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

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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 (summery 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

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citation query to include pertinent articles, which referenced those already identified, using the Cited Reference Search application available through the Web of Science. All articles selected for inclusion in our analyses were verified by a second reviewer.

We abstracted relative risks (RRs) and 95% CIs or p-values from selected articles. We used estimates adjusted for multiple confounders when available and calculated standard errors from the 95% CIs or p-values. We decided apriori to use a random-effects model to calculate the summary RR estimates and 95% CIs [5]. Q tests for heterogeneity were used to evaluate the consistency of findings among studies and Begg's and Egger's tests were used to assess publication bias [6,7]. We conducted meta-regression analyses to assess whether effect estimates differed by study design (i.e., case–control versus cohort versus other design) and by population studied (i.e., general population versus BRCA mutation carriers) [8]. In secondary analyses, we conducted meta-regression analyses in subsets of the studies to assess whether the effect estimates differed by age at procedure, years since procedure, and, for the tubal ligation analysis, by histological subtype (i.e., serous, mucinous, endometrioid, clear cell, other). All analyses were conducted using the Stata/SE 10.0 for Windows.

Results

Database search

We identified 30 studies that provided estimates of the risk of ovarian cancer in relation to tubal ligation as well as the p-value or 95% confidence interval (CI) [9-37] to include in the meta-analysis (Figure 1). One of the studies examined the risk of ovarian cancer death [28] and three studies were conducted in BRCA carriers [13,18,20]. Therefore, we conducted sensitivity analyses examining the influence of these studies, which are detailed below. For the examination of hysterectomy and ovarian cancer, we identified 24 studies to include in the meta-analysis (Figure 1) [9,10,12,13,15,16,23-26,29,31,32,38-47]. Nine of the studies reported effect estimates for simple hysterectomy, [23,25,29,32,38,42,43,45] seven provided estimates for hysterectomy with unilateral oophorectomy, [23,29,32,38,42,45] and 15 did not distinguish whether or not women with hysterectomy underwent a unilateral oophorectomy [9,10,12,13,15,16,24,26,31,39-41,44,46,47]. 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].

