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Familial risk of epithelial ovarian cancer after accounting for gynaecological surgery: a population-based study

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ABSTRACT

Background Uptake of risk-reducing surgery has increased among women at high risk of epithelial ovarian cancer. We sought to characterise familial risk of epithelial ovarian cancer histotypes in a population-based study after accounting for gynaecological surgeries, including bilateral oophorectomy.

Methods We compared risk of epithelial ovarian cancer in relatives of 3536 epithelial ovarian cancer cases diagnosed in 1966–2016 and relatives of 35 326 matched controls. We used Cox competing risk models, incorporating bilateral oophorectomy as a competing risk, to estimate the relative risk of ovarian cancer in first-degree (FDR), second-degree (SDR) and third-degree (TDR) relatives from 1966 to 2016. We also estimated relative risks in time periods before (1966–1994, 1995–2004) and after (2005–2016) formal recommendations were made for prophylactic oophorectomy among women with pathogenic variants in *BRCA1/2*.

Results The relative risks of epithelial ovarian cancer in FDRs, SDRs and TDRs of cases versus controls were 1.68 (95% CI 1.39 to 2.04), 1.51 (95% CI 1.30 to 1.75) and 1.34 (95% CI 1.20 to 1.48), respectively. Relative risks were greatest for high-grade serous, mucinous and 'other epithelial' histotypes. Relative risks were attenuated for case FDRs, but not for SDRs or TDRs, from 2005 onwards, consistent with the timing of recommendations for prophylactic surgery.

Conclusion Familial risk of epithelial ovarian cancer extends to TDRs, especially for high-grade serous and mucinous histotypes. Distant relatives share genes but minimal environment, highlighting the importance of germline inherited genetics in ovarian cancer aetiology. Increased ovarian cancer risk in distant relatives has implications for counselling and recommendations for prophylactic surgeries that, from our data, appear only to reach FDRs.

Key messages

What is already known on this topic

⇒ Increased ovarian cancer risk among first-degree relatives of ovarian cancer cases may reflect shared genetics and lifestyle factors, while increased ovarian cancer risk among third-degree relatives likely reflects shared genetics only.

What this study adds

⇒ After accounting for oophorectomy status, overall ovarian cancer risk was greatest among relatives of high-grade serous, mucinous and 'other epithelial' ovarian cancer cases.

⇒ Familial ovarian cancer risks appeared attenuated for first-degree, but not for second-degree or third-degree, relatives from 2005 onwards, consistent with the timing of recommendations for prophylactic surgery.

How this study might affect research, practice and/or policy

⇒ Future risk variant discovery may be most fruitful in studies that characterise ovarian cancer histotypes.

⇒ We provide suggestive evidence that clinical recommendations for genetic counselling and subsequent risk-reducing surgery should be extended to more distant relatives of ovarian cancer cases.

INTRODUCTION

Ovarian cancer is a highly fatal malignancy, with a 5-year survival of only 46%.[1] Understanding the aetiology of epithelial ovarian cancer, the most common ovarian malignancy, is critical to improving prevention, early detection and treatment strategies. Recent advances in our understanding of epithelial ovarian cancer aetiology have centred on the discovery that epithelial ovarian cancer is a heterogeneous disease that is comprised of multiple histologically defined subtypes (ie, histotypes). The most common of these histotypes is high-grade serous carcinoma (HGSC); other ovarian cancer histotypes include low-grade serous, endometrioid, mucinous and clear cell carcinomas, carcinosarcomas, and malignant Brenner tumours.[2 3] It is widely accepted that ovarian cancer histotypes have different tissues of origin, risk profiles and gene expression.[4–8] The magnitude of association between genetic risk variants and epithelial ovarian cancer also varies by histotype for some, but not all, SNPs.[2 9 10]

Family history, particularly among first-degree relatives (FDRs), is one of the strongest ovarian cancer risk factors.[11–17] An early, population-based study of family history and ovarian cancer risk in the Utah Population Database (UPDB) reported a statistically significant 4.31-fold increased ovarian cancer risk among FDRs, a statistically significant 2.12-fold increased risk among second-degree

relatives (SDRs) and a non-statistically significant 1.48-fold increased risk among third-degree relatives (TDRs) of ovarian cancer cases.[11] This increased risk of ovarian cancer among relatives, especially FDRs, has subsequently been observed in multiple settings, including the Ovarian Cancer Cohort Consortium (OC3) and the Swedish Family-Cancer Database.[12–15]

More recent studies have taken analyses of familial risk a step further, considering specific family relationships and ovarian tumour histology.[12–14] For example, researchers with the Swedish Family-Cancer Database reported a greater increased risk of ovarian cancer among women with an affected sister compared with an affected mother,[13 14] and an even greater increased risk of ovarian cancer among women with both an affected sister and an affected mother.[13] Studies from the Swedish Family-Cancer Database and OC3 also reported a stronger association between family history of ovarian cancer and risk of serous ovarian cancer, although findings for other histotypes were mixed.[12 13 15] These findings suggest there is more to be learnt from family history, especially in settings where it is possible to consider multiple relationship types, and to estimate ovarian cancer risk by histotype using the updated WHO guidelines for ovarian tumour histotyping.[3] Further, as the last 25 years have seen an increase in bilateral salpingo-oophorectomy for ovarian risk reduction among individuals at high risk of the disease, it is important to consider familial ovarian cancer risk accounting for oophorectomy status.[18–20]

