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Tubal Ligation and Fatal Ovarian Cancer in a Large Prospective Cohort Study

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Several studies suggest that tubal sterilization may decrease the risk of ovarian cancer. Data from the Cancer Prevention Study II were analyzed to examine the relation between tubal ligation and ovarian cancer mortality in a large prospective study. A total of 396,114 women who had not had hysterectomies and who had no prior history of cancer (except nonmelanoma skin cancer) were followed prospectively for approximately 9 years from 1982 to 1991. During this time, 799 ovarian cancer deaths were observed. Tubal ligation was significantly associated with a decreased risk of ovarian cancer mortality in an age- and race-adjusted Cox proportional hazards model (hazard ratio (HR) = 0.64, 95% confidence interval (CI) 0.42–0.96), and the results were essentially unchanged when controlling for potential ovarian cancer risk factors (HR = 0.68, 95% CI 0.45–1.03). The protective effect appeared to be greater in the first 20 years after the procedure (HR = 0.49, 95% CI 0.24–0.99) than later (HR = 0.80, 95% CI 0.48–1.34). No interactions between ever having had a tubal ligation and other covariates were observed. These data suggest that tubal ligation reduces the risk of fatal ovarian cancer. *Am J Epidemiol* 1997;145:349–57.

cohort studies; ovarian neoplasms; sterilization, tubal

Ovarian cancer is the second most common gynecologic cancer in the United States and is the most fatal gynecologic malignancy (1). Among women with the disease, fewer than 44 percent will survive 5 years from the time of diagnosis (2). Environmental and lifestyle factors may play an important role in ovarian cancer risk; studies have consistently identified an inverse association of ovarian cancer with use of oral contraceptives (3–7) and parity (5, 7–14).

Among women using contraception in 1990, 30 percent relied on female sterilization (15), making tubal ligation the first choice of contraception in that year. An estimated 10 million US women had undergone tubal sterilization by 1991. Because female sterilization is most widely used by older women who have completed their childbearing years, the prevalence of sterilization as a contraceptive choice will probably increase among US women with the continued aging of the baby boom generation (15).

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Abbreviations: CI, confidence interval; HR, hazard ratio.

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An inverse association between tubal ligation and ovarian cancer incidence has been reported in nine retrospective case-control studies (3–5, 16–21) and one prospective cohort study (22). Six of these were statistically significant at the 0.05 level (4, 5, 17, 20–22). Two additional studies did not find any reduction in risk with tubal ligation (23, 24). Although there are several biologic mechanisms supporting a protective effect of tubal ligation on ovarian cancer, it is possible that the lower risk results from ovarian screening that sometimes accompanies pelvic surgery. A screening effect is suggested by several studies that found risk was lowest in the 10–15 years after the procedure (3, 20, 21).

The poor prognosis of ovarian cancer reinforces the need for research to identify modifiable risk factors for this disease. To investigate further the relation of fatal ovarian cancer to tubal ligation and to determine whether risk varies with increasing time since the procedure, we examined the data from a large prospective cohort study of US women. This study is the largest ever conducted of this relation and is the second prospective cohort study.

MATERIALS AND METHODS

Women in this study were selected from 676,526 women in the Cancer Prevention Study II, an ongoing

prospective mortality study of 1.2 million men and women begun in 1982 by the American Cancer Society. Participants were enrolled from all 50 states, the District of Columbia, and Puerto Rico by 77,000 American Cancer Society volunteers.

At the time of enrollment, each participant completed a self-administered four-page questionnaire that included personal identifiers, demographic characteristics, smoking history, diet, alcohol intake, occupational exposures, menstrual and reproductive history, medication use, and personal and family history of cancer and other illnesses. The median age of female participants in 1982 was 56 years.

