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ORIGINAL RESEARCH ARTICLE

Long-term risk of cancer among the first-degree relatives of epithelial ovarian cancer patients: A cohort study with 48 years of follow up

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Abstract

Introduction: The long-term risk of cancer among first-degree relatives of ovarian cancer patients, especially their offspring, is of apparent clinical importance. Risks caused by known inherited factors such as *BRCA1* or *BRCA2* pathogenic variants are well established, but these account for only about 15% of ovarian cancer cases. Less is known about the possible familial risks of sporadic ovarian cancers.

Material and methods: Using registry data, we conducted a retrospective cohort study with a total of 6501 first-degree relatives of 559 epithelial ovarian cancer patients. We studied the occurrence of overall cancer and cancer in specific sites known or suspected to be associated with ovarian cancer (breast, cervix, colon, endometrium, lung and trachea, skin melanoma, ovary, pancreas, prostate, rectum, and stomach).

Results: The overall number of cancers was not increased among the first-degree relatives of epithelial ovarian cancer patients during the up to 48 years of follow up. Among female relatives, the standardized incidence ratio for ovarian cancer was 1.92 (95% CI 1.27–2.79), mostly explained by a 2.30-fold (95% CI 1.46–3.45) risk among the patients' sisters. There was a decreasing trend in the standardized incidence ratio for ovarian cancer among patients' sisters by increasing age of the index patient.

Conclusions: In our study cohort, we did not observe an increase in the overall cancer risk among the first-degree relatives of epithelial ovarian cancer patients in comparison with the general population. The risk for ovarian cancer, however, was increased. Current recommendations suggest prophylactic removal of the fallopian tubes and ovaries only with identified inherited risk factors. Our results emphasize the role of genetic counseling and testing, particularly in young ovarian cancer patients and their close female relatives.

KEYWORDS
cancer risk, epithelial ovarian cancer, first-degree relatives, ovarian cancer risk, standardized incidence ratio

Abbreviations: BRCA, breast cancer gene; *BRCA1*, breast cancer gene 1; *BRCA2*, breast cancer gene 2; CI, confidence interval; EOC, epithelial ovarian cancer; SIR, standardized incidence ratio.

1 | INTRODUCTION

With almost 300 000 incident cases per year, ovarian cancer is the third most common gynecological cancer in the world.[1] It has the worst prognosis among the gynecological malignancies—even in high-income countries only half of the patients survive for 5 years. Worldwide, ovarian cancer causes more than 180 000 deaths each year.[1]

A vast majority of ovarian cancers, approximately 95%, are of epithelial origin. The main type of epithelial ovarian cancer (EOC) is high-grade serous carcinoma, the majority of which are considered to have an origin in the fallopian tube. Other malignant ovarian tumors, such as germ cell and sex cord stromal tumors occur rarely. Approximately 15% of the ovarian cancers are related to a known inherited risk factor, such as *BRCA1* or *BRCA2* pathogenic variant or, to a lesser extent, Lynch syndrome or Peutz-Jeghers syndrome.[2,3] Hence, most ovarian cancer cases are considered sporadic, although some inherited susceptibility is assumed.

The poor prognosis of ovarian cancer is mostly related to the intra-abdominal location of the tumor. Developing or early-stage cancers are virtually asymptomatic and unlikely to be detected. Hence, symptomatic patients mostly have advanced disease, which is usually not curable. However, the introduction of new medications, especially poly-ADP ribose polymerase inhibitors, have given completely new insights into the long-term treatment options of selected ovarian cancer patients.[4,5]

To date, there is no effective screening for ovarian cancer. The only means for prevention is risk-reducing surgery for women with an increased risk. Surgical removal of the ovaries and fallopian tubes at around 40 years of age is generally recommended to women with a known *BRCA1* or *BRCA2* pathogenic variant.[2] For the family members of ovarian cancer patients negative for BRCA or known homologous recombination deficiencies, prophylactic surgery is generally not recommended because of the inconclusive evidence on the benefits of risk-reducing surgery, and the known harmful effects of early surgical menopause.[3]

Most ovarian cancer patients wish to receive counseling, not only about the ovarian cancer and treatment options but also about the possible risk of ovarian or other cancers for their family members. For *BRCA1* mutation carriers, the cumulative risk of breast cancer is 72% and the risk of ovarian cancer is 44% up to the age of 80 years.[6] For *BRCA2* carriers, the cumulative risks are 69% and 17%, respectively. For the more recently identified genes, *RAD51C* or *RAD51D*, the cumulative ovarian cancer risks up to the age of 80 years are 11% and 13%, respectively, and for *PALB2* they are both 5%.[7,8] In Lynch syndrome, colon cancer and endometrial cancer are more common than ovarian cancer, for which the cumulative risk up to age of 75 years is 10%–17% depending on the gene.[9] To lower their risks, many women with known inherited risk choose risk-reducing salpingo-oophorectomy, if this option is offered.[10]

