Ovarian cancer incidence and death in average-risk women undergoing bilateral salpingo-oophorectomy at benign hysterectomy

Maria C. Cusimano, MD, PhD; Sarah E. Ferguson, MD; Rahim Moineddin, PhD; Maria Chiu, PhD; Suriya Aktar, MSc; Ning Liu, MSc, PhD; Nancy N. Baxter, MD, PhD, FRCS, FACS

BACKGROUND: Opportunistic bilateral salpingo-oophorectomy is often offered to patients undergoing benign hysterectomy to prevent ovarian cancer, but the magnitude of risk reduction obtained with bilateral salpingo-oophorectomy in this population remains unclear and must be weighed against potential risks of ovarian hormone deficiency.

OBJECTIVE: This study aimed to quantify the relative and absolute risk reduction in ovarian cancer incidence and death associated with bilateral salpingo-oophorectomy at the time of benign hysterectomy.

STUDY DESIGN: We performed a population-based cohort study of all adult women (≥20 years) undergoing benign hysterectomy from 1996 to 2010 in Ontario, Canada. Patients with ovarian pathology, previous breast or gynecologic cancer, or evidence of genetic susceptibility to malignancy were excluded. Inverse probability of treatment—weighted Fine-Gray subdistribution hazard models were used to quantify the effect of bilateral salpingo-oophorectomy on ovarian cancer incidence and death while accounting for competing risks and adjusting for demographic characteristics, gynecologic conditions, and comorbidities. Analyses were performed in all women and specifically in women of postmenopausal age (≥50 years) at the time of hysterectomy.

RESULTS: We identified 195,282 patients (bilateral salpingo-oophorectomy, 24%; ovarian conservation, 76%) with a median age of 45 years (interquartile range, 40–51 years). Over a median follow-up of 16 years (interquartile range, 12–20 years), 548 patients developed ovarian cancer (0.3%), and 16,170 patients (8.3%) died from any cause. Bilateral salpingo-oophorectomy was associated with decreased ovarian cancer incidence (hazard ratio, 0.23; 95% confidence interval, 0.14–0.38; P < .001) and decreased ovarian cancer death (hazard ratio, 0.30; 95% confidence interval, 0.16–0.57; P < .001). At 20 years follow-up, the weighted cumulative incidences of ovarian cancer were 0.08% and 0.46% with bilateral salpingo-oophorectomy and ovarian conservation, respectively, yielding an absolute risk reduction of 0.38% (95% confidence interval, 0.32–0.45; number needed to treat, 260). After restricting to women aged ≥50 years at hysterectomy, the absolute risk reduction was 0.62% (95% confidence interval, 0.47–0.77; number needed to treat, 161).

CONCLUSION: Bilateral salpingo-oophorectomy resulted in a significant absolute reduction in ovarian cancer among women undergoing benign hysterectomy. Population-average risk estimates derived in this study should be balanced against other potential implications of bilateral salpingo-oophorectomy to inform practice guidelines, patient decision-making, and surgical management.

Key words: gynecologic surgical procedures, hysterectomy, ovarian cancer, ovariectomy

Introduction

Ovarian cancer (including epithelial carcinoma of the ovary, fallopian tube, and peritoneum) is typically diagnosed at an advanced stage with limited prospects for cure.1,2 Opportunistic bilateral salpingo-oophorectomy (BSO) is therefore considered at the time of clinically indicated hysterectomy, the most common major surgery performed in nonpregnant women worldwide, to prevent ovarian cancer later in life.3,4 Although BSO substantially reduces the rates of both ovarian cancer and all-cause death in women who carry pathogenic mutations in BRCA1 and BRCA2,5–8 its risk-to-benefit ratio in the general population undergoing hysterectomy remains unclear.4,9 BSO results in the complete cessation of ovarian estrogen production and therefore may have harmful effects that outweigh the benefit of ovarian cancer prevention in non–high-risk women. Studies to date suggest that BSO at benign hysterectomy may be associated with increased all-cause death compared with ovarian conservation when performed in women aged <50 years.10–14 It is also important to note that the residual risk of peritoneal carcinoma remains even after BSO.

Ovarian cancer risk reduction may remain a reasonable goal for women undergoing hysterectomy, particularly those aged ≥50 years.4 However, published guidelines provide no recommendation on whether BSO should be performed in this population,15–20 and the use of BSO varies substantially among surgeons, indicating ongoing uncertainty in practice.12 Estimates of the magnitude of ovarian cancer risk reduction obtained with BSO are needed to guide treatment standards and patient decision-making. Current data are derived from studies limited by selection bias,11,14,21–23 too few events for multivariable adjustment,13,14,21,23 and inclusion of patients with ovarian pathology at baseline.12 We therefore examined the effect of BSO on the incidence of ovarian cancer and ovarian cancer death in a large population-based cohort of
Why was this study conducted?
This study aimed to describe the extent to which opportunistic bilateral salpingo-oophorectomy (BSO) would reduce ovarian cancer incidence and death in non–high-risk women undergoing benign hysterectomy.

Key findings
In this population-based cohort study of 195,282 women, BSO was associated with absolute reductions of 0.38% (95% confidence interval [CI], 0.32–0.45) in ovarian cancer incidence and 0.18% (95% CI, 0.11–0.25) in ovarian cancer death for >20 years follow-up. Among women of postmenopausal age (≥50 years), absolute reductions in incidence and death were 0.62% (95% CI, 0.47–0.77; number needed to treat, 161) and 0.42% (95% CI, 0.26–0.60; number needed to treat, 237), respectively.

What does this add to what is known?
BSO effectively prevents ovarian cancer. This study uniquely quantified the absolute risk reduction and number needed to treat associated with BSO, which should be balanced against other potential implications of the procedure to inform practice guidelines and prevention strategies.

Materials and Methods

Study design and population
We performed a population-based retrospective cohort study using linked health administrative databases held at ICES (formerly the Institute for Clinical Evaluative Sciences), a nonprofit research institute evaluated to collect and use data on all residents of Ontario, Canada, for health system improvement. As Ontarians have universal access to hospital and physician services, these data are comprehensive. The research ethics board at the University of Toronto provided approval (approval number 38212).

We included adult women (≥20 years) in Ontario, Canada, undergoing hysterectomy for a benign indication by any surgical approach from January 1, 1996, to December 31, 2010. Validated codes were used to identify all cases of hysterectomy from the Canadian Institute of Health Information Discharge Abstract Database (DAD), Same Day Surgery database (SDS), and Ontario Health Insurance Plan (OHIP) database, which hold records of inpatient surgery, outpatient surgery, and billing claims for surgery, respectively (Appendix 1).9,24 Accrual dates were selected to (1) ensure sufficient follow-up for the development of ovarian cancer in all patients and (2) ensure clinical practice was consistent throughout the study so that the risk reduction associated with BSO could be accurately estimated. Surgeons in Canada routinely performed hysterectomy either with or without BSO before 2010 but began to adopt bilateral salpingectomy (BS) alone after publication of the tubal hypothesis in 2010,25–26 which postulated that high-grade serous cancers may originate in the fallopian tube and thus BS alone may reduce the risk of ovarian cancer.27 Although the potential risk reduction associated with BS is also unclear,28,29 we did not consider patients undergoing BS alone as a separate exposure in this study because of insufficient power and follow-up for that group.

We excluded (1) non-Ontario residents ineligible for universal health coverage, (2) patients undergoing emergent hysterectomy, (3) patients undergoing hysterectomy for a malignant indication, (4) patients with previous breast or gynecologic cancer, (5) patients whose index surgery or any previous surgery was performed for genetic susceptibility to malignancy, (6) patients who had previously undergone BSO, and (7) patients who had evidence of ovarian pathology or cysts at the index hysterectomy. These criteria were chosen to ensure our cohort represented a population that was not at high risk of ovarian cancer (Appendix 2; Figure 1).

Exposure assessment
The primary exposure was BSO, defined as removal of all ovarian tissue and corresponding fallopian tubes on the date of hysterectomy (index date). This included BSO in women with both ovaries and unilateral salpingo-oophorectomy in women with 1 remaining ovary because of a previous surgical procedure. We used procedure codes from DAD and SDS to identify salpingo-oophorectomy with a sensitivity of 99%, positive predictive value of 98%, and kappa of 99% (Appendix 1).24

We compared women undergoing BSO with women undergoing conservation of one or both ovaries, as this represents standard practice if surgery is done for ovarian cancer prophylaxis and reflects loss or retention of ovarian endocrine function, respectively. We considered BSO as a static covariate, as the overall rate of adnexal surgery following hysterectomy was only 1.6%.

Outcome assessment
The primary outcome was ovarian cancer, obtained from the Ontario Cancer Registry (OCR), which holds records of all incident cancers in the province from 1964 to 2019 and is over 95% complete (Appendix 3).30,31 The secondary outcome was ovarian cancer death. Date and cause of death were ascertained from the ICES Registered Persons Database and OCR, respectively, and were available from 1990 to 2017. Patients were therefore followed from the date of hysterectomy (time 0) to December 31, 2019, for ovarian cancer incidence and December 31, 2017, for ovarian cancer death.

