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Tubal ligation, hysterectomy, and epithelial ovarian cancer in the New England Case-Control Study

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Abstract

Previous studies have observed that tubal ligation and hysterectomy are associated with a decreased risk of ovarian cancer; however little is known about whether these associations vary bysurgical characteristics, individual characteristics, or tumor histology. We used logistic regression to examine tubal ligation, simple hysterectomy, and hysterectomy with unilateral oophorectomy in relation to risk of epithelial ovarian cancer in the New England Case-Control study. Our primary analysis included 2,265 cases and 2,333 controls. Overall, tubal ligation was associated with a lower risk of epithelial ovarian cancer (OR: 0.82, 95%CI: 0.68-0.97), especially for endometrioid tumors (OR=0.45, 95%CI: 0.29-0.69). The inverse association between tubal ligation and ovarian cancer risk was stronger for women who had undergone the procedure at the time of last delivery (OR=0.60, 95%CI: 0.42-0.84) rather than at a later time (OR=0.93, 95%CI: 0.75-1.15). Overall, simple hysterectomy was not associated with ovarian cancer risk (OR: 1.09, 95%CI: 0.83, 1.42), although it was associated with a non-significant decreased risk of ovarian cancer among women who underwent the procedure at age 45 or older (RR: 0.64, 95%CI: 0.40, 1.02) or within the last 10 years (OR=0.65, 95%CI: 0.38, 1.13). Overall, women who had a hysterectomy with a unilateral oophorectomy had significantly lower risk of ovarian cancer (OR=0.65, 95%CI: 0.45-0.94). In summary, tubal ligation and hysterectomy with unilateral oophorectomy were inversely associated with ovarian cancer risk in a large population-based case-control study. Additional research is necessary to understand the potential biologic mechanisms by which these procedures may reduce ovarian cancer risk.

Keywords

tubal ligation; tubal sterilization; hysterectomy; epithelial ovarian cancer

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Introduction

Tubal ligation and hysterectomy are among the most commonly performed operations in the United States [1, 2] and have been associated with a lower risk of ovarian cancer [3]. In a recent meta-analysis, the inverse association for tubal ligation was stronger for endometrioid tumors [3]; however, this finding was based on a small number of studies. In addition, few studies have examined whether the association with hysterectomy varies by histological subtype or whether details of the surgical procedures or individual characteristics of women undergoing these surgeries influence the associations with ovarian cancer risk. Better understanding of factors that may modify these associations could elucidate the mechanisms by which these gynecologic surgeries reduce the risk of ovarian cancer as well as identify populations who would benefit most from these procedures. Therefore, we examined the relationship between ovarian cancer risk and tubal ligation as well as hysterectomy in the New England Case-Control study (NECC), taking advantage of the large sample size to assess whether these associations vary by surgical characteristics, individual characteristics, and tumor histology.

Materials and Methods

Study Population

Details of the population-based NECC have been described previously [4-6]. In brief, NECC occurred in five phases; however, data from the first phase (NECC1, between 1978 and 1981) were not available and therefore were not included. For the subsequent four phases, participants were enrolled from 1984–1987 (NECC2), 1992–1997 (NECC3), 1998–2003 (NECC4), and 2003–2008 (NECC5). We recruited 2,274 epithelial ovarian cancer cases from ten hospitals in Boston (NECC2) and through statewide cancer registries and tumor boards in Eastern Massachusetts and the State of New Hampshire (NECC3-5).

For NECC2, 4, and 5, controls were recruited through town resident lists (MA) and through drivers' license lists (NH); of the potential eligible identified controls, 1,918 agreed to participate (55% of eligible). For NECC3, 421 controls (72% of eligible) were recruited via random-digit dialing and town resident lists for a total of 2,339 controls. Controls were frequency matched to cases based on age and state of residence. For this analysis, we excluded nine cases and five controls who had a hysterectomy, but did not report whether an ovary was removed. In addition, we excluded one control who reported that her tubal ligation was a salpingectomy.

