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# Familial aggregation of early-onset cancers in early-onset breast cancer families

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## Abstract

The risk of early-onset (EO) breast cancer is known to be increased in relatives of EO breast cancer patients, but less is known about the familial risk of other EO cancers. We assessed familial risks of EO cancers (aged ≤40 years) other than breast cancer in 54 753 relatives of 5562 women with EO breast cancer (probands) by using a population-based cohort from Finland. Standardized incidence ratios (SIRs) and 95% confidence intervals (CI) were estimated by using gender-, age- and period-specific cancer incidences of the general population as reference. The risk of any cancer excluding breast cancer in first-degree relatives was comparable to population cancer risk (SIR 0.99, 95% CI: 0.84-1.16). Siblings' children of women with EO breast cancer were at an elevated risk of EO testicular and ovarian cancer (SIR = 1.74, 95% CI: 1.07-2.69 and 2.69, 95% CI: 1.08-5.53, respectively). The risk of EO pancreatic cancer was elevated in siblings of the probands (7.61, 95% CI: 1.57-22.23) and an increased risk of any other cancer than breast cancer was observed in children of the probands (1.27, 95% CI: 1.03-1.55). In conclusion, relatives of women with EO breast cancer are at higher familial risk of certain discordant EO cancers, with the risk extending beyond first-degree relatives.

**KEYWORDS**
early-onset breast cancer, familial aggregation, ovarian cancer, pancreatic cancer, testicular cancer

## What's new?

Family members of early-onset breast cancer patients are at a higher risk of early-onset breast cancer. However, it is unclear whether the familial risk is limited to early-onset cancer of the same site. Here, the authors estimate the familial risks of discordant early-onset cancers in relatives of female early-onset breast cancer patients, using an extensive, prospective population-based cohort. The findings suggest that the familial risk extends to discordant early-onset cancers, including ovarian, testicular and pancreatic cancers, as well as beyond first-degree relatives.

**Abbreviations:** CI, confidence interval; EO, early-onset; FCR, Finnish Cancer Registry; PIS, Finnish Population Information System; SIR, standardized incidence ratio.

## 1 | BACKGROUND

It is well known that the risk of early-onset (EO) breast cancer is increased in women with a first-degree relative diagnosed with breast cancer.[1-3] The risk of developing EO breast cancer increases when the number of first-degree female relatives with breast cancer increases.[4] With only one affected first-degree relative, the risk is 2-fold compared to women with unaffected first-degree relatives.[4] The risk further increases to almost 3-fold with a second first-degree relative affected.[4] Furthermore, first-degree relatives of a breast cancer patient appear to be at increased risk of developing any type of cancer[5] with ovarian[6,7] and prostate[1,6,8] cancer risks showing the most consistent increases across studies.

It is less clear to what extent first-degree relatives of EO breast cancer patients are at risk of specific discordant EO cancers. A variety of associations across all ages have been established between breast and other cancers in first-degree relatives.[1,5] One of the most well-established relations is between breast and ovarian cancer[7,8] as both of these cancers are associated with germline mutations in *BRCA1*[9] and *BRCA2*.[10] Apart from ovarian cancer, previous research has suggested an increased risk of cancers of the prostate,[1,5,6,11] colon,[1,3,5] thyroid gland[1,5] and cervix[3,11] in first-degree relatives of women with EO breast cancer. These associations are not limited to EO cancers of the relatives and many of these discoveries are far from consistent and limited by small sample sizes. Concerning shared genetic factors, germline mutations in *BRCA1* and *BRCA2* genes do not confer increased risks only on the cancers of the breast and ovary; both BRCA1[9,12] and BRCA2[6,10] mutation carriers have been observed to have a higher than normal prevalence of prostate and pancreatic cancers.

Familial aggregation of cancer may be due to genetic susceptibility or acquired mutations caused by shared environmental factors. There are several known germline mutations predisposing to breast cancer with a prevalence of ~10% in all breast cancers.[13] At least 10% of EO breast cancer patients have germline mutations in *BRCA1* and *BRCA2*.[14] Despite their role as the most remarkable individual genetic factors in the etiology of breast cancer, data suggest that only a minor part of the familial excess risk of breast cancer is attributable to *BRCA1/2* mutations.[14] This suggests a considerable role of factors other than genetic predisposition or yet unidentified genetic factors impacting the familial aggregation of breast cancer.

