Risk of breast cancer in families of leukemia cases: a population-based study

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Summary
The main aim of this study was to assess whether the incidence of breast cancer was associated with a family history of leukaemia and to provide an in-depth analysis of how the type and subtype of leukemia, age at onset and sex of the proband might affect this incidence. We used Swedish population–based data to assess the risk of breast cancer in 28277 female relatives of 15906 leukemia patients and in 117026 relatives of 58828 matched controls from 1958 through 2001. The Cox regression model was used to evaluate the cause specific hazard of breast cancer in the relatives, adjusting for the disease status of the proband, sex of the proband, birth cohort of the relative and type of relative (mother, sister, daughter). We did not find any strong evidence of a familial association between leukemia and breast cancer (or early breast cancer) for any of the types or subtypes of leukemia. We did however observe a systematically higher breast cancer risk, especially if diagnosed before age 50, in sisters of girls/women with childhood and lymphatic leukemia that might be explained by genetic mutation or susceptibilities common to both cancers.

KEY WORDS: *neoplasm; familial risk; female relatives; family history; susceptibility; population registers.*

Introduction

In the last 20 years a number of studies have investigated the familial association between leukemia and breast cancer. Recently, the Shanghai Women's Health study showed that breast cancer risk was doubled in relatives of leukemia patients (incidence rate ratio=2.06, 95% confidence interval(CI): 1.02-4.15) (1). In a Swedish study investigating the familial association of breast cancer with cancers at other sites (2), results on breast cancer and leukemia were not clear-cut: the study found no increased risk of breast cancer in parents of leukemia probands (standardized incidence ratio (SIR)=1.04, 95%CI: 0.92, 1.16), but did find an increased incidence of early breast cancer (diagnosed before the age of 50), with SIR=1.29 (95%CI: 1.09, 1.5). However, in siblings of leukemia cases, the same study reported a SIR of 1.22 (95%CI: 0.83, 1.72) for breast-cancer and 0.88 (95%CI: 0.37, 1.74) for early breast cancer. From a case-control study in the US, Rauscher et al. (3) reported an association between adult acute leukemia and family history of breast cancer (odds ratio=1.7 95% CI:1.0,3.0), and showed that this association was stronger for earlier-onset cancers of both types. These authors also suggested family history of breast cancer as a possible marker of susceptibility to a range of leukemia risk factors (4). However, within the ESCALE case control study

in France, Rundant et al. did not find an association between childhood leukemia and history of breast cancer in relatives (5).
As far back as 1989, Linet (6) found a significantly higher risk of breast cancer in relatives of chronic lymphatic leukemia (CLL) cases (compared with the risk in relatives of controls). In another study, Pottern (7) found an increased risk of CLL in siblings of breast cancer cases, but no association between breast cancer and the broad class of leukemias. Infante-Rivard (8) observed a higher frequency of breast cancer in second degree relatives of childhood acute lymphatic leukemia (ALL) cases.
The inconsistent results regarding familial association between leukemia and breast cancer may be partly due to many of the studies using case-control designs where the family history of cancer is provided by interview. Furthermore, most of the studies were designed to evaluate the association between breast cancer or leukemia (or its subtypes) with a broad range of cancers in different contexts and populations.
We designed a population-based study specifically to assess whether the incidence of breast cancer was associated with a family history of leukemia, or subtypes of leukemia. The main aim of this study was to provide an in-depth analysis of how the type and subtype of leukemia, age at onset and sex of the proband might affect the risk of breast cancer in first degree relatives of leukemia patients.

Materials and Methods

Data Sources

The "Multi-Generation Register" maintained by Statistics Sweden contains information on all children born in Sweden since 1932 (and alive in 1960) and on their biological or adoptive parents.
The data extracted from this database for our study contained approximately 11 million individuals. For approximately 40% of offspring who died before 1991, the register is missing one or both parents (9) so that full siblings cannot be identified. Using the individually unique national registration number, the individuals were linked to the Swedish Cancer Register, to obtain all malignancies occurring between 1958 and 2001. Information in the cancer register permits identification of first and subsequent primary cancers. Cancers are coded according to the International Classification of Diseases, Seventh revision (ICD-7). During the period of our study, the Swedish Cancer Register was estimated to be at least 98% complete.
Further record linkages with the nationwide Cause of Death and Total Population registers allow complete follow-up with regard to vital status and date of death, as well as dates of emigration and immigration. The study was approved by the Stockholm regional ethics committee.

