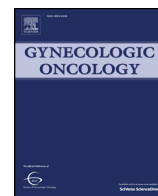




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## Q3 Effect of tubal sterilization technique on risk of serous ovarian and primary peritoneal carcinoma ☆,☆☆

Q4 Collette R. Lessard-Anderson<sup>a,1</sup>, Kathryn S. Handlogten<sup>b</sup>, Rochelle J. Molitor<sup>b</sup>, Sean C. Dowdy<sup>a</sup>, William A. Cliby<sup>a</sup>, Amy L. Weaver<sup>c</sup>, Jennifer St. Sauver<sup>d</sup>, Jamie N. Bakkum-Gamez<sup>a,\*</sup>

<sup>a</sup> Division of Gynecologic Surgery, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States

<sup>b</sup> Mayo Medical School, Mayo Clinic College of Medicine, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States

<sup>c</sup> Division of Biomedical Statistics and Informatics, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States

<sup>d</sup> Division of Epidemiology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States

### 10 HIGHLIGHTS

- Tubal sterilization reduces the risk of serous epithelial ovarian (EOC) and peritoneal cancer (PPC) by 41%.
- Excisional tubal sterilization reduces the risk of serous EOC and PPC by 65%.
- Prospective studies on the impact of salpingectomy on serous EOC and PPC development are needed.

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### ABSTRACT

**Objective.** To determine the effect of excisional tubal sterilization on subsequent development of serous epithelial ovarian cancer (EOC) or primary peritoneal cancer (PPC).

**Methods.** We performed a population-based, nested case–control study using the Rochester Epidemiology Project. We identified all patients with a diagnosis of serous EOC or PPC from 1966 through 2009. Each case was age-matched to 2 controls without either diagnosis. Odds ratios (ORs) and corresponding 95% CIs were estimated from conditional logistic regression models. Models were adjusted for prior hysterectomy, prior salpingo-oophorectomy, oral contraceptive use, endometriosis, infertility, gravidity, and parity.

**Results.** In total, we identified 194 cases of serous EOC and PPC during the study period and matched them with 388 controls (mean [SD] age, 61.4 [15.2] years). Fourteen cases (7.2%) and 46 controls (11.9%) had undergone tubal sterilization. Adjusted risk of serous EOC or PPC was slightly lower after any tubal sterilization (OR, 0.59 [95% CI, 0.29–1.17];  $P = .13$ ). The rate of excisional tubal sterilization was lower in cases than controls (2.6% vs 6.4%). Adjusted risk of serous EOC and PPC was decreased by 64% after excisional tubal sterilization (OR, 0.36 [95% CI, 0.13–1.02];  $P = .054$ ) compared with those without sterilization or with nonexcisional tubal sterilization.

**Conclusions.** We present a population-based investigation of the effects of excisional tubal sterilization on the risk of serous EOC and PPC. Excisional methods may confer greater risk reduction than other sterilization methods.

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**Abbreviations:** EOC, epithelial ovarian cancer; OR, odds ratio; PPC, primary peritoneal cancer; REP, Rochester Epidemiology Project; RRSO, risk-reducing salpingo-oophorectomy.

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\* Corresponding author. Fax: +1 507 266 9300.

E-mail addresses: [collettelessard@gmail.com](mailto:collettelessard@gmail.com) (C.R. Lessard-Anderson), [handlogten.kathryn@mayo.edu](mailto:handlogten.kathryn@mayo.edu) (K.S. Handlogten), [rochelle.molitor@gmail.com](mailto:rochelle.molitor@gmail.com) (R.J. Molitor), [dowdy.sean@mayo.edu](mailto:dowdy.sean@mayo.edu) (S.C. Dowdy), [cliby.william@mayo.edu](mailto:cliby.william@mayo.edu) (W.A. Cliby), [weaver@mayo.edu](mailto:weaver@mayo.edu) (A.L. Weaver), [stsauver.jennifer@mayo.edu](mailto:stsauver.jennifer@mayo.edu) (J.S. Sauver), [bakkum.jamie@mayo.edu](mailto:bakkum.jamie@mayo.edu) (J.N. Bakkum-Gamez).

<sup>1</sup> Present address: Altru Health System, Department of Obstetrics & Gynecology, 1000 South Columbia Road, Grand Forks, ND 58201, United States.

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## Introduction

Epithelial ovarian cancer (EOC) will be newly diagnosed in approximately 21,980 women in 2014 and account for 14,270 deaths, making it the most lethal gynecologic cancer in the United States [1]. Serous EOC accounts for approximately 70% to 75% of EOC subtypes and has a high propensity to metastasize beyond the reproductive tract [2,3]. In a recent report, 67% of ovarian cancers among *BRCA1* and *BRCA2* mutation carriers were of serous histology [4]. At least 20% of ovarian carcinomas appear to be hereditary [5], and, in high-risk patients, risk-reducing salpingo-oophorectomy (RRSO) is recommended [6]. However, most women with EOC have no identifiable risk factors or precursor lesions [7], and few effective screening tools exist for early diagnosis [7].

