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JNCI J Natl Cancer Inst (2015) 107(2): dju410

doi:10.1093/jnci/dju410
First published online January 27, 2015
Article

ARTICLE

Ovarian Cancer Risk After Salpingectomy: A Nationwide Population-Based Study

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Abstract

Background: Recent genetic and morphologic studies have challenged the traditional view on the pathogenesis of ovarian cancer; suggesting that ovarian cancer predominantly arises within the fallopian tubes or the uterus. We hypothesize that surgical removal of the fallopian tubes is associated with a reduced risk for ovarian cancer.

Methods: In this population-based cohort study, we used data on women with previous surgery on benign indication (sterilization, salpingectomy, hysterectomy, and bilateral salpingo-oophorectomy [BSO], hysterectomy; n = 251 465) compared with the unexposed population (n = 5 449 119) between 1973 and 2009 and analyzed with Cox regression models. The effects of one- and two-sided salpingectomy were considered in a subanalysis. All statistical tests were two-sided.

Results: There was a statistically significantly lower risk for ovarian cancer among women with previous salpingectomy (HR = 0.65, 95% CI = 0.52 to 0.81) when compared with the unexposed population. In addition, statistically significant risk reductions were observed among women with previous hysterectomy (HR = 0.79, 95% CI = 0.70 to 0.88), sterilization (HR = 0.72, 95% CI = 0.64 to 0.81), and hysterectomy with BSO (HR = 0.06, 95% CI = 0.03 to 0.12). Bilateral salpingectomy was associated with a 50% decrease in risk of ovarian cancer compared with the unilateral procedure (HR = 0.35, 95% CI = 0.17 to 0.73, and 0.71, 95% CI = 0.56 to 0.91, respectively).

Conclusion: Salpingectomy on benign indication is associated with reduced risk of ovarian cancer. These data support the hypothesis that a substantial fraction of ovarian cancer arises in the fallopian tube. Our results suggest that removal of the fallopian tubes by itself, or concomitantly with other benign surgery, is an effective measure to reduce ovarian cancer risk in the general population.

Ovarian cancer is the most lethal gynecological cancer in developed countries and, in spite of recent advances in surgical treatment, the prognosis remains poor. Because of vague symptoms and lack of reliable screening methods, ovarian cancer is commonly diagnosed at a late stage. The visual appearance of invasive lesions has prompted the hypothesis that ovarian cancer arises within the ovarian epithelium and/or ovarian inclusion cysts. Studies of high-risk populations (ie, *BRCA* mutation carriers) have led to new insights regarding the underlying pathology.

Microdissected tubes from women undergoing prophylactic BSO have been shown to harbor both preinvasive and invasive carcinomas, whereas the ovaries appeared benign (1). In addition, recent genetic studies suggest that endometriosis, a common benign gynecological condition, together with borderline ovarian tumors (BOT), may constitute preneoplastic conditions for ovarian cancer (2). Studies emerging from The Cancer Genome Atlas (TCGA) have shed further light on the genetics of ovarian cancer. Gene expression signatures clearly demonstrate

Received: May 26, 2014; **Revised:** August 11, 2014; **Accepted:** November 5, 2014

the pivotal role of *TP53* mutations and, to a lesser extent, *BRCA1/2* mutations in high-grade serous carcinomas (HGSC) (3,4). These findings seem to be associated with prognosis and may ultimately lead to improved treatment strategies.