Study design

Cases were defined as individuals in the Multi-Generation Register who were born in Sweden and had a first primary diagnosis of any type of Leukemia (International Classification of Diseases Seventh Revision (ICD7) codes 204, 205, 206, 207) recorded in the Swedish Cancer Register in the period from 1st January 1958 to 31st December 2001. Since our objective was to estimate breast cancer risk, we included only cases with at least one female relative. We defined cases as childhood leukemia if they were younger than 15 years on the date of diagnosis, and older cases were defined as adult leukemia. We stratified cases by the type of leukemia: lymphatic (ICD7 204), myeloid (ICD7 205), monocytic (ICD7 206) and other (ICD7 207), and further stratified as acute or chronic using the 4th digit of the ICD7 code. For each case, we randomly sampled from our database up to five controls born in Sweden who were cancer-free at the time of diagnosis of the case. Controls were matched to the case for gender, year of birth and county of residence at the previous census year closest to the diagnosis. This last matching was to account for regional variability in diagnosing and reporting of malignancies.
We will refer to the cases and controls as "probands". For each proband, we identified all first degree female relatives (mothers, sisters and daughters) and checked for registration of a primary breast cancer (ICD7 170) as the first recorded malignancy for the individual. Early breast cancer was defined as a diagnosis before age 50.

Study Subjects

From the linked database, we identified 31 544 ca-

ses born in Sweden who had a first primary diagnosis of any type of leukemia between 1958 and 2001. For 16 825 of these, we could identify at least one female relative. We excluded 394 (5.5%) cases due to missing data on county of residence. Matched controls were found for all but one case and 524 of the matched controls had no female relative. The remaining 15 906 cases and their 58 828 controls had at least one recorded female relative. The 15 906 matched sets included a total of 28 417 unique female relatives of cases and 118 134 unique female relatives of controls. Among the relatives identified, 1 248 could not be included in the analysis because they contributed no follow-up time in the period 1958-2001, leaving 28 277 case relatives and 117 026 control relatives available for analysis.

Statistical Methods

The aim of our study was to compare the risk of breast cancer in first-degree relatives of leukemia case probands and first-degree relatives of their matched controls. We used a Cox model to evaluate the cause specific hazard of breast cancer in all relatives using age as the time scale and adjusting for the disease status of the proband, sex of the proband, birth cohort of the relative and type of relative (mother, sister, daughter). Data were left-truncated at 1958 (start of the Swedish Cancer Register) and censored at the end of the study (31st December 2001). For the analysis of early breast cancer, relatives were censored at their 50th birthday.

Separate Cox regression models were fit for the relatives of probands with childhood leukemia and adult leukemia, and with lymphatic leukemia and myeloid leukemia. For lymphatic and myeloid leukemia we further stratified for acute and chronic disease. Finally, we considered separately the relatives of male and female probands, and the mo-

Table 1. Numbers of relatives and age at entry by different types of leukemia diagnoses for the case proband.

TYPE OF LEUKEMIA IN CASE PROBANDS	Relatives of cases		Relatives of controls	
	No. of females	age at entry median (1st - 3rd quartile)	No. of females	age at entry median (1st - 3rd quartile)
ANY LEUKEMIA (ICD7 204-207)	28 277	10(0-19)	117 026	8(0-19)
Adulthood*	23 802	11(1-20)	92 692	11(0-21)
Childhood**	4 475	0(0-10)	24 334	0(0-9)
LYMPHATIC (ICD7 204)	14 017	9(0-17)	55 435	7(0-17)
Acute (ICD7 204.0)	4 752	1(0-13)	23 909	0(0-12)
Childhood acute**(ICD7 204.0)	*2 907*	*0(0-7)*	*15 103*	*0(0-6)*
Chronic (ICD7 204.1)	9 067	11(3-19)	30 776	11(1-20)
MYELOID (ICD7 205)	11 301	10(0-20)	48 198	9(0-21)
Acute (ICD7 205.0)	6 920	10(0-19)	29 428	9(0-21)
Childhood acute**(ICD7 205.0)	*483*	*0(0-11)*	*2 595*	*0(0-10)*
Chronic (ICD7 205.1)	3 550	10(0-21)	15 476	10(0-23)

**diagnosed at or after the age of 15; **diagnosed before the age of 15.*

Table 2. Numbers and rates of breast cancers in case and control relatives and hazard ratio estimates stratified by various types of leukaemia in the case probands.