Bilateral tubal sterilization has been associated with a decreased risk of sporadic and hereditary EOC [8,9]. Risk reduction theories have suggested that tubal sterilization decreases ovarian blood supply or interrupts the pathway for environmental carcinogens from the lower genital tract to reach the ovaries [8,10,11]. However, the exact mechanism of risk reduction remains unclear, and more recent literature has suggested that the fallopian tube may be a source of serous EOC and primary peritoneal cancer (PPC). Within the *BRCA1/2* population, a substantial proportion of clinically occult serous malignancies (2%–17%) have been identified in the fallopian tube during RRSO [12–15] and histopathologic assessment suggests that the fimbriated portion of the tube is the most common site of origin [16]. In addition, prospective assessment of the “section and extensively examine the fimbriae” (SEE-FIM) protocol has identified up to 75% of pelvic serous carcinomas to have endosalpinx involvement. Over 70% of these cases also have tubal intraepithelial carcinoma (TIC) and more than 90% of TICs are identified in the distal fallopian tubes and involve the fimbriae [17]. Kim and colleagues provided further evidence of the tube as the source of EOC in their *Dicer-Pten* double knock out (DKO) mouse model. In *Dicer-Pten* DKO mice that underwent bilateral oophorectomy, with fallopian tubes remaining intact, high grade serous cancers developed. In contrast, among mice that underwent bilateral salpingectomy, with ovaries remaining intact, high grade serous cancers did not develop [2].

Given the increasing evidence indicating the fallopian tube as a primary site of serous EOC carcinogenesis, we sought to determine whether excisional tubal sterilization techniques account for the observed decrease in risk of serous EOC and PPC development among women who have undergone tubal sterilization.

## Materials and methods

A population-based, case-control study was designed using the Rochester Epidemiology Project (REP). The REP is a research infrastructure that links the medical records of virtually all persons who have resided in Olmsted County, Minnesota, between January 1, 1966, and the present. As of 2010, the REP contained information on 502,820 persons and their respective medical records from 65 different health care facilities in Olmsted County, including Mayo Clinic, Olmsted Medical Center, and providers in private practice. Most residents of Olmsted County receive their medical care from only a few practices in southeastern Minnesota, making effective population-based research feasible. Most patients receive cancer care at Mayo Clinic, which has a common medical records system of both inpatient and outpatient data, linking its 2 affiliated hospitals (Saint Marys and Rochester Methodist). Patients provide their consent to be part of the REP. The study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center, both in Rochester, Minnesota.

Using the REP and the Mayo Clinic Cancer Registry, we searched for all cases of serous EOC and PPC between January 1, 1966, and December 31, 2009. Cases were selected by review of pathology reports by one investigator (C.R.L.-A.). Patients were excluded if they did not have EOC or

PPC or did not reside in Olmsted County at the time of diagnosis, if they had fallopian tube carcinoma, or if the cancer was of non-serous histology. Each case was matched by age within 2 years to 2 women from the general population residing in Olmsted County and free of EOC or PPC in the index year (i.e., year of EOC or PPC diagnosis for the matched case). Data abstracted from the medical record for all patients included date of birth, race, body mass index, personal and family history of cancer, personal history of abdominal radiation or chemotherapy, smoking history, reproductive history (gravidity and parity; breastfeeding; ages of menarche and menopause; perimenopausal symptoms; oral contraceptive use and duration; other contraceptive use; hormone therapy use and duration; Papanicolaou test results; diagnoses of pelvic inflammatory disease, endometriosis, and infertility), *BRCA* status if known, gynecologic surgery history (prior hysterectomy, tubal sterilization and type, unilateral or bilateral salpingo-oophorectomy), and date of last follow-up. For case patients, information on primary tumor site, histology, stage, and grade was also abstracted.

Original operative and pathology reports were reviewed to determine the type of tubal sterilization performed. Excisional tubal sterilization was considered to be complete salpingectomy, distal fimbriectomy, or partial salpingectomy (i.e., Pomeroy or Parkland methods). All other methods of tubal sterilization were considered nonexcisional, unless not specified. Nonexcisional sterilization was defined as the use of monopolar coagulation, bipolar coagulation, clips, or rings. Among patients with clear documentation in their surgical history of having a prior tubal sterilization, but for whom the operative and pathology reports were not available to review, the tubal sterilization type was considered “not specified.”

The aim of the study was to determine whether the proportion of any type of tubal sterilization (primary study objective) or excisional tubal sterilization (secondary study objective) was lower among women with (cases) than without (controls) serous EOC and PPC. Demographic and baseline characteristics were compared between the cases and controls using the  $\chi^2$  test or Fisher exact test for categorical variables, the 2-sample *t* test for age, and the Wilcoxon rank sum test for all other continuous measures. The association between development of serous EOC/PPC and tubal sterilization was evaluated by fitting conditional logistic regression models. Associations were summarized using odds ratios (ORs) with corresponding 95% CIs. We adjusted for potential confounders, including prior hysterectomy, prior salpingo-oophorectomy, oral contraceptive use (yes vs no vs unknown), endometriosis, infertility, gravidity (0 vs  $\geq 1$ ), and parity (0 vs  $\geq 1$ ). All calculated *P* values were 2-sided, and *P* < .05 was considered statistically significant. The SAS software package version 9.2 (SAS Institute Inc.) was used for all statistical analyses. Rates of tubal sterilization during the study period were estimated using historical and contemporary reports [18,19]. On the basis of prior publications, we expected 240 cases of serous EOC and PPC among Olmsted County women during the 44-year study period [20,21]. Based on a sample size of 240 cases and 480 matched controls, we anticipated 80% power to detect a difference in tubal sterilization rates of 27% (controls) [18,19] vs 17.6% (cases), which corresponds to an OR of 0.58. This calculation was based on a 2-sided  $\chi^2$  test with a type I error rate of .05 and assuming no correlation between the exposure of matched cases and controls.

## Results

### Demographics and cancer characteristics

During the study period, 194 cases of serous EOC and PPC were diagnosed in women residing in Olmsted County; these cases were matched with 388 controls. Mean (SD) age was 61.4 (15.2) years in both groups (Table 1). Mean body mass index was similar in cases and controls (27.9 [7.0] vs 27.0 [5.8] kg/m<sup>2</sup>), and most patients were white (83.5% vs 87.6%). The rate of prior breastfeeding was the same for both groups

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