Published in final edited form as:
Gynecol Oncol. 2014 December ; 135(3): 423–427. doi:10.1016/j.ygyno.2014.10.005.

Effect of Tubal Sterilization Technique on Risk of Serous Ovarian and Primary Peritoneal Carcinoma

Collette R. LESSARD-ANDERSON, MD[a,e], **Kathryn S. HANDLOGTEN, BS**[b], **Rochelle J. MOLITOR, BA**[b], **Sean C. DOWDY, MD**[a], **William A. CLIBY, MD**[a], **Amy L. WEAVER, MS**[c], **Jennifer ST. SAUVER, PhD**[d], and **Jamie N. BAKKUM-GAMEZ, MD**[a]

Collette R. LESSARD-ANDERSON: collettelessard@gmail.com; Kathryn S. HANDLOGTEN: handlogten.kathryn@mayo.edu; Rochelle J. MOLITOR: rochelle.molitor@gmail.com; Sean C. DOWDY: dowdy.sean@mayo.edu; William A. CLIBY: cliby.william@mayo.edu; Amy L. WEAVER: weaver@mayo.edu; Jennifer ST. SAUVER: stsauver.jennifer@mayo.edu; Jamie N. BAKKUM-GAMEZ: bakkum.jamie@mayo.edu

[a]Division of Gynecologic Surgery, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States

[b]Mayo Medical School, Mayo Clinic College of Medicine, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States

[c]Division of Biomedical Statistics and Informatics, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States

[d]Division of Epidemiology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, United States

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.

Corresponding Author: Jamie N. Bakkum-Gamez, MD, Division of Gynecologic Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905; bakkum.jamie@mayo.edu; Telephone number: (507) 538-5867; Fax number: (507) 266-9300.
[e]Present Address: Altru Health System, Department of Obstetrics & Gynecology, 1000 South Columbia Road, Grand Forks, ND 58201
Reprints: Jamie N. Bakkum-Gamez, MD, Division of Gynecologic Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (bakkum.jamie@mayo.edu).

The authors report no conflict of interest.

Presented at the 2013 Society of Gynecologic Oncology Annual Meeting on Women's Cancer, Los Angeles, California, March 9–12, 2013.

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.

Keywords

fimbriectomy; salpingectomy; serous ovarian cancer; serous primary peritoneal cancer; tubal sterilization

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 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 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 (ie, 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 (ie, Pomeroy or Parkland methods). All other methods of tubal sterilization were considered nonexcisional, unless not

specified. Non-excisional 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 χ^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 ≥1), and parity (0 vs ≥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 χ^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^2), and most patients were white (83.5% vs 87.6%). The rate of prior breastfeeding was the same for both groups (13.9%), but breastfeeding data were available for less than half the patients. The mean age of menarche was 13.1 years in both cases and controls. Among case patients, 75.3% had reached menopause at the index date compared with 77.1% in control patients. According to the medical records, only 5 patients (4 cases, 1 control) were tested for *BRCA* mutations; 2 of the case patients were positive for mutations, and the control patient was negative.

Cancer histology, stage, and grade were documented for the 194 cases (Table 2). Per the search criteria, all cases had serous histology, with 24.2% having mixed histology with a serous component, and most were EOC (90.7%). The majority of patients had advanced-

stage disease at diagnosis (61.3% stage III; 7.7% stage IV). Serous borderline tumors accounted for 13.4% of the cases.

Tubal Sterilization Incidence, Techniques, and Development of Serous EOC or PPC

The rate of any type of tubal sterilization before the index date was 7.2% (14/194) among cases and 11.9% (46/388) among controls, and the rates of excisional tubal sterilization were 2.6% and 6.4%, respectively (Table 3). Among those who had tubal sterilization, the procedure was excisional in 25 of 46 controls (55%) and 5 of 14 cases (36%). Notably, 13% (6/46) of controls undergoing sterilization had a complete salpingectomy, compared with 0% of cases. Unipolar coagulation and bipolar coagulation were the only 2 methods of non-excisional tubal sterilization utilized in this study.

