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Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses' Health Studies

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Abstract

Objective—To prospectively examine if the association between tubal ligation, hysterectomy, unilateral oophorectomy, and ovarian cancer varied by patient, tumor, and surgical characteristics.

Design—Two prospective cohort studies (Nurses' Health Study and NHSII).

Setting—Participants were identified from across the US and followed for up to 34 years.

Patient(s)—A cohort of 121,700 married US female nurses, aged 30 to 55 at baseline and another cohort of 116,430 US female nurses aged 25 to 42 at baseline.

Intervention(s)—We obtained data on gynecologic surgeries and ovarian cancer incidence through biennial questionnaires. We calculated hazard ratios and 95% confidence intervals adjusted for known and suspected ovarian cancer risk factors.

Main Outcome Measure(s)—Confirmed incident epithelial ovarian cancer.

Results—Overall, tubal ligation was associated with a decreased risk of ovarian cancer HR: 0.76, 95%CI: 0.64–0.90). The inverse association was stronger for non-serous tumors (HR: 0.57, 95%CI: 0.40–0.82) and among women younger than 35 at surgery HR: 0.67, 95%CI: 0.49–0.90). Hysterectomy was associated with a decreased risk of ovarian cancer (HR: 0.80, 95%CI: 0.66–0.97) and was somewhat stronger for non-serous tumors (HR: 0.70, 95%CI: 0.49–1.02). Unilateral oophorectomy was associated with a 30% lower risk (HR: 0.70, 95%CI: 0.53–0.91), which did not differ by histologic subtype.

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COMPETING INTERESTS
The authors have no competing interests to declare.

Conclusions—Our study provides further support that tubal ligation reduces the risk of ovarian cancer, particularly for non-serous tumors and when conducted prior to age 35. The inverse association with hysterectomy along with the stronger associations for non-serous tumors supports shared biologic mechanisms for tubal ligation and hysterectomy.

Keywords

Tubal ligation; hysterectomy; unilateral oophorectomy; ovarian cancer

INTRODUCTION

Tubal ligation and hysterectomy are commonly performed operations (1, 2) that have been associated with a lower risk of ovarian cancer, particularly endometrioid tumors (3, 4). We recently reported that the benefits of tubal ligation were stronger for women who received the procedure at the time of last delivery and a suggestion that hysterectomy is more protective at older ages in a case-control study of ovarian cancer (4). Few other studies have examined the impact of details of the surgical procedures or characteristics of the women receiving these surgeries on the associations between tubal ligation or hysterectomy and ovarian cancer. A clearer definition of who benefits from these procedures could improve our understanding of the mechanisms by which they reduce the risk of ovarian cancer as well as better target ovarian cancer preventive surgeries. In addition, few studies have examined the association between unilateral oophorectomy and ovarian cancer risk independent of hysterectomy. Therefore, we sought to replicate our previous findings for tubal ligation and hysterectomy using prospective data and also examined the association between unilateral oophorectomy and ovarian cancer risk in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

METHODS

Study population

In 1976, 121,700 married US female registered nurses, 30 to 55 years of age completed an initial questionnaire, forming the NHS cohort. The NHSII began in 1989, when 116,430 female registered nurses in the United States, aged 25 to 42, completed an initial questionnaire. Follow-up questionnaires were mailed biennially to update exposure and covariate information and to ascertain incident diseases.

Ascertainment of ovarian cancer cases

Incident cases of epithelial ovarian cancer were identified through the biennial questionnaires from 1976 through 2010 in the NHS and from 1989 through 2011 in the NHSII. For women reporting a new ovarian cancer diagnosis or cases identified through death certificates, we obtained related medical records and pathology reports. A gynecological pathologist, who was blinded to tubal ligation, hysterectomy, and unilateral oophorectomy status, reviewed the records to confirm the diagnosis and abstract invasiveness, stage, and histologic subtype. For a subset of 215 ovarian cancer cases, we compared the histologic type abstracted from the pathology report with a standardized review of pathology slides completed by a gynecologic pathologist. As the concordance was

98 percent for invasiveness and 83 percent for histology, we used histologic type from the medical record for all cases.