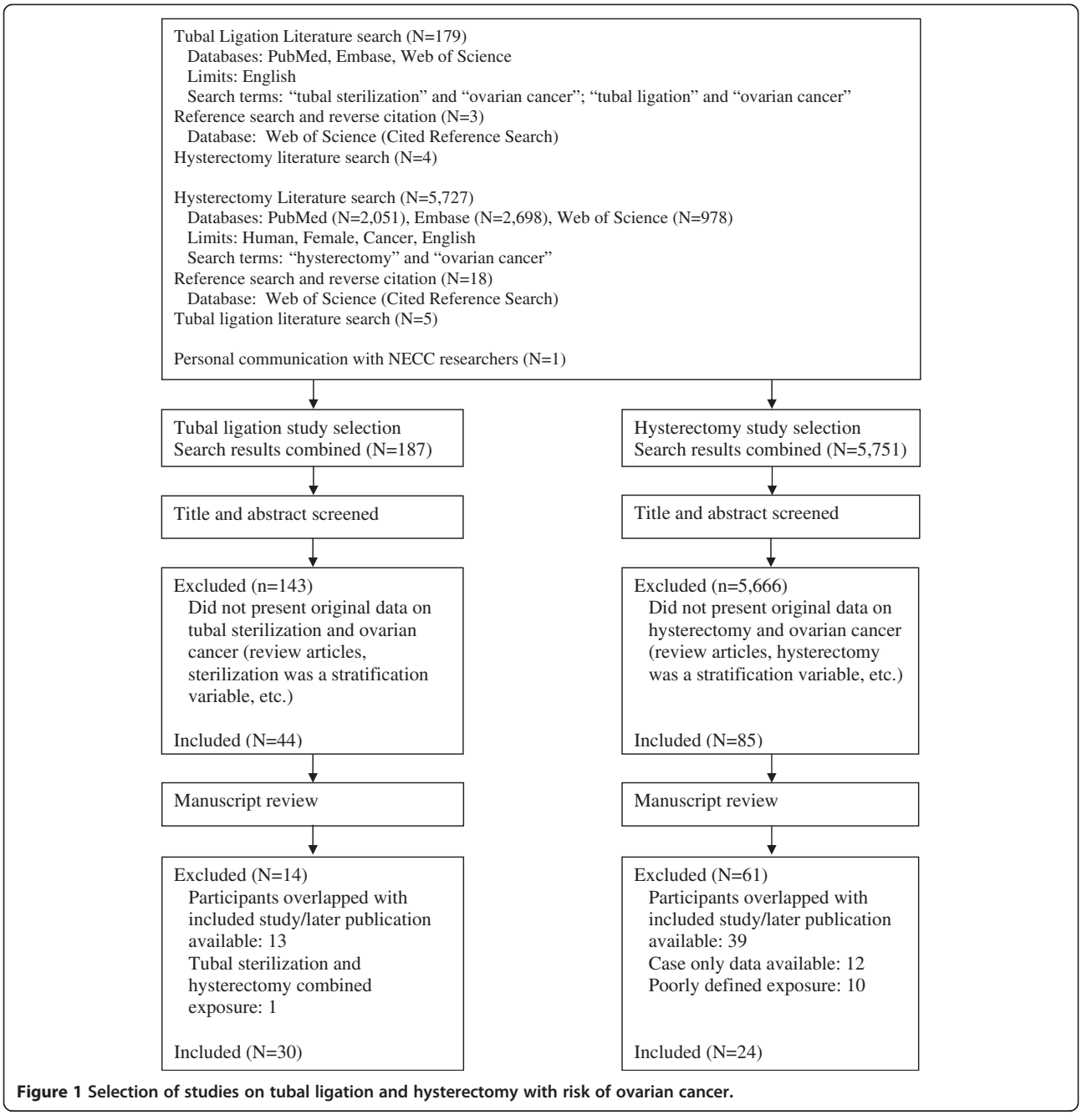

Figure 1 Selection of studies on tubal ligation and hysterectomy with risk of ovarian cancer.

Tubal ligation

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

Table 1 Epidemiologic Studies of the Association Between Tubal Ligation and Risk of Ovarian Cancer

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.

Table 1 Epidemiologic Studies of the Association Between Tubal Ligation and Risk of Ovarian Cancer *(Continued)*

Tworoger et al. 2007 (USA) [17]	Prospective cohort	Incident invasive epithelial ovarian cancer N=612 cases	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) N=799 cases BRCA1 N=670 BRCA2 N=128 BRCA1/2 N=1	Age, mutation type, country of residence, parity, breastfeeding, oral contraceptive use, ethnicity.	BRCA1+2 carriers: 0.78 (0.60, 1.00) BRCA1: 0.80 (0.59, 1.08) BRCA2: 0.63 (0.34, 1.15)	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 N=2098 cases	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 N=75 invasive cases N=21 borderline cases	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 N=36 BRCA1 cases N=381 noncarrier cases	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 N=477 cases	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 N=1124 cases	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 N=43 mucinous cases N=279 non-mucinous cases	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 N=108 observed cases in tubal ligation subcohort	Age, calendar year, length of follow-up	0.57 $p<0.001$	Calculated observed over expected events. Sensitivity analysis excluding borderline malignancies similar.

Table 1 Epidemiologic Studies of the Association Between Tubal Ligation and Risk of Ovarian Cancer *(Continued)*

Green, Purdie, et al. 1997 (Australia) [26]	Case-control	Incident, primary epithelial ovarian cancer N=824 cases	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 ca, 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.

Table 1 Epidemiologic Studies of the Association Between Tubal Ligation and Risk of Ovarian Cancer *(Continued)*

Koch et al. 1984 (Canada) [35]	Retrospective cohort	Ovarian cancer N=4 cases	Age, nulliparity	2.4 (0.9, 6.7)	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.

