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Epidemiologic Evidence for Uterine Growth Factors in the Pathogenesis of Ovarian Cancer

DANIEL W. CRAMER, MD, ScD, AND HUIJUAN XU, MPH

ABSTRACT

To examine the association between ovarian cancer and prior hysterectomy or tubal ligation in light of various interpretations, we combined data from two previously conducted case–control studies of ovarian cancer. This included 450 women with histologically verified epithelial ovarian cancer and 454 age-matched women from the general population for whom data on prior pelvic surgery were available to estimate exposure odds ratios. Overall there was a nonsignificant deficit of case patients who had had a hysterectomy or tubal ligation (odds ratio (OR) = 0.9; 95% confidence interval (CI), 0.6 to 1.3). A protective effect of prior hysterectomy or tubal ligation was more apparent among women who had the surgery 20 or more years previously (OR = 0.6; 95% CI, 0.3 to 1.1), women who had not used talc in their hygiene (OR = 0.6; 95% CI, 0.4 to 1.0), and women with mucinous tumors of the ovary (OR = 0.3; 95% CI, 0.1 to 1.0). Although these data do not clearly establish the validity of or mechanisms for an association between prior pelvic surgery and ovarian cancer, we speculate that such an association exists and may be mediated through absent or reduced uterine growth factors that reach the ovaries through the uteroovarian circulation, with mucinous tumors most dependent on such factors. Ann Epidemiol 1995;5:310–314.

KEY WORDS: Ovarian neoplasia, hysterectomy, tubal ligation, mucinous tumors, growth factors.

INTRODUCTION

Multiple studies have suggested that tubal ligation or hysterectomy (even without removal of ovaries) may protect against ovarian cancer (1–12). Various interpretations have been proposed including confounding, a screening effect offered by visualization of the ovaries at the time of such operations, an effect due to closure of the female tract, or some type of hormonal effect. Data from two previously completed case–control studies of ovarian cancer are combined to examine the association between ovarian cancer and tubal ligation or hysterectomy and to investigate various interpretations. An explanation not previously considered is proposed.

METHODS

Between 1978 and 1981, 215 women with epithelial ovarian cancer recently diagnosed in hospitals in the greater Boston area were interviewed about a variety of risk factors. From the same hospitals, 235 women with epithelial ovarian cancer were interviewed between 1984 and 1987. Slides of tumor specimens were reviewed and the histopathologic type of epithelial ovarian cancer confirmed. Tumors of borderline malignancy were included. In both studies, control subjects were selected from the general population and matched by age and precinct of residence to case patients; there were 215 control subjects in the first study and 239 in the second study. Informed consent was obtained from subjects under protocols approved at the participating hospitals. Women who had had a hysterectomy with both ovaries removed were excluded as control subjects but women who had had a hysterectomy and were certain that at least one ovary had been retained were included. Further details on study methods are discussed in other articles about these studies (13–18).

While a variety of risk factors have been investigated and reported from these studies (see above-cited references), no detailed examination of tubal ligation or hysterectomy has been conducted. In this report, both data sets are combined to look at uterine or tubal surgery as risk factors for ovarian cancer in 450 women with epithelial ovarian cancer and 454 control subjects. Crude and adjusted exposure odds ratios (ORs) for ovarian cancer associated with prior hysterectomy or tubal ligation were determined by logistic regression.

From the Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Address reprint requests to: Daniel W. Cramer, MD, ScD, Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115.

Received August 22, 1994; accepted November 1, 1994.