Population-based research on familial epithelial ovarian cancer risk is important in the assessment and refinement of risk stratification and precision prevention strategies. The UPDB is a state-wide, population-based resource that contains data from >11 million past and current Utah residents, >5 million of whom have ≥3 generations of genealogy data.[21 22] By linking records from the UPDB to the Utah Cancer Registry (UCR) and other state-wide data sources, we sought to quantify the familial risk of ovarian cancer histotypes in FDRs, SDRs and TDRs using updated histotype classifications and accounting for oophorectomy status. Given a prior finding that increased parity is not protective against ovarian cancer among women with a family history of ovarian cancer,[11] we also tested for effect modification by family history of epithelial ovarian cancer for the associations between two established ovarian cancer risk factors, parity and hysterectomy, and epithelial ovarian cancer risk.

METHODS

This large, population-based cohort study is nested within the UPDB. We compared risk of epithelial ovarian cancer in the relatives (FDR, SDR and TDR) of cancer proband groups with risk of epithelial ovarian cancer in the relatives (FDR, SDR, TDR) of matched non-cases, hereafter referred to as 'controls'. Our largest proband group consisted of all eligible epithelial ovarian cancer cases, and proband subgroups were defined by histotype or year of diagnosis. A family defined by a proband or matched control contributed to the analysis whenever at least one female FDR, SDR or TDR of the proband or matched control was living in Utah and contributing person-time to the study. Data were accessed from the UPDB and used to estimate familial risk of epithelial ovarian cancer as described below.

Identification and histotyping of ovarian cancer cases

We evaluated the study eligibility of 6811 women with a UCR record of ovarian cancer (Surveillance, Epidemiology, and End Results Program [SEER] code 27040) diagnosed from 1 January 1966 to 31 December 2016. Of these women, 2309 were excluded because they did not have at least three generations of genealogy data in the UPDB and at least one female FDR, SDR or TDR living in Utah during study follow-up. Another 241 cases were excluded because the ovarian cancer listed in UCR records was not invasive, and 178 were excluded due to a suspected ovarian cancer diagnosis prior to 1 January 1966.

We assigned histotypes to the 4083 remaining ovarian cancer cases using International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphology and behaviour codes in conjunction with tumour grade, as reported in the UCR record. Consistent with the 2020 WHO guidelines for classification of epithelial ovarian cancer, we assigned cases to the following ICD-O-3 code groupings: serous (8020, 8021, 8022, 8050, 8120, 8130, 8260, 8441, 8442, 8450, 8460, 8461, 8462, 8463, 9014), endometrioid (8380, 8381, 8382, 8383, 8482, 8570), mucinous (8470, 8471, 8472, 8480, 8481, 9015) and clear cell (8290, 8310, 8313, 8443, 8444). Then, using grade information, we subdivided serous ovarian cancers into low-grade serous (grade=1) or high-grade serous (grade ≥2 or unknown).[23] Cases with ICD-O-3 codes that could be classified as carcinosarcoma (8575, 8950, 8951, 8980, 8981), malignant Brenner (9000), carcinoma 'not otherwise specified' (NOS; 8010, 8046, 8140, 8230, 8440) or mixed (8255, 8323) were grouped into a category of 'other epithelial ovarian cancer' due to relatively low case counts for all except the carcinoma NOS group, and the 546 remaining miscellaneous epithelial ovarian cancers (8012, 8041, 8246, 8070, 8071, 8560, 8330) were excluded from analyses, as has been done previously.[23] This left 3536 cases whose FDRs, SDRs and TDRs contributed person-time to analyses.

To assess the accuracy of our record-based histotyping approach, two gynaecological pathologists, JA and EAJ, reviewed H&E stained tumour slides from a convenience sample of 132 UPDB ovarian cancer cases diagnosed in 1982–2018. We compared our expert pathology histotype review with record-based histotypes using Cohen's kappa and per cent agreement. Overall, agreement was good (Cohen's kappa=0.63, 95% CI 0.51 to 0.76; online supplemental table 1).

Selection of matched controls to define a comparison cohort

We used incidence density sampling to match 10 controls to each proband on birth year and birth location (in/out of Utah) to improve comparability of data quality within the cohorts of relatives. Women were eligible to be selected as a matched control if they did not have a UCR record of an ovarian cancer diagnosis (SEER code 27040), and if they had a minimum of three generations of genealogy data in the UPDB, and at least one female FDR, SDR or TDR living in Utah on or after 1 January 1966. The FDRs, SDRs and TDRs of all eligible controls contributed person-time to analyses.

