Tubal Ligation, Hysterectomy and Ovarian Cancer: A Meta-Analysis

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Tubal ligation, hysterectomy and ovarian cancer: A meta-analysis

Megan S Rice1,2,3*, Megan A Murphy1,2,3 and Shelley S Tworoger1,2,3

Abstract

Purpose: The purpose of this meta-analysis was to determine the strength of the association between gynecologic surgeries, tubal ligation and hysterectomy, and ovarian cancer. 

Methods: We searched the PubMed, Web of Science, and Embase databases for all English-language articles dated between 1969 through March 2011 using the keywords “ovarian cancer” and “tubal ligation” or “tubal sterilization” or “hysterectomy.” We identified 30 studies on tubal ligation and 24 studies on hysterectomy that provided relative risks for ovarian cancer and a p-value or 95% confidence interval (CI) to include in the meta-analysis. Summary RRs and 95% CIs were calculated using a random-effects model.

Results: The summary RR for women with vs. without tubal ligation was 0.70 (95%CI: 0.64, 0.75). Similarly, the summary RR for women with vs. without hysterectomy was 0.74 (95%CI: 0.65, 0.84). Simple hysterectomy and hysterectomy with unilateral oophorectomy were associated with a similar decrease in risk (summary RR = 0.62, 95% CI: 0.49-0.79 and 0.60, 95% CI: 0.47-0.78, respectively). In secondary analyses, the association between tubal ligation and ovarian cancer risk was stronger for endometrioid tumors (summary RR = 0.45, 95% CI: 0.33, 0.61) compared to serous tumors.

Conclusion: Observational epidemiologic evidence strongly supports that tubal ligation and hysterectomy are associated with a decrease in the risk of ovarian cancer, by approximately 26-30%. Additional research is needed to determine whether the association between tubal ligation and hysterectomy on ovarian cancer risk differs by individual, surgical, and tumor characteristics.

Keywords: Ovarian neoplasms, Sterilization, Tubal, Hysterectomy

Introduction

Ovarian cancer is the fifth leading cause of cancer death in US women [1], yet primary prevention recommendations are limited. Gynecological surgeries including tubal ligation and hysterectomy may alter ovarian cancer risk by protecting the ovary from ascending carcinogens or damaging the utero-ovarian artery altering hormonal function. In addition, tubal ligation may increase immunity against the surface glycoprotein human mucin 1 (MUC1) [2-4]. While tubal ligation and hysterectomy generally have been found to be inversely associated with ovarian cancer, effect estimates vary between studies and little is known about potential effect modifiers of these associations. Therefore, we conducted a meta-analysis of the association between ovarian cancer and tubal ligation as well as hysterectomy.

Materials and methods

Through searches in the PubMed, Web of Science, and Embase databases, we sought to identify all English-language articles with quantitative data on the association between tubal ligation or hysterectomy and the risk of ovarian cancer. Database searches encompassed articles dated 1969 through March 2011. We identified articles using the keywords “ovarian cancer” and “tubal ligation” or “tubal sterilization” as well as “ovarian cancer” and “hysterectomy.” In addition, we reviewed the references of selected articles to identify studies missed through our search. We also completed a reverse
and 15 did not distinguish whether or not women with hysterectomy underwent unilateral oophorectomy [9,10,12,13,15,16,24,26,29,31,39-41,44,46,47]. Two of the studies included in the primary meta-analysis for both tubal ligation and hysterectomy were pooled analyses [9,31], one was comprised of eight studies [31] and another was comprised of four studies [9]. For these studies, we included the pooled estimates in our meta-analysis as we were unable to obtain the study-specific effect estimates for all studies through our literature search. One of the studies identified in our tubal ligation and hysterectomy literature searches was a study in the New England case-control study (NECC) [Cramer]. However, in this study the reference category for the odds ratios for tubal ligation and hysterectomy was comprised of women who did not have any pelvic surgeries, including cesarean sections. In order for the effect estimates from the NECC to be comparable to other studies, we requested and obtained from NECC researchers the odds ratio for ovarian cancer comparing women who had a tubal ligation to those who did not have the procedure as well as the odds ratio comparing women with hysterectomy to those who did not have a hysterectomy. We also obtained odds ratios for the secondary analyses described below.