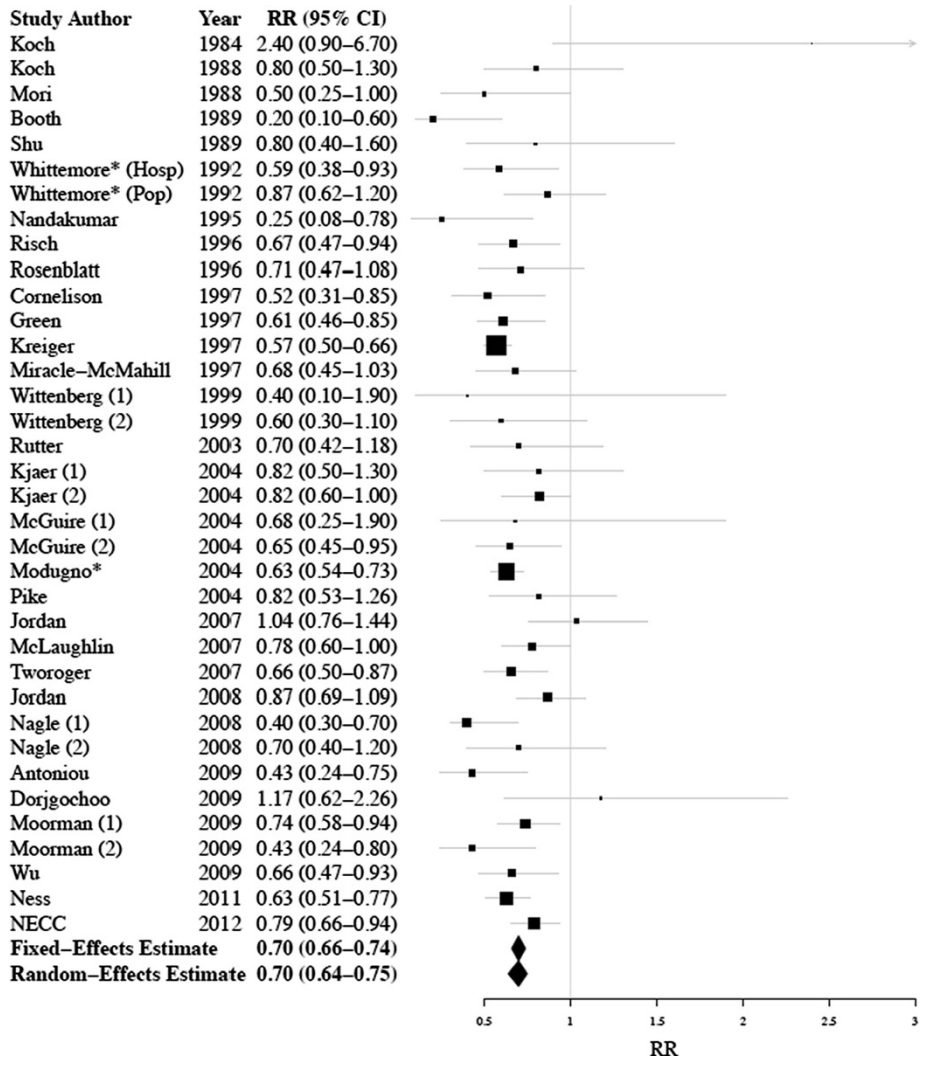

Figure 2 Forest plot for 30 studies of the association between tubal ligation and ovarian cancer risk. Forest plot summarizing individual effect estimates from 30 studies [9-37] contributing to summary effect estimates describing the association between tubal ligation and ovarian cancer risk. Black boxes mark the effect estimate for individual studies and the size of the black boxes represent the weight of individual studies in the summary estimate; horizontal gray lines demonstrate the width of the 95%CIs associated with each individual study; the black diamonds represent summary effect estimates; stars indicate pooled studies.

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-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

	Number of contributing studies	Random-effects RR (95%CI)
Study design	30 studies	
Cohort study		0.67 (0.50, 0.90)
Case-control study		0.70 (0.63, 0.75)
Other study design		0.95 (0.63, 1.43)
BRCA status	30 studies	
BRCA positive		0.64 (0.43, 0.96)
General population		0.70 (0.64, 0.76)
Geographic location	30 studies	
US		0.68 (0.63, 0.73)
Non-US		0.71 (0.61, 0.82)
Histologic subtype	11 studies	
Serous		0.75 (0.65,0.88)
Endometrioid		0.45 (0.33,0.61)
Mucinous		0.88 (0.70,1.09)
Clear cell		0.72 (0.55,0.94)
Other		0.80 (0.63,1.01)
Age at tubal ligation	7 studies	
<35 years of age		0.69 (0.59,0.81)
35+ years of age		0.79 (0.68,0.92)
Years since tubal ligation	6 studies	
<10 years		0.69 (0.59,0.79)
10+ years		0.68 (0.54,0.87)

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 RRs 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 note 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*-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

Table 3 Epidemiologic Studies of the Association Between Hysterectomy and Risk of Ovarian Cancer

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 and invasive 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, tubal ligation	Hysterectomy only: 1.10 (0.83-1.46) Hysterectomy with unilateral oophorectomy: 0.68 (0.46-0.99)	NECC 2012 (USA) [Personal communication with Dr. Daniel Cramer]
Annegers et al. 1979 (USA) [38]	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) [13]	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) BRCA1:0.68 (0.22, 2.12) BRCA2: 0.35 (0.08, 1.58)	Includes prevalent and incident cases. Mean difference between age at diagnosis and interview: 6.7 years
Beard et al. 2000 (USA) [40]	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)	
Booth et al 1989 (England) [32]	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)	Cases less than 65 years old and diagnosed within 2 years. Age-matched hospital-based controls.
Braem et al. 2010 (Netherlands) [41]	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) [42]	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) [26]	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) [43]	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) [10]	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) [16]	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)*