In unadjusted, matched conditional logistic regression analyses, having any prior tubal sterilization procedure before the index date conferred a 46% decreased risk of serous EOC and PPC (OR, 0.54 [95% CI, 0.28–1.04]; *P*=.07), and excisional tubal sterilization alone (vs no sterilization and nonexcisional techniques combined) conferred a 63% decreased risk of development of serous EOC and PPC (OR 0.37 [95% CI, 0.14–1.00]; *P*=.051). However, control patients had significantly more pregnancies and live births, a higher rate of oral contraceptive pill use, and higher likelihood of prior hysterectomy and unilateral or bilateral salpingo-oophorectomy than case patients (Table 1). These are well-recognized reproductive factors associated with a decreased risk of ovarian cancer.

Because of the significant differences in reproductive and gynecologic surgery histories between cases and controls, we adjusted for these potential confounders in multivariable conditional logistic regression models. In the adjusted analyses, which accounted for prior hysterectomy, prior salpingo-oophorectomy, oral contraceptive use (yes vs no vs unknown), endometriosis, infertility, gravidity (0 vs ≥1), and parity (0 vs ≥1), having any prior tubal sterilization was associated with a nonstatistically significant 41% decreased risk of serous EOC and PPC (OR, 0.59 [95% CI, 0.29–1.17]; *P*=.13). There appeared to be greater risk reduction associated with excisional tubal sterilization techniques (vs no sterilization and nonexcisional techniques combined) of 64% (OR, 0.36 [95% CI, 0.13–1.02]; *P*=.054). Although this finding was not statistically significant, there was an additional 23% risk reduction associated with excisional techniques.

Because tubal sterilization may not affect borderline tumor development [22], we further excluded the 26 cases with serous borderline tumors and their matched controls. In these analyses, the rate of any tubal sterilization before the index date was 7.7% (13/168) among cases and 11.6% (39/336) among controls, and the rates of excisional tubal sterilization were 3.0% and 6.6%, respectively. In the adjusted conditional multivariable logistic regression analyses, having any prior tubal sterilization was associated with a 38% decrease in the risk of serous EOC and PPC (adjusted OR, 0.62 [95% CI, 0.30–1.28]; *P*=.20). The risk reduction associated with an excisional tubal sterilization technique (vs no sterilization and nonexcisional techniques combined) was 62% (adjusted OR, 0.38 [95% CI, 0.14–1.10]; *P*=.07).

Because the proportion of the tube removed during a partial salpingectomy is variable, and is unlikely to remove much, if any, of the fimbria, we performed additional analyses excluding partial salpingectomy as an excisional sterilization technique. In this analysis, we only considered distal fimbriectomy and complete salpingectomy as excisional techniques, leaving only 1 of 194 cases (0.5%) and 9 of 388 controls (2.3%) with an excisional tubal sterilization technique. In this adjusted analysis, the decrease in risk associated with complete salpingectomy or distal fimbriectomy (vs no sterilization, the previously defined nonexcisional techniques, and partial salpingectomy combined) was 78% (OR, 0.22 [95% CI, 0.03–1.87]; *P*=.17). When serous borderline tumors were removed from this analysis, the results were similar, with a 77% decrease in risk (OR, 0.23 [95% CI, 0.03–2.02]; *P*=.19).

Discussion

Existing epidemiologic literature on the effect of reproductive factors on EOC development have described 34% to 67% decreases in risk after tubal sterilization [8–11, 23–25]. However, the specific tubal sterilization techniques and their impact on EOC development have not been previously detailed. Given the increasing evidence that a large proportion of serous cancers arise from the distal fallopian tube [26–28], sterilization procedures that remove a portion or all of the tube may account for the EOC risk reduction previously reported to be associated with tubal sterilization.

In our present study, excisional tubal sterilization techniques conferred a greater decrease in the risk of serous EOC and PPC (64%) than did all tubal sterilization techniques combined (41%), even when controlling for other factors previously shown to be associated with decreased risk of EOC. The decrease in risk was even greater when only distal fimbriectomy and complete salpingectomy were considered (78%). This suggests that excision of the fimbriae may confer the greatest serous EOC and PPC risk reduction from tubal sterilization in the general female population.

Strengths of this study include the use of a population-based cohort over a 44-year period. The results are applicable to the general female population, and the time period covered many changes in tubal sterilization techniques. Additionally, we controlled for multiple potential reproductive and surgical confounders. Although it was not possible to pre-select controls matched on reproductive history, such as parity and OCP use, these factors were controlled for in the analysis. Serous borderline tumors were included in the primary analyses given the potential for these cases, as we relied on pathology reports for diagnoses, to truly represent invasive serous cancers. Additional analyses excluding the 26 borderline tumors revealed essentially the same findings, suggesting that tubal sterilization has a larger effect on invasive disease.