During the first 6 years of follow-up, vital status of the participants was ascertained every 2 years through personal inquiries by the volunteers who enrolled the study participants. Since 1988, all follow-up has been conducted biannually through linkage with the National Death Index (25). Mortality follow-up at the time of this analysis was complete through December 31, 1991. At that time, 59,439 women (8.8 percent) were known to have died and of these, 97.1 percent of the death certificates have been collected. Certificates were coded by a nosologist according to the *International Classification of Diseases*, Ninth Revision (26). Follow-up was censored for 2,078 (0.3 percent) women in 1988 due to missing name or date of birth information necessary for linkage with the National Death Index.

Ideally, only women who had ovaries and who were therefore at risk of dying from ovarian cancer should be included in this analysis. Women in this study were not explicitly asked about the number of intact ovaries they had at the time of the interview or, if they reported a hysterectomy, whether the hysterectomy included removal of the ovaries. Therefore we excluded all women who may have had one or both ovaries surgically removed based on their report of prior hysterectomy, surgical menopause, or previous ovarian surgery. Postmenopausal women who did not specify whether their menopause was natural or surgical, and women who did not specify their menopause status, were excluded. In addition, we excluded from analyses women who had incomplete data on race or who reported prevalent cancers (except nonmelanoma skin cancer) at baseline. After all exclusions, 799 ovarian cancer deaths were observed in an eligible cohort of 396,114 women who were cancer free in 1982 (table 1). Ovarian cancer deaths were defined as those women who died between September 1, 1982, and December 31, 1991, and whose underlying cause of death was coded as ovarian cancer (*International Classification of Diseases,* Ninth Revision codes 183.0–183.9).

TABLE 1. Exclusion criteria and eligible cohort for analysis, Cancer Prevention Study II, United States, 1982–1991

	Women	Ovarian cancer deaths
Total cohort	676,526	1,481
Exclusions		
Incomplete race data	3,275	2
Reported cancer at interview*		
Ovarian	1,318	202
Other	55,543	203
Unknown no. of ovaries		
Prior hysterectomy	184,455	215
Incomplete menopause data	23,799	43
Ovarian surgery	12,022	17
Analytic cohort	396,114	799

* Except for nonmelanoma skin cancer.

Tubal ligation was classified as ever/never having had the procedure, age at the time of the procedure in years (<35, ≥35), years since the procedure (<20, ≥20), and calendar year of the procedure (<1960, 1960–1969, 1970 and beyond). Women were asked to give "age first used" and "number of years of use" for several specified birth control methods, including tubal ligation. If a woman gave a response for either age or years for a tubal ligation, she was classified as ever having had a tubal ligation; otherwise she was classified as never having had the procedure. If age at the time of tubal ligation was missing or invalid (2.0 percent of the women who had the procedure), it was defined as the difference between a woman's age at study entry and her years of use of the procedure. The number of years since tubal ligation was calculated by first subtracting a woman's age at the time of the procedure from her age at study entry and then allowing time between enrollment and the end of the follow-up to contribute as a time-varying variable. Reported years of use was used to calculate years since the procedure if age at the time of the procedure was missing or invalid. Calendar year of the procedure was analyzed as a surrogate for possible changes in methods or techniques of the procedure over time. All results presented are compared with the referent group of women with no prior tubal ligation.

The survival data were analyzed using Kaplan-Meier survival curves (27), log-rank tests (28), and Cox proportional hazards modeling (29), using the PHREG procedure in SAS (30). All multivariate Cox models included the following risk factors for ovarian cancer: age at baseline (continuous), race (white/other), age at menarche in years (≤12, 13, 14, ≥15),

body mass index in kg/m^2 (≤21, >21 to ≤27, >27), years of education (<12, ≥12), years of oral contraceptive use (never, ≤5, ≥6), marital status (ever, never), smoking status (ever, never), family history of breast cancer in a mother or sister (yes, no), family history of ovarian cancer in a mother or sister (yes, no), use of estrogen replacement therapy (ever, never), age periods stopped (pre- or perimenopausal, <45 years, ≥45 years), number of full-term pregnancies (0, 1–2, 3, ≥4), and number of miscarriages (0, 1, ≥2).

