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Breast and ovarian cancers in women: familial clustering, second primary cancer and cause of death

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Person-year, estimate of the actual year-at-risk that all persons contributing to a study.

Incidence rate, the number of new cases per population at risk in a given time period. When the denominator is the sum of the person-time of the at risk population, it is also known as the incidence density rate or person-time incidence rate.

Relative risk, the ratio of the incidence of the group of interest to that of the reference group.

Familial relative risk, the ratio of the incidence of the individuals with family history to that of the individuals without family history.

Survival rate, the percentage of people who are still alive for a certain amount of time since the diagnosis or the treatment of the disease such as cancer.

Cause of death, the disease or injury that initiates the train of morbid events leading directly to death or the circumstances of the accident or violence that produced the injury.

Second primary cancer, an additional primary cancer that occurs in a person who has had one cancer in the past.

Familial second primary cancer, second primary cancer that occurs in families more often than would be expected by chance.

List of Abbreviations

BRCA1, breast cancer 1, early onset

BRCA2, breast cancer 2, early onset

BRIP1, BRCA1 Interacting Protein C-Terminal Helicase 1

CDH1, Cadherin 1

CHEK2, Checkpoint Kinase 2

CI, Confidence interval

CUP, cancer of unknown primary

FCD, Family Cancer Database

FDR, First-degree relative

FRR, Familial relative risk

GLM, Generalized linear model

HBOC syndrome, hereditary breast and ovarian cancer syndrome

HNPCC syndrome, hereditary nonpolyposis colorectal cancer syndrome

ICD, the International Classification of Diseases

IDC, invasive ductal carcinoma not otherwise specified

IDC-NST, invasive ductal carcinoma

LKB1, Liver kinase B1

MLH, MutL Homolog 1

MMR genes, Mismatch repair genes

MSH2, MutS Homolog 2

MSH6, MutS Homolog 6

NHL, Hodgkin lymphoma

PAD, A code for histological type (WHO/HS/CANC/24.1 Histology Code, ‘PAD’) used in FCD since 1958

PTEN, Phosphatase And Tensin Homolog

RAD51C, RAD51 Paralog C

RAD51D, RAD51 Paralog D

RR, relative risk

SEER data, Surveillance, Epidemiology, and End Results data

SNOMED code, Systematized Nomenclature of Medicine code

SPC, second primary cancer

1 INTRODUCTION

1.1 Female cancer burden

Cancer was the second leading cause of death and disability after cardiovascular disease causing 8.93 million deaths worldwide in 2016 (Naghavi *et al.*, 2017). Cancers of breast, cervix, endometrium and ovary, predominantly known as female cancers add up to an approximate 44% of all cancer diagnosis and 12% of all cancer deaths among women globally (Ferlay *et al.*, 2013). Among those cancers, breast cancer is the most commonly diagnosed cancer with estimated 2.1 million new cases and an estimated 626,679 deaths worldwide in 2018 (Bray *et al.*, 2018). Compared to the other three female cancers, ovarian cancer has lower incidence and mortality with 295,414 new cases and 184,799 deaths in 2018 (Bray *et al.*, 2018), but it is a relatively fatal disease, for which no screening program is widely conducted and it is called "whispering disease" or "a silent killer" because of its vague abdominal symptoms and signs (Henderson *et al.*, 2018). In US ovarian cancer contributes just 2.5% of all cancer diagnoses in women, but 5% of cancer deaths due to the disease's low survival rate (Siegel *et al.*, 2018). The cancer incidence varies in different countries and regions. The highest incidence rates of breast cancer are presented in North America, Australia, New Zealand, and Northern and Western Europe (**Figure 1**). Similarly, the high incidence rates of ovarian cancer are observed in Northern and Eastern Europe (**Figure 2**).

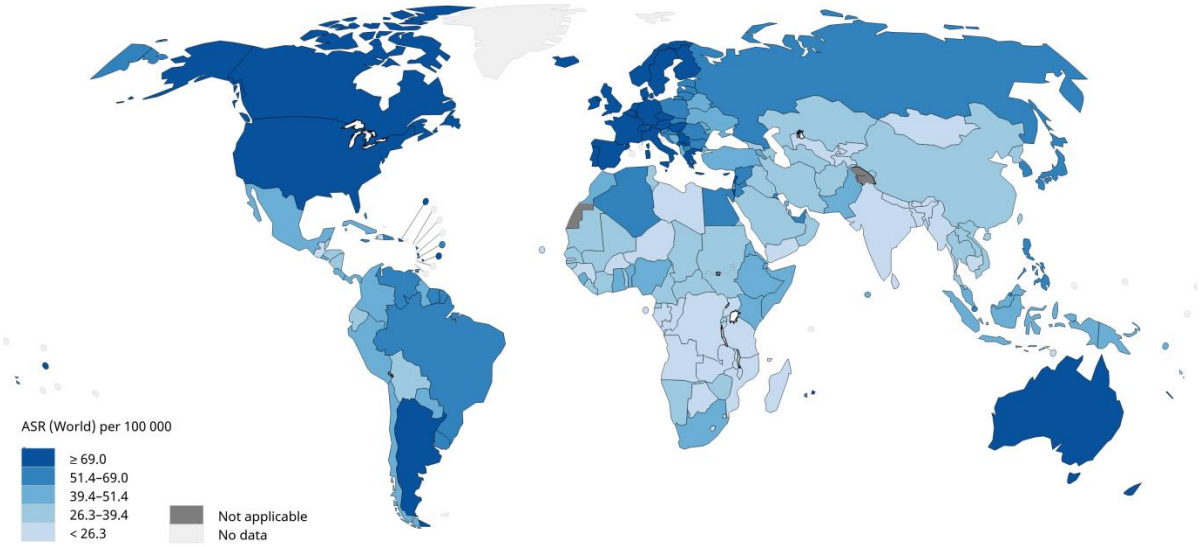

Figure 1 Regional differences of age-standardized incidence rates of breast cancer in women. Available from: http://globocan.iarc.fr, accessed on 18/09/2019.

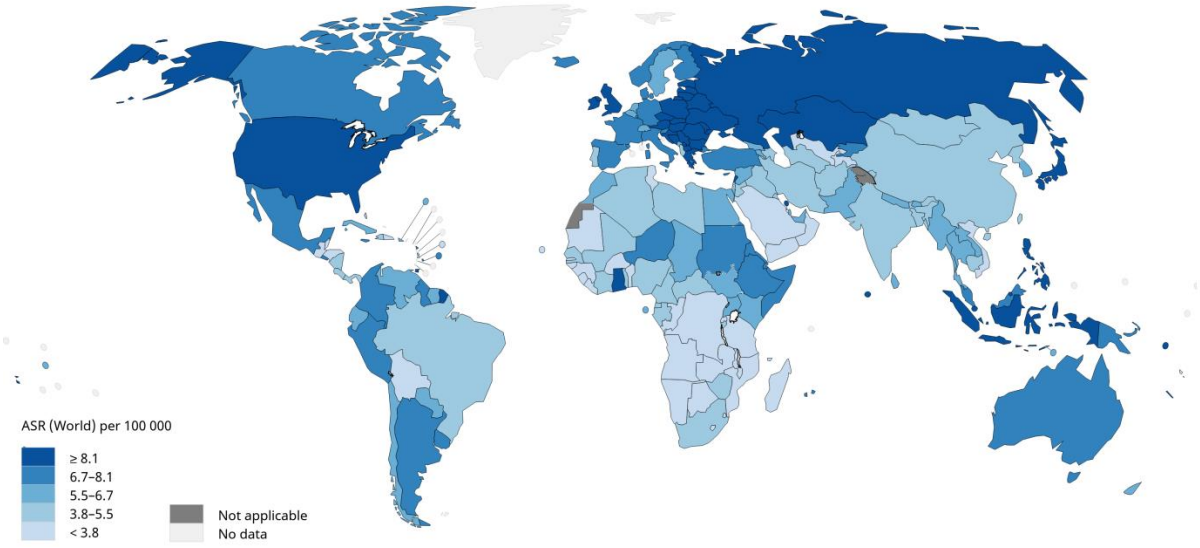

Figure 2 Regional differences of age-standardized incidence rates of ovarian cancer in women. Available from: http://globocan.iarc.fr, accessed on 18/09/2019.

1.2 Classification of histology

Cancer is a heterogeneous disease and it can be categorized into biologically and clinically meaningful subgroups according to histology grade and histological type. Grade is an assessment

of the degree of differentiation and proliferative activity of a tumor, and mirrors its aggressiveness. On the other hand, histological type refers to the growth pattern of the tumors. Specific types of cancer may present distinctive risk factors, genetic characteristics, clinical behavior and prognosis.

Invasive breast cancers were classified as ductal and lobular based on the sites where the tumor originated (Lakhani, 2012). However this sort of tumor growth is found not related to the site or the cell origin. Accounting for 80% of all types of breast cancer, ductal breast carcinoma is the most common type. According to cell type, amount, type and location of secretion, architectural features and immunohistochemical profile, it can be classified into diverse subtypes, among which invasive ductal carcinoma not otherwise specified (IDC-NST) constitutes about 75% of invasive ductal carcinoma (Lakhani, 2012). Other special types of IDC include tubular, mucinous, medullary, invasive papillary and so on. Tubular and mucinous usually occurs in elderly women (Makki, 2015). Medullary carcinoma has better outcome and favorable prognosis than common IDC (Makki, 2015). Invasive lobular carcinoma is the second major histology-specific breast cancer, accounting for 5%-15%. Invasive lobular carcinoma has five distinctive histological variants. With efforts concentrating on molecular characteristics, the breast cancers are classified as follows according to their gene signature in order to better predict tumor behavior and improve therapeutic strategies: luminal A, luminal B, *HER2* overexpression and basal like (Weigelt *et al.*, 2010).

Ovarian cancer is commonly classified into epithelial and non-epithelial types. Non-epithelial ovarian cancer contains a diversity of tumor types such as granulosa cell and germinal malignancies, teratomas, and dysgerminomas, totally occupying for less than 10% of all ovarian cancer cases (Alifrangis and Seck, 2017). Histologically epithelial ovarian cancers is classified

into two subgroups (type I and II) according to their distinctive clinicopathologic and molecular genetic features (Kurman and Shih, 2010). Type I group consists of low-grade serous, low-grade endometrioid, clear cell and mucinous carcinomas, which are indolent and have a good prognosis. While tumors in type II group present more aggressive, including high-grade serous carcinoma, high- grade endometrioid carcinoma, carcinosarcomas and undifferentiated carcinomas. In comparison with low-grade serous carcinoma, high-grade serous, endometrioid, clear cell, mucinous carcinomas may evolve from different pathways and originate outside of ovary: for instance, high-grade serous carcinoma is considered from fallopian tube and on the other hand, endometroid and clear cell carcinoma may originate from endometrium passing through the fallopian tube leading to endometriosis (Kurman and Shih, 2010).

1.3 Protective and risk factors

Cancer risk increases with aging. Besides, ovarian cancer is strongly influenced by reproductive and menstrual factors. Risk of ovarian cancer is reduced in the condition with any factors that can decrease the total number of ovulatory cycles including pregnancy, breastfeeding and use of oral contraceptives and is increased in the condition with any factors that prolong exposure to ovulation including low parity, early menarche and late menopause (Glance, 2009). As for oral contraceptive use, it is a commonly recognized protective factor for ovarian cancer and the widespread use in recent decades is considered as the main factor that contributed to the decreased incidence of ovarian cancer (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008). An exception is that users of oral contraceptives were observed increased risk of mucinous ovarian cancer (Riman *et al.*, 2002; Soegaard *et al.*, 2007; Wentzensen *et al.*, 2016). High parity is a protective factor for ovarian cancer, which is well confirmed and is most strongly related to endometrioid and clear cell carcinomas (Wentzensen *et al.*, 2016). Hormone

replacement therapy is considered to increase the risk of ovarian cancer (Reid *et al.*, 2017). Some gynecologic conditions have been studied as risk factors for ovarian cancer, such as endometriosis and pelvic inflammatory disease (Chiang *et al.*, 2018; Stewart *et al.*, 2018). The strongest associations between ovarian cancer and endometriosis are observed with endometrioid and clear cell subtypes (Wentzensen *et al.*, 2016). Besides reproductive factors, other factors associated with ovarian cancer risk include smoking and body size (represented as height or body mass index) (CollaborativeGrouponEpidemiologicalStudiesofOvarianCancer, 2012; Gates *et al.*, 2010). The increased risk associated with obesity may be specific to non-serous and low-grade serous subtypes (CollaborativeGrouponEpidemiologicalStudiesofOvarianCancer, 2012; Olsen *et al.*, 2013). Mucinous ovarian cancer was commonly found associated with smoking in a dose-response manner (Kurian *et al.*, 2005; Modugno *et al.*, 2002; Wentzensen *et al.*, 2016),

Similar to ovarian cancer, breast cancer is also sensitive to female hormones. Any factor that can increase exposure to these hormones is a potential risk factor. Specifically, reproductive factors associated with elevated exposure to endogenous estrogens generated from the ovaries, for example earlier menarche, low parity, late age at first birth, and late menopause can increase the risk of breast cancer (Glance, 2009). Analogously, exposure to exogenous hormones (for instance, menopausal hormone therapy, oral contraceptives use) is often associated with an increased risk of breast cancer. Lobular carcinoma is reported to be more strongly related to hormonal levels than ductal carcinoma; for example, late age at birth and estrogen and progestin hormone replacement therapy use were found only associated with the increased risk of lobular breast cancer (Li *et al.*, 2000; Nyante *et al.*, 2013). In addition, lifestyle related factors including alcohol consumption and postmenopausal obesity are related to development of breast cancer and those two factors can also be explained by hormonal factors as they are involved in higher

circulating estrogen levels. The protective effect of black tea was only found in premenopausal women with lobular histology (Baker *et al.*, 2006).

1.4 Familial clustering

Evidence suggests that the cancer risk increases with having family member(s) diagnosed with the same cancer. Approximately 14% of women with breast cancer have a mother or a sister diagnosed with breast cancer and the familial risk is 1.80 (Frank *et al.*, 2014; Frank *et al.*, 2015). RR of ovarian cancer is estimated to be 2.0 to 4.0 with mother or sisters affected by ovarian cancer (Frank *et al.*, 2017c; Hemminki and Granström, 2003; Hemminki *et al.*, 2011b; Jervis *et al.*, 2013; Teerlink *et al.*, 2012). The risk increases when multiple first-degree relatives are affected. For women with one, two and three or more first-degree relatives diagnosed with breast cancer, RRs of breast cancer were respectively 1.80, 2.93 and 3.90 compared to the women who had no affected relatives (Cancer, 2001). The RR of ovarian cancer reached 24 when mother and sister were both diagnosed with ovarian cancer (Hemminki and Granström, 2003). The familial risk was higher for early-onset patients and the risk was also higher when the relatives were diagnosed at the younger age (Negri *et al.*, 2003; Ziogas *et al.*, 2000). The familial aggregation can be caused by the environmental factors commonly shared among family members, such as smoking, alcohol consumption, low physical activity and toxicant substance exposure, as well as by the genetic factors inherited from parents. One twin study carried out among more than 200,000 same-sex twins sheds light on the important role of genetic factors in familial aggregation of breast and ovarian cancers, as cumulative risks of these two cancers were found significantly higher in monozygotic than in dizygotic twins (Mucci *et al.*, 2016). Cancers that are diagnosed at younger ages tend to have more influential hereditary background than late onset cancers (Brandt *et al.*, 2008; Goldgar *et al.*, 1994; Kharazmi *et al.*, 2012).

Up to 20% of familial breast cancers have been estimated as possible carriers of a germline variant associated with the increased risk of breast cancer (Cobain *et al.,* 2016). Women with mutations in the most common high-risk genes *BRCA1/2*, which are known for hereditary breast and ovarian cancer (HBOC) syndrome, have a 40 to 85% lifetime risk of breast cancer and also a high risk (10 to 60%) of ovarian cancer (Yurgelun *et al.*, 2015). In the population belonging to the central-European decent as well as that with African American ancestry, population frequency of deleterious *BRCA1/2* mutations was reported to be around 1.4% of all breast cancers (Palomaki, 2015). Sporadic studies that seldom reports a much larger heritability is due to bias introduced by patient selections or founder populations. Additionally, some other high- or moderate-risk genes susceptible to breast cancer have also been found (Cobain *et al.*, 2016), for example, germline mutation in *TP53, PTEN, LKB1* and *CDH1*. A number of (around 100) low-penetrant risk loci despite being discovered were found to contribute to less than 20% towards familial susceptibility (Skol *et al.*, 2016). Medullary breast cancer is reported to be associated with *BRCA1* mutations (Stratton, 1997). Germline mutation of *CDH1* increases the risk of lobular breast cancer (Corso *et al.*, 2018).

Collectively, known cancer syndromes account for 36% of ovarian familial risk (Bahcall, 2013). Apart from *BRCA1/2* genes, mutations in *mismatch repair (MMR)* genes that are common in hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, also known as Lynch syndrome, are the other major high-penetrance susceptibility genes for ovarian cancer. In women with *MLH1*, *MSH2* and *MSH6* mutations, the cumulative risk of ovarian cancer by age of 70 years old is 20%, 24% and 1% respectively (Barrow *et al.*, 2013). *MMR* gene mutations were reported associated with endometriod and clear cell carcinomas (Geary *et al.*, 2008; Watson *et al.*, 2001). In contrast, *BRCA1/2* mutations predisposing to ovarian cancer are associated with high-grade

serous histology (Lakhani *et al.*, 2004; Pal *et al.*, 2005). Ovarian cancer risk can be also contributed by some other moderate and low penetrant genes mutations such as *BRIP1, RAD51C* and *RAD51D* with 12%, 5.8% and 5.2% life time risk (Norquist *et al.*, 2016; Ramus *et al.*, 2015; Song *et al.*, 2015).

Risks for other, i.e. discordant, cancers can also be elevated by those high- and moderate-risk genes that predispose to breast or ovarian cancers. Prostate, pancreatic and some other cancers were observed in the carriers with *BRCA1/2* mutations (Rahman, 2014), and endometrial, colorectal, liver, stomach cancers were observed in carriers with *MMR* gene mutations (Barrow *et al.*, 2013). Furthermore, some environmental and lifestyle factors are shared among some cancers. Smoking is confirmed as the cause of several cancers. Reproductive factors that are related to hormonal levels are associated with most of the female cancers. In population study, familial clustering of breast and ovarian cancers has been reported with prostate and with few other cancers with lower statistical significance (Bermejo *et al.*, 2004; Hemminki *et al.*, 2012c). In addition, there are limited studies focusing on the familial association with specific histological types or with specific gender in relatives. The data on associated concordant and discordant cancers can be helpful for genetic counseling, and may provide evidence on the shared genetic or environmental factors for the related cancers.

1.5 Multiple primary cancer

Breast cancer patients are surviving longer due to improved early detection measures and breast cancer treatment as the 5-year survival has increased from 75% in 1976 to 91% in 2017 (Siegel *et al.*, 2017). Similarly, survival of ovarian cancer also is increasing and the reported 5-year relative survival in USA is around 46% (Jemal *et al.*, 2017). With continuous improvement in cancer survival, the occurrence of multiple primary cancers is increasing. Most of the multiple

primary cancers are second primary cancers (SPCs). The prevalence of multiple primary cancers in cancer patients is reported to range from 2% to 17% (Buiatti *et al.*, 1997; Coyte *et al.*, 2014; Karahalios *et al.*, 2009; Rosso *et al.*, 2009; Weir *et al.*, 2013). It is reported that in Sweden 23.1% of cancer patients developed additional cancers in 2016 (NationalBoardofHealthandWelfare, 2017). In comparison with the risk of first primary cancer, around 1.5-fold increased risk for SPC was found, and remarkably high risk was observed with connective tissue, small intestinal cancers and for leukemia (Hemminki *et al.*, 2003a). The development of SPCs can be the results of various factors, such as the treatment of the first cancer, shared etiologic background that trigger the first primary cancers such as family history and environmental determinants (Schaapveld *et al.*, 2015; Travis *et al.*, 2013; Wood *et al.*, 2012). Regarding family history, Hodgkin lymphoma patients who had first-degree relatives diagnosed with these cancers were reported to have excess risk of second lung, colorectal and breast cancers (Sud *et al.*, 2017).

About half of the cancer patients have a first-degree relative diagnosed with some other (discordant) cancers and for breast and ovarian cancers the respective proportions are 46% and 56% (Frank *et al.*, 2017c), which implies the importance of cancer family history on the risk of SPC. Cancer patients carrying high-risk genetic lesion have increased probability of developing multiple primary malignancy (of the same or different type). For breast cancer patients with *BRCA1* and *BRCA2* mutation, the 10-year risk of the subsequent ovarian cancer is estimated to be 12.7% and 6.8%, respectively (Metcalfe *et al.*, 2005). The concept that risk of SPCs may be increased by the genetic risk factors that drive the first primary cancer, can also be applied for individuals with unknown genetic background since high penetrant mutations are rare due to selection (Allan, 2008). It is suggested that genetic risk for multiple primary malignancies

depends on the cumulated effect from a number of low- and moderate-penetrance inherited risk alleles susceptible to malignancy, where all risk alleles are responsible for temporal aggregation of polygenetic risk resulting in substantial increase in susceptibility subject to co-inheritance (Peto, 2002; Pharoah *et al.*, 2002).

1.6 Cause of death

Cancer is the second leading cause of death in the world (Naghavi *et al.*, 2017). In cancer patients, the cause of death is diverse, and they can die from the diagnosed cancer, other cancer, non-cancer diseases such as cerebrovascular event, infection and from suicide. Previously, the cause of death in breast and prostate cancer patients was explored based on the Swedish Family-Cancer Database and the results showed that approximately half of the patients died of breast and prostate cancer respectively and cardiovascular diseases were most common competing causes of death in these patients (Riihimaki *et al.*, 2012; Riihimäki *et al.*, 2011). The US Surveillance, Epidemiology, and End Results (SEER) data reported that prostate, breast and testicular cancer patients are least likely to die of their cancer and patients with lung, pancreas and brain tumors are most likely to die of their cancer (Zaorsky *et al.*, 2016). The data on the cause of death in cancer patients with a second cancer diagnosis are limited. The SEER data also indicates that for the common cancers with an additional cancer, 55% of the patients died of their second primary malignancy (Donin *et al.*, 2016). Assessing the difference in cause of death between cancer patients with and without a SPC is of interest, which can guide the management of cancer patients.

1.7 Genetic counselling in clinical practice

In genetic counseling, cancer patients can learn about genetic conditions such as gene mutations probably involving in breast or ovarian cancers, find out their chances of being affected by or

families with a genetic disorders, and make informed decisions about their treatment. The demand for clinical genetic counseling is increasing, and the quantity of DNA-based genetic counseling has increased three times between 1996 and 2002 in Germany (Schmidtke *et al.*, 2005). With the ongoing technical improvement and the increasing capabilities of next generation sequencing, large-scale, high-throughput genetic testing has become more and more cost- and time- effective and thus, available for a variety of clinical and research applications (Durmaz *et al.*, 2015).

Genetic counseling might have good implications for mutational testing of known cancer predisposing genes, but for individuals without well-established familial cancer syndromes it is less competent. According to the guidelines from the American Cancer Society, only for limited cancer sites such as breast, prostate, colorectal, endometrial and ovarian cancers, family history is regarded as a sign for genetic screening or surveillance and the emphasis is mainly on mutation testing (Smith *et al.*, 2011). With the widespread use of next generation sequencing and the increasing focus on genetic testing (Samuel *et al.*, 2014), it is wasteful and dangerous if the easily accessible information on family history is still not properly used. It is reported that no more than 50% of medical record in the US had information on family history; even if it's documented, the information were not complete, for example only having or not having family history and lack of age at diagnosis (Murff *et al.*, 2007). One of the reasons can be that the data on familial risk is limited and physicians have not been aware of the possible relevance of family history to the cancer risk. Therefore, family history has not been made full use in the current busy clinical oncology practice. However, family history is of importance for identification of individuals susceptible to both first and subsequent primary malignancies and for identification of those most likely to benefit from genetic counseling (Wood *et al.*, 2014).

1.8 Aim of the study

The aim of the study was to highlight the familial clustering of breast and ovarian cancers with themselves and other cancers as well as with SPCs. Additionally cause of death in these two cancers were to be assessed based on the diagnosis of SPCs. To this end the recent update of Swedish Family-Cancer Database was used to:

1) Analyze RR of breast and ovarian cancers in offspring with first-degree relatives diagnosed with these cancers considering the familial risk stratified by proband type, age at diagnosis and histological type;

2) Explore discordant familial associations of the two cancers with other cancers, with additional stratification on histological type;

3) Assess the impact of family history in first-degree relatives on the risk of the same cancer as SPC in breast and ovarian cancer patients;

4) Compare the cause of death in breast and ovarian cancer patients with a diagnosis of SPC to those without a diagnosis.