Covariates
Covariates were ascertained at the time of the index hysterectomy. Demographic characteristics were age, rural or urban residence, era of surgery (1996–2000, 2001–2005, 2006–2010), residential income quintile, ethnicity (general
population, South Asian, Chinese), and immigration status (immigrant, long-
term resident). Residential income quintile is an area-level socioeconomic
index derived from Canadian census data on median neighborhood income
and is assigned to patients based on their postal code of residence.\(^3^2\) Immigration
status was assigned to patients based on their landing date in Ontario\(^3^3\) (long-
term resident: landing date absent or <1985). Ethnicity was assigned using
validated surname lists that accurately identify South Asian and Chinese in-
dividuals, Canada’s 2 largest visible mi-
nority groups.\(^3^4\)

Clinical characteristics were gynecologic conditions documented at the index
hysterectomy (abnormal uterine bleeding, fibroids, endometriosis, pre-
malignant conditions [endometrial hyperplasia, cervical dysplasia], pelvic pain
or inflammation, prolapse),\(^3^5\)\(^3^6\) surgical approach (abdominal, vaginal), hyster-
ectomy type (total, subtotal), overall comorbidities (0–5, 6–9, \(\geq 10\)),\(^3^8\) spe-
cific comorbidities (hypertension, diabetes mellitus, chronic obstructive
pulmonary disease, previous malignancy, cardiovascular disease), previous ovarian
surgery, and previous tubal ligation. Because our exposure was meant to reflect
the loss or retention of ovarian endocrine function, we did not exclude patients
based on previous adnexal procedures unless they had already undergone BSO
and instead adjusted for previous ovarian surgery and previous tubal ligation as
covariates in our analysis. Gynecologic conditions and surgical history were
ascertained with DAD and SDS and OHIP codes; of note, abdominal surgery
included open, laparoscopic, robotic-assisted, and laparoscopic-assisted
vaginal hysterectomies (Appendix 4).\(^3^5\)\(^3^7\)\(^3^9\) Comorbidities were catego-
rized into Aggregated Diagnosis Groups using the Johns Hopkins Adjusted Clin-
ic Group System (version 10).\(^3^8\)\(^4^0\) Specific comorbidities were ascertained from
validated registries of Ontarians affected by these conditions (Appendix 5).\(^4^1\)\(^4^4\)

**Statistical analysis**

Datasets were linked using unique encoded identifiers and analyzed at
ICES. We compared baseline character-
istics between patients undergoing BSO
and ovarian conservation using 2-
sample \(t\) tests or Mann-Whitney \(U\) tests
for continuous variables and chi-square
tests for categorical variables. We quan-
tified the difference in means and pro-
portions of baseline characteristics
between the 2 groups using standardized
differences.\(^4^5\)

We used inverse probability of treat-
ment (IPT) weighting to adjust for differ-
ences between patients undergoing
BSO and ovarian conservation; IPT
weighting uses weights based on the
propensity score to create a synthetic
sample in which the distribution of
baseline covariates is independent of
treatment status.\(^4^6\)\(^4^7\) Propensity
scores were obtained using logistic regression,
modeling BSO as the outcome and all
demographic and clinical characteristics
previously described as covariates.\(^4^8\)
To ensure that systematic differences in
exposed and unexposed subjects were
eliminated, we modeled age as a
restricted cubic spline with 5 knots\(^4^9\) and
added individual interaction terms be-
tween age and both surgical approach
and prolapse.\(^4^8\)\(^5^0\) Furthermore, we
generated stabilized IPT weights for each
patient, equal to the inverse probability
of undergoing the surgery received,
multiplied by the probability of under-
going that surgery in the overall sam-
ple.\(^4^6\) We again used standardized
differences to assess for balance in
baseline characteristics after applying
stabilized IPT weights.

We used IPT-weighted Fine-Gray
subdistribution hazard models to esti-
mate the relative effect of BSO on each
outcome; Fine-Gray models are time-to-
event models that account for competing
risks.\(^5^1\)\(^5^2\) The model for incident
ovarian cancer treated death as a
competing risk, and the model for
ovarian cancer death treated death owing
to other causes as a competing risk.
Patients were censored at loss to follow-up
(defined as loss of eligibility for provin-
cial health insurance) or end of follow-
up (December 31, 2019, for ovarian
cancer or December 31, 2017, for
ovarian cancer death). Models used
robust variance estimators to account for
IPT weighting and were presented with
subdistribution hazard ratios (HRs) and
corresponding 95% confidence intervals
(CIs).
| Characteristic                          | Unweighted cohort | Weighted cohort |
|----------------------------------------|-------------------|-----------------|
|                                        | Total (N=195,282) |                 |
|                                        | No BSO (n=148,621) | BSO (n=46,661) |
|                                        | Standard difference | Standard difference |
|                                        | No BSO | BSO | | No BSO | BSO | |
| Age (y)                                | 47.2 (40–52) | 46.1 (39–49) | 50.7 (45–55) | 0.44 | 47.5 | 47.9 | 0.04 |
| Area of residence                      |                |                |                |      |      |      |      |
| Urban                                  | 161,821 (82.9) | 122,366 (82.3) | 39,455 (84.6) | 0.06 | 82.84 | 82.09 | 0.02 |
| Rural                                  | 33,378 (17.1) | 26,201 (17.6) | 7177 (15.4) | 0.06 | 17.16 | 17.91 | 0.02 |
| Missing                                | 83 (0.0) | 54 (0.0) | 29 (0.1) | 0.01 | — | — | — |
| Era of surgery                         |                |                |                |      |      |      |      |
| 1996–2000                              | 69,598 (35.6) | 49,744 (33.5) | 19,854 (42.5) | 0.19 | 35.61 | 35.33 | 0.01 |
| 2001–2005                              | 64,628 (33.1) | 49,838 (33.5) | 14,790 (31.7) | 0.04 | 33.43 | 34.30 | 0.02 |
| 2006–2010                              | 61,056 (31.3) | 49,039 (33.0) | 12,017 (25.8) | 0.16 | 30.96 | 30.37 | 0.01 |
| Income quintile                        |                |                |                |      |      |      |      |
| Quintile 1 (low)                       | 36,253 (18.6) | 27,983 (18.8) | 8270 (17.7) | 0.03 | 18.59 | 17.80 | 0.02 |
| Quintile 2                             | 39,750 (20.4) | 30,540 (20.5) | 9210 (19.7) | 0.02 | 20.52 | 20.09 | 0.01 |
| Quintile 3                             | 40,993 (21.0) | 31,422 (21.1) | 9571 (20.5) | 0.02 | 21.02 | 20.70 | 0.01 |
| Quintile 4                             | 40,417 (20.7) | 30,747 (20.7) | 9670 (20.7) | 0.00 | 20.77 | 21.49 | 0.02 |
| Quintile 5 (high)                      | 37,348 (19.1) | 27,521 (18.5) | 9827 (21.1) | 0.06 | 19.10 | 19.92 | 0.02 |
| Missing                                | 521 (0.3) | 408 (0.3) | 113 (0.2) | 0.01 | — | — | — |
| Immigration status                     |                |                |                |      |      |      |      |
| Long-term resident                     | 178,229 (91.3) | 135,623 (91.3) | 42,606 (91.3) | 0.00 | 91.40 | 91.76 | 0.01 |
| Immigrant                              | 17,053 (8.7) | 12,998 (8.7) | 4055 (8.7) | 8.60 | 8.24 |
| Ethnicity                              |                |                |                |      |      |      |      |
| General population                     | 187,678 (96.1) | 143,132 (96.3) | 44,546 (95.5) | 0.04 | 96.15 | 96.24 | 0.00 |
| South Asian                            | 3675 (1.9) | 2766 (1.9) | 909 (1.9) | 0.01 | 1.82 | 1.77 | 0.00 |
| Chinese                                | 3929 (2.0) | 2723 (1.8) | 1206 (2.6) | 0.05 | 2.03 | 1.98 | 0.00 |
| Surgical approach                      |                |                |                |      |      |      |      |
| Abdominal                              | 133,519 (68.4) | 90,378 (60.8) | 43,141 (92.5) | 0.81 | 69.04 | 69.44 | 0.01 |
| Vaginal                                | 61,763 (31.6) | 58,243 (39.2) | 3520 (7.5) | 30.96 | 30.56 |
| Hysterectomy type                      |                |                |                |      |      |      |      |
| Total                                  | 178,184 (91.2) | 135,212 (91.0) | 42,972 (92.1) | 0.04 | 91.29 | 91.05 | 0.01 |
| Subtotal                               | 17,098 (8.8) | 13,409 (9.0) | 3689 (7.9) | 8.71 | 8.95 |
| Abnormal uterine bleeding              |                |                |                |      |      |      |      |
| Yes                                    | 91,763 (47.0) | 73,729 (49.6) | 18,034 (38.6) | 0.22 | 46.21 | 45.91 | 0.01 |
| No                                     | 103,519 (53.0) | 74,892 (50.4) | 28,627 (61.4) | 53.79 | 54.09 |
| Fibroids                               |                |                |                |      |      |      |      |
| Yes                                    | 89,415 (45.8) | 63,916 (43.0) | 25,499 (54.6) | 0.23 | 45.45 | 46.95 | 0.03 |
| No                                     | 105,867 (54.2) | 84,705 (57.0) | 21,162 (45.4) | 54.55 | 53.05 |

Casimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022. (continued)
We generated IPT-weighted cumulative incidence functions to estimate the absolute effect of BSO on ovarian cancer and ovarian cancer death.\textsuperscript{52,53} We plotted weighted cumulative incidence curves for patients undergoing BSO and ovarian conservation and used \( P \) values from respective Fine-Gray models to test the equality of curves across

![Table 1](image-url)
groups.\textsuperscript{52,53} We computed the risk difference in weighted cumulative incidence functions between the 2 groups, which in this setting corresponded to the absolute risk reduction (ARR), at 10, 15, and 20 years of follow-up. We took the inverse of the ARR to compute the number needed to treat (NNT) to prevent 1 case or 1 death by each time point.\textsuperscript{54} We generated 95\% CIs for all estimates using the 2.5th and 97.5th percentile of 1000 bootstrapped estimates.

To estimate the ARR associated with BSO in postmenopausal women, we repeated the analyses in a subcohort of women aged ≥50 years at the time of hysterectomy. To ensure that our estimates accurately represented the effect of BSO in patients who were not at high risk of ovarian cancer, we repeated the analyses (1) after excluding patients with any previous malignancy and (2) after excluding a small proportion of patients in the ovarian conservation group who underwent BS alone. To determine whether our findings were robust to multiple approaches for confounder control, we repeated all analyses using conventional multivariable Fine-Gray subdistribution hazard models rather than IPT weighting.

The proportionality assumption was confirmed by testing for an interaction between BSO status and time, which was not significant for either outcome. Tests were 2-sided, with \( P < 0.05 \) and standardized differences of ≥0.1 considered significant. Complete case

### TABLE 1
Baseline characteristics of patients undergoing benign hysterectomy with BSO or ovarian conservation, both before and after inverse probability of treatment weighting (continued)

| Characteristic                  | Unweighted cohort | Weighted cohort |
|--------------------------------|-------------------|-----------------|
|                                | Total (N=195,282) | No BSO (n=148,621) | BSO (n=46,661) | Standard difference\textsuperscript{a} | No BSO | BSO | Standard difference\textsuperscript{a} |
| Previous tubal ligation        |                   |                  |                |                                |        |     |                                 |
| Yes                            | 28,187 (14.4)     | 24,773 (16.7)   | 3414 (7.3)     | 0.29                           | 14.13  | 13.61 | 0.02 |
| No                             | 167,095 (85.6)    | 123,848 (83.3)  | 43,247 (92.7)  |                                | 85.87  | 86.39 |      |

Data are presented as number (percentage), unless otherwise indicated.