Lifestyle and environmental factors associated with the risk of breast cancer, such as alcohol consumption,[15] low physical activity,[16] body weight[17] and several endogenous[18] and exogenous[19] hormonal factors are of great interest as exposure to many of them is avoidable unlike exposure to genetic risk factors. Concerning hormonal factors, for example, early age at menarche[20] and late age at menopause are associated with an increased risk of breast cancer,[17,21] presumably due to longer lifetime exposure to estrogen.[21,22] The role of body weight is not as straightforward as being obese or overweight throughout adulthood before menopause seems to act as a protective factor against premenopausal breast cancer[23] but predisposes to postmenopausal breast cancer.[17] Independent of adulthood obesity, some studies have shown a protective effect of higher body fatness during childhood and young adulthood on both premenopausal[20,24] and postmenopausal breast cancer.[20,24] Independent risk factors of premenopausal breast cancer are mostly unidentified, but it may be assumed that they at least partly overlap with those of postmenopausal breast cancer.

Familial clustering of cancer is associated with earlier age of onset[9] and the inherited component seems to contribute more to EO cancers.[1,25] In addition, it is known that the familial risk of breast cancer is the highest in the offspring when their mother has been diagnosed with breast cancer at a young age.[3,7] As an earlier age of onset is generally suggestive of a hereditary component in the etiology of the disease, it therefore makes investigating the associations between discordant EO cancers a useful tool for evaluating the etiology of familial aggregation of discordant cancers. We estimate the relative risks of other EO cancers than breast cancer (discordant cancer) in family members of EO breast cancer probands by utilizing a prospective population-based familial cohort in Finland.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

Our data consists of 54 753 relatives in 5562 families of females diagnosed with EO breast cancer during the period 1970 to 2012. The data of the prospective observational familial cohort were obtained from the Finnish Cancer Registry (FCR) and the Finnish Population Information System (PIS) maintained by the Digital and Population Data Services Agency. The FCR provides a population-based database of all cancer cases diagnosed in Finland starting from 1953. These data contain details of the cancers and the patients' personal identity codes which can be used to reliably link persons between different registries. The FRC has 96% and 86% coverage for solid and nonsolid tumors, respectively, which makes it nearly complete.[26] Data retrieved from the PIS include the personal identity codes, family relations, and dates of birth and death of Finnish residents alive in 1967 or born from there on. Linkage to the offspring and siblings is systematically available for persons born after 1955 and alive in 1967. For offspring, links are nonsystematically available for children born after 1940.

The first member of the family who was diagnosed with female breast cancer aged 40 or younger from 1 January 1970 to 31 December 2012, in Finland was selected as the proband. The probands and their family members (offspring, mother, father and siblings of the proband, siblings' offspring and spouses of the probands and siblings of the spouses) were linked with the PIS. There is only one proband in each family, but the same person may appear more than once in the cohort if they belong to different families. Spouses of the probands and siblings of the spouses are included in the same category. We did not include probands' grandparents or other older second-degree relatives in the study as the information could not be fully retrieved from the PIS. Additionally, we are missing information on some parents of the probands. Information on both parents was

missing for 26.3% of the probands, whereas 7% had information on one parent only.

Cancers were considered familial if they occurred in a family with a female diagnosed with a preceding EO breast cancer and were diagnosed at age 40 or younger. Cancers were classified according to the International statistical classification of diseases and related health problems (ICD-10). Discordant (other than breast) cancers included in the analysis and their corresponding ICD-10 codes are listed in Data S1 (Table A1). Follow-up of the family members started either from 1 January 1953, or at the date of the family members' birth. Depending on the event whichever happened first, the subjects of the study were followed up either for cancer diagnosis, death, emigration, 31 December 2017 or to the date the subject turned 41 years (early-onset follow-up). For the analysis of late-onset familial aggregation, the follow-up was started at the age of 41 and was terminated on the cancer diagnosis, death, emigration or 31 December 2017, whichever happened first (late-onset follow-up). Multiple cancer diagnoses were included only if they were primary cancers of different locations. Follow-up periods were modified to avoid immortal time bias which is a period of time when cancer could not be diagnosed due to study design. Therefore, family members of the proband were not considered to be at risk of cancer between 1 January 1970, and the date of diagnosis of the proband (immortal period). Immortal periods were left out when estimating the SIRs to avoid bias when evaluating familial aggregation.[27] In families with at least one breast cancer diagnosed in addition to the proband's, the original clinical and pathology notifications from the FCR data were examined and any notes indicating the presence of BRCA1/2 gene mutation were extracted. No BRCA1/2 gene mutation carriers were reported in families with multiple breast cancers but it should be noted that the pathological reports were available only until the year 2014.[27]

