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Tubal Sterilization and Risk of Cancer of the Endometrium

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Objective. **Surgical sterilization is a common method of contraception among U.S. women. Most surgical sterilizations are tubal ligations, but few studies have investigated their potential impact on endometrial cancer risk.**

Methods. **A case–control study included 405 women diagnosed with endometrial cancer at 5 U.S. medical centers between 1987 and 1990 and 297 age-, race-, and location-matched controls who were identified by random-digit-dialing. Questionnaires ascertained information on tubal sterilization, and logistic regression models generated odds ratios (ORs) to estimate relative risk.**

Results. **The OR and 95% confidence interval for tubal sterilization, which was reported by 47 cases and 40 controls, was 0.9 (0.6–1.4) before adjustment and 1.4 (0.8–2.4) after adjustment for age, parity, and oral contraceptive use. Age at surgery, years since surgery, or calendar years of surgery were not associated with endometrial cancer, and associations did not vary according to parity or stage of disease at diagnosis.**

Conclusions. **Tubal sterilization is not substantially associated with endometrial cancer.**

Key Words: **endometrial cancer; surgical sterilization; tubal sterilization.**

INTRODUCTION

Surgical sterilization is a popular method of contraception among U.S. women [1] that also reduces risk of subsequent ovarian cancer [2] through hypothesized mechanisms of blocking access of vaginal contaminants to the ovaries [3] or modifying ovarian hormone levels [4]. The procedure's influence on two other hormone-sensitive female cancers—breast and endometrium—is less clear. Tubal sterilization may interrupt blood flow to the ovaries, and thus alter circulating levels of reproductive hormones in the breast or uterus. Breast cancer studies show increased [5], decreased [6], and unchanged risks [7], while endometrial cancer studies also reveal modestly increased [8] and decreased [9] risks. The two studies of endometrial cancer included primarily younger women [8, 9], in whom tubal sterilization is more common but for whom the absolute risk of endometrial cancer is low [10]. We therefore investigated this issue in a case–control study that included larger numbers of older women.

MATERIAL AND METHODS

This study, previously described [11], included 20- to 74-year-old women who were diagnosed with pathologically confirmed epithelial endometrial cancer between June 1987 and May 1990 at five U.S. medical centers (Chicago, IL; Hershey, PA; Irvine and Long Beach, CA; Minneapolis, MN; and Winston-Salem, NC). Random digit dialing identified age-, race-, and location-matched (i.e., in the same residential telephone exchange as the index case) controls for younger (<65 years) cases, while random selection from Health Care Financing Administration files identified matched controls for older (≥ 65) cases. Home interviews were obtained from 434 of 498 of eligible cases (87.1%) and 313 of 477 of eligible controls (65.6%). This analysis includes only the 405 epithelial cancer cases and their 297 matched controls.

Interviews ascertained whether women had ever had a female sterilization operation and the year of that procedure. Unconditional logistic regression generated odds ratios (ORs) to estimate relative risk (RR), with 95% confidence intervals (CI). Regression models included adjustment for continuous age, parity (0, 1, 2, 3, 4, or ≥ 5), and duration of oral contraceptive use (no use, <5 years, or ≥ 5 years). Although smoking, weight, and menopausal hormones were associated with endometrial cancer [12, 13], adjustment for these factors did not change any of the parameter estimates for tubal sterilization. This study had 80% power to detect an association of 2 or higher.

RESULTS

Forty-seven cases and 40 controls reported a tubal sterilization, which was not associated with endometrial cancer when adjusted for age only (OR = 0.9, 95% CI = 0.6–1.4; Table 1). Additional adjustment for parity and years of oral contracep-

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TABLE 1
Odds Ratios for Tubal Sterilization

	Cases *N*[a]	Controls *N*	OR[b]	OR[c]	95% CI
Tubal sterilization					
No	357	257	1.0	1.0	Reference
Yes	47	40	0.9	1.4	0.8–2.3
Age at surgery (years)					
<30	16	14	0.9	1.1	0.5–2.5
30–39	20	20	0.8	1.3	0.7–2.6
≥40	11	6	1.4	2.2	0.8–6.2
Time since surgery (years)					
<10	6	7	0.7	1.0	0.3–3.3
10–19	21	22	0.8	1.4	0.7–2.9
≥20	20	11	1.3	1.4	0.7–3.2
Date of surgery					
Before 1970	23	12	1.4	1.6	0.8–3.4
1970–1975	13	17	0.6	1.1	0.5–2.4
1976 or later	11	11	0.8	1.4	0.6–3.6

[a] Tubal sterilization status was unknown for one case.
[b] Adjusted for age only.
[c] Adjusted for age, parity, and years of oral contraceptive use.

tive use generated a weak positive association (OR = 1.4, 95% CI = 0.8–2.3). Neither time since surgery nor calendar year of surgery were associated with endometrial cancer. Surgery after age 40 was positively associated with endometrial cancer (OR = 2.2, 95% CI = 0.8–6.2), but this was based on only six exposed controls.