Assessment of tubal ligation

On the 1976 through 1982 NHS biennial questionnaires, as well as all NHSII biennial questionnaires, women were asked if they used various forms of contraception, including tubal ligation. In 1997, NHSII women were asked what type of tubal ligation they had undergone (i.e., cautery/coagulation, ligation, clip/band/ring, other/don't know). Lastly, NHS women were asked in 1994 whether they had ever had a tubal ligation and at what age (i.e., <25, 25–29, 30–34, 35–39, 40–44, 45+). To calculate years since tubal ligation in the NHS, we assumed women underwent the procedure at the midpoint of the age category in which they reported having the procedure. In the NHSII, we assumed women underwent the procedure one year prior to the first report of a tubal ligation. We were able to estimate age at and years since tubal ligation for all NHS women who responded to the 1994 question as well as for all NHSII women who had a tubal ligation after the study baseline in 1989.

Assessment of hysterectomy and oophorectomy

On all of the NHS and NHSII questionnaires through 1992/1993, participants were asked if their menstrual periods had ceased permanently, if it was due to surgery, and, if so, how many ovaries were removed. Beginning in 1980 in the NHS and at baseline in the NHSII, if a woman reported natural menopause, she was asked if she had a subsequent surgery to remove her ovaries and/or her uterus. Beginning in 1994/1995 (NHS/NHSII), all participants were asked if they had ever had their uterus or either or both ovaries removed.

Statistical analysis

Participants accrued person-time from the return date of the baseline questionnaire until the date of ovarian cancer diagnosis, diagnosis of any other cancer (except non-melanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up (2010 in NHS, 2011 in NHSII). At baseline, we excluded women with cancer other than non-melanoma skin cancer (NHS: N=3315; NHSII N=1050), bilateral oophorectomy (NHS: N=7668; NHSII N=2225), or menopause due to pelvic irradiation NHS: N=99; NHSII N=30). We used Cox regression with time-dependent covariates stratified by age, time period, and cohort to estimate hazard ratios (HR) and 95% confidence intervals (CIs). Women who never had a tubal ligation, women who never had a hysterectomy, or women who never had a unilateral oophorectomy were the reference groups. We adjusted for body mass index (BMI), parity, age at first birth, breastfeeding, oral contraceptive use, age at menarche, menopausal status, family history of breast and ovarian cancer, smoking status, talc use (NHS only), postmenopausal hormone use (PMH), and for the other gynecologic surgeries. We used interaction terms and stratified analyses to assess effect modification by use of PMH (never, ever; among postmenopausal women only), oral contraceptive use (never, ever), family history of breast or ovarian cancer (no, yes), talc use (never, ever; NHS only), and the other gynecologic surgeries (never, ever). Missing indicators for covariates were included in multivariate models. We used Cox proportional hazards competing risk analysis, stratified by time period and cohort to allow for different associations by tumor histology.(5) We assumed that the tumor subtypes were mutually exclusive. The estimates

for the gynecologic surgeries, as well as age, parity, breastfeeding, and estrogen only PMH use, were allowed to vary by tumor histology based on prior analyses, whereas estimates for the remaining covariates were constrained to a single effect estimate across subtypes.(6) To test for heterogeneity by tumor subtype, we compared a model allowing each of our exposures of interest to vary by subtype to a model that constrained the estimates to be the same across subtypes. We also tested for heterogeneity by cohort using a likelihood ratio test comparing a model with an interaction term between the surgery and cohort to a model without the interaction term. As a sensitivity analysis, women in the NHS who were postmenopausal at baseline, and therefore may not have answered the question about contraception during the study period, entered the analysis in 1994 when all women were asked if they ever had a tubal ligation. Due to the high prevalence of tubal ligation at study entry, we restricted our analysis to women who did not have a tubal ligation at baseline as a sensitivity analysis. We considered a two-sided p-value of less than 0.05 to be statistically significant and used SAS version 9.2 (SAS Institute, Cary, NC) for all analyses. This investigation was approved by the Institutional Review Board at the Brigham and Women's Hospital.