A previous meta-analysis suggested a 3.1-fold ovarian cancer risk for the first-degree relatives of ovarian cancer patients, with daughters having the highest risk.[11] A more recent study using the Swedish Family-Cancer Database found an approximately 2.5-fold risk of ovarian cancer of any histology for women with mother or sister diagnosed with ovarian cancer, and the risk was more than 10-fold for those with both a mother and sister having the diagnosis.[12] Previously, an increased risk of breast and endometrial cancers in the first-degree relatives of ovarian cancer patients was reported based on data from the same Swedish database.[13] The risk of, especially, pancreatic cancer but also of prostate cancer has been suggested to be increased among the first-degree relatives of patients with hereditary ovarian cancers, mostly due to *BRCA2* pathogenic variants or Lynch syndrome.[14,15] More recently, familial ovarian cancer risks have also been related to rare germline variants.[3,16,17]

In a Finnish cohort study of family members of EOC patients diagnosed during 1980–1982, no increase in overall cancer risk was observed in a follow up ending in 1993, but the risk of ovarian cancer among first-degree relatives was 2.8-fold compared with the risk in the general population.[18] Due to the relatively short follow-up time, results concerning patients' children remained uninformative. In the present study, we aimed to assess the long-term risk of cancer among the first-degree relatives of ovarian cancer patients by using the same historical population-based cohort with full family histories as the basis.

Key message

First-degree female relatives of epithelial ovarian cancer patients have a nearly two-fold risk of ovarian cancer. The risk seems highest for the sisters of young ovarian cancer patients. In the current study, no excess risk of other cancers was observed.

2 | MATERIAL AND METHODS

The collection of the baseline data has been described elsewhere in detail.[18] Briefly, the nationwide Finnish Cancer Registry was used to identify all women with an EOC diagnosed up to the age of 75 years during 1980–1982. The first-degree family members of these patients were traced from the national Population Registry and from local parish records. Of the 863 EOC patients, it was possible to obtain complete information on parents, siblings, and children for 559 patients (65%). Tracking of mothers, fathers, and siblings of the index patients was done mainly manually from local parish records. Tracing of the parents, most born in the 19th century, was complicated due, for example, to their movement caused by the First and Second World Wars in Finland. Also, some of the manual local parish records had been destroyed by fires or other disasters. Only the 559 patients with complete information on the first-degree relatives ($N = 6501$) were included in the study. In the original article by Auranen et al., a total of 3072 family members were reported as being at risk during the study period from the 1 January 1967

onwards, when the personal ID code system was available for reliable registry linkages.[18] In the current study, the number of family members at risk was 3073, as one more daughter was identified. The study was approved by the Finnish Institute for Health and Welfare. According to Finnish legislation on registry-based studies, informed consents were not required from individual patients.

For the current study, dates of death or emigration were obtained from the Population Information System maintained by the Digital and Population Data Services Agency in Finland. Information on cancer diagnoses until the end of the study period, defined as 31 December 2014, were collected from the Finnish Cancer Registry. Information on organ removal surgery was gathered from the Care Register for Health Care (HILMO).

For the parents of the index patients, the follow up for cancer was started at the date of birth of the index patient or on 1 January 1967, whichever came last. For all other relatives, the follow up for cancer was started at their date of birth or on 1 January 1967, whichever was later. The follow up ended at death, at emigration, or on 31 December 2014, whichever came first.

2.1 | Statistical analyses

The numbers of observed cancer cases and person-years at risk were calculated for the first-degree relatives by sex, age (5-year categories), and calendar period of follow up (1967–1975, 1976–1984, 1985–1993, and 1994–2004), separately for parents, siblings, and children. Numbers of observed cancers and person-years at risk were also stratified according to the age of diagnosis of the index patient; these figures were eventually reported for ovarian cancer. Our main focus was on the occurrence of cancer in specific sites previously known or suspected to be associated with ovarian cancer. Hence, our main analyses included cancers of the breast, cervix, colon, endometrium, lung and trachea, skin melanoma, ovary, pancreas, prostate, rectum, and stomach.