2 MATERIALS AND METHODS

2.1 The Swedish Family-Cancer Database

The Swedish Family-Cancer Database (FCD) was created by linking the Multigeneration Registry, the Swedish Cancer Registry, national censuses and the Cause of Death Registry (Hemminki, 2001). In the Multigeneration Registry, children (offspring) born since 1932 are registered with their biological parents (**Figure 3**). Except misinformation due to registration mistakes and inaccuracies which primarily affects the offspring population belonging to the first decade of the registry and in addition to some discrepancies for some groups of emigrants and immigrants, the registry is complete. The cancer notification in the Swedish Cancer Registry started from 1958 (**Figure 3**). The reliability of the Cancer Registry is considered very high. About 98% of the cases are morphologically verified, and in comparisons with the National Patient Register, under reporting is only 3.7% (Barlow *et al.*, 2009). As cancer identification from Death Registry is not used in the Swedish Cancer Registry, data from these two registries can be used to estimate the underreporting of cancers. Among individuals identified from Death Registry who had cancer as underlying cause of death, the average agreement rate were about 80% between the cancers recorded in Cancer registry and in Hospital Charge Registry (Ji *et al.*, 2012). The agreement rate varied across cancer site. In the same study breast cancer was reported with very low underreporting and pancreatic and lung cancers with high underreporting (Ji *et al.*, 2012). Additional linkage was conducted to obtain, individual's socio-economic index, geographical region of residence and educational level in the FCD. The linkages were performed by using the national registration number. In the final matched records, individuals cannot be identified because those numbers were removed (Hemminki, 2001).

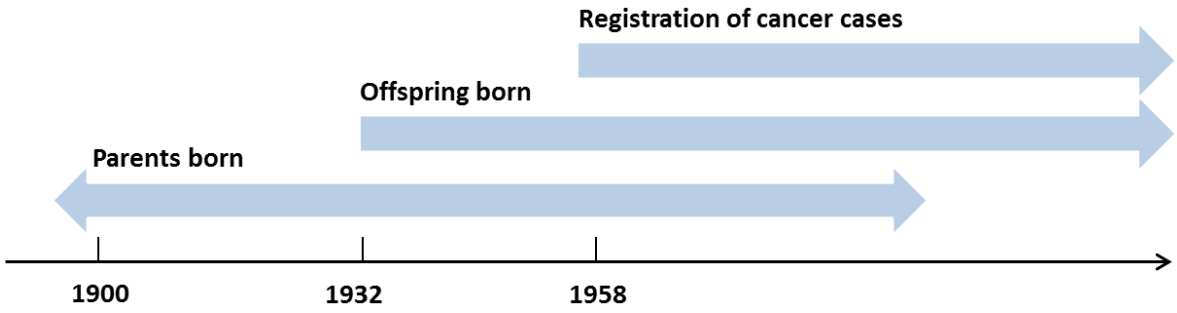

Figure 3 General information on the structure of the populations and cancer registration in FCD.

In the FCD, cancers are coded using three digits of international classification of diseases (ICD). In the beginning, ICD-7 was used to record the cancer sites. Later ICD-9 was used in 1987, ICD-O/2 in 1993 and ICD-O/3 in 2005. All the coding are translated to ICD-7 in order to facilitate identifying cancers over long time periods in the following version of FCD. Table 1 shows the ICD-7 codes for all the cancer sites in the FCD. As for some cancers in ICD-7 encompass cancers in multiple sites; for example, endocrine gland cancer includes cancers in adrenal parathyroid, thymus, pituitary, insuloma of pancreas and some other sites related to endocrine gland. Four digits of ICD-7 were also used to identify the detailed cancer sites of liver, endocrine gland and leukemia. The four digits codes for some cancers in subsite are shown in **Supplementary Table 1**.

Table 1 ICD-7 code in FCD for the cancer sites

Cancer sites	ICD-7 code (first 3 digits)
Upper aerodigestive tract (UAT)	140, 141, 143-148, 161
Salivary glands	142
Esophagus	150
Stomach	151
Small intestine	152
Colorectum	153 and 154 (except 1541)
Colon	153
Rectum	154 (except 1541)
Anus	1541
Liver	155-156
Pancreas	157
Nose	160
Lung	162-163
Breast	170
Cervix	171
Endometrium	172
Uterus	173
Ovary	175
Other female genital	176
Prostate	177
Testis	178
Other male genital	179
Kidney	180
Bladder	181
Melanoma	190
Skin	191
Eye	192
Nervous system	193
Thyroid gland	194
Endocrine glands	195
Bone	196
Connective tissue	197
Non-Hodgkin lymphoma (NHL)	200, 202
Hodgkin disease	201
Myeloma	203
Leukaemia	204-209
Cancer od unknown primary (CUP)	199

Histological types are also reported in the FCD. Before 1993, WHO/HS/CANC/24.1 histological codes ("PAD") were used. In 1993 and later, The Systematized Nomenclature of Medicine (SNOMED) was applied in order to give more detailed histological information. The confirmation of the SNOMED histology as PAD histologies was reported closed to 100% and

compared to PAD codes, the SNOMED codes provided more information for breast and thyroid cancers and for melanoma (Hemminki *et al.*, 2010b). However, PAD codes can be used to distinguish malignant melanoma (PAD=”176”) from retinoblastoma medulloblastoma (PAD=”436”) for eye cancer (shown in **Supplementary Table 1**). The SNOMED code for the main histological types of breast and ovarian cancer is displayed in **Table 2**. Particularly, thecoma was used to represent non-epithelial type as it accounts the most of this type.

Table 2 SNOMED code in FCD for the histological types of breast and ovarian cancers

Breast cancer	
Histological type	**SNOMED code**
Ductal	85003
Lobular	85203
Mucinous	84803
Tubular	82113
Medullary	85103
Ovarian cancer	
Histological type	**SNOMED code**
Undifferentiaed	83203
Clear cell	83103
Endometrioid	83803
Serous	84413, 84603
Mucinous	84703
Thecoma	86203

2.2 Study population and Follow-up time

FCD has been updated regularly since its creation. In this thesis, two versions of the database were used: the 10th version, which assembled in 2012 and the 11th version, assembled in 2015. The first one is for the analyses of familial association in breast cancer patients, which includes 15.7 million individuals and 1.8 million cancer patients diagnosed between 1958 and 2012 and aged 0-80 years old. The second one is for the analyses of second cancer risk and cause of death in breast cancer patients and all the analyses in ovarian cancer patients, which contains 16.1 million individuals and more than 2.0 million cancer cases aged 0-83 years old until the end of

2015.

There is a lack of information on the death cases before 1958 when the Cancer Registry started. Therefore, offspring generation was followed for the cancer diagnosis from 1958 (for histological analysis it was 1993), the birth year, or the immigration year, whichever occurred latest. The follow-up was terminated in the year when the person was diagnosed with cancer, emigrated or died, or at the end of 2012 (for breast cancer) or 2015 (for ovarian cancer), whichever came first. In the follow-up for the second cancer risk, it started from the diagnosis of first cancer, and ended at the diagnosis of second cancer, emigration or death, or at the end of 2015, which came earliest.

Based on the follow-up period, the corresponding cases and person-years were assigned into different strata according to sex, age group (17 groups with 5-year gap), calendar year (10-year-gap), residential area (big cities, South Sweden, North Sweden, or unspecified) and socioeconomic status (blue-collar worker, white-collar worker, farmer, private, professional, or other/unspecified). For the study purpose, cases and person-years were also allocated to different strata based on family history of cancer for familial clustering analysis or personal history of cancer for SPC risk estimation individually. Additionally when estimating breast or ovarian cancer risk, the adjustment for parity (0, 1, 2, 3 and ≥4 child births) was also performed.

2.3 Familial clustering

Familial history was defined as the concordant or discordant cancer diagnosis in first-degree relatives (including parents and/or siblings). RRs, estimated for the offspring generation, were used for the assessment of familial risk, which were obtained by comparing incidence rates of cancer for individuals with cancer family history to incidence rates for those who had no relatives affected by cancer (reference group).

2.3.1 Concordant familial associations

For concordant familial risk analysis stratified by proband type, diagnosis of breast or ovarian cancer in first-degree relatives was regarded as having family history. For ovarian cancer, only family history in the relationship of mother-daughter, sister-sister and mother-two daughters was taken into account. On the contrary, the family history from father and brother were also included for breast cancer. Estimation of familial risk stratified by the age at diagnosis (over or below 50 years old) was performed. In order to see the role of histology in the familial association in breast and ovarian cancer, a two-way comparison was applied, the detail of which is shown in **Figure 6**. In this method, estimation for two sets of RRs were performed, i.e. RR for overall (histology-specific) breast or ovarian cancer with cancer diagnosis of histology-specific breast or ovarian cancer in first-degree relatives, and conversely, RRs for histology-specific breast or ovarian cancer with cancer diagnosis of overall (histology-specific) breast or ovarian cancer in first-degree relatives.

2.3.2 Discordant familial associations

The two-way comparison was performed to estimate the familial associations of breast and ovarian cancers with other cancers. Firstly, RR for breast or ovarian cancer was calculated when first-degree relatives were diagnosed with discordant cancer X, and then in the reverse order RR for cancer X was calculated when first-degree relatives were diagnosed with breast or ovarian cancer. In addition, gender-specific association and histology-specific association were considered for breast and ovarian cancer respectively. The two-way analysis is displayed in **Figure 4**. On the left side, RR was calculated for breast or ovarian cancer; person-years at risk were calculated for all offspring; probands were all first-degree relatives. The reverse analysis was shown on the right side: RR for cancer X was estimate.

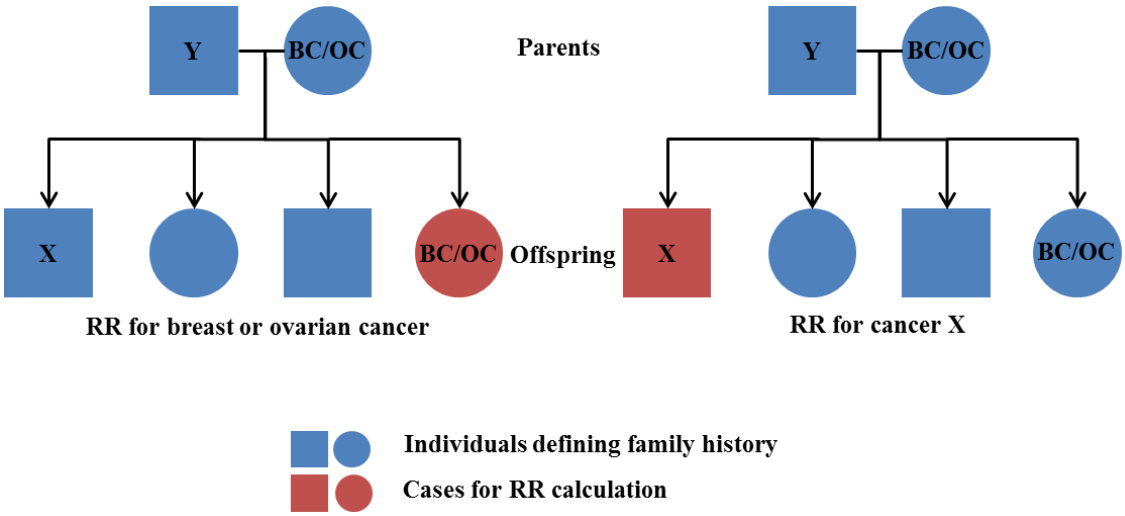

Figure 4 The structure of the two-way analysis for RR estimates in the association of breast or ovarian cancer with cancer X. On the left, RR of breast or ovarian cancer was calculated when first-degree relatives were diagnosed with cancer X; on the right, RR of cancer X was calculated when female first-degree relatives were diagnosed with breast or ovarian cancer. In addition, gender-specific association and histology-specific association were considered for breast and ovarian cancer respectively. BC, breast cancer, OC, ovarian cancer, X and Y are both other cancers.

The two-way comparisons are independent for the family relationship between parents and offspring which was the main familial cases) while for the relationship between siblings the pairs of cases are the same (Hemminki *et al.*, 2010b). Although a bi-directional signal allude to true association, but absence of it in no way an evidence against it, as case numbers and age distributions may vary among two-way analyses.

2.4 Impact of family history on development SPC

Invasive cancer diagnosed after breast or ovarian cancers, including synchronous second malignancies (diagnosed within 1 year after breast or ovarian cancer diagnoses) were identified as SPC. The risk of second endometrial cancer after ovarian cancer was not considered as the primary treatment for ovarian cancer is surgery usually including uterus removal. However, for the overall calculation we kept second endometrial cancer. For the risk of particular SPC, the diagnosis of this cancer in first-degree relatives was considered as family history. In situ cancers

in breast, colorectum, melanoma and skin (squamous cell) in family members were also included in family history because familial risk in these in situ cancers are approximately equally as high as in invasive cancers (Hussain *et al.*, 2008; Lorenzo Bermejo and Hemminki, 2005a). For risk estimation for any cancer as SPC, any invasive cancer diagnosis in first-degree relatives was regarded as family history.

The impact of family history on the development of SPC was assessed by comparing the RRs of SPC in breast or ovarian cancer patients who had first-degree relative diagnosed with this cancer to the RRs without this family history. In risk estimation for SPC, the incidence of this cancer as first primary cancer in the population without family history of this cancer and breast cancer was used as reference. Cumulative incidence of SPC with or without a family history of concordant cancer stratified over age at SPC diagnosis were calculated considering death as a competing event.

We performed sensitivity analyses for ovarian cancer by deleting families which might be carriers of the known high-risk genes in the risk estimation of SPC. Families with increased likelihood of having *BRCA1/2* carriers can be defined with any of the following situations: 1) with male first-degree relatives diagnosed with breast cancer; 2) with two or more first-degree relatives diagnosed with breast cancers before age 50 years; 3) with at least one first-degree relative diagnosed with bilateral breast cancers counted as two independent cases when diagnosed <50 years (Lorenzo Bermejo and Hemminki, 2005b). High risk families possibly associated with *MMR* mutations were defined as families with patients with colorectal or endometrial cancer diagnosed before 50 years (Bermejo *et al.*, 2005). Based on the above criteria, 14,854 (0.35%) women among all the women followed in the database and 79 (0.70%) among 11,300 ovarian cancer patients were identified from possible high-risk family associated

with *BRCA1/2* mutations. For possible high-risk families associated with *MMR* mutations, the respective numbers were 25,188 (0.60%) and (0.96%).

2.5 Relative risk estimation

Generalized liner model (GLM) fitted by Poisson regression was used to estimate the RR in this thesis, since this approach is possible to be used to perform hypothesis tests comparing familial risks for different family relationships. The model was formulated by Nelder et al. in 1972 (82), which is a flexible generalization of ordinary linear regression that allows error distribution models of response variables to have distribution not limited to a normal distribution. Briefly, GLMs model the relation between a response variable Y and a set of explanatory variables X (covariates) with the assumption that Y possesses a probability density function of exponential form and its distribution parameters depend on the linear predictor X through a link function, where β is called the regression coefficients. Poisson regression is a generalized model used to model count data and contingency tables, in which the count response Y is assumed to be a discrete random variable following a Poisson distribution with probability mass function f:

$$f(y_i; \mu_i) := P(Y = y_i) = \frac{e^{-\mu_i}\ \mu_i{}^{y}}{y_i!} \qquad y_i = 0, 1, 2, \ldots; \mu_i > 0 .$$

In the regression model the observed count is represented by y_i, of which i is used to emphasize the modeling of various observations y_i (i=1,…,N) with a set of K covariates $x_i' = (1, x_{i1}, \ldots, x_{iK})$. In Poisson distribution, one of the unique features is that the variance equals the mean, which is called *equidispersion*. To conform to an equidispersed variance function, the link was adjusted with an offset variable. Based on the regression equation

$$\ln \mu_i = x_i' \beta,$$

μ_i is linked to the linear predictor $x_i'\beta$ through the natural logarithm which is the link function for

Poisson regression. The regression coefficients β are estimated by maximizing the log-likelihood function.

$$l(\beta|X,Y):=\sum_{i=1}^{N}[y_i(x_i'\beta)-e^{x_i\beta}-\ln y_i!]$$

As described previously, cases and person-years were stratified among different strata based on the follow-up data. Let n_j be the number of person-years and d_j denote the number of newly diagnosed cancers among individuals with a positive family history (for analysis of familial clustering) or with the prior breast or ovarian cancer diagnosis (for analysis of SPC risk) in the jth stratum, j=1,…, J different settings of K covariates (the confounders used for stratification) that will be presented as x_j below. Assuming d_j to follow Poisson distribution with mean μ_j, the mean incidence rate E $(\frac{d_j}{n_j})$ was derived as

$$\mathrm{E}\left(\frac{d_j}{n_j}\right)=\frac{\mu_j}{n_j}$$

and the regression equation could be described as

$$\ln\left(\frac{\mu_j}{n_j}\right)=x_j'\beta$$

or, in another way, as

$$\ln\mu_j=x_j'\beta+\ln n_j,$$

$\ln n_j$ is termed *offset* variable.

Each combination of covariates $x_j'=(1, x_{j1}, \ldots, x_{jj})$ consisted of the binary information on family history (diagnosis of breast or ovarian cancer) x_{j*} which was coded $x_{j*}=0$ for negative family history for familial association study and no diagnosis of breast or ovarian cancer for second

cancer risk study and correspondingly x_{j*}=1 for positive family history and diagnosis of breast or ovarian cancer. The fitted incidence rate for any stratum j was derived by μ_j/n_j. With the assumption that values of all other covariates from x_j were constant except of x_{j*}, then $(\mu_j/n_j)^+$ represented the incidence rate given x_{j*}=1 and $(\mu_j/n_j)^-$ was the corresponding rate for x_{j*}=0. The ratio of both rates was only depended on β^* other than j. Therefore, the RR was obtained by

$$\text{RR}=\frac{(\mu_j/n_j)^+}{(\mu_j/n_j)^-}=e^{\beta*}.$$

Wald Chi-square estimates for β^* were used to test for the significance of family history (diagnosis of breast or ovarian cancer) as a risk factor and provide CIs for RRs. Familial risk (risk of SPC) was regarded to be significantly increased or decreased with the lower bound of the RR's 95% CI over 1.00 or with the upper bound below 1.00, respectively.

For the analysis of familial clustering, if different family histories (for example, only one mother, only one sister or both mother and sister affected by cancer) were examined together in one regression model, x_{j*} was converted into a set of dummy variables using reference cell coding to calculate the corresponding RRs analogously to the binary case.

In the analyses for familial clustering, to know whether there was dose-response relationship between familial risk and affected first-degree relatives i.e. the familial risk increases with the increasing number of the affected relatives, trend tests were carried out by adjusting the Poisson regression with the number of affected relatives treated as a continuous variable for the analyses of familial clustering. P value of the trend test (P-trend) calculated from non-parameter test (Median test) was used to assess the impact of family history on the risk of SPC. In the non-parameter test, 100 000 bootstrapped samples of a particular second cancer risk in breast or ovarian cancer patients with family history of this cancer (RR positive family history) were

compared to those same number of samples in patients without family history among first-degree relatives (RR negative family history).

To avoid chance finding and more importantly falsely discovered signals, a cautious sensitivity adjustment measure needs to be employed in studies where a large number of tests are to be performed (Brown, 1975). To this end adjustments for multiple testing were implicated with calculation of multiple confidence intervals (CIs). In this study, besides 95%, 99% and 99.9% confidence intervals (CIs) from Poisson regression models were also calculated in order to differentiate the likely true associations from likely chance findings, as a single 95%CI is not very informative in the context of multiple comparisons. All the statistical tests are based on two-tailed hypothesis. SAS version 9.4 was used to perform the statistical analysis.

2.6 Cause of death

Underlying and contributing cause of death were obtained from the Swedish Cause of Death Register and its coding system was based on the ICD codes (ICD7 for 1961; ICD8 for 1969-1986; ICD9 for 1987-1996; ICD10 for 1997-2015). For ovarian cancer, all cancer related deaths were grouped into ovarian cancer, SPC and 'other cancer'. For breast cancer, all cancer related deaths were stratified into breast cancer, SPC, higher order primary cancer and 'other cancer'. In breast cancer patients with second breast cancer diagnosis, the cause of death was assigned to breast cancer even though it was not known whether first or second breast cancer killed the patient. 'Other cancer' included cancers diagnosed at the issue of death certificates and they were not the first cancer, SPC or higher order primary cancer. As mentioned before, unlike other Nordic Cancer Registries, Swedish Cancer Registry death does not use cancer notifications from Death Registry (Brooke *et al.*, 2017; Ji *et al.*, 2012; Pukkala *et al.*, 2017). Multiple cancers and cancer of unknown primary (CUP) were often included in the death certificate notifications,

which were considered as metastases in our previous study (Riihimaki *et al.*, 2014a; Riihimaki *et al.*, 2016). In the present analysis, cause of death was assigned into the reported primary cancer if this site was consistent with the death certificate notification. However, when cancer reported from Cancer Registry was different from death certificate notification, the classification for cause of death was to "other cancer". In some analyses higher order primary cancers including third, fourth, fifth primary cancer, were reported separately. Other non-cancer cause of death such as suicide and heart attack were classified as 'other cause'.

3 RESULTS

3.1 Familial clustering of breast cancer

3.1.1 Characteristics of breast cancer patients

There are 235,316 breast cancer patients diagnosed between 1958 and 2012 in the database and among them, 76,060 were diagnosed in the offspring generation for which RRs were calculated (**Table 3**). Among breast cancer patients in offspring generation, 63,794 (83.9%) were from families without first-degree relatives affected by breast cancer, while 11,351 (14.9%) with one and 915 (1.2%) with at least two first-degree relatives affected by breast cancer. On the contrary, 39.8% of women had one first-degree relative diagnosed with discordant cancer and 14.7% had at least two first-degree relatives diagnosed with discordant cancer. More than half of the breast cancer patients in the offspring generation were diagnosed in the recent 15 years. Most of the women (43.5%) had two children and 14.4% of the women had no children. Approximately half of the patients were living in big cities. Most of the patients were blue collar or worker upon the diagnosis of the breast cancer. In the patients with record of histological types, 69.2% of them were ductal, followed by lobular (12.9%).

Table 3 Characteristics of breast cancer patients in offspring generation (1958-2012)

No. of females followed		4,139,937
No. of breast cancer cases		76,060
No. of breast cancer cases (1993-2012)		64,209
Median age at diagnosis of breast cancer		55 years old
No. of breast cancer cases with family history of breast cancer	In one first-degree relative	11,351 (14.9%)
	In two first-degree relatives	889 (1.2%)
	In at least three first-degree relatives	26
No. of breast cancer cases with family history of discordant cancers	In one first-degree relative	30,239 (39.8%)
	In two first-degree relatives	9,317 (12.2%)
	In at least three first-degree relatives	1898 (2.5%)
Diagnosed period (year)	1958-1970	139 (0.2%)
	1971-1980	1413 (1.9%)
	1981-1990	7,285 (9.6%)
	1991-2010	21,277 (28.0%)
	2011-2012	45,946 (60.4%)
Parity	0 child	10,800 (14.2%)
	1 child	12,820 (16.9%)
	2 children	33,070 (43.5%)
	3 children	14,788 (19.4%)
	≥ 4 children	4,582 (6.0%)
Residential area	Big city	35,557 (46.7%)
	South	6,270 (8.2%)
	North	2,310 (3.0%)
	Other	3,1923 (42.0%)
Socioeconomic status	Agriculture	622 (0.8%)
	Private	2,253 (3.0%)
	Professional	6,965 (9.2%)
	Blue collar	30,888 (40.6%)
	Worker	23,004 (30.2%)
	Other	12,328 (16.2%)
Histological type (1993-2012)	Ductal	44,376 (69.2%)
	Lobular	8,240 (12.9%)
	Mucinous	856 (1.3%)
	Tubular	3,065 (4.8%)
	Medullary	6,84(1.1%)
	Others	6,988 (10.9%)

Others include histological types of other breast cancers such as papillary, neuroendocrine breast cancers.

3.1.2 Familial clustering of breast cancer with concordant cancer

3.1.2.1 Familial risk by number of affected FDRs

The RR for breast cancer was 1.76 (95%CI, 1.72-1.79, P<0.001) for women from families with one first-degree relative diagnosed with breast cancer and it went up to 2.76 (2.58-2.95, P<0.001)

with two first-degree relatives diagnosed but it increased no further (1.70, 1.16-2.50, P<0.001) with three or more first-degree relatives diagnosed (**Figure 5**). The proportion of invasive and in situ female breast cancer was calculated when there were zero, one, two and more than three first-degree relatives diagnosed with breast cancer (invasive) and the more affected first-degree relatives with breast cancer in family, the larger proportion of in situ breast cancer compared to invasive breast cancer (**Supplementary Table 2**).