Familial aggregation was estimated by using standardized incidence ratios (SIR) to compare sex-, age- and period-specific cancer incidence among family members to that in the population of Finland. The age groups were divided into 5-year intervals with an exception: 0 to 4, 5 to 9, ..., 35 to 40, 41 to 44, 45 to 49, ..., 85 to .... Calendar periods were split into 5-year intervals from 1953 to 2017. Age groups from 41 to 85 to ... were included in the analysis to confirm the validity of the data. SIRs were calculated for all first-degree relatives of the proband (offspring, siblings, mother and father of the proband) combined and separately for subgroups of family members according to relatedness to the proband. Additionally, familial aggregation was evaluated for siblings' offspring and spouses of the probands and siblings. As some cancers only occur in one sex, we account for sex in the estimation of SIR by considering only sex-specific target population, such as only female population for ovarian cancer and only male population for testicular cancer. Stratified analyses of familial aggregation were performed by histological subtypes of breast cancer (ductal and lobular) and testicular cancer (seminoma and non-seminoma).

## 3 | RESULTS

The numbers of families, relatives, and discordant (other than breast cancer) EO cancers of relatives of EO breast cancer probands for each cancer site are shown in Table 1. Only 5.5% of the probands' families had another family member with any discordant EO cancer. The most common discordant familial EO cancers were cancers of the testicle (0.6% of the families) and the thyroid gland (0.6%).

Standardized incidence ratios (SIR) for discordant EO cancers among relatives of probands are presented in Table 2 (full table available in Table A2). The SIR for any discordant cancer in first-degree relatives was 0.99 (95% CI: 0.84-1.16). Children of the probands had a significantly increased risk (SIR 1.27, 95% CI: 1.03-1.55) but the siblings did not have an increased risk for any discordant cancer (SIR 0.93, 95% CI: 0.68-1.25). A decreased risk for any cancer was seen in fathers (SIR 0.43, 95% CI: 0.17-0.88), mothers (SIR 0.48, 95% CI: 0.22-0.91) and spouses (SIR 0.58, 95% CI: 0.40-0.81). The risk in siblings' children was comparable to population cancer risk (SIR 1.16, 95% CI: 0.97-1.37).

Regarding site-specific familial cancer risks, the SIR for testicular cancer was increased in siblings' children (SIR 1.74, 1.07-2.69), in whom we observed 20 males with testicular cancer while only 11.5 was expected. The SIR for ovarian cancer in siblings' children was 2.69, 95% CI: 1.08-5.53 (7 observed cases vs 2.61 expected). Neither testicular nor ovarian cancer showed significantly increased risks in other subgroups or first-degree relatives. In siblings of the probands, we found a significantly elevated risk of EO pancreatic cancer (SIR 7.61, 95% CI: 1.57-22.23) The risk for thyroid cancer was nonsignificantly increased in children of the probands (SIR 1.86, 95% CI: 0.99-3.19).

To consider the possible role of sex-linked inheritance or hormonal factors in EO testicular and ovarian cancers, we stratified the siblings' children's risk by the siblings' gender (Table 3). The risk of EO ovarian cancer was significantly elevated in daughters of the probands' brothers (SIR 4.65, 95% CI: 1.71-10.13) and the risk of EO testicular cancer was significantly elevated in sons of the proband's sisters (SIR 1.99, 95% CI: 1.03-3.47).

When stratifying by the histological subtype (ductal or lobular) of EO breast cancer, siblings' children of EO ductal breast cancer probands had an elevated risk of EO kidney cancer (SIR 3.34, 95% CI: 1.23-7.27; Table A3). In addition, significantly increased risks were seen for late-onset ovarian cancer in any first-degree relatives (SIR 1.40, 95% CI: 1.10-1.75), mothers (SIR 1.32, 95% CI: 1.00-1.72) and sisters (SIR 1.78, 95% CI: 1.10-2.73; Table A3). No increase in cancer risk was observed in relatives of probands with lobular breast cancer. There were no other major differences in familial risk of discordant EO cancers by histological subtypes of breast cancer.