In secondary analyses, we identified studies that reported the relative risk of ovarian cancer by characteristics of surgery, such as age at or years since procedure, as well as by histological subtype of ovarian cancer. We identified eight studies that reported stratum-specific estimates of ovarian cancer risk by years since tubal ligation (Additional file 1: Table S1) [14,19,25,26,28,29,48] and nine studies that reported stratum-specific estimates for age at tubal ligation (Additional file 1: Table S2) [13,14,19,25,27-29,48]. In addition, 13 studies specified effect estimates for invasive ovarian cancer [10,12,15,17-23,31,33] and 11 studies on tubal ligation reported estimates for at least one histological subtype of ovarian cancer (Additional file 1: Table S3) [9,10,15,16,19,22,24,26,29,49]. Eight studies on hysterectomy reported stratum-specific estimates of ovarian cancer risk by years since the procedure (Additional file 1: Table S4) [25,26,29,31,43,45,46] and five studies reported stratum-specific estimates for age at hysterectomy (Additional file 1: Table S5) [25,29,31,43]. In addition, nine studies reported effect estimates for invasive ovarian cancer ([10,12,15,23,31,40-42], Cramer]. Separate analyses were performed examining risk of ovarian cancer and characteristics of surgery, including years since and age at procedure. For six of the eight studies reporting stratum-specific estimates for years since tubal ligation, we were able to derive estimates for less than 10 years since tubal ligation and 10 or more years since tubal ligation [19,25,26,29,48]. For seven of the nine studies that reported risks by age at tubal ligation, we were able to derive estimates for age less than 35 at tubal ligation and 35 years of age or older [13,19,27-29,48]. For seven of the eight studies reporting stratum-specific estimates for years since hysterectomy, we were able to derive estimates for less than 10 years since hysterectomy and 10 or more years since hysterectomy [22,25,26,31,43,45]. For the five studies that reported risks by age at hysterectomy, we were able to derive estimates for age less than 40 or 45 at hysterectomy and 40 or 45 years of age or older [25,29,31,43] [NECC].
The estimated RRs for ovarian cancer associated with tubal ligation versus no tubal ligation ranged from 0.2 to 2.4 (Table 1). Twenty-seven of the 30 studies reported lower risks of ovarian cancer in women who had a tubal ligation compared to those who had not had the procedure. The three studies that observed an elevated risk of ovarian cancer did not achieve statistical significance [14,16,35]. The summary RR was 0.70 (95%CI: 0.64, 0.75), demonstrating a statistically significant inverse association between tubal ligation and ovarian cancer (Figure 2). Some studies in our analysis did not specify whether borderline cases were included in the analyses. However, when we restricted our analysis to 13 studies that reported the association for invasive ovarian cancer, specifically the summary RR was very similar (summary RR = 0.72; 95%CI: 0.66, 0.72). Since there was evidence of heterogeneity among the 30 studies ($P = 0.02$), we examined the contribution of study characteristics to the heterogeneity. We did not observe statistically significant evidence of heterogeneity by study design (i.e., cohort study, case–control study, or other) or residence of study.
| Author (Country) | Study Design | Case definition | Covariates | OR, RR, or SIR (95%CI) | Comments |
|-----------------|--------------|-----------------|------------|------------------------|----------|
| NECC 2012 (USA) [personal communication with Dr. Daniel Cramer] | Case-control | Borderline or invasive epithelial ovarian cancer N=2076 | age, study center, BMI, study phase, smoking, family history of ovarian and breast cancers, talc use, OC use, parity, breast feeding, age at menarche, post-menopausal status, use of post-menopausal hormones, hysterectomy | 0.79 (0.66-0.94) | |
| Ness et al. 2011 (USA) [11] | Case-control | Invasive or borderline epithelial ovarian cancer N=867 | Age, number of pregnancies, race, infertility, family history of ovarian cancer, ever use of oral contraceptives, ever use of IUDs, ever use of barriers, vasectomy | 0.63 (0.51-0.77) | |
| Moorman et al. 2009 (USA) [12] | Case-control North Carolina Ovarian Cancer Study | Invasive epithelial ovarian cancer N=746 White cases N=111 African-American cases | Age, parity, age at menarche, duration of OC use, family history of breast/ovarian cancer, BMI | Whites: 0.74 (0.58, 0.94) African-Americans: 0.43 (0.24, 0.80) | |
| Antoniou et al. 2009 (Europe and Canada) [13] | Retrospective Cohort | Ovarian cancer (only BRCA 1/2 carriers) N=201 BRCA1 cases N=52 BRCA2 cases | Age, duration of OC use, parity | BRCA 1/2: 0.43 (0.24, 0.75) BRCA1: 0.42 (0.22, 0.80) BRCA2: 0.47 (0.18, 1.21) | Includes prevalent and incident cases. Mean difference between age at diagnosis and interview: 6.7 years |
| Wu et al. 2009 (USA) [37] | Case-control | Invasive and borderline ovarian cancer N=609 cases | Race/ethnicity, age, education, family history of ovarian cancer, menopausal status, use of oral contraceptives, parity | 0.66 (0.47, 0.93) | |
| Dorjgochoo T. et al. 2009 (China) [14] | Prospective cohort | Ovarian cancer N=94 cases | Age, education, age at menarche, parity, breastfeeding, BMI, physical activity, smoking, menopausal status, family history of cancer, other contraceptive methods. | 1.17 (0.62, 2.26) | Cohort N=66,661 76.1% participation rate |
| Nagle et al. 2008 (Australia) [15] | Case-control | Invasive epithelial endometrioid and clear cell ovarian cancer N=142 endometrioid cases N=90 clear cell cases | Age, education, parity, and hormone contraceptive use | Endometrioid: 0.4 (0.3, 0.7) Clear cell: 0.7 (0.4, 1.2) | 47% participation rate in controls |
| Jordan et al. 2008 (Australia) [10] | Case-control | Invasive epithelial serous ovarian cancer N=627 cases | Parity, hormonal contraceptive use, history of breast or ovarian cancer, age, education | Serous (invasive): 0.87 (0.69-1.09) | |
| Jordan et al. 2007 (Australia) [16] | Case-control | Epithelial benign serous tumors (N=230) and benign mucinous tumors (N=133) | Age, state of residence, education, parity, hormonal contraceptive use, hysterectomy, smoking status | Combined: 1.04 (0.76-1.44) Mucinous: 1.00 (0.61-1.64) Serous: 1.08 (0.75-1.57) | 65% participation rate in cases, 47% in controls. |
| Study | Design | Endpoint | Risk Factors Considered | Odds Ratio (95% CI) | Note |
|-------|--------|----------|-------------------------|---------------------|------|
| Tworoger et al. 2007 (USA) [17] | Prospective cohort | Incident invasive epithelial ovarian cancer | Age, BMI, parity, smoking history, age at menarche, age at menopause, duration of postmenopausal hormone use, duration of oral contraceptive use | 0.66 (0.50, 0.87) | Update of Hankinson et al. 1993 |