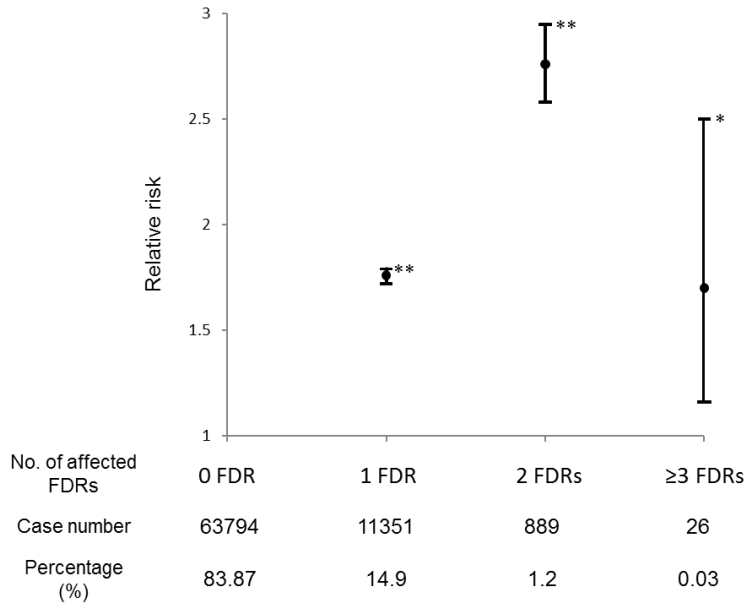

Figure 5 Relative risk of female breast cancer with family history of breast cancer in first-degree relatives (parents or siblings). FDR: first-degree relatives; *significant at 0.01 level, ** significant at 0.001 level.

3.1.2.2 Familial risk by proband type and age at diagnosis

Table 4 shows the familial risk of breast cancer stratified by proband type and age at diagnosis. Among all the breast cancer in offspring generation, 8,584 and 5,438 of them had only mother and only one sister diagnosed with breast cancer respectively, and the risk of breast cancer with one affected mother was similar to that with one affected sister (1.71, 95%CI:1.69-1.76, 1.75, 1.71-1.80, respectively). Accordingly, the risk when at least two sisters were affected by breast

cancer (2.52, 2.29-2.78) was found close to the risk when mother and at least one sister were affected (2.78, 2.59-2.98). However, in the families with mother and at least two sisters with breast cancer diagnoses, the risk of breast deceased (1.95, 1.35-2.82). When one brother was diagnosed with breast cancer, the breast cancer risk (2.64, 1.88-3.72) was higher than the risk with father affected by breast cancer (1.65, 1.26-2.16). In families with mother and father diagnosed with breast cancer, the risk of breast cancer increased up to 6.51 (3.78-11.21). When mother, sister and brother all were affected by breast cancer, the familial risk is extremely high, reaching 16.15 (4.04-64.6), but based on only two families of this kind. The familial risk of breast cancer was found higher in younger patients (<50 years old) no matter what proband type was affected.

Table 4 Familial risk of female breast cancer according to proband type and age at diagnosis

Affected first-degree relatives	Overall			<50 years			>= 50 years		
	N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	*N*	*RR*	*95%CI*
Female relatives									
Only mother	8584	***1.72***	1.69-1.76	3236	***1.95***	1.88-2.02	5348	***1.63***	1.59-1.68
Only one sister	5438	***1.75***	1.71-1.80	1406	***2.02***	1.92-2.14	4032	***1.69***	1.64-1.75
At least two sisters	407	***2.52***	2.29-2.78	108	***3.47***	2.87-4.19	299	***2.33***	2.08-2.61
Mother + one sister	798	***2.78***	2.59-2.98	262	***3.70***	3.28-4.18	536	***2.53***	2.32-2.76
Mother + at least two sister	28	***1.95***	1.35-2.82	10	***3.23***	1.74-6.01	18	**1.61**	1.02-2.56
Male relatives									
Only father	53	***1.65***	1.26-2.16	21	***2.26***	1.47-3.46	32	**1.42**	1.00-2.00
Only brother	33	***2.64***	1.88-3.72	10	***3.80***	2.04-7.06	23	***2.38***	1.58-3.58
Female and male relatives									
Father + at least one sister	6	**2.81**	1.26-6.26	2	3.89	0.97-15.56	4	2.53	0.95-6.75
At least one sister + one brother	2	1.19	0.30-4.76	1	2.32	0.33-16.5	1	0.80	0.11-5.69
Mother + at least one brother	3	**3.30**	1.06-10.22	1	4.76	0.67-33.79	2	2.93	0.73-11.72
Both mother + father	13	***6.51***	3.78-11.21	8	***9.55***	4.78-19.10	5	***4.59***	1.91-11.02
Mother + sister + brother	2	***16.15***	4.04-64.6	0			2	***20.36***	5.09-81.43

Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively.

3.1.2.3 Familial risk by histological types

The familial associations of overall breast cancer and histology-specific breast cancer are shown in **Table 5**. The familial risks were similar between histological types and in the two way

comparisons the RRs ranged from 1.50 to 2.06.

Table 5 Familial associations between overall breast cancer and histology-specific breast cancers

Histological type	Risk of overall breast cancer			Risk of histology-specific breast cancer		
	N	***RR***	***95%CI***	***N***	***RR***	***95%CI***
Ductal	4893	***1.72***	1.67-1.77	9206	***1.78***	1.74-1.82
Lobular	1028	***1.73***	1.63-1.84	1785	***1.87***	1.77-1.97
Mucinous	157	***1.50***	1.28-1.75	170	***1.63***	1.38-1.92
Tubular	380	***1.97***	1.78-2.18	619	***1.97***	1.8-2.15
Medullary	74	***2.06***	1.64-2.59	119	***1.71***	1.4-2.07

Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively.

3.1.2.4 Familial risk among histological types

Familial associations among different histology-specific breast cancers are shown in **Table 6**. Family history of all the histological types in first-degree relatives were found related to the risk of the concordant type of breast cancer and the risk with family history of concordant histology showed the highest compared to the risk with discordant subtypes apart from ductal carcinoma, among which medullary carcinoma presented the highest risk (7.88, 2.54-24.50). Furthermore, ductal carcinoma in first-degree relatives was observed with the increased risk of all the other subtypes of breast cancer, among which risk of tubular carcinoma was the highest (1.92, 1.67-2.20). In addition, risk of ductal breast cancer elevated with family history of any other histology-specific breast cancers. Risks of tubular carcinoma increased when first-degree relatives were diagnosed with lobular breast cancer (1.75, 1.30-2.37). In the reverse analysis, family history of tubular carcinoma was associated with the risk of lobular type (1.91, 1.43-2.55).

Table 6 Familial associations between histology-specific breast cancers

Histological type		Risk of overall breast cancer		
First-degree relative	**Offspring**	***N***	***RR***	***95%CI***
Ductal	Ductal	3471	***1.73***	1.67-1.79
	Lobular	614	***1.73***	1.59-1.87
	Mucinous	53	**1.38**	1.04-1.82
	Tubular	221	***1.92***	1.67-2.20
	Medullary	42	**1.46**	1.07-1.99
Lobular	Ductal	731	***1.76***	1.64-1.89
	Lobular	154	***2.06***	1.75-2.41
	Mucinous	8	0.99	0.49-1.98
	Tubular	43	***1.75***	1.30-2.37
	Medullary	7	1.19	0.56-2.51
Mucinous	Ductal	113	***1.55***	1.29-1.86
	Lobular	15	1.13	0.68-1.87
	Mucinous	6	***4.21***	1.89-9.40
	Tubular	2	0.45	0.11-1.80
	Medullary	0	0.45	0.04-4.62
Tubular	Ductal	275	***2.05***	1.82-2.31
	Lobular	46	***1.91***	1.43-2.55
	Mucinous	5	1.90	0.79-4.57
	Tubular	22	***2.68***	1.76-4.08
	Medullary	4	2.08	0.78-5.57
Medullary	Ductal	52	***2.06***	1.57-2.71
	Lobular	7	1.58	0.75-3.32
	Mucinous	1	2.09	0.29-14.88
	Tubular	2	1.40	0.35-5.60
	Medullary	3	***7.88***	2.54-24.5

Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively.

3.1.3 Familial clustering of breast cancer with discordant cancer

3.1.3.1 Risk of breast cancer with first-degree relatives affected by other cancer

A group of 20 discordant cancers with significance in the two-way comparison or trend test were included in **Table 7** and **Table 8**. Results on risk of breast cancer with first-degree relatives affected by discordant cancers are shown in **Table 7**. A total of 17 cancer sites showed at least one significant association. RRs of breast cancer displayed a ‘dose-response’ relationship with numbers of first-degree relatives affected by prostate cancer (trend test P<0.0001): RR was 1.08 (1.06-1.10) when one first-degree relative was affected by prostate cancer, 1.15 (1.06-1.25) when two first-degree relatives affected and 1.38 (1.09-1.71) when at least three were affected. The

trend test was also observed highly significant in families with ovarian cancer patients (trend test P<0.0001, RR, 2.44, 1.66-3.59) in families with two women diagnosed with ovarian cancer). In addition, significance was shown in families with lung cancer patients (trend test P=0.0002) although the RRs were modest. Besides those three cancers, only a single significant RR was found for the rest of the 14 cancer sites. Curiously, RRs for breast cancer were not elevated when only one first-degree relative diagnosed with melanoma, non-Hodgkin lymphoma or leukemia patient but high RRs were shown when two first-degree relatives were diagnosed with those diseases (1.56, 1.23-1.98, 1.48, 1.05-2.09 and 1.50,1.07-2.11, respectively). When first-degree relatives had any cancers, RRs for breast cancer were highly significant and it was 1.63 (1.58-1.69) in families with three or more first-degree relatives affected by any cancer. When breast cancer was excluded from any cancer diagnosis in first-degree relatives, the respective familial risk decreased to 1.22 (1.17-1.28).

Table 7 Relative risks for female breast cancer in families where parents or siblings were diagnosed with cancers

Cancer site	Cases with one FDR			Cases with two FDRs			Cases with ≥ three FDRs			*P- trend*
	N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Stomach	2265	**1.05**	1.01-1.09	41	1.30	0.96-1.77	2	1.85	0.46 – 7.39	**0.0080**
Colorectum	6474	***1.06***	1.03-1.08	300	1.09	0.97-1.22	11	0.83	0.46 - 1.50	**<0.0001**
Liver	1579	**1.05**	1.00-1.10	11	0.81	0.45-1.46	-	-	-	0.0773
Pancreas	1618	**1.06**	1.00-1.11	13	0.82	0.48-1.41	-	-	-	0.0571
Lung	4242	***1.06***	1.02-1.09	161	**1.18**	1.01-1.38	6	1.05	0.47-2.35	**0.0002**
Breast	11351	***1.76***	1.72-1.79	889	***2.76***	2.58-2.95	26	***1.70***	1.16-2.50	**<0.0001**
Endometrium	1709	**1.06**	1.01-1.11	20	1.25	0.81-1.94	1	1.49	0.21-10.59	**0.0122**
Ovary	1640	***1.26***	1.20-1.32	26	***2.44***	1.66-3.59	-	-	-	**<0.0001**
Prostate	8808	***1.08***	1.06-1.10	564	***1.15***	1.06-1.25	71	***1.38***	1.09-1.71	**<0.0001**
Testis	223	**1.14**	1.00-1.31	-	-	-	-	-	-	0.0490
Bladder	2824	**1.05**	1.01-1.09	45	0.99	0.74-1.32	4	2.26	0.85-6.02	0.0089
Melanoma	1922	1.02	0.98-1.07	67	***1.56***	1.23-1.98	2	1.63	0.41-6.52	0.0752
Skin, squamous cell	2373	0.99	0.95-1.03	51	1.09	0.83-1.43	-	-	-	0.6013
Eye	201	**1.16**	1.01-1.33	-	-	-	-	-	-	0.0408
Nervous	1761	**1.05**	1.00-1.10	22	0.91	0.60-1.39	-	-	-	0.0739
Thyroid gland	504	1.08	0.99-1.18	4	1.38	0.52-3.67	-	-	-	0.0645
Endocrine glands	1071	**1.08**	1.02-1.15	9	0.99	0.52-1.91	-	-	-	**0.0112**
Connective tissue	381	1.01	0.92-1.12	1	1.54	0.22-10.96	-	-	-	0.7469
Non-Hodgkin lymphoma	1781	1.02	0.97-1.07	32	**1.48**	1.05-2.09	1	3.03	0.42-21.49	0.2690
Leukemia	1664	1.03	0.98-1.08	33	**1.50**	1.07-2.11	1	1.78	0.25-12.61	0.0852
Cancer of unknown primary	1971	**1.05**	1.01-1.10	16	0.91	0.56-1.48	-	-	-	**0.0320**
All cancers[a]	31348	**1.17**	1.16-1.19	12929	***1.36***	1.33-1.39	3393	***1.63***	1.58-1.69	**<0.0001**
All cancers[b]	30239	**1.08**	1.06-1.09	9317	***1.11***	1.09-1.14	1898	***1.22***	1.17-1.28	**<0.0001**

FDR: first-degree relatives (parents or siblings);
Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;
a: all cancers include breast cancers and all other cancers; b: all cancers include all other cancers except breast cancer.

To acknowledge the association of breast cancer risk with specific cancer sites. We did subtype analyses for eye, endocrine gland tumor and leukemia. The increase in risk of breast cancer in families with eye cancer patients was associated with uveal melanoma (N= 158, RR 1.16, 1.00-1.35); only family history of the parathyroid tumors was related to increased breast cancer risk in families with endocrine gland tumor patients (708, 1.07, 1.00-1.16); chronic myeloid leukemia showed the only significance in the analyses for leukemia (181, 1.19, 1.03-1.38).

3.1.3.2 Risk of other cancer with first-degree relatives affected by breast cancer

RRs for discordant cancers in families with breast cancer patients are displayed in Table 8. A total of 14 cancers showed significant results in the two-way analysis (Table 7 and Table 8) among the 20 discordant pairs of cancer. Risks of 16 cancers were associated with family history of breast cancer, among which connective tissue tumors only showed significance in the trend test. Elevated risks for ovarian and stomach cancers were observed in families with one and two family members diagnosed with breast cancer patients; risk for CUP was increased in families with one and three or more family members affected by breast cancer (2.28, 1.02-5.07). The RR of nervous system tumors was 1.99 (1.00-3.98) when at least three first-degree relatives were diagnosed with breast cancer and it was 1.90 (1.38-2.63) for thyroid cancer (significant at 0.1% level) when two first-degree relatives were diagnosed with breast cancer.

Table 8 Relative risks for cancers in offspring in families where mother or sisters were diagnosed with breast cancer

Cancer site	Cases with 1 FDR			Cases with 2 FDRs			Cases with ≥3 FDRs			*P-trend*
	N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Stomach	531	**1.10**	1.01-1.21	44	***1.69***	1.26-2.28	3	1.90	0.61-5.89	**0.0005**
Colorectum	3256	1.03	0.99-1.07	183	1.09	0.94-1.26	5	0.53	0.22-1.28	0.3322
Liver	520	1.00	0.92-1.10	26	0.93	0.63-1.36	3	1.78	0.57-5.52	0.9535
Pancreas	664	***1.13***	1.04-1.22	35	1.08	0.78-1.51	3	1.51	0.49-4.68	**0.0037**
Lung	2253	1.03	0.99-1.08	135	1.12	0.94-1.32	7	0.98	0.47-2.05	0.0866
Breast	11342	***1.76***	1.72-1.79	876	***2.72***	2.55-2.91	26	***1.71***	1.16-2.51	**<0.0001**
Endometrium	1072	**1.07**	1.01-1.14	65	1.20	0.94-1.54	2	0.74	0.18-2.95	**0.0149**
Ovary	1045	***1.23***	1.15-1.31	61	***1.45***	1.13-1.86	3	1.44	0.46-4.45	**<0.0001**
Prostate	6499	***1.12***	1.09-1.15	343	1.06	0.96-1.18	26	1.35	0.92-1.98	**<0.0001**
Testis	621	***1.14***	1.05-1.23	19	0.99	0.63-1.56	-	-	-	**0.0053**
Bladder	1304	1.03	0.97-1.09	79	1.15	0.92-1.43	6	1.48	0.66-3.29	0.1183
Melanoma	2615	***1.06***	1.02-1.11	128	1.16	0.97-1.37	6	1.07	0.48-2.38	**0.0007**
Skin, squamous cell	1141	***1.10***	1.04-1.17	55	1.01	0.78-1.32	3	1.03	0.33-3.20	**0.0056**
Eye	170	***1.25***	1.07-1.47	7	1.12	0.53-2.35	-	-	-	**0.0103**
Nervous system	1763	1.02	0.97-1.07	80	1.07	0.86-1.33	8	**1.99**	1.00-3.98	0.2047
Thyroid gland	478	1.05	0.96-1.16	37	***1.90***	1.38-2.63	1	1.02	0.14-7.27	**0.0157**
Endocrine glands	880	**1.07**	1.00-1.15	41	1.06	0.78-1.44	2	0.99	0.25-3.95	0.0678
Connective tissue	323	1.10	0.98-1.23	20	1.48	0.95-2.30	-	-	-	**0.0332**
Non-Hodgkin lymphoma	1289	**1.06**	1.00-1.12	58	0.96	0.74-1.24	4	1.18	0.44-3.14	0.1076
Leukemia	1175	***1.08***	1.02-1.15	62	1.27	0.99-1.63	2	0.75	0.19-3.00	**0.0026**
Cancer of unknown primary	894	***1.11***	1.04-1.19	49	1.13	0.85-1.49	6	**2.28**	1.02-5.07	**0.0011**
All cancers[a]	44003	***1.18***	1.17-1.19	2620	***1.38***	1.33-1.43	132	***1.27***	1.07-1.50	**<0.0001**
All cancers[b]	32661	***1.06***	1.05-1.07	1744	***1.10***	1.05-1.16	106	***1.19***	0.99-1.44	**<0.0001**

FDR: first-degree relatives (mother or sisters);
Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;
a: all cancers include breast cancers and all other cancers; b: all cancers include all other cancers except breast cancer.

In the analysis for subtype cancer sites, uveal melanoma was found likely related to the increased risk for eye cancer (N= 97, RR 1.29, 95%CI 1.04-1.59); pituitary tumors was the only site among all the endocrine gland tumors associated with family history of breast cancer (257, 1.16, 1.02-1.32); the association between risk of acute and chronic myeloid leukemia and breast cancer family history may contributed to the increased risk of leukemia: the increased risk of chronic myeloid leukemia was observed when two first-degree relatives were diagnosed with breast

cancer (10, 2.06, 1.11-3.85), and the RRs for acute and chronic myeloid leukemia were marginally significant in families with one first-degree relative affected by breast cancer (231, 1.13, 0.98-1.29 and 125, 1.18, 0.98-1.42, respectively).

3.1.3.3 Familial association of female breast cancer with other cancers limited by sex

The two-way analysis with stratification on gender of first-degree relatives was performed for the association of breast cancer and other cancers. When considering other cancer risk in female relatives (**Supplementary Table 3**), risks for kidney (3.90, 1.26-12.08) and bladder (3.60, 1.16-11.17) cancers and for myeloma (4.87, 1.22-19.49) were found high when three or more female family members were affected by breast cancer, however each association was only based on one or three familial cases. When considering the familial association with other cancer in male relatives (**Supplementary Table 4)**, RR of breast cancer was remarkably high in two families with three or more male relatives diagnosed with stomach cancer (24.03, 6.03-96.08) and it was 1.88 (1.14-3.12) in 15 families with two patients affected by squamous cell skin cancer. Specifically, the results for colorectal cancer are summarized in Table 9. Breast cancer risk was not increased when female relatives were diagnosed with colorectal cancer. On the contrary, a 'dose-response' trend was found between breast cancer risk and number of male relatives having colorectal cancers and the RR increased up to 2.67 (1.11-6.40) with three or more patients ($p < 0.0001$).

Table 9 Familial association of female breast cancer with female and male colorectal cancer

Calculation item	Cases with 1 FDR			Cases with 2 FDRs			Cases with ≥3 FDRs			*P-trend*
	N	***RR***	***95%CI***	***N***	***RR***	***95%CI***	***N***	***RR***	***95%CI***	
BC by female CRC	3242	1.02	0.98-1.06	46	1.03	0.77-1.38	1	0.77	0.11-5.38	0.2946
Female CRC by BC	1433	1.02	0.96-1.08	92	**1.25**	1.02-1.54	3	0.80	0.26-2.48	0.1553
BC by male CRC	3605	***1.08***	1.04-1.11	75	**1.27**	1.01-1.59	5	**2.67**	1.11-6.40	**<0.0001**
Male CRC by BC	1823	1.04	0.99-1.09	91	0.96	0.78-1.19	2	0.35	0.09-1.40	0.2998

FDR: first-degree relatives; BC: breast cancer; CRC: colorectal cancer

Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively.

3.2 Familial clustering of ovarian cancer

3.2.1 Characteristics of ovarian cancer patients

A group of 46,227 ovarian cancer cases were identified in the database from 1958 to 2015. The median age was 63 years among 11,301 ovarian cancer cases in the offspring generation (**Table 10**). Since 1993 a total of 8,850 ovarian cancer cases in the offspring generation were diagnosed with SNOMED codes, and non-epithelial ovarian cancers accounted for 11.9% of them. Regarding family history of discordant cancer, 4526 (40.0%) cases in the offspring generation were from families with one first-degree relative diagnosed with by any discordant cancer and 2395 (21.2%) cases were from families with at least two first-degree relatives diagnosed with any discordant cancer. For family history of concordant cancer, 467 (4.3%) cases were from families with one first-degree relative diagnosed with ovarian cancer and 20 (0.2%) cases were from families with two first-degree relatives diagnosed with ovarian cancer.

Most of the ovarian cancer patients were diagnosed in the latest decades (1991-2010). More than half of the patients (51.0%) had no children. A total of 40.8% patients were living in big cities upon ovarian cancer diagnosis. A large portion of patients were blue collars and workers, accounting for 35.6% and 33.4% respectively. Among the patients with histology types, serous carcinoma accounts for the most (46.9%).

Table 10 Characteristics of ovarian cancer patients in offspring generation (1958-2015)

No. of females followed		4,216,676
No. of ovarian cancer cases		11,301
No. of ovarian cancer cases (1993-2015)		8850
Median age at diagnosis of ovarian cancer		63 years old
No. of ovarian cancer cases with family history of ovarian cancer	In one first-degree relative	467 (4.3%)
	In at least two first-degree relatives	20 (0.2%)
No. of ovarian cancer cases with family history of discordant cancers	In one first-degree relative	4526 (40.0%)
	In at least two FDRs	2395 (21.2%)
Diagnosed period (year)	1958-1970	199 (1.7%)
	1971-1980	511 (4.5%)
	1981-1990	1233 (10.9%)
	1991-2010	3045 (26.9%)
	2011-2015	6313 (55.9%)
Parity	0 child	5760 (51.0%)
	1 child	1493 (13.2%)
	2 children	2391 (21.2%)
	3 children	1119 (9.9%)
	≥ 4 children	538 (4.8%)
Residence area	Big city	4614 (40.8%)
	South	1035 (9.2%)
	North	369 (3.3%)
	Other	5283 (46.7%)
Socioeconomic status	Agriculture	151 (1.3%)
	Private	331 (2.9%)
	Professional	780 (6.9%)
	Blue collar	4023 (35.6%)
	Worker	3775 (33.4%)
	Other	2241 (19.8%)
Histological type (1993-2015)	Undifferentiated	193 (2.2%)
	Clear cell	511 (5.8%)
	Endometrioid	999 (11.3%)
	Serous	4149 (46.9%)
	Mucinous	726 (8.2%)
	Non-epithelial	1053 (11.9%), 300 of them were thecoma
	Others	1219 (13.8%)

Others include histological types of other ovarian cancers such as papillary ovarian cancer, as well as unspecified ovarian cancers.

3.2.2 Familial clustering of ovarian cancer with concordant cancer

The total number of familial ovarian cancer cases was 807 among daughters and mothers; among them a total of 487 were daughters. Thus 4.31% (487/11,301) of invasive ovarian cancer cases were familial in Sweden. The overall familial risk of ovarian cancer was 2.51 (2.29-2.75, P <0.001) with any first-degree relative diagnosed with ovarian cancer. The RR was 2.42 (2.21-

2.66) in families with one first-degree relative diagnosed with ovarian cancer and it increased up to 11.36 (7.33-17.62) with two affected first-degree relatives, both of which were significant at a 0.001 level.