We also studied familial aggregation of testicular cancer by histological subtypes (seminoma or non-seminoma) in subtypes (ductal and lobular) of the proband's breast cancer (Tables A3 and A4). The SIR for EO non-seminoma was elevated in siblings' sons of the probands both overall (SIR 2.17, 95% CI: 1.22-4.29) and when the proband had ductal carcinoma (SIR 2.00, 95% CI: 1.00-3.58). The risk of non-

**TABLE 1** Number of families, relatives and familial early-onset cancers (≤40 years) for the most common discordant familial cancers.

| Cancer | ICD-10 | Families | Relatives | Number of cancers other than breast among family members | | | | | Number of families with familial cancers | Percentage of families with familial cancers |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 0 | 1 | 2 | 3 | Total | | |
| Any other than breast | C00-49, C51-96, D09.0-1, D32-33, D41-43, D45-47, D76 | 5562 | 54 753 | 5258 | 289 | 15 | 0 | 319 | 304 | 5.5 |
| Testicle | C62 | 5490 | 30 007 | 5457 | 33 | 0 | 0 | 33 | 33 | 0.6 |
| Thyroid gland | C73 | 5562 | 54 753 | 5529 | 33 | 0 | 0 | 33 | 33 | 0.6 |
| Melanoma of the skin | C43 | 5562 | 54 753 | 5535 | 27 | 0 | 0 | 27 | 27 | 0.5 |
| Brain | C70-72 | 5562 | 54 753 | 5537 | 25 | 0 | 0 | 25 | 25 | 0.4 |
| Hodgkin lymphoma | C81 | 5562 | 54 753 | 5537 | 24 | 1 | 0 | 26 | 25 | 0.4 |
| Colon and rectum | C18-20 | 5562 | 54 753 | 5541 | 21 | 0 | 0 | 21 | 21 | 0.4 |
| Ovary | C56, C57.1-4, C48.1-2 | 5189 | 24 746 | 5171 | 18 | 0 | 0 | 18 | 18 | 0.3 |
| Acute lymphoblastic leukemia/ lymphoma | C91.0 | 5562 | 54 753 | 5545 | 17 | 0 | 0 | 17 | 17 | 0.3 |

seminoma testicular cancer was not increased in relatives of lobular breast cancer probands. Familial risks of seminoma type of testicular cancer were not increased.

As a sensitivity analysis, we estimated SIRs for discordant cancers in relatives of probands when the relatives were ≥41 years at the time of diagnosis (late-onset, Table A5). Most importantly, statistically significant elevations in SIRs were seen for ovarian cancer in first-degree relatives (SIR 1.49, 95% CI: 1.22-1.81), mothers (SIR 1.44, 95% CI: 1.13-1.81) and siblings (SIR 1.70, 95% CI: 1.11-2.49) of probands.

## 4 | DISCUSSION

We found increased familial risks of EO testicular and ovarian cancers in siblings' children and pancreatic cancer in siblings of women with EO breast cancer. In addition, an increased risk of any other EO cancer than breast cancer was observed in offspring of females with EO breast cancer. In our data, most of the EO cancers were nonfamilial (95%) and it was rare (5%) to have at least one other family member affected with a discordant cancer in addition to proband's breast cancer. The most common familial cancers combined with proband's breast cancer were testicular and thyroid gland cancers occurring in 33 (0.6%) and in 33 (0.6%) families, respectively.

We found a moderately increased risk of any other EO cancer than breast cancer in offspring of the probands. Increased overall cancer risk in offspring of mothers with breast cancer diagnosed at a young age has been reported earlier by Anderson et al.[7] The results of our study are not fully comparable to those of Anderson and colleagues as their data included also breast cancers of the offspring, which were left out from our analysis. Increased cancer risk in offspring might be due to inherited genetical or shared environmental factors but as the offspring share both genetical and environmental similarities with their mothers it is challenging to separate the exact contribution of each. Concerning genetic predisposition, highly penetrant *BRCA1/2* gene mutations account for only around 10% of EO breast cancers[14] and therefore, it is possible that there exists yet undiscovered genetical susceptibility factors that are shared across cancer sites. Besides genetic factors, lifestyle patterns which increase the risk of cancer, such as smoking,[28] physical inactivity[28] and dietary factors,[28] are commonly shared among family members.

