GYNECOLOGY

Examining indicators of early menopause following opportunistic salpingectomy: a cohort study from British Columbia, Canada

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BACKGROUND: The fallopian tube may often be the site of origin for the most common and lethal form of ovarian cancer, high-grade serous ovarian cancer. As a result, many colleges of obstetrics and gynecology, which include the American College of Obstetricians and Gynecologists, are recommending surgical removal of the fallopian tube (bilateral salpingectomy) at the time of other gynecologic surgeries (particularly hysterectomy and tubal sterilization) in women at general population risk for ovarian cancer, collectively referred to as opportunistic salpingectomy. Previous research has illustrated no increased risk of complications after opportunistic salpingectomy. However, most studies that have examined potential hormonal consequences of opportunistic salpingectomy have had limited follow-up time and have focused on surrogate hormonal markers.

OBJECTIVE: We examine whether there are differences in physician visits for menopause and filling a prescription for hormone replacement therapy among women who undergo opportunistic salpingectomy in the population of British Columbia, Canada.

STUDY DESIGN: We identified all women who were ≤50 years old in British Columbia who underwent opportunistic salpingectomy from 2008—2014. We compared women who underwent opportunistic salpingectomy at hysterectomy with women who underwent hysterectomy alone and women who underwent opportunistic salpingectomy for sterilization with women who underwent tubal ligation. We used Cox Proportional hazards models to model time to physician visits for menopause and for filling a prescription for hormone replacement therapy. We calculated adjusted hazards ratios for these outcomes and adjusted for other gynecologic conditions, surgical approach, and patient age. We performed an age-stratified analysis (<40, 40—44, 45—49 years) and conducted a sensitivity analysis that included only women with ≥5 years of follow up.

RESULTS: We included 41,413 women in the study. There were 6861 women who underwent hysterectomy alone, 6500 who underwent hysterectomy with opportunistic salpingectomy, 4479 who underwent hysterectomy with bilateral salpingo-oophorectomy, 18,621 who underwent tubal ligation, and 4952 who underwent opportunistic salpingectomy for sterilization. In women who underwent opportunistic salpingectomy, there was no difference in time to the first physician visit related to menopause for both women who underwent hysterectomy with opportunistic salpingectomy (adjusted hazard ratio, 0.98; 95% confidence interval, 0.88—1.09) and women who underwent opportunistic salpingectomy for sterilization (adjusted hazard ratio, 0.92; 95% confidence interval, 0.77—1.10). There was also no difference in time to filling a prescription for hormone replacement therapy for women who underwent hysterectomy with opportunistic salpingectomy or opportunistic salpingectomy for sterilization (adjusted hazard ratio, 0.82; 95% confidence interval, 0.72—0.92; and adjusted hazard ratio, 1.00; 95% confidence interval, 0.89—1.12; respectively). In contrast, we report significantly increase hazards for time to physician visit for menopause (adjusted hazard ratio, 1.95; 95% confidence interval, 1.78, 2.13) and filling a prescription for hormone replacement therapy (adjusted hazard ratio, 3.80; 95% confidence interval, 3.45, 4.18) among women who underwent hysterectomy with bilateral salpingo-oophorectomy. There were no increased hazards for physician visits for menopause or initiation of hormone replacement therapy among women who underwent opportunistic salpingectomy in any of the age-stratified analyses, nor among women with at least 5 years of follow up.

CONCLUSION: Our results reveal no indication of an earlier age of onset of menopause among the population of women who underwent hysterectomy with opportunistic salpingectomy and opportunistic salpingectomy for sterilization as measured by physician visits for menopause and initiation of hormone replacement therapy. Our findings are reassuring, given that earlier age at menopause is associated with increased mortality rates, particularly from cardiovascular disease.

Key words: bilateral salpingectomy, hysterectomy, menopause, ovarian cancer, sterilization

Ovarian cancer remains an important cause of death in the developed world, accounting for more deaths than any other cancer of the female reproductive tract.[1] Currently, there remains no effective screening methods because no mortality benefit has been demonstrated, even with strict adherence to screening protocols,[2–6] and no recent advances in treatment have significantly improved overall survival.[7] We now recognize that epithelial ovarian cancer encompasses 5 distinct diseases that differ in histologic appearance, clinical presentation, response to therapy, likelihood of recurrence, molecular aberrations, and, most important for prevention purposes, site of origin.[8,9] There has been a growing body of evidence pointing to the fallopian tube as the origin of the most common form of ovarian cancer, high-grade serous carcinoma.[10–13]

Many professional associations are recommending that clinicians discuss the removal of the fallopian tubes (bilateral salpingectomy) among women at general population risk of ovarian cancer who have completed childbearing

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AJOG at a Glance

Why was this study conducted?

The purpose of this study was to examine whether opportunistic salpingectomy, the removal of fallopian tubes at the time of hysterectomy or in lieu of tubal ligation for the purpose of ovarian cancer prevention, is associated with a decreased age of onset of menopause.

