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AOGS MAIN RESEARCH ARTICLE

Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: a nationwide case–control study

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Key words
Ovarian cancer, borderline ovarian tumor, histologic subtype, tubal ligation, salpingectomy

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The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Objective. According to the recent theories on the ovarian cancer origin, any protective effect of tubal ligation may vary with histologic subtype of ovarian cancer. Furthermore, bilateral salpingectomy may represent an opportunity for surgical prevention of serous ovarian cancer. *Design.* Nationwide register-based case–control study. *Setting.* Denmark during 1982–2011. *Population.* Cases were all Danish women diagnosed with epithelial ovarian cancer (n = 13 241) or borderline ovarian tumor (n = 3605) in the study period. Age-matched female population controls were randomly selected by risk set sampling. We required that cases and controls have no previous cancer and that controls have no previous bilateral oophorectomy. *Methods.* Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals, adjusting for potential confounders. *Main outcome measures.* Epithelial ovarian cancer and borderline ovarian tumors stratified according to histology. *Results.* Tubal ligation reduced overall epithelial ovarian cancer risk (odds ratios 0.87; 95% confidence interval 0.78–0.98). We observed significant risk variation according to histology (p = 0.003) with the strongest risk reductions associated with endometrioid cancer (odds ratios 0.66; 95% confidence interval 0.47–0.93) and epithelial ovarian cancer of "other" histology (odds ratios 0.60; 95% confidence interval 0.43–0.83). Tubal ligation was not associated with risk of borderline ovarian tumors. Finally, bilateral salpingectomy reduced epithelial ovarian cancer risk by 42% (odds ratios 0.58; 95% confidence interval 0.36–0.95). *Conclusions.* We confirmed that tubal ligation reduces the risk of epithelial ovarian cancer and particularly endometrioid cancer. To our knowledge, this is the first observational publication to report on salpingectomy and ovarian cancer risk and our promising findings warrant further investigation.

Abbreviations: CI, confidence interval; ICD, International Classification of Disease; ICD-O-3, ICD for Oncology; OR, odds ratio.

Key Message

Consistent with recent theories on ovarian cancer origin, we observed that tubal ligation reduced the risk of particularly endometrioid ovarian cancer. Albeit with limited statistical precision; bilateral salpingectomy reduced the risk of epithelial ovarian cancer by approximately 40%.

Introduction

Traditionally, epithelial ovarian cancer was thought to originate from the ovarian surface epithelium (1). However, more recently it has been suggested that the origin is extra-ovarian and that the ovary is involved subsequently (2,3). According to these new theories, serous

tumors, the most common histologic subtype of epithelial ovarian cancer, may develop from the Fallopian tube (3,4). Endometrioid and clear cell tumors may originate from the endometrium, whereas mucinous tumors may arise from the tubal–mesothelial junction where the fimbriae touch the peritoneum (3).

Recent theories on the origin of ovarian cancer add to our understanding of the suggested inverse association between tubal ligation and ovarian cancer risk (5–7). If tubal ligation mechanically prevents the migration of endometrial tissue passing through the Fallopian tube, one would expect the largest risk reduction for endometrioid and clear cell ovarian cancers (7,8). Subtype-specific effects of tubal ligation compatible with these theories have recently been observed in two meta-analyses (5,6) and two large case–control studies (7,9). However, although the existing literature on the association between tubal ligation and ovarian cancer risk is extensive, all studies except for two (10,11) have been based on self-reporting, implying a risk of recall bias. Furthermore, if the Fallopian tube is the site of origin of serous ovarian cancer, bilateral salpingectomy may represent a potential opportunity for surgical prevention of serous ovarian cancer with preservation of the ovarian hormone production (12). To our knowledge, no previous publication has presented observational data on the association between salpingectomy and ovarian cancer risk.

To further elucidate the role of tubal ligation and salpingectomy in the etiology of epithelial ovarian cancer, we conducted a large register-based case–control study including all women in Denmark diagnosed with epithelial ovarian cancer or borderline ovarian tumor in the period 1982–2011. Analyses were stratified according to histologic subtype, and potential effect modification was explored by timing of tubal ligation and other case characteristics.