3.2.2.1 Familial risk by proband type and age at diagnosis

Table 11 displays familial RRs of ovarian cancer with stratification of proband type and age at diagnosis. In families with only mother, only sister and both mother and sisters affected by ovarian cancer, familial RRs were respectively 2.40 (2.14-2.68), 2.59 (2.21-3.03) and 10.40 (6.16-17.57), and all of them were significant at the 0.001 level. The corresponding risks went up to 2.74 (2.29-3.26), 3.86 (3.01-4.96) and 16.05 (7.20-35.74) when only considering women diagnosed before the age of 50 years (P <0.001 for all). While the respective risks were relatively lower, 2.22 (1.93-2.56), 2.12 (1.73-2.60) and 8.33 (4.16-16.67) when considering the age at diagnosis over 50 years, but the results were still highly significant (P <0.001). Notably, in the older age group similarly high risks were observed for women having only mother and only sister with diagnosis of ovarian cancer, compared to the younger counterpart. For group with RR 10.40, ten out of the 14 patients had recorded histological type and they were serous (N=5), non-specified adenocarcinomas (2), clear cell (1), endometrioid (1) and undifferentiated (1).

Table 11 Familial risk of ovarian cancer in daughters by proband type and age of diagnosis

Age at diagnosis (years)	Only mother			Only sisters			Mother and sister		
	N	***RR***	***95%CI***	***N***	***RR***	***95%CI***	***N***	***RR***	***95%CI***
< 50	120	***2.74***	2.29-3.26	63	***3.86***	3.01-4.96	6	***16.05***	7.20-35.74
≥50	195	***2.22***	1.93-2.56	95	***2.12***	1.73-2.60	8	***8.33***	4.16-16.67
All	315	***2.40***	2.14-2.68	158	***2.59***	2.21-3.03	14	***10.40***	6.16-17.57

Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively.

3.2.2.2 Familial risk by histological types

Table 12 displays familial associations between ovarian cancer and histology- specific ovarian

cancers. Overall ovarian cancer risk was increased no matter which type of ovarian cancers was diagnosed in first-degree relatives. The histological types with RRs in descending order were undifferentiated (4.79, 2.49-9.21, *P* <0.001), endometrioid (3.81, 2.65-5.49, *P* <0.001), non-epithelial (2.72, 1.02-7.25), mucinous (2.21, 1.26-3.90, *P* <0.01), clear cell (2.16, 1.03-5.54) and serous (2.15, 1.70-2.73, *P* <0.001) type. In the reverse analysis, when mother or sisters had ovarian cancer, risks for all histology specific ovarian cancers increased apart from mucinous and non-epithelial types. The histological types was undifferentiated (5.45, 3.36-8.86, *P* <0.001), serous (2.96, 2.58-3.40, *P* <0.001), endometrioid (2.81, 2.10-3.75, *P* < 0.001) and clear cell (1.67, 1.00-2.80).

Table 12 Familial associations of overall ovarian cancer with ovarian cancer of specific histological type

Histological type	Overall risk of ovarian cancer in daughters				Risk of histology-specific ovarian cancer in daughters			
	N1	*N2*	*RR*	*95% CI*	*N1*	*N2*	*RR*	*95% CI*
Undifferentiated	8841	9	***4.79***	2.49-9.21	175	18	***5.45***	3.36-8.86
Clear cell	8843	7	**2.16**	1.03-4.54	496	15	**1.67**	1.00-2.80
Endometrioid	8821	29	***3.81***	2.65-5.49	951	48	***2.81***	2.10-3.75
Serous	8780	70	***2.15***	1.70-2.73	3934	215	***2.96***	2.58-3.40
Mucinous	8838	12	***2.21***	1.26-3.90	708	18	1.51	0.94-2.41
Non-epithelial	8846	4	**2.72**	1.02-7.25	295	5	1.10	0.46-2.66

N1: Number of cases without family history in first-degree relatives; N2: Number of cases with family history in first-degree relatives;
Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;

3.2.2.3 Familial associations among histological types

Table 13 presents familial associations among different histological types of ovarian cancers in offspring and their relatives. Risk of undifferentiated ovarian cancer elevated when mother or sisters were affected by ovarian cancer with clear cell (15.44, 2.16-110.37, *P* <0.01), serous (6.01, 2.23-16.20, *P* <0.001) or mucinous (9.23, 1.29-65.89) types. Having first-degree relatives with endometrioid ovarian cancer was related to the increased risk of same histological type of

ovarian cancer (3.59, 1.15-11.14); in families with patients diagnosed with undifferentiated (9.27, 2.31-37.12, *P* <0.01) and serous (2.26, 1.13-4.53) ovarian cancer, risk of endometrioid ovarian cancer was also elevated. Diagnoses of all the other histological types except clear cell type in mother or sisters were related to risk of serous ovarian cancer. Familial risk of mucinous ovarian cancer risk was increased in families with family members diagnosed with mucinous (6.91, 2.22-21.49, *P* <0.001) or undifferentiated (7.08, 1.00-50.33) ovarian cancer. Non-epithelial showed increased risk in families with ovarian cancer patients of clear cell type (9.70, 1.36-69.12).

Table 13 Familial associations among different histological types of ovarian cancers

Histological type		**Cases without family history**	**Cases with family history**			
Offspring	**First-degree relative**		***N***	***RR***	***95%CI***	
Undifferentiated	Clear cell	175	1	***15.44***	2.16	110.37
	Serous	175	4	***6.01***	2.23	16.2
	Mucinous	175	1	**9.23**	1.29	65.89
Endometrioid	Undifferentiated	951	2	***9.27***	2.31	37.12
	Endometrioid	951	3	**3.59**	1.15	11.14
	Serous	951	8	**2.26**	1.13	4.53
Serous	Undifferentiated	3934	4	***4.80***	1.80	12.8
	Clear cell	3934	3	2.08	0.67	6.45
	Endometrioid	3934	12	***3.50***	1.99	6.17
	Serous	3934	36	***2.47***	1.78	3.43
	Mucinous	3934	6	**2.44**	1.09	5.43
	Non-epithelial	3934	3	***4.62***	1.49	14.33
Mucinous	Undifferentiated	708	1	**7.08**	1.00	50.33
	Endometrioid	708	2	3.26	0.81	13.05
	Serous	708	4	1.56	0.58	4.17
	Mucinous	708	3	***6.91***	2.22	21.49
Non-epithelial	Clear cell	295	1	**9.70**	1.36	69.12
	Serous	295	2	1.97	0.49	7.93

Only items with at least two cases with family history, or with significant results are displayed in Table 13. No such items were found for clear cell type of ovarian cancer.
Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;

We summarized the familial associations between different histological types of ovarian cancers in **Supplementary Figure 1**, based on the two-way association in **Table 13**.

3.2.3 Familial clustering of ovarian cancer with discordant cancer

3.2.3.1 Risk of ovarian cancer with first-degree relatives affected by other cancer

Risk of ovarian cancer when first-degree relatives were diagnosed with discordant cancers are displayed in **Table 14**, which only includes the cancer sites with more than 30 familial cases with family history of corresponding cancer or those with significant results. Eight discordant cancers displayed significant familial associations. Family history of breast cancer presented a dose-response on ovarian cancer risk (P trend test <0.0001), with a RR of 1.20 (1.14-1.28) when one first-degree relative was diagnosed with breast cancer (P<0.001) and a RR of 1.47 (1.20-1.82) when two first-degree relatives were affected (P<0.01). We found increased ovarian cancer risk in families with one first-degree relative diagnosed with colorectal (1.06, 1.00-1.13), liver (1.20, 1.06-1.35, P <0.01), pancreatic (1.14, 1.01-1.28) and endometrial (RR 1.27, 1.14-1.42, P <0.001) cancers, melanoma (1.12, 1.00-1.25) and CUP (1.25, 1.13-1.38 P<0.001). For the subtypes of liver cancer (N=277), risk of ovarian cancer was increased in families that had members diagnosed with gallbladder cancer (N=95, 34.3% of all liver cancer; RR=1.27, 95%CI 1.03-1.55; **Supplementary Table 5**). Risk of ovarian cancer was found to be elevated in families with one individual diagnosed with any cancer (1.13, 1.09-1.18), and RR was 1.29 (1.23-1.36) in families with two individuals affected by cancer. When only considering the family history of discordant cancers (excluding family history of ovarian cancer), we found the risk of ovarian cancer was still significantly increased. Cancer sites with significant results are shown in **Figure 6.**

Table 14 Relative risk of ovarian cancer in families where parents or siblings were diagnosed with other cancers

Cancer site	Cases with 1 FDR			Cases with ≥ 2 FDRs			*P-trend*
	N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Upper aerodigestive tract	239	1.08	0.95-1.23	4	1.46	0.55-3.90	0.1887
Esophagus	70	0.94	0.74-1.19	0	-	-	-
Stomach	349	1.08	0.97-1.2	3	0.57	0.18-1.76	0.2887
Small intestine	41	1.02	0.75-1.38	1	4.07	0.57-28.93	0.7269
Colorectum	1009	**1.06**	1.00-1.13	58	1.16	0.89-1.50	0.0377
Colon	659	1.04	0.96-1.13	28	1.33	0.92-1.92	0.141
Rectum	395	1.07	0.97-1.19	10	1.48	0.80-2.76	0.0974
Liver	277	***1.20***	1.06-1.35	4	1.64	0.62-4.38	0.0024
Pancreas	271	**1.14**	1.01-1.28	2	0.70	0.18-2.80	0.0595
Lung	655	1.05	0.97-1.14	27	1.04	0.71-1.52	0.2382
Breast	1243	***1.20***	1.14-1.28	88	***1.47***	1.20-1.82	<.0001
Cervix	184	1.14	0.98-1.32	0	-	-	-
Endometrium	317	***1.27***	1.14-1.42	4	1.40	0.53-3.73	<.0001
Other female genitals	39	0.94	0.69-1.29	0	-	-	-
Prostate	1320	1.02	0.96-1.08	121	1.14	0.95-1.36	0.2174
Testis	35	1.20	0.86-1.68	1	4.37	0.62-31.03	0.1904
Other male genitals	30	***1.74***	1.21-2.49	0	-	-	-
Kidney	276	1.08	0.96-1.22	3	0.89	0.29-2.75	0.2458
Bladder	403	0.96	0.87-1.06	14	1.57	0.93-2.66	0.8195
Melanoma	339	**1.12**	1.00-1.25	8	1.02	0.51-2.04	0.0573
Skin, squamous cell	387	0.98	0.88-1.08	12	1.20	0.68-2.11	0.8309
Nervous system	279	1.08	0.96-1.22	2	0.49	0.12-1.97	0.2972
Thyroid gland	75	1.04	0.83-1.31	0	-	-	-
Endocrine glands	148	0.97	0.83-1.14	1	0.72	0.10-5.10	0.6948
Connective tissue	61	1.06	0.83-1.37	0	-	-	-
Non-Hodgkin lymphoma	296	1.08	0.96-1.21	5	1.27	0.53-3.05	0.1882
Hodgkin lymphoma	52	1.28	0.97-1.68	0	-	-	-
Myeloma	141	1.07	0.90-1.26	0	-	-	-
Leukemia	250	0.99	0.87-1.12	2	0.50	0.13-2.01	0.6704
Cancer of unknown primary	396	***1.25***	1.13-1.38	4	1.08	0.40-2.87	<.0001
All cancers[a]	4553	***1.13***	1.09-1.18	2589	***1.29***	1.23-1.36	<.0001
All cancers[b]	4340	***1.10***	1.06-1.15	2315	***1.20***	1.14-1.27	<.0001

FDR, first-degree relative (parents or siblings);
Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;
a: all cancers include ovarian cancers and all other cancers; b: all cancers include all other cancers except ovarian cancer.

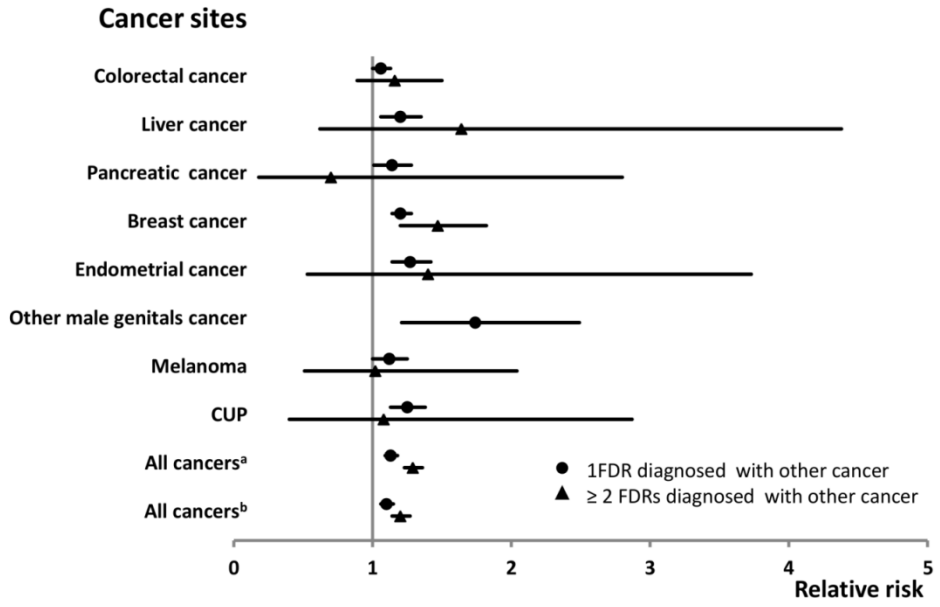

Figure 6 Relative risk of ovarian cancer according to the number of the first-degree relatives affected by other cancers. Only cancer sites with significance are displayed. CUP, cancer of unknown primary; a: all cancers include ovarian cancers and all other cancers; b: all cancers include all other cancers apart from ovarian cancer.

3.2.3.2 Risk of other cancers with first-degree relatives affected by ovarian cancer

Reversely the overall risk for any cancer in the offspring generation increased with first-degree relatives diagnosed with ovarian cancer (**Table 15**). When one first-degree relative had diagnosis of ovarian cancer, the overall risk for any cancer was 1.12 (, 1.10-1.14, P<0.001) and when two or more relatives were diagnosed the risk increased up to 1.49 (1.27-1.75, P<0.001). When only considering cancers other than ovarian cancer, the RRs were 1.09 (1.07-1.11, P<0.001) and 1.31(1.10-1.56, P<0.01) with respectively one and at least two relatives affected. In combination with the results from **Table 14**, cancers in colorectum, liver, breast, endometrium and CUP presented significant familial associations with ovarian cancer in the two-way comparison. In addition, the effect of family history of ovarian cancer on the risk of liver and breast cancers and CUP had dose-response trend. Although based on two families, the RR of Hodgkin lymphoma was high (4.11, 1.03-16.46, P <0.01) for individuals having first-degree relatives with diagnosis

of ovarian cancer. Increased risks were also found for lung (1.10, 1.01-1.19) and prostate (1.05, 1.00-1.10) cancers in families with one ovarian cancer patient. While declined risk of esophageal (0.76, 0.58-1.00) cancer was observed in families with one ovarian cancer patient. All the significant cancer sites are displayed in **Figure 7**.

Table 15 Relative risk of other cancer in families where mother or sisters were diagnosed with ovarian cancer

Cancer site	Cases with 1 FDR			Cases with ≥ 2 FDRs			*P-trend*
	N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Upper aerodigestive tract	220	1.02	0.89-1.17	3	1.32	0.43-4.09	0.7011
Esophagus	52	**0.76**	0.58-1.00	1	1.29	0.18-9.16	0.0552
Stomach	134	1.11	0.94-1.32	3	2.29	0.74-7.10	0.1435
Small intestine	54	1.29	0.98-1.68	0	-	-	-
Colorectum	884	**1.07**	1.00-1.15	6	0.70	0.31-1.56	0.0708
Colon	552	1.06	0.98-1.16	2	0.38	0.09-1.50	0.2651
Rectum	332	1.09	0.97-1.21	4	1.23	0.46-3.27	0.1264
Liver	167	**1.20**	1.03-1.40	4	**2.66**	1.00-7.10	0.0083
Pancreas	157	0.97	0.82-1.13	2	1.14	0.28-4.54	0.6918
Lung	634	**1.10**	1.01-1.19	5	0.80	0.33-1.92	0.0320
Breast	1981	***1.24***	1.19-1.30	30	***2.13***	1.49-3.05	<.0001
Cervix	165	1.08	0.92-1.26	2	1.65	0.41-6.61	0.3036
Endometrium	304	***1.22***	1.09-1.36	2	0.86	0.21-3.44	0.0014
Uterus	6	**2.63**	1.16-5.95	0	-	-	-
Other female genitals	27	0.89	0.61-1.30	0	-	-	-
Prostate	1727	**1.05**	1.00-1.10	29	1.40	0.97-2.01	0.0149
Testis	117	1.15	0.95-1.37	0	-	-	-
Other male genitals	22	1.16	0.76-1.77	0	-	-	-
Kidney	226	1.10	0.96-1.25	5	2.30	0.96-5.53	0.0905
Bladder	333	0.99	0.89-1.10	4	1.07	0.40-2.85	0.8401
Melanoma	628	1.07	0.99-1.16	7	1.29	0.62-2.71	0.0645
Skin, squamous cell	333	1.06	0.95-1.18	2	0.62	0.16-2.49	0.3549
Nervous system	380	1.04	0.94-1.15	3	0.89	0.29-2.77	0.4900
Thyroid gland	111	1.11	0.92-1.34	1	1.18	0.17-8.35	0.2767
Endocrine glands	193	1.01	0.88-1.16	2	1.13	0.28-4.51	0.8776
Connective tissue	70	1.01	0.79-1.28	0	-	-	-
Non-Hodgkin lymphoma	327	1.11	0.99-1.24	3	0.99	0.32-3.08	0.0751
Hodgkin lymphoma	71	1.20	0.95-1.51	2	**4.11**	1.03-16.46	0.0732
Myeloma	107	1.09	0.90-1.32	0	-	-	-
Leukemia	248	0.98	0.86-1.11	3	1.22	0.39-3.79	0.8095
Cancer of unknown primary	227	**1.14**	1.00-1.30	6	**2.81**	1.26-6.26	0.0157
All cancers[a]	10492	***1.12***	1.10-1.14	147	***1.49***	1.27-1.75	<.0001
All cancers[b]	10025	***1.09***	1.07-1.11	127	***1.31***	1.10-1.56	<.0001

FDR: first-degree relative (mother or sisters);
Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;
a: all cancers include ovarian cancers and all other cancers; b: all cancers include all other cancers except ovarian cancer.

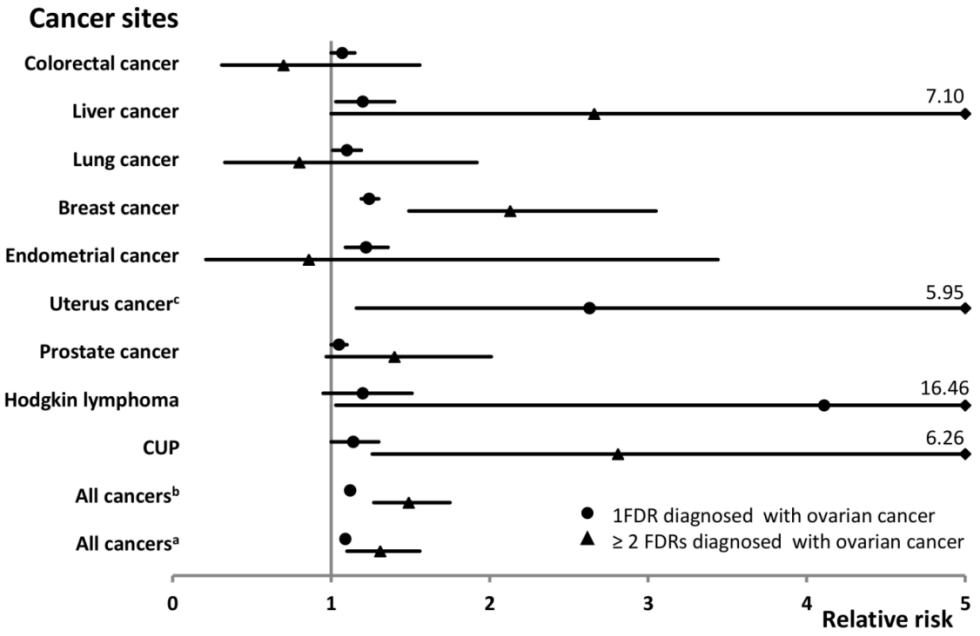

Figure 7 Relative risk of other cancer according to the number of first-degree relatives affected by ovarian cancer. Only cancer sites with significance are displayed. CUP, cancer of unknown primary; a: all cancers include ovarian cancers and all other cancers; b: all cancers include all other cancers apart from ovarian cancer.

3.2.3.3 Familial clustering of ovarian cancer with other cancer by histological type

Familial associations of ovarian cancer of different histological types with other cancers in the two-way analysis were shown in **Table 16**. The pairs (histological type-cancer site) significant in the two-way comparison were clear cell-pancreas, endometrioid-nose, endometrioid-breast ($P < 0.05$ and $P < 0.001$), endometrioid- endometrium (both $P < 0.001$), serous-breast (both $P < 0.001$), serous-male genitals ($P<0.05$ and $P<0.001$), mucinous-gallbladder ($P < 0.01$ and $P < 0.001$; see **Supplementary Table 6**). For familial association between endometrioid ovarian cancer and cancer of nose, the histological type for the latter included squamous cell carcinomas (N=2) and adenocarcinomas (N=1). Of note, only few cases were used for the familial clustering of non-epithelial ovarian cancer.

Table 16 Familial associations of histology-specific ovarian cancer with other cancers

Histological type	Cancer site	Risk of ovarian cancer			Risk of invasive cancer		
		N	***RR***	***95% CI***	***N***	***RR***	***95% CI***
Undifferentiated	Stomach	11	**1.95**	1.06-3.60	2	1.65	0.41-6.61
	Liver	8	2.00	0.99-4.06	4	**2.76**	1.04-7.36
	Pancreas	5	1.16	0.48-2.81	7	***4.07***	1.94-8.55
	Lung	17	1.48	0.90-2.44	11	**1.85**	1.02-3.34
	Hodgkin lymphoma	3	**4.35**	1.39-13.61	1	2.35	0.33-16.71
Clear cell	Pancreas	18	**1.69**	1.05-2.70	7	**2.23**	1.06-4.68
	Testis	3	2.19	0.70-6.81	6	***3.94***	1.77-8.76
Endometrioid	Stomach	35	1.25	0.89-1.75	11	**2.15**	1.19-3.88
	Nose	4	**3.08**	1.15-8.21	2	**4.02**	1.00-16.10
	Lung	58	0.98	0.75-1.28	37	**1.43**	1.04-1.97
	Breast	121	**1.24**	1.02-1.49	94	***1.35***	1.10-1.65
	Endometrium	49	***2.22***	1.67-2.96	22	***2.04***	1.34-3.09
	Other female genitals	6	1.65	0.74-3.69	4	**3.08**	1.16-8.22
	Kidney	34	**1.50**	1.07-2.12	12	1.41	0.80-2.49
	Connective tissue	8	1.54	0.77-3.09	6	**2.53**	1.13-5.63
Serous	Breast	515	***1.27***	1.15-1.39	373	***1.24***	1.12-1.38
	Other male genitals	12	**1.87**	1.06-3.29	8	***2.42***	1.20-4.85
	Thyroid gland	38	**1.42**	1.03-1.96	14	0.89	0.53-1.51
	Cancer of unknown primary	134	**1.23**	1.04-1.47	39	1.06	0.77-1.45
Mucinous	Upper aerodigestive tract	23	***1.73***	1.14-2.63	11	1.70	0.94-3.08
	Nose	3	**3.43**	1.10-10.67	0	-	-
	Breast	83	1.23	0.98-1.54	67	***1.38***	1.08-1.75
	Bladder	37	**1.46**	1.05-2.04	11	1.15	0.64-2.08
Non-epithelial	Thyroid gland	5	**2.82**	1.17-6.48	1	1.20	0.17-8.50
	Connective tissue	5	***3.69***	1.52-8.94	1	1.81	0.25-12.84
	Non-Hodgkin lymphoma	6	0.90	0.40-2.02	7	***2.72***	1.30-5.71
	Cancer of unknown primary	14	***2.25***	1.31-3.86	3	1.66	0.54-5.15

Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;
a: all cancers include all other cancers as well as ovarian cancer; b: all cancers include all other cancers apart from ovarian cancer.

Familial associations of different histological type of ovarian cancer with any cancer including or excluding ovarian cancer are shown in **Table 17**. When considering ovarian cancer into other cancers, all the histological types showed significance in the association with any cancer apart from clear cell and non-epithelial types. Additionally, familial associations for undifferentiated, endometrioid (both P <0.001) and serous (P<0.05 and P <0.001) types were significant in the two-way analysis. When removing ovarian cancer from other cancers, endometrioid, serous and mucinous types were still in the significant familial associations with any other cancers.

However, only the result of endometrioid carcinoma showed significance in the two-way analysis (P<0.01 and P <0.001).