Effect modification between ever/never had a tubal ligation and all other covariates was assessed by entering multiplicative interaction terms into the multivariate Cox model one at a time. The statistical significance of the interaction terms was assessed at the $p = 0.05$ level using the likelihood ratio test (31). Tests of linear trend for time since tubal ligation, age at tubal ligation, and calendar year of tubal ligation were performed by entering a continuous variable for the exposure into the Cox models and assessing the significance of the term using the Wald chi-square test (32). Women with no prior tubal ligation were not included in the tests of trend (33).

In Cox models, ties in follow-up time were handled using the Breslow method (34). This technique was checked by comparing the results with models using exact tie-handling methods. The proportional hazards assumption was rigorously checked for each covariate in these models by scrutinizing log cumulative hazard curves plotted against follow-up time and by including multiplicative interaction terms between each covariate and a function of the follow-up time in individual models (35). Any variables that broke the proportional hazards assumption by either method were used as stratification factors in multivariate Cox models (age and race in these data) (35). To avoid losing observations by excluding women with missing data for any covariate, missing values for each covariate were assigned using imputation techniques (36, 37). Missing data for inherently continuous variables were assigned to the mean value using the available data, and missing data on categorical variables were assigned to the category with the largest percentage of data. Only one variable (estrogen replacement therapy) was missing for more than 5 percent of the women in the analytic cohort. Age- and race-adjusted models for each covariate were fit before and after assignment of missing data to compare differences in effects (36). In addition, multivariate models containing only women with known data for all variables ($n = 287,552$) were compared with the assigned data multivariate models ($n = 396,114$) to assess any differences in the models caused by assignment of the missing data (36).

RESULTS

A prior tubal ligation was reported by 8.1 percent of women in this analytic cohort. The median age at tubal ligation was 35 years (95 percent of tubal ligations were performed by age 45) and the median calendar year of procedure was 1973. In table 2, the age-adjusted percentages of women by tubal ligation status across categories of other potential ovarian cancer risk factors are presented. Tubal ligation status varied considerably across levels of some covariates. Women with a prior tubal ligation were much younger at interview (median age of 46 compared with 56), had higher educational attainment, and had a greater number of full-term pregnancies and miscarriages. Also, women with a tubal ligation were more likely to have ever married, to use or have used estrogen replacement therapy, and to have used oral contraceptives.

Using the Kaplan-Meier method (27), estimated freedom from ovarian cancer death among women who reported ever having had a tubal ligation was significantly higher than in those who had never had the procedure (log rank test p value = <0.001 (figure 1)). Results for the association of tubal ligation history and ovarian cancer mortality in age- and race-adjusted models and in multivariate models are shown in table 3. Women who had undergone tubal ligation had a greater than 30 percent lower risk of fatal ovarian cancer as compared with women who had never had this procedure (multivariate hazard ratio (HR) = 0.68, 95 percent confidence interval (CI) 0.45–1.03). When we analyzed the relation between years since the operation and fatal ovarian cancer, a more recent operation appeared to be more protective than one that occurred in the distant past. The risk for women having a tubal ligation in the past 19 years was 0.49 (95 percent CI 0.24–0.99); and for women having a tubal ligation 20 or more years ago, the risk was 0.80 (95 percent CI 0.48–1.34). We examined shorter length of time categories in years (<10, 10–19, 20–29, ≥30) to determine whether the protective effect observed for the <20-year category was consistent over the 20-year time period and to observe more closely any possible trends across years since tubal ligation. The results revealed a significant protective effect in the 10- to 19-year category (HR = 0.39, 95 percent CI 0.16–0.95) but failed to show a significant reduction in risk of ovarian cancer mortality in the other categories. Reduction of ovarian cancer risk among sterilized women did not vary by age at time of the procedure. In terms of calendar years, procedures performed most recently (in the 1970s) appeared most protective in this cohort (HR = 0.47, 95 percent CI 0.22–1.02). Given the small number of tubal ligation deaths, it was not possible in these data to separate the highly correlated

