273	646	1250	617	65	568
Ovary	713	348	673	450	18	205
Other germ cell	203	92	196	121	2	73
Carcinomas and other malignant epithelial neoplasms‡						
Thyroid	1724	1232	2779	1527	47	1205
Cervix	707	547	1209	1133	15	61
Uterus	70	21	39	35	0	4
Breast	1710	1289	2569	2245	43	281
Stomach	367	233	470	408	15	47
Colon	918	590	1277	673	45	559
Urinary bladder	166	119	283	161	12	110
Melanoma	1584	1081	2303	1234	83	986
Other carcinomas	1423	891	1944	1254	60	630

				Offspring born		
Primary Site of Parent	**Patients**	**Parents**	**Offspring**	**before**	**within 9 months***	**after**
Other and unspecified malignant neoplasms	335	186	406	248	9	149
Total	25,784	12,735	26,331	15,708	746	9,877

*Includes offspring of male and female patients.

‡The carcinomas and other malignant neoplasms group is further divided into major subsites to account for the different malignancy patterns among young adults.

Table 2

Standardized incidence ratios (SIR) for overall cancer among offspring born at different time-points relative to their parent's cancer diagnosis, as well as among offspring of sibs

	Offspring of Patients								Offspring of Siblings			
	All cases				Sporadic							
	Obs	Exp	SIR	95% CI	N	Exp	SIR	95% CI	N	Exp	SIR	95% CI
All offpsring	305	213.7	1.43	1.27–1.59	229	212.61	1.08	0.94–1.22	239	222.67	1.07	0.94–1.21
Born after diagnosis	65	38.95	1.67	1.29–2.12	40	38.76	1.03	0.74–1.40				
Born after diagnosis	8	4.92	1.63	0.70–3.20	6	4.89	1.23	0.45–2.67				
Born before diagnosis	232	169.84	1.37	1.20–1.54	183	168.97	1.08	0.93–1.25				

Table 3

Standardized incidence ratios (SIRs) with 95% confidence intervals (CI) for malignant neoplasms, including and excluding hereditary cases, observed among offspring born >9 months after parent's cancer diagnosis.

PRIMARY CANCER AMONG OFFSPRING	OFFSPRING BORN >9 MO AFTER DIAGNOSIS							
	All cases				Sporadic cases			
Primary site	**Obs**	**Exp**	**SIR**	**95% CI**	**Obs**	**Exp**	**SIR**	**95% CI**
Person-years			146794				146352	
All sites	65*	38.95	1.67	1.29–2.12	40*	38.76	1.03	0.74–1.40
Leukemia	11	6.55	1.68	0.84–3.00	11	6.54	1.68	0.84–3.01
Non-Hodgkin lymphoma	2	2.51	0.80	0.10–2.87	2	2.50	0.80	0.10–2.89
Hodgkin lymphoma	2	2.35	0.85	0.10–3.07	1	2.34	0.43	0.01–2.38
Brain and CNS	19	8.36	2.27	1.37–3.55	10	8.33	1.20	0.58–2.21
Neuroblastoma	1	1.17	0.86	0.02–4.76	1	1.17	0.86	0.02–4.77
Eye	5	0.56	8.98	2.91–20.94	0	0.56	0	0–6.64
Kidney	2	1.43	1.40	0.17–5.04	0	1.43	0	0–2.58
Liver	1	0.33	2.99	0.08–16.66	1	0.33	3.00	0.08–16.73
Bone	1	0.81	1.24	0.03–6.88	1	0.81	1.24	0.03–6.90
Soft tissues	3	1.12	2.68	0.55–7.84	1	1.11	0.90	0.02–5.00
Thyroid gland	4	1.82	2.19	0.60–5.61	3	1.81	1.65	0.34–4.83
Skin, non-melanoma	1	0.37	2.71	0.07–15.11	0	0.37	0	0–10.06
Breast	5	3.19	1.57	0.51–3.66	3	3.15	0.95	0.20–2.78
Testis	3	1.77	1.70	0.35–4.95	3	1.76	1.70	0.35–4.97
Colon and rectum	2	1.55	1.29	0.16–4.66	1	1.54	0.65	0.02–3.62

*All sites includes 2 sporadic tumors of 'Other sites': 1 stomach and 1 urinary bladder. Additionally there is one hereditary case of cortical carcinoma of the adrenal gland in a survivor-offspring pair with Li Fraumeni syndrome.