ADGs, Aggregated Diagnosis Groups; BSO, bilateral salpingo-oophorectomy; IQR, interquartile range.

\textsuperscript{a} Standardized differences comparing patients who did and did not undergo BSO.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.

### TABLE 2
Ovarian cancer outcomes of patients undergoing benign hysterectomy with BSO or ovarian conservation

| Outcome                  | No BSO (n=148,621) | BSO (n=46,661) | Total (N=195,282) |
|--------------------------|-------------------|---------------|-------------------|
| Ovarian cancer           |                   |               |                   |
| Yes                      | 498 (0.3)         | 50 (0.1)      | 548 (0.3)         |
| No                       | 148,123 (99.7)    | 46,611 (99.9) | 194,734 (99.7)    |
| Age at ovarian cancer (y)\textsuperscript{a} |                   |               |                   |
| Median (IQR)             | 59.7 (50.9–73.0)  | 58.6 (53.9–67.7) | 59.6 (51.3–72.3) |
| Follow-up for ovarian cancer (y) |               |               |                   |
| Median (IQR)             | 16 (12–20)        | 17 (13–21)    | 16 (12–20)        |
| Ovarian cancer death     |                   |               |                   |
| Alive                    | 138,786 (93.4)    | 42,941 (92.0) | 181,727 (93.1)    |
| Death owing to ovarian cancer | 214 (0.1)       | 26 (0.1)      | 240 (0.1)         |
| Death owing to other causes | 9621 (6.5)    | 3694 (7.9)    | 13,315 (6.8)      |
| Follow-up for ovarian cancer death (y) |               |               |                   |
| Median (IQR)             | 14 (10–18)        | 15 (11–19)    | 14 (10–18)        |

Data are presented as number (percentage), unless otherwise indicated.

BSO, bilateral salpingo-oophorectomy; IQR, interquartile range.

\textsuperscript{a} Age at diagnosis among patients who developed ovarian cancer.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
analyses were performed as data were rarely missing (area of residence, <0.1%; residential income quintile, <0.3%). Analyses were performed in SAS (version 9.4; SAS Institute Inc, Cary, NC).

**Results**

**Study population**

A total of 266,434 women (≥20 years) underwent elective hysterectomy from January 1, 1996, to December 31, 2010 (Figure 1). After exclusions, our cohort included 195,282 women with a mean age of 47.2 years. BSO was performed in 46,661 women (23.9%) and ovarian conservation in 148,621 women (76.1%); the proportion of women undergoing BSO each year from 1996 to 2010 is included in Appendix 6. Nearly 70% of all hysterectomies were performed abdominally, by either an open approach or a minimally invasive approach.

Patients undergoing BSO were older (50.7 vs 46.1 years; *P*<0.001), more likely to have multiple comorbidities (33.6% vs 28.4%; *P*<0.001), and more likely to have a premalignant disease (12.5% vs 6.5%; *P*<.001) or endometriosis (32.7% vs 21.2%; *P*<0.001) than patients undergoing ovarian conservation. After applying IPT weights, the groups were balanced on all baseline characteristics (standardized differences, <0.1) (Table 1; Appendix 7).

**Ovarian cancer incidence**

Median follow-up for incident ovarian cancer was 16 years (interquartile range [IQR], 12–20); during that time, 548 women (0.3%) developed ovarian cancer, and 16,170 women (8.3%) experienced the competing event of death from any cause (Table 2). The median age at diagnosis of ovarian cancer was 59.6 years (IQR, 51.3–72.3) (Table 2).

BSO was associated with reduced ovarian cancer (HR, 0.23; 95% CI, 0.14–0.38; *P*<.001) compared with ovarian conservation. The 20-year weighted cumulative incidences of ovarian cancer were 0.08% and 0.25% with BSO and ovarian conservation, respectively. The ARRs associated with BSO at 10, 15, and 20 years follow-up were 0.15% (95% CI, 0.11–0.19), 0.25% (95% CI, 0.20–0.30), and 0.38% (95% CI, 0.32–0.45), corresponding to NNTs of 634, 405, and 260, respectively (Figure 2; Table 3).

**Ovarian cancer death**

Median follow-up for ovarian cancer death was 14 years (IQR, 10–18); during that time, 240 women (0.1%) died from ovarian cancer, and 13,315 women (6.8%) experienced the competing event of death from other causes (Table 2). BSO was associated with reduced ovarian cancer death (HR, 0.30; 95% CI, 0.16–0.57; *P*<.001) compared with ovarian conservation. The 20-year weighted cumulative incidences of ovarian cancer death were 0.07% and 0.25% with BSO and ovarian conservation, respectively. The ARRs associated with BSO at 10, 15, and 20 years follow-up were 0.06% (95% CI, 0.02–0.09), 0.11% (95% CI, 0.06–0.15), and 0.18% (95% CI, 0.11–0.25), corresponding to

![FIGURE 2](https://example.com/figure2.png)

Weighted cumulative incidence (%) of ovarian cancer and ovarian cancer death in patients undergoing benign hysterectomy with bilateral salpingo-oophorectomy or ovarian conservation. Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
NNTs of 1806, 939, and 569, respectively (Figure 2; Appendix 8).

Sensitivity analyses
In a subcohort of women aged ≥50 years undergoing hysterectomy (n = 57,736) (Appendices 9 and 10), BSO was associated with reduced ovarian cancer (HR, 0.16; 95% CI, 0.07–0.32; P<.001) and ovarian cancer death (HR, 0.26; 95% CI, 0.11–0.62; P<.001). Because women aged ≥50 years were observed until older ages when ovarian cancer typically develops, the ARRs associated with BSO were slightly greater than the total cohort. The ARRs for ovarian cancer at 10, 15, and 20 years follow-up were 0.30% (95% CI, 0.19–0.41), 0.45% (95% CI, 0.32–0.57), and 0.62% (95% CI, 0.47–0.77), corresponding to NNTs of 334, 223, and 161, respectively. The ARRs for ovarian cancer death followed the same pattern (Table 3; Appendix 8).

Results were similar after excluding patients with a previous malignancy (n=2688 [1.4%]; ovarian cancer: HR, 0.22; 95% CI, 0.14–0.38; P<.001; ovarian cancer death: HR, 0.31; 95% CI, 0.16–0.58; P<.001); after excluding patients who underwent BS alone (n=2450 [1.3%]; ovarian cancer: HR, 0.23; 95% CI, 0.14–0.38; P<.001; ovarian cancer death: HR, 0.30; 95% CI, 0.16–0.57; P<.001); and after using traditional multivariable Fine-Gray models rather than IPT weighting (ovarian cancer: HR, 0.23; 95% CI, 0.17–0.32; P<.001; ovarian cancer death: HR, 0.28; 95% CI, 0.17–0.44; P<.001).

Discussion
Principal findings
In this population-based cohort study of >195,000 non–high-risk women undergoing benign hysterectomy, BSO was associated with significant decrease in the incidence of ovarian cancer and ovarian cancer death. At 20 years follow-up, the absolute reduction in ovarian cancer incidence was 0.38% (95% CI, 0.32–0.45). Although the 20-year ARR was greater in a subset of women aged ≥50 years at hysterectomy (0.62%; 95% CI, 0.47–0.77), young women would likely be similarly protected on reaching a comparable age. In comparison, existing modalities for screening have not been shown to reduce ovarian cancer deaths by any margin.5

Results and implications
Our study provided population-average risk reduction estimates for ovarian cancer and ovarian cancer death after BSO at benign hysterectomy that in combination with other data can help inform practice guidelines, patient counseling, and surgical management. Previous studies have reported absolute incidences of ovarian cancer in a similar range (Table 4) but enrolled selected cohorts of women that may not represent typical women undergoing benign hysterectomy (ie, Nurses’ Health Study,13 Women’s Health Initiative,21 Cancer Prevention Study II23) and did not adjust risk estimates for differences in patients undergoing BSO and ovarian conservation.13,14,21 A cohort study by Chan et al22 is most comparable with ours in its use of administrative data and design focused specifically on ovarian cancer outcomes. Among 56,692 women undergoing benign hysterectomy from the Kaiser Permanente of Northern California database, BSO was associated with a decrease in the rate of ovarian cancer (HR, 0.12; 95% CI, 0.05–0.28) based on 40 cases identified over a median follow-up of 5 years. Our estimates are precise, based on 584 ovarian cancer cases identified over a median 16 year follow-up; better reflect outcomes of the general population undergoing benign hysterectomy; and account for demographic factors, gynecologic conditions, and comorbidities.

Decisions on whether to perform BSO must weigh the magnitude of the benefit illustrated here against other possible risks of the surgery. The addition of BSO to hysterectomy does not increase the complexity of the procedure and is not thought to appreciably influence short-term surgical risk; studies that adjust for underlying gynecologic disease have not shown an increase in complications or length of stay with BSO, except

### Table 3

| Year of follow-up | No BSO | BSO | ARR | NNT |
|-------------------|--------|-----|-----|-----|
| **All women**     |        |     |     |     |
| 10                | 0.20%  | 0.05%| 0.15%|664 |
| 15                | 0.31%  | 0.07%| 0.25%|405 |
| 20                | 0.46%  | 0.08%| 0.38%|260 |
| **Women aged ≥50 y at BSO** |        |     |     |     |
| 10                | 0.38%  | 0.08%| 0.30%|334 |
| 15                | 0.54%  | 0.10%| 0.45%|223 |
| 20                | 0.72%  | 0.10%| 0.62%|161 |