Material and methods

Since 1968, all citizens in Denmark have been assigned a unique personal identification number, comprising information on date of birth and gender, registered in the Civil Registration System (13), which also contains information on dates of death, and migration to and from Denmark. Using the personal identification numbers as key identifiers it is possible to ensure correct linkages between registries. Our case–control study was nested in the entire Danish female population, using data from the Civil Registration System and several other nationwide registries including the Danish Cancer Registry, the Pathology Data Bank, the National Patient Register, the Danish Prescription Registry, and the Danish Fertility Database.

The Danish Cancer Registry (14) has accurate and almost complete data on incident cancer cases in Denmark since 1943. Cancer diagnoses are recorded according to the International Classification of Diseases, version 10 (ICD-10) and the ICD for Oncology (ICD-O-3) for topography and morphology codes. The Danish Pathology Data Bank (15) contains detailed information on cytologic and histologic diagnoses performed at pathology departments in Denmark. The Pathology Data Bank was established in 1997, but the majority of pathology departments have transferred information on diagnoses from 1997 and back to 1978. The National Patient Register (16) holds information on virtually all diagnoses and surgical procedures performed at hospitals since 1977, and on outpatient visits since 1995. Diagnoses are coded according to the ICD-8 from 1977 to 1993, and ICD-10 from 1994 onwards. Surgical procedures are classified according to the Danish Classification of Surgical Procedures and Therapies until the end of 1995 and thereafter according to the Nordic Classification of Surgical Procedures. The Danish Prescription Registry (17) includes information on all prescription drugs dispensed at pharmacies in Denmark since 1995 classified by the Anatomical Therapeutic Chemical Index (18). The Danish Fertility Database (19) contains data on reproductive variables for all women in Denmark aged 13–49 years in 1980 and onwards.

Detailed information on codes used to identify cases, tubal ligation, unilateral and bilateral salpingectomy, and potential confounders are listed in the Supporting information (Table S1).

Eligible cases were all women in Denmark with a first diagnosis of histologically verified epithelial ovarian cancer or borderline ovarian tumor during 1982–2011. We further required that women were 30–84 years of age at diagnosis, were resident in Denmark on date of diagnosis (index date), and with no previous cancer (except for nonmelanoma skin cancer). Cases were classified according to histology of epithelial ovarian cancer or borderline ovarian tumor, that is, serous, endometrioid, mucinous, clear cell, and "other" subtypes (for example Brenner and squamous cell tumors).

For each case, we randomly selected 15 female population controls, matched on date of birth ($\pm$1 month), from the Civil Registration System (13) using risk-set sampling (20). Hence, controls were alive and at risk of a first cancer (except nonmelanoma skin cancer) at the time the corresponding case was diagnosed, and women were eligible as controls before they became cases. The controls fulfilled the same selection criteria as cases and, in addition, we excluded controls with previous bilateral oophorectomy or salpingo-oophorectomy.

Information on tubal ligation and salpingectomy (unilateral and bilateral) was obtained from the Patient

Register (16), which also provided information on hysterectomy, endometriosis, pelvic inflammatory disease, and infertility. Infertility was defined as the diagnosis in the Patient Register and/or use of fertility drugs (the Prescription Registry). We disregarded all surgical procedures, hospital diagnoses and drug use in the year before index date. We calculated parity based on information from the Fertility Database (19) and classified cases and controls according to number of births at 1 year before index date, i.e. 0 (nulliparous), 1, 2 and ≥3.

Information on use of oral contraceptives and hormone replacement therapy was obtained solely from the Prescription Registry (17) and therefore these variables were only available from 1995. Finally, for women born after 1953 we were able to assess family history of ovarian or breast cancer among their sisters and mothers by linking the Civil Registration System (13) and the Danish Cancer Registry (14).

Statistical analysis

The association between tubal ligation and risk of epithelial ovarian cancer or borderline ovarian tumors was estimated using conditional logistic regression by estimating age- and multivariable-adjusted odds ratios (ORs) and two-sided 95% confidence intervals (CIs). Analyses were performed for epithelial tumors overall and for each of the histologic subtypes. Although for borderline ovarian tumors, numbers permitted analyses of serous and mucinous tumors only. Confounding factors were selected a priori based on the literature and availability and included age, parity, infertility, endometriosis, pelvic inflammatory disease and hysterectomy. In a sub-analysis including exclusively women born after 1953, we were able to further adjust for a family history of ovarian or breast cancer, and use of oral contraceptives and hormone replacement therapy.

