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Cancer incidence in first-degree relatives of a population-based set of cases of early-onset breast cancer

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ABSTRACT

Reliable determination of familial risks for cancer is important for clinical counselling, cancer prevention and understanding cancer aetiology. Family-based gene identification efforts may be targeted if the risks are well characterised and the mode of inheritance is identified. Early-onset breast cancer in a family member is a risk indicator for cancer among first-degree relatives; however, the familial risk pattern has not been assessed fully in population-based incidence studies. We estimated the risks for cancers of the breast, ovary and other sites among the first-degree relatives of 8868 patients in whom breast cancer was diagnosed before they reached the age of 50 years (diagnosed during the period 1943–1999). Population registers and parish records were used to identify 31,235 first-degree relatives, who were followed up to 31 December 2002 for occurrence of cancer by linkage to the Danish Cancer Registry. The observed incidence rates were compared with national rates adjusted for age, sex and calendar period. Overall, 39% of the 674 cases of breast cancer and 43% of the 143 cases of ovarian cancer among relatives were associated with a diagnosis of early-onset breast cancer in a family member. Among relatives under 50 years of age, the proportions were 56% and 58%, respectively, and among relatives 50 years or above the proportions were approximately 30% and 10%. In addition, a slightly but significantly increased risk for cancer of the cervix uteri was observed among relatives, and among those under 50 years of age, we found significantly increased risks for cancers of the colon and gall-bladder. In conclusion, the excess risk for breast cancer in first-degree relatives is large and remains sizable in the subgroup of female relatives aged 50 years or older, and that mutations in *BRCA1/2* seem to explain only half of breast cancer cases attributable to family history.

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1. Introduction

A familial history of early-onset breast cancer is a strong predictor of risk for breast cancer among female relatives, making estimates of familial cancer risk an important tool for clinical counselling.[1,2] Little is known about other causes of early-onset breast cancer, as only 5–10% of breast cancers diagnosed before the age of 40 years can be explained by mutations in the *BRCA1/2* or other known heritable genes.[3] Germ-line mutations in *BRCA1/2* substantially increase the lifetime risks for developing breast and ovarian cancer and have also been associated with higher risks for other types of cancer. Thus, in carriers of a *BRCA1* mutation, the risks for cancers of the pancreas and colon are reported to be significantly increased[4–6] Carriage of *BRCA2* mutations has been related to cancers of the pancreas, prostate, gall-bladder, bile duct and stomach and to malignant melanoma.[7–12] Nevertheless, the findings of increased risks for cancers other than of

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the breast and ovary in carriers of *BRCA1/2* mutations are far from consistent across studies, perhaps because of small sample sizes. In a recent Swedish study of first-degree relatives of patients eligible for *BRCA1/2* mutation testing by criteria proposed by the German Consortium for Hereditary Breast and Ovarian Cancer, increased risks were found for cancers of the breast, ovary, pancreas, prostate and stomach.[13,14] The risks for cancers of the prostate, cervix and non-melanoma skin were found to be increased among the first-degree relatives of early-onset breast cancer patients who tested negative for a *BRCA* gene mutation.[15] Thus, for effective counselling, more information is needed about the general cancer risk profiles of individuals with a family history of early-onset breast cancer. Our study, based on registered national data on cancer incidence in nuclear families during the period 1943–2002, provides additional knowledge for assessing the predictive value of early-onset breast cancer for the risk pattern of cancer among first-degree relatives at the population level.

2. Patients and methods

A population-based study was conducted in Denmark (5.2 million inhabitants in 2000) to investigate the risks for breast and other cancers among first-degree relatives of patients in whom early-onset breast cancer had been diagnosed.