| McLaughlin JR et al. 2007 (International) [18] | Case-control | Invasive ovarian cancer (only BRCA 1/2 carriers) | Age, mutation type, country of residence, parity, breastfeeding, oral contraceptive use, ethnicity. | BRCA1+2 carriers: 0.78 (0.60, 1.00) | Includes prevalent and incident cases. Results similar when restricted to women interviewed within 3 years of diagnosis. |
| Modugno et al. 2004 (USA) [9] | Pooled case-control | Epithelial ovarian cancer | Study site, age, family history, duration of oral contraceptive use, parity | 0.63 (0.54, 0.73) | Pooled analysis from four studies. |
| Kjaer et al. 2004 (Denmark) [19] | Population-based follow-up study | Invasive ovarian cancer and borderline ovarian tumor | Age and calendar year | Invasive: 0.82 (0.6, 1.0) Borderline: 0.82 (0.5, 1.3) | Observed number of cancer cases in cohort of women who underwent tubal ligation was compared to the expected number of cases based on the age and calendar year specific rates from the Danish Cancer Registry. |
| McGuire et al. 2004 (USA) [20] | Case-control | Invasive epithelial ovarian cancer | Age, parity, duration of OC use, race/ethnicity | BRCA 1 carriers: 0.68 (0.25, 1.90) Noncarriers: 0.65 (0.45, 0.95) | |
| Pike et al. 2004 (Los Angeles, USA) [21] | Case-control | Invasive ovarian cancer | Age, ethnicity, SES, education, family history of ovarian cancer, use of talc, BMI, parity, age at last birth, number of incomplete pregnancies, OC use, menopausal status, age at menopause, hormone replacement therapy | 0.82 (0.53-1.26) | |
| Rutter et al. 2003 (Israel) [23] | Case-control | Invasive epithelial ovarian cancer or primary peritoneal cancer | Age, ethnicity, parity, years of oral contraceptive use | 0.70 (0.42, 1.18) | Participation rate was 79% for case patients and 66% for controls. |
| Wittenberg et al. 1999 (USA) [24] | Case-control | Mucinous and non-mucinous epithelial ovarian cancer | Age at diagnosis, parity, duration of OC use | Mucinous: 0.4 (0.1, 1.9) Non-mucinous: 0.6 (0.3, 1.1) | 64% participation rate in cases, 72% in controls. Included both borderline and invasive. |
| Kreiger et al, 1997 (Canada) [25] | Historical cohort study | Invasive and borderline ovarian cancer | Age, calendar year, length of follow-up | 0.57 p<0.001 | Calculated observed over expected events. Sensitivity analysis excluding borderline malignancies similar. |
| Study                                      | Study Design          | Study Group                          | Variables                                                                 | Odds Ratio (95% CI) | Notes                                                                 |
|--------------------------------------------|-----------------------|--------------------------------------|---------------------------------------------------------------------------|---------------------|----------------------------------------------------------------------|
| Green, Purdie, et al. 1997 (Australia) [26] | Case-control          | Incident, primary epithelial ovarian cancer | Age, education, BMI, parity, OC duration, smoking, family history of ovarian cancer | 0.61 (0.46, 0.85)   | 90% participation rate in cases, 73% in controls.                   |
| Cornelison et al. 1997 (USA) [27]          | Case-control          | Ovarian cancer N=300 cases           | Age, SES, marital status, parity, age at first pregnancy, age at menarche, age at menopause, irregular menses, breast-feeding duration, BMI, OC use | 0.52 (0.31,0.85)   | Patient controls with no malignancy or ovarian disease.             |
| Miracle-McMahill, et al. 1997 (USA) [28]   | Prospective Cohort Study | Ovarian cancer mortality N=799 ovarian cancer deaths | Age, race, BMI, education, family history of ovarian cancer, family history of breast cancer, parity, marital status, age at menarche, OC use, ERT, age at menopause, miscarriages smoking status | 0.68 (0.45, 1.03)   |                                                                      |
| Rosenblatt, et al. 1996 (International) [29] | Case-control          | Borderline or malignant epithelial ovarian cancer N=385 cases | Age, hospital, year of interview, parity OC use | 0.71 (0.47, 1.08)   | No differences observed for borderline and malignant tumors.        |
| Risch et al. 1996 (Canada) [22]            | Case-control          | Epithelial ovarian cancer N=450 cases Borderline N=83 Invasive N=376 | Age, parity, years of OC use, average lactation/pregnancy, total years of ERT, hysterectomy, family history of breast cancer | 0.67 (0.47-0.94)    | Invasive and borderline tumors included.                            |
| Nandakumar et al. 1995 (India) [30]        | Case-control          | Ovarian cancer N=97 cases            | Age, residential area, parity, age at first birth | 0.25 (0.08, 0.78)   | Restricted to ever-married women. Hospital-based controls.          |
| Whittemore et al. 1992 (USA) [31]          | Pooled case-control   | Invasive epithelial ovarian cancer N=2197 cases | Age, study, parity, OC use | Hospital-based studies: 0.59 (0.38, 0.93) Population-based studies: 0.87 (0.62, 1.20) | Restricted to white women. 6 hospital based studies and 6 population-based studies. |
| Booth et al 1989 (England) [32]            | Case-control          | Epithelial ovarian cancer N=235 cases | Age, social class, gravidity, unprotected intercourse | 0.2 (0.1, 0.6)     | Cases were less than 65 years old and interviewed within 2 years of diagnosis. Age-matched hospital-based controls. |
| Shu et al 1989 (China) [33]                | Case-control          | Invasive epithelial ovarian cancer N=172 cases | Age, education, parity, age at menarche, ovarian cyst | 0.8 (0.4, 1.6)     | 89% participation rate in cases, 100% in controls. All <70 years of age. |
| Koch et al 1988 (Canada) [34]              | Case-control          | Epithelial ovarian cancer N=200 cases | None | 0.8 (0.5, 1.3) | 47% participation rate in controls. Age-matched, but did not control for age in analyses. |
| Mori et al 1988 (Japan) [36]               | Case-control          | Primary epithelial ovarian cancer N=110 cases | Age, parity, marital status, number of induced abortions | 0.5 (0.25, 1.00)    | Controls were hospital in-patients with gynecological complaints other than ovarian cancer and OB/GYN outpatients without a malignant ovarian disorder. 100% participation rate in cases and controls. |
| Study                | Design          | Disease                        | Cases | Age, Nulliparity | OR   | Comments                                                                                                                                 |
|---------------------|-----------------|--------------------------------|-------|------------------|------|------------------------------------------------------------------------------------------------------------------------------------------|
| Koch et al. 1984    | Retrospective   | Ovarian cancer                 | N=4 cases | Age, nulliparity | 2.4  | Population who underwent tubal ligation were mental patients. 34% were lost to follow-up. Many underwent the procedure at young ages (i.e. 10-19). Expected rates calculated from a previous retrospective study. Incomplete adjustment for parity. |