Covariate information

We obtained demographic and health information for all cancer probands, matched controls, and their FDRs, SDRs and TDRs. Demographic data obtained from the UPDB included sex, race (white/non-white/unknown), ethnicity (non-Hispanic/Hispanic/unknown), birth month and year, birth location (Utah/other/unknown), death month and year, and last month and year known to be a resident of Utah. Health data focused on reproductive and surgical histories as these are associated with risk of epithelial ovarian cancer and its histotypes.[2 5 12] To evaluate parity, we considered UPDB birth certificate and genealogy data. Dates listed on Utah birth certificates allowed for a time-varying assessment of parity in Utah (ever/never) and number

of births in Utah. To account for children without known birth dates (eg, children born before their mother moved to Utah, but referenced on a sibling's birth certificate), we also included an indicator variable. To evaluate gynaecological surgical history, we obtained data from two comprehensive, state-wide databases linked to the UPDB: (1) Utah's State Inpatient Records and (2) Utah's State Ambulatory Surgery Records. State-wide data on surgical procedures first became available in 1996 and were updated from that point forward. To capture the occurrence of relevant surgical procedures, we identified all ICD-9, ICD-10 and Current Procedural Terminology (CPT) codes associated with oophorectomy, salpingectomy, hysterectomy, tubal ligation and pelvic surgery NOS. From 1996 onwards, we assumed that women who continuously lived in Utah and did not have a pelvic surgery recorded in Utah had not undergone a pelvic surgery.

All research was conducted under a waiver of informed consent.

Statistical analysis

We used Cox competing risk models to assess the familial relative risk (FRR) of epithelial ovarian cancer in female FDRs, SDRs and TDRs of probands compared with the same relatives of controls. Separate FRRs were estimated for each relationship type. Models were adjusted for birth year, whether born in Utah, race, ethnicity, parity (ever/never in Utah, number of live births in Utah and a proxy for births outside of Utah: a record of a birth with an unknown birth date), ever unilateral oophorectomy, ever salpingectomy, ever hysterectomy and ever tubal ligation. Time was measured in years, and individuals were followed from birth or 1 January 1966, whichever occurred later, and right-censored at the time of death, ovarian cancer diagnosis, bilateral oophorectomy or pelvic surgery NOS with suspected bilateral oophorectomy. All FDRs, SDRs and TDRs of each proband and control were included in the analyses, even if a relative had been previously counted as a relative of another cancer proband or control.[24] Huber-White sandwich estimators of variance of regression parameters were used to correct for non-independence of observations.[25]

To evaluate how family history modifies the associations between reproductive factors (parity, number of live births among parous women and hysterectomy) and risk of epithelial ovarian cancer, we estimated these associations stratified by family history. Similar to the main analysis, we used Cox standard competing risk models adjusted for matching factors and ovarian cancer risk factors. We tested for multiplicative effect modification by family history for FDRs, SDRs and TDRs using a likelihood ratio test that compared nested models with and without an interaction term. There were low case numbers for less common histotypes and we were interested in evaluating if the results differ by histotype, so we condensed the histotypes into two groups for analyses: type 1 cancers (low-grade serous, endometrioid, clear cell and mucinous) and type 2 cancers (high-grade serous and 'other epithelial ovarian cancer').[7]

Analyses were conducted using R V.3.6.1. All statistical tests were two-sided and a p value <0.05 was considered statistically significant. Consistent with UPDB confidentiality policies, we masked all counts and percentages that reflect <11 cases.

RESULTS

In total, the relatives of probands contributed 4 153 530 person-years to this analysis, and the relatives of controls contributed 43 238 382 person-years. Demographic factors and parity did not differ substantially for the relatives of probands versus controls for any of the three relationship types: FDR, SDR or TDR (table 1). History of gynaecological surgery was more common among relatives of cases, with the greatest differences in FDRs (table 1). For example, 9.1% of case FDRs but only 7.8% of control FDRs had a record of hysterectomy, and 7.5% of case FDRs but only 4.8% of control FDRs had a record of bilateral oophorectomy. Diagnosis of ovarian cancer was also more common among FDRs, SDRs and TDRs of cases compared with relatives of controls (table 1).

The results from our main analysis were consistent with an increased risk of epithelial ovarian cancer among the FDRs, SDRs and TDRs of epithelial ovarian cancer cases (table 2). Considering all 3536 epithelial ovarian cancer cases as probands, the FRR of epithelial ovarian cancer in proband FDRs compared with control FDRs (FRR_{FDR}) was 1.68 (95% CI 1.39 to 2.04). Relative risks decreased in magnitude for more distantly related family members, but remained statistically significant (FRR_{SDR}=1.51, 95% CI 1.30 to 1.75; FRR_{TDR}=1.34, 95% CI 1.20 to 1.48).

To understand variation in the familial risk of epithelial ovarian cancer by histotype, we defined groups of probands by histotype and estimated the FRR of any epithelial ovarian cancer in relatives separately for each group. We observed the

Table 1 Demographic characteristics and history of gynaecological surgeries for FDR, SDR and TDR of ovarian cancer cases and matched controls