Limitations of this study include the statistical power. We estimated 240 cases of serous EOC and PPC during the time period to detect an OR of 0.58 [17,18]; although the observed adjusted OR of 0.59 was similar, we were limited to 194 cases. Given the 44-year time span, we relied on pathology reports to confirm serous histology, and central pathology review was not performed. Data on family history were missing for a substantial proportion of patients, which prevented a meaningful analysis of familial cancers. Retrospective collection

of the reproductive histories of our cases and controls was limited by data available in the medical record, and there was missing data in this area (Table 1). Also, given that formulations and doses of OCPs changed over the time period studied, detailed data regarding the impact of specific hormones and doses could not be elucidated. Operative reports were not available to determine the tubal sterilization technique for 6 cases and 13 controls; although this did not influence our primary analysis, the specific sterilization technique data would have allowed a more comprehensive secondary analysis. Also, when partial salpingectomy was excluded from the analysis as a non-excisional sterilization technique, this further limited the numbers in our statistical analysis.

Evidence on the effect of salpingectomy on EOC development is emerging. Salpingectomy in the *Dicer-Pten* DKO mouse model prevents high-grade serous EOC development, but oophorectomy does not [2]. While this in vivo model supports the fallopian tube as the source of serous carcinogenesis, the effects of salpingectomy may not be readily translated from an animal model to humans. Additionally, serous cancers in *Dicer-Pten* DKO mice appear to arise within the tubal stroma [2], whereas the site of serous carcinogenesis identified in human fallopian tubes is the tubal epithelium [3, 29]. In humans, more than 70% of invasive serous cancers are associated with a TIC [17] and among women with *BRCA* mutations who undergo RRSO, clinically occult tubal cancers are discovered in 2% to 17% [12, 13, 15]. The collective data suggests the fallopian tube as a potential site of serous carcinogenesis and the results of this current population-based study demonstrate a trend that provides further support to consider the fallopian tube as a site of pelvic serous carcinogenesis.

While tubal sterilization clearly reduces the risk of EOC (8–11, 23–25), there may be more than one mechanism through which this occurs. The risk of endometriosis-associated EOCs may be reduced by interrupting retrograde menstruation; and as mucinous and transitional cell EOC may originate in paratubal epithelial nests, tubal sterilization methods may also contribute to reducing the risk of these cancers (30). Given the growing evidence that the tube is a site of serous carcinogenesis, the clinical question of whether total salpingectomy or fimbriectomy provide the greatest risk reduction among the surgical techniques and truly decrease serous EOC and PPC risk in the general female population warrants prospective study. The implications of EOC risk reduction conferred by excisional tubal sterilization could ultimately influence the choice of tubal sterilization approach and technique. Reports identifying tubal sterilization as a risk-reducing factor for EOC existed before some contemporary sterilization techniques (eg, hysteroscopic) were developed; the effects of these newer techniques on EOC development are unknown. In addition, the practice of tubal excision during benign hysterectomy has been increasing and deserves further exploration [31]. Early reports of coincidental salpingectomy and hysterectomy suggest that it is safe and does not appear to affect ovarian function [32–35]. Such an alternative to bilateral salpingo-oophorectomy may provide some cancer risk reduction while avoiding the detrimental effects of oophorectomy [36].

Although an effective screening tool for EOC does not exist, methods to decrease EOC risk have been the mainstay of management in the high-risk population (*BRCA* mutation carriers and hereditary breast and ovarian cancer syndrome). In the general female population, the

risks associated with oophorectomy may outweigh the benefit of RRSO; thus, salpingectomy may provide a risk-reduction compromise that spares ovarian function. Our findings raise several questions: 1) Should women undergoing permanent sterilization, regardless of EOC risk status, be counseled to have an excisional technique performed? 2) Is interval salpingectomy a reasonable bridge to complete adnexectomy for young, high-risk patients? 3) Should coincidental salpingectomy be offered at the time of benign hysterectomy in low-risk women? Larger scale prospective population-based trials are needed to better determine the impact of salpingectomy and/or fimbriectomy for tubal sterilization and intentional risk reduction on the development of serous EOC.

