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Original Research

Association between pelvic inflammatory disease and subsequent salpingectomy on the risk for ovarian cancer

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Abstract *Aim:* Salpingectomy is associated with a lower risk for ovarian cancer, suggesting that the fallopian tubes constitute the origin of the disease. It is unclear whether the observed effect is mediated by pelvic inflammatory disease (PID); a major indication for salpingectomy and implicated in the aetiology of ovarian cancer.

Methods: In this population-based cohort study, we used nationwide registry-based data on women exposed for PID with and without subsequent salpingectomy ($n = 97,912$) compared with the unexposed population ($n = 5,429,174$) between 1973 and 2010. The effect of hormone treatment was considered in a subanalysis.

Results: Of the exposed women, 9538 women underwent salpingectomy during the study period. There was a significant association between PID and ovarian cancer (hazard ratio [HR] 1.44, 95% confidence interval [CI] 1.31–1.59), whereas an inverse association was observed for exposed women with subsequent salpingectomy (HR 0.55, 95% CI 0.36–0.83). Salpingectomy performed on other indications ($n = 24,895$) was associated with a lower incidence of ovarian cancer (HR 0.72, 95% CI 0.56–0.93). No effect modification was observed for the use of oral contraceptives or hormonal replacement therapy.

Conclusion: Salpingectomy is associated with a lower incidence of ovarian cancer regardless of indication.

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1. Introduction

Ovarian cancer is commonly diagnosed at an advanced stage and is associated with a dismal prognosis. Risk-reducing salpingoophorectomy has considerable protective effect in high-risk populations (i.e. BRCA mutation carriers), but with detrimental effects on reproduction and quality of life [1–3]. A substantial body of evidence suggests that ovarian cancer may originate in the fallopian tubes as precursor cells for high-grade serous carcinomas [4,5]. It has also been suggested that the fallopian tubes allow ovarian seeding of endometrial cells giving rise to clear-cell and endometrioid ovarian cancer subtypes [6].

Robust epidemiological data underpin the association between removal of the fallopian tubes and a subsequent reduction of incident ovarian cancer in the general population [7,8]. As such, salpingectomy may provide an opportunity for ovarian cancer prevention also among non-high-risk populations. However, there is paucity of data from prophylactic salpingectomy *per se* as most procedures have been performed for various conditions including pelvic inflammatory disease (PID). This has spurred a discussion as to what extent confounding by indication (i.e. PID) accounts for the observed effect of salpingectomy on the incidence of ovarian cancer: a notion that has limited consensus on the use of salpingectomy for ovarian cancer prevention. Certainly, chronic inflammation has been implicated in the aetiology of several malignancies and is estimated to precede up to 25% of all cancers [9]. The role of PID on the risk of ovarian cancer is uncertain and pooled analyses of case–control studies show conflicting results [10,11]. Most of these studies were limited by the lack of serological data on PID agents but recent prospective data suggest that chlamydia trachomatis antibodies are associated with a two-fold ovarian cancer risk [12]. In this population-based cohort study, we hypothesized that salpingectomy on benign indications is associated with a reduction of ovarian cancer irrespective of the indication for the procedure. To test the hypothesis, we studied a nationwide cohort of women in Sweden exposed to PID with, or without, subsequent salpingectomy.

2. Methods

2.1. Data sources

Data from nationwide health care registers were used to establish a cohort of Swedish women aged 18 years or older between 1973 and 2009. Records of these registers are identified by the unique national registration number individually assigned to all nationals at birth or immigration, allowing unambiguous record linkage across these registers.

Exposed women were identified using the Swedish Patient Register, established in 1964, which contains data on individual hospital discharges including date and discharge diagnoses according to the International Classification of Diseases (ICD) versions 7 through 10. Correct coding for surgical procedures is achieved in 98% of cases [13]. Incident cases of primary ovarian/tubal cancer were identified in the Swedish Cancer Register. The register, established in 1958, includes histologically verified incident cancers, is more than 95% complete and is uniformly classified according to ICD-7. Classification of tumour morphology according to the Systemized Nomenclature of Medicine is available from 1993. Using national registration numbers, all individual records were also linked with the Cause of Death Register, the Swedish Medical Birth Register, the Swedish Education Registry, the Swedish Prescribed Drug Register and the Population Register. Data were available for the entire study period except for data from the newly established Swedish Prescribed Drug Register (available from 2005).

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).