Table 4

Standardized incidence ratios (SIRs) with 95% confidence intervals (CI) for malignant neoplasms, including and excluding hereditary cases, observed among offspring born before diagnosis.

PRIMARY CANCER AMONG OFFSPRING	OFFSPRING BORN BEFORE DIAGNOSIS							
	All cases				Sporadic cases			
Primary site	**Obs**	**Exp**	**SIR**	**95% CI**	**Obs**	**Exp**	**SIR**	**95% CI**
Person-years		398558				397432		
All sites	232*	169.80	1.37	1.20–1.54	183*	168.97	1.08	0.93–1.25
Leukemia	13	13.99	0.93	0.49–1.58	13	13.96	0.93	0.50–1.59
Non-Hodgkin lymphoma	9	9.71	0.93	0.42–1.76	9	9.67	0.93	0.43–1.76
Hodgkin lymphoma	9	8.31	1.08	0.50–2.05	8	8.28	0.97	0.42–1.90
Brain and CNS	46	24.37	1.89	1.38–2.52	33	24.29	1.36	0.94–1.91
Neuroblastoma	1	1.71	0.58	0.01–3.24	1	1.71	0.58	0.01–3.25
Eye	3	1.19	2.52	0.52–7.37	3	1.19	2.53	0.52–7.39
Kidney	7	4.70	1.49	0.60–3.06	5	4.68	1.07	0.35–2.49
Liver	1	1.12	0.90	0.02–4.98	1	1.11	0.90	0.02–5.01
Bone	2	2.67	0.75	0.09–2.70	1	2.66	0.38	0.01–2.09
Soft tissues	9	3.42	2.63	1.20–4.99	7	3.41	2.05	0.83–4.22
Thyroid gland	23	9.50	2.42	1.53–3.63	17	9.45	1.80	1.05–2.88
Skin, melanoma	12	10.03	1.20	0.62–2.08	12	9.98	1.20	0.62–2.10
Breast	30	28.67	1.05	0.71–1.49	21	28.42	0.74	0.46–1.12
Cervix	4	3.59	1.11	0.30–2.84	4	3.57	1.12	0.31–2.86
Ovary	5	4.12	1.21	0.39–2.83	5	4.09	1.22	0.40–2.85
Testis	6	6.51	0.92	0.34–2.00	6	6.49	0.92	0.34–2.01
Colon and rectum	23	9.23	2.49	1.58–3.73	13	9.18	1.42	0.75–2.42

* For sporadic cases 'All sites' included 24 tumors of 'Other sites': 10 lung, 1 stomach, 1 pancreas, 1 malignant neurilemmoma, 1 female external genitalia, 1 vagina, 2 prostate, 4 urinary bladder, 1 malignant pheocromocytoma, 2 unknown primary site. Additionally, there were 5 tumors that were considered hereditary in 'Other sites': stomach, pancreas, uterus, malignant pheocromocytoma, unknown primary site.

Appendix A

Clinical details about survivor parents and offspring born >9months after diagnosis. Comments in bold indicate hereditary cases and criteria for exclusion from sporadic cancer risk estimates.