					For serous tumors by surgical indication:
				Mucinous: 0.95 (0.55-1.67)	Non-hormonal: 1.1 (0.5-2.7)
				Serous: 2.75 (1.90-3.96)	Hormonal: 3.0 (2.1-4.5)
Kreiger et al. 1997 (Canada) [25]	Historical cohort study	Ovarian cancer N=169 observed cases in hysterectomy subcohort	Age, calendar year, length of follow-up	Hysterectomy only: 0.72 p<0.001	Calculated observed over expected events.
					Sensitivity analysis excluding borderline malignancies similar.
Loft et al. 1997 (Denmark) [44]	Prospective historical cohort study	Ovarian cancer N=71	Age	Hysterectomy with and without unilateral oophorectomy: 0.78 (0.60-0.96)	N=22,135 women w/ hysterectomy (3940 of whom had unilateral oophorectomy)
					Follow-up=12.5 years
Luoto et al. 1997 (Finland) [39]	Historical cohort study	Ovarian cancer N=53 cases with partial hysterectomy	Adjusted for education, parity, and follow-up. Non-hysterectomized women had similar distributions of age and municipality.	Partial hysterectomy: RR=0.94 (0.68-1.30)	Ovarian status not assessed.
		N=91 cases with total hysterectomy		Total hysterectomy: RR=0.62 (0.48-0.80)	
Modugno et al. 2004 (USA) [9]	Pooled case-control	Epithelial ovarian cancer N=2098 cases	Study site, age, family history, duration of oral contraceptive use, parity, endometriosis, tubal ligation	Hysterectomy with or without unilateral oophorectomy: 0.99 (0.83-1.18)	Pooled analysis from four studies. Analyzed by endometriosis status.
Moorman et al. 2009 (USA) [12]	Case-control North Carolina Ovarian Cancer Study	Invasive epithelial ovarian cancer N=746 White cases	Age, parity, age at menarche, duration of OC use, family history of breast/ovarian cancer, BMI	Hysterectomy with or without unilateral oophorectomy:	
		N=111 African-Am cases		Whites: 1.22 (0.97, 1.54) African-	
				Americans: 1.07 (0.61, 1.87)	
Nagle et al. 2008 (Australia) [15]	Case-control	Invasive epithelial endometrioid and clear cell ovarian cancer	Age, education, parity, and hormone contraceptive use	Hysterectomy with or without unilateral oophorectomy:	47% participation rate in controls
		N=142 endometrioid cases		Endometrioid: 1.2 (0.8, 1.9)	
		N=90 clear cell cases		Clear cell: 0.9 (0.5, 1.6)	
Parazzini et al. 1993 (Italy) [45]	Case-control study	Epithelial ovarian cancer N=953 cases	Age, education, parity, oral contraceptive use, menarche, menopause	Hysterectomy only: 0.6 (0.5-0.9)	
				Hysterectomy with unilateral	
				oophorectomy: 0.6 (0.3-1.3)	
Risch et al. 1994 (Canada) [46]	Case-control	Epithelial ovarian cancer N=450 cases	Age, duration of OC use, number of full-term pregnancies	Hysterectomy with or without unilateral oophorectomy: 0.51 (0.36-0.72)	
Rosenblatt et al. 1996 (Multi-national) [29]	Case-control (Multi-site/country)	Borderline or invasive epithelial ovarian cancer N=385 cases	Age, date of diagnosis, center, parity, OC use	Hysterectomy only: 0.41 (0.14-1.21)	

Table 3 Epidemiologic Studies of the Association Between Hysterectomy and Risk of Ovarian Cancer *(Continued)*

				Hysterectomy with unilateral oophorectomy: 1.06 (0.34-3.29) Combined: 0.58 (0.27-1.28)	
Rutter et al. 2003 (Israel) [23]	Case-control	Epithelial ovarian cancer or primary peritoneal cancer N=1124 cases	Age, ethnicity, parity, years of oral contraceptive use	Hysterectomy only: 0.69 (0.50-0.95) Hysterectomy with unilateral oophorectomy: 0.46 (0.25-0.86)	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 N=2197 cases	Age, study, parity, OC use	Hysterectomy with or without unilateral oophorectomy: Hospital-based studies: 0.66 (0.50-0.86) Population-based studies: 0.88 (0.72-1.1)	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 N=43 mucinous cases N=279 non-mucinous cases	Age at diagnosis, parity, duration of OC use	Hysterectomy with or without unilateral oophorectomy: Mucinous: 0.2 (0.1, 1.0) Non-mucinous: 1.1 (0.7, 1.6)	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.