Restriction to cases and controls who were older than 55 had minimal impact on the overall OR (OR = 1.6, 95% CI = 0.7–3.4) or the ORs for age at, years since, or calendar year of surgery. Similar associations with tubal sterilization emerged for endometrial cancers diagnosed at early stages (OR = 1.5, 95% CI = 0.7–3.2) and late stages (OR = 1.3, 95% CI = 0.8–2.2).

Excluding nulliparous women (90 cases and 28 controls, including one who reported a tubal sterilization) did not alter the association for tubal sterilization (OR = 1.2, 95% CI = 0.8–2.0), and associations did not differ according to parity (Table 2). Table 2 shows weight stratum-specific ORs adjusted only for age and parity; models with years of oral contraceptive use were no different. ORs did not differ according to smoking status or use of menopausal estrogens. The majority of women who reported a tubal sterilization had never used menopausal hormones.

DISCUSSION

These results indicate that tubal sterilization introduces little change in endometrial cancer risk. As seen in other investigations [8, 9], parity confounded the initial negative associations, which disappeared after adjustment. Castellsagué *et al.* found a nonsignificant 13% decreased risk among 437 cases and 3200 controls who were under the age of 54 [8], Rosenblatt and Thomas reported a nonsignificant 26% increased risk among 136 parous cases and 1218 parous controls from eight centers in six countries [9], and Kelsey *et al.* observed a nonsignificant 50% decreased risk associated with tubal sterilization in a U.S. study of 167 cases and 903 controls [14]. Each study adjusted for appropriate confounders. Adding ours to this group balances the numbers of positive and negative studies and fortifies the Rosenblatt and Thomas conclusion [9] that chance accounts for the apparent association. Our data also suggest that older women who have had a surgical sterilization are at no greater or lesser risk than their younger peers. However, the suggestive associations with tubal sterilization in heavier women may be of interest because of the reported interactions between weight and established endometrial cancer risk factors, such as estrogen replacement therapy, oral contraceptives, and smoking [13, 15].

Numerous studies have attempted to characterize biologic changes and clinical outcomes associated with tubal sterilization. Endometrial cancer reflects an excess balance of estrogens to progestogens [16], and therefore the reports of decreased progesterone levels after tubal sterilization [17, 18] imply that lower progesterone levels after surgical sterilization might increase risk. Other studies, however, reported higher progesterone or lower estrogen levels following tubal sterilization [19], which would be expected to decrease risk. These conflicting results may arise from methodologic differences, or they could suggest that tubal sterilization has diverse effects in

TABLE 2
ORs for Tubal Sterilization, with Potential Effect Modification by Parity and Weight

	Cases		Controls			
Tubal sterilization?:	Yes	No	Yes	No	OR[a]	95% CI
Never pregnant	0	90	1	27		
Parous women only	47	267	39	230	1.2	0.8–2.0
No. pregnancies						
1	1	65	2	29	0.3	0.0–3.0
2	12	73	10	77	1.6	0.6–4.2
3	12	59	10	47	1.2	0.5–3.2
4	10	39	4	31	2.1	0.6–7.3
≥5	12	31	13	46	1.3	0.5–3.7
Weight[b]					OR[c]	
<125 lbs	7	55	8	48	0.7	0.2–2.6
125–149 lbs	7	95	13	85	0.8	0.3–2.3
150–174 lbs	6	56	13	65	1.3	0.4–4.2
175–199 lbs	8	48	4	33	1.9	0.5–7.9
≥200 lbs	18	99	2	25	2.8	0.6–14.2

[a] Adjusted for age only.
[b] Weight was unknown for five cases and one control; BMI was unknown for five cases and five controls.
[c] Also adjusted for parity; additional adjustment for years of oral contraceptive use produced similar results.

different patients. They also raise the question of whether hormone levels after sterilization change sufficiently to influence endometrial carcinogenesis.

Recall bias and misreporting of tubal sterilization are concerns, but women appear to accurately report this procedure [20]. Women who undergo tubal sterilization may experience heightened surveillance and detection at or after surgery, but the absence of stronger associations among subjects with shorter intervals since surgery or among cases diagnosed at earlier stages implies that such a bias did not dramatically impact our data. Our questionnaire lacked procedural details about the self-reported surgeries, and therefore whether different surgical techniques introduce particular risk or confer differential benefit remains unknown. Year of surgery (a proxy for techniques that have changed over time) indicated no particular association, but an exploration of outcomes associated with different surgeries may be warranted. The prevalence of tubal sterilization increased dramatically in the past 30 years, but appears to have recently plateaued [1]. To fully understand potential outcomes associated with this procedure, future investigations should include larger numbers of exposed women and specific details about the procedures used and reason for tubal sterilization.

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