Key findings

There are no differences in time to physician visits for menopause or time to the initiation on hormone replacement therapy among women who undergo opportunistic salpingectomy compared with women who undergo hysterectomy alone or tubal ligation.

What does this add to what is known?

This study adds to the existing body of evidence that opportunistic salpingectomy is a safe alternative to hysterectomy alone or tubal ligation, with the potential benefit of ovarian cancer risk reduction.

and are undergoing (1) hysterectomy with ovarian preservation and (2) tubal ligation. This procedure is known as opportunistic salpingectomy (OS). Recommendations for OS were made by the Ovarian Cancer Research team in British Columbia in 2010. Since then, the American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynecologists of Canada have endorsed the recommendation.[14,15]

Previous research has indicated a substantial uptake of OS in both the United States[16–18] and Canada.[19–21] The safety research done to date that has examined both major perioperative events[18,20] and minor complications[22] has been reassuring. All data indicate that OS poses no additional risk to hysterectomy alone or tubal ligation. Studies that have examined ovarian function after these procedures have often been small and have focused on surrogate hormonal markers. For example, measurement of ovarian sonographic parameters and hormonal assays were reassuring, with no differences seen in women who undergo hysterectomy with OS vs hysterectomy alone.[23–27] One series has reported up to 5 years of follow-up data with no negative impact on reported ovarian parameters.[28] However, a recent Swedish Registry study found an increased risk of menopausal symptoms 1 year after hysterectomy among women who underwent hysterectomy with bilateral salpingectomy compared with hysterectomy alone (relative risk, 1.33; 95% confidence interval [CI], 1.04–1.69).[29] Given that an earlier age at menopause has been associated with increased mortality rates,[30–32] it is imperative that we understand whether OS decreases the age of onset of menopause. Herein, we use population-based data in British Columbia, Canada, to examine indicators of menopause, namely physician visits for menopause or the initiation of hormone replacement therapy (HRT) among women who undergo OS and women who undergo comparator surgeries.

Methods

We conducted a population-based retrospective cohort study of all women who were ≤50 years old at the time that they underwent a hysterectomy or tubal sterilization in the Canadian province of British Columbia, Canada, (population 4.6 million) from 2008–2014. We obtained approvals from all relevant data stewards and worked with Population Data British Columbia to access the British Columbia Cancer Registry,[33] vital statistics death data,[34] the Discharge Abstract Database,[35] which contains all hospital stays and day surgeries in the province, thus capturing all women who underwent a relevant surgical procedure. These data were then linked with data on all physician visits,[36] and the British Columbia PharmaNet (a database that contains all prescriptions drugs dispensed in an outpatient setting).[37] Ethics approval was obtained from the University of British Columbia's Behavioural Research Ethics Board. All inferences, opinions, and conclusions are those of the authors and do not reflect the opinions or policies of the Data Stewards.

Women who underwent any of the relevant surgical procedures were identified with the use of the Canadian Classification of Health Intervention codes. This system separately identifies each procedure that is performed in the same surgery. For example, a woman who undergoes a hysterectomy with a bilateral salpingectomy has a code that indicates the removal of her uterus and a code that indicates the removal of her fallopian tubes. These codes also indicate the surgical approach for each surgery (ie, open, laparoscopic, or vaginal). We excluded women who were <15 years old or >50 years old at the time of the surgery. We excluded women who had a diagnosis of gynecologic cancer and women who had <183 days (approximately 6 months) of follow-up time after their surgery. We grouped women according to their procedures and stratified the data into 5 groups: (1) women who had undergone a hysterectomy with no concomitant oophorectomy or salpingectomy (referred to as hysterectomy alone), (2) women who underwent a hysterectomy and a bilateral salpingectomy (hysterectomy with OS), (3) women who underwent a hysterectomy with a bilateral salpingo-oophorectomy (BSO), (4) women who underwent a tubal ligation, and (5) women who had a bilateral salpingectomy alone with a diagnosis code that indicated the procedure was for sterilization (International Classification of Diseases, 10th revision [ICD-10], CM Z.30.2). We did not include women who underwent hysteroscopic tubal occlusion. We also used diagnostic codes in the hospital stay to examine other gynecologic conditions that were present in each woman, which included endometriosis (ICD-10, CA N80.X), leiomyoma (ICD-10, CA