The potential paradigm shift in the understanding of ovarian cancer is substantiated by epidemiological data showing that occlusion of the fallopian tubes (ie, sterilization) protects against future ovarian cancer development (5). Although the underlying mechanism remains unknown, it has been speculated that the obstruction of the fallopian tubes prevents outflow of preinvasive or invasive components into the peritoneal cavity. Furthermore, case-control series suggest that hysterectomy on benign indication is associated with a statistically significant risk reduction of ovarian cancer (6). However, data available from observational studies are generally limited by small sample sizes, hospital-based study populations, insufficient control for the effects of oophorectomy, or inability to account for the temporal aspects of the association. Taken together, clinical and epidemiological studies introduce a novel view on the pathogenesis of ovarian cancer. In this population-based cohort study, we hypothesize that removal of the fallopian tubes on benign indication is associated with a reduction for ovarian cancer. For comparison, the previously reported risk-reducing procedures hysterectomy and sterilization were analyzed in relation to ovarian cancer. To test the hypothesis, we studied a cohort of women in Sweden from 1973 through 2009 to evaluate the association between previous gynecologic surgery for benign reasons and ovarian cancer risk.

Methods

Data Sources

We used data from nationwide health-care registers supervised by the Swedish Board of Health and Welfare (http://www.socialstyrelsen.se/english). Records of these registers are identified by the unique national registration numbers (NRNs) individually assigned to all nationals at birth or immigration, allowing unambiguous record linkage across these registers.The Swedish Inpatient Register, established in 1964, contains data on individual hospital discharges, and the records contain the dates of hospital admission and discharge, discharge diagnoses according to the International Classification of Diseases (ICD) versions 7 through 10, and operation codes according to the Swedish Classification of Operations and Major Procedures. The register has a less than 1% yearly loss to registration, and correct coding for surgical procedures is achieved in 98% of cases (7).

The Swedish Cancer Register, established in 1958, includes histologically verified incident cancers, is more than 95% complete, and is uniformly classified according to ICD-7. The Cause of Death Register, established in 1952, includes information about date and cause of death on all Swedish residents with a completeness exceeding 99%. The Swedish Medical Birth Registry includes prospectively collected information during pregnancy, delivery, and the neonatal period on virtually all births in Sweden since 1973. The Swedish Education Registry includes education and completion on a yearly basis for all Swedish residents age 16 to 74 years. The Register of Population includes information about dates of birth, death, emigration, and immigration of all Swedish residents.

The study was approved by the Research Ethics Committee at Karolinska Institutet, Stockholm, Sweden, and conforms to the STROBE guidelines for reporting observational studies (www.strobe-statement.org).

Exposure, Covariates, and Study Population

Using the Swedish Classification of Operations and Major Procedures, we identified as exposures four gynecological surgical procedures (hysterectomy, hysterectomy and concomitant BSO, salpingectomy, sterilization) in the Swedish Inpatient Register. Women with hysterectomy and concomitant salpingectomy constituted a small group (n = 2646) and were excluded from analyses. Oophorectomy (uni/bilateral) without concomitant hysterectomy was not considered a unique exposure. Women with oophorectomy prior to any of the four exposures contributed person-years until oophorectomy and time after was censored.

To address the potential impact of one- vs two-sided salpingectomy, we performed a subanalysis where the exposures of interest were one- and two-sided salpingectomy. The Swedish Classification of Operations and Major Procedures have two coding systems for the two different periods of calendar years, before and after January 1, 1997. For the post-1997 codes, supplementary codes for laterality were added, but the consistency in reporting one- or two-sided procedures turned out to be very low (data available from authors), precluding the identification of one- and two-sided salpingectomy after 1997. We therefore restricted the exposure and the study population to the period between January 1, 1973 and December 31, 1996, but followed the population through December 31, 2009.

From the Medical Birth Register, we obtained parity of each woman, which is known to have influence on ovarian cancer. Parity was categorized as three groups, none, one to two, and three or more. From the Education Register we extracted education level as a proxy of socioeconomic status, which was categorized into three groups (high = college or university studies, middle = two or three years of high school, low = zero to nine years of primary and secondary school).

Because information on the number of childbirths was available only from 1973 according to the Medical Birth Register, we restricted the exposures to the period between January 1, 1973 and December 31, 2009. In accordance with the exposure restriction, we identified as our study population all women above age 18 years during the period between January 1, 1973 and December 31, 2009, from the Register of Population (n = 5 703 758).