TABLE 2. Age-adjusted distribution of potential ovarian cancer risk factors and their association with tubal ligation status, Cancer Prevention Study II, United States, 1982–1991

Variable	Prior tubal ligation (n = 31,692) (%)	No prior tubal ligation (n = 364,422) (%)
Age (years)		
≤49	70.1	28.9
50–59	22.3	33.3
60–69	6.3	24.8
≥70	1.3	13.0
Race		
White	94.2	93.2
Black	5.8	6.8
Education		
<High school graduation	8.3	12.6
High school graduation	90.7	86.0
Missing	1.0	1.5
Marital status		
Ever married	99.3	94.0
Never married	0.2	5.5
Missing	0.5	0.5
Body mass index (kg/m^2)		
≤21	18.5	19.9
>21, ≤27	56.3	55.0
>27	23.8	22.9
Missing	1.5	2.2
Age at menarche (years)		
≤12	42.5	41.3
13	29.1	28.4
14	15.3	15.5
≥15	11.6	12.1
Missing	1.5	2.9
Oral contraceptive use		
Never	64.1	68.0
≤5 years of use	19.9	17.3
≥6 years of use	12.9	9.8
Missing years of use	1.3	1.2
Missing	1.8	3.7
Estrogen replacement therapy use		
Ever	27.8	19.7
Never	65.5	69.0
Missing	6.6	11.3
Age periods stopped		
Pre-/perimenopausal	40.1	38.2
<45 years	5.6	7.3
≥45 years	50.9	49.7
Missing	3.5	4.9
Smoking status		
Ever	45.4	42.6
Never	51.1	52.9
Missing	3.6	4.5
No. of full-term pregnancies		
0	1.8	12.9
1–2	26.6	35.7
3	26.6	21.1
≥4	40.7	23.8
Parous, no. unknown	3.4	3.4
Missing	1.0	3.1
No. of miscarriages		
0	66.9	71.3
1	20.1	16.0
≥2	9.9	7.7
Missing	3.2	5.0
Family history of ovarian cancer		
Yes	0.6	0.5
No	99.4	99.5
Family history of breast cancer		
Yes	7.6	7.1
No	92.4	92.9

effects of age at time of the procedure, years since the procedure, and calendar year of the procedure.

No statistically significant trends were observed for years since the procedure, age at time of the procedure, or calendar year of the procedure (see table 3). No effect modification between tubal ligation status was observed with any of the covariates. In addition, none of the exposure definitions of tubal ligation history broke the proportional hazards assumption.

It is unlikely that assignment of missing data in these analyses resulted in inappropriate models for assessing the relation of tubal ligation and ovarian cancer mortality. The parameter estimates and confidence intervals from the complete case model (n = 287,552) and the assigned data model were similar in both models for all covariates (parameter estimates were not different by more than 10 percent, and the 95 percent CI intervals for each covariate overlapped). The results for the tubal ligation exposure definitions using the complete case cohort (multivariate HR for ever/never tubal ligation = 0.67, 95 percent CI 0.42–1.05) were essentially the same as seen in the assigned data model. Use of exact methods for handling ties in follow-up time did not alter the results from those obtained using the Breslow technique.

DISCUSSION

In these data, a history of tubal ligation was strongly and inversely associated with ovarian cancer mortality. The reduction in risk was greatest during the 19-year period after the tubal ligation procedure. Risk did not vary by age at time of the procedure, and

procedures performed most recently (in the 1970s) were most strongly associated with a decreased risk of ovarian cancer.