Table 17 Familial associations of histology-specific ovarian cancer with any cancer

Histological type	Cancer site	Risk of ovarian cancer			Risk of invasive cancer		
		N	***RR***	***95% CI***	***N***	***RR***	***95% CI***
Undifferentiated	All cancers[a]	134	**1.45**	1.07-1.97	119	**1.23**	1.03-1.48
	All cancers[b]	116	1.29	0.94-1.77	110	1.16	0.96-1.40
Clear cell	All cancers[a]	302	0.99	0.82-1.18	168	1.01	0.87-1.18
	All cancers[b]	287	0.96	0.80-1.15	161	0.99	0.85-1.16
Endometrioid	All cancers[a]	675	***1.41***	1.23-1.61	477	***1.21***	1.11-1.32
	All cancers[b]	627	***1.34***	1.17-1.54	448	***1.16***	1.06-1.27
Serous	All cancers[a]	2663	***1.19***	1.12-1.27	1781	**1.04**	1.00-1.09
	All cancers[b]	2448	***1.13***	1.04-1.23	1711	1.02	0.98-1.07
Mucinous	All cancers[a]	439	**1.19**	1.02-1.38	290	1.05	0.94-1.18
	All cancers[b]	421	**1.17**	1.00-1.37	278	1.03	0.91-1.16
Non-epithelial	All cancers[a]	159	1.00	0.79-1.27	80	1.03	0.83-1.28
	All cancers[b]	154	1.00	0.79-1.27	76	1.00	0.80-1.25

Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;
a: all cancers include all other cancers as well as ovarian cancer; b: all cancers include all other cancers apart from ovarian cancer.

3.3 Influence of family history on the risk of SPC in breast cancer patients

3.3.1 Familial demography of breast cancer population

Among 87,752 breast cancer patients diagnosed at the median age of 55 years (**Table 18**), 14,952 patients (17.0%) developed SPC at the median age of 63 years, and among them 8653 (57.9%) was second breast cancer. In the 8626 patients who had second breast cancer diagnosis and had data on cancer side, 42.1% developed second breast cancer on the same side as previous one and 57.9% developed contralateral tumors. The median follow-up time from diagnosis of first breast cancer to SPCs was five years. However, it was only one year to second breast cancer diagnosis while it was eight years to other SPC. In the patients with diagnosis of second cancer, 68.8% had a first-degree family history of any cancer. In patients with SPC as well as with a cancer family history, 2228 (21.6%) of the SPCs were the same (concordant) cancer that was diagnosed in the

first-degree relatives, and for 8052 (77.4%) patients it was a different (discordant) familial cancer. Third primary cancers occurred in 2543 (17.0%) patients who had SPCs.

Table 18 Familial demography of breast cancer population followed during 1958-2015

No. of females followed	4,216,676
NUMBER OF CASES	
A. No. of BC diagnoses	87,752
B. No. of SPC diagnoses in BC patients	14,952 (17.0% of all BC survivors, B/A)
C. Familial SPC	10,280 (68.8% of all BC survivors with SPC, C/B)
D. Familial SPC (concordant)	2,228 (21.6% of all familial SPC, D/C)
E. Familial SPC (discordant)	8,052 (77.4% of all familial SPC,D/C)
F. No. of third primary cancer diagnoses	2,543 (17% of all BC survivors with SPC, F/B)
NUMBER OF DEATHS	
G. Deaths among all BC patients	18,998 (21.6% of all BC patients, G/A)
H. Deaths among BC patients with SPC	4,828 (32.3% of all diagnosed with SPC, H/B)
I. Deaths among SPC patients with positive family history	3,356 (32.6% of all familial SPC diagnoses, I/C)
J. Deaths among SPC patients with negative family history	1,472 (31.5% of all SPC patients with negative family history, J/(B-C))
K. Deaths among BC patients without SPC	14,170 (16.1% of all BC survivors without SPC, K/(A-B))

BC, breast cancer; SPC, second primary cancer.

3.3.2 Influence of family history on the SPC risk in breast cancer patients

In the assessment of influence of family history on SPC risk (**Table 19**), breast cancer patients with family history of any cancer (RR, 3.54, 95%CI, 3.46-3.62) presented with higher risk for any cancer as SPC in comparison with patients without family history (3.00, 2.91-3.09). When taking SPCs other than breast cancer into consideration, the corresponding RRs were 1.51 (1.49-1.58) and 1.25 (1.19-1.31), indicating an attributable risk proportion of 18.3% ((1.53-1.25) /1.53) for family history of cancer. The trend tests showed significance for 14 site-specific SPCs, including stomach, colorectal, liver, pancreatic, lung, breast, endometrial, ovarian, bladder, skin (squamous cell) and endocrine gland cancers, and melanoma, non-Hodgkin lymphoma and CUP. The maximum risk was observed with ovarian cancer (6.28, 4.50-8.75 with family history *vs.* 1.49, 1.34-1.65 without family history of ovarian cancer). Patients either with or without family history of breast cancer were both presented with high RRs for second breast cancer (4.89, 4.67-

5.12 and 3.90, 3.80-4.00, respectively). The major disease burden for familial SPCs was found for breast cancer (1909, of these 100 with only family history of in situ breast cancer), followed by colorectal (112, of these 12 with only family history of in situ colorectal cancer), lung (96) and skin (79, of these 41 with only family history of in situ skin cancer) cancers.

Table 19 Relative risk of second primary cancers according to family history of the same cancer in breast cancer patients

Site of second primary cancer	Breast cancer patients						*P- Trend*
	Negative family history			Positive family history			
	N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Upper aerodigestive tract	138	***1.38***	1.16-1.64	5	2.31	0.96-5.56	0.17
Esophagus	44	***1.56***	1.15-2.11	0	-	-	-
Stomach	93	***1.37***	1.11-1.69	8	***3.14***	1.57-6.28	**0.003**
Small intestine	46	***1.54***	1.14-2.07	0	-	-	-
Colorectum	683	***1.17***	1.08-1.26	112	***1.50***	1.25-1.81	**<.001**
Colon	499	***1.16***	1.06-1.27	45	**1.35**	1.01-1.81	**<.001**
Rectum	233	**1.15**	1.01-1.32	18	***1.90***	1.19-3.01	**<.001**
Anus	37	1.38	0.99-1.92	0	-	-	-
Liver	139	***1.25***	1.06-1.49	7	**2.54**	1.21-5.32	**0.007**
Pancreas	176	**1.20**	1.03-1.39	9	***2.35***	1.22-4.52	**0.02**
Nose	9	1.29	0.66-2.51	0	-	-	-
Lung	744	***1.54***	1.43-1.66	96	***2.93***	2.40-3.58	**<.001**
Breast	6744	***3.90***	3.80-4.00	1909	***4.89***	4.67-5.12	**<.001**
Cervix	95	1.07	0.87-1.31	2	1.58	0.39-6.32	0.16
Endometrium	627	***1.42***	1.31-1.54	37	***3.32***	2.40-4.58	**<.001**
Uterus	1	2.38	0.32-17.49	0	-	-	-
Ovary	364	***1.49***	1.34-1.65	35	***6.28***	4.50-8.75	**<.001**
Other female genitals	53	1.09	0.83-1.44	0	-	-	-
Kidney	180	***1.44***	1.24-1.68	7	**2.12**	1.01-4.44	0.24
Bladder	189	***1.30***	1.12-1.51	14	***2.21***	1.31-3.74	**0.005**
Melanoma	423	***1.32***	1.19-1.45	26	***1.97***	1.34-2.89	**<.001**
Skin, squamous cell	339	***1.35***	1.21-1.51	79	***3.47***	2.78-4.33	**<.001**
Eye	25	1.42	0.95-2.12	0			
Nervous system	204	1.01	0.88-1.17	6	1.16	0.52-2.57	0.10
Thyroid gland	90	***1.72***	1.39-2.12	1	2.73	0.38-19.42	0.31
Endocrine gland	172	**1.17**	1.01-1.37	8	***3.50***	1.75-6.99	**0.004**
Bone	10	1.83	0.96-3.48	0	-	-	-
Connective tissue	66	***2.15***	1.67-2.76	0	-	-	-
Non-Hodgkin lymphoma	224	***1.21***	1.05-1.38	10	**2.03**	1.09-3.77	**0.01**
Hodgkin lymphoma	15	1.29	0.77-2.17	0	-	-	-
Myeloma	79	1.06	0.85-1.33	2	2.08	0.52-8.31	0.15
Leukaemia	222	***1.38***	1.20-1.57	5	1.32	0.55-3.17	0.18
Cancer of unknown primary	253	***1.37***	1.21-1.55	10	1.82	0.98-3.38	**0.01**
All cancers [a]	4672	***3.00***	2.91-3.09	10280	***3.54***	3.46-3.62	**<.001**
All cancers [b]	1905	***1.25***	1.19-1.31	4394	***1.53***	1.49-1.58	**<.001**

a: Breast cancer is included into all cancers; b: Breast cancer is excluded from all cancers
Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not

overlapped with 1.00 respectively;

Cumulative incidence rates for second primary endometrial, lung, ovarian, colorectal and skin cancers and melanoma are shown in **Figure 8** (A-F) based on age at diagnosis of SPCs. The cumulative incidence of SPC in breast cancer patients having a family history of concordant cancer was high at individual age compared to those patients without family history. Ovarian cancer was found with a large difference; for patients with ovarian cancer diagnosis in first-degree relatives, the cumulative incidence of second ovarian cancer increased up to 6% at the age of 75 years, compared to 1% for those without a family history.

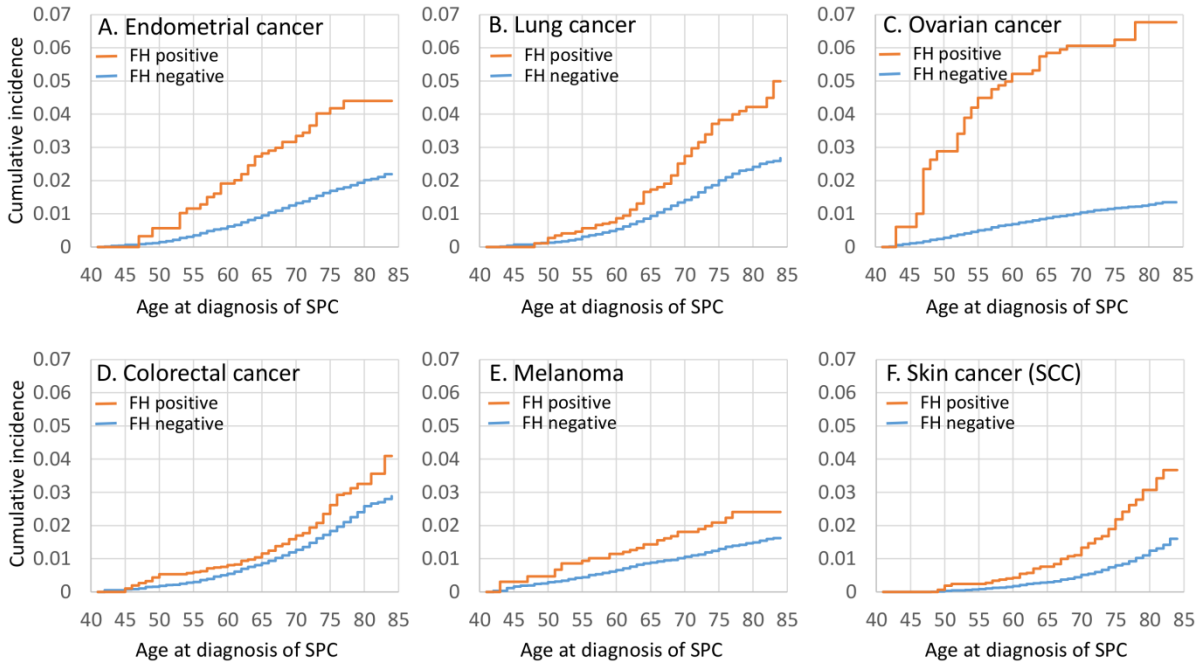

Figure 8 Cumulative incidence of second primary cancers (SPCs) at each age of breast cancer patients according to family history. SPC, second primary cancer. FH positive (negative), breast cancer patients had (had no) first-degree family history of specific cancer (for example, endometrial cancer in Fig.1-A).

3.3.3 Cause of death in breast cancer with and without SPC diagnosis

A number of 18,998 (21.6%) deaths were identified during the follow-up time in breast cancer patients (**Table 18**, lower part). A total of 4,828 (32.3%) deaths occurred among the 14,952

patients diagnosed with SPCs. The death rate was identical for patients who developed SPCs, either with or without a family history (32.6% and 31.5%, respectively). However, the death rate in the patients who only had breast cancer (16.1%) was half of the rate in those who had SPC.

The cause of death for BC patients in different follow-up time from diagnosis of breast cancer is displayed in **Table 20** according to the occurrence of SPC. In patients with diagnosis of SPCs, most of the deaths throughout the follow-up time were due to breast cancer and SPC and the former included largely patient with second breast cancer. Deaths resulted from SPCs other than breast cancer were responsible for 34.3% of deaths, but when considering second breast cancer also as SPC (30.6%), the joint SPC contributed to 64.9 % of all deaths. In the beginning after diagnosis of breast cancer, second breast cancer accounted for large proportion of deaths (first year, 42.6%) while after 10 years of diagnosis the proportion dropped to 23.2%. The proportion of death due to SPCs other than breast was constant throughout the follow-up ranging from 30% to 35%. For the death caused by higher order primary cancer, the proportion increased from 2.1% in the first year to 7.6% after 10 years of breast cancer diagnosis. Breast cancer was the leading cause of death for women who only had breast cancer during the follow-up period and other causes were responsible for approximately 15% of all deaths but went up to 32.1% after 10 years of breast cancer diagnosis.

Table 20 Cause of death according to follow-up time since first cancer diagnosis in breast cancer patients with or without second primary cancer

Breast cancer	Cause of death	<1 year (% in column)	1-4 years (% in column)	5-10 years (% in column)	>10 years (% in column)	All (% in column)
With SPC	Breast cancer a	11 (7.7)	86 (10.1)	138 (9.2)	211 (9.1)	466 (9.6)
	Breast cancer b	61 (42.6)	344 (40.4)	533 (35.4)	540 (23.2)	1478 (30.6)
	SPC	40 (30.0)	258 (30.3)	543 (36.0)	815 (35.0)	1656 (34.3)
	Higher order primary cancer	3 (2.1)	26 (3.0)	56 (3.7)	177 (7.6)	262 (5.4)
	Other cancers	11 (7.7)	54 (6.3)	100 (6.6)	252 (10.8)	417 (8.6)
	Other causes	17 (11.9)	83 (9.8)	136 (9.0)	333 (14.3)	569 (11.8)
	All (% in row)	143 (3.0)	851 (17.6)	1506 (31.2)	2328 (48.2)	4828 (100.0)
Without SPC	Breast cancer	817 (77.0)	4032 (86.2)	4006 (81.1)	2190 (62.7)	11045 (77.9)
	Other cancers	48 (4.5)	104 (2.2)	152 (3.1)	184 (5.3)	488 (3.4)
	Other causes	196 (18.5)	541 (11.6)	779 (15.8)	1121 (32.1)	2637 (18.6)
	All (% in row)	1061 (7.5)	4677 (33.0)	4937 (34.8)	3495 (24.7)	14170 (100.0)

a, breast cancer patients diagnosed with non-breast second primary cancer and dying of breast cancer; b, breast cancer patients diagnosed with second breast cancer and dying of breast;
SPC, second primary cancer;
Higher order primary cancer, third, fourth or fifth primary cancer.

Supplementary Table 7 displays the same data as **Table 20** but covers only the follow-up time from 2001 to 2015. For patients with second breast cancer diagnoses, the overall proportions of deaths due to breast cancer decreased from 30.6% in **Table 20** to 28.1% in **Supplementary Table 7**. A concomitant increase was found in deaths due to non-breast SPC (from 34.3 to 38.5%).

The distribution of the cause of death in patients with SPCs when SPC conferred at least 50 deaths is shown in **Figure 9**. Second pancreatic, lung, liver, breast, stomach and ovarian cancers individually accounted for more than 70% of the deaths in breast cancer patients with the corresponding SPC, while skin and endometrial cancers and CUP appeared least fatal, accounting for less than 30% of deaths. The proportions of death caused by breast cancer and other causes were reversed in these two groups of cancers; for example, large proportions of death in the least fatal SPCs (skin and endometrial cancers) were caused by breast cancer and

other cause instead of SPC. Other cancers were a minor cause of death, but not for CUP, for which half of the deaths were caused by other cancers. Details of the distribution of the cause of deaths for all SPCs are presented in **Supplementary Table 8**.

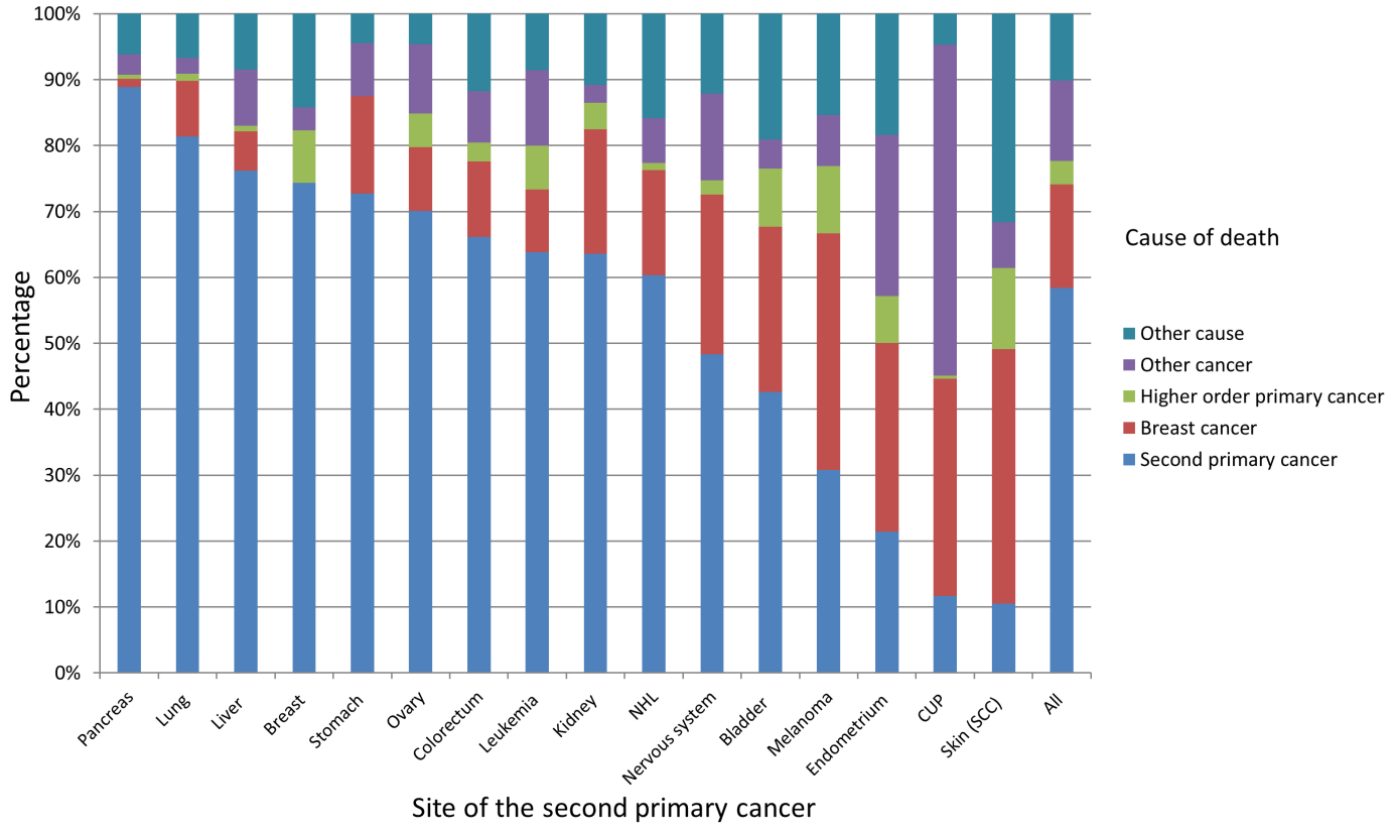

Figure 9 Distribution of cause of death (second primary cancer, breast cancer, higher order primary cancer, other cancers and other causes) in breast cancer patients with diagnosis of second primary cancer. Only cancer sites with more than 50 death cases are displayed.

3.4 Influence of family history on the risk of SPC in ovarian cancer patients

3.4.1 Familial demography of ovarian cancer population

One patient was excluded from the 11,301 ovarian cancer patients in the offspring generation, as the second cancer diagnosis of this patient was later than the time of death. A total of 1,111 patients (9.8%) among the 11,300 patients developed SPC during the follow-up (**Table 21**). Among patients with SPC, 67.6% (751) were from families with at least one first-degree relative having cancer diagnosis. For 622 patients, the site of the SPC was different (discordant) from site of the cancer diagnosed in their first-degree relatives and for the rest 129, the site of SPC was the same (concordant) as the cancer site in family members. The median age at diagnosis of first primary cancer was 50 years in ovarian cancer patients who were diagnosed with SPC later and it was 62 years for the diagnosis of SPC. In the ovarian cancer patients with SPC diagnosis, the median follow-up time from diagnosis of first primary to that of SPC was eight years. Additionally11.0% (122) of those patients developed a third primary at the end of the follow-up.

Table 21 Familial demography of population followed during 1958-2015

No. of females followed	4,216,676
NUMBER OF CASES	
A. No. of OC diagnoses	11,300
B. No. of SPC diagnoses	1,111 (9.8% of all OC survivors, B/A)
C. Familial SPC	751(67.6% of all OC survivors with SPC, C/B)
D. Familial SPC (concordant)	129 (16.2% of all familial SPC, D/C)
E. Familial SPC (discordant)	622 (83.8% of all familial SPC,D/C)
NUMBER OF DEATHS	
F. Deaths among all OC patients	5,559 (49.2% of all OC patients, F/A)
G. Deaths among OC patients with SPC	544 (49.0% of all diagnosed with SPC, G/B)
H. Total deaths among SPC patients with positive family history	362 (48.2% of all familial SPC diagnoses, H/C)

OC, ovarian cancer; SPC, second primary cancer;

3.4.2 Influence of family history on the SPC risk in ovarian cancer patients

Table 22 shows the influence of cancer diagnosis in first-degree relatives on the development of this cancer as SPC in ovarian cancer patients without removal of possible high risk families, and for the risk estimation, the reference group is the general population without neither ovarian cancer nor a family history of SPC of any cancer. With a cancer family history, the risk for any cancer as SPC was higher (RR, 1.74 95%CI, 1.64-1.87) than that without family history (1.49, 1.34-1.65). Small intestinal (3.23, 1.73-6.03), connective tissue (3.13, 1.73-5.67) and bladder (2.72, 2.01-3.69) cancers and CUP (2.69, 2.06-3.52) were noted with high risks as SPC in ovarian cancer. The trend test was found significant for risks of SPC with concordant family history of four cancers, including colon, colorectal, lung and breast cancers. Furthermore, the trend test was found marginally significant for skin (squamous cell) cancer as SPC with a family history (3.25, 1.05-10.02) compared to that without a family history (0.74, 0.48-1.15). The RRs for pancreatic and bladder cancer and CUP as SPC with a concordant family history were high although based on few cases. Breast (52 patients) and colorectal cancers (29 patients) were found as the most common familial SPCs. Of note, cancer sites with less than 10 total cases are not shown in this and the subsequent tables, but they contributed to the estimation for 'All cancer'. In the 122 patients identified with third primary cancers, 58% of third primary were breast (32), colorectal (27) and lung (12) cancer. The influence of cancer diagnosis in first-degree relatives on the probability of developing this cancer as SPC was still of significance even though individuals from possible high risk families were removed in the analysis (**Supplementary Table 9**).