In contrast, the risk of any other EO cancer than breast cancer was decreased in mothers and fathers of the probands. One reasonable explanation behind this observation is that both female and male EO cancer survivors have a significantly lower probability of parenthood[29] compared to healthy young adults. This cannot be taken into account when calculating SIRs and therefore, might be reflected as reduced risk of EO cancer in parents of the probands. Additionally, information on either one or both parents was missing for 33.3% of the probands. Also, the observed decrease in cancer risk among spouses may at least partially be due to lesser, or later, marrying of cancer survivors.[30] Spouses may also have adopted a somewhat healthier lifestyle after the proband has been diagnosed with cancer.

EO cancer of the testicles showed an elevated SIR of 1.74 (95% CI: 1.07-2.69) among siblings' sons of the probands. The association between testicular and breast cancers has not been reported earlier in a manner where a significant increase was observed only in second-degree relatives but not in first-degree relatives. Furthermore, there is no previous evidence of a relationship between EO breast cancer and

**TABLE 2** Site-specific standardized incidence ratios (SIR) and 95% CIs for early-onset. cancer in relatives of females with EO breast cancer.

| Cancer | ICD-10 | Relative | Cancers | SIR | 95% CI |
|---|---|---|---|---|---|
| Any other than breast | [a] | First deg[b] | 157 | 0.99 | 0.84-1.16 |
| | | C[c] | 97 | 1.27 | 1.03-1.55 |
| | | F[d] | 7 | 0.43 | 0.17-0.88 |
| | | M[e] | 9 | 0.48 | 0.22-0.91 |
| | | S[f] | 44 | 0.93 | 0.68-1.25 |
| | | SC[g] | 129 | 1.16 | 0.97-1.38 |
| | | SP[h] | 33 | 0.58 | 0.40-0.81 |
| Liver | C22 | First deg | 3 | 3.63 | 0.75-10.61 |
| | | C | 1 | 2.38 | 0.06-13.27 |
| | | F | 0 | 0.00 | 0.00-50.81 |
| | | M | 0 | 0.00 | 0.00-44.54 |
| | | S | 2 | 7.97 | 0.97-28.81 |
| | | SC | 0 | 0.00 | 0.00-5.83 |
| | | SP | 0 | 0.00 | 0.00-12.34 |
| Pancreas | C25 | First deg | 4 | 3.23 | 0.88-8.27 |
| | | C | 1 | 2.09 | 0.05-11.66 |
| | | F | 0 | 0.00 | 0.00-14.91 |
| | | M | 0 | 0.00 | 0.00-30.90 |
| | | S | 3 | 7.61 | 1.57-22.23 |
| | | SC | 1 | 1.59 | 0.04-8.86 |
| | | SP | 1 | 1.95 | 0.05-10.85 |
| Ovary | C56, C57.1-4, C48.1-2 | First deg | 7 | 1.37 | 0.55-2.83 |
| | | C | 3 | 1.41 | 0.29-4.12 |
| | | M | 2 | 1.38 | 0.17-4.99 |
| | | S | 2 | 1.31 | 0.16-4.73 |
| | | SC | 7 | 2.69 | 1.08-5.53 |
| | | SP | 4 | 2.63 | 0.72-6.72 |
| Testicle | C62 | First deg | 11 | 1.07 | 0.53-1.91 |
| | | C | 8 | 1.13 | 0.49-2.22 |
| | | F | 0 | 0.00 | 0.00-5.13 |
| | | S | 3 | 1.19 | 0.25-3.48 |
| | | SC | 20 | 1.74 | 1.07-2.69 |
| | | SP | 2 | 0.70 | 0.08-2.52 |
| Kidney | C64 | First deg | 1 | 0.27 | 0.01-1.52 |
| | | C | 0 | 0.00 | 0.00-2.45 |
| | | F | 0 | 0.00 | 0.00-12.50 |
| | | M | 1 | 2.94 | 0.07-16.40 |
| | | S | 0 | 0.00 | 0.00-2.42 |
| | | SC | 6 | 2.62 | 0.96-5.71 |
| | | SP | 1 | 0.55 | 0.01-3.08 |
| Melanoma of the skin | C43 | First deg | 11 | 0.76 | 0.38-1.36 |
| | | C | 8 | 0.98 | 0.42-1.93 |
| | | F | 0 | 0.00 | 0.00-4.91 |
| | | M | 0 | 0.00 | 0.00-3.76 |
| | | S | 3 | 0.65 | 0.13-1.91 |
| | | SC | 15 | 1.27 | 0.71-2.09 |
| | | SP | 1 | 0.19 | 0.00-1.04 |