1047-2797/95/$9.50
SSDI 1047-2797(94)00098-E

TABLE 1. General characteristics of cases and controls from combined ovarian cancer studies

Variable	Case		Control		Odds ratio (95% CI)
	n	%	n	%	
Reference age (y)[a]					
< 40	89	19.8	91	20.0	
40–49	83	18.4	86	18.9	
50–59	120	26.7	116	25.6	
60–69	102	22.7	101	22.2	
⩾ 70	56	12.4	60	13.2	
Ever married					
No	86	19.1	50	11.0	1
Yes	364	80.9	404	89.0	0.5 (0.4–0.8)
Religion					
Catholic	244	54.2	260	57.3	1
Protestant	124	27.6	136	30.0	1.0 (0.7–1.3)
Jewish	61	13.6	44	9.7	1.5 (1.0–2.3)
Other	21	4.7	14	3.1	1.6 (0.8–3.2)
Education					
< college	318	70.7	328	72.2	1
⩾ college	132	29.3	126	27.8	1.1 (0.8–1.4)
Parity					
None	161	35.8	85	18.7	1
1–2	139	30.9	162	35.7	0.4 (0.3–0.6)
⩾ 3	150	33.3	207	45.6	0.4 (0.3–0.5)
Oral contraceptive use					
No	349	77.6	324	71.4	1
Yes	101	22.4	130	28.6	0.7 (0.5–1.0)[b]
Talc use					
No	249	55.3	300	66.1	1
Yes	201	44.7	154	33.9	1.6 (1.2–2.1)

[a] Age at diagnosis for cases and at interview for controls.
[b] P = 0.03.
CI, confidence interval.

RESULTS

Table 1 shows risk for ovarian cancer associated with several demographic or reproductive variables that have been shown to be risk factors for ovarian cancer or might confound or interact with the association between hysterectomy or tubal ligation and ovarian cancer. The case group was nearly identical in age distribution to the control group. There was a slight but not significant excess of women with Jewish religious background among the case patients, but no difference in educational status. Case patients with ovarian cancer were less likely to have ever been married, to have had children, or to have used oral contraceptives. Case patients were more likely to have used talc in their genital hygiene compared to control subjects.

Table 2 shows the distribution of case patients and control subjects by occurrence of tubal ligation or hysterectomy and by age at or recency of operation. There was a deficiency of ovarian cancer case patients who had either hysterectomy or tubal ligation, translating into a modest protective effect of these pelvic operations on ovarian cancer risk, but the finding was not statistically significant (OR = 0.9; 95% confidence interval (CI) 0.6 to 1.3). A protective effect of tubal ligation or hysterectomy was more apparent for women who had either hysterectomy or tubal ligation more than 20 years prior to the age at diagnosis or interview (OR = 0.6; 95% CI, 0.3 to 1.2).

Table 3 shows the risks for ovarian cancer associated with tubal ligation or hysterectomy in various subgroups of case patients and control subjects. The protective effect was more apparent in subjects 50 years and older, parous subjects, and subjects who had not used talc in their pelvic hygiene. The odds ratio in the latter group associated with prior hysterectomy or tubal ligation was 0.6 (95% CI, 0.4 to 1.0).

Table 4 examines the odds ratios for tubal ligation or hysterectomy among women with various histologic types of ovarian cancer. A history of pelvic surgery was most frequently observed among women with undifferentiated tumors, 6 (20%) of 30, and least frequently observed among women with mucinous tumors of the ovary, 3 (4.2%) of 72. Referenced against the 14.8% frequency of prior pelvic surgery observed in all control subjects, the odds ratio for a mucinous epithelial ovarian tumor associated with prior tubal ligation or hysterectomy was 0.3 with a 95% confidence interval of 0.1 to 1.0 after adjusting for parity.

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TABLE 2. Odds ratios of hysterectomy and tubal ligation for the risk of ovarian cancer from the combined data

Variable	Case		Control		Odds ratio[a] (95% CI)
	n	%	n	%	
No operation	398	88.4	387	85.2	1
Tubal ligation	16	3.6	23	5.1	0.9 (0.4–1.7)
Hysterectomy	36	8.0	47	10.4	0.8 (0.5–1.3)
Tubal ligation or hysterectomy	52	11.6	67[b]	14.8	0.9 (0.6–1.3)
Age (y) at first operation					
< 35	18	4.0	20	4.4	1.1 (0.6–2.1)
35–44	22	4.9	31	6.8	0.8 (0.4–1.4)
⩾ 45	12	2.7	16	3.5	0.8 (0.4–1.8)
Recency of last operation (y)					
< 10	10	2.2	12	2.6	1.0 (0.4–2.3)
10–19	26	5.8	27	5.9	1.1 (0.6–2.0)
⩾ 20	16	3.6	28	6.2	0.6 (0.3–1.2)

[a] Adjusted for parity (0, ⩾ 1).
[b] Three controls had both tubal ligation and hysterectomy.
CI, confidence interval.