Acknowledgments

The Rochester Epidemiology Project (REP) is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was also supported in part by the Office of Women's Health Research Building Interdisciplinary Careers in Women's Health (BIRCWH award K12 HD065987). The funding sources played no role in the design, conduct, or reporting of this study.

Abbreviations

EOC	epithelial ovarian cancer
OR	odds ratio
PPC	primary peritoneal cancer
REP	Rochester Epidemiology Project
RRSO	risk-reducing salpingo-oophorectomy

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan; 64(1):9–29. Epub 2014 Jan 7. [PubMed: 24399786]
2. Kim J, Coffey DM, Creighton CJ, Yu Z, Hawkins SM, Matzuk MM. High-grade serous ovarian cancer arises from fallopian tube in a mouse model. Proc Natl Acad Sci U S A. 2012 Mar 6; 109(10):3921–6. Epub 2012 Feb 13. [PubMed: 22331912]
3. Crum CP, Drapkin R, Kindelberger D, Medeiros F, Miron A, Lee Y. Lessons from *BRCA*: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res. 2007 Mar; 5(1):35–44. [PubMed: 17456833]
4. Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, et al. Pathology of breast and ovarian cancers among *BRCA1* and *BRCA2* mutation carriers: results from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). Cancer Epidemiol Biomarkers Prev. 2012 Jan; 21(1):134–47. Epub 2011 Dec 5. [PubMed: 22144499]
5. Pennington KP, Swisher EM. Hereditary ovarian cancer: beyond the usual suspects. Gynecol Oncol. 2012 Feb; 124(2):347–53. [PubMed: 22264603]
6. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. JAMA. 2010 Sep 1; 304(9):967–75. [PubMed: 20810374]
7. Nusbaum R, Isaacs C. Management updates for women with a *BRCA1* or *BRCA2* mutation. Mol Diagn Ther. 2007; 11(3):133–44. [PubMed: 17570734]

8. Tworoger SS, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. Am J Epidemiol. 2007 Oct 15; 166(8):894–901. Epub 2007 Jul 26. [PubMed: 17656616]

9. Antoniou AC, Rookus M, Andrieu N, Brohet R, Chang-Claude J, Peock S, et al. Reproductive and hormonal factors, and ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers: results from the International *BRCA1/2* Carrier Cohort Study. Cancer Epidemiol Biomarkers Prev. 2009 Feb; 18(2): 601–10. Epub 2009 Feb 3. [PubMed: 19190154]

10. Cibula D, Widschwendter M, Zikan M, Dusek L. Underlying mechanisms of ovarian cancer risk reduction after tubal ligation. Acta Obstet Gynecol Scand. 2011 Jun; 90(6):559–63. Epub 2011 Apr 15. [PubMed: 21355863]

11. Runnebaum IB, Stickeler E. Epidemiological and molecular aspects of ovarian cancer risk. J Cancer Res Clin Oncol. 2001 Feb; 127(2):73–9. [PubMed: 11216917]

12. Colgan TJ, Murphy J, Cole DE, Narod S, Rosen B. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with *BRCA* germline mutation status. Am J Surg Pathol. 2001 Oct; 25(10):1283–9. [PubMed: 11688463]

13. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002 May 23; 346(21):1609–15. Epub 2002 May 20. [PubMed: 12023992]

14. Powell CB, Kenley E, Chen LM, Crawford B, McLennan J, Zaloudek C, et al. Risk-reducing salpingo-oophorectomy in *BRCA* mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol. 2005 Jan 1; 23(1):127–32. [PubMed: 15625367]

15. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, et al. Prevention and Observation of Surgical End Points Study Group. Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. N Engl J Med. 2002 May 23; 346(21):1616–22. Epub 2002 May 20. [PubMed: 12023993]

16. Finch, et al. Clinical and pathological findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecologic Oncology. 2006; 100:58–64. [PubMed: 16137750]

17. Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. Am J Surg Pathol. 2007 Feb; 31(2):161–9. [PubMed: 17255760]

18. Peterson LS. Contraceptive use in the United States: 1982–90. Adv Data. 1995 Feb 14.(260):1–15. [PubMed: 10140578]

19. Westhoff C, Davis A. Tubal sterilization: focus on the US experience. Fertil Steril. 2000 May; 73(5):913–22. [PubMed: 10785216]