ARR, absolute risk reduction; BSO, bilateral salpingo-oophorectomy; NNT, number needed to treat.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
### TABLE 4
Cohort studies examining ovarian cancer incidence and death in women undergoing TH with or without BSO

| Study | Cohort | Group | Sample size | Cases | HR (95% CI) | Covariates |
|-------|--------|-------|-------------|-------|-------------|------------|
|       |        |       |             |       | Incidence   | Death      |
| Parker et al, 2009 and Parker et al, 2013 | Nurses’ Health Study (30–55 y at enrollment) | TH | 13,035 | 99 | Ref | Ref | Age |
|       |        |       |             |       |             |            |
|       |        |       |             |       | 0.04 (0.01–0.09) | 0.06 (0.02–0.21) |
| Jacoby et al, 2011 | Women’s Health Initiative (50–79 y at enrollment) | TH | 11,194 | 37 | NR | NR | N/A |
|       |        |       |             |       |             |            |
| Chan et al, 2014 | Kaiser Permanente Northern California (18–84 y at hysterectomy) | TH | 22,051 | 30 | Ref | Ref | Age, race |
|       |        |       |             |       |             |            |
|       |        |       |             |       | 0.76 (0.27–2.16) | NR |
| Gaudet et al, 2014 | Cancer Prevention Study II Nutrition (50–74 y at enrollment) | None | 41,397 | 303 | Ref | Ref | Age, race, education, parity, body mass index, hormone therapy use, age at first birth, age at menopause, lifestyle factors |
|       |        |       |             |       |             |            |
|       |        |       |             |       | 1.26 (1.03–1.78) | NR |
| Falconer et al, 2015 | Swedish Population Register (≥18 y at enrollment) | TH | 9655 | 86 | 0.12 (0.07–0.21) | NR |
|       |        |       |             |       |             |            |
|       |        |       |             |       | 0.79 (0.70–0.88) | NR |
| Mytton et al, 2017 | Hospital Episode Statistics Database (35–45 y at hysterectomy) | TH | 76,581 | 56 | Ref | Ref | Age group, deprivation, hysterectomy type, Charlson comorbidity score, previous admissions |
|       |        |       |             |       |             |            |
|       |        |       |             |       | 3.84 (2.70–5.26) | 4.76 (2.00–11.11) |

Casimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022. (continued)
possibly when performed via a vaginal approach. In contrast, the addition of BSO may influence long-term surgical risk because of the cessation of ovarian hormone production. BSO has been associated with increased all-cause mortality in women aged <50 years, who are likely premenopausal at the time of surgery. Similar findings have not been consistently identified in women aged >65 years. Other theoretical effects of BSO include reduced quality of life or sexual function, as the ovaries continue to produce androgens even after menopause, but most studies have not shown significant differences in these measures postoperatively.

This study addressed the main limitations of previous works. We included a large cohort with many incident cases of ovarian cancer at baseline were included in the study. Complete list of sociodemographic factors, gynecologic diagnoses, and comorbidities available in the Materials and Methods section.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.

### TABLE 4

| Study | Cohort | Group | Sample size | Cases | HR (95% CI) | Incidence | Death |
|-------|--------|-------|-------------|-------|-------------|-----------|-------|
| Cusimano et al, 2021 | ICES Ontario (≥20 y at hysterectomy) | TH | 148,621 | 498 | Ref | Ref |
|  | | TH-BSO | 46,661 | 50 | 0.23 (0.14–0.38) | 0.30 (0.16–0.57) |

BSO, bilateral salpingo-oophorectomy; CI, confidence interval; HR, hazard ratio; ICES, Institute for Clinical Evaluative Sciences; N/A, not applicable; NR, not reported; TH, total hysterectomy; USO, unilateral salpingo-oophorectomy.

Nonproportional hazards; excess ovarian cancer in BSO group occurred weeks after benign hysterectomy, suggesting patients with ovarian cancer at baseline were included in the study. Complete list of sociodemographic factors, gynecologic diagnoses, and comorbidities available in the Materials and Methods section.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
information on family history and genetic testing and could not definitively confirm whether patients were not at high risk. To mitigate this, we applied strict exclusion criteria, and the results were similar in sensitivity analyses restricted to patients without a previous malignancy. Second, we were unable to obtain information on factors that protect against ovarian cancer at baseline, including combined contraceptive use and parity for most women in our study. As women receiving ovarian conservation are more often parous and past contraceptive users,11,13 our results may be conservative estimates of the effect of BSO. Third, there were few incident ovarian cancer cases and ovarian cancer deaths throughout the study period. We addressed this by generating absolute and relative risk estimates, controlling for covariates with a propensity-based approach, and using bootstrapping to generate accurate 95% CI; moreover, it is also important to note that we identified many more events than previous studies (Table 4). Fourth, despite the high quality of our data sources overall, some covariates had limited sensitivity (eg, ethnicity) or relied on diagnostic or procedural codes with unknown accuracy (eg, gynecologic conditions). Any misclassification of these covariates is likely non-differential with respect to BSO status; therefore, adjustment will still likely reduce confounding bias.29 Finally, because of limited numbers and follow-up for patients undergoing surgery after 2010, we could not assess ovarian cancer outcomes following BSO alone.28,29 Our results did not change after excluding 2% of patients in the ovarian conservation group who also underwent BSO, but additional studies are required to determine the magnitude of benefit offered by BSO compared with BSO alone; we intended to complete this analysis as soon as sufficient follow-up has accrued for our cohort.

Conclusions

In the United States, >400,000 women undergo hysterectomy annually.70 The population-average risk estimates derived from this study were generalizable. Such estimates can be used to counsel patients on the value of concurrent BSO preoperatively, so they can make informed choices that weigh the magnitude of ovarian cancer prevention against other potential risks of the procedure.

Acknowledgments

Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information; the Ontario Ministry of Health & Long-Term Care; Cancer Care Ontario; Immigration, Refugees and Citizenship Canada Permanent Resident Database; the Ontario Registrar General and Ministry of Government and Customer; and Service-Ontario. However, the conclusions, opinions, and statements expressed in this manuscript are solely those of the authors and not those of the bodies listed. No endorsement by these bodies is intended or should be inferred.