DISCUSSION

Overall, in this study, we found a nonsignificant deficit of case patients who had had hysterectomy or tubal ligation. More apparent protection of prior hysterectomy or tubal ligation on ovarian cancer was observed among women who had had the surgery 20 or more years previously, women who had not used talc in their hygiene, and women with mucinous tumors of the ovary. Although these data, by themselves, do not clearly establish the validity of an association between prior hysterectomy or tubal ligation and ovarian cancer, it is more persuasive viewed in the perspective of existing data. A dozen studies reported a protective association between prior pelvic surgery and ovarian cancer (1–12). Our discussion will focus on explanations that have been offered for this possible association.

Biases that may pertain in epidemiologic studies, such as recall bias, generally lead to an excess of case patients with the exposure rather than a deficiency, which is observed for the hysterectomy and tubal ligation association. Confounding might explain this association, if there were some factor that protected against ovarian cancer but increased risk for hysterectomy or tubal ligation. The most obvious of such factors would be childbearing. High parity decreases the risk for ovarian cancer and most certainly is associated with the decision to have a tubal ligation. High parity has also been found to increase the risk for hysterectomy in both cohort (19) and cross-sectional studies (20). Parity is clearly the most important confounder that must be controlled for in investigating the association between ovarian cancer and hysterectomy or tubal ligation. Virtually all studies that

TABLE 3. Odds ratios for pelvic surgery (hysterectomy or tubal ligation) for the risk of ovarian cancer by various subgroups of cases and controls

Subgroups	Pelvic surgery	Case		Control		Odds ratio (95% CI)
		n	%	n	%	
Age < 50 y	No	153	89.0	155	87.6	1
	Yes	19	11.0	22	12.4	0.9 (0.5–1.7)
Age ⩾ 50 y	No	245	88.1	232	83.8	1
	Yes	33	11.9	45	16.2	0.7 (0.4–1.1)
Parity = 0	No	152	94.4	81	95.3	1
	Yes	9	5.6	4	4.7	1.2 (0.4–4.0)
Parity ⩾ 1	No	246	85.1	306	82.9	1
	Yes	43	14.9	63	17.1	0.8 (0.6–1.3)
Nontalc user	No	224	90.0	252	84.0	1
	Yes	25	10.0	48	16.0	0.6 (0.4–1.0)[a]
Talc user	No	174	86.6	135	87.7	1
	Yes	27	13.4	19	12.3	1.1 (0.6–2.1)

[a] $P = 0.04$.
CI, confidence interval.

TABLE 4. Odds ratios (ORs) for prior pelvic surgery (hysterectomy or tubal ligation) associated with histologic type or grade of ovarian cancer

Group	Total	Surgery		OR (95% CI)[a]
		n	%	
All controls	386	67	14.8	
Cancer type				
Serous	231	28	12.1	0.9 (0.5–1.4)
Mucinous	72	3	4.2	0.3 (0.1–1.0)[b]
Endometrioid	46	6	13.0	1.0 (0.4–2.5)
Clear cell	31	4	12.9	1.4 (0.5–4.6)
Undifferentiated	30	6	20.0	1.8 (0.7–4.6)
Other	41	5	12.2	1.0 (0.4–2.6)
Cancer grade				
Borderline	103	9	8.7	0.8 (0.4–1.6)
Malignant	348	43	12.4	0.9 (0.6–1.4)

[a] Adjusted for parity (0, ≥ 1).
[b] P = 0.06.

investigated the association between pelvic surgery and ovarian cancer have adjusted for parity and the association has persisted. Oral contraceptive use is another protective factor for ovarian cancer but there is little evidence to suggest that it predisposes to risk for tubal ligation or hysterectomy, and thus little reason to suspect it is a confounder.