RESULTS

Table 1 presents participant characteristics at study baseline (NHS:1976; NHSII:1989) by tubal ligation status and cohort. Women who underwent a tubal ligation were more likely to be parous and were more likely to have used OCs. Supplemental tables 1 and 2 present participant characteristics at study baseline cohort and by hysterectomy status and oophorectomy status, respectively. Over the study period, women with a hysterectomy were more likely to have ever used estrogen only PMH (data not shown).

Tubal ligation

In the multivariate-adjusted model, women who had undergone a tubal ligation had a 24 percent lower risk of ovarian cancer compared to women who did not undergo the procedure (95%CI: 0.64, 0.90) (Table 2). This effect estimate was similar to the age-adjusted hazard ratio (HR=0.71, 95%CI: 0.60, 0.84). The inverse association between tubal ligation and ovarian cancer was stronger for non-serous tumors (HR=0.57, 95%CI: 0.40, 0.82) compared to serous tumors (HR=0.89, 95%CI: 0.72, 1.10; p-heterogeneity=0.03) (Table 3). The association between tubal ligation and ovarian cancer did not significantly vary by family history of breast/ovarian cancer, PMH use (postmenopausal women only), hysterectomy status, or oophorectomy status (Supplementary table 3). The association between tubal ligation and ovarian cancer was suggestively stronger among women in the NHS who had ever used talc (HR=0.66, 95%CI: 0.46, 0.94) compared to those who did not (HR=0.90, 95%CI: 0.71, 1.14), although this difference did not reach statistical significance (p-heterogeneity=0.23). The inverse association also was suggestively stronger among women who underwent a tubal ligation prior to age 35 compared to women who were older at the time of surgery HR=0.67, 95%CI: 0.49, 0.90 and HR=0.97, 95%CI: 0.74, 1.26, respectively; p-heterogeneity=0.06) (Table 4). Interestingly, while the association between tubal ligation and ovarian cancer risk varied by age at surgery, there was no difference in the association by years since tubal ligation (HR, <10 years=0.81, 95%CI: 0.42, 1.54; HR, 10+ years=0.81,

0.65, 1.01; p-heterogeneity=0.99). Among women in the NHSII, the association was somewhat weaker for the cautery method (HR=0.84, 95%CI: 0.39, 1.80) as compared to ligation (HR=0.58, 95%CI: 0.31, 1.09) or ring (HR=0.48, 95%CI: 0.12, 1.93). This difference did not reach statistical significance (p-heterogeneity=0.68), although the sample size was limited. Finally, in NHSII we examined whether the association between tubal ligation and ovarian cancer risk varied by whether women reported a tubal ligation in the same questionnaire cycle as her last pregnancy or a later questionnaire cycle. Though the difference did not reach statistical significance (p-heterogeneity=0.39), the HR among women who reported a tubal ligation around the time of her last pregnancy was lower (HR=0.36, 95%CI: 0.09, 1.46) compared to the HR among women who had a tubal ligation at a later point in time (HR=0.66, 95%CI: 0.36, 1.23). The association between tubal ligation and ovarian cancer risk in the NHS was similar when women in the NHS who were postmenopausal at baseline entered the analysis in 1994 (HR=0.81, 95%CI: 0.66, 0.99) and when we restricted to women who did not have a tubal ligation at baseline (HR=0.66, 95%CI: 0.50, 0.88).