References

1. Berk JS, Kehoe ST, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2018;143(Supp2):59–78.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012: CA Cancer J Clin 2015;65:87–108.
3. McPherson K, Gor G, Scott M. International variations in a selected number of surgical procedures. 2013. Available at: https://library.villanova.edu/find/record/1441291/details. Accessed March 24, 2020.
4. Evans EC, Matteson KA, Orejuela FJ, et al. Salpingo-oophorectomy at the time of benign hysterectomy: a systematic review. Obstet Gynecol 2016;128:476–85.
5. Robbeek TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 2009;101:80–7.
6. Marchetti C, De Felice F, Palaia I, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA1 and BRCA2 mutation carriers. BMC Womens Health 2014;14:150.
7. Finch AP, Lubinski J, Moller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 2014;32:1547–53.
8. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. Am J Surg 2016;212:660–9.
9. Cusimano MC, Moineddin R, Chiu M, et al. Practice variation in bilateral salpingo-oophorectomy at benign abdominal hysterectomy: a population-based study. Am J Obstet Gynecol 2021;224:585.e1–30.
10. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol 2006;7:821–8.
11. Gr心仪 GL, Pfaffler RM, Patel DA, et al. Long-term overall and disease-specific mortality associated with benign gynecologic surgery performed at different ages. Menopause 2014;21:592–601.
12. Mirror J, Evison F, Chilton PJ, Lifford RJ. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and time to linkage. BMJ 2017;356:j372.
13. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses’ health study. Obstet Gynecol 2009;113:1027–37.
14. Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses’ health study. Obstet Gynecol 2013;121:709–16.
15. RANZCOG Research Foundation. C-Gyn 25: prophylactic oophorectomy at the time of hysterectomy for benign gynaecological disease. O&G Mag 2009;11:75–6. Available at: https://ranzcocg.edu.au/RANZCOG-MEDIA/Women’s%20Health/Statement%20and%20guidelines/Clinical%20-20%20Gynaecology/Managing-the-adenexae-at-the-time-of-hysterectomy-(C-Gyn-25)-March18.pdf?ext=pdf. Accessed October 18, 2021.
16. American Urogynecologic Society. Ten things physicians and patients should question. Choosing Wisely. 2015. Available at: https://www.choosingwisely.org/societies/american-urogynecologic-society/. Accessed March 24, 2020.
17. American Association of Gynecologic Laparoscopists. Five things patients and providers should question. Choosing Wisely. 2019. Available at: https://www.choosingwisely.org/societies/aagl/. Accessed March 24, 2020.
18. Thurston J, Munji A, Scattolini S, et al. No. 377-hysterectomy for benign gynaecologic indications. J Obstet Gynaecol Can 2019;41:543–57.
19. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 2005;90:3847–53.
20. Fogle RH, Stanczyk FZ, Zhang X, Paulson RJ. Ovarian androgen production in postmenopausal women. J Clin Endocrinol Metab 2007;92:3040–3.
21. Jacoby VL, Grady D, Wactawski-Wende J, et al. Oophorectomy vs ovarian conservation with hysterectomy: cardiovascular disease, hip fracture, and cancer in the Women’s Health Initiative Observational Study. Arch Intern Med 2011;171:760–8.
22. Chan JK, Urban R, Capra AM, et al. Ovarian cancer rates after hysterectomy with and without salpingo-oophorectomy. Obstet Gynecol 2014;123:65–72.
23. Gaudet MM, Gapstur SM, Sun J, Teras LR, Campbell PT, Patel AV. Oophorectomy and hysterectomy and cancer incidence in the Cancer Prevention Study-II Nutrition Cohort. Obstet Gynecol 2014;123:2475–5.
24. Juurlink D, Preya C, Crossford R, et al. Can-Canadian Institute for Health Information discharge abstrac database: a validation study. Available at: https://www.cics.on.ca/Publications/Atlases-and-Report/2006/Canadian-Institute-for-Health-Information. Accessed March 24, 2020.
25. McAlpine JN, Hanley GE, Woo MM, et al. Opportunistic salpingectomy: uptake, risks, and complications of a regional initiative for ovarian cancer prevention. Am J Obstet Gynecol 2014;210:471.e1–11.
26. Sandoval C, Fung-Kee-Fung M, Gilks B, Murphy KJ, Rahal R, Bryant H. Examining the use of salpingectomy with hysterectomy in Canada. Curr Oncol 2013;20:173–5.
27. Kurman RJ, Shih IeM. The origin and path-ogenesis of epithelial ovarian cancer: a pro-posed unifying theory. Am J Surg Pathol 2010;34:433–43.
28. Salvador S, Scott S, Francis JA, Agrawal A, Giede C. No. 344-opportunistic salpingectomy and other methods of risk reduction for ovarian/ Fallopian tube/peritoneal cancer in the general population. J Obstet Gynaecol Can 2017;39:480–93.
29. ACOG Committee Opinion No. 774: opportunistic salpingectomy as a strategy for epithelial ovarian cancer prevention. Obstet Gynecol 2019;133:e279–84.
30. McLaughlin JR, Kreiger N, Marrett LD, Holowaty EJ. Cancer incidence registration and improve cardiovascular health and health-care services. Circ Cardiovasc Qual Outcomes 2018;11:932–9.
31. Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. J Clin Epidemiol 1988;41:495–501.
32. Canadian Institute for Health Information. Health Indicators 2013: definitions, data sources, and rationale. 2013. Available at: https://www.cifi.ca/sites/default/files/document/health-indicators-2013-en.pdf. Accessed March 24, 2020.
33. Chiu M, Lebenbaum M, Lam K, et al. Describing the linkages of the immigration, refugees and citizenship Canada permanent resident data and vital statistics death registry to Ontario’s administrative health database. BMC Med Inform Decis Mak 2016;16:135.
34. Shah BR, Chiu M, Amin S, Ramani M, Sady S, Tu JV. Surname lists to identify South Asian and Chinese ethnicity from secondary data in Ontario, Canada: a validation study. BMC Med Res Methodol 2010;10:42.
35. Hall RE, Cohen MM. Variations in hysterectomy rates in Ontario: does the indication matter? CMAJ 1994;151:1713–9.
36. Banis-Matharu L, Gurd-Urganci I, Mahmood TA, Templeton A, van der Meulien JH, Cromwell DA. Rates of subsequent surgery following endometrial ablation among English women with menorrhagia: population-based cohort study. BJOG 2013;120:1500–7.
37. Reeves GK, Balkwill A, Cairns BJ, Green J, Beral V. Million Women Study Collaborators. Hospital admissions in relation to body mass index in UK women: a prospective cohort study. BMC Med 2014;12:45.
38. Austin PC, van Walraven C, Wodchis WP, Newman A, Anderson GM. Using the Johns Hopkins Aggregated Diagnosis Groups (ADGs) to predict mortality in a general adult population cohort in Ontario, Canada. Med Care 2011;49: 932–9.
39. Ministry of Health and Long-Term Care. Quality-based procedures clinical handbook for hysterec- tomy. 2016. Available at: https://www. health.gov.on.ca/en/pro/programs/ecfa/docs/ hb_hysterectomy.pdf. Accessed March 24, 2020.
40. The Johns Hopkins ACG® case-mix sys-tem version 10.0 release notes. The Johns Hopkins University Bloomberg School of Public Health, Health Services Research & Develop-ment center. The Johns Hopkins University; 2011.
41. Lipscombe LL, Hveee J, Webster L, Shah BR, Booth GL, Tu K. Identifying diabetes cases from administrative data: a population-based validation study. BMC Health Serv Res 2018;18:316.
42. Tu K, Chen Z, Lipscombe LL, Canadian Hypertension Education Program Outcomes Research Taskforce. Prevalence and incidence of hypertension from 1995 to 2005: a population-based study. CMAJ 2008;178:1429–35.
43. Gershon AS, Wang C, Guan J, Vasilevska- Ristovska J, Cicuttto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. COPD 2009;6: 388–94.
44. Tu JV, Chu A, Donovan LR, et al. The car-diovascular Health in Ambulatory Care Research Team (CANHEART): using big data to measure and improve cardiovascular health-care services. Circ Cardiovasc Qual Outcomes 2015;8:204–12.
45. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28: 3083–107.
46. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treat-ment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34: 3661–79.
47. Austin PC. The use of propensity score methods with survival or time-to-event out-comes: reporting measures of effect similar to those used in randomized experiments. Stat Med 2014;33:1242–58.
48. Austin PC. An introduction to propensity score methods for reducing the effects of con-founding in observational studies. Multivariate Behav Res 2011;46:399–424.
49. Harrell FE. Regression modelling strategies: with applications to linear models, logistic regression, and survival analysis. New York, NY: Springer-Verlag New York; 2010.
50. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79: 516–24.
51. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol 2009;170:244–56.
52. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601–9.
53. Austin PC, Fine JP. Practical recommendation for reporting Fine-Gray model analyses for competing risk data. Stat Med 2017;36: 4391–400.
54. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event out-comes. J Clin Epidemiol 2010;63:46–55.
55. US Preventive Services Task Force, Grossman DC, Curry SJ, et al. Screening for ovarian cancer: US Preventive Services Task Force recommendation statement. JAMA 2019;321:589–94.
56. Falconer H, Yin L, Grönh berg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. J Natl Cancer Inst 2015;107:duu410.
57. Gross CP, Nicholson W, Powe NR. Factors affecting prophylactic oophorectomy in post-menopausal women. Obstet Gynecol 1999;94: 962–8.
58. Lai JC, Chen HH, Huang SM, et al. In-hos-pital complications of vaginal versus laparoscopic-assisted benign hysterectomy among older women: a propensity score-matched cohort study. Menopause 2016;23: 1233–8.
59. Asante A, Whiteman MK, Kulkarni A, Cox S, Marchbanks PA, Jamieson DJ. Elective oph-rectomy in the United States: trends and in-hospital complications, 1998-2006. Obstet Gynecol 2010;116:1088–95.
60. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar G, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. Obstet Gynecol 2005;106:219–26.
61. Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual func-tioning in oophorectomized women. Psychoso-med 1987;49:397–409.
62. Shifren JL. Androgen deficiency in the oophorectomized woman. Fertil Steril 2002;77(Suppl4):S60–2.
63. Labirle F, Martel C, Balser J. Wide distribution of the serum dehydroepiandrosterone and sex steroid levels in postmenopausal women: role of the ovary? Menopause 2011;18:30–43.
64. Chen X, Guo T, Li B. Influence of prophylactic oophorectomy on mood and sexual
function in women of menopausal transition or postmenopausal period. Arch Gynecol Obstet 2013;288:1101–6.

65. Rodríguez MC, Chedraui P, Schwager G, Hidalgo L, Pérez-López FR. Assessment of sexuality after hysterectomy using the Female Sexual Function Index. J Obstet Gynaecol 2012;32:180–4.

66. Sözeri-Varma G, Kalkan-Oğuzhanoğlu N, Karadağ F, Ozdel O. The effect of hysterectomy and/or oophorectomy on sexual satisfaction. Climacteric 2011;14:275–81.

67. Aziz A, Bergquist C, Brännström M, Nordholm L, Silfverstolpe G. Differences in aspects of personality and sexuality between perimenopausal women making different choices regarding prophylactic oophorectomy at elective hysterectomy. Acta Obstet Gynecol Scand 2005;84:854–9.

68. Aziz A, Bergquist C, Nordholm L, Möller A, Silfverstolpe G. Prophylactic oophorectomy at elective hysterectomy. Effects on psychological well-being at 1-year follow-up and its correlations to sexuality. Maturitas 2005;51:349–57.

69. Ogburn EL, VanderWeele TJ. On the non-differential misclassification of a binary confounder. Epidemiology 2012;23:433–9.

70. Wright JD, Herzog TJ, Tsui J, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. Obstet Gynecol 2013;122:233–41.

**Author and article information**

From the Department of Obstetrics and Gynaecology, University of Toronto, Toronto, Ontario, Canada (Drs Cusimano and Ferguson); Institute of Health Policy, Management, and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Drs Cusimano, Chiu, and Baxter); Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, Ontario, Canada (Drs Cusimano and Baxter); Division of Gynecologic Oncology, Princess Margaret Cancer Centre and Sinai Health Systems, Toronto, Ontario, Canada (Dr Ferguson); ICES (formerly the Institute for Clinical Evaluative Sciences), Toronto, Ontario, Canada (Drs Moeneddin and Chiu, Ms Aktar, and Drs Liu and Baxter); Biostatistics Division, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Dr Moineddin); Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada (Dr Moineddin); Department of Surgery, University of Toronto, Toronto, Ontario, Canada (Dr Baxter); and Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia (Dr Baxter).

Received March 13, 2021; revised Sept. 7, 2021; accepted Sept. 17, 2021.

The authors report no conflict of interest.

M.C.C. is supported by the American College of Surgeons Resident Research Scholarship and the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship. This study was supported by ICES (formerly known as the Institute for Clinical Evaluative Sciences), which is funded by an annual grant from the Ontario Ministry of Health & Long-Term Care (MOHLTC). The funding sources had no role in any part of the study, and the opinions, results, and conclusions reported in this manuscript are those of the authors and are independent from the funding sources. No endorsement by ICES or the MOHLTC is intended or should be inferred.

The findings in this study were presented at the Society of Gynecologic Oncology Annual Meeting (Virtual) in March 19–25, 2021.

Corresponding author: Nancy N. Baxter, MD, PhD, FRCSC, FACS. Nancy.Baxter@unimelb.edu.au
### SUPPLEMENTAL TABLE 1  
**Codes for hysterectomy and salpingo-oophorectomy**

| Procedure               | Technique | DAD and SDS codes | Years 1996−2001 | Years 2002+ | OHIP codes |
|-------------------------|-----------|-------------------|------------------|-------------|------------|
| Total hysterectomy      | Open      | 1.RM.89.LA        | 80.3             |             | S710, S757, S758, S759, S763, S769, S810, S816 |
|                         | Laparoscopic | 1.RM.89.DA, 1.RM.89.AA | N/A             |             |            |
|                         | Vaginal   | 1.RM.89.CA        | 80.4             |             |            |
|                         | Robotic   | 1.RM.89.− + 7.SF.14.ZX | N/A             |             |            |
| Subtotal hysterectomy   | Open      | 1.RM.87.LA        | 80.2             |             |            |
|                         | Laparoscopic | 1.RM.87.DA, 1.RM.87.BA, 1.RM.87.CA | N/A             |             |            |
|                         | Robotic   | 1.RM.87.− + 7.SF.14.ZX | N/A             |             |            |
| Radical hysterectomy    | Open      | 1.RM.91.LA        | 80.5             |             |            |
|                         | Laparoscopic | 1.RM.91.DA, 1.RM.91.AA | N/A             |             |            |
|                         | Vaginal   | 1.RM.91.CA        | 80.6             |             |            |
|                         | Robotic   | 1.RM.91.− + 7.SF.14.ZX | N/A             |             |            |
| Salpingo-oophorectomy   | Unilateral | 1.RB.89., 1.RD.89.− [location attribute (L)eft/(R)ight] | 77.2, 77.3     | N/A         |            |
|                         | Bilateral | 1.RB.89., 1.RD.89.− [location attribute (B)ilateral] | 77.41, 77.42, 77.51, 77.52 |             |            |
| Salpingectomy           | Unilateral | 1.RF.89.− [location attribute (L)eft/(R)ight] | 78.1            | N/A         |            |
|                         | Bilateral | 1.RF.89.− [location attribute (B)ilateral] | 78.21, 78.22    |             |            |

Patients required a procedure code for hysterectomy in the DAD or SDS and a surgeon billing claim for hysterectomy in the OHIP database within 6 weeks of each other to be eligible for inclusion.