TABLE 1
Characteristics of women according to their surgery type

Variable	Hysterectomy alone (n=6891)	Hysterectomy with opportunistic salpingectomy (n=6500)	*P* value[a]	Hysterectomy with bilateral salpingo-opphorectomy (n=4479)	*P* value[a]	Tubal ligation (n=18,621)	Opportunistic salpingectomy for sterilization (n=4952)	*P* value
Year of surgery, calendar year mean (SD)	2009.6 (1.6)	2011.8 (1.5)	<.001	2010.5 (1.6)	<.001	2010.1 (1.8)	2012.3 (1.2)	<.001
Age at time of surgery, y[b]	41.5±5.7	42.0±5.3	<.001	43.4±5.5	<.001	35.3±5.6	36.3±5.4	<.001
Mean length of follow-up, y[b]	4.8±1.5	2.7±1.5	<.001	3.9±1.8	<.001	4.3±1.8	2.2±1.1	<.001
Age category, y (%)								
<40	2419 (35.3)	2040 (31.4)		1029 (23.0)		14634 (78.6)	3652 (73.7)	
40–44	2244 (32.7)	2224 (34.2)		1262 (28.2)		3287 (17.7)	1032 (20.8)	
45–50	2198 (32.0)	2236 (34.4)	<.001	2188 (48.9)	<.001	701 (3.8)	270 (5.5)	<.001
Delivered a baby in the same hospital stay, n (%)	65 (1.0)	14 (0.2)	<.001	13 (0.3)	<.001	7790 (41.8)	1777 (35.9)	<.001
Income quintile, n (%)								
1	1275 (18.8)	1237 (19.3)		873 (19.8)		4194 (22.9)	1073 (21.9)	
2	1396 (20.6)	1298 (20.2)		942 (21.3)		4275 (23.3)	1055 (21.5)	
3	1450 (21.4)	1339 (20.9)		946 (21.4)		3840 (20.9)	1040 (21.2)	
4	1455 (21.4)	1386 (21.6)		878 (19.9)		3386 (18.5)	971 (19.8)	
5	1209 (17.8)	1153 (18.0)	.898	777 (17.6)	.262	2654 (14.5)	759 (15.5)	.009
Comorbid gynecologic conditions, y (%)								
Endometriosis	1269 (18.5)	1378 (21.2)	<.001	1639 (36.6)	<.001	427 (2.3)	196 (4.0)	<.001
Uterine leiomyoma	2590 (37.8)	2832 (43.6)	<.001	1833 (40.9)	.001	154 (0.8)	42 (0.9)	.886
Benign uterine or ovarian neoplasm	73 (1.1)	117 (1.8)	<.001	429 (9.6)	<.001	119 (0.6)	89 (1.8)	<.001
Prolapse	912 (13.3)	450 (7.0)	<.001	132 (3.0)	<.001	118 (0.6)	30 (0.6)	.824
Abnormal bleeding	4210 (61.4)	4096 (63.0)	.049	1806 (40.3)	<.001	1251 (6.7)	498 (10.0)	<.001
Pelvic inflammatory disease	200 (2.9)	219 (3.4)	.132	487 (10.9)	<.001	322 (1.7)	147 (3.0)	<.001
Hydrosalpinx	27 (0.4)	103 (1.6)	<.001	179 (4.0)	<.001	168 (0.9)	28 (0.6)	.004
Surgical approach, n (%)								
Abdominal/open	2976 (43.4)	3000 (46.2)	.001	3104 (69.3)	<.001	8036 (43.2)	1908 (38.5)	<.001
Laparoscopic	568 (8.3)	2620 (40.3)	<.001	1194 (26.7)	<.001	10,493 (56.4)	3128 (63.1)	<.001
Vaginal	3259 (47.5)	1104 (17.0)	<.001	364 (8.1)	<.001	2039 (11.0)	691 (14.0)	<.001

[a] Reference group is hysterectomy alone; probability values were obtained with the use of chi-squared tests for categoric variables and independent sample *t*-tests for continuous variables; [b] Data are given as mean±standard deviation.

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TABLE 2
Rates of physician visits for menopause and hormone replacement therapy after surgery

Variable	Hysterectomy alone (n=6891)	Hysterectomy with opportunistic salpingectomy (n=6500)	*P* value[a]	Hysterectomy with bilateral salpingo-ophorectomy (n=4479)	*P* value[a]	Tubal ligation (n=18,621)	Opportunistic salpingectomy for sterilization (n=4952)	*P* value
Physician visit for menopause, n (%)	1233 (18.0)	820 (12.6)	<.001	1443 (32.3)	<.001	1280 (6.9)	205 (4.1)	<.001
Median time to first physician visit for menopause, d (interquartile range)[b]	891 (269, 1448)	264 (43, 751)	<.001	479 (156, 905)	<.001	1056 (508, 1573)	432 (143, 735)	<.001
Any hormone therapy, n (%)	939 (13.7)	583 (9.0)	<.001	1907 (42.6)	<.001	2510 (13.5)	453 (9.1)	<.001
Estrogen only hormone replacement therapy, n (%)	761 (11.1)	439 (6.8)	<.001	1798 (40.1)	<.001	410 (2.2)	65 (1.3)	<.001
Median time to hormone replacement therapy use, d (interquartile range)[b]	604 (141, 1157)	316 (76, 728)	<.001	28 (3, 119)	<.001	505 (176, 977)	315 (97, 590)	<.001

[a] Reference group is hysterectomy alone; probability values were obtained with the use of chi-squared tests for categoric variables and independent sample *t*-tests for continuous variables; [b] Only among women with physician visits for menopause or hormone replacement therapy use.

