

### Short Communication

## Reduced Risk of Ovarian Cancer in Women with a Tubal Ligation or Hysterectomy<sup>1</sup>

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Neoplasia and Steroid Contraceptives

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### Abstract

Possible relationships between tubal ligation and hysterectomy and epithelial ovarian cancer were assessed in data that were collected for a multinational hospital-based case-control study conducted between 1979 and 1988. Histologically confirmed incident cases ( $n = 393$ ) were compared with controls ( $n = 2563$ ) matched on age, hospital, and year of interview. A nonsignificant reduction in risk was observed for tubal ligation [odds ratio (OR), 0.72; 95% confidence interval (CI), 0.48-1.08] and hysterectomy (OR, 0.58; 95% CI, 0.26-1.27). There was no trend in risk with time since tubal ligation. The possible protective effect of tubal ligation was greatest in women of parity less than four. The apparent protective effect for tubal ligation was seen only for clear cell (OR, 0.32; 95% CI, 0.006-2.50) and endometrioid (OR, 0.20; 95% CI, 0.046-1.46) tumors, suggesting a hormonal mechanism for the observed associations.

### Introduction

A reduced risk of ovarian cancer has been associated with tubal ligation (1-7), although not consistently so (8-10). Possible protective effects against ovarian cancer have been observed for hysterectomy (11-13). There have been several hypothesized theories for these observations, including a screening effect (14), blockage of particles coming into contact with the ovaries (8), a decrease in the blood supply to the ovaries (1), and a decrease in uterine growth factors that may be involved in ovarian cancer development (8).

In this report, we present findings on the relationship between tubal ligation and hysterectomy and risk of ovarian cancer from a multinational study that was conducted largely in developing countries.

### Subjects and Methods

The methods used in this study have been described previously (15). Briefly, newly diagnosed cases of breast, uterine cervix, uterine corpus, ovarian, and hepatobiliary cancers were identified from admissions to hospitals in nine centers in seven countries (Australia, Chile, China, Israel, Mexico, the Philippines, and Thailand). All study subjects must have been older than 15 years, born after 1925 or 1930, depending on when steroid contraceptives became available locally, and must have resided in a defined area served by the hospital of ascertainment for at least 1 year. Ascertainment of study subjects began in October 1979 and continued until 1988 in some centers. Cases were included in the analysis for this report if they had been confirmed by a reference pathologist as borderline or malignant epithelial ovarian carcinomas.

Approximately two controls of the same ages as the cases were selected for each case of the five neoplasms investigated. Women were not eligible for control selection if they had been admitted to the hospital for selected conditions that might have altered their use of steroid contraceptives or had had a previous bilateral oophorectomy or ovarian cancer. For the present study, up to eight women from this pool of controls were individually matched to each case on age, hospital, and date of diagnosis.

Of all subjects, 95.4% of cases and 95.7% of controls agreed to be interviewed. Standardized questionnaires were administered in the local language. Histological slides were sent to one reference laboratory for review by one of two pathologists. One hundred four (26.2%) of the 385 epithelial ovarian tumors were classified as borderline malignant potential, and the remaining were judged to be malignant.

Conditional logistic regression (16) was used to calculate ORs<sup>3</sup> and 95% CIs as estimates of RRs. When cell sizes were small, exact logistic regression was used (17). ORs were controlled for the number of live births and oral contraceptive use along with the three matching variables (age, date of diagnosis, and center) after examining numerous variables as potential confounding factors.

### Results

Because there was no significant heterogeneity of the relationships of ovarian cancer with tubal ligation ( $P = 0.265$ ) or hysterectomy ( $P = 0.169$ ) between centers, data from all centers were combined. A nonsignificant reduction in risk of ovarian cancer was associated with tubal ligation (Table 1). No trend with time since tubal ligation was observed, but the possible protective effect was not evident more than 20 years since the operation. The apparent association with reduced risk also was stronger if the tubal ligation was performed after age 35 years, and there is a modest trend in risk with age at tubal

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<sup>3</sup> The abbreviations used are: OR, odds ratio; CI, confidence interval; RR, relative risk.

**Table 1** ORs for epithelial ovarian cancer in relation to time since and age at tubal ligation and hysterectomy: WHO Collaborative Study of Steroid Contraceptives and Neoplasia, 1979–1988

	Cases	Controls	OR <sup>a</sup>	95% CI
Never sterilized	351	2060	1.00	
Tubal ligation	34	426	0.71	0.47–1.08
Time since tubal ligation, (yr)				
1–5	9	95	0.96	0.46–1.98
6–10	8	134	0.58	0.28–1.24
11–15	5	77	0.60	0.23–1.52
16–20	2	59	0.27	0.063–1.15
>20	10	48	1.44	0.66–3.15
Missing	0	19	<i>P</i> = 0.275 <sup>b</sup>	
Age at tubal ligation (yr)				
≤27	11	104	0.92	0.46–1.84
28–30	7	89	0.76	0.33–1.69
31–35	8	101	0.77	0.36–1.64
>35	8	119	0.59	0.28–1.24
Missing	0	19	<i>P</i> = 0.095 <sup>b</sup>	
Hysterectomy	8	84	0.58	0.27–1.28
Hysterectomy alone	4	57	0.41	0.14–1.21
Hysterectomy with unilateral oophorectomy	4	27	1.06	0.34–3.29
Time since hysterectomy (yr)				
1–5	5	32	1.04	0.37–2.90
>5	3	47	0.37	0.11–1.24
Age at hysterectomy (yr)				
≤40	4	46	0.50	0.17–1.50
>40	4	33	0.78	0.25–2.40