(Continues)

**TABLE 2** (Continued)

| Cancer | ICD-10 | Relative | Cancers | SIR | 95% CI |
|---|---|---|---|---|---|
| Thyroid gland | C73 | First deg | 16 | 1.38 | 0.79-2.23 |
| | | C | 13 | 1.86 | 0.99-3.19 |
| | | F | 0 | 0.00 | 0.00-15.00 |
| | | M | 0 | 0.00 | 0.00-4.89 |
| | | S | 3 | 0.82 | 0.17-2.40 |
| | | SC | 12 | 1.26 | 0.65-2.20 |
| | | SP | 5 | 1.27 | 0.41-2.95 |
| Hodgkin lymphoma | C81 | First deg | 14 | 1.22 | 0.67-2.05 |
| | | C | 11 | 1.65 | 0.83-2.96 |
| | | F | 1 | 0.70 | 0.02-3.91 |
| | | M | 0 | 0.00 | 0.00-3.86 |
| | | S | 2 | 0.82 | 0.10-2.97 |
| | | SC | 11 | 1.06 | 0.53-1.89 |
| | | SP | 1 | 0.31 | 0.01-1.71 |
| Colon and rectum | C18-20 | First deg | 8 | 0.91 | 0.39-1.79 |
| | | C | 3 | 0.67 | 0.14-1.96 |
| | | F | 0 | 0.00 | 0.00-4.18 |
| | | M | 0 | 0.00 | 0.00-4.44 |
| | | S | 5 | 1.92 | 0.62-4.48 |
| | | SC | 9 | 1.45 | 0.66-2.76 |
| | | SP | 4 | 1.29 | 0.35-3.31 |

[a]See Appendix (Table A1).
[b]Father, mother, sibling or child of the proband.
[c]Child.
[d]Father.
[e]Mother.
[f]Sibling.
[g]Sibling's child.
[h]Spouse, either sibling's or proband's.

**TABLE 3** Early-onset testicular and ovarian cancers of offspring of proband's siblings by sex of the sibling.

| Cancer | Relative | Cancers | Expected | SIR | 95% CI |
|---|---|---|---|---|---|
| Testicle | Brother's son | 8 | 5.45 | 1.47 | 0.63-2.89 |
| | Sister's son | 12 | 6.04 | 1.99 | 1.03-3.47 |
| Ovary | Brother's daughter | 6 | 1.29 | 4.65 | 1.71-10.13 |
| | Sister's daughter | 1 | 1.33 | 0.75 | 0.02-4.20 |

EO testicular cancer. However, a few studies have reported an increased risk of testicular cancer at any age in men with a family history of breast cancer.[31,32] These studies also found a greater risk of testicular cancer in sons of mothers who were diagnosed with breast cancer at an earlier age.[31,32]

Seikkula et al described an increased risk of EO testicular cancer in sons of siblings' of men with testicular cancer but not in sons of the testicular cancer probands themselves, utilizing the same Finnish Cancer Registry data as our study.[33] A significant risk observed only in second-degree relatives can be partly explained by the difference in the number of children of probands and their siblings, impacting the statistical power. The number of siblings' sons in our data was nearly double the number of probands' sons which makes the SIR estimate of siblings' sons statistically more powerful and therefore limits the possibility that this is a chance finding. The expected number of testicular cancers in offspring might be a little lower in reality as it does not take into account that women with a history of EO cancer tend to have a lower relative probability of having children compared to their healthy counterparts.[29]

Both testicular and breast cancers are known to have a strong familial association[34] with testicular cancer having consistently one of the highest familial risks reported in different studies.[5,34] One

epidemiological study has suggested a recessive mode of inheritance or susceptibility loci linked to the X chromosome.[35] An X chromosome-linked inheritance pattern could also contribute to the observation that sons of the proband's sisters were at an elevated risk of testicular cancer, but sons of the brothers were not. No highly penetrant predisposition genes have been discovered regarding testicular cancer and it has been concluded that the inherited component is multifactorial.[36] Recently, germline variants in *CHEK2* have been linked to an increased risk of testicular cancer[37] besides its known association with breast cancer.[38]