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D25.X), benign ovarian or uterine neoplasm (ICD-10, CA D26.X, D27.X, D28.7), abnormal bleeding (ICD-10, CA N92.X, N93.X), pelvic organ prolapse (ICD-10, CA N81.X), pelvic inflammatory disease (ICD-10, CA N73.X, N74.X), and hydrosalpinx (ICD-10, CA N70.X).

Indicators of menopause

We examined 2 separate indicators that a woman was having menopausal symptoms. The first was a physician visit for menopausal or postmenopausal disorders (ICD-9th revision, CM 627), which includes visits for menopausal symptoms. Our data included all physician visits for all women in our dataset, regardless of the provider or the indication for the visit. The second indicator was filling a prescription for HRT, which included all formulations of estrogen alone and all formulations of estrogen, including vaginal, topical and transdermal, and progestin (identified with the use of Anatomical Therapeutic Chemical Classification 3 codes G03A, G03C, G03D, and Anatomical Therapeutic Chemical Classification 4 code L02AA).

Statistical analysis

We examined differences between rates of visits to physicians and the initiation of HRT between women who underwent OS or hysterectomy with BSO and women who underwent the comparator surgery (hysterectomy alone is the comparator for all hysterectomies and tubal ligation is the comparator for OS for sterilization) with the use of chi-squared tests for categoric variables and independent sample *t*-tests for continuous variables. All statistical tests were 2-sided, and a probability value of <.05 was considered to indicate statistical significance. We used Cox Proportional hazards models to model time to physician visits for menopause and for filling a prescription for HRT and controlled for patient age at surgery, other gynecologic conditions (listed earlier), year of surgery, and surgical approach. We censored our data when a woman died and when she moved outside of the province. An age-stratified analysis

TABLE 3
Time to first menopause-related physician visit and time to initiation of hormone replacement therapy by surgery type

Hazard ratio (95% confidence interval)	Hysterectomy alone (n=6861)	Hysterectomy with opportunistic salpingectomy (n=6500)	Hysterectomy with bilateral salpingo-oophorectomy (n=4479)	Tubal ligation (n=18,621)	Opportunistic salpingectomy for sterilization (n=4952)
Crude: time to menopause-related physician visit	1.00 (Reference)	1.11 (1.02–1.22)	2.41 (2.23–2.60)	1.00 (Reference)	1.39 (1.19–1.62)
Adjusted: time to menopause-related physician visit[a]	1.00 (Reference)	0.98 (0.88–1.09)	1.95 (1.78–2.13)	1.00 (Reference)	0.92 (0.77–1.10)
Crude: time to hormone replacement therapy initiation	1.00 (Reference)	0.81 (0.73–0.90)	4.39 (4.06–4.75)	1.00 (Reference)	1.01 (0.91–1.11)
Adjusted: time to hormone replacement therapy initiation[a]	1.00 (Reference)	0.82 (0.73–0.92)	3.80 (3.45–4.18)	1.00 (Reference)	1.00 (0.89–1.12)

[a] Adjusted for year of surgery, age at the time of surgery, gynecologic comorbidities, and surgical approach.

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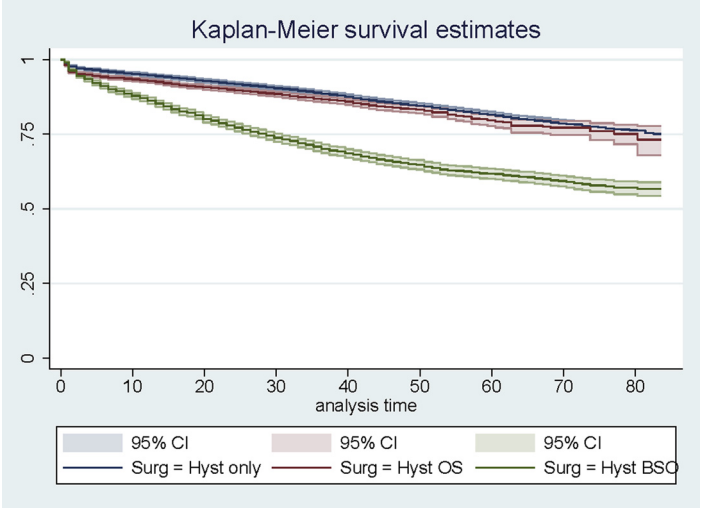
(<40, 40–44, 45–49 years old) was performed and controlled for the same variables as the non–age-stratified analysis, except for age. We also conducted a sensitivity analysis that included only women with at least 5 complete years of follow up and only women who had reached age 50 by the end of follow up.