In-person interviews were administered to all study participants to obtain detailed data on lifestyle factors, reproductive history, medical history, body size, and family history of breast and ovarian cancer. We ascertained information on exposures occurring at least one year prior to diagnosis (cases) or study enrollment (controls) to avoid the potential impact of preclinical disease on these factors. This study was approved by the Institutional Review Board at Brigham and Women's Hospital in Boston, MA and the Geisel School of Medicine at Dartmouth in Hanover, NH. Written informed consent was obtained from all study participants.

Exposure, Covariate, and Outcome Assessment

The primary exposures of interest were self-reported tubal ligation (no, yes), simple hysterectomy (i.e., removal of the uterus without removal of an ovary) (no, yes) and hysterectomy with unilateral oophorectomy (i.e., removal of the uterus as well as the removal of one ovary) (no, yes). The following self-reported surgical characteristics were available for subsets of NECC participants: timing of tubal ligation (at time of last delivery [vaginal or caesarian section] or after last delivery) in NECC3-5 (n=4,063), type of tubal

ligation (by tying, banding, burning) in NECC4-5 (n=2,809), and type of hysterectomy (abdominal, vaginal) in NECC3-5 (n=4,128). In addition, we calculated age at, time since, and year of both tubal ligation and hysterectomy for participants in all four phases. Interview questions on tubal ligation and hysterectomy varied slightly across study phases [Supplemental Table 1]. We used data from in-person interviews for the following covariates: age (continuous), parity (nulliparous, 1, 2, 3, 4+ live born), breastfeeding duration (continuous), family history of ovarian cancer and/or early onset breast cancer (yes, no), oral contraceptive (OC) use (<3 months, 3 months to <1 year, 1 to < 3, 3 to <6, 6 to <12, 12+ years), genital talc use (yes, no), body mass index (BMI) (<23, 23 to <25, 25 to <30, 30+ kg/m^2), smoking status (never, former, current), age at menarche (<12, 12, 13, 14, 15+ years), menopausal status (premenopausal, postmenopausal), estrogen only postmenopausal hormone (PMH) use (never, ever), estrogen and progesterone PMH use (never, ever), and other PMH use (never, ever). Data on PMH use was only available for NECC phases 2, 4, and 5. Pathology reports were collected for all cases and reviewed by a gynecologic pathologist who classified tumors by behavior and histology (serous - borderline, serous – invasive, mucinous – borderline, mucinous – invasive, endometrioid, clear cell, other).

Statistical Analysis

We used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for epithelial ovarian cancer by tubal ligation, simple hysterectomy and hysterectomy with unilateral oophorectomy. Polytomous logistic regression was used to estimate ORs and 95%CIs for ovarian cancer defined by behavior and histological subtype. In secondary analyses, we modeled timing and type of surgery as well as age at, time since, and year of the surgery as categorical exposures. Likelihood ratio tests were used to assess whether ORs for ovarian cancer varied by histological subtype as well as by surgical and individual characteristics. In addition, for age at, time since, and year of surgery we also conducted ordinal trend tests.

Minimally-adjusted models included age, study center (MA, NH), and study phase (NECC2-5). Multivariate models additionally adjusted for putative or established ovarian cancer risk factors including breastfeeding duration, parity, OC use, BMI, smoking status, age at menarche, PMH use, family history of ovarian cancer and/or early onset breast cancer, genital talc use, menopausal status, hysterectomy (in the tubal ligation analyses) and tubal ligation (in the hysterectomy analyses). In the polytomous models, we allowed the relationship between ovarian cancer and age, parity, PMH use, and breastfeeding to vary by subtype and constrained all other covariates to obtain the best adjustment for potential confounding based on previous findings.

In addition, we evaluated whether the following individual characteristics modified the associations with ovarian cancer risk: parity (nulliparous, parous), genital talc use (ever, never), endometriosis (ever, never), OC use (ever, never), family history of ovarian cancer and/or early onset breast cancer (yes, no), and age at diagnosis/interview (<50, 50+). We conducted likelihood ratio tests comparing multivariate models with and without multiplicative interaction terms to determine whether the associations varied significantly by these factors.

For all analyses, two-sided $p < 0.05$ was considered statistically significant. We performed all analyses using SAS software release version 9.3 (Cary, NC) and STATA version 11 (College Station, TX).