Weiss and colleagues (3, 21) proposed that the protective effect of hysterectomy or tubal ligation might represent a screening effect such that visualization of the pelvis permitted at the time of pelvic surgery may lead to the diagnosis and removal of ovaries with premalignant conditions. They further proposed that this screening effect would lead to the greatest protection being observed in the immediate years after operation and waning with time since surgery. Although this was observed in some studies (3, 11), it was not seen in the majority of studies including this one.

Turning to explanations that have a more obvious biologic basis, we note that hysterectomy or tubal ligation closes the female tract. Thus tubal effluences or vaginal contaminants are no longer able to reach the pelvic cavity and ovaries. Although many vaginal contaminants could be proposed, talc use in genital hygiene may be an important one (13, 18). However, Hankinson and coworkers (12) did not find that the protective effect of pelvic surgery was confined to women who had used talc in genital hygiene, and in this study, the protective effect of pelvic surgery was more apparent among those who never used talc in their genital hygiene. A patent female tract is not a necessary cause for ovarian cancer, as there is a case report of an epithelial ovarian tumor in a woman with vaginal agenesis (22). Thus, it seems unlikely that closure is the key mechanism to explain the protective effect of pelvic surgery on ovarian cancer risk.

Cattanach (23) observed that many types of tubal ligation interrupt the uteroovarian circulation, and proposed that this could lead to localized hypertension and damage to the ovary, resulting in decreased estrogen production. However, the reduced estrogen levels he reported following tubal ligation were not observed by others nor have consistent effects of hysterectomy been seen on gonadotropins and steroid hormone levels (24–26). Nevertheless, the circulatory changes Cattanach (23) suggested may offer another previously unconsidered explanation for the protective effect of tubal ligation on ovarian cancer risk.

We propose that there are uterine growth factors involved in ovarian cancer pathogenesis that are eliminated or reduced after pelvic surgery. Hysterectomy obviously removes the source of uterine growth factors and interrupted uteroovarian circulation after tubal ligation would reduce the concentration of growth factors that reaches the ovaries directly from the uterus. There is increasing evidence that growth factors are produced by uterine stroma or smooth muscle in a variety of species during estrous and pregnancy (27, 28). These may include epidermal growth factor, insulin growth factor-I, and colony-stimulating factor-I, and have paracrine effects on the uterine epithelium or trophoblast or endocrine effects at distant sites on estrogen-sensitive tissue. Of particular note, Sirbasku (29) demonstrated that estrogen-dependent tumor cell lines in mice could be stimulated by growth factors from rodent uteri.

The observation that uterine growth factors may be stimulated by pregnancy might potentially be relevant to our observation that the protective effect of hysterectomy or tubal ligation was most apparent for mucinous tumors of the ovary. In series describing tumors arising during pregnancy (30–32), dermoids (mature teratomas) are most common; however, among the epithelial tumors, mucinous tumors appear to account for a disproportionately higher frequency in pregnant women than they do among nonpregnant women. These observations could indicate that dermoids and mucinous tumors of the ovary are those most likely to depend on a uterine growth factor for their initiation or

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growth. Parenthetically, Scully (33) reviewed evidence that some mucinous tumors may arise from germ cells as monophyletic teratomas. However, given the small number of mucinous tumors in this series, chance must also be considered as an explanation for our finding and further study will be necessary.

In conclusion, we report a protective effect of prior hysterectomy or tubal ligation for ovarian cancer and offer several explanations. A novel and speculative explanation we propose is that protection may derive from removal of the source of uterine growth factors by hysterectomy or from a reduction of such factors that reach the ovaries directly by interruption of the uteroovarian circulation by tubal ligation. We further speculate that the epithelial tumors most likely to depend on uterine growth factors are mucinous types. Further research on the role of uterine growth factors in the initiation or progression of ovarian cancer would likely be informative.

This study was supported by grant RO1 CA 42008 from the National Cancer Institute.

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