20. Bakkum-Gamez JN, Langstraat CL, Martin JR, Lemens MA, Weaver AL, Allensworth S, et al. Incidence of and risk factors for postoperative ileus in women undergoing primary staging and debulking for epithelial ovarian carcinoma. Gynecol Oncol. 2012 Jun; 125(3):614–20. Epub 2012 Feb 24. [PubMed: 22370599]

21. Beard CM, Hartmann LC, Atkinson EJ, O'Brien PC, Malkasian GD, Keeney GL, et al. The epidemiology of ovarian cancer: a population-based study in Olmsted County, Minnesota, 1935–1991. Ann Epidemiol. 2000 Jan; 10(1):14–23. [PubMed: 10658685]

22. Harlow BL, Weiss NS, Roth GJ, Chu J, Daling JR. Case-control study of borderline ovarian tumors: reproductive history and exposure to exogenous female hormones. Cancer Res. 1988 Oct 15; 48(20):5849–52. [PubMed: 3167840]

23. Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer: a prospective study. JAMA. 1993 Dec 15; 270(23): 2813–8. [PubMed: 8133619]

24. Sieh W, Salvador S, McGuire V, Weber RP, Terry KL, Rossing MA, et al. Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. Int J Epidemiol. 2013 Apr; 42(2):579–89. [PubMed: 23569193]

25. Whittemore AS, Wu ML, Paffenbarger RS Jr, Sarles DL, Kampert JB, Grosser S, et al. Personal and environmental characteristics related to epithelial ovarian cancer, II. Exposures to talcum powder, tobacco, alcohol, and coffee. Am J Epidemiol. 1988 Dec; 128(6):1228–40. [PubMed: 3195564]

26. Cass I, Holschneider C, Datta N, Barbuto D, Walts AE, Karlan BY. BRCA-mutation-associated fallopian tube carcinoma: a distinct clinical phenotype? Obstet Gynecol. 2005 Dec; 106(6):1327–34. [PubMed: 16319259]
27. Crum CP. Intercepting pelvic cancer in the distal fallopian tube: theories and realities. Mol Oncol. 2009 Apr; 3(2):165–70. Epub 2009 Feb 3. [PubMed: 19383378]
28. Semmel DR, Folkins AK, Hirsch MS, Nucci MR, Crum CP. Intercepting early pelvic serous carcinoma by routine pathological examination of the fimbria. Mod Pathol. 2009 Aug; 22(8):985–8. Epub 2009 May 1. [PubMed: 19407856]
29. Karst AM, Levanon K, Drapkin R. Modeling high-grade serous ovarian carcinogenesis from the fallopian tube. Proc of Nat Acad of Sciences. 2011 May; 108(18):7547–7552.
30. Kumar RJ, Shih IeM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer —shifting the paradigm. Hum Pathol. 2011 Jul; 42(7):918–31. [PubMed: 21683865]
31. Sandoval C, Fung-Kee-Fung M, Gilks B, Murphy KJ, Rahal R, et al. Examining the use of salpingectomy with hysterectomy in Canada. Curr Oncol. 2013 Jun; 20(3):173–5. [PubMed: 23737686]
32. Morelli M, Venturella R, Mocciaro R, Di Cello A, Rania E, Lico D, et al. Prophylactic salpingectomy in premenopausal low-risk women for ovarian cancer: primum non nocere. Gynecol Oncol. 2013 Jun; 129(3):448–51. Epub 2013 Apr 2. [PubMed: 23558052]
33. McAlpine, et al. Opportunistic salpingectomy: uptake, risks, and complications of a regional initiative for ovarian cancer prevention. Am Jour Obstet Gynecol. 2013 Oct; 210(5):471.e1–471.e11. [PubMed: 24412119]
34. Strandell A, Lindhard A, Waldenström U, Thorburn J. Prophylactic salpingectomy does not impair the ovarian response in IVF treatment. Human Reprod. 2001 Jun; 16(6):1135–9.
35. Strandell A, Lindhard A, Waldenstrom U, Thorburn J. Hydrosalpinx and IVF outcome: cumulative results after salpingectomy in a randomized controlled trial. Human Reprod. 2001 Nov; 16(11): 2403–10.
36. Schuster LT, Gostout BS, Grossardt BR, Rocca WA. Prophylactic oophorectomy in premenopausal women and long-term health. Menopause Int. 2008 Sep; 14(3):111–6. [PubMed: 18714076]

Research Highlights

- Tubal sterilization reduces the risk of serous 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.