2.1. *Index patients*

From the Danish population born in 1935 or later, we identified 8868 women in whom early-onset breast cancer had been diagnosed, defined here as breast cancer diagnosed in women under 50 years of age. Of these, 4096 women were diagnosed before they were 40 years of age during the period 1943–1999, and 4772 were diagnosed when they were 40–49 years of age during the period 1991–1999 (Table 1). Patients were identified from the files of the Danish Cancer Registry, which also provided the patients' names, dates of birth and personal identification numbers. The last, which incorporates sex and date of birth and permits accurate linkage of information between registers, was available for 8859 women alive on 1 April 1968, when the Central Population Register (CPR) was established in Denmark, or born thereafter. Linkage to the files of the CPR also provided the date of death or date of emigration. For 9 women who died before 1 April 1968, the date of death was obtained manually from the death certificate file at the National Board of Health.

2.2. *Identifying relatives*

Parents of these women were identified either through a computerised search in the CPR or through manual searches in relevant local population registers. When the personal identification number of the index patient was available, computerised linkage with the files of the CPR usually gave the name, identification number and date of death or emigration (if applicable) of the parents. For the oldest group of index patients, born around 1955 or before ($n = 5410$), no information on the parents was available in the CPR. For almost all women, diagnosed before the age of 40 years, who had limited familial data in the CPR, we were able to retrieve data on parents by a diligent manual search of the population registers of the localities in which the families had lived at the date of birth of the index patient. For index patients whose cancer was diagnosed when they were 40–49 years of age, no additional local search for parental data was attempted, which implies that the tracing of families for patients in this age group was incomplete. In the few cases in which either the breast cancer patient or one or both of the parents had died before 1 April 1968, CPR linkage was not feasible, and information about the parents had to be obtained manually from the local population registers, as described above.

Sisters and brothers of the index patients were also located in the files of the CPR (by using the personal identification number of the mother of the index patient) or from local parish registers. All the offspring of the index patients were located through the CPR by use of the personal identification number of the index patient.

Table 1 – 8868 Index patients with breast cancer before the age 50, 1943-1999

	Year of diagnosis of breast cancer					
	<1999	1991–1999	All		Cumulative	
Age at diagnosis			No.	%	No.	%
10–14	1	0	1	0,01	1	0,01
16–19	2	0	2	0,02	3	0,03
20–24	40	10	50	0,56	53	0,60
25–29	268	93	361	4,07	414	4,67
30–34	807	344	1151	12,98	1565	17,65
35–39	1739	792	2531	28,54	4096	46,19
40–44	0	1728	1728	19,49	5824	65,67
45–46	0	3044	3044	34,33	8868	100,00
Year of birth						
1930–39	487	0	487	5,49	487	5,49
1940–49	1564	2703	4267	48,12	4754	53,61
1950–59	770	2718	3488	39,33	8242	92,94
1960–69	36	564	600	677	8842	99,71
1970–79	0	26	26	0,29	8868	100,00

2.3. Probands

In order to define first-degree relatives of the early-onset breast cancer patients unambiguously, we had to decide who was to be the proband of each family. If the index patient was the only female member of the nuclear family who was affected by early-onset breast cancer, she became by definition the proband of the family. The tracing of first-degree relatives disclosed, however, that two times 49 index patients were pair-wise sisters and two times 12 index patients were pair-wise mother and daughter. For these 61 families, the woman whose breast cancer was diagnosed earliest was regarded as the proband in the family, while the other woman was regarded as a familial case of breast cancer. Overall, 31,235 first-degree relatives of 8807 probands with early-onset breast cancer were identified including 8571 parents, 6703 siblings and 15,970 offspring (Table 2). Six mothers of probands were also sisters of other probands and three fathers of probands were repeated as brothers of other probands.

2.4. Identifying cancer in first-degree relatives

Data on relatives were linked to the Danish Cancer Registry, by personal identification number or, if they had died before 1 April 1968, their date of birth, date of death and name. With the exception of female breast cancer, the period of follow-up for the occurrence of cancer among parents started from the date of birth of the proband and that among siblings and offspring from their respective date of birth. The period of follow-up for the occurrence of breast cancer among female relatives started from the date of diagnosis of breast cancer in the proband, the 40th birthday of female relatives of probands in whom cancer was diagnosed between 1950 and 1990 or the 50th birthday of female relative of probands in whom cancer was diagnosed between 1991 and 1999, whichever came first. Follow-up of relatives was ended at the date of death or emigration or 31 December 2002, whichever came first. Cancers, including benign tumours of the brain and papillomas of the urinary tract, were classified according to the modified Danish version of the International Classification of Diseases, 7th Revision (ICD–7) (World Health Organisation (WHO), 1957).