We also performed analyses to estimate potential effect modification by age at tubal ligation (continuously and categorized as ≤35 and >35 years), time since tubal ligation (continuously and divided into 1–9, 10–19, ≥20 years), and year of tubal ligation (continuously). Year of tubal ligation reflects changes or improvements in the surgical procedure over time. The variable was modeled only continuously because we had no information on calendar periods for marked changes in the tubal ligation procedure to have occurred in Denmark during our study period (21,22).

Potential effect measure modification was estimated by including interaction terms between tubal ligation and histologic subtype, endometriosis, infertility, pelvic inflammatory disease, parity (nulliparous and ≥1), and age at diagnosis of ovarian cancer (≤50 years and >50 years), respectively. We furthermore compared the effects of tubal ligation for the nonserous histologic subtypes of ovarian cancer with the effect of tubal ligation for serous ovarian cancer by means of Wald tests. The association between unilateral and bilateral salpingectomy and risk of epithelial ovarian cancer was estimated by conditional logistic regression. Due to limited statistical power, this analysis was adjusted only for age, parity, and tubal ligation.

All statistical tests were likelihood ratio tests performed using the statistical software R, version 3.0.2. A significance level of 5% was applied. The data were handled anonymously and the study was approved by the Danish Data Protection Agency (file number 2013-41-1883), and Statens Serum Institute and Statistics Denmark (file number 704327).

Results

We identified a total of 13 241 cases with epithelial ovarian cancer and 3605 cases with borderline ovarian tumors during 1982–2011. Table 1 shows characteristics of cases and age-matched controls. The majority of the women with ovarian cancer were over 50 years old at diagnosis (82.1%) and serous tumors constituted the most common histologic subtype (46.5%). Tubal ligation was slightly more common among controls compared with ovarian cancer cases (3.2% vs. 2.6%). In contrast, ovarian cancer cases were more likely than controls to be nulliparous (38.4% vs. 33.7%) and have a history of infertility (1.9% vs. 1.2%).

Among cases with borderline ovarian tumors, 45.9% were 50 years or younger at diagnosis. Most tumors were either serous (46.6%) or mucinous (49.1%). The prevalence of tubal ligation was similar among borderline cases and controls (5.3% and 5.6%), whereas more cases than controls were nulliparous (28.3% vs. 22.0%) and had a history of endometriosis (2.1% vs. 1.2%), infertility (5.5% vs. 3.4%), or pelvic inflammatory disease (8.0% vs. 5.3%).

Epithelial ovarian cancer

Tubal ligation significantly reduced the risk of overall epithelial ovarian cancer (OR = 0.87; 95% CI 0.78–0.98) (Table 2). The risk estimate was not changed materially among women born after 1953 after additional adjustment for a family history of ovarian and breast cancer, use of oral contraceptives, and hormone replacement therapy (data not shown).

We observed a significant variation in risk according to histologic subtype of epithelial ovarian cancer ($p = 0.003$). The strongest risk reductions associated with tubal ligation were observed for endometrioid tumors

Table 1. Characteristics of women with epithelial ovarian cancer and borderline ovarian tumors and matching controls.

	Epithelial ovarian cancer				Borderline ovarian tumors			
	Cases (n = 13 241)		Controls (n = 194 689)		Cases (n = 3605)		Controls (n = 53 322)	
Characteristics	n	%	n	%	n	%	n	%
Histologic subtype								
Serous	6157	46.5	–	–	1679	46.6	–	–
Mucinous	1414	10.7	–	–	1770	49.1	–	–
Endometrioid	1713	12.9	–	–	44	1.2	–	–
Clear cell	633	4.8	–	–	7	0.2	–	–
"Other"	3324	25.1	–	–	105	2.9	–	–
Age at diagnosis/index date (years)								
30–40	535	4.0	8042	4.1	687	19.1	10 296	19.3
41–50	1842	13.9	27 452	14.1	966	26.8	14 400	27.0
51–60	3172	24.0	46 590	23.9	865	24.0	12 717	23.8
61–70	3883	29.3	56 734	29.1	635	17.6	9283	17.4
71–80	3123	23.6	45 744	23.5	360	10.0	5279	9.9
>80	686	5.2	10 127	5.2	92	2.6	1347	2.5
Parity								
Nulliparous	5085	38.4	65 649	33.7	1020	28.3	11 716	22.0
One	2624	19.8	36 124	18.6	746	20.7	9664	18.1
Two	3497	26.4	55 850	28.7	1224	34.0	20 056	37.6
Three or more	2035	15.4	37 066	19.0	615	17.1	11 886	22.3
Tubal ligation								
Yes	345	2.6	6201	3.2	191	5.3	2989	5.6
Hysterectomy								
Yes	738	5.6	10 147	5.2	216	6.0	2868	5.4
Endometriosis								
Yes	147	1.1	1667	0.9	75	2.1	645	1.2
Pelvic inflammatory disease								
Yes	444	3.4	5780	3.0	287	8.0	2852	5.3
Infertility								
Yes	258	1.9	2385	1.2	198	5.5	1807	3.4