TYPE OF LEUKEMIA IN CASE PROBANDS	Relatives of cases			Relatives of controls			Hazard Ratio	
	No. of Breast Cancers	PY at risk	rate per 1000 PY	No. of Breast Cancers	PY at risk	rate per 1000 PY	HR	95%CI
ANY LEUKEMIA	686	1049647	0.654	2583	4101026	0.630	1.03	0.95,1.12
Adulthood*	632	904758	0.699	2294	3367149	0.681	1.05	0.96,1.14
Childhood**	54	144889	0.373	289	733877	0.394	0.91	0.68,1.22
LYMPHATIC	334	515855	0.647	1173	1939492	0.605	1.03	0.91,1.16
Acute	78	158045	0.494	344	752637	0.457	1.04	0.82,1.33
Childhood acute*	*25*	*91137*	*0.274*	*143*	*453923*	*0.315*	*0.88*	*0.58,1.34*
Chronic	254	350400	0.725	804	1160733	0.693	1.06	0.92,1.22
MYELOID	273	421966	0.647	1099	1707752	0.644	1.04	0.91,1.19
Acute	163	259190	0.629	646	1046123	0.618	1.07	0.90,1.27
Childhood acute*	*6*	*15663*	*0.383*	*34*	*78273*	*0.434*	*0.87*	*0.37,2.08*
Chronic	96	132144	0.726	380	545168	0.697	1.06	0.85,1.32

**diagnosed at or after the age of 15; **diagnosed before the age of 15; PY: person-years*

thers and sisters of probands.
Data linkage and analysis were performed using SAS 9.1

Results

Among the 15 906 case probands (9 306 males), there were 8 011 lymphatic, 6 235 myeloid and 217 monocytic leukemia. Table 1 presents a breakdown of the 28 277 relatives of these case probands and 117 026 relatives of 58 828 controls in terms of type of leukemia of the case probands and the median age at which they begin to be observed by the cancer register: this "age at entry" provides indirect information about the birth cohort and is quite similar between case and control relatives.
Table 2 indicates that the overall rate of breast cancer in the relatives of leukemia cases (0.65 per 1000 person-years) was very similar to that in the relatives of controls (0.63 per 1000 person-years), and as expected the hazard was very similar in the two groups (Hazard Ratio, HR=1.03, 95% CI: 0.95, 1.12).
The breast cancer rate for the relatives of adult probands is almost double the risk for relatives of childhood probands, both for relatives of cases and controls suggesting age/calendar effects. The early breast cancer rate is lower than the overall breast cancer rate (Table 3) and similar in relatives of adult and child probands. The com-

Table 3. Numbers and rates of early breast cancers in case and control relatives and hazard ratio estimates, stratified by various types of leukaemia in the case probands.

	Relatives of cases			Relatives of controls			Hazard Ratio	
TYPE OF LEUKEMIA IN CASE PROBANDS	No. of Early Breast Cancers	PY at risk	rate per 1000 PY	No. of Early Breast Cancers	PY at risk	rate per 1000 PY	HR	95%CI
ANY LEUKEMIA	251	861472	0.291	890	3291470	0.270	1.02	0.88,1.17
Adulthood*	221	730150	0.303	739	2621980	0.282	1.03	0.88,1.19
Childhood**	30	131322	0.228	151	669490	0.226	1.03	0.70,1.51
LYMPHATIC	125	431043	0.290	435	1599853	0.272	0.98	0.80,1.20
Acute	33	139573	0.236	140	663554	0.211	1.07	0.74,1.56
Childhood acute*	*16*	*86107*	*0.186*	*84*	*429486*	*0.196*	*1.00*	*0.60,1.69*
Chronic	91	285217	0.319	287	914413	0.314	0.99	0.78,1.25
MYELOID	91	340478	0.267	330	1329975	0.248	1.04	0.82,1.31
Acute	53	210386	0.252	187	820718	0.228	1.07	0.79,1.46
Childhood acute*	*0*	*14079*	*0.000*	*17*	*70480*	*0.241*	-	
Chronic	34	104783	0.324	114	416207	0.274	1.13	0.77,1.65

**diagnosed at or after the age of 15; **diagnosed before the age of 15; PY: person-years.*

parison of the risk in case and control relatives gave a similar result as for overall breast cancer: the HR of early breast cancer was 1.02 (95% CI: 0.88, 1.17) and was also close to 1 for relatives of adult, childhood, lymphoid or myeloid leukemia cases.