Abbreviations: OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; OC, oral contraceptive; BMI, body mass index; SES, socio-economic status; ERT, estrogen replacement therapy.
participants (i.e., USA or non-USA) \( (P > 0.05) \) (Table 2). Interestingly, the relative risk among BRCA carriers (RR = 0.64, 95%CI: 0.43-0.96) was similar to the relative risk among population-based studies (RR = 0.70, 95%CI: 0.64-0.76) (Table 2). Overall, we found that if any single study was removed from the meta-analysis, the effect estimate did not change substantially (data not shown). In addition, we found no evidence of publication bias using either the Begg \( (P = 0.12) \) or the Egger \( (P = 0.22) \) method for assessing bias.

Eight of the studies examined years since tubal ligation. In a meta-regression of six of these studies, we did not observe a difference in the relative risk of ovarian cancer between women who had a tubal ligation less than 10 years ago (summary RR = 0.69, 95%CI: 0.59, 0.79) and those women who had a tubal ligation 10 or more years ago (summary RR = 0.68, 95%CI: 0.54, 0.87) \( (P\text{-heterogeneity} = 0.78) \) (Table 2). Of the other studies, a prospective cohort study of ovarian cancer mortality reported tubal ligation to be associated with a reduced risk for women who had the procedure within 20 years, with a smaller non-significant reduced risk for those who had the procedure 20 or more years ago.[19] However, a prospective cohort study based in China observed a non-significant increase in risk that was similar for both women who had a tubal ligation less than 33 years ago and women who had a tubal ligation 33 or more years ago [14].
### Table 2 Summary relative risks for tubal ligation and ovarian cancer by selected characteristics