<sup>a</sup> Adjusted for parity and oral contraceptive use.<sup>b</sup> Test for trend.

ligation. A possible protective effect of hysterectomies was restricted to women without concomitant unilateral oophorectomy and to those whose surgery was performed more than 5 years prior to reference date.

Women of low parity exhibited the lowest risk associated with tubal ligation, and no relationship was observed for women with four or more children (Table 2). Exclusion of the few nulliparous women from the analysis did not appreciably alter the results. Associations of tubal ligation with reduced risk were observed only for women with clear cell and endometrioid tumors (Table 3). No differences in risk were observed for borderline and malignant tumors (not shown).

## Discussion

Although our results did not reach statistical significance, the RR estimate of 0.71 for women with a tubal ligation is only slightly higher than that observed in a meta-analysis of previous studies (RR, 0.63; 95% CI, 0.44–0.91; Ref. 1).

The RR estimate of less than 1 for hysterectomy has been consistently observed in many studies (1–6, 11–13, 18), and our RR estimate is less than that observed in a pooled analysis of 12 case-control studies (OR, 0.66; 95% CI, 0.50–0.85 for hospital case studies; OR, 0.88; 95% CI, 0.72–1.1 for population-based studies; Ref. 4). Our nonsignificant results could have been due to the small number of exposed subjects in this study.

Cramer and Xu (8) observed that low risk associated with sterilization was strongest for mucinous tumors (OR, 0.3; 95% CI, 0.1–1.0). In contrast, we observed the strongest apparent protective effects of tubal ligation to occur for clear cell and endometrioid tumors. Our findings may differ from those of Cramer and Xu (8) because of chance, due to the small numbers of exposed individuals within histological subtype groups.

**Table 2** ORs for epithelial ovarian cancer associated with tubal ligation stratified by parity: WHO Collaborative Study of Steroid Contraceptives and Neoplasia, 1979–1988

Parity	Tubal ligation		Never sterilized		OR <sup>a</sup>	95% CI
	Cases	Controls	Cases	Controls		
0–2	7	92	242	1006	0.33	0.14–0.77
3	9	116	51	340	0.56	0.26–1.20
4–5	11	132	29	388	1.16	0.55–2.42
>5	7	86	29	326	1.02	0.43–2.44

<sup>a</sup> Adjusted for oral contraceptive use; ORs calculated for tubal ligation within parity strata.**Table 3** ORs for epithelial ovarian cancer associated with tubal ligation by cell type: WHO Collaborative Study of Steroid Contraceptives and Neoplasia, 1979–1988

Histological cell type	Tubal ligation		Not sterilized		OR <sup>a</sup>	95% CI
	Cases	Controls	Cases	Controls		
Serous	17	141	154	893	0.98	0.53–1.80
Mucinous	15	139	91	578	0.88	0.46–1.69
Clear cell	1	61	34	167	0.33 <sup>b</sup>	0.007–2.68
Endometrioid	1	73	48	273	0.21 <sup>b</sup>	0.048–1.49
Other	0	12	24	148	0 <sup>b</sup>	0–3.44

<sup>a</sup> Adjusted for parity and oral contraceptive use.<sup>b</sup> Estimated by exact methods.

Both Weiss *et al.* (19) and La Vecchia *et al.* (20) found that the risk for endometrioid tumors is increased after postmenopausal hormone exposure, and Cramer *et al.* (21) found that there was an increase in the incidence of endometrioid and clear cell carcinomas in the United States, following the period in which postmenopausal hormones were used frequently. If endogenous estrogen exposure stimulates the development of endometrioid and clear cell ovarian tumors the same way that exogenous hormone exposure does, then a reduction in the production of endogenous hormones, particularly estrogens, would specifically reduce the risk of the most estrogen-responsive ovarian tumors (*i.e.*, endometrioid and clear cell histological types). Tubal ligations (22, 23) and hysterectomies (24) appear to inhibit the production of estrogen and progesterone by the ovary, perhaps due to the decrease in blood supply to the ovary (25). Cattanaach (26) has suggested that the reduction is greater for estrogen than progesterone and that this, therefore, reduces the estrogen/progesterone ratio.

We suggest that other studies be conducted that include a standardized histological review to investigate the relationship of specific types of ovarian carcinomas to hysterectomy and tubal ligation to confirm either our findings or those of Cramer and Xu (8).

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