(OR = 0.66; 95% CI 0.47–0.93) and epithelial ovarian cancer of "other" histology (OR = 0.60; 95% CI 0.43–0.83) (Table 2). In the age-adjusted analysis, data also indicated that tubal ligation may decrease the risk of serous and clear cell ovarian cancer, but after adjustment for potentially confounding factors, the association attenuated. In contrast to the nonmucinous subtypes of epithelial ovarian cancer, we observed a nonsignificantly increased risk of mucinous ovarian cancer associated with tubal ligation (OR = 1.25; 95% CI 0.94–1.67).

Compared with serous ovarian cancer, the protective effect of tubal ligation was significantly larger for endometrioid ovarian cancer (p = 0.047) and epithelial ovarian cancer of "other" histology (p = 0.018), whereas the effect of tubal ligation for clear cell tumors did not differ significantly from that for serous tumors (p = 0.880). Lastly, the OR of tubal ligation associated with risk of mucinous ovarian cancer seemed to be larger compared with the OR associated with serous ovarian cancer (p = 0.052) (data not shown).

The risk of overall epithelial ovarian cancer did not seem to vary with time since tubal ligation (p-value for trend = 0.759), age at tubal ligation (p-value for trend = 0.551) or year of tubal ligation (p-value for trend = 0.301) (Table 3). Based on small numbers, we observed no consistent pattern in timing of tubal ligation with regard to risk for each of the histologic subtypes of epithelial ovarian cancer. Risk of endometrioid ovarian cancer was halved among women who had tubal ligation performed at a younger age (OR = 0.49; 95% CI 0.24–1.00). For epithelial ovarian cancer of "other" histology, we found significantly reduced OR associated with tubal ligation performed at 20 years or longer ago (OR = 0.47; 95% CI 0.26–0.87) and irrespective of age at tubal ligation (≤35 years: OR = 0.51; 95% CI 0.26–1.00; >35 years: OR = 0.63; 95% CI 0.43–0.91).

We observed no effect modification by endometriosis, infertility, pelvic inflammatory disease, parity or age at diagnosis on the association between tubal ligation and risk of epithelial or serous ovarian cancer, and the data

Table 2. Risk of epithelial ovarian cancer and histologic subtype by tubal ligation history.

Histologic type of epithelial ovarian cancer by tubal ligation history	Cases		Controls		Age-matched		Adjusted	
	n	%	*n*	%	OR	95% CI	OR	95% CI[a]
All epithelial								
No	12 896	97.4	188 488	96.8		ref		ref
Yes	345	2.6	6201	3.2	0.81	0.72–0.90	0.87	0.78–0.98
Serous								
No	5967	96.9	87 153	96.5		ref		ref
Yes	190	3.1	3196	3.5	0.87	0.74–1.01	0.92	0.79–1.08
Mucinous								
No	1357	96.0	20 146	96.5		ref		ref
Yes	57	4.0	730	3.5	1.18	0.88–1.57	1.25	0.94–1.67
Endometrioid								
No	1676	97.8	24 318	96.5		ref		ref
Yes	37	2.2	887	3.5	0.60	0.43–0.84	0.66	0.47–0.93
Clear cell								
No	611	96.5	8905	95.8		ref		ref
Yes	22	3.5	392	4.2	0.82	0.52–1.28	1.03	0.65–1.62
"Other"								
No	3285	98.8	47 966	98.0		ref		ref
Yes	39	1.2	996	2.0	0.56	0.40–0.77	0.60	0.43–0.83

CI, confidence interval; OR, odds ratio.
[a]Adjusted for age, parity (0, 1, 2, ≥3), infertility (yes, no), endometriosis (yes, no), pelvic inflammatory disease (yes, no), and hysterectomy (yes, no).

did not allow meaningful evaluation of the nonserous histologic subtypes (data not shown).