The expected numbers of cancer cases overall and for specific cancer types were calculated by multiplying the number of person-years in a stratum by the corresponding cancer incidence rate in Finland. Standardized incidence ratios (SIRs) were calculated as ratios of the observed to the expected numbers of cancer, and 95% confidence intervals (CIs) were defined presuming the numbers of observed cancer cases to follow a Poisson distribution.

2.2 | Ethics statement

The original study conducted in the 1990s was approved by the National Research and Development Centre for Welfare and Health on January 11, 1993 (Diary number 3415/95/92), more recently known as the Finnish Institute for Health and Welfare. A new permission to cover the updated registry linkages and analyses was granted by the Finnish Institute for Health and Welfare on May 28, 2018 (Diary number THL/499/5.05.00/2018). According to Finnish legislation, patients' consents for performing this study or publishing the results were not required.

3 | RESULTS

Within the study period of 48 years (1967–2014), we did not observe an increase in the overall number of cancers in the first-degree relatives of EOC patients compared with the general population (Table 1). The mean follow-up time ranged from 15 years for the patients' fathers to more than 45 years of follow up among the daughters of EOC patients (Table 1).

Of the 11 specific cancers analyzed, the only statistically significant increase in cancer risk among the first-degree relatives was observed for ovarian cancer, which was nearly two-fold (SIR 1.92, 95% CI 1.27–2.79) (Table 2). This was mostly explained by a 2.30-fold (95% CI 1.46–3.45) risk among sisters of ovarian cancer patients. The SIR was 0.47 for the mothers and 1.54 for the daughters, but these did not reach statistical significance.

There was a slightly decreasing trend in the ovarian cancer risk of the sisters by the increasing age of the index patient (Table 3). The highest SIR of ovarian cancers was observed for the sisters aged 30–44 years; they had a 7.09-fold risk of ovarian cancer compared with

TABLE 1 Observed and expected numbers of cancers (all sites combined) and standardized incidence ratios (SIR) with 95% confidence intervals (CI) for first-degree relatives of epithelial ovarian cancer patients.

Relative	Number of relatives	Mean length of follow up (y)	Expected cancers	Observed cancers	SIR	95% CI
Female	1606	35.0	344.1	334	0.97	0.87–1.07
Mother	287	18.5	57.4	47	0.82	0.60–1.08
Sister	918	35.6	239.4	240	1.00	0.88–1.13
Daughter	401	45.6	47.4	47	0.99	0.73–1.31
Male	1467	33.2	361.9	361	1.00	0.90–1.10
Father	171	15.0	44.3	56	1.26	0.95–1.64
Brother	861	31.3	270.7	266	0.98	0.87–1.10
Son	435	44.3	46.9	39	0.83	0.59–1.13

TABLE 2 Observed and expected numbers and standardized incidence ratios (SIR) with 95% confidence intervals (CI) of specific cancers in first-degree relatives of epithelial ovarian cancer patients.

Site	Observed cancers	Expected cancers	SIR	95% CI
Breast, female	78	87.5	0.89	0.70–1.11
Cervix	7	6.7	1.05	0.42–2.16
Colon				
Female	22	22.4	0.98	0.62–1.48
Male	21	17.4	1.21	0.75–1.84
Endometrium	25	20.6	1.22	0.79–1.79
Lung and trachea				
Female	16	16.3	0.98	0.56–1.59
Male	64	70.1	0.91	0.70–1.17
Skin melanoma				
Female	8	8.7	0.92	0.40–1.80
Male	8	8.9	0.89	0.39–1.76
Ovary	27	14.1	1.92	1.27–2.79*
Pancreas				
Female	14	14.7	0.96	0.52–1.60
Male	19	13.0	1.47	0.88–2.29
Prostate	91	85.8	1.06	0.85–1.30
Rectum				
Female	11	12.5	0.88	0.44–1.57
Male	13	13.8	0.94	0.50–1.61
Stomach				
Female	20	17.6	1.14	0.70–1.76
Male	31	21.4	1.45	0.99–2.06

*$p < 0.01$.

TABLE 3 Observed numbers of ovarian cancer and standardized incidence ratios (SIR) with 95% confidence intervals (CI) for sisters of epithelial ovarian cancer (EOC) patients, by age of diagnosis for both the index patient and the sister.