2.5. Statistical analysis

The age-, sex- and period-specific national incidence rates of each type of cancer and of all types combined, were applied to the person-years of observation for each study group, to obtain number of cancers expected. The statistical methods were chosen on the basis of the assumption that the observed number of cases of cancer in any specific category follows a Poisson distribution. Significance and confidence intervals (CIs) for the standardised incidence ratio (SIR)–the ratio of the observed to the expected number of cancers–were calculated with Miettinen exact confidence limits if the observed number of cases was small; otherwise, an accurate asymptotic approximation was used.[16] Account was also taken of the age of the proband at the time of the initial diagnosis of breast cancer and the age of the relatives at the time of cancer diagnosis.

3. Results

Table 1 gives some descriptive characteristics of the 8868 index patients in whom breast cancer was diagnosed before the age of 50 years; 4096 (46.2%) received their diagnosis before the age of 40 years and 4772 (53.8%) in the age range 40–49 years. For the group of 8807 patients who were eligible as probands, 31,235 first-degree relatives were identified: 4351 mothers, 4220 fathers, 3184 sisters, 3519 brothers, 7776 daughters and 8194 sons (Table 2). Six mothers of probands were also sisters of other probands and three fathers of probands were repeated as brothers of other probands. During follow-up, a total of 3153 first-degree relatives were diagnosed with 3860 cancers, of which 768 occurred before the age of 50 years and 3092 at age 50 years or older (Table 2). First-degree relatives diagnosed with cancer before the age of 50 years were ranked as sisters (6.9%) > mothers (4.1%) > brothers (3.0%) > fathers (1.8%) > daughters (1.1%) > sons (0.8%). Relatives diagnosed with cancer at age 50 years or older were ranked as fathers (33%) > mothers (31.1%) > sisters (6.8%) > brothers (4.5%).

Table 3 shows observed numbers and SIRs for cancer at all sites combined and for a selected number of site specific cancers diagnosed among the entire group of first-degree relatives. The risks were significantly increased for cancers of

Table 2 – 31235 first-degree relatives of 8807 probands with early-onset breast cancer

Relationship	Numbers	Year of birth (range)	Diagnosed with cancer before the age of 50 years		Diagnosed with cancer after the age of 50 years	
			n	%	*n*	%
Mothers	4351	1891–1954	180	4.1	1356	31.1
Fathers	4220	1866–1950	75	1.8	1391	33.0
Sisters	3184	1914–1986	220	6.9	215	6.8
Brothers	3519	1914–1983	109	3.0	158	4.5
Daughters	7776	1953–2002	89	1.1	0	0.0
Sons	8194	1953–2002	67	0.8	0	0.0
All relatives	31235[a]	1891–2002	740	2.6	3120	10.0

a Six mothers of probands are also sisters of other probands and three fathers of probands are repeated as brothers of other probands.

Table 3 – Cancer by site among first degree relatives of 8807 Probands at different ages