	FDR of case (n=11 197) n (%)	FDR of control (n=117 591)n (%)	SDR of case (n=32 524) n (%)	SDR of control (n=347 069) n (%)	TDR of case (n=86 059) n (%)	TDR of control (n=895 049) n (%)
Follow-up duration (years)*†	36.7±14.3	37.1±14.3	33.2±15.2	33.1±15.3	30.9±15.6	30.6±15.7
Birth year†	1937.1±25.6	1938.8±26.5	1949.8±33.8	1952.0±33.8	1954.8±36.2	1956.2±36.4
Born in Utah†	9602 (85.8)	102 925 (87.5)	29 843 (91.8)	320 953 (92.5)	80 084 (93.1)	837 138 (93.5)
White	10 817 (96.6)	113 776 (96.8)	30 929 (95.1)	330 145 (95.1)	80 896 (94.0)	839 935 (93.8)
Non-Hispanic	8798 (78.6)	91 913 (78.2)	24 025 (73.9)	255 725 (73.7)	62 626 (72.8)	651 446 (72.8)
Nulliparous*	781 (7.0)	8039 (6.8)	1987 (6.1)	20 758 (6.0)	1046 (1.2)	10 328 (1.2)
Ever tubal ligation*	229 (2.0)	2354 (2.0)	1098 (3.4)	10 704 (3.1)	2368 (2.8)	23 659 (2.6)
Ever hysterectomy*	1022 (9.1)	9144 (7.8)	2440 (7.5)	25 348 (7.3)	4949 (5.8)	50 288 (5.6)
Ever bilateral oophorectomy*	843 (7.5)	5614 (4.8)	1385 (4.3)	13 035 (3.8)	2696 (3.1)	26 481 (3.0)
Ever bilateral salpingectomy*	835 (7.5)	5722 (4.9)	1431 (4.4)	13 668 (3.9)	2807 (3.3)	27 706 (3.1)
Ever diagnosed with ovarian cancer*	120 (1.1)	735 (0.6)	206 (0.6)	1387 (0.4)	476 (0.6)	3576 (0.4)

*From start of follow-up to the end of 2016.
†Matching factor for case probands and controls.
FDR, first-degree relative; SDR, second-degree relative; TDR, third-degree relative.

Table 2 Risk of epithelial ovarian cancer in relatives of ovarian cancer probands versus relatives of controls in the Utah Population Database (1966–2016)

	FRR of ovarian cancer among FDRs of probands vs controls			FRR of ovarian cancer among SDRs of probands vs controls			FRR of ovarian cancer among TDRs of probands vs controls		
Proband type	Case FDRs (% matching proband histotype) (n=11 197)	Control FDRs (% matching proband histotype) (n=117 591)	FRR* (95% CI)	Case SDRs (% matching proband histotype) (n=32 524)	Control SDRs (% matching proband histotype) (n=347 069)	FRR* (95% CI)	Case TDRs (% matching proband histotype) (n=86 059)	Control TDRs (% matching proband histotype) (n=895 048)	FRR* (95% CI)
All EOC	120	733	1.68 (1.39 to 2.04)	205	1384	1.51 (1.30 to 1.75)	475	3574	1.34 (1.20 to 1.48)
HGSC	56 (62.5)	372 (51.6)	1.45 (1.10 to 1.91)	110 (66.4)	660 (51.1)	1.66 (1.38 to 1.99)	241 (50.2)	1684 (49.8)	1.41 (1.25 to 1.58)
EC	12 (0)	74 (9.5)	1.65 (0.94 to 2.90)	18 (0)	126 (6.3)	1.30 (0.87 to 1.92)	34 (5.9)	310 (11.3)	1.15 (0.92 to 1.44)
CCC	† (0)	27 (3.7)	1.19 (0.42 to 3.32)	† (0)	47 (2.1)	0.91 (0.42 to 1.96)	16 (0)	101 (4.0)	1.55 (1.09 to 2.22)
MC	† (40.0)	60 (13.3)	1.75 (0.99 to 3.10)	13 (15.4)	123 (14.6)	1.60 (1.08 to 2.37)	34 (2.9)	344 (7.0)	1.37 (1.10 to 1.71)
LGSC	† (N/A)	† (0)	‡	† (0)	28 (0)	0.79 (0.25 to 2.53)	† (0)	64 (1.6)	1.08 (0.66 to 1.75)
Other epithelial	39 (38.4)	194 (29.9)	2.07 (1.51 to 2.84)	60 (23.3)	400 (32.5)	1.72 (1.39 to 2.14)	142 (25.4)	1071 (32.7)	1.48 (1.30 to 1.68)

'Other epithelial': an amalgamation of carcinoma not otherwise specified, mixed tumours, carcinosarcoma and malignant Brenner.
*Results were generated using competing risk Cox proportional hazards models with censoring at death, bilateral oophorectomy or loss to follow-up, and adjustment for birth year, born in Utah, race, ethnicity, ever parous, number of live births, births outside of Utah, ever unilateral oophorectomy, ever unilateral salpingectomy, ever bilateral salpingectomy, ever tubal ligation and ever pelvic surgery not otherwise specified.
†Consistent with the Utah Department of Health confidentiality policies, we have masked low counts (n<11) and any counts that could be used to re-create the low counts.
‡Model does not converge.
CCC, clear cell carcinoma; EC, endometrioid carcinoma; EOC, epithelial ovarian cancer; FDR, first-degree relative; FRR, familial relative risk; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; N/A, Not applicable; SDR, second-degree relative; TDR, third-degree relative.