Finally, the potential association between salpingectomy and ovarian cancer risk was examined (Table 4). The analysis was based on few exposed cases. However, we found that bilateral salpingectomy was associated with a 42% decreased risk of epithelial ovarian cancer (OR = 0.58; 95% CI 0.36–0.95). We also observed an inverse association between unilateral salpingectomy and ovarian cancer, but the risk reduction was smaller and nonsignificant (OR = 0.90; 95% CI 0.72–1.12).

Epithelial borderline ovarian tumors

Tubal ligation was not associated with the risk of overall epithelial borderline ovarian tumors (OR = 1.03; 95% CI 0.89–1.21) or with borderline tumors of serous (OR = 1.00; 95% CI 0.80–1.26) or mucinous (OR = 1.04; 95% CI 0.83–1.30) histology (Table 5). Risk estimates did not change when the analysis was restricted to women born after 1953 with further adjustment for a family history of ovarian and breast cancer, use of oral contraceptives, and hormone replacement therapy (data not shown).

For epithelial borderline ovarian tumors, we also investigated potential effect modification by timing of tubal ligation. We observed no difference in risk estimates according to time since tubal ligation (p-value for trend = 0.874), age at tubal ligation (p-value for trend = 0.557), and year of tubal ligation (p-value for trend = 0.166). Similar analyses were performed for serous and mucinous borderline ovarian tumors, and we observed no differences in risk according to timing of tubal ligation. Moreover, the association between tubal ligation and risk of epithelial borderline ovarian tumors was not affected by endometriosis, infertility, pelvic inflammatory disease, parity, or age at diagnosis (data not shown).

Discussion

In this large nationwide register-based case-control study, tubal ligation significantly reduced the risk of overall epithelial ovarian cancer. We found significant risk variation according to histology with the largest risk reduction observed for endometrioid ovarian cancer and epithelial ovarian cancer of "other" histology. In contrast, there was no association between tubal ligation and risk of borderline ovarian tumors. Finally, albeit with limited statistical precision, we observed that bilateral salpingectomy significantly reduced the risk of epithelial ovarian cancer by approximately 40%.

Several hypotheses have been suggested to explain the inverse association between tubal ligation and ovarian cancer risk. Tubal ligation may reduce blood flow to the ovaries and thereby alter levels of growth factors and

Table 3. The association between tubal ligation and risk of epithelial ovarian cancer and histologic subtype by time since tubal ligation, age at tubal ligation, and year of tubal ligation.

	Overall epithelial OC			Serous OC			Mucinous OC			Endometrioid OC			Clear cell OC			"Other" OC		
		Adjusted			Adjusted			Adjusted			Adjusted			Adjusted			Adjusted	
Timing of tubal ligation	Cases (*n*)	OR	95% CI[a]	Cases (*n*)	OR	95% CI[a]	Cases (*n*)	OR	95% CI[a]	Cases (*n*)	OR	95% CI[a]	Cases (*n*)	OR	95% CI[a]	Cases (*n*)	OR	95% CI[a]
No tubal ligation	12 896		ref	5967		ref	1357		ref	1676		ref	611		ref	3285		ref
Time since tubal ligation																		
1–9	82	0.93	0.74–1.17	34	0.86	0.60–1.22	22	1.62	1.03–2.56	9	0.64	0.33–1.26	6	1.19	0.51–2.76	11	0.72	0.39–1.34
10–19	137	0.84	0.70–1.00	72	0.86	0.68–1.10	24	1.16	0.76–1.79	15	0.63	0.37–1.07	9	1.03	0.52–2.07	17	0.63	0.39–1.04
≥20	126	0.88	0.73–1.06	84	1.01	0.81–1.27	11	0.98	0.52–1.83	13	0.72	0.41–1.28	7	0.92	0.42–2.01	11	0.47	0.26–0.87
p-value for trend			0.759			0.580			0.375			0.935			0.909			0.609
Age at tubal ligation																		
≤35	112	0.92	0.76–1.12	70	1.09	0.85–1.39	21	1.26	0.80–1.99	8	0.49	0.24–1.00	4	0.61	0.22–1.67	9	0.51	0.26–1.00
>35	233	0.86	0.75–0.98	120	0.85	0.70–1.03	36	1.25	0.88–1.79	29	0.73	0.50–1.08	18	1.21	0.74–1.99	30	0.63	0.43–0.91
p-value for trend			0.551			0.120			0.988			0.306			0.195			0.586
Year of tubal ligation																		
p-value for trend			0.301			0.665			0.910			0.216			0.845			0.319

CI, confidence interval; OC, ovarian cancer; OR, odds ratio.