Results

This analysis included 2,265 cases and 2,333 controls. Tubal ligation and hysterectomy with unilateral oophorectomy were less common in cases than controls (12.8% vs. 18.5% and 2.5% vs. 3.2%, respectively) [Table 1]. However, a similar proportion of cases and controls underwent simple hysterectomy (6.1% vs. 5.7%). Overall, cases were less likely to have ever used OCs, to have ever used estrogen and progesterone PMH, or be parous and were more likely to be talc users and have a family history of ovarian and/or early breast cancer compared to controls.

In our minimally-adjusted model, women who had a tubal ligation had a 36 percent lower risk of ovarian cancer compared to women who did not have a tubal ligation (OR=0.64, 95%CI: 0.54-0.75) [Table 2]. The odds ratio was somewhat attenuated when we adjusted for known and suspected ovarian cancer risk factors, mainly due to the effect of parity (OR=0.82, 95%CI: 0.68-0.97). In minimally or multivariate-adjusted models, there was no association between ovarian cancer risk and simple hysterectomy (OR=1.07, 95%CI: 0.84-1.37 and OR=1.09, 95%CI: 0.83-1.42, respectively). Hysterectomy with unilateral oophorectomy was suggestively inversely associated with ovarian cancer risk in the minimally-adjusted model (OR=0.78, 95%CI: 0.55-1.11) and significantly inversely associated after adjustment for ovarian cancer risk factors, especially PMH use (OR=0.65, 95%CI: 0.45-0.94).

While there was no statistically significant difference by histological subtype (p-for-heterogeneity=0.47), tubal ligation was more strongly associated with endometrioid tumors (OR=0.45, 95% CI=0.29-0.69) and invasive mucinous tumors (OR=0.47, 95%CI: 0.22-0.99) compared to other histologic types. There was significant heterogeneity by histological subtype for hysterectomy with unilateral oophorectomy ($p<0.01$), with a significant inverse association for invasive serous tumors (OR=0.62, 95%CI: 0.40-0.98).

We next examined whether the association between tubal ligation and ovarian cancer risk varied by participant or surgical characteristics. Women who had tubal ligation postpartum (i.e., at the time of last delivery) had a 40 percent lower risk of ovarian cancer compared to women who never had a tubal ligation (OR=0.60, 95%CI: 0.42-0.84) [Table 3]. In contrast, tubal ligation at a later time was not associated with ovarian cancer risk (OR=0.93, 95% CI=0.75-1.15, p-for-heterogeneity=0.02). Among women who had a tubal ligation at the time of their last delivery, those who had a cesarean section had a suggestively stronger lower risk of ovarian cancer (OR=0.48, 95% CI=0.28-0.82) compared to those whose last delivery was a vaginal birth (OR=0.68, 95% CI=0.44-1.05; p-heterogeneity=0.31). Tubal ligation was strongly associated with risk among women who underwent the procedure 30 or more years ago (OR=0.54, 95%CI: 0.35-0.83). In addition, tubal ligation was not associated with ovarian cancer among women who were 40 or older at time of the surgery (OR=1.07, 95%CI: 0.73-1.56). However, differences in the associations for tubal ligation by age at tubal ligation, years since tubal ligation, or type of surgery (by tying, banding or burning) did not reach statistical significance. Lastly, tubal ligation was inversely associated with ovarian cancer risk among women who underwent the procedure in the 1980's or the 1990's, but not among women who had a tubal ligation in the 1970s or earlier (p for heterogeneity=0.21, p for trend=0.03).

We did not observe differences in the associations between simple hysterectomy or hysterectomy with unilateral oophorectomy with ovarian cancer risk by type of hysterectomy (abdominal vs vaginal), years since hysterectomy, or year of hysterectomy. However, simple hysterectomy was suggestively inversely associated with ovarian cancer risk among women who were age 45 or older at the time of the procedure (OR=0.64,

95%CI: 0.40-1.02, p for heterogeneity=0.05) as well as among women who underwent a hysterectomy within the last 10 years (OR=0.65, 95%CI: 0.38, 1.13, p for heterogeneity=0.06). [Supplemental Table 2].