Cancer site	Cancers diagnosed before 50 years				Cancers diagnosed after 50 years			
	obs.	exp.	SIR	95%-Cl	obs.	exp.	SIR	95%-Cl
All malignant neoplasms (140–205)	768	581.6	**1.3**	(1.2–1.4)	3092	2810.8	1.1	(1.1–1.2)
Stomach (151)	7	11.3	0.6	(0.3–1.3)	78	82.6	0.9	(0.8–1.2)
Colon (153)	31	19.2	**1.6**	(1.1–2.3)	222	217.2	1.0	(0.9–1.2)
Rectum (154)	9	11.4	0.8	(0.4–1.5)	135	127.4	1.1	(0.9–1.3)
Gallbladder (155.1)	6	1.5	**4.1**	(1.5–8.8)	17	22.4	0.8	(0.4–1.2)
Pancreas	4	5.5	0.7	(0.2–1.9)	79	75.9	1.0	(0.8–1.3)
Lung (162.0.1)	31	24.6	1.3	(0.9–1.8)	363	384.5	0.9	(0.9–1.1)
Breast (170)	185	80.3	**2.3**	(2.0–2.7)	489	328.6	**1.5**	(1.4–1.6)
Cervix uteri (171)	79	64.1	**1.2**	(1.1–1.5)	59	46.5	**1.3**	(1.1–1.6)
Endometrium (172)	9	8.5	1.1	(0.5–2.0)	75	73.7	1.0	(0.8–1.3)
Ovary (175)	46	19.4	**2.4**	(1.7–3.2)	97	62.2	**1.6**	(1.3–1.9)
Prostrate (177)	0	–	–	–	163	167.3	1.0	(0.8–1.1)
Kidney (180)	10	11.2	0.9	(0.4–1.7)	85	73.7	1.2	(0.9–1.4)
Bladder (181)	11	12.0	0.9	(0.5–1.6)	190	168.5	1.1	(1.0–1.3)
Melanoma of skin (190)	38	36.4	1.0	(0.7–1.4)	44	52.6	0.8	(0.6–1.3)
Other skin (191)	66	60.3	1.1	(0.9–1.4)	427	396.0	1.1	(1.0–1.2)
Brain and nervous system (193)	57	50.2	1.1	(0.9–1.5)	67	63.48	1.1	(0.8–1.3)
Thyroid	8	6.9	1.2	(0.5–2.3)	12	8.2	1.5	(0.8–2.6)
Bone (196)	3	5.7	0.5	(0.1–1.6)	0	–	–	–
Connective tissues (197)	10	6.1	1.6	(0.8–3.0)	11	7.7	1.4	(0.7–2.6)
Non-Hodgkin lymphoma (200,202)	12	17.7	0.7	(0.4–1.2)	72	54.8	1.3	(1.0–1.6)
Hodgkin's disease (201)	26	16.7	**1.6**	(1.1–2.3)	10	7.1	1.4	(0.7–2.6)
Leukemia (204)	40	27.3	**1.5**	(1.1–2.0)	61	61.5	1.0	(0.8–1.3)
Others and unspecified cancers	80	84.2	0.9	(0.8–1.2)	336	326.9	1.0	(0.9–1.1)

obs, number of cases observed; exp, expected number of cases; SIR, standardised incidence ratio.

the breast, ovary, cervix, colon, and gallbladder along with leukaemia and Hodgkin's disease in the analysis restricted to include the age range below 50 years. In the age range 50 years or above, the risk among first-degree relatives was significantly increased only for cancers of the breast, ovary and cervix, and for non-Hodgkin's lymphoma.

Table 4 – Cancer by site among first degree relatives of 8807 probands diagnosed before 50 years