Hysterectomy

In the age-adjusted model, hysterectomy was not significantly associated with ovarian cancer risk (HR=0.94, 95%CI: 0.81, 1.08) (Table 2). However, after adjustment for additional covariates, particularly PMH use, hysterectomy was associated with a 20% lower risk of ovarian cancer (95%CI: 0.66, 0.97). While this association was somewhat stronger for non-serous tumors (HR=0.70, 95%CI: 0.49, 1.02) compared to serous tumors HR=0.96, 95%CI: 0.76, 1.21), this difference was not statistically significant (p-heterogeneity=0.15) (Table 3). The association between hysterectomy and ovarian cancer did not significantly vary by family history of breast/ovarian cancer, OC use, talc use, tubal ligation, or unilateral oophorectomy (Supplementary table 3). Though not statistically significantly different (p-heterogeneity=0.18), the association was somewhat stronger among postmenopausal women who had never used PMH (HR=0.81, 95%CI: 0.54, 1.20) compared to those who had ever used PMH (HR=1.10, 95%CI: 0.77, 1.57). Similar to tubal ligation, there was no difference in the association between hysterectomy and ovarian cancer risk by years since hysterectomy (HR, <10 years=0.77, 95%CI: 0.55, 1.06; HR, 10+=0.85, 95%CI: 0.68, 1.07; p-heterogeneity =0.57) (Table 4).

Unilateral oophorectomy

In the multivariate model, women who had a unilateral oophorectomy had a 30% lower risk of ovarian cancer (95%CI: 0.53, 0.91). This effect estimate was similar to the age-adjusted HR (HR=0.74, 95%CI: 0.58, 0.96). There was no difference in the association by serous histology (p-heterogeneity=0.60). In addition, the association did not significantly vary by OC use, talc use, tubal ligation, or hysterectomy (p-heterogeneity≥0.17). There was no association among women with a family history of breast/ovarian cancer (HR=1.10, 95%CI: 0.62, 1.97), but a significantly lower risk associated with unilateral oophorectomy among those with no family history (HR=0.62, 95%CI: 0.46, 0.85; p-heterogeneity=0.21). There was no difference in the association by age at or time since surgery (p-heterogeneity=0.76 and 0.50, respectively) (Table 4).

DISCUSSION

Consistent with prior studies, tubal ligation was associated with a lower risk of ovarian cancer in our study, particularly for non-serous tumors. Our data further suggest that tubal ligation is more strongly associated with risk among women who had the procedure earlier in life. Similarly, hysterectomy was suggestively more strongly inversely associated with risk for non-serous tumors. Women who had a unilateral oophorectomy had a lower risk of ovarian cancer; however the association did not differ by tumor subtype or age at surgery.

As discussed in our previous meta-analysis,(3) tubal ligation is a well-established preventive factor for ovarian cancer(3, 7) and studies generally support a stronger association among women who had the procedure before age 35.(3) While the association between hysterectomy and ovarian cancer risk is more variable across studies, overall previous data support an inverse association, with some studies suggesting that the surgery is more protective among younger women.(3) For both tubal ligation and hysterectomy, there is little evidence of a difference in the association by time since surgery, strengthening the argument that the inverse associations with these surgeries cannot be accounted for by screening bias.(3) Consistent with our findings, two previous meta-analyses reported that tubal ligation is more strongly associated with non-serous tumors (7, 8). The similar inverse associations for tubal ligation and hysterectomy with non-serous tumors suggest that tubal ligation and hysterectomy may share common protective mechanisms, such as prevention of retrograde menstruation (important in premenopausal women) or reduction of blood supply to the ovaries, thereby reducing ovarian function and estrogen production.(9–12) Tubal ligation also may act to lower ovarian cancer risk through the induction of anti-MUC-1 antibodies(13). Consistent with previous analysis in the New England Case-Control (NECC) study, we observed a suggestively stronger inverse association for tubal ligation that was conducted around the time of last birth which may be attributed to more effective closing of the fallopian tubes or heightened anti-MUC1 response.(4)

Fewer studies have examined the association between unilateral oophorectomy and ovarian cancer risk. One study compared observed rates of ovarian cancer among women who had a unilateral oophorectomy to the expected rates based on registry data and observed an increase in ovarian cancer risk within two years of surgery, but no association afterwards.(14) Women in a cohort study who reported a unilateral oophorectomy had over four times the risk of ovarian cancer; however, this cohort was restricted to women who were receiving medical care for infertility and likely do not represent women in the general population.(15) Consistent with our study, four case-control studies reported an inverse association for unilateral oophorectomy, with odds ratios ranging from 0.2–0.9. (16–19) We did not observe any difference in the association by histologic subtype, consistent with the hypothesis that unilateral oophorectomy would lower ovarian cancer risk by reducing the amount of ovarian tissue available for malignant transformation or implantation by putative precursor lesions.