The associations between the tubal ligation or hysterectomy and ovarian cancer risk did not vary significantly by parity, OC use, age at diagnosis/interview or family history of ovarian cancer/early onset breast cancer [data not shown]. However, simple hysterectomy was associated with a significantly higher risk of ovarian cancer among women who ever used genital talc, but a non-significant lower risk of ovarian cancer among those who never used genital talc (OR=0.81, 95% CI=0.59-1.13 in never users; OR=1.96, 95% CI=1.20-3.10 in ever users, p-for-heterogeneity=0.01). Though not statistically significant, we observed a stronger inverse association for tubal ligation in women with endometriosis (OR=0.56, 95% CI=0.28-1.09) compared to those without (OR=0.85, 95%CI=0.70-1.02; p-interaction=0.07) as well as a stronger inverse association for nulliparous women (OR=0.43, 95%CI: 0.21, 0.90) compared to parous women (OR=0.85, 95%CI: 0.71, 1.02; p-interaction=0.09).

Discussion

The results of this large population based case-control study support previous findings that tubal ligation is inversely associated with ovarian cancer, particularly endometrioid tumors. Our data further suggest that tubal ligation is more strongly associated with risk if conducted at the time of last delivery, as opposed to a later time. We did not observe an overall association between simple hysterectomy and ovarian cancer, but hysterectomized women who had used talc were at increased risk and those 45 years of age or older at surgery appeared to have a decreased risk. Overall, hysterectomy with unilateral oophorectomy was inversely associated with epithelial ovarian cancer.

Many studies have observed a strong inverse association between tubal ligation and ovarian cancer risk [7-19] and several have suggested the association is stronger among women who were younger at and had a longer time since tubal ligation [10-12, 15, 20-23]. However, it is difficult to separate these factors because women who were younger at tubal ligation generally have a longer time between surgery and diagnosis. Our results suggest that tubal ligation conducted before age 40 or conducted 30 or more years ago may be more strongly associated with a lower risk of ovarian cancer. Additionally, two previous meta-analyses reported that tubal ligation is most strongly associated with endometrioid tumors [24, 25]. Overall, our findings are consistent with these previously reported results. Importantly, we observed that the association for tubal ligation was similar for women with versus without a family history of ovarian and/or early breast cancers, consistent with studies observing an inverse association in BRCA positive women [15, 26, 27].

Several biologic mechanisms may explain the inverse association observed between tubal ligation and ovarian cancer. Tubal ligation may impede inflammatory agents, such as endometrial tissue, from traveling up the fallopian tubes to the ovaries [28-30] and thereby prevent the inflammation induced tumor promotion that has been proposed as an etiologic pathway for endometrioid and clear cell ovarian tumors [31]. Endometriosis consistently has been linked to endometrioid and clear cell tumors [31, 32] and may lead to inflammation-induced tumor promotion [33]. Our observations of stronger inverse associations for endometrioid tumors and among women reporting a diagnosis of endometriosis support this hypothesis. Alternatively, tubal ligation may lower cancer risk through the induction of anti-MUC1 antibodies. MUC1 is heavily expressed on reproductive tract epithelia and injury of this tissue, including tubal ligation and caesarian section, is associated with elevated MUC1 antibodies [34]. As MUC1 is overexpressed on ovarian tumors these antibodies may help clear ovarian cancer cells.

We observed that tubal ligation at time of last delivery was more protective than at later times. Further, our data suggested that tubal ligation after cesarean section was most protective. Tubal ligation occurring within hours of birth may be advantageous because there is easy access to the tubes, which may result in more effective sterilization, protecting not only from subsequent pregnancies, but also from ascending carcinogens [35]. However, data regarding the quality of post-partum tubal sterilzation is inconsistent [36]. Alternatively, an immune response, characterized by elevated anti-MUC1 antibodies, previously noted for tubal ligation may be more robust immediately following pregnancy, especially with a cesarean section, when both MUC1 and anti-MUC1 antibodies are known to be elevated [37, 38].