2.2. Exposure, covariates and study population

Using the Swedish Classification of Operations and Major Procedures, we identified as exposures women with a diagnosis of salpingitis (ICD-7: 622, 623, 624, 625; ICD-8: 612, 613, 614, 615.10; ICD-9: 614; ICD10: N70) and all women subjected to salpingectomy during the study period. To address the potential impact of hormonal treatment (oral contraceptives and/or hormonal replacement treatment), we performed a sensitivity analysis considering the use of these pharmaceuticals.

The analyses were adjusted for known confounders for ovarian cancer risk, including parity, age and educational level (proxy of socioeconomic status).

In accordance with the exposure restriction, we identified as our study population all women above 18 years of age during the period between 1st January 1973 and 31st December 2009, from the Register of Population ($n = 5,703,758$).

Women were excluded from analysis if they had any gynaecological surgical procedure before entering the cohort ($n = 9434$), if they had primary ovarian cancer before entering the cohort ($n = 4035$), if they had other inconsistencies of their data ($n = 119$), and if they emigrated out of Sweden before entering the cohort ($n = 225,255$). The largest source of ‘other inconsistencies’ were women older than 110 years of age at the end of follow-up ($n = 15,796$) and was mainly due

Table 1
Characteristics of the study population.

	PID without salpingectomy	PID with salpingectomy	Salpingectomy without PID	Unexposed ^a
n	93,242	9538	24,895	5,429,174
Follow-up years, mean (SD)	21.9 (10.9)	18.3 (6.6)	17.8 (10.8)	22.8 (12.5)
Age at entry, mean (SD)	29.1 (10.2)	38.8 (8.8)	34.5 (8.7)	35.9 (20.6)
Education, n				
Low	10,722	1254	2812	2,563,445
Middle	59,954	6032	15,181	1,934,459
High	22,566	2252	6902	931,270
Parity ^b , n				
0	66,861	5629	18,479	3,903,868
1	16,099	2015	7998	549,521
2–	10,282	1894	7956	975,785
Age at surgery, years, n				NA
–30	89,398	1563	7441	
30–39	2365	3807	12,773	
40–49	1245	3237	3663	
50–59	217	807	540	
60–69	15	86	211	
70–	2	38	267	
Salpingectomy, n (%) ^c				
Unilateral		4912 (73)	14,640 (92)	
Bilateral		1775 (27)	1276 (8)	
Topography ovarian/tubal cancer, n (%)				
Ovarian	368 (88)	22 (100)	58 (98)	29,512 (97)
Tubal	49 (12)	0	1 (2)	820 (3)
Histologic subtypes ^d , n (%)				
Total	294	17	45	12,403
Epithelial	279 (95)	17 (100)	42 (93)	11,668 (94)
Serous	190 (68)	14 (82)	31 (74)	7893 (68)
Mucinous	24 (9)	1 (6)	4 (10)	1087 (9)
Endometrioid	44 (16)	2 (12)	2 (5)	1507 (13)
Clear cell	13 (5)	0	5 (12)	532 (5)
Other	8 (3)	0	0 (0)	649 (6)
Non-epithelial	15 (5)	0	3 (7)	735 (6)

PID, pelvic inflammatory disease.

^a The entire cohort during unexposed period.

^b Parity for exposed is the one at time of surgery. Parity for unexposed is the parity of the entire cohort during the follow-up.

^c Laterality available between 1973 and 1997.

^d Histologic subtypes available from 1993.

to emigration without reporting to authorities. After exclusions, the final cohort comprised 5,449,119 women.

2.3. 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 tumours were excluded from analyses. The following cohorts were considered in the analyses: women with PID and subsequent salpingectomy, women with PID without salpingectomy, women with salpingectomy without prior PID and finally women with neither PID and salpingectomy (unexposed). To isolate the effect of salpingectomy on benign indications, women with ovarian cancer occurring within 1 year after exposure were considered as unexposed in the analyses.

The end of follow-up in this study was the earliest date of ovarian/tubal cancer, emigration from Sweden, death or 31st December 2009.

2.4. Data analyses

We calculated the incidence rate of ovarian cancer as the number of cases per 100,000 person-years, with 95% confidence intervals (CIs) based on the Poisson distribution. Cox proportional hazard models were used to estimate the hazard ratios (HRs) for ovarian/tubal cancer among the exposed compared to 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, that is, time since exposure, which is of direct interest in this study. Age, calendar year and parity were modelled as time-dependent variables, where age of each woman was divided into 5-year intervals, calendar year was divided into 10-year periods, and parity was calculated according to age intervals. Two-tailed 95% CIs and p-values were given, with $p < 0.05$.

regarded as significant. All variables (i.e. the exposures and covariates) 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.