Table 22 Relative risk of second primary cancers according to family history of concordant cancer in ovarian cancer patients

Site of second primary cancer	Patients with ovarian cancer						*P-trend*
	Negative family history			Positive family history			
	N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Upper aerodigestive tract	12	1.10	0.62-1.94	0	-	-	-
Stomach	16	***2.21***	1.35-3.62	1	3.43	0.48-24.4	0.31
Small intestine	10	***3.23***	1.73-6.03	0	-	-	-
Colorectum	114	***1.84***	1.53-2.22	29	***4.17***	2.09-6.00	**<0.001**
Colon	89	***2.00***	1.63-2.47	16	***4.95***	3.03-8.09	**<0.001**
Rectum	37	***1.72***	1.24-2.37	1	1.30	0.18-9.21	0.32
Liver	22	***1.89***	1.24-2.88	1	3.17	0.45-22.52	0.34
Pancreas	36	***2.35***	1.69-3.27	3	***8.38***	2.70-25.98	0.52
Lung	74	***1.45***	1.16-1.83	12	***3.32***	1.88-5.84	**<0.001**
Breast	209	1.01	0.88-1.15	52	***2.08***	1.58-2.73	**<0.001**
Other female genitals	11	**2.07**	1.14-3.75	0	-	-	-
Kidney	21	**1.61**	1.05-2.48	1	2.56	0.36-18.17	0.32
Bladder	42	***2.72***	2.01-3.69	3	**5.32**	1.72-16.52	0.15
Melanoma	38	1.06	0.77-1.46	2	1.81	0.45-7.24	0.15
Skin, squamous cell	20	0.74	0.48-1.15	3	**3.25**	1.05-10.02	0.06
Nervous system	16	0.68	0.42-1.12	2	3.04	0.76-12.15	>0.99
Thyroid gland	10	1.57	0.84-2.92	0	-	-	-
Endocrine glands	22	1.35	0.89-2.06	0	-	-	-
Connective tissue	11	***3.13***	1.73-5.67	0	-	-	-
Non-Hodgkin lymphoma	17	0.87	0.54-1.40	1	1.45	0.20-10.29	0.32
Leukemia	29	**1.67**	1.16-2.40	0	-	-	-
Cancer of unknown primary	54	***2.69***	2.06-3.52	3	**3.98**	1.28-12.36	0.58
All cancers [a]	360	***1.49***	1.34-1.65	751	***1.74***	1.62-1.87	**<0.001**
All cancers [b]	334	***1.38***	1.24-1.54	714	***1.66***	1.54-1.74	**<0.001**

Values with bold, italic or underlined format indicate their 95% CI, 99% CI and 99.9% CI were not overlapped with 1.00 respectively;
a, all cancers including second ovarian cancer; b, all cancers excluding second ovarian cancer.

Cumulative incidence for second primary breast and colorectal cancers after diagnosis of ovarian cancer is shown in **Figure 10** stratified over age at SPC diagnosis. For SPCs with a concordant family history of breast or colorectal cancer, cumulative incidence increased steeply from about age 45 to 60, and less steeply at older ages. Having first-degree relatives diagnosed with breast cancer, the cumulative incidence for second primary breast cancer was 5.0% at age over 80 years, approximately two-fold larger compared to that without a family history (2.5%). Similarly, the respective cumulative incidence for second primary colorectal cancer was 5.0% and 1.5%.

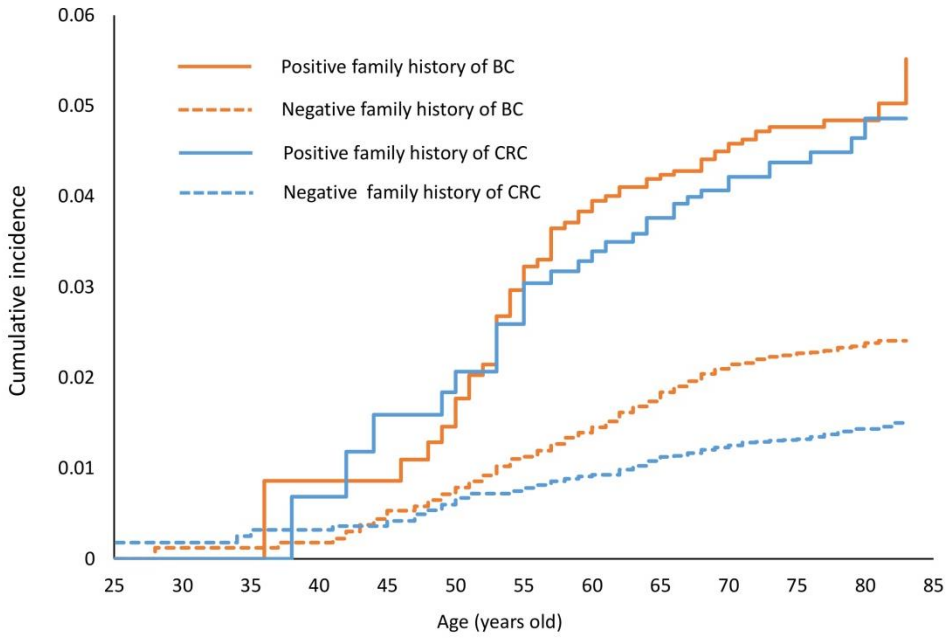

Figure 10 Cumulative incidence of second primary cancers (SPCs) at each age of ovarian cancer patients according to family history. SPC, second primary cancer.

3.4.3 Cause of death in ovarian cancer with and without SPCs diagnosis

As a whole, 49.19% (5,559) of all the ovarian cancer patients died during the follow-up time. Similarly, the death rate was 48.96% for patients with SPC and 48.20% for those with SPC and a family history (**Table 21**, bottom part).

Causes of deaths were classified into ovarian cancer, SPC (if present), other cancer and other (non-neoplastic) cause for the analysis of distribution of causes of deaths in ovarian cancer patients with and without diagnosis of SPC in the different time period after first primary cancer diagnosis (**Table 23**). Among the patients with SPC, in the first 5 years since follow-up, ovarian cancer was observed as the main cause of death. However, SPC accounted around half of the death cases in the last two periods (43.1%, 5-10 years and 50.9%, >10 years) and overall follow-up time (42.1%), which presented as the leading death cause in those times. Others causes was

only responsible for a small portion of the death cases, reaching 15.1% after 10 year diagnosis of ovarian cancer. On the contrary, ovarian cancer was the main cause of death throughout the follow-up time for patients free of SPC and larger proportion of those patients died of other causes in the last follow-up period (32.5%). Among 102 death cases due to other cancers, many multiple and poorly localized cancers or tumors with undefined behavior were observed and CUP was responsible for 19 death cases.

Table 23 Cause of death according to follow-up time since first cancer diagnosis in ovarian cancer patients with or without second primary cancer

Ovarian cancer	Cause of death	<1 year (% in column)	1-4 years (% in column)	5-10 years (% in column)	>10 years (% in column)	All (% in column)
With SPC	Ovarian cancer	10 (45.4)	71 (58.7)	47 (40.5)	31 (10.9)	159 (29.2)
	SPC	8 (36.4)	26 (21.5)	50 (43.1)	145 (50.9)	229 (42.1)
	Other cancers	4 (18.2)	19 (15.7)	13 (11.2)	66 (23.2)	102 (18.8)
	Other causes	0	5 (4.1)	6 (5.2)	43 (15.1)	54 (9.9)
	All (% in row)	22 (4.0)	121 (22.2)	116(21.3)	285 (52.4)	544 (100.0)
Without SPC	Ovarian cancer	849 (86.5)	2238 (90.5)	950 (86.9)	269 (57.6)	4306 (85.9)
	Other cancers	88 (9.0)	177 (7.2)	75 (6.9)	46 (9.8)	386(7.7)
	Other causes	44 (4.5)	59 (2.4)	68 (6.2)	152 (32.5)	323 (6.4)
	All (% in row)	981(19.6)	2474 (49.3)	1093 (21.8)	467 (9.3)	5015 (100.0)

SPC, second primary cancer

The distribution of cause of death in the 544 patients with SPC diagnoses is shown in **Supplementary Table 10**. As a whole, 29.2% (159) of the deaths was due to ovarian cancer, 42.1% (229) was SPC, 18.8% (102) was other cancer and 9.9% (54) was other causes. In the 102 deaths due to other cancers, higher order primaries (third, fourth and fifth primaries) were responsible for 28 deaths and the rest were cancers identified as the cause of death by the death registry. The death codes indicated eight patients had identical second and third primary cancers and cause of death (three were breast cancer and the rest were other individual cancers) among the 28 deaths due to higher order primaries. For all the patients with SPC, the leading cause was

breast (88), colorectal (75) and lung (66) cancers and CUP (47). The distribution of causes of death is displayed in **Figure 11** for the patients with SPC and for the site of SPC with at least 10 death cases. Pancreatic cancer, leukemia (seven acute myeloid leukemia, three acute monocytic leukemia and one megakaryocytic), liver and lung cancers were most fatal as SPCs since 70% of deaths were due to them individually. While in patients with second melanoma and CUP, SPC only accounted a small portion of the deaths.

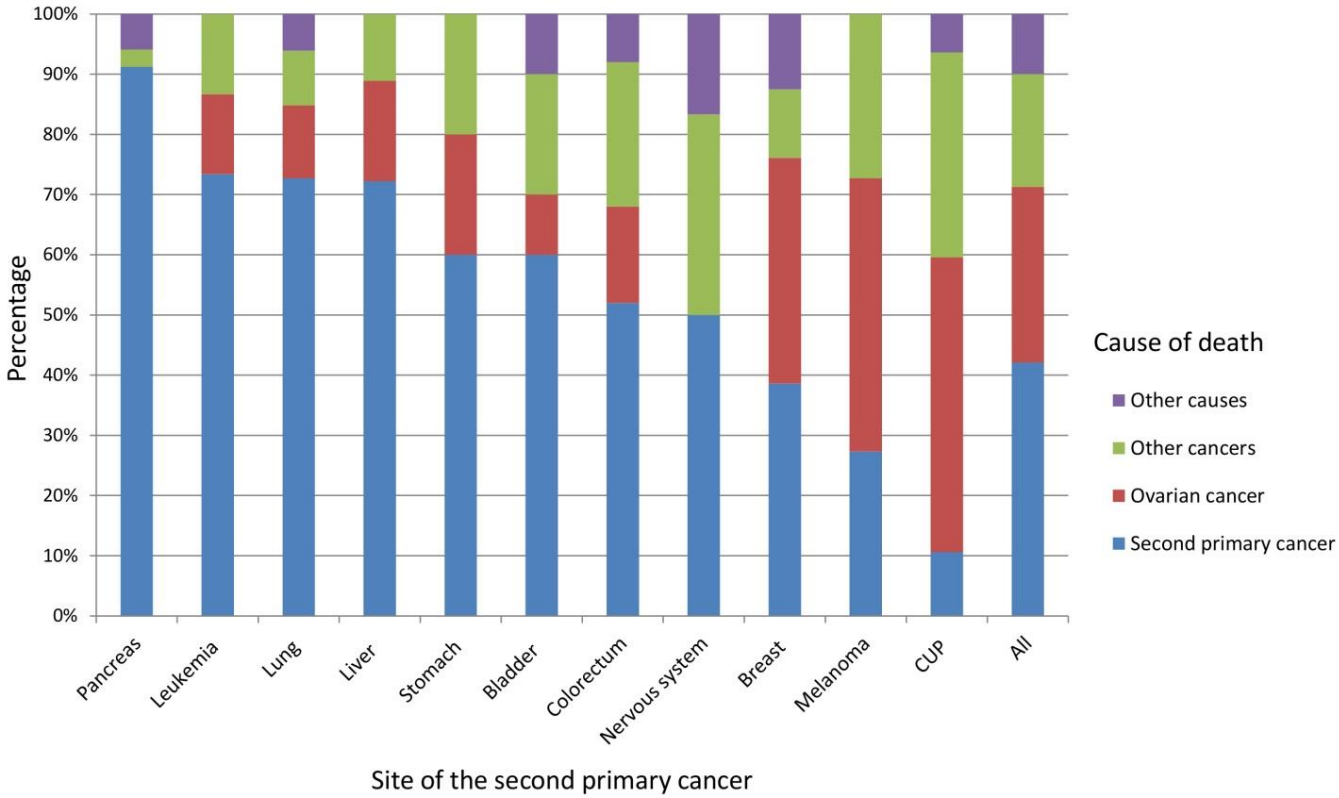

Figure 11 Distribution of cause of death (second primary cancer, ovarian cancer, other cancers and other causes) in ovarian cancer patients with diagnosis of second primary cancer. Only cancer sites with more than 10 death cases are displayed.

4 DISCUSSION

4.1 Familial clustering

4.1.1 Familial clustering of breast cancer with concordant cancer

The risk of breast cancer was decreased in families with three or more first-degree relatives diagnosed with breast cancer compared to the families that had two breast cancer patients. This may result from the intensified screening activity in families with multiple affected patients, as the proportion of in situ breast cancer was observed the largest in families with multiple breast cancer patients.

In the search of familial risk stratified by different proband type, family history from mother and sister individually had similar effect on breast cancer risk (mother vs. sister; mother and one sister vs. two sisters). Contextually, male breast cancer is a very rare disease, which is reported associated with *BRCA2* mutation (Liede *et al.*, 2004). Breast cancer risk was lower in family with father diagnosed with breast cancer compared to that with one brother diagnosed; for the latter, risk was identical to that with two sisters affected. Individuals with a father diagnosed with breast cancer showed similar risk to those with an affected mother. When both mother and father were diagnosed with breast cancer, the risk was extremely high, which suggests strong interactions between female and male risk genotype with much weaker effects when they are functioning individually. Women with mother and brother affected, also had high risk of breast cancer, but the results were based on only three families.

Familial association between breast cancer and histology-specific breast cancer were found significant in the two-way comparison. Interestingly, the RRs were homogeneous, around 2.00, indicating that for different histological types, they share similar familial risk. In the analysis of

familial association among histology-specific breast cancers, highest risk with family history of concordant histological type was observed for medullary tumor despite three familial cases. Medullary breast cancer is reported particularly common in carriers of *BRCA1* mutations (Stratton, 1997). There are limited data on the familial risk of histology-specific breast cancer. In Utah population, excess familial risk was found for lobular breast cancer and the familial risk was slightly higher than the present study with lobular breast cancer risk to be 2.38 in families with any type of breast cancer and 4.61 in families with lobular breast cancer. To be noted, germline mutation of *CDH1* gene increases the risk of lobular breast cancer (Corso *et al.*, 2018).

4.1.2 Familial clustering of breast cancer with discordant cancer

Breast cancer was previously reported in familial associations with discordant cancers such as ovarian, endometrial, prostate, colon and thyroid cancers, melanoma and non-Hodgkin lymphoma but among which only ovarian and prostate cancers were frequently reported (Amundadottir *et al.*, 2004; Jervis *et al.*, 2013; Teerlink *et al.*, 2012). The familial associations between breast cancer and other cancers were previously reported based on the earlier version of the Swedish Family-Cancer Database. In that study the familial risk was analyzed separately in siblings and parents-offspring pairs in order to avoid chance finding and ovarian and prostate cancers showed significance in both analyses (Hemminki *et al.*, 2012c). In the present study, additional significant associations were found for small intestinal, colorectal and lung cancers as well as for non-Hodgkin lymphoma. Compared to other studies, the advantage of the present one is in the large sample size and the extensively stratified statistical analyses. Significant discordant associations in the two-way comparison together with a ‘dose-response’ trend in the increasing RRs with the increasing number of affected first-degree relatives increased credibility for the findings. Additionally, considering ‘dose-response’ model is helpful in the identification

of the underlying genetic risk (penetrance) and high penetrance may be noted in families with many members diagnosed with the same cancers.

Genetic and hormonal factors contribute the most for the significant familial associations of breast cancer with discordant cancers, as only few common environmental factors can explain the association between breast cancer and other cancers apart from the association with female sex hormone/reproductive factor related cancers. The environmental factor was estimated to contribute only 29% of the familial risk of female breast cancer and breast cancer risk was observed to remain uninfluenced by the age difference of sisters diagnosed with breast cancer which indicates an important role of genetic factors instead of the influence from environmental sharing (Couto and Hemminki, 2007; Hemminki and Li, 2004).

It is known that *BRCA1* carriers have an increased risk of ovarian cancers and *BRCA2* carriers are at excess risks of ovarian, prostate and pancreatic cancers (Rahman, 2014). Esophageal, stomach and colorectal cancers were also reported in *BRCA1* mutation carriers (Levy-Lahad and Friedman, 2007; Moran *et al.*, 2012; Sopik *et al.*, 2015). In some studies uveal melanoma as well as cutaneous melanoma was found related to *BRCA2* mutations. Result from a breast cancer clinic reported that *BRCA1/2* mutations in breast cancer families were entirely responsible for ovarian cancer risk (Ingham *et al.*, 2013). *BRCA1/2* mutation frequencies are not well known in Sweden but in one study *BRCA1* mutations were estimated responsible for less than 1% of unselected breast cancers and another study found mutation frequency of *BRCA2* is one third of that of the *BRCA1* in early onset patients (Loman *et al.*, 2001; Margolin *et al.*, 2004). Although many cancers have been reported in *BRCA1/2* carriers, the question if those really present excess risks has remained unresolved. In this study, familial breast cancer accounted for 16.1% of all and if 1% of it is related to *BRCA1/2*, it can be concluded that the associations found here were

dominated by other factors. As mutations in other high risk genes are much less frequent than those in *BRCA1/2*, their contribution to breast cancer is most likely small (Tung *et al.*, 2016). *CHEK2**1100delC is a moderate-penetrance gene related to breast cancer which can also predispose to other cancers (Meijers-Heijboer *et al.*, 2002). Results from Copenhagen Gerneral Population Study based on 80,000 individuals showed that in addition to breast cancer (RR=2.08), *CHEK2*1100delC* heterozygosity is related to 15% to 82% increased risk for at least some cancers, including stomach (5.76), kidney (3.61) and prostate (1.60) cancers and sarcoma (3.45) (Naslund-Koch *et al.*, 2016).

In the present study breast cancer displayed one of the strongest two-way association with ovarian cancer (four significant RRs, three of which were significant at 0.001 level), suggesting the likely contribution of hormonal effects and/or *BRCA1/2* mutations. The association with prostate cancer was probably at least in part due to hormonal factors (Hemminki *et al.*, 2010a; Risbridger *et al.*, 2010). The associations with eye cancer were linked by uveal melanoma which may be related to the *BRCA2* mutation (Levy-Lahad and Friedman, 2007; Moran *et al.*, 2012). The significant association with leukemia may be due to chronic myeloid leukemia. In the two-way analyses with endocrine tumors, parathyroid and pituitary tumors were observed with solitary associations.

CUP is a rare disease in which the origin of the malignant (cancer) cell cannot be found. Compared to cancer with known primary, CUP is fatal as it is usually at a metastatic stage upon diagnosis (Pavlidis and Pentheroudakis, 2012). Familial association of CUP with many primary cancers, including breast cancer, was reported previously based on the earlier version of the database (Hemminki *et al.*, 2011a) . In that study the primary cancers in relatives were hypothesized to indicate the place where the primary cancer began in CUP patients. In the

current study familial association of breast cancer with CUP suggested the probable primary site for CUP may be the breast (Hemminki *et al.*, 2012b; Hemminki *et al.*, 2013; Hemminki *et al.*, 2016). Significance in one-way analysis cannot provide strong evidence for the association in the present kind of studies. However, some rare yet unknown high penetrant genes may contribute to the associations with female kidney and bladder cancers and with myeloma in families of three or more breast cancer patients, or the associations may be found simply by chance or unknown environmental burden. The association of breast cancer with 'All cancers' was notable because of the high RRs. When at least three cancers including breast cancer were identified in the family, the RR for breast cancer was 1.63 (**Table 7**), which is as high as the risk for concordant breast cancer (**Figure 5**, 1.70). However, a total of 3393 breast cancer patients were found in such families with diverse cancer diagnoses whereas only 26 breast cancer patients had family history of breast cancer in family. This also allude to a shared familial risk among multiple cancers (Frank *et al.*, 2017a; Frank *et al.*, 2017b; Frank *et al.*, 2017c; Yu *et al.*, 2017).

Even though these findings can provide evidence for germline genetics of cancer, the problem is in application of the information in clinical practice. Firstly, genetic counseling for suspected genetic risk factors should be encouraged based on the result showing significant breast cancer burden in families with prior history of diverse cancers. Secondly, according to **Table 7**, breast cancer risk was especially high for women with two family members affected by non-Hodgkin lymphoma, leukemia or melanoma. Thirdly, even by leveraging high-throughput sequencing merely a moderate number of genes are identified in multiple independent families that predispose to cancers. Hence a desirable technique to address such polygenic predisposition paradigm should include dynamic assessment of multiple cancer phenotypes compared to that of a single phenotype based process. These may increase the awareness of counselors about the

cancer patterns clustering in families although they are not related to clinical routine.

4.1.3 Familial clustering of ovarian cancer with concordant cancer

In the estimation of familial risks of ovarian cancer according to proband type, familial risk was higher in families with one sister diagnosed with ovarian cancer, compared to that in families that only had affected mother. This may implicate recessive inheritance or shared environmental factors among sisters. Familial risks for the mother or sister history were identical when only including cases diagnosed after 50 years of age, indicating that the excess risk for sisters may only influence women with early diagnosis with likely involvement of sex-related hormone levels. Notably high familial risk was found in families where both mother and sisters were affected by ovarian cancer suggesting possible involvement of high penetrant risk genes. Unfortunately, histology information are only available for 8 cases among the 14 cases with high familial risk and histological type of 5 cases was serous suggesting possible involvement of *BRCA1/2* (Lakhani *et al.*, 2004; Pal *et al.*, 2005). One study from UK reported that germline mutations in *BRCA1/2* contributed to around 24% of the familial risk of epithelial ovarian cancer, and for the relatives of cases without *BRCA1/2* mutations the familial RR was reported at 2.24 (Jervis *et al.*, 2013). Serous ovarian cancer was found with higher familial risk compared to the non-serous type in that study, which may support the association with *BRCA* mutations; however, no obvious differences were observed in the current study. Without information on mutation status, information lacking data on ovariectomies is one of the caveats in population-observational investigations on ovarian cancer. Contextually, familial risk of serous cancers may be affected by oophorectomy in mutation carriers.

The present study on 46,227 ovarian cancer cases is by far one of the largest family studies for ovarian cancer stratified by particular histological type in cases and their first-degree relatives. In

a combined cohort study performed by the international Ovarian Cancer Cohort Consortium covering 5,584 invasive ovarian cancers, the overall familial risk was 1.48 and only serous carcinoma was found related to the family history of concordant type with relative risk (RR) of 1.61(Wentzensen *et al.*, 2016). This is in contrast to the current data in which the overall familial risk was 2.51 and all histological types here showed significance in the two-way comparison, although mucinous and non-epithelial types were significant only in one-way analyses. In the present study, the risks for serous ovarian cancer in the two-way analyses were 2.15 and 2.96. The familial risks for ovarian cancer in this study (2.51) are far larger than those reported by the Ovarian Cancer Cohort Consortium (1.48). However, it can be speculated that family risk was underestimated in that study as the estimated risks were not compared with values from other studies (Frank *et al.*, 2017c; Hemminki and Granström, 2003; Hemminki *et al.*, 2011b; Jervis *et al.*, 2013; Teerlink *et al.*, 2012). Information on family history is subjected to ambiguity when it is self-reported instead of being procured from registered resources and it was reported that the positive predictive value of correct reporting for ovarian cancer in first-degree relatives was just 69% (Murff *et al.*, 2004).

The histology-specific analyses in cases and probands, although novel, were based on small number of familial cases. Significant risks for concordant histological type were observed for serous, endometrioid and mucinous ovarian cancers. However, an interesting finding was that among all the familial associations between concordant or discordant histological types, all the association between discordant histological types were observed with highest RRs except mucinous ovarian cancer. For instance, the endometrioid-endometrioid RR was 3.59 and undifferentiated-undifferentiated RR was not significant while the endometrioid-undifferentiated RR was 9.27. This may suggest that for familial ovarian cancer histological type is not specific.

Histological type of ovarian cancer may not be decided by the genes or polygenes responsible for familial aggregation or may be decided by those genetic factors together with the effects of hormone and environmental factors in variable levels.

Clear cell and endometrioid ovarian cancers were reported to arise in the context of endometriosis (Campbell *et al.*, 2004; Catasús *et al.*, 2004; Obata *et al.*, 1998; Sato *et al.*, 2000). Unsupervised clustering of risk factors found that endometrioid and clear cell carcinomas share many common risk factors, including oral contraceptive use, history of tubal ligation, endometriosis and parity (Wentzensen *et al.*, 2016). In contrast, the present results found no shared familial risks between these two histological types, which is consistent with genetic factors playing more important roles than environmental factors on familial clustering.

4.1.4 Familial clustering of ovarian cancer with discordant cancer

Ovarian cancer showed the strongest association with breast cancer (four significant RRs, of which three were significant at 0.001 level) and additionally familial association of serous carcinoma with breast cancer was significant in the two-way comparison. The possible explanation can be the involvement of *BRCA1/2* mutations (Lakhani *et al.*, 2004; Pal *et al.*, 2005). Only one weak association was found with prostate cancer here despite that *BRCA2* is reported to have association with prostate cancer (BreastCancerLinkageConsortium, 1999; Moran *et al.*, 2012). *BAP1* mutations are considered as risk factors for cutaneous and eye melanomas and ovarian cancers, which may be responsible for the weakly increased risk with cutaneous melanoma and the associations with eye cancer (one of two was melanoma) in **Table 7** (BreastCancerLinkageConsortium, 1999; Carbone *et al.*, 2013). The present study may not support the aggregation of HNPCC syndrome that clusters colorectal and ovarian cancers with presentation of only a weak association between these two cancers and insignificant associations

of endometrioid or clear cell ovarian cancers with colorectal cancer. However, the indication of the HNPCC link can be indicated in the strong association between endometrioid ovarian cancer and endometrial cancer in the two-way analyses. *MSH6* mutations are related to ovarian cancer of endometrioid and clear cell types (Pal *et al.*, 2012). A tendency of high risk for endometrial cancer was reported in carriers with *MSH6* germline mutations compared to low risk for colorectal cancer (Castellsagué *et al.*, 2015).