Our study has some limitations. Gynecologic surgery status was based on self-report, however, tubal ligation, hysterectomy, and unilateral oophorectomy were assessed prior to ovarian cancer diagnosis and are generally well-reported.(20) Therefore any misclassification of exposures, and resulting bias, should be small and non-differential. We

did not have detailed data on the date of the gynecological surgeries, therefore there is likely non-differential misclassification of our estimates of age at and time since surgery. Forty-seven percent of NHSII women who responded to the type of tubal ligation question on the 1997 questionnaire answered "other/don't know," resulting in low power to detect differences by method. In addition, most women who reported tubal ligation had the procedure prior to the beginning of the NHS/NHSII studies, which limited our ability to assess whether the procedure occurred around the time of their last pregnancy. We do not have information on why women had a hysterectomy or a unilateral oophorectomy. In general, factors associated with these surgeries, such as endometriosis, uterine fibroids, or ovarian cysts, are either not associated or associated with an increase in ovarian cancer risk. (19, 21) Therefore, any bias due to confounding by indication for these surgeries would likely cause an underestimate of the true associations. The primary strengths of our study include prospective assessment of exposures, large cohort sizes, and detailed covariate and tumor information.

CONCLUSION

The consistent and strong inverse association between tubal ligation and ovarian cancer risk in this and many other studies is unlikely to be due to confounding or screening bias and supports the hypothesis that tubal ligation is causally associated with risk. Women considering a tubal ligation should be counseled on the potential benefit for ovarian cancer risk, along with other benefits and risks associated with the procedure. Future studies should examine what, if any, other long-term benefits or risks are associated with tubal ligation to allow women to make informed decisions about their long-term health risks. In addition, further studies into whether the inverse association with ovarian cancer risk varies type of procedure are warranted. The inverse association with hysterectomy along with the stronger association for non-serous tumors supports shared biologic mechanisms for tubal ligation and hysterectomy. 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.