Cancer site	All Female first degree relatives				All male first degree relatives			
	obs.	exp.	SIR	95%-Cl	obs.	exp.	SIR	95%-Cl
All malignant neoplasms (140–205)	510	350.3	**1.5**	(1.3–1.6)	258	231.3	1.1	(1.0–1.3)
Stomach (151)	2	4.4	–	–	5	6.9	0.7	(0.2–1.7)
Colon (153)	17	10.9	1.6	(0.9–2.5)	14	8.3	1.7	(0.9–2.8)
Rectum (154)	3	5.6	0.5	(0.1–1.6)	6	5.8	1.0	(0.4–2.3)
Gallbladder (155.1)	4	0.8	**4.8**	(1.3–12.4)	2	0.7	–	–
Pancreas (157)	1	2.3	–	–	3	3.1	1.0	(0.2–2.8)
Lung (162.0.1)	14	10.3	1.4	(0.7–2.3)	17	14.3	1.2	(0.7–1.9)
Breast (170)	182	80.0	**2.3**	(2.0–2.7)	3	0.3	**10.4**	(2.1–30.4)
Cervix uteri (171)	79	64.1	**1.2**	(1.1–1.5)	–	–	–	–
Endometrium (172)	9	8.5	1.1	(0.5–2.0)	–	–	–	–
Ovary (175)	46	19.4	**2.4**	(1.7–3.2)	–	–	–	–
Kidney (180)	4	4.6	0.9	(0.2–2.2)	6	6.5	0.9	(0.3–2.0)
Bladder (181)	3	3.2	0.9	(0.2–2.8)	8	8.9	0.9	(0.4–1.8)
Melanoma of skin (190)	20	23.6	0.8	(0.5–1.3)	18	12.8	1.4	(0.8–2.2)
Other skin (191)	35	32.6	1.1	(0.8–1.5)	31	27.7	1.1	(0.8–1.6)
Brain and nervous system (193)	26	23.8	1.1	(0.7–1.6)	31	26.4	1.2	(0.8–1.7)
Thyroid (194)	7	5.1	1.4	(0.6–2.9)	1	1.9	–	–
Connective tissue (197)	4	2.9	1.4	(0.4–3.5)	6	3.2	1.9	(0.7–4.0)
Non-Hodgkin lymphoma (200,202)	6	6.6	0.9	(0.3–2.0)	6	11.1	0.5	(0.2–1.2)
Hodgkin's disease (201)	8	6.8	1.2	(0.5–2.3)	18	9.9	**1.8**	(1.1–2.9)
Leukemia (204)	19	11.8	**1.6**	(1.1–2.5)	21	15.6	1.3	(0.8–2.1)
Others and unspecified cancers	20	22	0.9	(0.8–1.2)	59	66	0.9	(0.1–1.3)

obs, number of cases observed; exp, expected number of cases; SIR, standardised incidence ratio. SIR and 95% CI were not calculated when obs. cases were below 3.

Table 5 – Standardised incidence ratios (SIRs) of breast and ovarian cancers among first-degree female relatives (mothers and sisters) of probands by age of the relative and by age of the proband when her own breast cancer was diagnosed

Age (years) of female relatives at diagnosis	Age (years) of proband at breast cancer diagnosis		
	<30	30–39	40–49
	SIR (obs)	SIR (obs)	SIR (obs)
Breast cancer			
<30	24.6[a](2)	3.3[a](2)	3.5[a](2)
30–49	2.7[a](18)	2.3[a](145)	1.5[a](13)
⩾50	1.4(28)	1.5[a](360)	1.5[a](98)
Ovarian cancer			
<30	–(0)	–(0)	2.1(2)
30–49	1.9(3)	2.7[a](37)	2.2(4)
⩾50	2.3[a](11)	1.6[a](75)	1.2(11)

obs, number of cases observed; SIR, standardised incidence ratio.
a $P < 0.05$.

The risk analysis among first-degree relatives below age 50 years was further stratified by sex (Table 4). We saw statistically increased risks for cancers of the breast (SIR, 2.3), ovary (2.4), cervix (1.2) and gallbladder (4.8; based on only four observed cases) along with leukaemia (1.6) in women, and for breast cancer (10.4; three observed cases) and Hodgkin's disease (1.8) in men. The SIRs for breast cancer diagnosed before the age of 50 years was 1.8 (95% CI 1.6–1.9) for mothers, 2.5 (95% CI 2.2–2.9) for sisters, and 3.7 (2.3–5.5) for daughters. The SIRs for ovarian cancer was 1.5 (95% CI 1.2–1.8) for mothers, 2.6 (1.8–3.8) for sisters and 1.4 (95% CI 0.3–4.1) for daughters. Table 5 shows the standardised incidence ratios (SIRs) of breast and ovarian cancer among first-degree female relatives (mothers and sisters) of probands by age of the relative as well as the age of the proband. SIRs are higher in younger age groups compared with older groups and particularly high at the combination of young ages of female relatives and probands.