Women were excluded from analysis if they had any gynecological surgical procedure before entering the cohort (n = 9495), if they had primary ovarian cancer before entering the cohort (n = 4140), if they had other inconsistencies of their data (n = 15 810), or if they emigrated out of Sweden before entering the cohort (n = 225 194). The largest source of "other inconsistencies" were women older than age 110 years at the end of follow-up (n = 15 796) and was mainly because of emigration without reporting to authorities.

Outcome and Follow-up

From the Cancer Register, we identified ovarian and tubal cancer as outcome (ICD-7 codes 175.0 and 175.1). Borderline tumors were excluded from analyses. The end of the observation period was December 31, 2009. Women were considered unexposed before surgery but exposed after surgery. The follow-up of each woman was accordingly divided into two periods: an unexposed one before surgery and an exposed one after surgery. To isolate surgery on benign indication, we used the following algorithm: if a woman had ovarian cancer within one year after the gynecological surgery, she was then considered having the cancer in the unexposed period while not having an exposed period.

A woman without any surgery had only an unexposed period. As a result, the end of follow-up of this study was the earliest date of ovarian/tubal cancer, emigration from Sweden, death, or December 31, 2009.

Statistical Analysis

Cox proportional hazard models were used to estimate the hazard ratios for ovarian/tubal cancer among the exposed compared with unexposed, with either partial adjustment for age, calendar year, or with full adjustment, which also included parity and education level. The proportional hazards assumption was assessed using the Schoenfeld residuals and the Kolmogorov-type supremum test. The time axis was time on study, ie, time since exposure, which is of direct interest in this study. Age, calendar year, and parity were modeled as time-dependent variables, where age of each woman was divided into five-year intervals, calendar year was divided into ten-year periods, and parity was calculated according to age intervals. Two-sided 95% confidence intervals and *P* values were given, with *P* of less than .05 regarded as significant. All variables (ie, the exposures and covariables) were discrete with a small number of categories, and the proportionality assumption of the Cox model was of limited relevance in the analyses. The statistical software package SAS 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

After exclusions, the cohort consisted of 5 449 119 women during the unexposed period, then 251 465, among whom 98 026 had hysterectomy, 37 348 had hysterectomy and BSO, 34 433 had salpingectomy, and 81 658 had sterilization. In the subanalysis, 3051 women were identified with two-sided salpingectomy and 19 552 with one-sided salpingectomy. Table 1 shows some characteristics of the study population. For the unexposed period of the cohort, mean age at entry was 35.9 years (SD = 20.6 years) and the mean follow-up was 23.1 years (SD = 12.4 years).

Table 2 gives hazard ratios and incidence ratios for ovarian/tubal cancer comparing exposed with unexposed women in partial adjustment for age and calendar year and in full adjustment, which also includes parity and education. Women with previous hysterectomy, sterilization, or salpingectomy benefited from a statistically significant reduction of ovarian cancer risk (HR = 0.79, 95% CI = 0.70 to 0.88; HR = 0.72, 95% CI = 0.64 to 0.81; HR = 0.65, 95% CI = 0.52 to 0.81, respectively). As expected, hysterectomy combined with BSO eventuated in an almost complete risk cessation (HR = 0.06, 95% CI = 0.03 to 0.12). The observed incidence ratio (IR) for the group of women with hysterectomy was slightly higher than for the unexposed group, whereas the hazard ratio was considerably lower. This difference was because of the confounding by age. When age (ie, attained age in five-year intervals) was added to the unadjusted model, the hazard ratio for hysterectomy changed from 1.033 to 0.709. The other variables (calendar time, education, and parity) had only minor influence on the hazard ratio for hysterectomy.