Age of the index patient at EOC diagnosis (y)	Age of the sister during follow up (y)	Observed ovarian cancers	SIR	95% CI
<45	30–44	1	7.35	0.19–40.9
	45–59	1	2.14	0.05–11.9
	60–74	1	2.40	0.06–13.4
	75+	0	0.00	0.00–42.7
	All ages	3	2.65	0.55–7.75
45–54	30–44	1	5.98	0.15–33.3
	45–59	3	3.41	0.70–9.95
	60–74	2	1.46	0.18–5.27
	75+	1	1.72	0.04–9.59
	All ages	7	2.33	0.94–4.79
55–75	30–44	1	8.32	0.21–46.4
	45–59	3	1.99	0.41–5.81
	60–74	7	1.90	0.76–3.91
	75+	2	0.72	0.09–2.60
	All ages	13	1.61	0.86–2.74
All	30–44	3	7.09	1.46–20.7*
	45–59	7	2.45	0.99–5.04
	60–74	10	1.83	0.88–3.35
	75+	3	0.87	0.18–2.54
	All ages	23	1.88	1.19–2.82**

*$p < 0.05$; **$p < 0.01$.

the general population. For the sisters aged 45–59 years, the SIR was almost 2.5 (Table 3).

Of all female relatives, one mother, 43 sisters, and 43 daughters had both fallopian tubes and ovaries removed during the study period, and an additional two sisters and one daughter had bilateral oophorectomy without salpingectomy. The average age of adnexal surgery was 59.1 years for the sisters and 50.7 years for the daughters; the only mother with salpingo-oophorectomy was 78 years at the time of surgery.

Breast cancers were not observed more often than expected. The SIR for mothers was 0.80 (95% CI 0.34–1.57), for sisters was 0.89 (95% CI 0.67–1.17), and for daughters was 0.93 (95% CI 0.55–1.47).

Concerning male relatives, the point estimates for prostate and pancreatic cancers were somewhat elevated but did not reach statistical significance. Among the fathers of ovarian cancer patients, cancers of the digestive organs (esophagus, stomach, small intestine, colon, rectum, liver, gallbladder, biliary system, pancreas, and other/unspecified) were observed more often than expected (SIR 1.85, 95% CI 1.16–2.79). The other male relatives did not have an excess number of these or other cancers.

4 | DISCUSSION

Based on the current follow-up study on relatives of EOC patients, we did not detect any increase in overall cancer occurrence even with a very long follow-up time, the mean of which was over 30 years for the patients' siblings and over 40 years for their children. The only significantly increased cancer risk observed was for ovarian cancer, which was roughly two-fold. This increased risk concerned especially sisters of the index patients. For them, the risk was most pronounced (SIR seven-fold) when the index patient had early-onset ovarian cancer (diagnosed before the age of 45 years). Furthermore, sisters also tended to have ovarian cancer at a younger age than the population average. In absolute numbers, an excess of 13 ovarian cancer cases, in addition to the 14 expected, was observed among the 918 sisters during the entire follow-up period. The point estimate for ovarian cancer risk was also elevated for daughters, but this finding was not statistically significant. Mothers' low risk estimate should be interpreted with caution, as many of them were born in the 19th century and individual cancer data were only available from 1967 onwards; hence, our results mainly come from old age categories.

For male family members, there was little evidence on a possible increased risk of specific cancers, namely prostate and pancreatic cancers, that could be due to families with *BRCA1* or *BRCA2* pathogenic variants.

Our results are in line with previous studies that showed an increase in the risk of ovarian cancer for the first-degree relatives of ovarian cancer patients.[11–13] In contrast to the Swedish study by Hemminki and Granström,[13] we did not detect an increased risk of breast and endometrial cancer in our cohort. Our study could only add weak support to the earlier findings on an increased risk of pancreatic and prostate cancer among male relatives.[14,15]

In the first analysis of this cohort in the beginning of the 1990s, we observed that in 27 out of the 559 families, ovarian cancer was also diagnosed in a sister or mother of the index patient.[18] Histological samples from 51 tumors in 23 of these families were obtained in 1999, and screening of BRCA mutations was performed on these samples for the Finnish founder mutations then identified. A pathogenic variant was detected in only 26% of the 23 families, including all families with three first-degree relatives with ovarian cancer, and the only breast-ovarian cancer family with an early-onset (45 years) breast cancer.[19] It is noteworthy that due to strong founder mutations in Finland, pathogenic variants in *BRCA2* are as common as in *BRCA1*. As the ovarian cancer risk is significantly lower for *BRCA2* carriers, this may explain the relatively low number of BRCA-positive families and why we do not find a relation between ovarian and breast cancer in the studied families. The entire study cohort could not be screened for BRCA variants, as at the time of the diagnosis of the index patients (1980–1982), genetic testing for BRCA genes was not available. Nevertheless, genetic etiology of ovarian epithelial cancer is heterogeneous, including high-risk genes, moderate-risk genes and several low penetrance loci.[20,21] Hence, the genetic susceptibility and higher risk for ovarian cancer for first-degree female relatives, particularly for sisters, is likely to be explained by several different genetic mechanisms.