[a]Adjusted for age, parity (0, 1, 2, ≥3), infertility (yes, no), endometriosis (yes, no), pelvic inflammatory disease (yes, no), and hysterectomy (yes, no).

Table 4. Risk of epithelial ovarian cancer by unilateral and bilateral salpingectomy.

Salpingectomy history	Cases (*n*)	Controls (*n*)	Age-matched		Adjusted	
			OR	95% CI	OR	95% CI[a]
No salpingectomy	13 135	192 896	ref		ref	
Unilateral	89	1382	0.94	0.76–1.18	0.90	0.72–1.12
Bilateral	17	411	0.61	0.37–0.99	0.58	0.36–0.95

CI, confidence interval; OR, odds ratio.

[a]Adjusted for age, parity (0, 1, 2, ≥3), and tubal ligation.

hormones (8,23,24), or inhibit endometrial tissue or retrograde menstruation ascending from the uterus to the Fallopian tubes and ovaries (6,8). Moreover, tubal ligation may prevent infection or other carcinogenic agents (e.g. talc and asbestos) from the external genitalia from spreading to the Fallopian tubes and ovaries and causing inflammation (6,8). Finally, it is also suggested that surgeons may remove suspicious ovarian tissue during tubal ligation (6,8). According to the more recent theories on the origin of epithelial ovarian cancer, endometrioid and clear cell cancers arise from endometrial cells passing up through the Fallopian tube (3). Therefore, it has been hypothesized that tubal ligation is more protective for endometrioid and clear cell tumors compared with the other histologic subtypes of epithelial ovarian cancer (5,7).

Consistent with these theories, we observed that tubal ligation reduced the risk of endometrioid ovarian cancer substantially and to a greater extent than the risk reduction for serous cancer. Two previous meta-analyses (5,6) followed by two large studies (7,9), one of which pooled data from 13 case–control studies (7), have also reported the most profound risk reduction for endometrioid cancer and similar to our findings, in these studies it was observed that the magnitude of risk reduction was greater for endometrioid compared with serous (6,7) or other subtypes of epithelial ovarian cancer (5,9). Hence, the literature on tubal ligation and endometrioid cancer seems to be rather consistent, although in one multicenter case–control study no association was noted (25). With regard to clear cell tumors, our study did not confirm the hypothesis that tubal ligation may have a particularly strong protective effect. This negative finding is in agreement with one recent study (9), whereas most other studies reporting risk estimates specifically for clear cell cancer have described substantial risk reductions associated with tubal ligation (6,7,25).

Considering the hypothesis that the majority of serous tumors arise in the Fallopian tube (2–4), it is plausible that tubal ligation may provide only limited protection

Table 5. Risk of borderline ovarian tumor and histologic subtype by tubal ligation history.

Histologic type of epithelial borderline ovarian tumors by history of tubal ligation	Cases		Controls		Age-matched		Adjusted	
	n	%	*n*	%	OR	95% CI	OR	95% CI[a]
All epithelial								
No	3414	94.7	50 333	94.4		ref		ref
Yes	191	5.3	2989	5.6	0.94	0.81–1.10	1.03	0.89–1.21
Serous								
No	1593	94.9	23 408	94.3		ref		ref
Yes	86	5.1	1415	5.7	0.89	0.71–1.12	1.00	0.80–1.26
Mucinous								
No	1676	94.7	24 751	94.5		ref		ref
Yes	94	5.3	1436	5.5	0.97	0.78–1.21	1.04	0.83–1.30

OR, odds ratio.

[a]Adjusted for age, parity (0, 1, 2, ≥3), infertility (yes, no), endometriosis (yes, no), pelvic inflammatory disease (yes, no), and hysterectomy (yes, no).

against serous ovarian cancer (7,26). In line with this we found no strong association between tubal ligation and risk of serous cancer. Although our finding is consistent with one recent case–control study (9), most previous data have shown that tubal ligation reduces the risk of serous cancer (5–7,25). We also observed a substantial risk reduction of epithelial ovarian cancer of "other" histology. Previous studies have indicated that tubal ligation reduces risk of this group of epithelial ovarian cancers, but risk estimates have not been statistically significant (6,9).