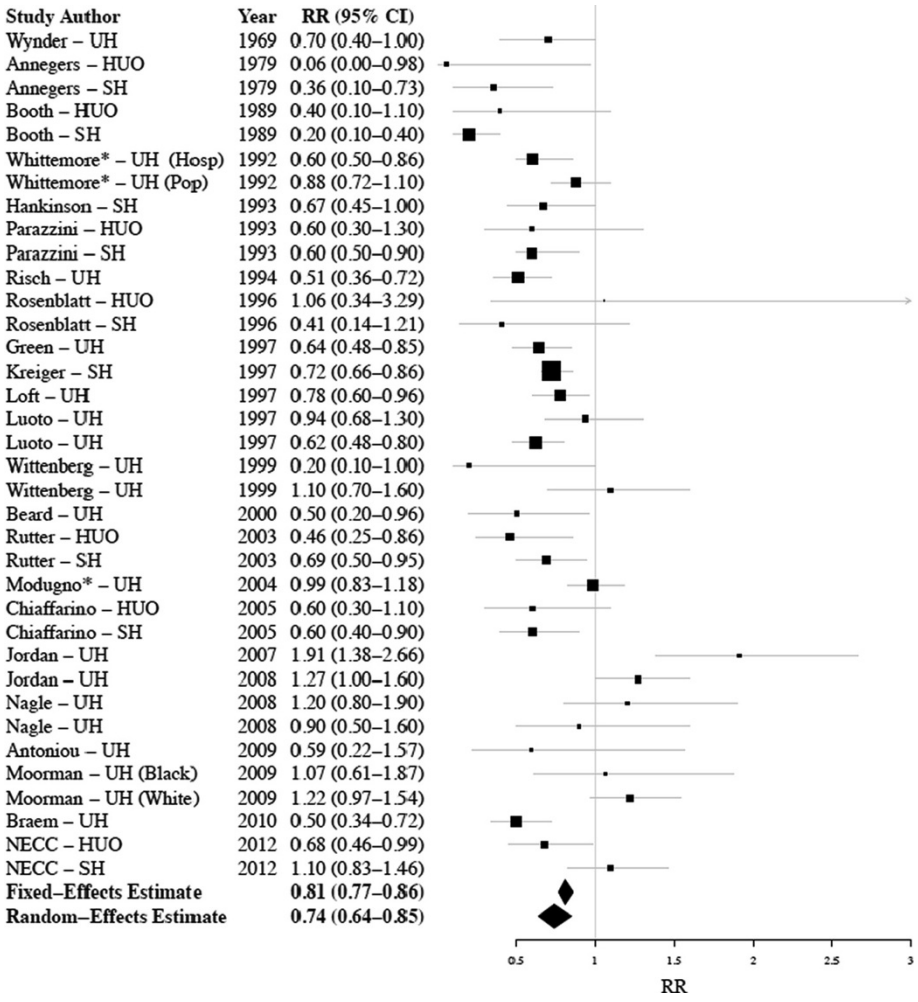

Figure 3 Forest plot for 24 studies of the association between hysterectomy and ovarian cancer risk. Forest plot summarizing individual effect estimates from 24 studies [9,10,12,13,15,16,23,26,29,31,32,38-47] contributing to summary effect estimates describing the association between hysterectomy and ovarian cancer risk. Black boxes mark the effect estimate for individual studies and the size of the black boxes represent the weight of individual studies in the summary estimate; horizontal gray lines demonstrate the width of the 95% CIs associated with each individual study; the black diamonds represent summary effect; stars indicate pooled studies. HUO=hysterectomy with unilateral oophorectomy, SH=simple hysterectomy, UH=unknown type of hysterectomy.

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

Table 4 Summary relative risks for hysterectomy and ovarian cancer by selected characteristics

	Number of contributing studies	Random-effects RR (95%CI)
Study design	24 studies	
Cohort study		0.73 (0.63, 0.85)
Case-control study		0.73 (0.62, 0.86)
Geographic location	24 studies	
US		0.81 (0.67, 0.97)
Non-US		0.70 (0.59, 0.84)
Type of hysterectomy	24 studies	
With unilateral oophorectomy		0.60 (0.47, 0.78)
Without oophorectomy		0.62 (0.49, 0.79)
Unknown oophorectomy		0.83 (0.71, 0.98)
Age at hysterectomy	5 studies	
<40/45 years of age		0.70 (0.55, 0.89)
40/45+ years of age		0.83 (0.72, 0.96)
Years since hysterectomy	7 studies	
<10 years		0.69 (0.60, 0.79)
10+ years		0.77 (0.66, 0.89)

able to visualize abnormal changes in the ovaries during tubal 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 analysis as there was a strong inverse association even more than 10 years after surgery. Another potential mechanism 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 was highest among women who used talc and did not have a tubal ligation or hysterectomy and lowest among women who had surgical sterilization, but did not use talc [26]. However, in the Nurses' Health Study (NHS), there was no variation in RR estimates of tubal ligation and ovarian cancer by talc use, and in a large case–control study, the inverse association of tubal ligation and hysterectomy was limited to non-talc users, contrary to the ascending carcinogen hypothesis [43,50].

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 associated with breast cancer risk during other periods when methods that caused less tissue destruction were common. To our knowledge, only one study examined ovarian 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 compared 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 ovarian cancer., however when we restricted to studies that reported effect estimates for invasive ovarian cancer the summary RRs were very similar. Few studies reported effect 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 associated with survival after ovarian cancer diagnosis then the inclusion of prevalent cases may bias the effect estimates. However, a recent systematic review did not support an association between tubal ligation or hysterectomy and survival from ovarian cancer [58].