| Study design          | Number of contributing studies | Random-effects RR (95%CI) |
|-----------------------|--------------------------------|--------------------------|
| Cohort study          | 30 studies                     | 0.67 (0.50, 0.90)        |
| Case-control study    | 30 studies                     | 0.70 (0.63, 0.75)        |
| Other study design    | 30 studies                     | 0.95 (0.63, 1.43)        |
| BRCA status           | 30 studies                     | 0.64 (0.43, 0.96)        |
| General population    | 30 studies                     | 0.70 (0.64, 0.76)        |
| Geographic location   | 30 studies                     | 0.68 (0.63, 0.73)        |
| US                    | 11 studies                     | 0.71 (0.61, 0.82)        |
| Non-US                | 11 studies                     | 0.75 (0.65, 0.88)        |
| Histologic subtype    | 11 studies                     | 0.88 (0.70, 1.09)        |
| Serous                | 7 studies                      | 0.72 (0.55, 0.94)        |
| Endometrioid          | 7 studies                      | 0.80 (0.63, 1.01)        |
| Mucinous              | 7 studies                      | 0.79 (0.68, 0.92)        |
| Clear cell            | 7 studies                      | 0.69 (0.59, 0.81)        |
| Other                 | 7 studies                      | 0.79 (0.68, 0.92)        |
| Age at tubal ligation | 6 studies                      | 0.69 (0.59, 0.79)        |
| 35 years of age       | 6 studies                      | 0.68 (0.54, 0.87)        |
| 35+ years of age      | 6 studies                      | 0.54 (0.33, 0.88)        |
| Years since tubal ligation | 5 studies                  | 0.60 (0.47, 0.78)        |
| <10 years             | 5 studies                      | 0.74 (0.65, 0.84)        |
| 10+ years             | 5 studies                      | 0.72 (0.55, 0.94)        |

Nine studies examined age at tubal ligation on ovarian cancer risk. In a meta-regression of seven of these studies, the relative risk for ovarian cancer was non-significantly lower among women who had a tubal ligation when they were younger than 35 (summary RR = 0.69, 95%CI: 0.59, 0.81) compared to at 35 years of age or older (summary RR = 0.79, 95%CI: 0.68, 0.92), although the difference was not statistically significant \( (P_{for-heterogeneity} = 0.22) \) (Table 2). In addition, the Shanghai Women’s Health Study noted a non-significant increase in ovarian cancer risk only among women who were less than 30 when they underwent the procedure and no association among those aged 30 or more at time of surgery [14]. In a historical cohort study, tubal ligation was associated with a reduced risk of ovarian cancer among women aged 25–44 at time of the procedure \( (RR = 0.54, p < 0.001) \), but not among women aged 45–64 at the time of their tubal ligation \( (RR = 1.18, p = 0.68) \) [25].

Eleven studies reported effect estimates by at least one histologic subtype. In a meta-analysis regression we observed that the association was stronger for endometrioid tumors compared to serous tumors \( (P < 0.01) \). The summary RR for serous tumors was 0.75 \( (95\% CI: 0.65, 0.88) \) compared to 0.45 \( (95\% CI: 0.33, 0.61) \) for endometrioid tumors. The summary RRs for mucinous \( (summary \ RR = 0.88, 95\% CI: 0.70,1.09) \), clear cell \( (summary \ RR = 0.72, 95\% CI: 0.55, 0.94) \), and other tumor types \( (summary \ RR = 0.80, 95\% CI: 0.63,1.01) \) did not significantly differ from serous tumors \( (p > 0.05) \).

### Hysterectomy

The study-specific RR for ovarian cancer associated with hysterectomy (with or without unilateral oophorectomy) ranged from 0.06 to 1.91 (Table 3). The summary RR was 0.74 \( (95\% CI: 0.65, 0.84) \), demonstrating a statistically significant inverse association between hysterectomy and ovarian cancer (Figure 3). When we restricted to nine studies that reported effect estimates for invasive ovarian cancer, the association was similar \( (summary \ RR = 0.81; 95\% CI: 0.68, 0.97) \). We also calculated summary estimates for simple hysterectomy and hysterectomy with unilateral oophorectomy (Table 4). We observed that the reduced risk of ovarian cancer associated with hysterectomy with unilateral oophorectomy \( (RR = 0.60, 95\% CI: 0.47-0.78) \) was similar to the reduced risk associated with simple hysterectomy \( (RR = 0.62, 95\% CI: 0.49-0.79) \). We examined the contribution of other study characteristics to the heterogeneity between studies, since the p-heterogeneity \(< 0.01\). We did not observe evidence for statistically significant heterogeneity by study type \( (i.e., \ case-control, \ cohort, \ other) \) or geographic location \( (i.e., \ USA \ vs \ non-USA) \) \( (P > 0.05) \) (Table 4). Overall, if any single study was removed from the meta-analysis, the effect estimate did not change substantially \( (data \ not \ shown) \). We did not evidence of publication bias using the Egger \( (P = 0.01) \) method for assessing bias, but not for the Begg method \( (P = 0.11) \).