Table 1

Demographics and Baseline Characteristics

Characteristic	Study Group[a] Cases (n=194)	Controls (n=388)	*P* value[b]
Age at index date, y	61.4 (15.2)	61.4 (15.2)	.97
BMI, kg/m^2	26.5 (22.9–30.5) (n=185)	25.9 (22.8–30.3) (n=372)	.38
Race			.92[c]
White	162 (83.5)	340 (87.6)	
Other	6 (3.1)	12 (3.1)	
Not specified	26 (13.4)	36 (9.3)	
Ever breastfeeding			.10[c]
No	66 (34.0)	82 (21.1)	
Yes	27 (13.9)	54 (13.9)	
Unk	101 (52.1)	252 (65.0)	
Age at menarche, y	13.1 (1.3) (n=79)	13.1 (1.4) (n=232)	.75
Menopausal status at index date			.87[c]
Premenopausal	38 (19.6)	75 (19.3)	
Postmenopausal	146 (75.3)	299 (77.1)	
Unk	10 (5.1)	14 (3.6)	
OCP use			.10[d]
Never	74 (38.1)	119 (30.7)	
<5 y	10 (5.2)	23 (5.9)	
5–10 y	2 (1.0)	13 (3.4)	
>10 y	2 (1.0)	6 (1.5)	
Duration unk	23 (11.9)	47 (12.1)	
Unk	83 (42.8)	180 (46.4)	
HRT use			.44[d]
Never	41 (21.1)	92 (23.7)	
<5 y	11 (5.7)	34 (8.8)	
5–10 y	10 (5.2)	17 (4.4)	
>10 y	7 (3.6)	34 (8.8)	
Duration unk	15 (7.7)	33 (8.5)	
Unk	110 (56.7)	178 (45.9)	
Gravidity	2 (1–4) (n=192)	3 (2–5) (n=384)	.003
Parity	2 (0–3) (n=193)	3 (1–4) (n=384)	.007
Hx of abnormal Pap result			.78[c]
No	157 (80.9)	322 (83.0)	
Yes	16 (8.3)	30 (7.7)	
Unk	21 (10.8)	36 (9.3)	
Hx of pelvic inflammatory disease	4 (2.1)	8 (2.1)	.99

	Study Group[a]		
Characteristic	**Cases (n=194)**	**Controls (n=388)**	***P* value[b]**
Hx of polycystic ovary syndrome	2 (1.0)	3 (0.8)	.99
Hx of infertility	10 (5.2)	15 (3.9)	.47
Hx of endometriosis	9 (4.6)	13 (3.4)	.44
Prior hysterectomy	30 (15.5)	125 (32.2)	<.001
Prior salpingo-oophorectomy	9 (4.6)	69 (17.8)	<.001

Abbreviations: BMI, body mass index; HRT, hormone replacement therapy; Hx, history; OCP, oral contraceptive pill; Pap, Papanicolaou test; Unk, unknown.

[a] Values are No. (%), unless otherwise stated.

[b] The χ^2 or Fisher exact test was used for categorical variables, 2-sample *t* test for age, and Wilcoxon rank sum test for all other continuous measures.

[c] Comparisons based on ignoring those with unknown information.

[d] Comparisons based on ever vs never usage, ignoring those with unknown information.

Table 2

Oncologic Characteristics Among Cases (n=194)

Characteristic	No. of Cases (%)
Primary site	
Ovarian	176 (90.7)
Primary peritoneal	18 (9.3)
FIGO grade	
Borderline	26 (13.4)
1	15 (7.7)
2	20 (10.3)
3	131 (67.5)
Not documented	2 (1.0)
FIGO stage	
I	40 (20.6)
II	19 (9.8)
III	119 (61.3)
IV	15 (7.7)
Not documented	1 (0.5)
Histology	
Serous	146 (75.3)
Mixed serous	47 (24.2)
Not documented	1 (0.5)

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

Table 3

Tubal Sterilization Techniques

	Study Group[a]	
Tubal sterilization	**Cases (n=194)**	**Controls (n=388)**
No	180 (92.8)	342 (88.1)
Yes	14 (7.2)	46 (11.9)
Excisional		
Complete salpingectomy	0	6
Partial salpingectomy	4	16
Distal fimbriectomy	1	3
Nonexcisional		
Unipolar coagulation	2	0
Bipolar coagulation	1	8
Type not specified	6	13

[a]Values are No. or No. (%)