Results

There were 51,352 women who had undergone a hysterectomy alone, a hysterectomy with OS, a hysterectomy with BSO, a tubal ligation, or an OS for sterilization from 2008–2014 in British Columbia, Canada. We eliminated women who were ≤15 years old at the time of surgery (number omitted because of small cell size) and women who were ≥50 years old (n=6078). We also excluded women who had <183 days of follow up (n=3041) or women who were coded as having a gynecologic cancer (n=819), which resulted in a final cohort of 41,413 women. In this study population, 6861 women underwent hysterectomy alone; 6500 underwent hysterectomy with OS; 4479 underwent hysterectomy with BSO; 18,621 underwent tubal ligation, and 4952 underwent OS for sterilization.

Table 1 illustrates characteristics of women who underwent each of these procedures in our cohort. Because recommendations for OS were published in September 2010, the mean year of surgery is significantly later among women who underwent OS. Women who underwent hysterectomy with OS were significantly more likely to experience comorbid gynecologic conditions compared with women who underwent hysterectomy alone, except that they were significantly less likely to have a prolapse (7.0% vs 13.3%; $P<.001$) and that there was no difference in rates of pelvic inflammatory disease. Women who underwent hysterectomy with BSO had even higher rates of the comorbid gynecologic conditions, with the exception of prolapse and abnormal bleeding, which were slightly less common in this group. There were no differences in income quintiles, and women who

FIGURE 1
Kaplan Meier Survival curve for time to physician visit for menopause according to whether a woman underwent hysterectomy alone, hysterectomy with OS or hysterectomy with BSO



Kaplan Meier curve for time to physician visit for menopause among women who underwent hysterectomy.

BSO, bilateral salpingo-oophorectomy; *CI*, confidence interval; *Hyst*, hysterectomy; *OS*, opportunistic salpingectomy; *Surg*, surgery.

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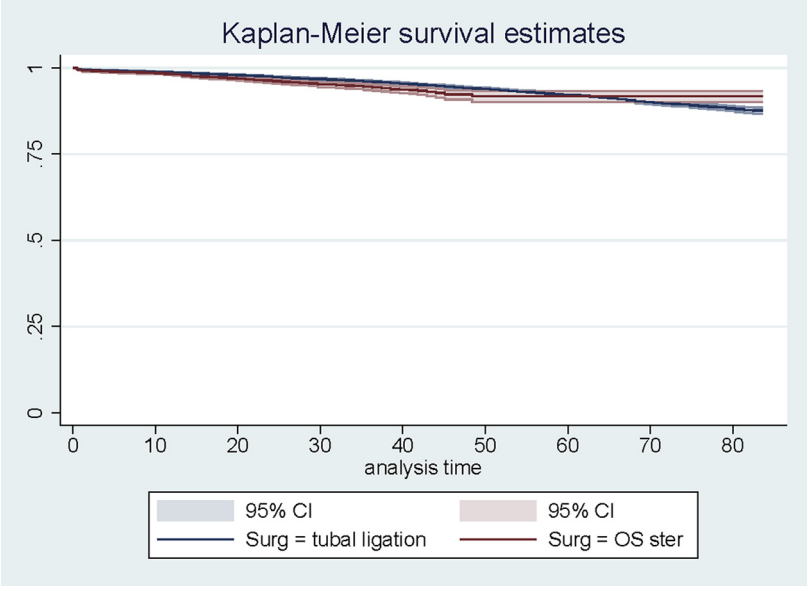
FIGURE 2
Kaplan Meier Survival curve for time to physician visit for menopause according to whether a woman underwent OS for sterilization or tubal ligation



Kaplan Meier curve for time to physician visit for menopause among women who underwent permanent contraception.

CI, confidence interval; *OS*, opportunistic salpingectomy; *ster*, sterilization *surg*, surgery.

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underwent hysterectomy with BSO were significantly older at surgery (43.4 vs 41.5 years; $P<.001$). The mean length of follow up was longer in women who underwent hysterectomy alone (4.8 years) compared with women who underwent hysterectomy with OS (2.7 years).

Women who underwent OS for sterilization were slightly older (36.3 vs 35.3 years; $P<.001$) were less likely to have delivered a baby in the same hospital stay (35.9% vs 41.8%; $P<.001$) and were of higher income ($P=.009$) than women who underwent tubal ligation. They were more likely to have endometriosis (4.0% vs 2.3%; $P<.001$), a benign uterine or ovarian neoplasm (1.8% vs .6%; $P<.001$), abnormal bleeding (10.0% vs 6.7%; $P<.001$), and pelvic inflammatory disease (3.0% vs 1.7%; $P<.001$). There were no differences in rates of uterine leiomyoma and prolapse, and they were less likely to have hydrosalpinx (0.6% vs 0.9%; $P=.004$). The mean length of follow up was longer in women who underwent tubal ligation (4.3 years) compared with women who underwent hysterectomy with OS (2.2. years).