Literature offers controversial evidence regarding environmental risk factors to testicular cancer. However, most of the suggested risk factors are thought to derive from fetal life with the most well-known being cryptorchidism.[31,39] There is inconsistency concerning the role of prenatal exposure to estrogen as some of the studies have shown a strong association with testicular cancer[39,40] while others have not observed such connection at all.[31] Estrogen exposure could serve as a common etiological factor since premenopausal breast cancer is thought to be associated with higher estrogen exposure.[21,22] Finnish men are known to have a relatively low incidence of testicular cancer compared to other Nordic countries.[41] However, a recent study discovered that Finland has had the highest relative increase in testicular cancer incidence among Nordic countries during the past years.[41] By observing the speed of the increase, it is unlikely that genetic factors would explain such a rapid increase in incidence. Ekbom et al studied the incidence of testicular cancer in Finnish immigrants in Sweden and found that the reduced risk of testicular cancer was retained independent of age at immigration or duration of stay which greatly supports the theory of early exposure to environmental as a strong predictor of testicular cancer incidence.[42] Supporting the major role of environmental factors are observations that the descendants of the Finnish immigrants do not retain the same reduced risk as their fathers[43] and that a smaller age difference between brothers contributes to a greater risk of testicular cancer.[44]

For now, it remains unexplained what could have caused sons of the probands' siblings to be exposed to these shared etiological factors that the probands' offspring seem to avoid. Perhaps, the explanatory mechanism behind this connection is not a single shared etiological component but an interplay between different common predisposition factors as this connection does not seem to follow any known inheritance pattern nor offer any obvious cues of common etiology. Our findings are interesting but raise some questions about unknown genetical and environmental mechanisms that need to be further studied.

We further stratified testicular cancers by their histological subtypes to see if the clustering with breast cancer was associated specifically either with seminoma or non-seminoma as they are thought to have partially different etiological backgrounds.[45] Non-seminoma showed an increased SIR in probands' siblings' sons while the risk of seminoma was at the population level in all relatives of probands. A similar pattern of inheritance was detected in a study conducted by Seikkula et al using the same data as in our study.[33] Non-seminomatous testicular cancer tends to occur at lower ages than seminomatous testicle cancer[46] which could explain why we did not see an increased risk of seminoma as our cohort was restricted to patients aged 40 years or less.

Ovarian cancer is the most commonly reported discordant cancer in association with EO breast cancer[3,11] as the risk of ovarian cancer is substantially increased in carriers of highly penetrant *BRCA1* and *BRCA2* gene variants.[9,10] However, we observed a statistically significant increase in SIR for EO ovarian cancer only in siblings' offspring but not in the first-degree relatives of the proband. All subgroups of first-degree relatives had elevated SIRs for EO ovarian cancer although none of them statistically significantly. Increased ovarian cancer risk in second-degree relatives of women with EO breast cancer has been described earlier[11] but not unaccompanied by increased risk in first-degree relatives. However, it should be noted that this elevation was detected in relatives with known *BRCA* mutation carriage and the age of the relatives was not restricted.[11]

Although we did not have comprehensive information on every proband's mutation statuses, it has been approximated that 44% of the Finnish breast-ovarian cancer families and 21% of families with multiple breast cancer cases are attributable to *BRCA1/2* gene mutations.[47] Consequently, it is probable that less penetrant gene mutations are common in hereditary breast-ovarian cancer families in the Finnish population, and as the incidence of EO ovarian cancers is low, the statistical power to detect aggregation caused by low penetrance gene mutations is weaker. Furthermore, almost all of the EO ovarian cancers were detected in daughters of the probands' brothers (6 out of 7 in total). Both probands and their sisters might be less willing to have children after being tested positive for *BRCA1/2* mutation carriage[48] and therefore, the number of ovarian cancers in their offspring is reduced. In contrast, male carriers have been reported to have similar fertility intentions compared to noncarriers.[48]

We did, however, see significant increases in SIR for late-onset (>40 years) ovarian cancer in mothers, sisters, and all first-degree relatives, which are in line with previous literature.[6,49] Olsen et al found SIRs for ovarian cancer of 1.7 for mothers and 1.9 for sisters of EO breast cancer patients[49] which is similar to our estimates, 1.4 for mothers and 1.7 for sisters.

There was a notable difference in SIRs for late-onset ovarian cancer when breast cancer was separated into subtypes. The increased SIR was seen in first-degree relatives overall, siblings, and mothers of breast cancer patients when the breast cancer was ductal but was absent when the cancer was lobular. Part of this association might be explained by etiological differences between lobular and ductal subtypes as the ovarian cancer susceptibility gene *BRCA1* is clearly more prevalent in ductal than in lobular breast cancer.[50] Additionally, as ductal carcinoma is more common than lobular carcinoma the statistical power is higher for ductal breast cancer than that for lobular.