The subanalysis of salpingectomy according to laterality is presented in Table 3. One-sided salpingectomy was associated with a statistically significant risk reduction, and bilateral salpingectomy was associated with an additional 50% decrease in risk of ovarian cancer compared with the unilateral procedure (unilateral: HR = 0.71, 95% CI = 0.56 to 0.91; bilateral salpingectomy: HR = 0.35, 95% CI = 0.17 to 0.73). The small difference in unexposed women between the main study and the subanalysis (30 749 vs 30 682) is because women who entered the main study after January 1, 1997 were too young to develop ovarian/tubal cancer.

Table 4 gives the temporal aspect of ovarian cancer according to surgical procedures in five-year bands. Apart from the group of women with concomitant hysterectomy and BSO, statistically significant hazard ratios were only observed more than 10 years after surgery among women with sterilization or salpingectomy. Similar results were observed in the subanalysis according to one- or two-sided salpingectomy. A borderline significant result was detected in the group of women with hysterectomy over 10 years after surgery. In Table 5, the number of ovarian cancer cases and person-years

Table 1. Characteristics of the study population (presented as means and SDs)

Characteristic	Hysterectomy	Hysterectomy and BSO	Salpingectomy	Sterilization	Unexposed*
n	98026	37348	34433	81658	5449119
Follow-up, y	11.3 (8.3)	8.0 (6.6)	18.0 (10.5)	21.4 (7.5)	23.1 (12.4)
Age at entry, y	51.2 (11.7)	63.1 (12.0)	35.7 (8.9)	37.9 (4.8)	35.9 (20.6)
Education					
Low	23443	7088	9154	17570	935162
Middle	52472	15604	21213	53503	1947572
High	22111	14656	4066	10585	2566385
Parity†					
0	47194	27376	18479	24238	3911511
1	16665	4949	7998	18392	553401
2-	34167	5023	7956	39028	984207
Age at surgery, y					
-30	530	59	9004	5102	NA
30–39	10545	536	16580	47473	
40–49	45783	4140	6900	28941	
50–59	45783	11827	1347	134	
60–69	8426	9395	297	7	
70-	10055	11391	305	1	

* The whole cohort during unexposed period. BSO = bilateral salpingoophorectomy.
† Parity for exposed is the one at time of surgery. Parity for unexposed is the parity of the whole cohort during the follow-up.

Table 2. Hazard ratios and incidence rates for ovarian cancer according to surgical procedures

Surgery	No. of OC (person-years)	IR (95% CI)‡	Adjusted*		Fully adjusted†	
			HR (95% CI)	P	HR (95% CI)	P
Hysterectomy	278 (1103317)	25.2 (22.4 to 28.3)	0.79 (0.70 to 0.89)	<.0001	0.79 (0.70 to 0.88)	<.0001
Hysterectomy and BSO	7 (298829)	2.3 (1.1 to 4.9)	0.06 (0.03 to 0.12)	<.0001	0.06 (0.03 to 0.12)	<.0001
Salpingectomy	81 (620873)	13.0 (10.5 to 16.2)	0.67 (0.54 to 0.83)	.0003	0.65 (0.52 to 0.81)	.0001
Sterilization	284 (1744474)	16.3 (14.5 to 18.3)	0.69 (0.62 to 0.78)	<.0001	0.72 (0.64 to 0.81)	<.0001
Unexposed	30749 (125790992)	24.4 (24.2 to 24.7)	Referent		Referent	

* Adjusted for age and calendar time. Analyzed with Cox regression models. All statistical tests were two-sided. BSO = bilateral salpingoophorectomy; CI = confidence interval; HR = hazard ratio; OC = ovarian or tubal cancer.
† Adjusted also for education status and parity. Analyzed with Cox regression models. All statistical tests were two-sided.
‡ Incidence rate calculated per 100 000 person-years. The 95% confidence interval calculated by assuming that the number of OCs follows the Poisson distribution.