Laparoscopic approach (40.3% vs 8.3%; $P<.001$) and abdominal approach (46.2% vs 43.4%; $P<.001$) was more common in women who underwent hysterectomy with OS than in women who underwent hysterectomy alone; the vaginal approach was significantly less common in women who underwent hysterectomy with OS (17.0% vs 47.5%; $P<.001$). Abdominal approach was less common in women who underwent OS for sterilization (38.5% vs 43.2%; $P<.001$), and the laparoscopic approach (63.1% vs 56.4%; $P<.001$) and vaginal approach (14.0% vs 11.0%; $P<.001$) were more common than in women who underwent tubal ligation.

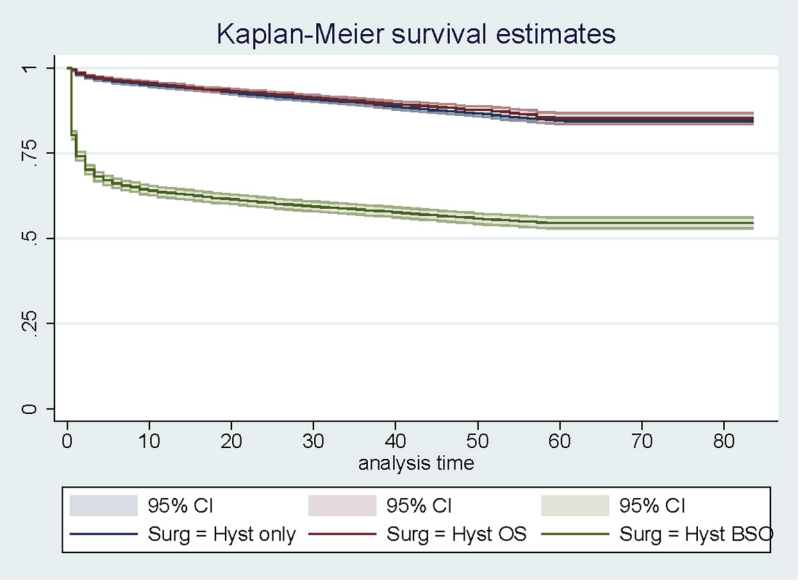
With respect to crude rates of physician visits and HRT after surgery (Table 2), women who underwent hysterectomy with OS had significantly lower rates of physicians' visits for menopause (12.6% vs 18.0%; $P<.001$) but a shorter median time to first physician visit (264 vs 891 days; $P<.001$). Women who underwent hysterectomy with BSO had the highest rate of

physician visits for menopause (32.3%; $P<.001$). Women who underwent OS for sterilization were also less likely to have a physician visit for menopause than those who underwent tubal ligation (4.1% vs 6.9%; $P<.001$) but had a shorter median time to first visit than women who underwent tubal ligation (432 vs 1056 days; $P<.001$).

With respect to HRT, again rates of use were lower among women who underwent hysterectomy with OS than women who underwent hysterectomy alone (9.0% vs 13.7%; $P<.001$), but time to initiation was shorter (453.4 vs 685.5 days; $P<.001$). Rates of HRT were highest among those who underwent hysterectomy with BSO (42.6%), and time to initiation was shortest in this group (28 days). Women who underwent OS for sterilization were less likely to initiate HRT (9.1% vs 13.5%; $P<.001$), and medium time to initiation was significantly shorter (315 vs 505 days; $P<.001$) than among women who underwent tubal ligation (Table 2).

The crude Cox proportional hazards models (Table 3) reveal that women who underwent hysterectomy with OS have increased hazard ratios for a physician visit for menopause (hazard ratio [HR], 1.11; 95% CI, 1.02−1.22); however, this risk is attenuated entirely after being controlled for year of surgery, age at the time of surgery, gynecologic comorbidities, and surgical approach (adjusted HR, 0.98; 95% CI, 0.88−1.09). All HRs for women who underwent hysterectomy with BSO were significantly >1. This is also reflected in the Kaplan Meier survival estimates for time to physician visits for menopause among women who underwent hysterectomy, where women who underwent hysterectomy with BSO have a significantly shorter time to visits for menopause than women who underwent hysterectomy alone or hysterectomy with OS. There is no significant difference between hysterectomy alone and hysterectomy with OS (Figure 1). Figure 2 reveals no significant difference in the Kaplan Meier survival curves for time to menopause related physician visits in the sterilization cohort. The same pattern is reflected in Figure 3 that illustrates time to the initiation of HRT.

FIGURE 3
Kaplan Meier curve for time to initiation on hormone replacement therapy according to whether a woman underwent hysterectomy alone, hysterectomy with OS or hysterectomy with BSO



Kaplan Meier curve for time to hormone replacement therapy use among women who underwent hysterectomy.

BSO, bilateral salpingo-oophorectomy; *CI*, confidence interval; *Hyst*, hysterectomy; *OS*, opportunistic salpingectomy; *Surg*, surgery.