following distribution of histotypes in our probands: 47.9% high-grade serous, 10.5% endometrioid, 3.8% clear cell, 9.0% mucinous, 2.0% low-grade serous and 27.0% 'other epithelial ovarian cancer' (88.3% carcinoma NOS, 7.1% carcinosarcoma and 4.6% malignant Brenner or mixed). We observed the strongest familial risk estimates among relatives of cases diagnosed with 'other epithelial ovarian cancer' (table 2). Increased familial risk out to TDRs was also observed for high-grade serous and mucinous ovarian cancer (table 2). The FRR of epithelial ovarian cancer in the FDRs of high-grade serous probands versus the FDRs of controls ($FRR_{FDR\text{-}HGSC}$) was 1.45 (95% CI 1.10 to 1.91), $FRR_{SDR\text{-}HGSC}$ was 1.66 (95% CI 1.38 to 1.99) and $FRR_{TDR\text{-}HGSC}$ was 1.41 (95% CI 1.25 to 1.58). For 'other epithelial ovarian cancer' probands, the following were the corresponding relative risks: $FRR_{FDR\text{-}other}$ 2.07 (95% CI 1.51 to 2.84), $FRR_{SDR\text{-}other}$ 1.72 (95% CI 1.39 to 2.14) and $FRR_{TDR\text{-}other}$ 1.48 (95% CI 1.30 to 1.68). The proportion of FDRs diagnosed with a histotype concordant with the proband histotype was also higher than expected for these three groups: high-grade serous (62.5% vs 47.9%), 'other epithelial ovarian cancer' (38.4% vs 27.0%) and mucinous (40.0% vs 9.0%). Enrichment for each proband histotype of interest was not observed in the relatives of controls (table 2). The results for endometrioid, clear cell and low-grade serous ovarian cancers did not follow the same patterns of familial risk as high-grade serous, mucinous and 'other epithelial ovarian cancer', did not have enrichment for concordant histotypes, and were not consistently statistically significant, although sample size was limited (table 2).

To consider how the relative risk of ovarian cancer varies by relationship to the affected FDR, we estimated $FRR_{FDR\text{-}M}$ for FDRs with affected mothers versus FDRs with unaffected mothers, $FRR_{FDR\text{-}S}$ for FDRs with affected sisters versus FDRs with unaffected sisters, and $FRR_{FDR\text{-}D}$ for FDRs with affected daughters versus FDRs with unaffected daughters. We observed the largest increased ovarian cancer risk among those with affected daughters ($FRR_{FDR\text{-}D}$=2.19, 95% CI 1.45 to 3.32) and the smallest increased ovarian cancer risk among those with affected sisters ($FRR_{FDR\text{-}S}$=1.63, 95% CI 1.07 to 2.46; table 3). This pattern was also observed for high-grade serous ovarian cancer, the most common histotype, for which we observed a statistically significant 2.07-fold (95% CI 1.17 to 3.65) increased risk of ovarian cancer among women with affected daughters, and non-statistically significant 1.60-fold (95% CI 0.90 to 2.85) and 1.47-fold (95% CI 0.86 to 2.52) increased risks of ovarian cancer among women with an affected mother or an affected sister, respectively. The magnitudes of the point estimates were even higher for 'other epithelial ovarian cancers', while subgroup analyses for the remaining histotypes were less informative due to small numbers (table 3).

Prophylactic oophorectomy for women at high risk of ovarian cancer started in the early 1990s and was formally recommended in 2005.[18 19] To assess how the risk of ovarian cancer among relatives changed following these recommendations, we evaluated the relative risks pre-1995, from 1995 to 2004, and from 2005 to 2016. The results for the pre-1995 time period did not differ substantially from the main analysis, with or without controlling for known history of gynaecological surgeries, while the results for 1995–2004 were higher than the pre-1995 time period for FDRs, similar for SDRs and attenuated in TDRs (table 4). For the 2005–2016 time period, the FRR_{FDR} was close to 1 and not statistically significant (FRR_{FDR}=1.02, 95% CI 0.36 to 2.90). In contrast, the point estimates for SDRs (FRR_{SDR}=1.26, 95% CI 0.61 to 2.63) and TDRs (FRR_{TDR}=1.37, 95% CI 0.88 to 2.13) remained similar to the main analysis.

Table 3 Risk of epithelial ovarian cancer in FDRs of ovarian cancer probands versus FDRs of controls in the Utah Population Database (1966–2016)

	FRR of ovarian cancer among women with affected mothers (FDR-M) vs women with unaffected mothers (FDR-CM)			FRR of ovarian cancer among women with affected sisters (FDR-S) vs women with unaffected sisters (FDR-CS)			FRR of ovarian cancer among women with affected daughters (FDR-D) vs women with unaffected daughters (FDR-CD)		
	FDR-M (n=4131)	FDR-CM (n=33 695)	FRR* (95% CI)	FDR-S (n=4053)	FDR-CS (n=32 164)	FRR* (95% CI)	FDR-D (n=1809)	FDR-CD (n=13 070)	FRR* (95% CI)
All EOC	33	144	1.91 (1.30 to 2.79)	50	253	1.63 (1.07 to 2.46)	30	104	2.19 (1.45 to 3.32)
HGSC	14	76	1.60 (0.90 to 2.85)	23	134	1.47 (0.86 to 2.52)	16	60	2.07 (1.17 to 3.65)
EC	†	14	1.30 (0.27 to 6.21)	†	25	1.76 (0.65 to 4.73)	†	21	2.37 (0.94 to 6.01)
CCC	†	†	2.16 (0.23 to 19.95)	†	†	0.75 (0.08 to 6.72)	†	†	1.39 (0.26 to 7.53)
MC	†	11	3.89 (1.41 to 10.71)	†	28	0.87 (0.26 to 2.90)	†	11	2.03 (0.54 to 7.65)
LGSC	†	†	‡	†	†	‡	†	†	‡
Other epithelial	12	51	1.93 (1.02 to 3.63)	21	85	2.25 (1.30 to 3.90)	†	18	3.66 (1.48 to 9.02)