Table 3. Hazard ratios and incidence rates for ovarian cancer according to one- and two-sided salpingectomy 1973–1996

Surgery	No. of OC (person-years)	IR (95% CI)‡	Partially adjusted*		Fully adjusted†	
			HR (95% CI)	P	HR (95% CI)	P
Unilateral Salpingectomy	68 (472263)	14.4 (11.4 to 18.3)	0.73 (0.57 to 0.92)	.0092	0.71 (0.56 to 0.91)	.0054
Bilateral salpingectomy	7 (70566)	9.9 (4.7 to 20.8)	0.36 (0.17 to 0.75)	.0064	0.35 (0.17 to 0.73)	.0042
Unexposed	30682 (121433033)	25.3 (25.0 to 25.6)	Referent		Referent	

* Adjusted for age and calendar time. Analyzed with Cox regression models. All statistical tests were two-sided. CI = confidence interval; HR = hazard ratio; OC = ovarian cancer.
† Adjusted also for education status and parity. Analyzed with Cox regression models. All statistical tests were two-sided.
‡ Incidence rate calculated per 100 000 person-years. The 95% confidence interval calculated by assuming that the number of OCs follows the Poisson distribution.

Table 4. Hazard ratios for ovarian cancer over time since surgery according to surgical procedures*

Surgery	Time since surgery, y†		
	0–4	5–9	10+
Hysterectomy	0.55 (0.25 to 1.20)	0.94 (0.38 to 2.29)	0.87 (0.74 to 1.03)
Hysterectomy and BSO	0.05 (0.01 to 0.27)	0.07 (0.01 to 0.30)	0.06 (0.02 to 0.24)
Salpingectomy (all)	1.10 (0.48 to 2.49)	0.50 (0.17 to 1.43)	0.63 (0.48 to 0.81)
Unilateral	1.44 (0.60 to 3.48)	0.64 (0.21 to 1.93)	0.68 (0.52 to 0.90)
Bilateral	0.61 (0.08 to 4.61)	No cases	0.39 (0.18 to 0.87)
Sterilization	0.46 (0.19 to 1.10)	0.75 (0.29 to 1.97)	0.76 (0.66 to 0.86)
Unexposed	Referent	Referent	Referent

* Presented as hazard ratios and confidence intervals. Cox proportional hazard models were used to estimate hazard ratios; two-sided 95% confidence intervals are given. BSO = bilateral salpingoophorectomy.
† Adjusted for age, calendar time, education status, parity.

Table 5. Number of ovarian cancer cases (person-years) over time since surgery according to surgical procedures*

Surgery	Time since surgery, y		
	0–4	5–9	10+
Hysterectomy	40 (352629)	91 (323693)	147 (426995)
Hysterectomy and BSO	2 (125388)	3 (98805)	2 (74636)
Salpingectomy (all)	13 (129741)	10 (140068)	58 (351064)
Unilateral	8 (77461)	8 (95253)	59 (299549)
Bilateral	1 (12025)	0 (14652)	6 (43887)
Sterilization	15 (321372)	40 (384976)	229 (1038126)
Unexposed	3818 (20888662)	4632 (23569449)	22299 (81332880)

* BSO = bilateral salpingoophorectomy.

in relation to follow-up are presented. The number of ovarian cancer cases increased with time, but the association seems independent of the follow-up time (P values for equality of different follow-up periods were .72 for hysterectomy, .99 for hysterectomy and BSO, .53 for salpingectomy, and .80 for sterilization).

Discussion

In this population-based cohort study encompassing more than 30 000 individual case patients with ovarian cancer, we found that a history of hysterectomy, sterilization, or salpingectomy on benign indications was associated with a reduced risk of ovarian cancer. Except for the group of women with hysterectomy and BSO, the most pronounced protective effect was observed for women with bilateral salpingectomy. These data provide robust epidemiological support for the hypothesis that ovarian cancer arises primarily in gynecological organs outside the ovaries. Given the lack of effective screening and detection for ovarian cancer, our results may portend important public health implications.