In summary, we observed a consistent inverse association 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 procedure, 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

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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References
1. Society AC: *Cancer facts & Figures 2008*. 2008. In.
2. Moorman PG, Schildkraut JM, Calingaert B, Halabi S, Vine MF, Berchuck A: **Ovulation and ovarian cancer: a comparison of two methods for calculating lifetime ovulatory cycles (United States).** *Cancer Causes Control* 2002, **13**(9):807–811.
3. Lukanova A, Kaaks R: **Endogenous hormones and ovarian cancer: epidemiology and current hypotheses.** *Cancer Epidemiol Biomarkers Prev* 2005, **14**(1):98–107. doi:14/1/98.
4. Cramer DW, Titus-Ernstoff L, McKolanis JR, Welch WR, Vitonis AF, Berkowitz RS, Finn OJ: **Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer.** *Cancer Epidemiol Biomarkers Prev* 2005, **14**(5):1125–1131. doi:14/5/1125 10.1158/1055-9965.EPI-05-0035.
5. DerSimonian R, Laird N: **Meta-analysis in clinical trials.** *Control Clin Trials* 1986, **7**(3):177–188. doi:0197-2456(86)90046-2.
6. Begg CB, Mazumdar M, Egger M, Davey Smith G, Schneider M, Minder C, DerSimonian R, Laird N, Lau J, Ioannidis JP, Schmid CH: **Operating characteristics of a rank correlation test for publication bias Bias in meta-analysis detected by a simple, graphical test Meta-analysis in clinical trials Summing up evidence: one answer is not always enough.** *Biometrics* 1994, **50**(4):1088–1101.
7. Egger M, Davey Smith G, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test.** *BMJ* 1997, **315**(7109):629–634.
8. Lau J, Ioannidis JP, Schmid CH: **Summing up evidence: one answer is not always enough.** *Lancet* 1998, **351**(9096):123–127. doi:S0140-6736(97)08468-7 10.1016/S0140-6736(97)08468-7.
9. Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT: **Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis.** *Am J Obstet Gynecol* 2004, **191**(3):733–740. doi:S0002937804002819 10.1016/j.ajog.2004.03.035.
10. Jordan SJ, Green AC, Whiteman DC, Moore SP, Bain CJ, Gertig DM, Webb PM: **Serous ovarian, fallopian tube and primary peritoneal cancers: a comparative epidemiological analysis.** *Int J Cancer* 2008, **122**(7):1598–1603. doi:10.1002/ijc.23287.
11. Ness RB, Dodge RC, Edwards RP, Baker JA, Moysich KB: **Contraception methods, beyond oral contraceptives and tubal ligation, and risk of ovarian cancer.** *Ann Epidemiol*, **21**(3):188–196. doi:S1047-2797(10)00356-X 10.1016/j.annepidem.2010.10.002.
12. Moorman PG, Palmieri RT, Akushevich L, Berchuck A, Schildkraut JM: **Ovarian cancer risk factors in African-American and white women.** *Am J Epidemiol* 2009, **170**(5):598–606. doi:kwp176 10.1093/aje/kwp176.
13. Antoniou AC, Rookus M, Andrieu N, Brohet R, Chang-Claude J, Peock S, Cook M, Evans DG, Eeles R, Nogues C, Faivre L, Gesta P, van Leeuwen FE, Ausems MG, Osorio A, Caldes T, Simard J, Lubinski J, Gerdes AM, Olah E, Furhauser C, Olsson H, Arver B, Radice P, Easton DF, Goldgar DE: **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, **18**(2):601–610. doi:1055-9965.EPI-08-0546 10.1158/1055-9965.EPI-08-0546.
14. Dorjgochoo T, Shu XO, Li HL, Qian HZ, Yang G, Cai H, Gao YT, Zheng W: **Use of oral contraceptives, intrauterine devices and tubal sterilization and cancer risk in a large prospective study, from 1996 to 2006.** *Int J Cancer* 2009, **124**(10):2442–2449. doi:10.1002/ijc.24232.
15. Nagle CM, Olsen CM, Webb PM, Jordan SJ, Whiteman DC, Green AC: **Endometrioid and clear cell ovarian cancers: a comparative analysis of risk factors.** *Eur J Cancer* 2008, **44**(16):2477–2484. doi:S0959-8049(08)00544-3 10.1016/j.ejca.2008.07.009.
16. Jordan SJ, Green AC, Whiteman DC, Webb PM: **Risk factors for benign serous and mucinous epithelial ovarian tumors.** *Obstet Gynecol* 2007, **109**(3):647–654. doi:109/3/647 10.1097/01.AOG.0000254159.75977.fa.
17. 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, **166**(8):894–901. doi:kwm157 10.1093/aje/kwm157.
18. McLaughlin JR, Risch HA, Lubinski J, Moller P, Ghadirian P, Lynch H, Karlan B, Fishman D, Rosen B, Neuhausen SL, Offit K, Kauff N, Domchek S, Tung N, Friedman E, Foulkes W, Sun P, Narod SA: **Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case–control study.** *Lancet Oncol* 2007, **8**(1):26–34. doi:S1470-2045(06)70983-4 10.1016/S1470-2045(06)70983-4.
19. Kjaer SK, Mellemkjaer L, Brinton LA, Johansen C, Gridley G, Olsen JH: **Tubal sterilization and risk of ovarian, endometrial and cervical cancer. A Danish population-based follow-up study of more than 65 000 sterilized women.** *Int J Epidemiol* 2004, **33**(3):596–602. doi:10.1093/ije/dyh046 dyh046.
20. McGuire V, Felberg A, Mills M, Ostrow KL, DiCioccio R, John EM, West DW, Whittemore AS: **Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations.** *Am J Epidemiol* 2004, **160**(7):613–618. doi:10.1093/aje/kwh284 160/7/613.
21. Pike MC, Pearce CL, Peters R, Cozen W, Wan P, Wu AH: **Hormonal factors and the risk of invasive ovarian cancer: a population-based case–control study.** *Fertil Steril* 2004, **82**(1):186–195. doi:10.1016/j.fertnstert.2004.03.013 S0015028204005564.
22. Risch HA, Marrett LD, Jain M, Howe GR: **Differences in risk factors for epithelial ovarian cancer by histologic type. Results of a case–control study.** *Am J Epidemiol* 1996, **144**(4):363–372.
23. Rutter JL, Wacholder S, Chetrit A, Lubin F, Menczer J, Ebbers S, Tucker MA, Struewing JP, Hartge P: **Gynecologic surgeries and risk of ovarian cancer in women with BRCA1 and BRCA2 Ashkenazi founder mutations: an Israeli population-based case–control study.** *J Natl Cancer Inst* 2003, **95**(14):1072–1078.
24. Wittenberg J, Cook LS, Rossing MA, Weiss NS: **Reproductive risk factors for mucinous and non-mucinous epithelial ovarian cancer.** *Epidemiology* 1999, **10**(6):761–763.