Consistent with most previous work [9, 39-42], our data suggest that hysterectomy with unilateral oophorectomy is inversely associated with ovarian cancer. While many previous studies have observed an inverse association with simple hysterectomy [9, 12, 20, 29, 39-42], there was no association in the NECC. Contrary to findings in a previous meta-analysis [3], simple hysterectomy was suggestively associated with lower ovarian cancer risk among women who were 45 years of age or older at time of their hysterectomy or underwent the procedure within the last 10 years in the current study. However, given the overall null findings for hysterectomy in this study, these results may be due to chance. It is not clear why our results are inconsistent with most prior findings. While hysterectomy rates are lower in the Northeast US compared to other geographic regions, we would expect these lower rates to reduce power in our study rather than bias effect estimates.[43] As in most case-control studies, controls without ovaries or whose ovarian status was unknown were excluded from the study, which may have resulted in hysterectomy being underrepresented in the controls compared to the underlying study population.

Our study has some limitations. The average time between diagnosis and interview is 9 months suggesting we may have not included the most aggressive cases. As with all retrospective case-control studies, there is the possibility of recall bias. However, tubal ligation and hysterectomy are generally well-reported, therefore any misclassification of these procedures, and resulting bias, should be small. There is some evidence that there may be greater error in self-reported oophorectomy which could result in a greater potential for bias.[44] A large proportion of women who were asked about the type of procedure they underwent were unable to provide details of their surgery, limiting power for our secondary analyses. Last, our study population is limited to a largely Caucasian population in New England in which the prevalence of hysterectomy was low, thus our results may not be generalizable to other populations. The primary strengths of our study include a large sample of epithelial ovarian cases with excellent tumor classification, detailed epidemiologic information to control for potential confounding, and population-based controls.

Conclusion

Tubal ligation was associated with an 18% lower risk of ovarian cancer. We observed a stronger inverse association for endometrioid tumors and among women who underwent the procedure at the time of their last delivery. While hysterectomy with unilateral oophorectomy was associated with a 35% lower risk of ovarian cancer, there was no overall association with simple hysterectomy. Additional research is needed to understand the potential biologic mechanisms by which these procedures may reduce ovarian cancer risk. Further understanding of how these procedures may affect ovarian carcinogenesis could lead to improved prevention recommendations for ovarian cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PMH	postmenopausal hormone
OC	oral contraceptives
BMI	body mass index
OR	odds ratio
CI	confidence interval
NECC	New England Case-Control study

Novelty/Impact

In previous studies, tubal ligation and hysterectomy were inversely associated ovarian cancer risk; however little is known about whether these associations vary by surgical characteristics or tumor histology. In this large case-control study, the inverse association with tubal ligation was stronger for endometrioid tumors and among women who underwent the procedure after their last childbirth. While hysterectomy with unilateral oophorectomy was inversely associated with ovarian cancer risk, there was no overall association with simple hysterectomy.

Table 1

Reproductive and non-reproductive characteristics of cases and controls in the New England Case-Control study, 1984-2008.

		Case		Control	
Mean (SD)		**Mean**	**SD**	**Mean**	**SD**
Age[a]		52.3	12.4	52.3	12.7
BMI (kg/m2)		26.3	6.2	25.9	5.5
Age at menarche		12.7	1.7	12.8	1.7
Years of OC use		5.1	4.8	5.9	5
Parity (among parous)		2.5	1.3	2.7	1.4
Years breastfeeding (among parous)		0.5	0.9	0.7	1.2
Frequency (%)		**N**	**%**	**N**	**%**
Nulliparous	No	1538	67.9	1913	82.0
	Yes	727	32.1	420	18.0
Talc Use	No	1528	67.5	1698	72.8
	Yes	737	32.5	635	27.2
Oral contraceptive use	Never	1207	53.3	977	41.9
	Ever	1058	46.7	1356	58.1
Family history of ovarian cancer or early breast cancer	No	2060	91.0	2180	93.4
	Yes	205	9.1	153	6.6
Smoking status	Never	1047	46.2	1106	47.4
	Past	807	35.6	870	37.3
	Current	411	18.2	357	15.3
Menopausal status	Premenopausal	1011	44.6	1046	44.8
	Postmenopausal	1254	55.4	1287	55.2
Estrogen only use	Never	1129	90.0	1165	90.5
	Ever	125	10.0	122	9.5
Estrogen and Progesterone Use	Never	1086	86.6	1024	79.6
	Ever	168	13.4	263	20.4
Other PMH Use	Never	1247	99.4	1267	98.5
	Ever	7	0.6	20	1.6