DAD, Discharge Abstract Database; N/A, not applicable; OHIP, Ontario Health Insurance Plan; SDS, Same Day Surgery database.

Casimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
### SUPPLEMENTAL TABLE 2

**Inclusion and exclusion criteria with relevant codes**

| Criteria | Source | Codes |
|----------|--------|-------|
| **Inclusion criteria** | | |
| 1. Female patient | RPDB | SEX = F |
| 2. Age ≥ 20 y at index date | RPDB | Based on variables BDATE and BYEAR |
| 3. Record of hysterectomy in DAD and SDS and OHIP (± 6 wk) from January 1, 1996, to December 31, 2010, and performed on an elective basis | DAD | Hysterectomy codes: Appendix 1 |
| SDS | Admission category variable: ADMCAT = L |
| **Exclusion criteria** | | |
| 1. Non-Ontario residents ineligible for universal health insurance coverage | RPDB | - IKN = Invalid |
| | | - First 2 digits of PRCDDABL not 35 |
| | | - Death or loss of OHIP before the index date |
| 2. Suspected emergent hysterectomy | OHIP | - Surgery between 12:00 AM and 7:00 AM: E410 |
| DAD | - Peripartum indication for hysterectomy (PATSERV = 51, 53, or 59)¹ |
| SDS | | |
| 3. Malignant indication for hysterectomy or a previous breast cancer diagnosis | OCR | - Gynecologic cancer diagnosed any time before or up to 6 wk after index date (ICD-9: 179–184; ICD-10: C510–C58, C481, C48.2) |
| DAD | - Main indication for index surgical admission was either a cancer diagnosis or a gynecologic neoplasm of uncertain or unknown behavior: ICD-9: 140-208, 2360, 2362, 2361, 2363; ICD-10: C00—C97, D390, D391, D392, D397, D399 |
| SDS | - Documentation of prophylactic surgery for malignancy before or on the index date (mastectomy, hysterectomy, salpingo-oophorectomy): ICD-9: V50.4; ICD-10: Z40 |
| | - Breast cancer diagnosis before the index date: ICD-9: 174; ICD-10: C50 |
| 4. Bilateral salpingo-oophorectomy before the index date | DAD | Salpingo-oophorectomy codes: Appendix 1 |
| SDS | | |
| 5. Ovarian pathology documented at the time of the index hysterectomy | DAD | - ICD-9: 220, 2200, 6200, 6201, 6202, 2362 |
| SDS | - ICD-10: D27, N830, N831, N832, D391 |

DAD: Discharge Abstract Database; ICD-9: International Classification of Diseases, Ninth Revision; ICD-10: International Classification of Diseases, Tenth Revision; OHIP: Ontario Health Insurance Plan; RPDB: Registered Persons Database; SDS: Same Day Surgery database.

¹ Codes are derived from the Canadian Institute for Health Information—technical note: hysterectomy readmission (accessed at https://www.cihi.ca/en/technical-note-hysterectomy-readmission-09P14_039).

Casimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
### SUPPLEMENTAL TABLE 3
ICD-9 and ICD-10 codes for cancer of the ovary, fallopian tube, and peritoneum

| Cancer type                                           | ICD-9 | ICD-10 |
|-------------------------------------------------------|-------|--------|
| **Ovary**                                             |       |        |
| Malignant neoplasm of the ovary, unilateral            | 1830  | C56.0  |
| Malignant neoplasm of the ovary, bilateral             | 1830  | C56.1  |
| Malignant neoplasm of the ovary, unspecified or specified whether unilateral or bilateral | 1830  | C56.9  |
| **Fallopian tube**                                    |       |        |
| Malignant neoplasm of the fallopian tube, unilateral   | 1832  | C57.00 |
| Malignant neoplasm of the fallopian tube, bilateral    | 1832  | C57.01 |
| Malignant neoplasm of the fallopian tube, unspecified whether unilateral or bilateral | 1832  | C57.09 |
| **Peritoneum**                                        |       |        |
| Malignant neoplasm of the broad ligament               | 1833  | C57.1  |
| Malignant neoplasm of the round ligament               | 1835  | C57.2  |
| Malignant neoplasm of the parametrium                  | 1834  | C57.3  |
| Malignant neoplasm of the uterine adnexa, unspecified  | 1838, | C57.4  |
|                                                      | 1839  |        |
| Malignant neoplasm of the unspecified parts of peritoneum | 1588  | C48.1  |
| Malignant neoplasm of the peritoneum, unspecified      | 1589  | C48.2  |

ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

Casimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
### SUPPLEMENTAL TABLE 4
ICD-9 and ICD-10 codes for major gynecologic diagnoses documented on the inpatient or outpatient admission for hysterectomy

| Indication                                      | Definition                                               | ICD-10 codes               | ICD-9 codes |
|------------------------------------------------|----------------------------------------------------------|----------------------------|-------------|
| **Premalignant conditions**                    |                                                          |                            |             |
| Endometrial hyperplasia                        | N850, N851                                              | N870, N871, N872, N879     | 6213        |
| Cervical dysplasia                             | N890, N891, N892, N893                                  | 6221                       |             |
| Vaginal dysplasia                              | N900, N901, N902, N903                                  | N/A                        |             |
| Vulvar dysplasia                               | N900, N901, N902, N903                                  | N/A                        |             |
| CIS of the cervix                              | D060, D061, D067, D069                                  | 2331                       |             |
| CIS of the vagina                              | D072                                                    | N/A                        |             |
| CIS of the vulva                               | D071                                                    | N/A                        |             |
| CIS of the endometrium or uterus               | D070                                                    | 2332                       |             |
| CIS of the unspecified female genital organs   | D073                                                    | 2333                       |             |
| **Benign ovarian cysts**                       |                                                          |                            |             |
| Benign neoplasm of the ovary                   | D27                                                     | 220, 2200                  |             |
| Follicular ovarian cyst                        | N830                                                    | 6200                       |             |
| Corpus luteum cyst                             | N831                                                    | 6201                       |             |
| Other and unspecified ovarian cysts            | N832                                                    | 6202                       |             |
| Neoplasm of uncertain or unknown behavior of the ovary | D391                                                  | 2362                       |             |
| **Abnormal uterine bleeding**                  |                                                          |                            |             |
| Heavy menstrual bleeding                       |                                                          |                            |             |
| Excessive or frequent, regular cycle          | N920                                                    | 6262                       |             |
| Excessive or frequent, irregular cycle         | N921                                                    | 6262                       |             |
| Excessive in premenopause                      | N924                                                    | 6270                       |             |
| Irregular, other                               | N925                                                    | 6264, 6266                 |             |
| Irregular, unspecified                         | N926                                                    | 6264, 6266                 |             |
| Abnormal, other                                | N938                                                    | 6268                       |             |
| Abnormal, unspecified                          | N939                                                    | 6269                       |             |
| Excessive menstruation at puberty              | N922                                                    | 6263                       |             |
| Ovulation bleeding                             | N923                                                    | 6265                       |             |
| Postcoital and contact bleeding                | N930                                                    | 6267                       |             |
| Postmenopausal bleeding                        | N950                                                    | 6271                       |             |
| **Fibroids**                                   |                                                          |                            |             |
| Fibroids                                       | D25                                                     | 218                        |             |
| Submucous leiomyoma                            | D250                                                    | 2180                       |             |
| Intramural leiomyoma                           | D251                                                    | 2181                       |             |
| Subserosal leiomyoma                           | D252                                                    | 2182                       |             |
| Leiomyoma of the uterus, unspecified           | D259                                                    | 2189                       |             |

*Casimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.*

(continued)
| Indication | Definition | ICD-10 codes | ICD-9 codes |
|------------|------------|--------------|------------|
| Endometriosis | | | |
| Uterus | N800 | 6170 |
| Ovary | N801 | 6171 |
| Fallopian tube | N802 | 6172 |
| Pelvic peritoneum | N803 | 6173 |
| Rectovaginal septum or vagina | N804 | 6174 |
| Intestine | N805 | 6175 |
| Cutaneous scar | N806 | 6176 |
| Other, unspecified | N808, N809 | 6178, 6179 |
| Prolapse | | | |
| Female urethrocele | N810 | N/A |
| Cystocele | N811 | N/A |
| Incomplete uterovaginal prolapse | N812 | 6182 |
| Complete uterovaginal prolapse | N813 | 6183 |
| Uterovaginal prolapse, unspecified | N814 | 6184 |
| Vaginal enterocele | N815 | 6186 |
| Rectocele | N816 | N/A |
| Other female genital prolapse | N818 | 6188 |
| Female genital prolapse, unspecified | N819 | 6189 |
| Prolapse of vaginal wall | N/A | 6180 |
| Uterine prolapse | N/A | 6181 |
| Postoperative vaginal prolapse | N/A | 6185 |
| Old laceration of pelvic muscle | N/A | 6187 |
| Pelvic pain and inflammation | | | |
| Inflammation | | | |
| Salpingitis and oophoritis | N700, N701, N709 | 6140, 6141, 6142 |
| Inflammatory disease of the uterus | N710, N711, N719 | 6143, 6144, 6150, 6151, 6159 |
| Inflammatory disease of the cervix | N72 | 6160 |
| Parametritis, pelvic cellulitis, pelvic peritonitis, pelvic peritoneal adhesions, other or unspecified female pelvic inflammatory disease | N730, N731, N732, N733, N734, N735, N736, N738, N739 | 6145, 6146, 6147, 6148, 6149 |
| Pelvic inflammatory disease (tuberculous, syphilitic, gonococcal, chlamydial, other, unspecified) | N740, N741, N742, N743, N744, N748 | 614, 615 |
| Bartholin’s cyst, abscess, or disease | N750, N751, N758, N759 | 6162, 6163 |
| Vaginitis, vulvitis, or ulceration | N760, N761, N762, N763, N764, N765, N766, N768, N7680, N7688 | 6161, 61610, 61611, 6164, 6165, 61650, 61651 |
| Vulvovaginal ulceration and inflammation NEC | N770, N771, N778 | 6168, 6169 |
### SUPPLEMENTAL TABLE 4
ICD-9 and ICD-10 codes for major gynecologic diagnoses documented on the inpatient or outpatient admission for hysterectomy

| Indication                                      | Definition                                                                 | ICD-10 codes               | ICD-9 codes |
|-------------------------------------------------|---------------------------------------------------------------------------|----------------------------|-------------|
| Abdominal and pelvic pain                       | Acute abdomen, RUQ or LUQ, RLQ or LLQ, pelvic or perineal pain, other or unspecified abdominal pain | R100, R1010, R1011, R1012, R1019, R102, R1030, R1032 R1039, R104 | 7890        |
|                                                 | Acute, chronic, or other pain                                            | R520, R521, R522, R529     | N/A         |
| Menstrual pain                                  | Mittelschmerz                                                             | N940                       | 6252        |
|                                                 | Dyspareunia                                                               | N941                       | 6250        |
|                                                 | Vaginismus                                                                | N942                       | 6251        |
|                                                 | Premenstrual tension syndrome                                             | N943                       | 6254, 6255  |
|                                                 | Primary dysmenorrhea                                                      | N944                       | 6253        |
|                                                 | Secondary dysmenorrhea                                                    | N945                       | 6253        |
|                                                 | Dysmenorrhea, unspecified                                                | N946                       | 6253        |
| Other specified conditions associated with female genital organs and menstrual cycle | N948                       | N/A                       |
| Unspecified condition associated with female genital organs and menstrual cycle | N949                       | N/A                       |

Patients could have multiple diagnoses if relevant.