Ovarian cancer is a group of diseases with diverse histological types that present unique risk factors, genetic features and clinical manifestation. Similarly, analyses stratified by histology suggest that the familial clustering of ovarian cancer with other cancer may be histology-specific. Endometrial cancer was only in familial association with endometrioid cancer among all the histological types, accompanied by the strongest significance (both RR>2.00, both $P < 0.001$). Additionally, epithelial ovarian cancers of different histological types including endometrioid, serous and mucinous were associated with breast cancer individually with homogenous RRs between 1.20-1.40, which indicate that there is similarity of familial risk between epithelial ovarian cancers of different types and breast cancer. Mucinous ovarian cancer was found here associated with smoking related cancers including cancers in upper aerodigestive tract, nose, breast, bladder and gallbladder. This is consistent with the knowledge that smoking can increase the risk of mucinous ovarian cancer (Wentzensen *et al.*, 2016). However, lung cancer was not observed in association with mucinous ovarian cancer instead of undifferentiated and endometrioid types.

Liver cancer in the ICD-7 contains a group of cancers and the significant association of liver cancer with ovarian cancer in the two-way comparison indicated the need for analyses in subtype cancers. Only gallbladder cancer showed significant results and remarkably, with mucinous

carcinoma in the two-way analysis, which may be due to some risk factors like smoking and obesity that are commonly shared in family members (Campbell *et al.*, 2017; Pandey and Shukla, 2003; Wentzensen *et al.*, 2016).

Among notable associations were, cancer of nose significant in the two-way analysis with ovarian cancer of endometrioid histology as well as with mucinous ovarian cancer in one-way analysis. Known risk factors such as smoking and wood dust exposure, cannot adequately explain such finding (Greiser *et al.*, 2012). However, cancer of the nose has been associated with Epstein-Barr virus infection, particularly in transiently immunocompromised individuals, which can probably explain the present associations (Dong and Hemminki, 2001; WorldHealthOrganization, 2012) . Male and female genital cancers were the other rare cancers found in familial associations with ovarian cancer; most of the cases presented with squamous cell carcinoma and infection related human papilloma virus (de Martel *et al.*; WorldHealthOrganization, 2012; Zur Hausen, 2002). Hodgkin lymphoma is also related Epstein-Barr virus and the elevated risk was found based on two families where at least two patients were affected by ovarian cancer (WorldHealthOrganization, 2012). It should be noted that the association with virus related cancers may be found by chance due to the small number of familial cases. Nevertheless, this is an interesting finding, which can provide evidence for further researches. Socioeconomic factors and pro-inflammatory effects of obesity could be involved (Craig *et al.*, 2016). Familial associations of CUP, as here with ovarian cancer, may indicate in CUP patients the cancer may began in the ovary.

The proportion of the non-epithelial malignancies among all the ovarian malignancies is approximately 10% in our database and data on risk factor for this type of ovarian cancer is limited (Alifrangis and Seck, 2017). In this study although based on one single significant RR

familial association with thyroid gland and connective tissue cancers, non-Hodgkin lymphoma and CUP were found, which can help understand the etiology of non-epithelial malignancies.

4.2 Influence of family history on the risk of SPC

4.2.1 Influence of family history on the risk of SPC in breast cancer

Risk of subsequent cancer in breast cancer patients has been the topic of many studies with the improvement in breast cancer survival, and second endometrial, ovarian, stomach and colon cancers, and melanoma were reported to occur most frequently (Molina-Montes *et al.*, 2015). Besides these cancers, more second cancers were identified with elevated risks here. Additionally, cancer diagnosis in first-degree relatives of breast cancer patients was associated with the excess risk for the SPCs. No matter considering the presence of family history or not, risk of second breast cancer was very high, which is reasonable as first primary breast cancer should share more risk factors with second breast cancer compared to other SPC.

A fourfold excess risk for ovarian cancer as SPC was observed in breast cancer patients who had first-degree relatives diagnosed with ovarian cancer. Additionally, a threefold risk for liver and endocrine gland cancers, a two and half fold risk for skin (SCC) cancer, more than a twofold risk for endometrial cancer, close to a twofold risk for pancreatic and lung cancers and a one and half fold risk for rectal, kidney, bladder cancers, melanoma and non-Hodgkin lymphoma were observed. Some genetic and environmental factors, for the latter including reproductive and other behavioral factors, may contribute to the elevated risks for familial SPCs. High familial risk of second breast and ovarian cancers may be a consequence of *BRCA1/2* mutations (Metcalfe *et al.*, 2005; Rhiem *et al.*, 2012), which may be also responsible for the significant risk of second pancreatic cancer and melanoma (Moran *et al.*, 2012). On the other hand, the elevated familial

risk for second breast, ovarian and endometrial cancers may be attributable to hormone exposure. Smoking may be associated with the elevated familial risk of second lung, bladder and kidney cancers, and alcohol consumption with second liver cancer.

In patients who only had breast cancer diagnosis, death rate was half of that in those who had diagnosis of SPC (16.1% and 32.3% respectively). The possible reason can be the unfavorable survival in most of the cancers other than breast cancer which was demonstrated by high death rate in second stomach, pancreatic and liver cancers and CUP (**Figure 9**). On the contrary, for cancers that have relatively good survival, for example, melanoma, endometrial and skin cancers when diagnosed as SPC, the main cause of death was breast cancer. It was reported that death rate of breast cancer is not affected by family history (Chang *et al.*, 2009; Melvin *et al.*, 2016), which is in line with our study showing that death rate in patients with SPCs was independent on the family history of cancer.

4.2.2 Influence of family history on the risk of SPC in ovarian cancer

SPC occurred to 9.8% of all the ovarian cancer patients after a median follow-up time of 8 years since the initial diagnosis. First-degree relatives of 67.6% ovarian cancer patients with SPC had cancer diagnoses, which may contribute to the elevated risk of concordant SPC in ovarian cancer patients. A colon cancer diagnosis in first-degree relative was related to a nearly two and half fold risk of this cancer as SPC, and diagnosis of lung and breast cancers more than two fold risk. The primary clinical implication that is observed in the investigation is the allusion to emergence of multiple primary cancers based on an inherited susceptibility (Travis *et al.*, 2013; Vogt *et al.*, 2017). Hence, mutation carriers are largely expected to carry the disease burden, for instance *BRCA1/2* mutation carriers predispose to cancers in pancreas and breast (Moran *et al.*, 2012); *MMR* mutations associated with HNPCC give rise to colorectal cancer (Bonadona *et al.*, 2011).

Although frequency of deleterious alleles of *BRCA1/2* or *MMR* mutation carriers in Swedish population is in Sweden, the estimate frequency of *MMR* mutation carriers is 1/1200 (0.08%) (Lagerstedt-Robinson *et al.*, 2016). In European ancestry, with cumulative incidence of 10%, 1.4% of breast cancers are presumably due to *BRCA1/2* mutations. Therefore, the population frequency of such mutation would be 0.14% (Palomaki, 2015); the mutation prevalence among breast cancer in Sweden is 1.8%, which would extend to a population frequency of 0.18% (Li *et al.*, 2018). At the same time 11% of ovarian cancers were reported to be caused by germline mutations in the *BRCA1/2* and 2% of that in the *MMR* genes based on another Swedish study (Malander *et al.*, 2006). The possible influence of such high penetrant genes on the familial aggregation of discordant cancers was explored by removing individuals from high-risk families based on the criteria defined earlier due to lack of the information on mutation status (Bermejo *et al.*, 2005; Lorenzo Bermejo and Hemminki, 2005b). The significant impact on the risk of SPC with a positive family history remained even after eliminating those kinds of individuals. There may be additional genetic or environmental factors involving the development of SPC in ovarian cancer patients.

This study shows SPC, accounting for 42.1% of all deaths, is the main cause of death among ovarian cancer patients with SPC diagnosis. In contrast, ovarian cancer is responsible for the large amount of deaths (85.9%) in patients with only diagnosis of first primary cancer. The overall death rate in ovarian cancer patients was similar to that in patient whose first-degree relatives had cancer diagnosis despite that excess number of patients with diagnosis of SPCs was due to family history of cancer. Additional cancer diagnosis is supposed to worsen the prognosis especially for the cancer with good survival but SPC did not affect the survival in ovarian cancer patients due to its poor prognosis (Riihimaki *et al.*, 2012). However, according to **Figure 13**,

some fatal first primary cancers like pancreatic cancer can also exacerbate the survival when they were SPC.

CUP is recognized as a metastatic cancer conveying an unfavorable prognosis, resembling or often detrimental than pancreatic cancer (Hemminki *et al.*, 2012a; Riihimaki *et al.*, 2013; Riihimaki *et al.*, 2014b), however it did not show such unfavorable outcome in this study (**Figure 13)**. The likely reason for this discrepancy is the death registration practice in Sweden for CUP. The cause of death is reported by the death registrar reasoned as the cause that directly led to the death (Hemminki *et al.*, 2012b). Another deviance is that the 5-year survival of leukemia is 62.7% as first primary but it was the second fatal SPC in ovarian cancer patients. (Jemal *et al.*, 2017). Most of the cases (10/11) were diagnosed with acute leukemia, which may be the plausible explanation for the high mortality.

4.3 Strength and limitation

Some notable strength should be mentioned. As this study is based on registered resources with practically complete nationwide coverage of medically diagnosed cancers, it has all the advantages of registry data. Firstly, large sample size enables enough power of detection. Furthermore, population-based study is more generalizable compared to hospital based-study. Additionally, the estimates of familial risks are accurate given that the family relationship is documented without recalling bias.

In the analyses for familial clustering, a novel approach, bi-directional statistical analyses was applied to explore association of breast and ovarian cancers with other cancer. In addition, dose-response relationship between cancer risk and number of affected first-degree relatives is another way to prove the existing familial association. This study is the first one performed to explore the familial associations among different histological types in breast and ovarian cancer patients.

Regarding studies on SPCs, one of the concerns is to accurately differentiate SPC from metastases following the first cancer. It was reported that 98% of the second neoplasms in the Swedish Cancer Registry were correctly classified and no recorded SPC was found to be a metastasis (Frödin *et al.*, 1997). The additional challenge is to identify the true cause that killed patients who had multiple cancer diagnosis. An agreement of 77% was reported between the cause of death from death certificates and the expected cause of death according to case summaries in a Swedish study (Johansson *et al.*, 2009).

As for the limitation of the study, in the familial risk stratified by histological type, available information on histological type were only for cancer diagnosis since the introduction of SNOMED coding system in the cancer registry in 1993. The estimation for familial risk of cancer may be affected as the follow-up time is too short for intergenerational studies. In addition, with better understanding of ovarian cancer new histological classification for ovarian cancer has been proposed. However the histology in the cancer database is not updated yet. Breast and ovarian cancers are both hormone related cancers, but data on reproductive factors like age at menopause and exposure to exogenous hormones, are not available in the cancer registry. For the analysis for risk of second cancer, no clinical information such as tumor stage and treatment data are another shortage. No individual lifestyle data such as smoking and physical activity may confound the relationship between family history and cancer risk but socioeconomic factors were adjusted in the regression models, which can reducing the confounding to some extent (Hemminki *et al.*, 2003b). What should be noted with caution is that due to lack of individual genetic condition the familial aggregation of cancers was explained by conjecture.

4.4 Conclusions

1) The familial risks of breast and ovarian cancers with the concordant cancer family history are high for early-onset patients and multiple affected relatives; for breast cancer, risk are prominently high with mother and father both affected. Familial risk varies among histological types. Notably, causes for familial clustering of ovarian cancer seems not to define a specific histological type and this can allude to an underlying mechanistic link shared between various histological types of ovarian cancer.

2) Common risk factors are shared by breast cancer and a group of discordant cancers with possible involvement of gene-environment interactions related to hormonal and immunological pathways. Genetic counselors should alert the family members of breast cancer patients about high familial risk shared between breast cancer with some cancers, such as cancers in kidney and bladder in females and myeloma. A refurbished genetic approach, which was successful in discovery of *BRCA1/2* in breast and ovarian cancer families, may be useful for genetic research in families with clustering of breast and other related cancers.

3) A group of other cancers were found to share susceptibility with ovarian cancer and the associations with cancers in colorectum, breast, endometrium and liver and CUP showed significance in the two-way comparison. Histology-specific familial associations were presented in some cancers, such as the only significant association for endometrial cancer with endometrioid types and the pairs of breast cancer and endometrioid, serous and mucinous types with similar RRs. The association with rare cancers (in nose, male and female genitals) was interesting but calls further confirmation with mechanistic studies.

4) A group of 17% of breast cancer patients developed SPCs during the follow-up period, and 68.8% of them had first-degree relatives diagnosed with cancer. For breast cancer patients with

family history, 18.3% of SPCs other than breast cancer were estimated as the consequence of family history. Cancers that have common genetic, reproductive or behavioral risk factors shared with breast cancer were found with high familial risks. For the patients with diagnosis of SPC, the majority of deaths were due to SPC. Our findings indicate that cancer family history can provide evidence on potential risk of SPCs and it is helpful for the counseling about risk factors and disease surveillance in breast cancer patients.

5) SPC occurred in nearly 10% of all ovarian cancer patients and 67.6% of them had positive family history of cancer. Family history of cancer in first-degree relatives contributed to the elevated risk of concordant SPC regardless of including or excluding individuals from possible high-risk families. Breast and colorectal cancers were observed with high familial risks, which are acknowledged to develop in HBOC and HNPPC syndromes respectively. Therefore, the results together indicate the necessity for physicians to obtain cancer family history upon the diagnosis of ovarian cancer which is helpful for disease management and can benefit patients and their families.

The present results can be used in several ways. In clinical practice, these results can increase the awareness of clinicians to take family history during cancer diagnosis and make use of it in disease management. An important message to clinicians and patients is that family history may indicate the possible familial clustering with genetic background, for which different cancers may aggregate in different family members or in one individual presenting as multiple primary cancers.

5 NOVELTY

- This study was based on Swedish Family-Cancer Database, the largest of its kind in the world, which provided accurate family relationship and enabled most available power of detection.
- For the familial clustering with concordant cancer, diverse aspects of familial risk was explored, from different family relationships, number of affected family members, age at diagnosis to histological types.
- For the familial clustering with discordant cancers, the two-way comparison and trend test for dose-response relationship were performed to assess effects of family history on risk of cancer.
- In the analysis for familial clustering of breast cancer with other cancers, some cancers with high familial risk were observed when only considering cancer diagnosis in female or male first-degree relatives.
- For the analysis for familial clustering of ovarian cancer with other cancers, stratification of histology was considered and some remarkable associations were noted.
- The impact of family history on the risk of second primary cancer was explored by including or excluding individuals from possible high-risk families and the familial risk of second primary cancer was still significant after excluding these families
- Cause of death was assessed in breast and ovarian cancer patients with or without second primary cancer and second primary cancer was the leading cause of death for both cancer patients with diagnosis of second primary cancer.
- Different significant levels were implemented throughout the study, which can help with identification of the true association from the chance finding.

6 SUMMARY

Female cancers account for 44% among all cancer diagnoses in women globally, among which breast cancer is the most frequently diagnosed and ovarian cancer is a relatively fatal disease. Familial clustering of these two cancers with the same (concordant) cancer is well recognized, but the data on the aggregation with other (discordant) cancers is limited. How cancer family history impacts on risk of this cancer as second primary cancer (SPC) in breast and ovarian cancers and the related cause of death are also interesting questions for the fact that the cancer survival increases in recent years. Hence, this study is to analyze the familial clustering of breast and ovarian cancer with the concordant and discordant cancers as well as familial risk of SPC and related cause of death in breast and ovarian cancer patients.

Based on the Swedish Family-Cancer Database, familial risks of breast and ovarian cancers in families with first-degree relatives (parents or siblings) affected by the concordant and discordant cancers and the risks of other cancers in families with first-degree relatives affected by breast and ovarian cancers were estimated. The familial risks were also stratified by sex and histology. In the analysis for the impact of family history on SPC risk, the relative risk for SPC in breast and ovarian cancer patients in families with first-degree relatives diagnosed with the same cancer was compared with that of patients without family history. Based on the diagnosis of SPC cause of death in those patients was analyzed. ICD-7 was used to identify cancers and SNOMED was to histology. Poisson regression model was performed for risk estimation and calculation of their corresponding CIs for 95%, 99% and 99.9%.

The high familial risks of breast and ovarian cancers with the concordant cancer family history are shown for women with younger age diagnosis and those with multiple affected relatives and familial risk varies among histological types. Breast cancer shares susceptibility with a group of

other cancers for which gene-environment interactions with hormonal and immunological pathways could be involved and ovarian and prostate cancers showed most significant associations. Some novel associations of breast cancer were found with female kidney and bladder cancers and with myeloma. Ovarian cancer was also observed associated with a group of discordant cancers and among them colorectal, breast, endometrial and liver cancers and CUP showed significance in the two-way analysis. The novel associations with cancer of nose and that of male and female genitals were noted.

For breast cancer patients in families with individuals diagnosed with cancer, 18.3% of non-breast SPCs were due to family history. Prominent familial risks were found in cancers that share genetic, reproductive or behavioral factors with breast cancer. For ovarian cancer patients, high familial risks were found for breast and colorectal cancers, which are known to manifest in ovarian cancer-related syndromes. However, family history of a particular cancer contributed to the elevated risk of SPC in ovarian cancer patients at the same site regardless of inclusion or exclusion of possible high-risk families. SPC was the main cause of death in the breast and ovarian cancer patients with SPCs.

Our study suggested that family history may indicate the possible familial clustering with genetic background, for which different cancers may aggregate in different family members or in one individual presenting as multiple primary cancers, which provide useful information on genetic counseling and disease management in breast and ovarian cancer patients.

Zusammenfassung

44% der weltweit bei Frauen diagnostizierten Tumorerkrankungen betreffen die weiblichen Geschlechtsorgane, wobei Brustkrebs am häufigsten diagnostiziert wird und Ovarialkrebs im Vergleich eine tödliche Erkrankung darstellt. In beiden Fällen ist das familiäre Clustering innerhalb des jeweiligen Krebs bereits bekannt (konkordant), aber die Datengrundlage bezüglich des gehäuften Auftretens mit anderen Krebserkrankungen (diskordant) ist bisher noch beschränkt. Interessant erscheinen außerdem die Frage nach dem Einfluss der familiären Krebsvorgeschichte auf das Risiko, einen zweiten Primärtumor (second primery cancer, SPC) der selben Krebsart zu entwickeln, sowie die Frage nach der jeweiligen Todesursache im Falle des Brust- und des Ovarialkrebs. Dies ist besonders in Anbetracht der in den letzten Jahren steigenden Überlebensraten dieser Erkrankungen von großer Bedeutung. Daher nimmt sich diese Studie zum einen die Analyse des familiären Clusterings von Brust- und Ovarialkrebs mit konkordanten und diskordanten Krebsarten zum Ziel. Weiterhin sollen das Risiko der Entwicklung eines SPCs sowie die einhergehenden Todesursachen von Brust- und Ovarialkrebspatienten untersucht werden.

Basierend auf den Informationen schwedischer Datenbanken zu familiären Krebserkrankungen, wurde das familiäre Risiko des Brust- und Ovarialkrebs in Familien geschätzt, deren Mitglieder ersten Grades (Eltern oder Geschwister) konkordante und diskordante Krebsrerkrankungen zeigten. Zudem wurde das familiäre Risiko anderer Krebsarten in Familien geschätzt, welche im ersten Verwandtschaftsgrad Brust- und Ovarialkrebs aufwiesen. Einige der familiären Risiken wurden außerdem nach Geschlecht und Histologie stratifiziert.

In den Analysen des Einflusses der Familiengeschichte auf die Entwicklung eines SPCs wurde das relative Risiko eines SPCs bei Brust- und Ovarialkrebspatienten in Familien, deren

Mitglieder ersten Verwandtschaftsgrades am selben Krebs erkrankten, mit dem relativen Risiko bei Patienten ohne familiäre Krebsvorgeschichte verglichen. Basierend auf SPC-Diagnose, wurde die Todesursache dieser Patienten analysiert.

ICD-7 wurde für die Identifizierung des Krebs genutzt und SNOMED für die Histologie. Die Poisson-Regression wurde für die Risikoschätzung und die Berechnung der entsprechenden Konfidenzintervalle (CI) von 95%, 99% und 99,9%.

Das hohe familiäre Risiko von Brust- und Ovarialkrebs bei familiärer Vorgeschichte des konkordanten Krebs wurde für Frauen mit einer Diagnose im frühen Alter sowie bei Patientinnen mit mehreren betroffenen Verwandten beobachtet. Das familiäre Risiko variiert zudem zwischen den verschiedenen histologischen Typen. Brustkrebs hat die genetisch bedingte Anfälligkeit mit einer Gruppe anderer Krebserkrankungen gemeinsam, wobei Gen-Umwelt-Interaktionen, hormonellen und immunologischen Pathways folgend, eine Rolle spielen könnten. Hierbei zeigten sich Ovarial- und Prostatakrebs am stärksten miteinander assoziiert.

Einige neue Assoziationen von Brustkrebs mit weiblichem Nieren- und Blasenkrebs sowie dem Myelom wurden weiterhin gefunden. Außerdem konnte beobachtet werden, dass Ovarialkrebs mit einer Gruppe diskordanter Krebserkrankungen assoziiert ist, von welchen kolorektale Tumore, Brustkrebs, das Endometrium- und Leberkarzinom sowie CUP Signifikanz in der Zwei-Weg-Analyse zeigten. Die neue Assoziation mit Nasenkrebs und Krebserkrankungen der männlichen und weiblichen Genitalien wurde beobachtet.

In Familien mit diagnostiziertem Krebs wurden 18,3% der Nicht-Brustkrebs-SPCs bei Brustkrebspatienten der familiären Krebsvorgeschichte zugeschrieben. Auffällige familiäre Risiken wurden für Krebsarten gefunden, die genetische, reproduktive oder verhaltensbezogene Faktoren mit Brustkrebs gemeinsam hatten. Bei Ovarialkrebspatienten wurden hohe familiäre

Risikofaktoren für Brustkrebs und das kolorektale Karzinom gefunden. Diese treten bekannterweise im Rahmen Ovarialkrebs-assoziierter Syndrome auf. Die familiäre Vorgeschichte bestimmter Krebsarten trug zu einem erhöhten Risiko, dass Ovarialkrebspatienten einen SPC entwickeln, sowohl bei Inklusion, als auch bei Exklusion der potenziellen Hochrisiko-Familien bei. Bei Brust- und Ovarialkrebspatienten mit bekannten SPCs war dieser die hauptsächliche Todesursache.

Unsere Studie deutet darauf hin, dass die familiäre Vorgeschichte auf ein mögliches familiäres Clustering mit genetischem Hintergrund hinweist, welches verschiedene Krebsarten in unterschiedlichen Familienmitgliedern oder multiple Primärtumoren in einem Individuum zusammenfasst. Dies bietet nützliche Informationen für die genetische Beratung und Krankheitsbewältigung bei Brust- und Ovarialkrebspatienten.

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8 PUBLICATIONS

Publications related to this thesis:

#Zheng, G., Yu, H., Hemminki, A., Försti, A., Sundquist, K., & Hemminki, K. (2017). Familial associations of female breast cancer with other cancers. International journal of cancer, 141(11), 2253-2259. (Published)

Zheng, G., Yu, H., Kanerva, A., Försti, A., Sundquist, K., & Hemminki, K. (2018). Familial Ovarian Cancer Clusters with Other Cancers. Scientific reports, 8. (Published)

Zheng, G., Yu, H., Kanerva, A., Försti, A., Sundquist, K., & Hemminki, K. (2018). Familial risks of ovarian cancer by age at diagnosis, proband type and histology. PloS one, 13(10), e0205000. (Published)

Zheng, G., Chattopdhyay, S., Försti, A., Sundquist, K., & Hemminki, K. (2018). Familial risks of second primary cancers and mortality in ovarian cancer patients. Clinical Epidemiology, 10, 1457-1466. (Published)

Zheng, G., Hemminki, A., Försti, A., Sundquist, J., Sundquist, K., & Hemminki, K. Second primary cancer after female breast cancer: familial risks and cause of death. Cancer Medicine. (Accepted)

#The corresponding results for risk of breast cancer in this thesis (section 3.1.3) had been adjusted by parity, so there is slightly difference between them.