		Case		Control	
Mean (SD)		**Mean**	**SD**	**Mean**	**SD**
Tubal Ligation	No	1975	87.2	1901	81.5
	Yes	290	12.8	432	18.5
Hysterectomy	None	2071	91.4	2128	91.2
	Simple Hysterectomy	138	6.1	132	5.7
	Hysterectomy with oophorectomy	56	2.5	73	3.1

[a]Frequency matching factor

Table 2

Odd ratios for total epithelial ovarian cancer and by histologic subtypes by tubal ligation, simple hysterectomy or hysterectomy with unilateral oophorectomy in the New England Case-Control study, 1984-2008.

		Tubal Ligation			Simple hysterectomy			Hysterectomy with oophorectomy		
Cases (N)		**Minimally-Adjusted[a] OR (95%CI)**	**Multivariate-adjusted[b] OR (95%CI)**	**P for het[c]**	**Minimally-Adjusted[a] OR (95%CI)**	**Multivariate-adjusted[b] OR (95%CI)**	**P for het[c]**	**Minimally-Adjusted[a] OR (95%CI)**	**Multivariate-adjusted[b] OR (95%CI)**	**P for het[c]**
2265	All	**0.64 (0.54,0.75)**	**0.82 (0.68,0.97)**		1.07 (0.84,1.37)	1.09 (0.83,1.42)		0.78 (0.55,1.11)	0.65 (0.45,0.94)	
1008	Serous – invasive	**0.81 (0.66, 0.99)**	0.93 (0.75, 1.16)	0.47	1.23 (0.92, 1.65)	1.24 (0.91, 1.69)	0.80	0.76 (0.49, 1.16)	0.62 (0.40, 0.98)	<0.01
286	Serous – borderline	0.83 (0.58, 1.19)	1.09 (0.74, 1.59)		1.30 (0.71, 2.36)	1.35 (0.74, 2.47)		1.23 (0.94, 1.63)	1.23 (0.91, 1.64)	
116	Mucinous – invasive	**0.35 (0.17, 0.73)**	**0.47 (0.22, 0.99)**		0.33 (0.08, 1.35)	0.34 (0.08, 1.42)		0.88 (0.27, 2.87)	0.90 (0.27, 2.99)	
168	Mucinous - borderline	0.75 (0.46, 1.21)	0.94 (0.57, 1.57)		0.84 (0.33, 2.10)	0.78 (0.31, 2.00)		1.04 (0.32, 3.40)	0.92 (0.28, 3.06)	
365	Endometriod	**0.33 (0.22, 0.50)**	**0.46 (0.30,0.71)**		0.78 (0.45, 1.36)	0.83 (0.46,1.47)		0.73 (0.34,1.53)	0.63 (0.29,1.36)	
132	Clear Cell	**0.47 (0.26,0.85)**	0.87 (0.46,1.62)		0.54 (0.20, 1.51)	0.87 (0.20,1.66)		0.24 (0.03,1.74)	0.20 (0.03,1.53)	
190	Other	0.65 (0.42,1.00)	0.77 (0.49,1.22)		1.30 (0.74, 2.28)	1.17 (0.65,2.11)		0.59 (0.21,1.63)	0.47 (0.17,1.34)	

[a] Model adjusted for age one year prior to enrollment (continuous), study center (MA, NH) and study phase (NECC2-5).