Our findings are consistent with almost all past studies of tubal ligation and ovarian cancer incidence. Of 13 studies, 10 found a decrease in risk of ovarian cancer incidence for previous tubal sterilization patients. The magnitude of the risk ratio ranged from 0.2 to 0.9 (3–5, 16–21). Harlow et al. (3) found the association did not persist beyond 12 years after the procedure, and Irwin et al. (21) found that the protective effect remained up to 14 years. Whittemore et al. (20) reported that the reduced risk was greatest among women who had the surgery within the 10 years before the interview, but the effect was not significant when the procedure occurred more than 10 years before the interview. Shu et al. (19) reported no trend with increasing years since tubal sterilization, although the categories used were larger than those seen in other studies with the lowest group being ≤20 years since the procedure. The only prior prospective study (22) was unable to analyze years since the time of the tubal ligation procedure. In our analyses, a substantial and significant protective effect was observed for the 19-year period after tubal ligation.

Several biologic hypotheses have been advanced to explain the apparent protective effect of tubal ligation on ovarian cancer risk. First, risk of ovarian cancer is thought to increase with each ovulatory cycle due to repetitious cell division accompanying ovulation (38). After tubal ligation procedures, menstrual disorders are often reported (39–44), which may be a result of reduced ovarian blood flow (45). Ovarian blood supply is important in the regulation of the luteal phase (42); therefore a reduced blood supply to the ovaries after tubal sterilization could possibly result in inhibited ovulation. Although we were unable to address this issue specifically, tubal ligation did not act to reduce or vary age at natural menopause in these data. Second, tubal sterilization may act to reduce ovarian cancer risk by lowering estrogen and/or progesterone levels (46–49). Elevated estrogen or estrogen precursors and gonadotropins are likely involved in differentiation, proliferation, and eventual malignant transformation of entrapped epithelial cells (50). Third, tubal sterilization methods cause occlusion of the fallopian tube, therefore blocking a potential pathway of exposure for possible carcinogens (51). No information was collected in this study on possible carcinogens (such as perineal talc or asbestos exposure), which would be needed to address this question adequately. Finally, tubal ligation may eliminate or reduce the concentration of uterine growth factors that reach the ovaries through uteroovarian circulation. These