Analyses which considered the gender of the proband yielded very similar estimates of the overall risk of breast cancer for relatives of male and females probands (Table 4). For early breast cancer, the HR was systematically higher for relatives of female probands, in particular if diagnosed in childhood or with ALL, although none of these results were statistically significant.

Finally, breast cancer risk was evaluated separately in mothers and sisters of probands (Table 5). Borderline significantly increased risks were found for mothers of chronic leukemia patients, in particular increased risk of breast cancer in mothers of CLL probands (HR=1.31 95%CI: 0.99, 1.72), and higher risk of early breast cancer in mothers of myeloid probands (HR=2.09 95%CI: 1.00, 4.38). Furthermore, sisters of childhood and lymphatic leukemia probands showed a higher (though not statistically significant) risk of breast cancer and early breast cancer.

Discussion

The purpose of this study was to examine the risk

Table 4. Hazard ratio estimates for relatives of male and female probands stratified by various types of leukemia in the case probands.

TYPE OF LEUKEMIA IN CASE PROBANDS	CANCER IN RELATIVES							
	BREAST CANCER				EARLY BREAST CANCER			
	Relatives of male probands		Relatives of female probands		Relatives of male probands		Relatives of female probands	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
ANY LEUKEMIA	1.03	0.92,1.16	1.05	0.92,1.19	0.93	0.77,1.13	1.13	0.92,1.40
Adulthood*	1.04	0.93,1.17	1.07	0.93,1.22	0.95	0.77,1.16	1.12	0.90,1.40
Childhood**	0.99	0.68,1.43	0.81	0.52,1.28	0.90	0.54,1.52	1.23	0.68,2.20
LYMPHATIC	1.05	0.90,1.22	1.00	0.82,1.22	0.90	0.69,1.17	1.11	0.82,1.51
Acute	1.09	0.80,1.49	0.97	0.65,1.45	0.96	0.59,1.55	1.30	0.72,2.37
*Childhood acute***	*0.89*	*0.52,1.51*	*0.87*	*0.45,1.72*	*0.75*	*0.37,1.50*	*1.65*	*0.74,3.67*
Chronic	1.07	0.89,1.28	1.04	0.83,1.31	0.93	0.68,1.27	1.06	0.74,1.52
MYELOID	1.06	0.88,1.27	1.04	0.86,1.27	1.08	0.79,1.48	0.99	0.70,1.41
Acute	1.08	0.85,1.38	1.07	0.84,1.37	1.06	0.69,1.61	1.10	0.70,1.72
*Childhood acute***	*0.54*	*0.13,2.30*	*1.30*	*0.43,3.93*	-		-	
Chronic	1.08	0.80,1.46	1.03	0.73,1.45	1.27	0.78,2.08	0.95	0.51,1.75

**diagnosed at or after the age of 15; **diagnosed before the age of 15.*

of breast cancer in the relatives of patients diagnosed with various types of leukemia, with particular attention to the type and subtype of leukemia, and the age and gender of the proband. Our detailed analysis provides an overview that cannot be readily obtained from existing studies of different populations addressing various hypotheses, particularly for a rare cancer such as leukemia whose classification is difficult and subject to change (10, 11).

The breast cancer incidence rate was very similar in case and control families, but was lower when the proband was a child. The relatives of children with leukemia were younger than the relatives of adult patients at the start of the cancer register (as shown in Table 1), so that by the end of followup a majority of them would not have achieved the older ages at which breast cancer incidence is highest. Our results on breast cancer risk in female relatives do not support the few reports which found an increased risk in leukemia families (1, 3), but these reports were based on smaller case-control studies, in which the familial history of cancer was assessed by survey. In our population-based study of first degree relatives of leukemia patients, (overall or stratified by subtype), we did not observe a significant increased risk of breast cancer or of early breast cancer.