The emerging concept of ovarian cancer as a disease originating from extra-ovarian organs introduces novel opportunities for cancer prevention. Mutation analyses have revealed completely different patterns between the histological subtypes of ovarian cancer. Low-grade serous carcinomas (LGSCs), accounting for less than 5% of ovarian cancer, are associated with *KRAS* and *BRAF* mutations and share little resemblance with high-grade serous carcinomas (HGSC) that are commonly driven by *TP53* and *BRCA* mutations (8,9). LGSC usually develops from serous borderline neoplasms, whereas morphologic studies of fallopian tubes from *BRCA* mutation carriers have identified tubal dysplasia (STIC) as a precursor of HGSC (10). It has been hypothesized that STIC lesions are shed through the fallopian tubes and incorporated into ovarian surface inclusion cysts where they later transform into HGSC. Endometrioid and clear-cell carcinomas are believed to arise from atypical endometriosis with mutations in *PTEN*, *KRAS*, and *ARID1A* (2). The novel theory of ovarian cancer origin is supported by our results, suggesting that removal of the fallopian tubes or the uterus confers a substantial reduction of ovarian cancer risk.

We hypothesize that the decreased risk for ovarian cancer observed among women with salpingectomy reflects the effect of removed tubal epithelium and the subsequent loss of STIC formation. Indeed, the subanalysis demonstrates that complete removal of fallopian tissue (bilateral salpingectomy) more than halves the risk for ovarian cancer. Currently, high-risk populations (ie, *BRCA* mutation carriers) are recommended to have risk-reducing salpingo-oophorectomy (RRSO) at about the age of 40 years or after completing childbearing (11). While efficiently minimizing ovarian cancer risk (and also decreasing the risk for breast cancer), the removal of healthy ovaries is associated with a negative impact on health and general wellbeing as a result of estrogen deficiency (12). Limiting prophylactic surgery to salpingectomy only may constitute a feasible option for younger women at risk for ovarian cancer although the benefits (including decreased risk of cardiovascular disease secondary to premature menopause) of sparing the ovaries must be balanced against the remaining risk of breast cancer.

This study confirms previous observational data indicating that sterilization and hysterectomy is associated with a reduced risk of ovarian cancer. A recent meta-analysis of tubal ligation and the risk of ovarian cancer, analyzing data from 21 case-control and cohort studies, reported an overall hazard ratio of 0.69 (95% CI = 0.64 to 0.75) (5). A similar reduction in ovarian cancer risk was observed in a meta-analysis of women with previous hysterectomy on benign indication (HR = 0.74) (6). These results are similar to the data from more than 175 000 sterilized and hysterectomized women in the current study. In contrast to the vast majority of included studies in the meta-analyses, the utilization of data from high-quality population-based registers allowed us to control for age, parity, and temporal association, thereby efficiently reducing the risk of screening and selection bias. The most common indications for benign hysterectomy in Sweden include leiomyoma, dysfunctional bleedings, and uterine prolapse (13). Although we cannot entirely rule out that confounding by indication may to some extent have influenced our results, we consider the risk very limited. While epidemiological studies have linked endometriosis with an increased risk for ovarian cancer (14), endometriosis accounts for a minor part of hysterectomies performed in Sweden (14). Leiomyoma leading up to hysterectomy does not seem to confer any association with ovarian cancer (15), and whether dysfunctional bleedings or uterine prolapse are associated with ovarian cancer is unknown. Ectopic pregnancy and inflammatory processes in the fallopian tubes comprise main indications for salpingectomy. Ectopic pregnancy may constitute a protective factor for ovarian cancer, but the current data is limited to smaller studies, including also other types of failed pregnancies (miscarriage, abortion, and stillbirth) (16).