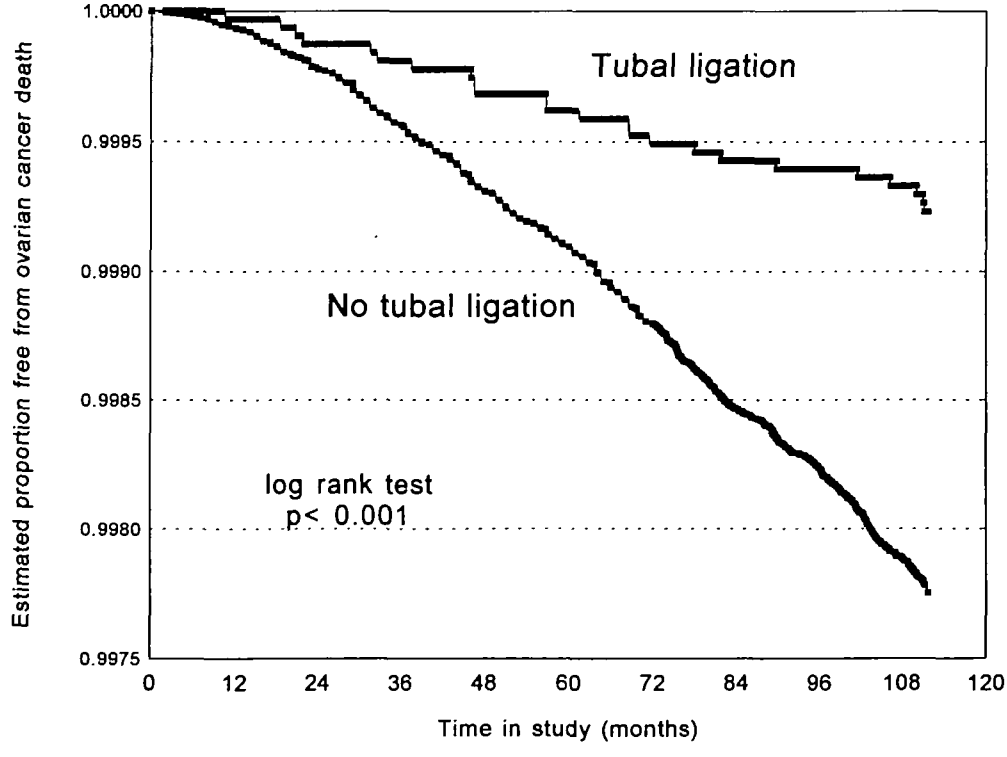

FIGURE 1. Estimated freedom from ovarian cancer death for women who had a prior tubal ligation versus women without a prior tubal ligation, Cancer Prevention Study II, United States, 1982–1991.

TABLE 3. Ovarian cancer mortality by tubal ligation history, Cancer Prevention Study II, United States, 1982–1991

Tubal ligation history	Ovarian cancer deaths	Person-years	Age and race adjusted		Multivariate*	
			HR†	95% CI†	HR	95% CI
Ever had a tubal ligation						
Yes	24	291,515	0.64	0.42–0.96	0.68	0.45–1.03
No	775	3,269,123	1.00		1.00	
Years since tubal ligation procedure‡						
<20	8	214,553	0.41	0.20–0.84	0.49	0.24–0.99
≥20	15	74,557	0.82	0.49–1.37	0.80	0.48–1.34
Never had	775	3,269,123	1.00		1.00	
<9	3	77,210	0.68	0.21–2.16	0.85	0.26–3.75
10–19	5	137,343	0.34	0.14–0.82	0.39	0.16–0.95
20–29	8	44,496	0.93	0.46–1.88	0.90	0.44–1.83
≥30	7	30,061	0.72	0.34–1.52	0.71	0.34–1.50
Never had	775	3,269,123	1.00		1.00	
p (trend)				0.540		0.835
Age at time of tubal ligation procedure‡ (years)						
<35	11	128,699	0.71	0.39–1.30	0.71	0.34–1.30
≥35	12	160,411	0.55	0.31–0.98	0.62	0.34–1.10
Never had	775	3,269,123	1.00		1.00	
p (trend)				0.411		0.651
Calendar year of procedure‡						
<1960	8	38,647	0.73	0.37–1.47	0.70	0.35–1.41
1960–1969	8	52,179	0.91	0.45–1.84	0.90	0.44–1.83
1970 and later	7	198,284	0.39	0.18–0.83	0.47	0.22–1.02
Never had	775	3,269,123	1.00		1.00	
p (trend)				0.390		0.791

* Multivariate results adjusted for age at interview, race, body mass index, education level, family history of ovarian cancer, family history of breast cancer, number of full-term pregnancies, marital status, age at menarche, oral contraceptive use, estrogen replacement therapy, age periods stopped, number of miscarriages, and smoking status.
† HR, hazard ratio; CI, confidence interval.
‡ Excludes one event and 2,405 person-years with inconsistent or invalid data values.

growth factors are possibly involved in ovarian cancer pathogenesis (52).

Our results could also be consistent with an effect of screening. Women undergoing tubal ligation may have had their ovaries screened at the time of the procedure, and those women with malignant or suspicious-appearing ovaries at the time of tubal ligation may have had them removed. Therefore these women would have been excluded from the present study. This could have created a bias toward more healthy ovaries among the tubal ligation patients included in this study. Furthermore, physicians may watch patients more carefully for symptoms of ovarian cancer if they see a problem with an ovary at the time of the procedure. This could result in earlier detection of cancer and better survival. If screening explains the results, one might expect the protective effect of tubal ligation to wane with increasing time since the procedure. Although this is suggested in these data, there was no significant trend associated with increasing years since the procedure. Also, a protective effect was still seen (HR = 0.71) in the group of women having had a tubal ligation 30 or more years in the past.