In our study, siblings of probands were at an increased risk (SIR 7.61, 95% CI: 1.57-22.23) of EO pancreatic cancer. In addition to the current study, previous research has established an association between EO pancreatic and breast cancers.[51] A major part of this association is likely to be explained by known shared susceptibility genes including highly penetrant *BRCA1*[12,51] and *BRCA2*[10,51] germline mutations.

Other cancers that have been suggested to be associated with EO breast cancer include cancers of the prostate,[1,6,11] colon,[1,3,5] cervix[3,11] and thyroid gland[1,5] along with a variety of other less consistently established cancer sites. We detected no prostate cancers in relatives of the probands which was expected as prostate cancer is extremely rare in young adults. Similarly, cancers of the GI-tract are rare in young patients. The incidence of cervical cancer is low in Finland due to an extensive screening program, explaining the very small number of EO cancer cases in our study. Regarding thyroid gland cancer, a nonsignificantly increased risk (SIR 1.86, 95% CI: 0.99-3.19) was observed among children of the probands.

Among the strengths of our study were the use of population-based registry data and its high coverage of malignant tumors[26] which limits the possibility of information or selection bias. The ability to link the cancer registry data with data obtained from the Population Information System enables gathering information on probands' and their relatives' cancer status, therefore making it possible to reliably examine familial aggregation of cancer. Another major strength was that follow-up of cancer incidence can be considered complete.

The relationships between EO cancers may indicate the existence of shared genetic susceptibility genes or early exposure to common environmental risk factors at a young age. The structure of our cohort is particularly powerful for detecting familial clustering of cancers and evaluating the etiology of the association as it includes only cancer patients diagnosed under the age of 41 linked to their relatives. By focusing on probands with EO cancers the number of sporadic cancers decreased and therefore the risk of overestimation of familial cancer risk was minimized. The inclusion of second-degree relatives and spouses brings more information on the difference of the genetic and environmental components of familial cancer risk as the proportion of shared genetic and environmental background is altered when the relationship changes.

A potential limitation of our study was the inability to accurately identify individuals with hereditary cancer syndromes and predisposition gene mutations in the families as registry data do not include comprehensive information on the gene mutation carriage status. The inclusion of hereditary cancer syndromes could possibly contribute to the increase in familial aggregation in offspring of the probands. However, the number of BRCA-carriers is likely to be low as we observed a low number of ovarian cancers in first-degree relatives of the probands. Also, it should be noted that since many of the probands have been diagnosed with breast cancer at reproductive age, they may have fewer children than their healthy counterparts, including their siblings. This might lead to a weaker statistical power to detect a positive association between the proband's breast cancer and the subsequent other cancer in the offspring.

## 5 | CONCLUSIONS

The offspring of female EO breast cancer patients were at an elevated risk of any EO cancer other than breast cancer. We also found an increased familial risk of EO testicular and ovarian cancers in offspring of siblings. Our results indicate the possible role of early exposure to estrogen or shared genetic factors in both ovarian and testicular cancers in families with EO breast cancer.

## AUTHOR CONTRIBUTIONS

**Jasmiina N. J. Rantala:** Designed the analysis; conceptualization; writing - original draft. **Sanna M. M. Heikkinen:** Designed the analysis; conceptualization; revised and edited the article. **Elli M. Hirvonen:** Conceptualization; statistical analyses and revised the article. **Tomas Tanskanen:** Conceptualization; revised the article. **Nea K. Malila:** Conceptualization; revised the article. **Janne M. Pitkäniemi:** Designed the analysis; conceptualization; revised and edited the article; supervised the work. All authors read and approved the final article. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author (Jasmiina N. J. Rantala) upon reasonable request and with permission of Finnish Cancer Registry.

## ETHICS STATEMENT

The study was approved by the Ethical Committee of the Finnish Institute of Health and Welfare (Permit no THL/1588/5.05.00/2019). All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki). Informed consent from study participants was unnecessary as the study utilized registry data not based on consent (based on the Finnish legislation), Act on the Finnish Institute for Health and Welfare 668/2008 (cancer information), Act on the Population Information System 661/2009 (other than health information) and the Act on the Secondary Use of Health and Social Data (552/2019).

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## SUPPORTING INFORMATION

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