To our knowledge, the current study is unique in the length of the follow up and completeness of the family data; for comparison, the study by Zheng et al. based on the Swedish Family-Cancer Database reported results for a follow up period of 22 years.[12] Our study data were drawn from the complete high-quality national cancer and population registries, which eliminates the risk of selection bias in the SIR estimates. Unfortunately, full family histories could not be detected for 35% of index patients despite thorough manual searches in addition to the family links available from the population registration system. Exclusion of incomplete families weakens the study power, which is too low to observe minor relative increases in cancer risks among the relatives of EOC patients.

Another limitation is that we were unable to perform histology-specific analysis due to both small numbers of the rarer histological subtypes, and the high number of unspecified histologies. At the time of diagnosis in 1980–1982, 26% of the cancers of the 559 index patients were classified as serous, 16% as mucinous, 9% as endometrioid, 4% as clear cell, 7% as anaplastic, and 38% as unspecified adenocarcinoma. It is likely, that if these histological diagnoses were re-evaluated now, some cancers would be re-classified. The historical cancer registry data do not allow similar histological classification of the reference incidence rates, and therefore it was not possible to stratify SIR estimates for ovarian cancer histology.

As one of our main interests was to study the long-term cancer risks among offspring of EOC patients, we wanted to explore the possible effect of organ removals on the results. Based on register linkages, the number of first-degree family members with salpingo-oophorectomies was small. Hence, analyses with follow up ending at organ removal would have shown almost identical results to those presented in this paper and, therefore, they were dropped.

Most (74/90) of the first-degree relatives with salpingo-oophorectomy also had partial or total hysterectomy at the same operation. Although it is not uncommon to perform hysterectomy concurrently with risk-reducing salpingo-oophorectomy to simplify possible estrogen replacement therapy, it is possible that hysterectomy in combination with salpingo-oophorectomy was performed for other gynecological indications. Therefore, we cannot be certain that these operations were carried out for risk-reducing purposes. The number of families with eventually identified germline BRCA mutation was small in our cohort. It is, however, possible that if a more extended genetic analysis had later been performed in some of the families and subsequently pathogenic variants found, it could have led to risk-reducing operations in those families. Routine tumor BRCA-testing and genetic counseling of newly diagnosed EOC patients started in Finland in 2015, right after the end of our study period. Since then, cascade testing has led to improved identification of BRCA mutation carriers in families of EOC patients, which presumably will increase the number of risk-reducing salpingo-oophorectomies.

For the EOC patients and their families, the current results seem somewhat reassuring: in general, the overall risk of cancer among the first-degree relatives appears similar to that in the general population. However, female family members, particularly of young ovarian cancer patients, should be informed of the disease risk, and genetic testing should be actively pursued. The genetic risk for ovarian cancer is now readily identified, as the updated treatment guidelines recommend genetic testing of all new ovarian cancer patients.[22,23] Current recommendations, in which risk-reducing removal of fallopian tubes and ovaries is suggested only for relatives of patients with known inherited susceptibility, appear adequate. Our results emphasize the role of genetic counseling and testing, particularly in young ovarian cancer patients and their close female relatives. This is especially important in countries with no routine genetic testing for all ovarian cancer patients at the time of diagnosis.

5 | CONCLUSION

Confirming the previous findings, in our study the first-degree female relatives of EOC patients have a nearly two-fold risk of ovarian cancer. The risk is highest among patients' sisters. On the other hand, in our study cohort no excess risk for other cancers was observed

among the first-degree relatives of EOC compared with the general population, even with up to 48 years of follow up.

AUTHOR CONTRIBUTIONS

LK-T contributed to conceptualization, formal analysis, writing the original draft, and visualization. EP contributed to conceptualization, methodology, software, formal analysis, writing the original draft, and visualization. KA contributed to writing the original draft and visualization. AA contributed to conceptualization, writing the original draft, visualization, and supervision. All the authors were responsible for editing, revewing and approving the final version of the manuscript.

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CONFLICT OF INTEREST

LK-T has received lecture honoraria between 2020 and 2022 from CampusPharma, MSD Finland, and Stragen Finland and writing fees from the Finnish Medical Society Duodecim. She is the current president of Finnish Colposcopy Society. All the other authors declare no conflicts of interest.

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