Acknowledgments

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ABBREVIATIONS

NHS Nurses' Health Study

PMH	postmenopausal hormones
OC	oral contraceptives
HR	hazard ratio

REFERENCES

1. DeFrances CJ, Lucas CA, Buie VC, Golosinskiy A. 2006 National Hospital Discharge Survey. National health statistics reports. 2008:1–20. [PubMed: 18841653]
2. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. National health statistics reports. 2009:1–25. [PubMed: 19294964]
3. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: A meta-analysis. J Ovarian Res. 2012; 5:13. [PubMed: 22587442]
4. Rice MS, Murphy MA, Vitonis AF, Cramer DW, Titus LJ, Tworoger SS, et al. Tubal ligation, hysterectomy and epithelial ovarian cancer in the New England Case-Control Study. Int J Cancer. 1002; 133:2415–2421. [PubMed: 23650079]
5. Lunn M, McNeil D. Applying Cox regression to competing risks. Biometrics. 1995; 51:524–532. [PubMed: 7662841]
6. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol. 1093; 171:45–53. [PubMed: 19910378]
7. Cibula D, Widschwendter M, Majek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. Hum Reprod Update. 2011; 17:55–67. Epub 2010 Jul 15. [PubMed: 20634209]
8. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: A meta-analysis. J Ovarian Res. 2012; 5:13. [PubMed: 22587442]
9. Hakverdi AU, Taner CE, Erden AC, Satici O. Changes in ovarian function after tubal sterilization. Adv Contracept. 1994; 10:51–56. [PubMed: 8030455]
10. Radwanska E, Headley SK, Dmowski P. Evaluation of ovarian function after tubal sterilization. J Reprod Med. 1982; 27:376–384. [PubMed: 6811740]
11. Cattanach J. Oestrogen deficiency after tubal ligation. Lancet. 1985; 1:847–849. [PubMed: 2858712]
12. Vlahos NF, Kalampokas T, Fotiou S. Endometriosis and ovarian cancer: a review. Gynecol Endocrinol. 1080; 26:213–219. [PubMed: 19718562]
13. Pinheiro SP, Hankinson SE, Tworoger SS, Rosner BA, McKolanis JR, Finn OJ, et al. Anti-MUC1 antibodies and ovarian cancer risk: prospective data from the Nurses' Health Studies. Cancer Epidemiol Biomarkers Prev. 1595; 19:1595–1601. [PubMed: 20501761]
14. Kreiger N, Sloan M, Cotterchio M, Parsons P. Surgical procedures associated with risk of ovarian cancer. Int J Epidemiol. 1997; 26:710–715. [PubMed: 9279601]
15. Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. Gynecol Oncol. 128:260–264. [PubMed: 23116937]
16. Chiaffarino F, Parazzini F, Decarli A, Franceschi S, Talamini R, Montella M, et al. Hysterectomy with or without unilateral oophorectomy and risk of ovarian cancer. Gynecol Oncol. 2005; 97:318–322. [PubMed: 15863124]
17. Beard CM, Hartmann LC, Atkinson EJ, O'Brien PC, Malkasian GD, Keeney GL, et al. The epidemiology of ovarian cancer: a population-based study in Olmsted County, Minnesota, 1935–1991. Ann Epidemiol. 2000; 10:14–23. [PubMed: 10658685]
18. Riman T, Dickman PW, Nilsson S, Correia N, Nordlinder H, Magnusson CM, et al. Risk factors for invasive epithelial ovarian cancer: results from a Swedish case-control study. Am J Epidemiol. 2002; 156:363–373. [PubMed: 12181107]

19. Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery. Cancer Causes Control. 2008; 19:1357–1364. [PubMed: 18704718]

20. Phipps AI, Buist DS. Validation of self-reported history of hysterectomy and oophorectomy among women in an integrated group practice setting. Menopause. 2009; 16:576–581. [PubMed: 19169161]

21. Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol. 2002; 155:217–224. [PubMed: 11821246]

Tubal ligation, hysterectomy and unilateral oophorectomy were independently associated with lower risks of ovarian cancer. The associations with tubal ligation and hysterectomy are stronger for non-serous tumors.

Table 1

Participant characteristics at baseline (1976 NHS/1 989 NHSII) by tubal ligation status

	NHS		NHSII	
	No tubal ligation (N=98,887; 89%)	**Tubal ligation (N=11,606; 11%)**	**No tubal ligation (N=95,391; 84%)**	**Tubal ligation (N=17,734; 16%)**
Mean (SD)				
Age (years)	42.9 (7.3)	38.9 (5.4)	34.2 (4.6)	37.5 (3.6)
BMI (kg/m2)	23.7 (4.1)	23.5 (4.0)	23.9 (4.9)	24.8 (5.1)
Age at menarche	12.5 (1.8)	12.4 (1.8)	12.4 (1.4)	12.3 (1.4)
Parity*	3.1 (1.5)	3.3 (1.3)	2.0 (0.9)	2.4 (0.8)
Age at first birth*	25.2 (3.4)	24.4 (2.9)	25.8 (4.0)	24.3 (3.8)
Breastfeeding (years)*	0.5 (0.9)	0.6 (0.9)	1.1 (1.1)	1.1 (1.1)
Duration OC use (yrs)†	1.9 (3.2)	2.4 (3.1)	3.5 (3.5)	3.7 (3.3)
Frequency (%)				
Nulliparous	7.1	1.1	35.2	4.9
Talc Use	31.4	32.3	--	--
Ever OC use	46.6	64.3	82.0	89.6
Family history of breast cancer	5.8	5.0	5.9	6.4
Family history of ovarian cancer	2.3	2.2	1.5	1.8
Smoking status				
Never	43.9	43.1	66.1	61.8
Past	23.1	23.2	21.1	22.2
Current	33.0	33.7	12.8	16.0
Postmenopausal	15.2	1.4	0.4	0.4
Hysterectomy				
No	78.3	94.3	95.3	96.9
Yes	14.0	0.1	3.7	2.4
Unknown	7.7	5.6	1.0	0.7
Oophorectomy				
None	86.8	94.3	99.1	99.5
Unilateral	2.5	0.2	0.9	0.5
Unknown	10.7	5.5	0.1	0.1