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Table 3 also reveals higher crude risk for physician visit for menopause among women who underwent OS for sterilization (HR, 1.29; 95% CI, 1.19−1.62), which was attenuated after adjustment for covariates (adjusted HR, 0.92; 95% CI, 0.77−1.10). Table 3 and Figure 4 also reveal no increased hazards for HRT among women who underwent OS at the time of hysterectomy or OS for sterilization (adjusted HR, 0.82; 95% CI, 0.72−0.92 and adjusted HR, 1.00; 95% CI, 0.89−1.12).

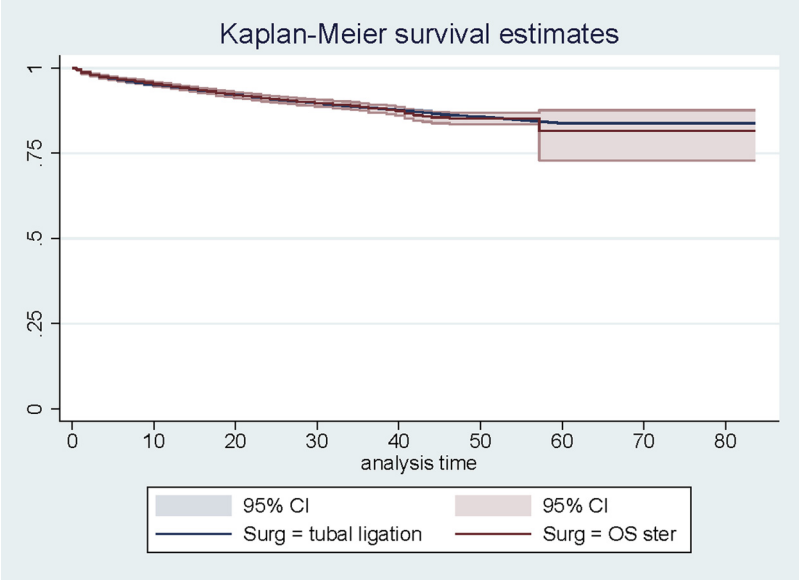
Finally, Table 4 reveals that there is no difference in our results in any of the age subgroups (women who underwent surgery at <40, 40−44, and 45−49 years old). Across all age groups and in both hysterectomy with OS and OS for sterilization, there are no increased hazards for physician visits for menopause or HRT compared with women who underwent hysterectomy alone or tubal ligation. The mean age was very similar across all of the procedures that were studied within each age group, with the largest difference being that women who had an OS for sterilization were 1.7 years older at the time of surgery. The same is true among women with at least 5 years of complete follow up and for women who reached age 50 years by the end of follow up; however, the results regarding OS for sterilization should be interpreted with caution because the numbers of women in that surgical group were low (n=26 for ≥5 years of follow up and n=72 for the number of women who reached age 50 by the end of the follow up period) the confidence intervals are very wide as a result. All hazards were increased significantly among women who underwent hysterectomy with BSO.

Comment

Principal findings

Our results reveal no indication of an earlier age of onset of menopause among the population of women who underwent hysterectomy with OS and OS for

FIGURE 4
Kaplan Meier curve for time to initiation on hormone replacement therapy according to whether a woman underwent OS for sterilization or tubal ligation



Kaplan Meier curve for time to hormone replacement therapy use among women who underwent permanent contraception.

CI, confidence interval; *OS*, opportunistic salpingectomy; *ster*, sterilization *surg*, surgery.

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sterilization as measured by physician visits for menopause and initiation of HRT. Women who underwent OS did not have significantly different adjusted HRs for these indicators from women who underwent hysterectomy alone or tubal ligation; there was no difference in Kaplan Meier survival curves between these groups. To determine whether our outcomes were accurately reflecting indicators for menopause, we also examined women who underwent hysterectomy with BSO, because we assumed that most of these women (being under the average age of onset of menopause of 51 years) would have entered premature surgical menopause. We report significantly increased hazards and decreased time to physician visits for menopause and initiation of HRT in this group, which suggests that our measures are reliable indicators of menopause. Finally, our age-stratified analyses reveal that our results hold for women who have their surgery at different ages (<40, 40−44, and 45−49 years), and our sensitivity analysis reveals that restricting the search to women with 5 full years of follow up and to women who were ≥50 years old at the end of follow up did not change our findings.

Results

Salpingectomy, when performed correctly, should not impact the ovarian blood supply and therefore should not have an impact on ovarian function (hormonal production, ovulation, age of menopause). However, there have been some small series after fallopian removal in a different clinical context, where short-term sonographic Doppler/blood flow has suggested a possible decreased ovarian blood supply,[38,39] which makes it important to continue examining menopausal outcomes in women who underwent OS. Our results are consistent with a retrospective series that involved approximately 160 premenopausal women who had total laparoscopic hysterectomy with or without bilateral salpingectomy that showed that the addition of salpingectomy to the hysterectomy did not change the effect on anti-Müllerian hormone levels.[24] The lack of a hormonal difference between the groups was also reported in a pilot randomized controlled trial that examined the short-term effects of salpingectomy during laparoscopic hysterectomy on ovarian reserve among 30 premenopausal women.[23] The only study with long-term follow up also failed to report any difference in OvAge (a statistical model that combines anti-Müllerian hormone, follicle-stimulating hormone, 3-dimensional antral follicle count, vascular index, flow index, and vascular flow index values), 3−5 years after their hysterectomy alone or hysterectomy with OS.[28] Our results conflict with a recent Swedish study in which women who underwent OS at the time of hysterectomy reported more menopausal symptoms 1 year after surgery than women who underwent hysterectomy alone.[29] If women in our cohort were experiencing menopausal symptoms differently according to OS status, they were not significant enough to change their care-seeking behaviors.