The strengths of our data include the population-based design with the ability to control for confounding factors. The cohort constitutes virtually all cases of ovarian cancer in Sweden from 1973 to 2009, and all of the previously specified primary gynecological surgeries on benign indication. A major source of concern in epidemiological studies of surgical exposures is the "healthy screenee effect." This bias refers to the identification of suspicious lesions during surgery and subsequent removal of malignant ovaries among supposedly healthy women (17). A causal relationship between salpingectomy and ovarian cancer would require a consistent effect over time, and our finding that the most prominent risk reduction was observed 10 years or more after salpingectomy is suggestive of a true association. However, it should be recognized that the group of women with bilateral salpingectomy in the subanalysis is relatively small. The changes in The Swedish Classification of Operations and Major Procedures unfortunately preclude analyses of one-sided vs two-sided salpingectomy after 1997, hence limiting the cohort size. Bilateral salpingectomy is a fairly uncommon procedure, and the indications mainly include hydrosalpinx, infections, and endometriosis. The common denominator for these conditions is acute or chronic inflammation, including pelvic inflammatory disease (PID), and endometriosis. Both PID and endometriosis have been recognized as risk factors for ovarian cancer; suggesting that the protective effect of bilateral salpingectomy in fact may be even larger then reported in this study (18,19). The use of oral contraceptives (OCs) is a well-established risk reducing factor for ovarian cancer (20). We were unable to control for the use of OC in the current study, and it could be argued that women wanting sterilization are more likely to be long-term OC users. However, other studies taking the use of OCs into account demonstrate a persistent effect of sterilization on the risk of ovarian cancer (5,21). Women with conditions eventually leading up to hysterectomy (dysfunctional bleeding, fibroids, and endometriosis) could potentially be prescribed OCs to control their symptoms prior to surgery. On the other hand, hysterectomy is uncommon in age groups below 40 (in the current study 11.3%), and the use of OC among women above 40 is only about 10% (22,23). We also find it unlikely that the pattern of OC use would differ between women at risk for one-sided salpingectomy and those who never undergo the procedure. Women with a family history of ovarian cancer (including *BRCA* mutation carriers) make up for a small proportion of the study population, especially because women were censored after oophorectomy (including RRSO). Nevertheless, informative censoring (ie, high-risk women having

surgery at an early age) may affect the results in the group of women with hysterectomy and BSO. However, the number of cases was very small in this group and the effect of informative censoring ought to be negligible. Finally, we want to point out that the registers used in this study rule out histological classification of ovarian cancer. According to the theory, removal of the fallopian tubes would mainly result in a reduction of HGSC. This histological subtype accounts for approximately 75% of all ovarian carcinomas, and we speculate that the observed risk reduction among women with bilateral salpingectomy mainly reflects a lower incidence of HGSC. However, a recent pooled analysis from 13 case-control studies demonstrated that sterilization not only reduces the risk of HGSC but also clear-cell, endometrioid, and mucinous subtypes of ovarian cancer (21). The effect on histological subtypes other than serous is probably mediated by the prevented reflux of cells originating from the endometrium and the subsequent ovarian seeding. Based on these data, it is possible that salpingectomy may have effects on histological subtypes other than HGSC.

Despite lack of clinical outcome data, the concept of the fallopian tubes as the originating organ for ovarian cancer has gradually gained acceptance. To the best of our knowledge, this is the first population-based study to describe an association between removal of both fallopian tubes and decreased risk of ovarian cancer. In addition, we confirm that hysterectomy on benign indications, as well as sterilization, is associated with a significant reduction of ovarian cancer risk. These findings may support a less radical approach in RRSO among *BRCA* mutation carriers. In a wider perspective, women scheduled for hysterectomy on benign indications should be informed of the risk-reducing effect of salpingectomy, and common procedures such as hysterectomy may be accompanied by bilateral removal of the fallopian tubes.

Funding

This work was supported by Stockholm County Council and Karolinska Institutet Funds, Sweden.

Notes

The authors had full access to the data and take full responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit the manuscript for publication. The funding sources had no influence on the design or conduct of the study. The data in this study were retrieved from the SIMSAM database (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden).

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