Table 6 shows the excess numbers of breast and ovarian cancers in first-degree female relatives in 11 consecutive age groups and the equivalent proportions estimated to be attributable to a family history of early-onset breast cancer. Table 6 shows that the proportions attributable to a family history were ranging from approximately 80% for breast cancer in age range below 40 years and 80–85% for ovarian cancer in the age range 40–49 years, to approximately 30% for breast cancer above age 55 years and 15% for ovarian cancer above age 70 years.

4. Discussion

Most studies of the accumulation of cancer in families are based on interview data, which makes them vulnerable towards a biased selection of relatives and a differential ascertainment of cases of cancer.[17,18] By contrast, our study relied on registered data of national coverage on familial relationships during the last 50 years from a central population register, supported with information from church registries, and on the occurrence of cancer in these families obtained through an unbiased linkage with the files of a national cancer registry. For women born before 1955 information on parents was generally not available in the Central Population Register; consequently, we were able to trace relatives for only a proportion of index patients diagnosed with breast cancer in the age range 40–49 years. However, as the incompleteness in tracing of relatives in this age group was determined by the temporal coverage of one of the registers used, we believe this is an unlikely cause of bias.

Familial accumulation of breast cancer is well established.[19,20] An unaffected woman, being a first-degree relative of a breast cancer patient has a two-fold increased risk for breast cancer; the relative risk is further increased if the patient is diagnosed before the age of 45 years. However, the relative risk estimates on breast cancer appear to be influenced by study type: the hospital-based studies tend to give higher estimates compared with those of the population-based studies. [2,21–24] In the present study, the overall estimate of a familial risk of breast cancer of 1.5 at age 50 years or above (when

Table 6 – Breast and ovarian cancers by age of diagnosis in first-degree female relatives of proband diagnosed with breast cancer before the age of 50 years

Age of diagnosis (years)	Breast			Ovary		
	Obs	Exp	Excess(%)	Obs	Exp	Excess(%)
20–29	6	1.3	4.70(78.4)	2	1.2	0.8(40.8)
30–34	18	3.4	14.59(81.0)	5	3.7	1.3(26.9)
35–39	31	6.5	24.45(78.9)	13	4.9	8.1(62.5)
40–44	56	28.2	27.84(49.7)	13	2.7	10.3(79.6)
45–49	71	40.6	30.41(42.8)	13	1.6	11.4(87.4)
50–54	95	58.0	36.96(38.9)	25	10.5	14.5(58.0)
55–59	93	59.8	33.17(35.7)	20	11.5	8.5(42.5)
60–64	75	60.1	14.87(19.8)	17	11.8	5.2(30.6)
65–69	83	53.6	29.41(35.4)	15	11.0	4.0(26.7)
70–74	58	43.1	14.90(25.7)	10	8.7	1.3(13.0)
>=75	82	53.7	28.35(34.6)	10	8.7	1.3(13.0)
All ages	668	408.4	259.63(38.9)	143	81.6	61.4(42.9)

obs, number of cases observed; exp, expected number of cases.

the proband is diagnosed before the age of 50 years) was similar to that of our earlier study and to that of other population-based studies.[25–27] We observed an overall SIR of 2.3 for breast cancer in family members at ages below 50 years, which was similar to the 2.4-fold increased risk reported by Lorenzo Bermejo and colleagues, but clearly lower than the estimate obtained from the Icelandic family database.[24,25]

Population-based studies from Iceland and the United Kingdom (UK) have also reported familial aggregation of incident or fatal cases of ovarian cancer in relatives of young breast cancer patients.[22,24,28] Our finding of a relative risk of 1.6 for ovarian cancer in relatives aged 50 years or more, and of a relative risk of 2.4 in relatives below the age of 50 years were comparable with the findings of earlier studies.[25,27]