25. Kreiger N, Sloan M, Cotterchio M, Parsons P: **Surgical procedures associated with risk of ovarian cancer.** *Int J Epidemiol* 1997, **26**(4):710–715.
26. Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, Ward B: **Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer.** *Survey of Women's Health Study Group. Int J Cancer* 1997, **71**(6):948–951. doi:10.1002/(SICI)1097-0215(19970611)71:6<948::AID-IJC6>3.0.CO;2-Y.
27. Cornelison TL, Natarajan N, Piver MS, Mettlin CJ: **Tubal ligation and the risk of ovarian carcinoma.** *Cancer Detect Prev* 1997, **21**(1):1–6.
28. Miracle-McMahill HL, Calle EE, Kosinski AS, Rodriguez C, Wingo PA, Thun MJ, Heath CW Jr: **Tubal ligation and fatal ovarian cancer in a large prospective cohort study.** *Am J Epidemiol* 1997, **145**(4):349–357.
29. Rosenblatt KA, Thomas DB: **Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives.** *Cancer Epidemiol Biomarkers Prev* 1996, **5**(11):933–935.
30. Nandakumar A, Anantha N, Dhar M, Ahuja V, Kumar R, Reddy S, Venugopal T, Rajanna VAT, Srinivas: **A case–control investigation on cancer of the ovary in Bangalore, India.** *Int J Cancer* 1995, **63**(3):361–365.
31. Whittemore AS, Harris R, Itnyre J: **Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case–control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group.** *Am J Epidemiol* 1992, **136**(10):1184–1203.
32. Booth M, Beral V, Smith P: **Risk factors for ovarian cancer: a case–control study.** *Br J Cancer* 1989, **60**(4):592–598.
33. Shu XO, Brinton LA, Gao YT, Yuan JM: **Population-based case–control study of ovarian cancer in Shanghai.** *Cancer Res* 1989, **49**(13):3670–3674.
34. Koch M, Jenkins H, Gaedke H: **Risk factors of ovarian cancer of epithelial origin: a case control study.** *Cancer Detect Prev* 1988, **13**(2):131–136.
35. Koch M, Starreveld AA, Hill GB, Jenkins H: **The effect of tubal ligation on the incidence of epithelial cancer of the ovary.** *Cancer Detect Prev* 1984, **7**(4):241–245.
36. Mori M, Harabuchi I, Miyake H, Casagrande JT, Henderson BE, Ross RK: **Reproductive, genetic, and dietary risk factors for ovarian cancer.** *Am J Epidemiol* 1988, **128**(4):771–777.
37. Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC: **Markers of inflammation and risk of ovarian cancer in Los Angeles County.** *Int J Cancer* 2009, **124**(6):1409–1415. doi:10.1002/ijc.24091.
38. Annegers JF, Strom H, Decker DG, Dockerty MB, O'Fallon WM: **Ovarian cancer: incidence and case–control study.** *Cancer* 1979, **43**(2):723–729.
39. Luoto R, Auvinen A, Pukkala E, Hakama M: **Hysterectomy and subsequent risk of cancer.** *Int J Epidemiol* 1997, **26**(3):476–483.
40. Beard CM, Hartmann LC, Atkinson EJ, O'Brien PC, Malkasian GD, Keeney GL, Melton LJ 3rd: **The epidemiology of ovarian cancer: a population-based study in Olmsted County, Minnesota, 1935–1991.** *Ann Epidemiol* 2000, **10**(1):14–23. doi:S1047-2797(99)00045-9.
41. Braem MG, Onland-Moret NC, van den Brandt PA, Goldbohm RA, Peeters PH, Kruitwagen RF, Schouten LJ: **Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study.** *Am J Epidemiol*, **172**(10):1181–1189. doi:kwq264 10.1093/aje/kwq264.