3. Results

After exclusions, the cohort consisted of 5,449,119 women, among whom 93,242 had PID without salpingectomy, 9538 had PID and salpingectomy and 24,895 had salpingectomy without previous PID. Table 1 gives the characteristics of the study population together with histologic subtypes and site of origin for ovarian/tubal cancer.

Table 2 gives HRs and incidence ratios for ovarian/tubal cancer comparing exposed to unexposed women in partial adjustment for age and calendar year and in full adjustment, which also includes parity and education. A history of PID without subsequent salpingectomy was associated with a higher risk for ovarian cancer (HR 1.44, 95% CI 1.31–1.59), whereas PID followed by salpingectomy was inversely associated with ovarian cancer (HR 0.55, 95% CI 0.36–0.83). Women with salpingectomy but without a previous history of PID had a lower incidence of ovarian cancer (HR 0.72, 95% CI 0.56–0.93). The observed associations were consistent over an observation period of 10 years (Table 3).

To address the potential confounding of exogenous oestradiol (hormone replacement therapy [HRT] and oral contraceptives), sensitivity analyses were performed for the last 5 years of the study period. Overall, use of oral contraceptives was associated with a lower risk for ovarian cancer (HR 0.64, 95% CI 0.51–0.80). For HRT use, a higher incidence of ovarian cancer (OC) was observed (HR 1.85, 95% CI 1.70–2.01). The adjusted HRs for exposure in the sensitivity analyses were nearly equal to the unadjusted estimates, implying that exogenous oestradiol was not confounding the estimates of the exposures. In the sensitivity analysis of oral contraceptives, the adjusted HR (95% CI) for exposures

Table 3

Hazard ratios (HR) and confidence intervals (CI) for ovarian cancer over time since exposure.

Exposure	Time since exposure (years) ^a		
	0–4	5–9	10+
PID without salpingectomy ^b	3.47 (2.44–4.93)	0.96 (0.53–1.75)	1.28 (1.14–1.43)
PID with salpingectomy ^c	1.41 (0.60–3.27)	0.12 (0.02–0.99)	0.50 (0.30–0.84)
Salpingectomy ^c	0.72 (0.30–1.75)	0.55 (0.22–1.40)	0.70 (0.52–0.94)
Unexposed ^d	Reference	Reference	Reference

PID, pelvic inflammatory disease.

^a Adjusted for age, calendar time, education status, parity.

^b Time since PID.

^c Time since surgery.

^d Time since entry into the cohort.

were 1.39 (1.11–1.74) for PID without salpingectomy, 0.62 (0.28–1.39) for PID with salpingectomy and 0.65 (0.37–1.15) for salpingectomy. In the sensitivity analysis for HRT, the adjusted HR (95% CI) for exposures were 1.34 (1.07–1.68) for PID without salpingectomy, 0.60 (0.27–1.34) for PID with salpingectomy and 0.63 (0.35–1.10) for salpingectomy.

4. Discussion

In this population-based cohort study, there was a clear association between PID and increased incidence of ovarian cancer. The risk decreased significantly in women with PID having had a salpingectomy as compared to those who did not, but it was equally clear that salpingectomy significantly decreased the risk for ovarian cancer also in women not having had a PID. Taken together with the fact that the protective effect was observed at long-term, irrespective of indication, our study corroborates previous data and provides solid epidemiological support for the preventive effect of salpingectomy on the risk for ovarian cancer.

The historic monolithic perception of ovarian cancer was questioned in the early 2000s by studies on micro-dissected fallopian tubes revealing dysplastic changes

Table 2

Hazard ratios (HRs) and incidence rates (IRs) with confidence intervals (CIs) for ovarian/tubal cancer according to exposure.

Exposure	Ovarian/tubal cancer, n (person years)	IR (95% CI) ^c	Adjusted HR ^a		Fully adjusted HR ^b	
			HR (95% CI)	P-value	HR (95% CI)	P-value
PID without salpingectomy	417 (2,043,404)	20.4 (18.5–22.5)	1.45 (1.31–1.60)	<0.0001	1.44 (1.31–1.59)	<0.0001
PID with salpingectomy	22 (174,443)	12.6 (8.3–19.2)	0.59 (0.39–0.89)	<0.0001	0.55 (0.36–0.83)	<0.0001
Salpingectomy without PID	59 (446,430)	13.2 (10.2–17.1)	0.73 (0.56–0.94)	0.0003	0.72 (0.56–0.93)	0.0001
Unexposed	30,332 (123,747,588)	24.5 (24.2–24.8)	Reference		Reference	

PID, pelvic inflammatory disease.

^a Adjusted for age and calendar time.

^b Adjusted also for education status and parity.