We found that the relative risk of cervical cancer among first-degree relatives of probands was moderately, but significantly, increased irrespective of age. In a recent study, a non-significantly elevated risk for cervical cancer was reported among first-degree relatives of probands diagnosed with breast cancer before the age of 50 years.[25] In the Swedish study of women with early-onset breast cancer, who were shown to be without a *BRCA* mutation, the incidence of cervical cancer was also found to be increased among first-degree relatives.[15] We are not aware of any reports on genes suspected to be associated with cervical cancer as well as breast cancer; moreover, human papillomaviruses (HPVs) are considered the single most important risk predictor for cervical cancer, indicating that the familiar accumulation of this cancer is likely a chance finding, or a result of confounding from known or unknown environmental risk factors for cervical cancer.

The clustering of early-onset breast cancer with leukaemia and colon cancer among young first-degree relatives may possibly be attributed to the inclusion in our study of some families with Li-Fraumeni syndrome.[29] However, we observed no increased risk for sarcomas in the study and we saw no cases of adrenocortical carcinoma, which are also regarded as part of that syndrome, indicating that such families are rare. The increased risk for Hodgkin's disease among first-degree relatives of probands with early-onset breast cancer was only significant among the sons of probands and only observed after 1990, which may indicate that this is a chance finding. Moreover, germ-line mutations of *BRCA1/2* are not common among the survivors of Hodgkin's disease.[30] The observation in our study of an increased risk for gall bladder cancer among first-degree relatives at ages below 50 years were seen in both sexes, although to a significant degree only in women. The Breast Cancer Linkage Consortium found that *BRCA2* mutations were associated with familial gall bladder cancers,[7] however this finding could not be verified in the study of Swedish families that were eligible for *BRCA1/2* mutation testing.[13]

We could not confirm earlier reports of an association of early-onset breast cancers with cancers of the endometrium, pancreas and prostate,[22,24,25,31,32] but our observation of a lack of association are consistent with the findings of other studies.[15,26,27]

We found that the excess risk for breast cancer in first-degree relatives attributable to a family history of breast cancer was 39% overall, which was similar to 39% recently reported from the Utah population database.[33] The percentage was as high as 80% in the age range 20–39 years, 45% in the age range 40–49 years and approximately 30% in the remaining lifetime, i.e. in the age range 50 years or above. It has been estimated that the prevalence of *BRCA1/2* mutations among women with breast cancer diagnosed before the age of 50 years is approximately 5%, and consequently that the prevalence among first-degree relatives is approximately 2.5%.[34] Thus, assuming a *BRCA1/2* mutation prevalence of 2.5% in first-degree relatives of our study and an associated life-time penetrance for breast cancer of 60% on average, these mutations were probably the cause of a total of 115 breast cancer cases in the combined study group of mothers and sisters. We in fact observed an excess number of breast cancers of 260, indicating that only approximately half of the excess number of cases can be attributed to the *BRCA* mutations.

The picture was somewhat different for ovarian cancer, as the excess risk attributable to a family history of breast cancer was highest in middle-aged women. The latter observation could be explained by a non-genetic nature of ovarian cancers diagnosed among very young adults.

In summary, apart from the clearly increased risks of cancers of the breast and ovary in first-degree relatives of women with early-onset breast cancer, we also observed a consistently, but moderately, increased risk of cervical cancer. Moreover, in relatives below the age of 50 years we saw an increased risk of cancer of the colon and leukaemia, which may be ascribed to the inclusion of some families with Li-Fraumeni syndrome, and of cancer of the gallbladder (both sexes) and Hodgkin's disease. The latter observation, however, is probably a chance finding. Finally, our study indicates that the excess risk for breast cancer in first-degree relatives is large and remains substantial in the subgroup of female relatives aged 50 years or older, and that the *BRCA* mutations seem to explain only a proportion of breast cancer cases attributable to a family history of breast cancer.

Conflict of interest statement

None declared.

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