Eight studies examined years since hysterectomy and ovarian cancer risk. In a meta-regression of seven of these studies, the RR of ovarian cancer between women who had the procedure 10 or more years ago was slightly lower compared to women who had a hysterectomy less than 10 years ago \( (summary \ RR = 0.69, 95\% CI: 0.60, 0.79 \) and summary \ RR = 0.77, 95\% CI: 0.66, 0.89 respectively) \( (P_{for-heterogeneity} = 0.33) \). In addition, a hospital-based case–control study reported an inverse association among women who underwent the procedure more than five years ago \( (RR = 0.37, 95\% CI: 0.11-1.24) \), but no association among those who had a hysterectomy within five years \( (RR = 1.04, 95\% CI: 0.37-2.90) \) [29]. Five studies examined age at hysterectomy on ovarian cancer risk, three dichotomized at age 40 and two at age 45. In a meta-regression, hysterectomy was more strongly inversely associated with ovarian cancer among women who were younger than 40 or 45 at surgery compared to 40 or 45 years of age or older, however the p for heterogeneity was not
| Author (Country) | Study Design       | Case definition                                      | Covariates                                                                 | OR, RR, or SIR (95%CI)                  | Comments                                      |
|-----------------|--------------------|------------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------|------------------------------------------------|
| NECC 2012 (USA) | Case-control       | Borderline and invasive ovarian cancer                | age, study center, BMI, study phase, smoking, family history of ovarian and breast cancers, talc use, OC use, parity, breast feeding, age at menarche, post-menopausal status, use of post-menopausal hormones, tubal ligation | Hysterectomy only: 1.10 (0.83-1.46)    | NECC 2012 (USA) [Personal communication with Dr. Daniel Cramer] |
| Annegers et al. 1979 (USA) | Case-control (Rochester Project) | Epithelial ovarian cancer N=116 cases | Controls matched on age and residence                                        | Hysterectomy only: 0.36 (0.10-0.73)    | Hysterectomy with unilateral oophorectomy: 0.06 (0.004-0.98) |
| Antoniou et al. 2009 (Europe and Canada) | Retrospective Cohort | Ovarian cancer (only BRCA 1/2 carriers) N=201 BRCA1 cases N=52 BRCA2 cases | Age, duration of OC use, parity                                               | Hysterectomy with or without unilateral oophorectomy: BRCA 1/2: 0.59 (0.22, 1.57) | Includes prevalent and incident cases. Mean difference between age at diagnosis and interview: 6.7 years |
| Beard et al. 2000 (USA) | Case-control (Rochester Project) | Invasive epithelial ovarian cancer N=103 cases | Controls matched on age and provider                                          | Hysterectomy with or without unilateral oophorectomy: 0.5 (0.2-0.96) | Cases less than 65 years old and diagnosed within 2 years. Age-matched hospital-based controls. |
| Booth et al. 1989 (England) | Case-control | Epithelial ovarian cancer N=235 cases | Age and social class                                                          | Hysterectomy only: 0.2 (0.1-0.4)       | Hysterectomy with unilateral oophorectomy: 0.4 (0.1-1.1) |
| Braem et al. 2010 (Netherlands) | Case-cohort study (Netherlands Cohort Study) | Invasive epithelial ovarian cancer N=375 | Age, OC use, parity                                                            | Hysterectomy with or without unilateral oophorectomy: 0.50 (0.34-0.72) | All women presumed to be postmenopausal |
| Chiaffarino et al. 2005 (Italy) | Multi-center case-control study | Incident invasive epithelial ovarian cancer N=1031 cases | Age, center, education, parity, OC use, family history of ovarian and breast cancer | Hysterectomy only: 0.6 (0.4-0.9)       | Hysterectomy and unilateral oophorectomy: 0.6 (0.3-1.1) |
| Green, Purdie, et al. 1997 (Australia) | Case-control | Incident, primary epithelial ovarian cancer N=824 cases | Age, education, BMI, parity, OC duration, smoking, family history of ovarian cancer | Hysterectomy with or without unilateral oophorectomy: 0.64 (0.48-0.85) | 90% participation rate in cases, 73% in controls. |
| Hankinson et al. 1993 (USA) | Cohort study (NHS) | Borderline and malignant epithelial ovarian cancer N=260 cases | Age, parity, duration of OC use, age at menarche, tubal ligation, smoking status, BMI | Hysterectomy only: 0.67 (0.45-1.00)   | 90% follow-up rate                            |
| Jordan et al. 2008 (Australia) | Case-control | Invasive epithelial serous ovarian cancer N=627 cases | Parity, hormonal contraceptive use, history of breast or ovarian cancer, age, education | Hysterectomy with or without unilateral oophorectomy: Serous (invasive): 1.27 (1.00, 1.60) | |
| Jordan et al. 2007 (Australia) | Case-control | Benign serous tumors (N=230) and benign mucinous tumors (N=133) | Age, state of residence, education, parity, hormonal contraceptive use, smoking status | Hysterectomy with or without unilateral oophorectomy: Combined: 1.91 (1.38-2.66) | 65% participation rate in cases, 47% in controls. |
Table 3 Epidemiologic Studies of the Association Between Hysterectomy and Risk of Ovarian Cancer (Continued)