CIS, carcinoma in situ; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; LLQ, left lower quadrant; LUQ, left upper quadrant; N/A, not applicable; NEC, necrotizing enterocolitis; RLQ, right lower quadrant.

* Codes for heavy menstrual bleeding have been previously used by Bansi-Matharu et al.36; b Codes for fibroids and prolapse have been previously used by Reeves et al.37

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
### SUPPLEMENTAL TABLE 5

Codes and algorithms used to ascertain specific comorbidities

| Comorbidity                              | Source                        | Relevant codes | Algorithm and citation |
|------------------------------------------|-------------------------------|----------------|------------------------|
| Previous malignancy                      | - Ontario Cancer Registry     | ICD-10: C00–C37 | Not applicable          |
|                                          |                               | ICD-9: 140–208  |                        |
| Hypertension                             | - Ontario Hypertension Database | ICD-9: 401, 402, 403, 404, 405 | Tu et al, 42 2008 |
|                                          |                               |                |                        |
|                                          | - DAD                         | ICD-10: I10, I11, I12, I13, I15 | SN: 72%                |
|                                          | - SDS                         | OHIP: 401, 402, 403, 404, 405 | SP: 95%                |
|                                          | - OHIP                        |                |                        |
| Diabetes mellitus                        | - Ontario Diabetes Database   | ICD-9: 250     | Lipscombe et al, 41 2018 |
|                                          |                               |                |                        |
|                                          | - DAD                         | ICD-10: E10, E11, E13, E14 | SN: 90.0%               |
|                                          | - SDS                         | OHIP: 250, K030, K045, K046, Q040 | SP: 97.7%                |
|                                          | - ODB                         |                |                        |
| COPD                                     | - COPD database               | OHIP: 491, 492, 496 | Gershon et al, 43 2009 |
|                                          | - OHIP                        | ICD-10: J41, J43, J44 | SN: 85.0%               |
|                                          | - DAD                         | SP: 78.4%      |                        |
|                                          | - SDS                         |                |                        |
| Previous cardiovascular disease          | - DAD                         | Ischemic heart disease | Tu et al, 44 2015 |
|                                          | - SDS                         | ICD-10: I20–I25 |                        |
|                                          | - NACRS                       | ICD-9: 410–414 |                        |
|                                          | - OHIP                        | OHIP: 410, 412, 413 |                        |
|                                          |                               | Stroke or transient ischemic attack | ICD-10: I60, I61, I63 (except I63.6), I64, H34.1, G45 (except G45.4), H34.0 |
|                                          |                               | ICD-9: 362.3, 430, 431, 434, 436, 435 |                        |
|                                          |                               | OHIP: 436, 432, 435 |                        |
|                                          |                               | Heart failure | ICD-10: I500, I501, I509 |
|                                          |                               | ICD-9: 428 |                          |
|                                          |                               | OHIP: 428 |                          |
|                                          |                               | Coronary revascularization | CCI: 1J50, 1J54, 1J57G0, 1J76 |
|                                          |                               | CCI: 3IP10 |                        |
|                                          |                               | CCI: 1J50, 1J54, 1J57G0, 1J76 |                        |
|                                          |                               | CCP: 4802, 4803, 481 |                        |
|                                          |                               | OHIP: Z434, G298, R742, R743 |                        |
|                                          |                               | Cardiac catheterization |                        |
|                                          |                               | CCI: 3IP10 |                        |
|                                          |                               | CCP: 4892, 4893, 4894, 4895, 4896, 4897, 4898, 4995, 4996, 4997 |                        |
|                                          |                               | OHIP: Z442 or G297 |                        |

CCI, Canadian Classification of Health Interventions; COPD, chronic obstructive pulmonary disease; DAD, Discharge Abstract Database; ICD, International Classification of Diseases; NACRS, National Ambulatory Care Reporting System; ODB, Ontario Drug Benefit Database; OHIP, Ontario Health Insurance Plan Database; SDS, Same Day Surgery database; SN, sensitivity; SP, specificity.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
Appendix 6

SUPPLEMENTAL FIGURE 1
Proportion of women undergoing hysterectomy who received BSO during each year of the study period

The total number of women undergoing hysterectomy and total number of women undergoing hysterectomy with BSO are indicated on the secondary axis.

BSO, bilateral salpingo-oophorectomy.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
Appendix 7

SUPPLEMENTAL FIGURE 2
Standardized differences before and after propensity score–based weighting
**SUPPLEMENTAL TABLE 6**
Weighted cumulative incidence of ovarian cancer death in women undergoing BSO or ovarian conservation, with corresponding ARR and NNT to prevent the occurrence of 1 additional outcome at 10, 15, and 20 years follow-up

| Year of follow-up | No BSO  | BSO     | ARR     | NNT  |
|-------------------|---------|---------|---------|------|
| Women ≥20 y       |         |         |         |      |
| 10                | 0.09% (0.07—0.11) | 0.03% (0.01—0.06) | 0.06% (0.02—0.09) | 1806 |
| 15                | 0.15% (0.12—0.18) | 0.04% (0.02—0.07) | 0.11% (0.06—0.15) | 940  |
| 20                | 0.25% (0.20—0.30) | 0.07% (0.03—0.12) | 0.18% (0.11—0.25) | 569  |
| Women ≥50 y       |         |         |         |      |
| 10                | 0.20% (0.15—0.25) | 0.08% (0.02—0.17) | 0.12% (0.02—0.20) | 852  |
| 15                | 0.35% (0.27—0.45) | 0.09% (0.03—0.18) | 0.26% (0.14—0.38) | 390  |
| 20                | 0.51% (0.38—0.67) | 0.09% (0.03—0.18) | 0.42% (0.26—0.60) | 237  |

ARR, absolute risk reduction; BSO, bilateral salpingo-oophorectomy; NNT, number needed to treat.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
### SUPPLEMENTAL TABLE 7
Baseline characteristics of patients (≥50 years) undergoing benign hysterectomy with BSO or ovarian conservation, both before and after inverse probability of treatment weighting

| Characteristic                               | Unweighted cohort | Weighted cohort | Standard difference<sup>a</sup> | Standard difference<sup>a</sup> |
|----------------------------------------------|-------------------|-----------------|----------------------------------|----------------------------------|
|                                              | Total (N=57,736)  | No BSO (n=35,196)| BSO (n=22,540)                   | No BSO                           | BSO                            |
| Age (y)                                      |                   |                 |                                  |                                  |                                |
| Mean (IQR)                                   | 60.9 (53–68)      | 62.9 (54–70)    | 57.9 (52–62)                     | 0.58                             | 61.0                           | 61.1                           | 0.01                          |
| Area of residence                            |                   |                 |                                  |                                  |                                |
| Urban                                        | 48,607 (84.2)     | 29,395 (83.5)   | 19,212 (85.2)                    | 0.05                             | 84.00                          | 83.42                          | 0.02                          |
| Rural                                        | 9105 (15.8)       | 5788 (16.4)     | 3317 (14.7)                      | 0.05                             | 16.00                          | 16.58                          | 0.02                          |
| Missing                                      | 24 (0.0)          | 13 (0.0)        | 11 (0.0)                         | 0.01                             | —                              | —                              | —                             |
| Era of surgery                               |                   |                 |                                  |                                  |                                |
| 1996–2000                                    | 19,562 (33.9)     | 10,656 (30.3)   | 8906 (39.5)                      | 0.19                             | 33.72                          | 31.89                          | 0.04                          |
| 2001–2005                                    | 18,721 (32.4)     | 11,488 (32.6)   | 7233 (32.1)                      | 0.01                             | 32.95                          | 34.60                          | 0.03                          |
| 2006–2010                                    | 19,453 (33.7)     | 13,052 (37.1)   | 6401 (28.4)                      | 0.19                             | 33.32                          | 33.51                          | 0.00                          |
| Income quintile                              |                   |                 |                                  |                                  |                                |
| Quintile 1 (low)                             | 9505 (16.5)       | 5955 (16.9)     | 3550 (15.7)                      | 0.03                             | 16.31                          | 15.96                          | 0.01                          |
| Quintile 2                                   | 11,219 (19.4)     | 6943 (19.7)     | 4276 (19.0)                      | 0.02                             | 19.60                          | 18.77                          | 0.02                          |
| Quintile 3                                   | 11,893 (20.6)     | 7252 (20.6)     | 4641 (20.6)                      | 0.00                             | 20.72                          | 19.91                          | 0.02                          |
| Quintile 4                                   | 12,087 (20.9)     | 7270 (20.7)     | 4817 (21.4)                      | 0.02                             | 21.23                          | 22.16                          | 0.02                          |
| Quintile 5 (high)                            | 12,901 (22.3)     | 7691 (21.9)     | 5210 (23.1)                      | 0.03                             | 22.15                          | 23.20                          | 0.03                          |
| Missing                                      | 131 (0.2)         | 85 (0.2)        | 46 (0.2)                         | 0.01                             | —                              | —                              | —                             |
| Immigration status                           |                   |                 |                                  |                                  |                                |
| Long-term resident                           | 53,660 (92.9)     | 32,724 (93.0)   | 20,936 (92.9)                    | 0.00                             | 93.11                          | 93.77                          | 0.03                          |
| Immigrant                                    | 4076 (7.1)        | 2472 (7.0)      | 1604 (7.1)                       | 6.89                             |                                |                                |                                |
| Ethnicity                                    |                   |                 |                                  |                                  |                                |
| General population                           | 55,385 (95.9)     | 33,797 (96.0)   | 21,588 (95.8)                    | 0.01                             | 96.03                          | 96.06                          | 0.00                          |
| South Asian                                  | 1133 (2.0)        | 696 (2.0)       | 437 (1.9)                        | 0.00                             | 1.84                           | 1.73                           | 0.01                          |
| Chinese                                      | 1218 (2.1)        | 703 (2.0)       | 515 (2.3)                        | 0.02                             | 2.13                           | 2.21                           | 0.01                          |
| Surgical approach                            |                   |                 |                                  |                                  |                                |
| Abdominal                                    | 29,014 (50.3)     | 8571 (24.4)     | 20,443 (90.7)                    | 1.81                             | 51.03                          | 51.45                          | 0.01                          |
| Vaginal                                      | 28,722 (49.7)     | 26,625 (75.6)   | 2097 (9.3)                       | 48.97                            |                                |                                |                                |
| Hysterectomy type                            |                   |                 |                                  |                                  |                                |
| Total                                        | 54,550 (94.5)     | 33,623 (95.5)   | 20,927 (92.8)                    | 0.12                             | 94.55                          | 94.36                          | 0.01                          |
| Subtotal                                     | 3186 (5.5)        | 1573 (4.5)      | 1613 (7.2)                       | 5.45                             |                                |                                |                                |
| Abnormal uterine bleeding                    |                   |                 |                                  |                                  |                                |
| Yes                                          | 11,973 (20.7)     | 4779 (13.6)     | 7194 (31.9)                      | 0.45                             | 21.25                          | 22.64                          | 0.03                          |
| No                                           | 45,763 (79.3)     | 30,417 (86.4)   | 15,346 (68.1)                    | 78.75                            |                                |                                |                                |