*Among parous women only

†Among oral contraceptive (OC) users only

Table 2

Hazard Ratios (HR) and 95% confidence intervals (CI) for ovarian cancer for tubal ligation, hysterectomy, and unilateral oophorectomy, NHS and NHSII

	NHS				NHSII				Combined				P-het*
	Cases	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Cases	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Cases	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	
Tubal ligation													
All	999	0.78 (0.64,0.95)	0.84 (0.69,1.02)	0.82 (0.67,1.00)	265	0.56 (0.41,0.77)	0.65 (0.46,0.90)	0.65 (0.47,0.91)	1264	0.71 (0.60,0.84)	0.77 (0.65,0.91)	0.76 (0.64,0.90)	0.19
Invasive	852	0.77 (0.62,0.96)	0.83 (0.67,1.03)	0.81 (0.65,1.01)	206	0.53 (0.37,0.76)	0.60 (0.41,0.88)	0.61 (0.42,0.89)	1058	0.69 (0.58,0.83)	0.75 (0.62,0.91)	0.75 (0.62,0.90)	0.16
Hysterectomy													
All	864	0.98 (0.84,1.15)	1.12 (0.94,1.33)	0.86 (0.70,1.06)	228	0.65 (0.40,1.04)	0.63 (0.37,1.07)	0.60 (0.32,1.09)	1092	0.94 (0.81,1.08)	1.05 (0.89,1.23)	0.80 (0.66,0.97)	0.13
Invasive	728	1.03 (0.87,1.22)	1.17 (0.97,1.41)	0.90 (0.72,1.12)	178	0.68 (0.40,1.14)	0.70 (0.40,1.24)	0.64 (0.33,1.26)	906	0.98 (0.84,1.15)	1.11 (0.93,1.32)	0.84 (0.68,1.04)	0.14
Unilateral Oophorectomy													
All	853	0.71 (0.53,0.94)	0.62 (0.46,0.84)	0.64 (0.48,0.87)	231	0.94 (0.53,1.67)	0.93 (0.50,1.72)	0.93 (0.50,1.72)	1084	0.74 (0.58,0.96)	0.68 (0.52,0.89)	0.70 (0.53,0.91)	0.37
Invasive	719	0.73 (0.54,0.99)	0.63 (0.45,0.86)	0.64 (0.47,0.88)	180	0.69 (0.33,1.42)	0.64 (0.29,1.39)	0.64 (0.29,1.39)	899	0.73 (0.55,0.96)	0.64 (0.48,0.86)	0.66 (0.49,0.88)	0.90

Model 1: Adjusted for age (continuous) and time period. The combined analysis additionally adjusted for cohort.

Model 2: Model 1 and BMI (continuous), nulliparity, parity (continuous), age at first birth (continuous), oral contraceptive use (never, <1 year, 1–5 years, 5–10 years, 10+years), age at menarche (<12, 12, 13, 14+), menopausal status (premenopausal/unknown, postmenopausal), family history of breast and ovarian cancer (yes/no), smoking status (never, past, current), talc use (yes, no; NHS only), and the other surgeries (tubal ligation yes/no, hysterectomy yes/no, unilateral oophorectomy yes/no).