| Study                  | Study Design       | Tumor Type                | Inclusion Criteria                                                                 | Surgical Indication | Estimation Method            | Odds Ratio (95% CI) | Additional Details |
|------------------------|--------------------|---------------------------|-------------------------------------------------------------------------------------|---------------------|-------------------------------|---------------------|-------------------|
| Kreiger et al. 1997    | Historical cohort  | Ovarian cancer            | N=169 observed cases in hysterectomy subcohort                                      | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (Canada) [25]          | cohort study       |                           | Age, calendar year, length of follow-up                                            | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Loft et al. 1997       | Prospective historical cohort study | Ovarian cancer | N=169 observed cases in hysterectomy subcohort                                      | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (Denmark) [44]         |                     |                           | Age, calendar year, length of follow-up                                            | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Luoto et al. 1997      | Historical cohort  | Ovarian cancer            | N=169 observed cases in hysterectomy subcohort                                      | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (Finland) [39]         | cohort study       |                           | Age, calendar year, length of follow-up                                            | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Modugno et al. 2004    | Pooled case-control| Epithelial ovarian cancer | N=2098 cases                                                                        | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (USA) [9]              |                    |                           | Study site, age, family history, duration of oral contraceptive use, parity, endometriosis, tubal ligation | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Moorman et al. 2009    | Case-control North Carolina Ovarian Cancer Study | Invasive epithelial ovarian cancer | N=746 White cases                                                                  | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (USA) [12]             |                    |                           | Age, parity, age at menarche, duration of OC use, family history of breast/ovarian cancer, BMI | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Nagle et al. 2008      | Case-control       | Invasive epithelial endometrioid and clear cell ovarian cancer                      | N=142 endometrioid cases                                                          | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (Australia) [15]       |                    |                           | Age, education, parity, and hormone contraceptive use                               | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Parazzini et al. 1993  | Case-control study | Epithelial ovarian cancer   | N=953 cases                                                                         | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (Italy) [45]           |                    |                           | Age, education, parity, oral contraceptive use, menarche, menopause                 | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Risch et al. 1994      | Case-control       | Epithelial ovarian cancer   | N=450 cases                                                                         | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (Canada) [46]          |                    |                           | Age, duration of OC use, number of full-term pregnancies                            | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Rosenblatt et al. 1996 | Case-control (Multi-site/country) | Borderline or invasive epithelial ovarian cancer | N=385 cases                                                                         | Mucinous: 0.95 (0.55-1.67) | Calculated observed over expected events. |                     |                   |
| (Multinational) [29]   |                    |                           | Age, date of diagnosis, center, parity, OC use                                       | Serous: 2.75 (1.90-3.96) | Non-hormonal: 1.1 (0.5-2.7)   | Hysterectomy only: 0.72 p<0.001 |                   |
| Study | Study Design | Study Population | Control Types | Study Methodology |
|-------|--------------|------------------|---------------|------------------|
| Rutter et al. 2003 (Israel) [23] | Case-control | Epithelial ovarian cancer or primary peritoneal cancer | Age, ethnicity, parity, years of oral contraceptive use | Participation rate was 79% for case patients and 66% for controls. Includes BRCA-specific analysis. |
| Whittemore et al. 1992 (USA) [31] | Pooled case-control (12 studies included) | Invasive epithelial ovarian cancer | Age, study, parity, OC use | Restricted to white women. 6 hospital-based studies and 6 population-based studies. All hysterectomies performed at least 2 years prior to reference date. |
| Wittenberg et al. 1999 (USA) [24] | Case-control | Mucinous and non-mucinous epithelial ovarian cancer | Age at diagnosis, parity, duration of OC use | 64% participation rate in cases, 72% in controls. Included both borderline and invasive. |
| Wynder et al. 1969 (USA) [47] | Case-control (Hospital based) | Epithelial ovarian cancer (N=150) plus miscellaneous ovarian tumors (N=8) | Age-matched controls | Hysterectomy with or without unilateral oophorectomy: 0.7 (0.04-1.0) |

Abbreviations: OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; OC, oral contraceptive; BMI, body mass index; SES, socio-economic status.
statistically significant ($P$-heterogeneity = 0.29). The summary RR for women less than 40 or 45 years of age was 0.70 (95%CI: 0.55, 0.89) compared to 0.83 (95%CI: 0.72, 0.96) for women over 40 or 45 years of age (Table 4).

**Discussion**

Observational epidemiologic evidence strongly suggests that there is a decreased risk of ovarian cancer among women who have had a tubal ligation or hysterectomy. We observed an approximately 26-30% reduction in ovarian cancer risk among women who had a tubal ligation or hysterectomy compared to women who never had a tubal ligation or hysterectomy, respectively. These estimates did not vary substantially by study design or population. We did not observe any significant differences in the effect estimates by years since procedure. For both hysterectomy and tubal ligation, the inverse association between these procedures and ovarian cancer risk was suggestively stronger among women who underwent the procedure at earlier ages. There was evidence that tubal ligation may be associated with a stronger reduced risk for endometrioid tumors compared to serous tumors; however this finding was based on studies with small numbers of cases of each subtype and should be interpreted cautiously.