Other epithelial: an amalgamation of carcinoma not otherwise specified, mixed tumours, carcinosarcoma and malignant Brenner.
*Results were generated using competing risk Cox proportional hazards models with censoring at death, bilateral oophorectomy or loss to follow-up, and adjustment for birth year, born in Utah, race, ethnicity, ever parous, number of live births, births outside of Utah, ever unilateral oophorectomy, ever unilateral salpingectomy, ever bilateral salpingectomy, ever tubal ligation and ever pelvic surgery.
†Consistent with the Utah Department of Health confidentiality policies, we have masked low counts (n<11) and any counts that could be used to re-create the low counts.
‡Model does not converge.
CCC, clear cell carcinoma; EC, endometrioid carcinoma; EOC, epithelial ovarian cancer; FDR, first-degree relative; FRR, familial relative risk; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma.

In addition to estimating the FRR of ovarian cancer, we were also interested in the role of family history as an effect modifier for established ovarian cancer risk factors. We did not observe consistent evidence of heterogeneity by family history for associations between parity or hysterectomy and risk of any epithelial ovarian cancer, type 1 ovarian cancer (endometrioid, clear cell, mucinous, low-grade serous) or type 2 ovarian cancer (high-grade serous or 'other epithelial') (table 5).

DISCUSSION

In this large, population-based study we observed an increased risk of epithelial ovarian cancer among FDRs, SDRs and TDRs of ovarian cancer cases. This is the first study to show clear evidence out to TDRs, who share substantial genes but not environment, and underscores the involvement of germline inherited genetics in ovarian cancer aetiology. Furthermore, since known susceptibility genes do not explain all familial clustering, it is likely that there are additional disease genes to be discovered.[26]

The ability to hone in on ovarian cancer phenotypes that have a more substantial genetic component is key to providing power for future gene discovery. Pertinent to this, we studied ovarian cancer histotypes. We observed robust evidence of increased ovarian cancer risk out to TDRs of women affected by high-grade serous ovarian cancer, and despite the low incidence of mucinous ovarian cancer, epithelial ovarian cancer risk among SDRs and TDRs of probands with mucinous ovarian cancer was

Table 4 Risk of epithelial ovarian cancer in family members of cases versus family members of controls in the Utah Population Database, stratified by year of diagnosis

	FRR of ovarian cancer among FDRs of cases vs controls			FRR of ovarian cancer among SDRs of cases vs controls			FRR of ovarian cancer among TDRs of cases vs controls		
	Case FDRs (cases/total)	Control FDRs (cases/total)	FRR (95% CI)	Case SDRs (cases/total)	Control SDRs (cases/total)	FRR (95% CI)	Case TDRs (cases/total)	Control TDRs (cases/total)	FRR (95% CI)
1966–1994									
Model 1*	67/11 124	409/116 350	1.65 (1.28 to 2.14)	123/29 929	785/312 899	1.55 (1.28 to 1.87)	310/72 196	2073/727 043	1.49 (1.31 to 1.70)
1995–2004									
Model 1*	20/4866	92/48 530	2.09 (1.29 to 3.38)	14/12 204	113/123 894	1.22 (0.70 to 2.12)	43/27 057	391/269 192	1.06 (0.73 to 1.55)
Model 2†	20/4866	92/48 530	2.10 (1.30 to 3.40)	14/12 204	113/123 894	1.22 (0.70 to 2.12)	43/27 057	391/269 192	1.06 (0.73 to 1.55)
2005–2016									
Model 1*	‡/2369	34/22 858	1.01 (0.36 to 2.87)	‡/6145	62/62 724	1.25 (0.60 to 2.61)	22/13 421	159/133 845	1.37 (0.88 to 2.12)
Model 2†	‡/2369	34/22 858	1.02 (0.36 to 2.90)	‡/6145	62/62 724	1.26 (0.61 to 2.63)	22/13 421	159/133 845	1.37 (0.88 to 2.13)

*Model 1: competing risk Cox proportional hazards models with censoring at death or loss to follow-up, and adjustment for birth year, born in Utah, race and ethnicity.
†Model 2: competing risk Cox proportional hazards models with censoring at death, bilateral oophorectomy or loss to follow-up, and adjustment for birth year, born in Utah, race, ethnicity, ever parous, number of live births, births outside of Utah, ever unilateral oophorectomy, ever unilateral salpingectomy, ever bilateral salpingectomy, ever tubal ligation and ever pelvic surgery not otherwise specified.
‡Consistent with the Utah Department of Health confidentiality policies, we have masked low counts (n<11) and any counts that could be used to re-create the low counts.
FDR, first-degree relative; FRR, familial relative risk; SDR, second-degree relative; TDR, third-degree relative.