Model 3: Model 2 and estrogen PMH use (never, past <5 years, past 5+ years, current <5 years, current 5+ years), estrogen and progesterone PMH use (yes, no), and other PMH use (yes, no).

*P-value for heterogeneity by cohort

Table 3

Hazard Ratios (HR) and 95% confidence intervals (CI) for ovarian cancer for tubal ligation, hysterectomy, and unilateral oophorectomy by histological subtype, NHS and NHSII

	Tubal Ligation			Hysterectomy			Unilateral oophorectomy		
	Cases	**HR (95%CI)**	**p-het**	**Cases**	**HR (95%CI)**	**p-het**	**Cases**	**HR (95%CI)**	**p-het**
Serous	740	0.89 (0.72, 1.10)	0.03	642	0.96 (0.76, 1.21)	0.15	636	0.71 (0.51, 0.99)	0.60
Non-serous	352	0.57 (0.40, 0.82)		305	0.70 (0.49, 1.02)		308	0.60 (0.35, 1.03)	
Mucinous	105	0.60 (0.33, 1.12)		89	0.70 (0.35, 1.40)		91	0.99 (0.42, 2.30)	
Endometrioid and clear cell	247	0.55 (0.36, 0.85)		216	0.71 (0.46, 1.09)		217	0.48 (0.24, 0.94)	

Adjusted for age (continuous), time period, cohort (NHS, NHSII), BMI (continuous), nulliparity, parity (continuous), age at first birth (continuous), oral contraceptive use (never, <1 year, 1–5 years, 5–10 years, 10+years), age at menarche(<12, 12, 13, 14+), menopausal status (premenopausal/unknown, postmenopausal), family history of breast and ovarian cancer (yes/no), smoking status (never, past, current), talc use (yes, no; NHS only), estrogen PMH use (never, past <5 years, past 5+ years, current <5 years, current 5+ years), estrogen and progesterone PMH use (yes,no), other PMH use(yes, no), and the other surgeries (tubal ligation yes/no, hysterectomy yes/no, unilateral oophorectomy yes/no).

Table 4

Hazard Ratios (HR) and 95% confidence intervals (CI) for ovarian cancer by age at and years since tubal ligation, hysterectomy, and unilateral oophorectomy, NHS and NHSII

	Tubal Ligation			Hysterectomy			Unilateral oophorectomy	
	MV-adjusted HR (95%CI)	**P-het**		**MV-adjusted HR (95%CI)**	**P-het**		**MV-adjusted HR (95%CI)**	**P-het**
Age at procedure			Age at procedure			Age at procedure		
<35	0.67 (0.49,0.90)	0.06	<50	0.80 (0.64,1.00)	0.43	<50	0.69 (0.50,0.97)	0.76
35+	0.97 (0.74,1.26)		50+	0.93 (0.66,1.30)		50+	0.75 (0.50,1.14)	
Years since procedure			Years since procedure			Years since procedure		
<10 years	0.81 (0.42,1.54)	0.99	<10 years	0.77 (0.55,1.06)	0.57	<10 years	0.63 (0.40,0.99)	0.50
10+ years	0.81 (0.65,1.01)		10+ years	0.85 (0.68,1.07)		10+ years	0.76 (0.55,1.05)	

Adjusted for age, time period, cohort, .BMI (continuous), nulliparity, parity (continuous), age at first birth (continuous), oral contraceptive use (never, <1 year, 1–5 years, 5–10 years, 10+years), age at menarche(<12, 12, 13, 14+), menopausal status (premenopausal/unknown, postmenopausal), family history of breast and ovarian cancer (yes/no), smoking status (never, past, current), talc use (yes, no) (NHS only), estrogen PMH use (never, past <5 years, past 5+ years, current <5 years, current 5+ years), estrogen and progesterone PMH use (yes,no), other PMH use(yes, no), and the other surgeries (tubal ligation yes/no, hysterectomy yes/no, oophorectomy yes/no).