Other publications:

Zheng, G., Yu, H., Hemminki, A., Försti, A., Sundquist, K., & Hemminki, K. (2017). Familial associations of male breast cancer with other cancers. Breast cancer research and treatment, 166(3), 897-902. (Published)

Chattopadhyay, S.*, **Zheng, G**.*, Sud, A.*, Yu, H., Sundquist, K., Sundquist, J., ... & Hemminki, K. (2018). Risk of second primary cancer following myeloid neoplasia and risk of myeloid neoplasia as second primary cancer: a nationwide, observational follow up study in Sweden. The Lancet Haematology, 5(8), e368-e377. (Published, *equal contribution)

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9 CURRICULUM VITAE

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11 APPENDIX

1. Supplementary Tables

Supplementary Table 1 ICD-7 or PAD code for the subtype cancer sites in FCD

Cancer sites		ICD-7 code (first 4 digits)	PAD code
Liver	Liver, primary	1550	-
	Gall bladder	1551	-
	Extrahepatic bile ducts	1552	-
	Ampulla of vater	1553	-
Eye	Melanoma	192	176
	Retinoblastoma	192	436
Endocrine glands	Adrenal	1950	-
	Parathyroid	1951	-
	Thymus	1952	-
	Pituitary	1953	-
	Insuloma of pancreas	1955	-
	Other	1957	-
	Multiple endocrine glands	1958	-
	Unspecified endocrine glands	1959	-
Leukemia	Acute lymphatic	2040	-
	Chronic lymphatic	2041	-
	Acute myeloid	2050	-
	Chronic myeloid	2051	-

Supplementary Table 2 Proportion of invasive and *in situ* female breast cancer when there were 0, 1, 2 and ≥3 first-degree relatives diagnosed with breast cancer

Breast cancer	0FDR		1FDR		2FDRs		3FDRs		Total
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	
Invasive	63794	95.2	11351	94.4	889	93.2	26	92.9	76060
In situ	3237	4.8	678	5.6	65	6.8	2	7.1	3982

FDR, first-degree relative

Supplementary Table 3 Familial association of female breast cancer with other cancers in female relatives

Other cancer site	Estimation item	Cases with 1 FDR			Cases with 2 FDRs			Cases with ≥3 FDRs			*P-trend*
		N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Upper aerodigestive tract	Risk of breast cancer	435	1.04	0.95-1.14	3	**4.18**	1.35-	-	-	-	0.3015
	Risk of other cancer	306	**1.13**	1.00-1.27	17	1.30	0.81-2.09	2	3.14	0.78-12.56	**0.0145**
Pancreas	Risk of breast cancer	772	1.03	0.96-1.11	6	2.12	0.95-4.72	-	-	-	0.2776
	Risk of other cancer	310	**1.14**	1.01-1.28	14	0.94	0.55-1.59	1	1.23	0.17-8.74	0.0692
Kidney	Risk of breast cancer	733	1.01	0.94-1.09	3	1.04	0.34-3.28	-	-	-	0.7435
	Risk of other cancer	295	1.00	0.89-1.13	11	0.74	0.41-1.33	3	**3.90**	1.26-12.08	0.9974
Bladder	Risk of breast cancer	700	1.06	0.99-1.14	2	0.71	0.18-2.83	-	-	-	0.1341
	Risk of other cancer	335	1.10	0.98-1.23	14	0.87	0.51-1.47	3	**3.60**	1.16-11.17	0.1224
Melanoma	Risk of breast cancer	1016	1.03	0.97-1.09	11	1.17	0.62-2.01	-	-	-	0.3575
	Risk of other cancer	1364	**1.07**	1.01-1.13	77	***1.41***	1.13-1.76	3	1.18	0.38-3.65	**0.0010**
Skin, squamous cell	Risk of breast cancer	984	0.91	0.86-0.98	6	0.91	0.41-2.02	-	-	-	**0.0062**
	Risk of other cancer	499	***1.16***	1.06-1.28	24	1.10	0.74-1.64	3	2.78	0.90-8.64	**0.0013**
Eye	Risk of breast cancer	96	1.18	0.97-1.44	-	-	-	-	-	-	0.1148
	Risk of other cancer	86	***1.38***	1.10-1.72	4	1.45	0.54-3.87	-	-	-	**0.0065**
Thyroid gland	Risk of breast cancer	360	1.08	0.97-1.20	2	1.23	0.31-4.92	-	-	-	0.1396
	Risk of other cancer	347	1.05	0.94-1.17	26	***1.89***	1.28-2.78	1	1.52	0.21-10.81	**0.0398**
Myeloma	Risk of breast cancer	367	0.97	0.87-1.07	3	2.43	0.78-7.53	-	-	-	0.6505
	Risk of other cancer	162	1.10	0.94-1.29	5	0.64	0.27-1.54	2	**4.87**	1.22-19.49	0.3341
Leukemia	Risk of breast cancer	722	0.99	0.92-1.07	4	1.08	0.40-2.87	-	-	-	0.8991
	Risk of other cancer	487	1.08	0.99-1.19	28	1.43	0.98-2.07	1	1.03	0.14-7.32	**0.0274**
Unknown primary	Risk of breast cancer	1098	1.04	0.98-1.11	4	1.42	0.51-3.77	-	-	-	0.1388
	Risk of other cancer	471	***1.14***	1.04-1.26	32	1.44	1.02-2.05	3	2.47	0.80-7.67	**0.0006**
All cancers[a]	Risk of breast cancer	26313	***1.26***	1.24-1.28	3632	***1.61***	1.56-1.67	453	***2.01***	1.81-2.21	**<0.0001**
	Risk of other cancer	24453	***1.28***	1.27-1.30	1599	***1.67***	1.59-1.76	69	***1.47***	1.16-1.86	**<0.0001**
All cancers[b]	Risk of breast cancer	18750	***1.04***	1.03-1.06	1377	**1.05**	1.00-1.11	118	**1.22**	1.02-1.47	**<0.0001**
	Risk of other cancer	13152	***1.04***	1.02-1.06	726	***1.14***	1.06-1.23	43	**1.36**	1.01-1.84	**<0.0001**

FDR: first-degree relatives;
Bolding, italic and underlining indicate that the 95% CI, 99% CI and 99.9% CI did not overlap with 1.00 respectively;
a: all cancers include breast cancers and all other cancers;b: all cancers include all other cancers except breast cancer.

Supplementary Table 4 Familial association of female breast cancer with cancers in male relatives

Other cancer site	Estimation item	Cases with 1 FDR			Cases with 2 FDRs			Cases with ≥3 FDRs			*P-trend*
		N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Stomach	Risk of breast cancer	1539	***1.07***	1.02-1.12	8	1.10	0.55-2.20	2	***24.03***	6.01-96.08	**0.0065**
	Risk of other cancer	342	1.11	0.99-1.24	29	***1.72***	1.19-2.48	2	1.82	0.45-7.27	**0.0034**
Small intestine	Risk of breast cancer	164	**1.19**	1.02-1.39		-	-	-	-	-	**0.0292**
	Risk of other cancer	91	0.92	0.74-1.14	9	1.75	0.91-3.37	1	3.21	0.45-22.83	0.8400
Anus	Risk of breast cancer	34	0.92	0.66-1.29		-	-	-	-	-	0.6169
	Risk of other cancer	21	0.60	0.39-0.94	1	0.53	0.07-3.76		-	-	**0.0128**
Liver	Risk of breast cancer	743	**1.08**	1.00-1.16	3	1.70	0.55-5.26	-	-	-	**0.0361**
	Risk of other cancer	291	1.02	0.90-1.15	17	1.10	0.68-1.77	3	2.98	0.96-9.26	0.4406
Pancreas	Risk of breast cancer	858	1.06	0.99-1.14	1	0.40	0.06-2.90	-	-	-	0.0989
	Risk of other cancer	354	**1.12**	1.01-1.25	21	1.20	0.78-1.85	2	1.70	0.43-6.82	**0.0230**
Lung	Risk of breast cancer	2939	***1.09***	1.05-1.13	42	1.24	0.91-1.68	-	-	-	**<0.0001**
	Risk of other cancer	1146	1.02	0.96-1.09	73	1.15	0.91-1.45	4	0.97	0.36-2.58	0.2705
Bladder	Risk of breast cancer	2178	**1.05**	1.01-1.10	19	0.97	0.62-1.51	2	1.91	0.48-7.62	**0.0227**
	Risk of other cancer	969	1.01	0.94-1.08	65	1.24	0.97-1.58	3	0.92	0.30-2.87	0.3608
Melanoma	Risk of breast cancer	1000	1.05	0.99-1.12	12	1.26	0.71-2.22	-	-	-	0.0676
	Risk of other cancer	1251	**1.06**	1.00-1.12	51	0.91	0.69-1.19	3	0.96	0.31-2.98	0.1597
Skin, squamous cell	Risk of breast cancer	1449	1.04	0.99-1.09	15	**1.88**	1.14-3.12	-	-	-	0.0792
	Risk of other cancer	642	1.06	0.98-1.15	31	0.90	0.64-1.29	-	-	-	0.3341
Endocrine gland	Risk of breast cancer	359	***1.17***	1.05-1.29		-	-	-	-	-	**0.0045**
	Risk of other cancer	352	**1.13**	1.01-1.26	17	1.08	0.67-1.75	-	-	-	**0.0353**
Connective tissue	Risk of breast cancer	206	1.02	0.89-1.17	-	-	-	-	-	-	0.7809
	Risk of other cancer	192	**1.20**	1.03-1.39	11	1.47	0.81-2.66	-	-	-	**0.0094**
Non-Hodgkin lymphoma	Risk of breast cancer	1015	1.04	0.97-1.11	5	1.03	0.43-2.47	-	-	-	0.2290
	Risk of other cancer	810	**1.09**	1.01-1.17	36	0.97	0.70-1.35	3	1.35	0.44-4.20	**0.0414**
Leukemia	Risk of breast cancer	989	***1.08***	1.02-1.15	7	1.19	0.57-2.50	-	-	-	**0.0114**
	Risk of other cancer	688	**1.08**	1.00-1.17	34	1.16	0.83-1.63	1	0.58	0.08-4.15	**0.0387**
All cancers[a]	Risk of breast cancer	26039	***1.08***	1.07-1.10	2972	***1.18***	1.14-1.22	379	***1.34***	1.21-1.48	**<0.0001**
	Risk of other cancer	19550	***1.07***	1.06-1.09	1021	**1.08**	1.01-1.14	63	1.09	0.85-1.40	**<0.0001**
All cancers[b]	Risk of breast cancer	25994	***1.08***	1.06-1.10	2958	***1.18***	1.13-1.22	376	***1.33***	1.20-1.47	**<0.0001**
	Risk of other cancer	19509	***1.07***	1.06-1.09	1018	**1.07**	1.01-1.14	63	1.09	0.85-1.40	**<0.0001**

FDR: first-degree relatives; Bolding, italic and underlining indicate that the 95% CI, 99% CI and 99.9% CI did not overlap with 1.00 respectively; a: all cancers include breast cancers and all other cancers; b: all cancers include all other cancers except breast cancer

Supplementary Table 5 Familial associations of ovarian cancer with liver cancers

Subtypes	Risk of ovarian cancer			Risk of liver cancers		
	N	*RR*	*95% CI*	*N*	*RR*	*95% CI*
Liver, primary	92	1.05	0.85-1.29	74	1.07	0.85-1.35
Gall bladder	95	**1.27**	1.03-1.55	30	1.05	0.73-1.51
Extrahepatic bile ducts	33	1.37	0.97-1.93	23	1.47	0.97-2.22
Ampulla of vater	14	1.40	0.83-2.37	9	1.27	0.66-2.46

Bolding, italic and underlining indicate that the 95% CI, 99% CI and 99.9% CI did not overlap with 1.00 respectively;

Supplementary Table 6 Familial associations of histology-specific ovarian cancers with gall bladder cancer

Subtypes	Histology	Risk of ovarian cancer			Risk of gall bladder cancer		
		N	*RR*	*95% CI*	*N*	*RR*	*95% CI*
Gall bladder	Undifferentiated	3	2.35	0.75-7.36	2	***6.95***	1.74-27.83
	Clear cell	3	0.92	0.29-2.85	0	-	-
	Endometrioid	7	1.09	0.52-2.29	2	1.62	0.40-6.49
	Serous	35	1.24	0.89-1.73	9	1.78	0.93-3.44
	Mucinous	12	***2.75***	1.56-4.88	4	***4.66***	1.75-12.42
	Non-epithelial	3	1.94	0.62-6.07	0	-	-

Bolding, italic and underlining indicate that the 95% CI, 99% CI and 99.9% CI did not overlap with 1.00 respectively;

Supplementary Table 7 Cause of death according to follow-up time since first cancer diagnosis in breast cancer patients with or without second primary cancer (2001-2015)

Breast cancer	Cause of death	<1 year (% in column)	1-4 years (% in column)	5-10 years (% in column)	>10 years (% in column)	All (% in column)
With SPC	Breast cancer a	8 (7.1)	55 (9.4)	70 (8.8)	25 (10.7)	158 (9.2)
	Breast cancer b	47 (41.6)	194 (33.2)	198 (25.0)	46 (19.7)	485 (28.1)
	SPC	32 (28.3)	203 (34.8)	345 (43.5)	83 (35.6)	663 (38.5)
	HPC	3 (2.6)	25 (4.3)	34 (4.3)	17 (7.3)	79 (4.6)
	Other cancers	9 (8.0)	36 (6.2)	61 (7.7)	26 (11.2)	132 (7.7)
	Other causes	14 (12.4)	71 (12.2)	85 (10.7)	36 (15.4)	206 (12.0)
	All (N, % in row)	113 (6.6)	584 (33.9)	793 (46.0)	233 (13.5)	1723 (100.0)
Without SPC	Breast cancer	538 (74.0)	2010 (81.1)	1591 (72.6)	268 (62.6)	4407 (75.7)
	Other cancers	36 (5.0)	74 (3.0)	91 (4.2)	15 (3.5)	216 (3.7)
	Other causes	153 (21.0)	393 (15.9)	510 (23.3)	145 (33.9)	1201 (20.6)
	All (N, % in row)	727 (12.5)	2477 (42.5)	2192 (37.6)	428(7.4)	5824 (100.0)

a, breast cancer patients diagnosed with non-breast second primary cancer and dying of breast cancer; b, breast cancer patients diagnosed with second breast cancer and dying of breast; SPC, second primary cancer; HPC, higher order (3^{rd}, 4^{th} or 5^{th}) primary cancer

Supplementary Table 8 Causes of death in breast cancer patients diagnosed with second primary cancer

Second cancer	Total number of deaths and % of all patient with SPC		Cause of death									
			Breast cancer		SPC		HPC		Other cancers		Other causes	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Upper aerodigestive tract	46	32.2	11	23.9	17	40.0	5	10.9	7	15.2	6	13.0
Esophagus	33	75.0	1	3.0	28	84.8	1	3.0	3	9.1	0	0.0
Stomach	88	87.1	13	14.8	64	72.7	0	0.0	7	8.0	4	4.5
Small intestine	15	32.6	3	20.0	9	60.0	0	0.0	2	13.3	1	6.7
Colorectum	307	38.6	35	11.4	203	66.1	9	2.9	24	7.8	36	11.7
Liver	117	80.1	7	6.0	89	76.1	1	0.8	10	8.5	10	8.5
Pancreas	162	87.6	2	1.2	144	88.9	1	0.6	5	3.1	10	6.2
Lung	610	72.6	51	8.4	496	81.3	7	1.1	15	2.4	41	6.7
Breast	1990	23.0	-	-	1478	74.3	159	8.0	70	3.5	283	14.2
Cervix	47	48.4	10	21.3	24	51.1	3	6.4	5	10.6	5	10.6
Endometrium	168	25.3	48	28.6	36	21.4	12	7.1	41	24.4	31	18.4
Ovary	237	59.4	23	9.7	166	70.0	12	5.1	25	10.5	11	4.6
Other female genitals	22	41.5	1	4.5	6	27.3	5	22.7	6	27.3	4	18.2
Kidney	74	39.6	14	18.9	47	63.5	3	4.0	2	2.7	8	10.8
Bladder	68	33.5	17	25.0	29	42.6	6	8.8	3	4.4	13	19.1
Melanoma	78	17.4	28	35.9	24	30.8	8	10.2	6	7.7	12	15.4
Skin, squamous cell	57	13.6	22	38.6	6	10.5	7	12.3	4	7.0	18	31.6
Eye	10	40.0	0	0.0	1	10.0	1	10.0	7	70.0	1	10.0
Nervous system	91	43.3	22	24.2	44	48.4	2	2.2	12	13.2	11	12.1
Thyroid gland	21	23.1	7	33.3	9	42.8	2	9.5	0	0.0	3	3.3
Endocrine gland	37	20.6	13	35.1	5	13.5	5	13.5	5	13.5	9	24.3
Bone	7	70.0	5	71.4	0	0.0	0	0.0	2	28.6	0	0.0
Connective tissue	32	48.5	7	21.9	11	34.4	2	6.2	7	21.9	5	15.6
Non-Hodgkin lymphoma	89	38.0	14	15.7	53	59.5	1	1.1	6	6.7	15	15.6
Hodgkin lymphoma	5	33.3	0	0.0	1	20.0	1	20.0	1	20.0	2	40.0
Meyloma	39	48.1	2	5.1	30	76.9	1	2.6	2	5.1	4	10.2
Leukemia	105	46.2	10	9.5	67	63.8	7	6.7	12	11.4	9	8.6
Cancer of unknown primary	213	81.0	70	32.9	25	11.7	1	0.5	107	50.2	10	4.7
All [a]	2838	45.0	446	15.7	1656	58.4	103	3.6	347	12.2	286	10.1

a:second breast cancer was excluded from all cancers; SPC, second primary cancer; HPC, higher (3^{rd}, 4^{th} or 5^{th}) primary cancer.

Supplementary Table 9 Relative risk of second primary cancers according to family history of concordant cancer in ovarian cancer patients after removing high risk families

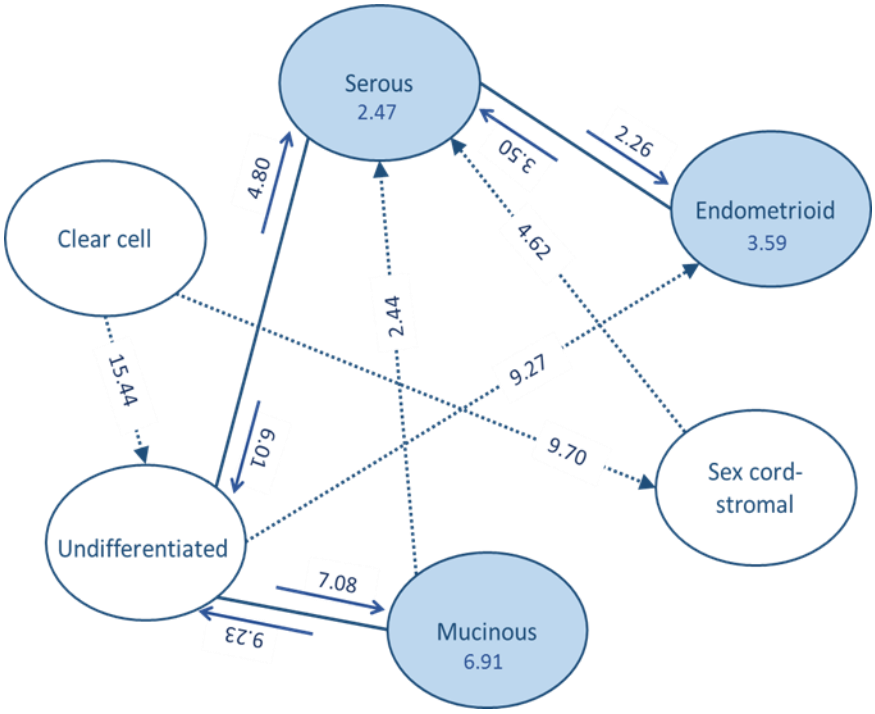
Cancer site	Patients with ovarian cancer						*P-trend*
	Negative family history			Positive family history			
	N	*RR*	*95%CI*	*N*	*RR*	*95%CI*	
Upper aerodigestive tract	12	1.12	0.64-1.97	0	-	-	-
Stomach	16	***2.25***	1.37-3.68	1	3.46	0.49-24.62	0.54
Small intestine	10	***3.29***	1.76-6.14	0	-	-	-
Colorectum	114	***1.94***	1.61-2.33	24	***3.80***	2.54-5.67	**<0.001**
Colon	86	***2.04***	1.65-2.52	14	***4.80***	2.94-8.11	**<0.001**
Rectum	37	***1.82***	1.32-2.51	1	1.42	0.20-10.11	0.33
Liver	21	***1.84***	1.20-2.82	1	3.17	0.45-22.5	0.32
Pancreas	36	***2.40***	1.73-3.33	3	***8.58***	2.77-26.62	0.52
Lung	74	***1.47***	1.17-1.85	12	***3.43***	1.95-6.04	**<0.001**
Breast	204	1.04	0.90-1.19	49	***2.24***	1.69-2.96	**<0.001**
Other female genitals	11	**2.11**	1.16-3.82	0	-	-	-
Kidney	21	**1.64**	1.07-2.53	1	2.59	0.36-18.38	0.32
Bladder	40	***2.64***	1.93-3.60	3	***5.46***	1.76-16.94	0.53
Melanoma	37	1.05	0.76-1.45	2	1.84	0.46-7.37	0.97
Skin, squamous cell	20	0.76	0.49-1.17	3	**3.30**	1.06-10.23	0.06
Nervous system	16	0.70	0.43-1.14	1	1.57	0.22-11.14	0.29
Thyroid gland	10	1.60	0.86-2.98	0	-	-	-
Endocrine glands	22	1.38	0.91-2.10	0	-	-	-
Connective tissue	11	***3.18***	1.75-5.76	0	-	-	-
Non-Hodgkin lymphoma	17	0.88	0.55-1.42	1	1.49	0.21-10.58	0.32
Leukemia	29	***1.70***	1.18-2.45	0	-	-	-
Cancer of unknown primary	51	***2.59***	1.97-3.42	3	**4.08**	1.32-12.66	0.56
All cancers [a]	360	***1.52***	1.37-1.68	734	***1.77***	1.64-1.90	**<0.001**
All cancers [b]	334	***1.41***	1.26-1.57	689	***1.67***	1.55-1.81	**<0.001**

a, all cancers including second ovarian cancer, b, all cancers excluding second ovarian cancer.

Supplementary Table 10 Causes of death in ovarian cancer patients diagnosed with second primary cancer

Second cancer	Total number of deaths and % of all patient with SPC		Cause of death							
			Ovarian cancer		SPC		Other cancers		Other causes	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Upper aerodigestive tract	2	16.7	1	50	1	50	0	0	0	0
Stomach	15	88.2	3	20.0	9	60.0	3	20.0	0	0
Small intestine	9	90.0	4	44.4	1	11.1	3	33.3	1	11.1
Colorectum	75	52.4	12	16.0	39	52.0	18	24.0	6	8.0
Liver	18	78.3	3	16.7	13	72.2	2	11.1	0	0
Pancreas	34	87.2	0	0	31	91.2	1	2.9	2	5.9
Lung	66	76.7	8	12.1	48	72.7	6	9.1	4	6.1
Breast	88	33.7	33	37.5	34	38.6	10	11.4	11	12.5
Other female genitals	5	45.5	1	20.0	1	20.0	3	60.0	0	0.0
Kidney	7	31.8	3	42.9	4	57.1	0	0	0	0.0
Bladder	20	44.4	2	10.0	12	60.0	4	20.0	2	10.0
Melanoma	11	27.5	5	45.4	3	27.3	3	27.3	0	0.0
Skin, squamous cell	7	30.4	4	57.1	0	0.0	1	14.3	2	28.6
Nervous system	12	66.7	0	0.0	6	50.0	4	33.3	2	16.7
Thyroid gland	2	20.0	0	0.0	2	100.0	0	0	0	0.0
Endocrine gland	4	18.2	1	25.0	0	0.0	0	0	3	75.0
Connective tissue	7	63.6	1	14.3	1	14.3	4	57.1	1	14.3
Non-Hodgkin lymphoma	8	44.4	0	0	1	12.5	6	75.0	1	12.5
Leukemia	15	51.7	2	13.3	11	73.3	2	13.3	0	0.0
Cancer of unknown primary	47	82.5	23	48.9	5	10.6	16	34.0	3	6.4
All	544	49.0	159	29.2	229	42.1	102	18.8	54	9.9

2. Supplementary Figures



Supplementary Figure 1 Risk of histology with grey background was significant within concordant histology of ovarian cancer. Risk of the two histologies between full lines was significant in the two-way comparison. Risk of the two histologies between imaginary line was significant in one way and the histology the arrow points to is from offspring.