Table 5 Associations* between nulliparity, number of live births and hysterectomy and risk of any epithelial ovarian cancer, type 1 epithelial ovarian cancer and type 2 epithelial ovarian cancer, by family history of epithelial ovarian cancer in FDRs, SDRs and TDRs

	Case FDRs HR (95% CI)	Control FDRs HR (95% CI)	P value for heterogeneity	Case SDRs HR (95% CI)	Control SDRs HR (95% CI)	P value for heterogeneity	Case TDRs HR (95% CI)	Control TDRs HR (95% CI)	P value for heterogeneity
Nulliparity									
Overall	1.61 (0.93 to 2.78)	1.41 (1.11 to 1.80)	0.500	1.27 (0.78 to 2.05)	1.81 (1.55 to 2.11)	0.098	1.95 (1.08 to 3.55)	2.44 (2.01 to 2.96)	0.530
Type 1	0.32 (0.05 to 2.23)	1.19 (0.70 to 2.01)	0.287	3.05 (1.51 to 6.15)	1.72 (1.30 to 2.28)	0.259	1.64 (0.67 to 4.01)	3.18 (2.49 to 4.04)	0.140
Type 2	1.93 (1.09 to 3.41)	1.43 (1.09 to 1.86)	0.300	1.05 (0.62 to 1.78)	1.81 (1.54 to 2.14)	0.028	2.04 (1.12 to 3.71)	2.33 (1.89 to 2.86)	0.751
Number of live births†									
Overall	0.89 (0.75 to 1.06)	0.90 (0.84 to 0.96)	0.451	0.95 (0.84 to 1.08)	0.92 (0.88 to 0.97)	0.901	0.85 (0.77 to 0.94)	0.85 (0.82 to 0.88)	0.363
Type 1	0.66 (0.39 to 1.10)	0.90 (0.80 to 1.00)	0.178	1.07 (0.86 to 1.34)	0.96 (0.89 to 1.04)	0.841	0.87 (0.76 to 1.00)	0.81 (0.77 to 0.86)	0.853
Type 2	0.95 (0.80 to 1.13)	0.90 (0.84 to 0.97)	0.224	0.95 (0.83 to 1.09)	0.93 (0.88 to 0.98)	0.813	0.86 (0.77 to 0.95)	0.86 (0.83 to 0.89)	0.343
Hysterectomy									
Overall	‡	0.49 (0.13 to 1.78)	‡	0.47 (0.07 to 3.21)	0.87 (0.52 to 1.46)	0.693	0.54 (0.11 to 2.78)	0.89 (0.59 to 1.36)	0.254
Type 1	‡	0.05 (0.00 to 2.82)	‡	‡	0.96 (0.89 to 1.04)	‡	1.22 (0.29 to 5.07)	1.62 (0.95 to 2.75)	0.302
Type 2	‡	0.47 (0.10 to 2.18)	‡	0.54 (0.08 to 3.68)	0.76 (0.42 to 1.38)	0.988	0.62 (0.12 to 3.17)	0.82 (0.52 to 1.30)	0.409

*HR estimated using competing risks Cox proportional hazards models with censoring at death, bilateral oophorectomy or loss to follow-up, and adjustment for birth year, born in Utah, race, ethnicity, ever parous (hysterectomy analysis only), number of live births (hysterectomy analysis only), births outside of Utah, ever unilateral oophorectomy, ever unilateral salpingectomy, ever bilateral salpingectomy, ever tubal ligation, ever pelvic surgery not otherwise specified and ever hysterectomy (parity analyses only).
†Number of live births evaluated among parous women only.
‡Models do not converge.
FDR, first-degree relative; SDR, second-degree relative; TDR, third-degree relative.

consistently elevated. These elevated risks reflect the known genetic aetiology of some high-grade serous ovarian cancers (eg, variants in *BRCA1/2* among others) and make both these histotypes excellent candidates for future family-based gene discovery studies.[27–29] It is also notable that although proband FDRs were enriched for the same histotype, other histotypes also occurred among relatives, suggesting potential for both unique and shared genetic aetiology across histotypes. Despite a prior report of effect modification by family history for the association between parity and risk of ovarian cancer,[11] family history of ovarian cancer did not alter the associations between parity or hysterectomy and ovarian cancer risk in this study population.

Recent years have seen a shift from family-based research, where relatives are studied directly, to population-based research, where family history is limited to self-report. This study reinforces how indepth characterisation of familial risk remains a valuable tool to form targeted hypotheses that can guide the design of genetic studies and disease prevention. Family-based studies have previously suggested that X linked and autosomal dominant modes of inheritance are most consistent with observed family configurations in epithelial ovarian cancer.[30 31] Our results were not restricted by parental lineage and so cannot provide evidence for X linked inheritance, but the evidence of familial risk among distant relatives strongly supports an aetiology that includes a dominant mode of inheritance. Beyond gene discovery, family-based designs also serve to improve counselling by understanding how risks vary for different family members. Familial risk for specific relative types informs this, yet the risks for specific FDR relationship types have been inconsistent. For example, in our study, FRRs were greatest for women with an affected daughter and lowest for women with an affected sister, while other studies have reported the greatest increase in risk when the affected FDR is a sister.[13 32] This discrepancy may reflect generational changes in risk reduction via prophylactic oophorectomy.