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.
### SUPPLEMENTAL TABLE 7

Baseline characteristics of patients (≥50 years) undergoing benign hysterectomy with BSO or ovarian conservation, both before and after inverse probability of treatment weighting (continued)

| Characteristic              | Unweighted cohort | Weighted cohort | Standard difference<sup>a</sup> |
|----------------------------|-------------------|-----------------|---------------------------------|
|                            | Total (N = 57,736) | No BSO (n = 35,196) | BSO (n = 22,540) | No BSO | BSO |
| Fibroids                   |                   |                 |                   |        |     |        |
| Yes                        | 23,553 (40.8)     | 10,631 (30.2)   | 12,922 (57.3)     | 0.57   | 40.89 | 42.64 | 0.04 |
| No                         | 34,183 (59.2)     | 24,565 (69.8)   | 9618 (42.7)       | 59.11  | 59.11 | 57.36 |
| Endometriosis              |                   |                 |                   |        |     |        |
| Yes                        | 9,586 (16.6)      | 4,472 (12.7)    | 5,114 (22.7)      | 0.26   | 17.08 | 17.02 | 0.00 |
| No                         | 48,150 (83.4)     | 30,724 (87.3)   | 17,426 (77.3)     | 82.92  | 82.92 | 82.98 |
| Pelvic pain or inflammation|                   |                 |                   |        |     |        |
| Yes                        | 6,133 (10.6)      | 2,698 (7.7)     | 3,435 (15.2)      | 0.24   | 11.55 | 10.99 | 0.02 |
| No                         | 51,603 (89.4)     | 32,498 (92.3)   | 19,105 (84.8)     | 88.45  | 88.45 | 89.01 |
| Premalignant disease       |                   |                 |                   |        |     |        |
| Yes                        | 6,498 (11.3)      | 2,288 (6.5)     | 4,210 (18.7)      | 0.37   | 11.97 | 12.03 | 0.00 |
| No                         | 51,238 (88.7)     | 32,908 (93.5)   | 18,330 (81.3)     | 88.03  | 88.03 | 87.97 |
| Prolapse                   |                   |                 |                   |        |     |        |
| Yes                        | 32,602 (56.5)     | 27,302 (77.6)   | 5,300 (23.5)      | 1.29   | 55.01 | 53.78 | 0.02 |
| No                         | 25,134 (43.5)     | 7,894 (22.4)    | 17,240 (76.5)     | 44.99  | 44.99 | 46.22 |
| Comorbidities (ADGs)       |                   |                 |                   |        |     |        |
| 0—5                        | 9,467 (16.4)      | 6,154 (17.5)    | 3,313 (14.7)      | 0.08   | 16.18 | 16.71 | 0.01 |
| 6—9                        | 29,737 (51.5)     | 18,235 (51.8)   | 11,502 (51.0)     | 0.02   | 51.09 | 50.44 | 0.01 |
| ≥10                        | 18,532 (32.1)     | 10,807 (30.7)   | 7,725 (34.3)      | 0.08   | 32.73 | 32.84 | 0.00 |
| Hypertension               |                   |                 |                   |        |     |        |
| Yes                        | 24,302 (42.1)     | 15,732 (44.7)   | 8,570 (38.0)      | 0.14   | 42.18 | 41.78 | 0.01 |
| No                         | 33,434 (57.9)     | 19,464 (55.3)   | 13,970 (62.0)     | 57.82  | 57.82 | 58.22 |
| Diabetes mellitus          |                   |                 |                   |        |     |        |
| Yes                        | 5,860 (10.1)      | 3,843 (10.9)    | 2,017 (8.9)       | 0.07   | 10.14 | 10.08 | 0.00 |
| No                         | 51,876 (89.9)     | 31,353 (89.1)   | 20,523 (91.1)     | 89.86  | 89.86 | 89.92 |
| Chronic obstructive pulmonary disease | | | |        |     |        |
| Yes                        | 5,206 (9.0)       | 3,336 (9.5)     | 1,870 (8.3)       | 0.04   | 9.18  | 8.86  | 0.01 |
| No                         | 52,530 (91.0)     | 31,860 (90.5)   | 20,670 (91.7)     | 90.82  | 90.82 | 91.14 |
| Previous malignancy        |                   |                 |                   |        |     |        |
| Yes                        | 1,369 (2.4)       | 845 (2.4)       | 524 (2.3)         | 0.01   | 2.47  | 2.45  | 0.00 |
| No                         | 56,367 (97.6)     | 34,351 (97.6)   | 22,016 (97.7)     | 97.53  | 97.53 | 97.55 |
| Previous cardiovascular disease | | | |        |     |        |
| Yes                        | 9,055 (15.7)      | 6,198 (17.6)    | 2,857 (12.7)      | 0.14   | 15.77 | 16.23 | 0.01 |
| No                         | 48,681 (84.3)     | 28,998 (82.4)   | 19,683 (87.3)     | 84.23  | 84.23 | 83.77 |

*Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.* (continued)
### SUPPLEMENTAL TABLE 7
Baseline characteristics of patients (≥50 years) undergoing benign hysterectomy with BSO or ovarian conservation, both before and after inverse probability of treatment weighting (continued)

| Characteristic                  | Unweighted cohort | Weighted cohort |
|--------------------------------|-------------------|-----------------|
|                                | Total (N=57,736)  | No BSO (n=35,196) | BSO (n=22,540) | Standard difference | No BSO | BSO | Standard difference |
| Previous ovarian surgery       |                   |                 |               |                   |        |     |                     |
| Yes                            | 984 (1.7)         | 475 (1.3)       | 509 (2.3)     | 0.07              | 1.82   | 1.68 | 0.01                |
| No                             | 56,752 (98.3)     | 34,721 (98.7)   | 22,031 (97.7) | 98.18             | 98.18  | 98.32|                    |
| Previous tubal ligation        |                   |                 |               |                   |        |     |                     |
| Yes                            | 1401 (2.4)        | 806 (2.3)       | 595 (2.6)     | 0.02              | 2.38   | 2.26 | 0.01                |
| No                             | 56,335 (97.6)     | 34,390 (97.7)   | 21,945 (97.4) | 97.62             | 97.62  | 97.74|                    |

Data are presented as number (percentage), unless otherwise indicated.

ADGs, Aggregated Diagnosis Groups; BSO, bilateral salpingo-oophorectomy; IQR, interquartile range.

*a Standardized differences comparing patients who did and did not undergo BSO.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.

### Appendix 10

### SUPPLEMENTAL TABLE 8
Ovarian cancer outcomes of patients (≥50 years) undergoing benign hysterectomy with BSO or ovarian conservation

| Outcome                        | No BSO (n=35,196) | BSO (n=22,540) | Total (N=57,736) |
|--------------------------------|-------------------|----------------|-----------------|
| Ovarian cancer                 |                   |                 |                 |
| Yes                            | 214 (0.6)         | 28 (0.1)        | 242 (0.4)       |
| No                             | 34,982 (99.4)     | 22,512 (99.9)   | 57,494 (99.6)   |
| Age at ovarian cancer (y)³     | Median (IQR)      |                 |                 |
|                                | 74.5 (67.3—80.7)  | 65.6 (58.0—73.0)| 73.8 (66.3—80.3)|
| Follow-up for ovarian cancer (y)| Median (IQR)      |                 |                 |
|                                | 14 (11—18)        | 16 (12—20)      | 15 (11—19)      |
| Ovarian cancer death           |                   |                 |                 |
| Alive                          | 28,369 (80.6)     | 19,841 (88.0)   | 48,210 (83.5)   |
| Death owing to ovarian cancer  | 130 (0.4)         | 18 (0.1)        | 148 (0.3)       |
| Death owing to other causes    | 6697 (19.0)       | 2681 (11.9)     | 9378 (16.2)     |
| Follow-up for ovarian cancer death (y)| Median (IQR) |                 |                 |
|                                | 12 (9—16)         | 14 (10—18)      | 13 (10—17)      |

Data are presented as number (percentage), unless otherwise indicated.

BSO, bilateral salpingo-oophorectomy; IQR, interquartile range.

*a Age at diagnosis among patients who developed ovarian cancer.

Cusimano et al. Ovarian cancer following bilateral salpingo-oophorectomy at benign hysterectomy. Am J Obstet Gynecol 2022.