42. Chiaffarino F, Parazzini F, Decarli A, Franceschi S, Talamini R, Montella M, La Vecchia C: **Hysterectomy with or without unilateral oophorectomy and risk of ovarian cancer.** *Gynecol Oncol* 2005, **97**(2):318–322. doi:S0090-8258(05)00085-5 10.1016/j.ygyno.2005.01.030.
43. Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE: **Tubal ligation, hysterectomy, and risk of ovarian cancer.** *A prospective study. JAMA* 1993, **270**(23):2813–2818.
44. Loft A, Lidegaard O, Tabor A: **Incidence of ovarian cancer after hysterectomy: a nationwide controlled follow up.** *Br J Obstet Gynaecol* 1997, **104**(11):1296–1301.
45. Parazzini F, Negri E, La Vecchia C, Luchini L, Mezzopane R: **Hysterectomy, oophorectomy, and subsequent ovarian cancer risk.** *Obstet Gynecol* 1993, **81**(3):363–366.
46. Risch HA, Marrett LD, Howe GR: **Parity, contraception, infertility, and the risk of epithelial ovarian cancer.** *Am J Epidemiol* 1994, **140**(7):585–597.
47. Wynder EL, Dodo H, Barber HR: **Epidemiology of cancer of the ovary.** *Cancer* 1969, **23**(2):352–370.
48. Irwin KL, Weiss NS, Lee NC, Peterson HB: **Tubal sterilization, hysterectomy, and the subsequent occurrence of epithelial ovarian cancer.** *Am J Epidemiol* 1991, **134**(4):362–369.
49. Tung KH, Goodman MT, Wu AH, McDuffie K, Wilkens LR, Kolonel LN, Nomura AM, Terada KY, Carney ME, Sobin LH: **Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case–control study.** *Am J Epidemiol* 2003, **158**(7):629–638.
50. Cramer DW, Xu H: **Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer.** *Ann Epidemiol* 1995, **5**(4):310–314. doi:1047-2797(94)00098-E.
51. Hakverdi AU, Taner CE, Erden AC, Satici O: **Changes in ovarian function after tubal sterilization.** *Adv Contracept* 1994, **10**(1):51–56.
52. Radwanska E, Headley SK, Dmowski P: **Evaluation of ovarian function after tubal sterilization.** *J Reprod Med* 1982, **27**(7):376–384.
53. Cattanach J: **Oestrogen deficiency after tubal ligation.** *Lancet* 1985, **1**(8433):847–849. doi:S0140-6736(85)92209-3.
54. Garza-Flores J, Vazquez-Estrada L, Reyes A, Valero A, Morales del Olmo A, Alba VM, Bonilla C: **Assessment of luteal function after surgical tubal sterilization.** *Adv Contracept* 1991, **7**(4):371–377.
55. Wu E, Xiao B, Yan W, Li H, Wu B: **Hormonal profile of the menstrual cycle in Chinese women after tubal sterilization.** *Contraception* 1992, **45**(6):583–593.
56. Eliassen AH, Colditz GA, Rosner B, Hankinson SE: **Tubal sterilization in relation to breast cancer risk.** *Int J Cancer* 2006, **118**(8):2026–2030. doi: 10.1002/ijc.21582.
57. Pinheiro SP, Hankinson SE, Tworoger SS, Rosner BA, McKolanis JR, Finn OJ, Cramer DW: **Anti-MUC1 antibodies and ovarian cancer risk: prospective data from the Nurses' Health Studies.** *Cancer Epidemiol Biomarkers Prev*, **19**(6):1595–1601. doi:1055–9965.EPI-10-0068 10.1158/1055-9965.EPI-10-0068.
58. Nagle CM, Bain CJ, Green AC, Webb PM: **The influence of reproductive and hormonal factors on ovarian cancer survival.** *Int J Gynecol Cancer* 2008, **18**(3):407–413. doi:IJG1031 10.1111/j.1525-1438.2007.01031.x.
59. Modugno F, Ness RB, Wheeler JE: **Reproductive risk factors for epithelial ovarian cancer according to histologic type and invasiveness.** *Ann Epidemiol* 2001, **11**(8):568–574. doi:S1047279701002137.

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