PAIR No.	PARENT			INTERVAL FROM DIAGNOSIS OF PARENT TO BIRTH OF OFFSPRING (YR)	OFFSPRING			COMMENTS
	Sex	AGE AT DIAGNOSIS (YR)	Primary site and morfology		Sex	AGE AT DIAGNOSIS (YR)	Primary site and morfology	
1	M	14	Nasopharynx, fibrosarcoma	9	M	8	Acute lymphoblastic leukemia	Li Fraumeni-like
		55	Salivary gland, adenocarcinoma					
2	M	31	Chest wall, rhabdomyosarcoma	6	F	10	Non-Hodgkin's lymphoma	Li Fraumeni-like
3	F	17	Leg, osteosarcoma	14	F	6	Acute lymphoblastic leukemia	Li Fraumeni-like
								Familial Hodgkin's lymphoma
4	F	22	I Head/neck, Hodgkin's lymphoma	6	M	15	Head/neck, HD mixed cellularity	**sdr**
		39	II Right breast, ductal ca					
		49	III Stomach, diffuse ca					
5	M	15	Cerebrum, malignant neoplasm	13	M	23	Cerebrum, malignant glioma	
6	M	31	Colon, adenocarcinoma	2	M	36	Colon, adenocarcinoma	**HNPCC**
7	F	6	Cerebrum, malignant glioma	20	M	3	Acute lymphoblastic leukemia	Li Fraumeni-like
8	F	20	Placenta, chorioncarcinoma	5	F	3	Acute lymphoblastic leukemia	
9	M	26	Colon, Adenocarcinoma	2	F	10	Lower limb, osteosarcoma	
		48	Colon, Adenocarcinoma					
10	M	24	Axilla, Hodgkin's lymphoma	5	F	39	Right breast,infiltrating ductal ca	
11	M	30	Acute myeloid leukemia	5	F	11	Cerebellum, medulloblastoma	
12	M	19	Multiple locations, Hodgkin's lymphoma	3	M	12	Cerebellum, medulloblastoma	
13	F	30	Thyroid, papillary adenocarcinoma	2	M	9	Lower limb/hip, synovial sarcoma	
14	F	17	CNS, neurofibroma	7	F	5	Cerebrum,pilocytic astrocytoma GrI	**Neurofibromatosis**
15	M	23	Lymph nodes, Hodgkin's lymphoma	6	M	37	Urinary bladder, papillary urothelial ca	
16	F	24	Right costa, chondrosarcoma	9	M	1	Acute erythroblastic leukemia	Li Fraumeni -like
17	M	26	Rectum, adenocarcinoma	6	F	3	Acute lymphoblastic leukemia	
18	F	22	I Upper limb, fibrous histiocytoma	3	M	2	Face, embryonal rhabdomyosarcoma	**Li Fraumeni syndrome**

PAIR No.	PARENT			INTERVAL FROM DIAGNOSIS OF PARENT TO BIRTH OF OFFSPRING (YR)	OFFSPRING			COMMENTS
	Sex	AGE AT DIAGNOSIS (YR)	Primary site and morfology		Sex	AGE AT DIAGNOSIS (YR)	Primary site and morfology	
		28	II Left breast, ductal carcinoma					
19	F	25	Thyroid, follicular adenocarcinoma	1	F	18	Craniopharyngioma	
20	F	20	Colon, carcinoid tumour	11	M	16	Testis, embryonal carcinoma	
21	F	23	I Thyroid, follicular adenocarcinoma	4	M	31	Head/neck, Hodgkin's lymphoma	
		50	II Scalp, basal cell carcinoma					
			I Right breast, ductal carcinoma					
22	F	31,35	II Left breast, ductal carcinoma	4	M	5	Cerebrum, glioblastoma Gr IV	**Li Fraumeni syndrome**
23	F	25	I Skin, fibrosarcoma	7	F	43	Colon, adenocarcinoma	
		70	II Left breast, lobular carcinoma					
24	M	28	Colon, adenocarcinoma	2	M	31	Testis, seminoma+teratoma	
25	F	29	Body, malignant melanoma	2	M	21	Thyroid, papillary carcinoma	
26	M	21	Head/neck, Hodgkin's lymphoma	11	M	4	Acute lymphoblastic leukemia	
27	F	29	Left breast, ductal carcinoma	3	M	1	Left adrenal gland, cortical carcinoma	**Li Fraumeni syndrome**
28	M	20	Leg, osteosarcoma	11	M	4	Left lateral ventricle, epedymoma GrIII	Both parents had cancer
29	F	27	Thyroid, papillary adenocarcinoma	6	F	3	Acute myeloid leukemia	
30	M	5	Retinoblastoma, unilateral	24	M	0	Retinoblastoma, unilateral	**RB**
31	F	34	Thyroid, papillary adenocarcinoma	3	F	4	Cerebellum, pilocytic astrocytoma GrI	
32	F	26	I Left acoustic neurinoma	1	M	30	I Neurinoma	**NF2**
		50	II Right acoustic neurinoma and meningioma			37	II Meningioma	SAME PARENT
32a				2	F	31	I Acoustic nerve, neurilemmoma	**NF2**
						35	II Spine, meningioma	
33	F	29	Thyroid, papillary adenocarcinoma	2	M	21	Trunk, sarcoma	**Li Fraumeni syndrome**
34	F	23	Ovary, fusocellular sarcoma	2	F	47	Meninges, meningioma	**NF1**
35	M	26	Cerebrum, histology unknown	1	M	22	Head/neck, Non-Hodgkin's lymphoma	
36	F	23	I Cerebrum, hemangiosarcoma	2	F	5	Acute lymphoblastic leukemia	
		39	II Eyelid, basal cell carcinoma					