Mucinous ovarian cancer differed from the nonmucinous subtypes as the risk estimate associated with tubal ligation was >1, although not significantly. Similar findings were also previously reported from Denmark (10) and America (27). However, the published data on the association between tubal ligation and mucinous cancer are inconclusive. Two meta-analyses (5,6) and the one pooled case–control study (25) reported reduced risk estimates with CIs including 1, whereas in another pooled case–control study (7) in addition to the study by Rice et al. (9) significant inverse associations were observed. One explanation of why the effect of tubal ligation may vary between mucinous and nonmucinous subtypes of epithelial ovarian cancer may be their origin, i.e. mucinous tumors are hypothesized to originate from the tubal–mesothelial junction where the fimbriae touch the peritoneum (3). Another explanation may be that a proportion of mucinous ovarian cancers may in fact be metastases from tumors in the gastrointestinal tract (28).

We also investigated tubal ligation with regard to the borderline category of epithelial ovarian tumors and in line with previous studies (5,7,9); we found no association between the procedure and risk of borderline ovarian tumors.

In view of the recent theories on the origin of epithelial ovarian cancer, it has been proposed that bilateral salpingectomy may represent a potential opportunity for surgical prevention of serous ovarian cancer (3,12,29). Although based on limited numbers we did actually observe that bilateral salpingectomy reduced the risk of epithelial ovarian cancer by approximately 40%. Unfortunately, our data did not permit subtype-specific analysis. Interesting data from the Rochester Epidemiology Project were presented by Lessard-Anderson et al. (30) at the 2013 Annual Meeting of the Society of Gynecologic Oncology. Based on 29 women (five cases and 24 controls) who had undergone excisional tubal sterilization, the authors reported that the surgical procedure reduced the risk of serous ovarian cancer and primary peritoneal cancer by more than 60% (OR = 0.38; 95% CI 0.14–1.06). These promising findings require confirmation by future studies and ideally with a larger sample size. At best, bilateral salpingectomy could represent a preventive intervention for women undergoing hysterectomy for benign disease or requesting permanent contraception or for women at high genetic risk of ovarian cancer with ovarian preservation (29,31).

The main strength of our study was that we assessed tubal ligation and salpingectomy from the National Patient Register, which eliminated risk of recall bias. Our use of nationwide registries with virtually complete coverage and continuously updated data on cancer diagnoses, surgical procedures and potential confounding factors minimized selection bias and provided us with data to perform the largest case–control study on tubal ligation and risk of epithelial ovarian cancer to date and furthermore, to be the first observational study to publish data on the association between unilateral and bilateral salpingectomy and epithelial ovarian cancer. Finally, our cases were histologically verified, which enhanced case validity.

Our study also had some limitations. Although we included a total of nearly 17 000 cases with epithelial ovarian cancer or borderline ovarian tumors, the low

prevalence of tubal ligation and salpingectomy in our study population limited the statistical precision. In particular, this limitation may explain why we were unable to conclude on the effect of timing of tubal ligation and effect modification by factors other than histology. Information on indication for a surgical procedure is not directly available in the Patient Registry. However, although not entirely complete, we reviewed the primary hospital diagnoses registered during the hospital admission where unilateral or bilateral salpingectomy was performed (as a proxy for surgical indication). Ectopic pregnancy was by far the most common primary diagnosis. Other common diagnoses included salpingitis, oophoritis, hydrosalpinx and benign tumors of the uterus or ovaries (in our study population, women did not have salpingectomy in connection with surgery for cancer because we excluded women with previous cancer and ignored surgical procedures performed in the year before index date).

Finally, information on a family history of ovarian and breast cancer, use of oral contraceptives and hormone replacement therapy were only available for women born after 1953. However, sensitivity analysis with additional adjustment for these factors did not change the overall risk estimates substantially, indicating that this was not a major limitation in our study.

Conclusion

Our study confirms that tubal ligation reduces the risk of epithelial ovarian cancer and particularly endometrioid ovarian cancer. We observed an even larger risk reduction of epithelial ovarian cancer associated with bilateral salpingectomy. Additional studies are needed to establish whether this translates into a potential preventive intervention for epithelial ovarian cancer.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Codes used in the analysis.