A systematic elevated risk of early breast cancer was observed for relatives of female probands with ALL and in particular with childhood leukemia. This increased magnitude, although not significant, is in agreement with the findings of Rauscher et al. who observed a strongest association for ear-

Table 5. Hazard ratio estimates for mothers and sisters of probands with various type of leukemia.

TYPE OF LEUKEMIA IN CASE PROBANDS	CANCER IN RELATIVES							
	BREAST CANCER				EARLY BREAST CANCER			
	Mothers of probands		Sisters of probands		Mothers of probands		Sisters of probands	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
ANY LEUKEMIA	1.06	0.93,1.21	1.11	0.87,1.43	0.98	0.72,1.32	1.07	0.74,1.55
Adulthood*	1.11	0.96,1.29	1.09	0.84,1.42	1.01	0.67,1.53	1.00	0.66,1.50
Childhood**	0.87	0.64,1.18	1.39	0.61,3.19	0.94	0.61,1.45	1.52	0.66,3.52
LYMPHATIC	1.13	0.92,1.38	1.23	0.86,1.76	0.91	0.58,1.41	1.26	0.73,2.19
Acute	1.00	0.75,1.34	1.34	0.62,2.91	1.09	0.69,1.74	0.86	0.25,2.93
Childhood acute*	*0.84*	*0.55,1.3*	*1.78*	*0.34,9.24*	*0.94*	*0.54,1.64*	*1.78*	*0.34,9.24*
Chronic	1.31	0.99,1.72	1.23	0.82,1.85	0.21	0.03,1.55	1.42	0.77,2.64
MYELOID	1.06	0.87,1.29	1.07	0.72,1.58	1.25	0.77,2.04	0.85	0.45,1.58
Acute	1.16	0.90,1.49	0.98	0.59,1.63	1.00	0.51,1.97	1.08	0.51,2.27
Childhood acute*	*0.98*	*0.41,2.36*	*0.00*	-	*0.00*	-	*0.00*	-
Chronic	1.01	0.71,1.42	1.06	0.53,2.13	2.09	1.00,4.38	0.66	0.20,2.15

**diagnosed at or after the age of 15; **diagnosed before the age of 15.*

ly onset of both leukemia and breast cancer (3). Moreover, the risks were higher for sisters of childhood and lymphatic leukemia probands, as found by Pottern (7), suggesting effects of shared childhood environment or recessive mode of inheritance. The latter is consistent with the significant increased risk of breast cancer only in second-degree relatives of childhood leukemia reported by Infant-Rivard and Guiguet (8). These findings could be partially explained by a rare genetic mutation in the p53 gene (the Li-Fraumeni Syndrome) that is common to both cancers (12).

We also found a borderline significant increased risk of breast cancer in the mothers of CLL cases (HR=1.31, P= 0.05), in agreement with the findings of Linet (6), and of early breast cancer in mothers of chronic myeloid leukemia cases (HR=2.09, P= 0.05). To our knowledge, only Pottern explored this association and reported an odds ratio of 1.9 (95%CI: 0.5-6.8) for breast cancer in mothers of chronic myeloid leukemia patients (7). The raised risk of breast cancer in mothers of patients with chronic leukemia deserves further investigation. In further analyses (data not shown), we applied

a more sophisticated Cox model that accommodated the correlation between cases in the same family and used a bootstrap estimate of confidence intervals (13). The results of this analysis were similar to those from the simpler model that we present here, and as expected from a method that produces more conservative confidence intervals, the borderline significantly increased risks were no longer significant.

The strength of our study is the population-based data from 40 years of cancer registration with consistent coding of cancer diagnoses (ICD7) throughout in addition to the most current coding system. Furthermore, the register-based data on cancer diagnoses protects our study from the reporting bias that is a concern in case-control studies. However, we did not have information on environmental or life-style risk factors or clinical information on biological markers, so that we could not explore the hypothesis of Rauscher et al. that family history of breast cancer is a marker of susceptibility to exposures associated with leukemia (4).

In conclusion, we did not find any strong evidence of a familial association between leukemia and breast cancer (or early breast cancer) for any of the types or subtypes of leukemia, or when limited to female leukemia probands. We did however observe a systematically higher breast cancer risk, especially if diagnosed before age 50, in sisters of childhood and lymphatic leukemia female probands, that may suggest genetic mutation or susceptibilities common to both cancers.

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