[b] Model adjusted for age one year prior to enrollment (continuous), study center (MA, NH), study phase (NECC2-5), breastfeeding duration (continuous), parity (nulliparous, 1, 2, 3, 4+ live born), OC use (<3 months, 3 months to <1 year, 1 to < 3 years, 3 to <6 years, 6 to <12 years, 12+ years), BMI (<23 kg/m^2, 23 to <25 kg/m^2, 25 to <30 kg/m^2, 30+ kg/m^2), smoking status (never, former, current), age at menarche (7 to <12, 12, 13, 14, 15+ years old), postmenopausal hormone (PMH) use (never, ever estrogen, ever estrogen plus progesterone, ever other type of hormone), family history of ovarian cancer or early onset breast cancer, talc use (yes, no), and menopausal status (premenopausal, postmenopausal) and hysterectomy status (never, ever) in TL model and TL (never, ever) in hysterectomy model. Simple hysterectomy and hysterectomy with unilateral oophorectomy were modeled simultaneously.

[c] p-heterogeneity was determined by a likelihood-ratio test comparing a polytomous logistic regression model which assumed that estimates by histologic subtype differed compared to a model which assumed estimates by histologic subtypes did not differ.

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Table 3

Odd ratios for epithelial ovarian cancer by surgical details of tubal ligation in the New England Case-Control study, 1984-2008.

	Cases (N)	Minimally-adjusted[a] OR	Multivariate- adjusted[b] OR	P for Heterogeneity[c]	P for trend
Timing of TL procedure					
At last delivery	57	**0.46(0.33,0.64)**	**0.60(0.42,0.84)**	**0.02**	
After last delivery	198	**0.73(0.60,0.89)**	0.93(0.75,1.15)		
Type of last delivery					
Vaginal	36	**0.51(0.34,0.78)**	0.68(0.44,1.05)	0.31	
C-section	21	**0.38(0.23,0.64)**	**0.48(0.28,0.82)**		
Type of TL procedure					
Tying	57	**0.66(0.47,0.94)**	0.81(0.56,1.16)	0.87	
Banding	12	0.55(0.27,1.12)	0.67(0.32,1.42)		
Burning	45	**0.60(0.41,0.88)**	0.73(0.49,1.09)		
Age at TL					
<30	62	**0.63(0.45,0.88)**	0.71(0.50,1.00)	0.39	0.21
30-34	89	**0.64(0.48,0.84)**	0.83(0.62,1.10)		
35-39	82	**0.55(0.42,0.73)**	0.75(0.56,1.01)		
40+	56	0.81(0.56,1.17)	1.07(0.73,1.56)		
Years since TL					
<10	36	**0.51(0.34,0.77)**	0.74(0.48,1.13)	0.15	0.32
10-20	99	**0.69(0.53,0.91)**	0.92(0.69,1.22)		
20-30	118	**0.71(0.56,0.92)**	0.88(0.68,1.15)		
30+	36	**0.47(0.31,0.71)**	**0.54(0.35,0.83)**		
Year of TL					
<1970	27	0.95(0.55,1.64)	1.13(0.64,1.99)	0.21	**0.03**
1970s	123	**0.73(0.57,0.93)**	0.92(0.71,1.19)		
1980s	108	**0.58(0.45,0.74)**	**0.73(0.56,0.95)**		
1990+	31	**0.44(0.28,0.68)**	**0.61(0.39,0.96)**		

[a]Model adjusted for age one year prior to enrollment (continuous), study center (MA, NH) and study phase (NECC2-5).

[b] Model adjusted for age one year prior to enrollment (continuous), study center (MA, NH), study phase (NECC2-5), breastfeeding duration (continuous), parity (nulliparous, 1, 2, 3, 4+ live born), OC use (<3 months, 3 months to <1 year, 1 to < 3 years, 3 to <6 years, 6 to <12 years, 12+ years), BMI (<23 kg/m^2, 23 to <25 kg/m^2, 25 to <30 kg/m^2, 30+ kg/m^2), smoking status (never, former, current), age at menarche (7 to <12, 12, 13, 14, 15+ years old), postmenopausal hormone (PMH) use (never, ever estrogen, ever estrogen plus progesterone, ever other type of hormone), family history of ovarian cancer or early onset breast cancer, talc use (yes, no), and menopausal status (premenopausal, postmenopausal) and hysterectomy status (never, ever.)

[c] P for heterogeneity was calculated for the multivariate-adjusted models.