Our study is limited by several factors including reliance on mortality rather than incidence data, dependence on a single self-administered questionnaire, incomplete data on the presence of ovaries, and inability to assess the method of tubal sterilization procedure. Because these data rely on mortality, factors that influence survival cannot be differentiated from those that influence incidence of ovarian cancer. However, because the overall 5-year survival rate from ovarian cancer is only 44 percent (2), mortality is not greatly different from incidence in the study of this cancer. Moreover, the results from this study are consistent with those found in studies of incident cases.

The data were collected at only one point in time (1982), introducing the possibility of misclassification

bias. However, it is unlikely that many women had a tubal ligation after 1982 given that 85 percent of the cohort were aged 45 years or older at that time. Self-reports of tubal sterilizations could also have caused misclassification bias. Although there have been no studies of the validity of self-reported tubal ligations, there is evidence to show that self-reported histories of hysterectomy and ovarian surgery agree well with medical records (22, 53–58).

No data were collected from participants regarding the specific method of tubal ligation performed. The surgical methods have been changing over time, and it has been noted that different methods of sterilization may lead to varying levels of menstrual disturbance, possibly caused by the varying degrees of tissue destruction of each method (40, 43, 46). In the 1960s and 1970s, the most common method was the Pomeroy procedure (usually a postpartum procedure). In the early 1970s, the electrocoagulation method was becoming increasingly popular; and by the late 1970s, it had become the most common method (59). Electric methods, the Silastic band technique, and the spring clip were introduced in the mid- to late 1970s to decrease the risk of bowel burns caused by coagulation methods using heat cauterization (59). The coagulation methods destroy the greatest amount of tissue; the Pomeroy technique, thermal techniques, and methods involving bands destroy less than the Pomeroy technique; and the newer methods using clips involve the least tissue destruction (59). It is possible that different methods of tubal sterilization may have varying effects on ovarian cancer risk. If menstrual disturbances following tubal ligation are a result of inhibited ovulation (caused by tissue destruction), then it is important to be able to identify which procedures are the most likely to cause this result. In our data, the median calendar year was 1973 for tubal ligation, and 90 percent of women had their tubal sterilization by 1980; therefore it is likely that most women in our cohort underwent sterilization by the Pomeroy technique.

The inability to assess directly whether a woman had ovaries was a limitation in this study. It is probable that in excluding any woman who reported a hysterectomy or ovarian surgery, some women who were at risk of ovarian cancer were excluded. This reduced the sample size; but because of the prospective design of the study, the validity of the results within the final analytic cohort were not affected. Also, because we could not identify women who had had a hysterectomy but had retained their ovaries, it was not possible to study the effects of hysterectomy on fatal ovarian cancer in this cohort. Most previous epidemiologic studies of the effects of tubal ligation have also looked at hysterectomy status. It is believed that they may have similar biologic effects on ovarian cancer risk. Finally, a woman could have had both ovaries removed during the follow-up period and have remained in the study even though she was no longer at risk for ovarian cancer. This would bias our estimates of risk downward if subsequent ovary removal were positively related to a prior tubal ligation. We suspect this did not occur in our data because women with a tubal ligation were less likely to have a subsequent hysterectomy than women without a prior tubal ligation (30.3 vs. 32.3 percent, respectively (age-adjusted)).

The strengths of this study include its prospective design, large size, information on numerous risk factors, small losses to follow-up, and completeness of death information. Prospective studies are less susceptible to selection or recall bias than case-control studies. This study is only the second prospective cohort study on this topic. The large size of the study and the fact that data were collected on multiple risk factors allowed for simultaneous examination and control of all known and potential risk factors for ovarian cancer.

More research is needed to study the association between specific tubal sterilization procedures and ovarian cancer risk. Differences in the risk ratios found in previous studies may be due to different proportions of procedure methods within study populations. Also, more research on time since the tubal ligation procedure is necessary to assess the possible impact of screening on the observed protective effect. As of 1990, tubal ligation was the most common choice of contraception among US women (15); understanding the potential impact of such a widespread procedure on subsequent ovarian cancer risk is an important public health issue.

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