PAIR No.	PARENT			INTERVAL FROM DIAGNOSIS OF PARENT TO BIRTH OF OFFSPRING (YR)	OFFSPRING			COMMENTS
	Sex	AGE AT DIAGNOSIS (YR)	Primary site and morfology		Sex	AGE AT DIAGNOSIS (YR)	Primary site and morfology	
37	M	29	Cerebrum,anaplastic oligodendroglioma	6	F	14	Cerebrum, pleomorphic xanthoastrocytoma	Li Fraumeni like
38	F	25	Right ovary, dysgerminoma	2	F	40	Right breast, infiltrating ductal ca	
39	M	28	Left testicle, seminoma	6	F	0	Neuroblastoma	
40	F	19	Head/neck, Hodgkin's lymphoma	6	F	28	Thyroid, papillary adenocarcinoma	
41	M	26	Colon, carcinoid	4	M	4	Cerebellum, medulloblastoma	
42	F	29	I Colon, carcinoid	4	F	43	Right breast, infiltrating ductal ca	
		52	II Left breast, infiltrating ductal carcinoma					
43		22	Axilla, Hodgkin's lymphoma	1	F	34	Thyroid, papillary adenocarcinoma	
								Hereditary kidney ca
44	F	30	Right kidney, hypernephroma	6	F	24	Right kidney, renal cell adenocarcinoma	**sdr**
45	F	11	Neuroblastoma	15	F	13	Liver, hepatocellular carcinoma	
46	F	5	I Left kidney, Wilms' tumor	13	M	28	Testis, seminoma	
		50	II Small intestine, leiomyosarcoma					
47	F	1	Retinoblastoma, unilateral	36	M	0	Retinoblastoma, laterality unknown	**RB**
48	M	27	Thyroid, medullary carcinoma	8	M	1	Thyroid, medullary carcinoma	**MEN2**
49	F	31	Cerebrum, hemangioma	4	M	17	Cerebrum, cavernous hemangioma	**von Hippel-Lindau**
		51	Cervix, squamous cell carcinoma					
50		3	Retinoblastoma, unilateral	26	M	0	I Retinoblastoma, bilateral	**RB**
50a					M	8	II Left eyelid, sebaceous carcinoma	
51	M	26	Right eye, malignant melanoma	3	F	34	Cerebrum, malignant astrocytoma Gr III	
52	M	0	Retinoblastoma, unilateral	31	M	0	Retinoblastoma, bilateral	**RB**
53	M	32	Cerebrum, malignant glioma	6	F	2	Acute lymphoblastic leukemia	Li Fraumeni like
54	M	23	Trunk, dermatofibrosarcoma	2	F	38	I Right breast, infiltrating ductal carcinoma	**Li Fraumeni syndrome**
					F	40	II Left breast, infiltrating ductal carcinoma	
55	M	24	I Cerebellum and medulla,hemangioblastoma	6	M	27	I Cerebellum, hemangioblastoma	**von Hippel Lindau**

PAIR No.	PARENT			INTERVAL FROM DIAGNOSIS OF PARENT TO BIRTH OF OFFSPRING (YR)	OFFSPRING			COMMENTS
	Sex	AGE AT DIAGNOSIS (YR)	Primary site and morfology		Sex	AGE AT DIAGNOSIS (YR)	Primary site and morfology	
		40	II Kidney, malignant neoplasm, bilateral			27	II Right kidney,clear cell carcinoma	
56	M	1	I Retinoblastoma, unilateral	22	F	0	Retinoblastoma, unilateral	**RB**
		15	II Lower limb, osteosarcoma	8				
57	F	7	Lower limb, Ewing sarcoma	22	M	1	Cerebellum, epedymoma	
58	F	33	I Left breast, carcinoma	6	F	41	Acute myeloid leukaemia	
		65	II Right breast, infiltrating ductal carcinoma					
		67	III Skin, basal cell carcinoma					
59	F	19	Parotid gland, sarcoma	3	F	33	Stomach, mucinous adenocarcinoma	Stomach, mucinous adenocarcinoma