Registry-based studies of familial risk in FDRs, consortia-based studies with self-reported family history and our findings all concur that ovarian cancers among family members may be concordant or discordant for ovarian cancer histotypes.[12 13 15] This observation is consistent with known risk variants. Many ovarian cancer risk variants (eg, *BRCA1*, *BRCA2*, *BRIP1*, *PALB2*, *RAD51C*, *RAD51D*) are shared across histotypes, while others (eg, *MLH1*, *MSH6*) are specific to one histotype or a small subset of histotypes.[2 9 10 27–29] Gene discovery in families relies on minimising intrafamilial heterogeneity, so knowledge of how ovarian cancer histotypes coaggregate will improve power of future family-based genetic research. Knowledge of shared aetiology by histology will also improve efficiency in the analysis and interpretation of Genome-Wide Association Study (GWAS) data.[21 33–35]

A more detailed understanding of familial risk may also contribute to improved identification of women who would benefit from enhanced screening, personalised chemoprevention or risk-reducing surgery. To date, *BRCA1/BRCA2* are the most well-studied ovarian cancer susceptibility genes,[27–29] although many others have been identified.[2 9 10 27–29] Testing for *BRCA1/BRCA2* pathogenic variants is recommended for women with a family or personal history consistent with increased risk of *BRCA1/2* pathogenic variants.[36] These include women with a family history of early-onset or male breast cancer, family history of breast and ovarian cancer in the same relative, family history of multiple *BRCA*-associated cancers, or of Ashkenazi Jewish

ancestry.[36] Women with *BRCA1/BRCA2* variants have an estimated lifetime risk of ovarian cancer ranging from 11% to 36% and are commonly referred for risk-reducing bilateral salpingo-oophorectomy,[37–39] a procedure that can reduce ovarian cancer risk by more than 90%.[20]

Risk-reducing salpingo-oophorectomy was first suggested for ovarian cancer risk reduction in the early 1990s and formally recommended in 2005.[18 19] Our Utah-based study observed a strong association between family history in FDRs overall and for the time periods ranging from 1966 to 1994 and from 1995 to 2004, but no association between family history in FDRs and risk of ovarian cancer from 2005 to 2016. This encouraging finding requires replication, but suggests that uptake of salpingo-oophorectomy may be dramatically reducing risk among women with a history of ovarian cancer in FDRs. Importantly, familial risk for SDRs and TDRs appeared similar across timeframes; therefore, an important next step for ovarian cancer prevention is to query ovarian cancer incidence in SDRs and TDRs and make sure women with affected SDRs and TDRs are aware of their elevated ovarian cancer risk and risk-management options.

Our study fills an important gap in the literature on family history of epithelial ovarian cancer by addressing three common limitations of prior familial risk studies: lack of data for more distant relatives (eg, SDR and TDR),[12 13] use of outdated histology guidelines to assign tumour histotypes[11–13 15] and inability to account for oophorectomy status.[11 13–17] By overcoming these limitations, we learnt that the strongest signals for histotype-specific family history occur when the proband case has a high-grade serous, mucinous or 'other epithelial' ovarian cancer. A limitation is the small sample size of other histotypes, although the count of mucinous cases was similar to that of both endometrioid and clear cell carcinomas. We also observed that patterns in familial risk are not clean-cut by histotype, suggesting that other phenotypes, such as molecular subtypes, may be important in describing familial disease. Further, we had an opportunity to observe that changing trends in risk-reducing salpingo-oophorectomy may be associated with a reduction in familial ovarian cancer risk that is strong enough to be perceived in a large, population-based study.

While this population-based study had many strengths, it also had several important limitations. One limitation was the lack of precise information on when study participants were under active follow-up in Utah. Lack of information on the exact timing and duration of study participants' ventures outside of Utah may have led us to underestimate important covariates such as parity, number of children and the occurrence of gynaecological surgeries. We addressed this limitation by matching controls to case probands on birth year and birth location to maximise the comparability of data quality among relatives. In doing so, we aimed to reduce the likelihood of differential misclassification of these important covariates by exposure status. A limitation we could not easily address was the potential for unmeasured confounding by medication use (eg, oral contraceptive or hormone therapy); however, the magnitude and direction of association for familial risk of ovarian cancer among FDRs were similar to that observed in studies with more complete covariate information.[12] Finally, we had some concern about the influence of misclassification of histotypes due to reliance on record-based classification, but our validation study suggested that concordance with histotypes assigned by modern histopathology review was good and any discordance occurred in the expected histotype groupings (eg, some cases previously considered endometrioid ovarian cancer were reclassified as high-grade serous).[23 40]

In summary, we illustrate that indepth characterisation of familial risk continues to have great value. Our findings provide new hypotheses for histotype-defined ovarian cancer phenotypes for family-based genetic studies and for prevention strategies that include more distant relatives. We also find preliminary evidence that prophylactic salpingo-oophorectomy is successfully reducing ovarian cancer risk. In the era of GWAS and whole genome sequencing studies, our findings may also help guide subset analyses to accelerate identification of additional common risk variants. Improved understanding of familial risk continues to offer opportunities for better ovarian cancer risk stratification, and we expect that familial data from this and other multisource databases will continue to inform advances in ovarian cancer prevention, detection and treatment.

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