Several mechanisms have been proposed to explain the observed inverse association between tubal ligation and hysterectomy and ovarian cancer risk. One potential explanation is a “screening effect” wherein surgeons are
able to visualize abnormal changes in the ovaries during
pubal sterilizations or hysterectomies and remove pre-
malignant lesions. If the inverse association was solely
due to screening of the ovaries, these procedures would
be associated with a lower risk for only a few years after
the surgery; however this was not supported in our ana-
lysis as there was a strong inverse association even more
than 10 years after surgery. Another potential mech-
anism is that tubal ligation and hysterectomy protect the
ovary from carcinogens, such as talc, or inflammatory
agents such as retrograde menstruation or endometriosis
ascending the genital tract. Green et al. reported that
ovarian cancer risk may be altered by decreased blood
supply to the ovary after surgery resulting in a decrease
in estrogen production. However, while some studies
have observed decreases in hormone levels after tubal
ligation or hysterectomy, [51-53] others have not
[54,55]. This mechanism may only apply to procedures
that cause substantial damage to the surrounding tissue.
In the NHS, women who had undergone tubal ligation
during the time period when the unipolar electrocautery
method was commonly used had a reduced risk of
breast cancer [56]. However, tubal ligation was not asso-
ciated with breast cancer risk during other periods when
methods that caused less tissue destruction were com-
mon. To our knowledge, only one study examined ovar-
ian cancer risk by type of tubal ligation and observed a
lower risk irrespective of technique [26]. However this
analysis was based on only 20 cases and 58 controls and
thus had limited power. Lastly, several cancers, including
ovarian cancers, over-express the surface glycoprotein
MUC1. It has been hypothesized that women who have
undergone events that trigger an immune response to
MUC1 have a decreased risk of ovarian cancer [4]. A
recent study reported higher anti-MUC1 antibodies were
associated with a decreased risk of ovarian cancer
among women less than 64 years of age [57]. In the
same study, women who had undergone a tubal ligation
had higher mean levels of anti-MUC1 antibodies com-
pared to women who had not undergone a tubal
ligation; however there were no differences in antibodies
levels by hysterectomy status [57]. Further research is
needed to determine the associations between surgical
procedures, anti-MUC1 antibodies, and subsequent
ovarian cancer risk.

Our analysis has several limitations. Not all studies
reported whether cases were restricted to invasive ovar-
ian cancer, however when we restricted to studies that
reported effect estimates for invasive ovarian cancer the
summary RRs were very similar. Few studies reported ef-
fect estimates by surgical characteristics or histological
subtype of ovarian cancer. In addition, when reported,
these stratum-specific estimates were often based on
small numbers of exposed cases. To pool effect estimates
for analysis of age at and years since tubal ligation, we
created very broad categories (e.g., age at tubal ligation
<35 years, ≥35 years; hysterectomy <10 years ago,
≥10 years ago), which may obscure important effects.
Some of the studies in the meta-analysis included both
prevalent as well as incident ovarian cancer cases and
the case definition for one study was ovarian cancer
mortality. If tubal ligation or hysterectomy were asso-
ciated with survival after ovarian cancer diagnosis then
the inclusion of prevalent cases may bias the effect esti-
mates. However, a recent systematic review did not sup-
port an association between tubal ligation or
hysterectomy and survival from ovarian cancer [58].

In summary, we observed a consistent inverse associ-
ation of tubal ligation and hysterectomy on ovarian cancer
risk that may be causal. We did not detect differences by
study design, study population, or years since the proc-
ure, although our statistical power in these analyses was
somewhat limited. While gynecologic surgery may be a
potential prevention strategy for women at high risk of
ovarian cancer, additional research is needed to determine

| Table 4 Summary relative risks for hysterectomy and ovarian cancer by selected characteristics |
|---------------------------------------------------------------|
| Study design | Number of contributing studies | Random-effects RR (95%CI) |
| Cohort study | 24 studies | 0.73 (0.63, 0.85) |
| Case-control study | 24 studies | 0.73 (0.62, 0.86) |
| Geographic location | 24 studies | 0.81 (0.67, 0.97) |
| US | Non-US | 0.70 (0.59, 0.84) |
| Type of hysterectomy | 24 studies | 0.60 (0.47, 0.78) |
| With unilateral oophorectomy | Without oophorectomy | 0.62 (0.49, 0.79) |
| Unknown oophorectomy | 0.83 (0.71, 0.98) |
| Age at hysterectomy | 5 studies | 0.70 (0.55, 0.89) |
| <40/45 years of age | 40/45+ years of age | 0.83 (0.72, 0.96) |
| Years since hysterectomy | 7 studies | 0.69 (0.60, 0.79) |
| <10 years | 10+ years | 0.77 (0.66, 0.89) |
whether the effect of tubal ligation and hysterectomy on ovarian cancer risk differs by individual and surgical characteristics as well as considering the potential negative health effects of these procedures. Additional research also is needed to further understand the mechanisms behind these reduced risks.

Additional file

Additional file 1: Table S1, Table S2, Table S3, Table S4, Table S5. Epidemiologic Studies of the Association Between Tubal Ligation and Risk of Ovarian Cancer by Years Since Procedure. Epidemiologic Studies of the Association Between Tubal Ligation and Risk of Ovarian Cancer by Age at Procedure. Epidemiologic Studies of the Association Between Tubal Ligation and Risk of Ovarian Cancer by Histological Subtype. Epidemiologic Studies of the Association Between Hysterectomy and Risk of Ovarian Cancer by Years Since Procedure. Epidemiologic Studies of the Association Between Hysterectomy and Risk of Ovarian Cancer by Age at Procedure. [59].

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

MSR participated in the design of the study, conducted the literature search for all tubal ligation articles, extracted data, analyzed the data and authored the manuscript. MAM conducted the literature search for all hysterectomy articles and extracted data. SST participated in the design of the study, reviewed the data extracted, and helped draft the manuscript. All authors read and approved the final manuscript.

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