^c Incidence rate calculated per 100,000 person years. The 95% CI calculated by assuming that the number of ovarian/tubal cancers follows Poisson distribution.

that could represent precursors for ovarian cancer [5]. Based on these findings, together with morphologic and genomic data, a shift from ‘one origin—one disease’ to a multipathway model was proposed [6]. The miniscule proportion of tubal cancers observed in this study underlines the current diagnostic dilemma and reinforces the need of an updated staging classification for ovarian cancer based on morphologic and genetic properties. Interestingly, a somewhat larger proportion of tubal cancer was observed among women with a previous history of PID without subsequent salpingectomy, suggesting that the presence of pre-existing tubal pathology may facilitate the topographic determination of ovarian cancer. Further support on the role of the fallopian tubes have been highlighted in cohort studies on women exposed to salpingectomy showing a convincing association between removal of the fallopian tubes and a lower incidence of ovarian cancer [7,14]. Indeed, bilateral salpingectomy was associated with a more than 50% reduction of incident ovarian cancer in Sweden [7]. Risk reductions of similar magnitudes have been shown in nested case–control studies also from Denmark and the United States of America [14,15].

PID is one of the primary indications for salpingectomy on benign indications and like other chronic inflammatory processes being linked to internal organ carcinogenesis, PID has been implicated in the aetiology of ovarian cancer [16]. However, data on the association between PID and ovarian cancer have been inconsistent and only a moderate effect was observed in a large pooled analysis of several smaller case–control studies [11]. In a recent in-depth analysis of the association between antibodies for *Chlamydia trachomatis* and ovarian cancer, a clear association was observed and PID should most likely be considered a risk factor for ovarian cancer [12]. We observed a significantly higher incidence of ovarian cancer among women with a history of PID, among whom salpingectomy significantly lowered the risk. However, the protective effect of salpingectomy was not limited to these women but also extended to women without a PID diagnosis. A protective effect of salpingectomy was further supported by the temporal analysis, showing a decrease in ovarian cancer risk when compared to women not having had a salpingectomy over the 10-year observation period. A temporal relationship between exposure and outcome may be considered a prerequisite for a biologically plausible relationship to exist as ovarian cancer incidence increases with age. In addition, the robustness of the association was supported by the lack of effect modification observed in the sensitivity analyses of exogenous administration of oestrogen.

The strengths of our data include the population-based design, the large number of cases, and the high-quality registers. Importantly, the study was able to control for the confounding effect of oral contraceptives, which substantially lower the risk for ovarian

cancer compared with women not using oral contraception. The cohort includes virtually all cases of ovarian cancer in Sweden during 1973–2010 together with coverage of selected exposures. Data from independently supervised registers using standardized nomenclature and diagnosis codes minimize selection and ascertainment bias. The study does, however, have some limitations including the inability to analyse uni- and bilateral salpingectomy separately because of the low number of cases. In addition, misclassification of exposure (PID) cannot be completely ruled out as we rely on data from the Swedish inpatient register and not actual cultures or patient serology. As a consequence, the role of *Chlamydia trachomatis* in ovarian cancer occurrence could not be confirmed and the association could not be explored further.

Fallopian tubes left *in situ* after pelvic surgery constitute a source of potentially precancerous transformation (regardless of carcinogenic pathway) and a significant proportion of these women require additional surgery to remove retained tubes [17]. Concerns regarding the effect of opportunistic salpingectomy on subsequent ovarian function have not been substantiated by clinical data and the potential harm if any ought to be outweighed by the oncological benefits [18]. Indeed, the incidence of opportunistic salpingectomy in conjunction with hysterectomy appears to have increased substantially the past 10 years [19,20]. Recent studies indicate that women have a high acceptance for salpingectomy, also in combination with non-gynaecological procedures [20,21]. Several societies have issued statements supporting opportunistic salpingectomy at the time of hysterectomy on benign indications [22–24]. Ongoing randomized controlled trials attempt to explore the potential impact of salpingectomy on quality of life and premature menopause [25,26].

The present analyses add to our previous work, showing a convincing reduction in incident ovarian cancer after salpingectomy irrespective of indication. We suggest that salpingectomy should be considered an effective preventive measure for ovarian cancer and that risk-reducing salpingectomy should be offered to women scheduled for gynaecological procedures including hysterectomy and sterilization, especially those with a history of PID.

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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

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Author contributions

Henrik Falconer, Conceptualization, methodology, investigation, writing – original draft, writing – review/editing, visualization. Li Yin, Methodology, formal analysis, writing – review/editing. Sahar Salehi, Formal analysis, writing – review/editing. Daniel Altman, Conceptualization, methodology, investigation, writing – review/editing.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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