Clinical Implications

Our results suggest that, if OS affects ovarian blood supply, it is not substantial enough to result in an earlier onset of menopause. This study adds to the body of evidence supporting the safety of OS.

Strengths and limitations

Our study is strengthened by its population-based nature and the long follow up of many women who were included. It is the first study to include women who underwent OS for sterilization, and the first study to examine women's care-seeking behaviors as indicators of menopause. However, we are limited by our use of surrogate markers for menopause. Ideally, future studies will use age at the time of a 12-month period amenorrhea as the outcome. We experienced limitations common to studies of administrative datasets. There is always a risk of imprecision, given the dependence on database accuracy

TABLE 4
Age stratified analyses and analysis of women with at least 5 years of follow up

Variable	Hysterectomy alone (n=6861)	Hysterectomy with opportunistic salpingectomy (n=6500)	Hysterectomy with bilateral salpingo-oophorectomy (n=4479)	Tubal ligation (n=18,621)	Opportunistic salpingectomy for sterilization (n=4952)
Mean age at surgery of women, y[a]					
<40	35.1±3.8	35.5±3.6	35.2±4.2	33.2±4.4	33.9±4.0
40–44	42.7±1.4	42.6±1.4	42.7±1.4	42.0±1.4	42.1±1.4
45–49	47.3±1.4	47.3±1.4	47.6±1.4	46.6±1.2	46.7(1.4)
Women with at least 5 years of follow-up, n (%)	41.7 (5.6)	41.1 (5.6)	43.8 (5.2)	35.4 (5.6)	37.1 (1.1)
Women with at least 5 years of follow up, n (%)	3749 (54.6)	472 (7.3)	1440 (32.2)	7500 (40.2)	26 (0.5)
Women who were >50 years old at the end of their follow-up, n	2219	1144	1738	668	72
Adjusted hazard ratio for time to menopause-related physician visit[b,c]					
<40 Y	1.00 (Reference)	1.24 (0.97, 1.59)	3.29 (2.63, 4.12)	1.00 (Reference)	0.84 (0.66, 1.08)
40–44 Y	1.00 (Reference)	1.01 (0.83, 1,22)	2.22 (1.87, 2.64)	1.00 (Reference)	1.11 (0.82, 1,51)
45–49 y	1.00 (Reference)	0.89 (0.77, 1.04)	1.54 (1.36, 1.74)	1.00 (Reference)	0.88 (0.56, 1.38)
Women with at least 5 years of follow up	1.00 (Reference)	1.11 (0.90, 1.37)	1.87 (1.65, 2.11)	1.00 (Reference)	1.40 (0.51, 3.83)
Women >50 years old at end of follow up	1.00 (Reference)	0.96 (0.82, 1.13)	1.56 (1.38, 1.77)	1.00 (Reference)	0.99 (0.51, 1.91)
Adjusted hazard ratio for time to hormone replacement therapy initiation[b,c]					
<40	1.00 (Reference)	0.79 (0.63, 1.00)	3.59 (2.97, 4.33)	1.00 (Reference)	0.97 (0.85, 1.11)
40-44	1.00 (Reference)	0.96 (0.77, 1.20)	4.57 (3.79, 5.51)	1.00 (Reference)	1.09 (0.83, 1.43)
45-49	1.00 (Reference)	0.76 (0.64, 0.91)	3.32 (2.90, 3.80)	1.00 (Reference)	1.10 (0.67, 1.81)
Women with at least 5 years of follow up	1.00 (Reference)	0.96 (0.75, 1.25)	3.73 (3.27, 4.27)	1.00 (Reference)	0.54 (0.19, 1.49)
Women >50 years old at end of follow up	1.00 (Reference)	0.93 (0.76, 1.13)	3.26 (2.85, 3.74)	1.00 (Reference)	1.84 (0.94, 3.57)

[a] Data are given as mean±standard deviation; [b] Data are given as hazard ratio (95% confidence interval); [c] Adjusted for year of surgery, age at the time of surgery, gynecologic comorbidities, and surgical approach.

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and physician coding. The fact that more women are using HRT in the hysterectomy with BSO group than are visiting their physicians for menopause also indicates how physician decisions that involve coding can lead to imprecision. Most likely, the physician prescribed the HRT at the same time as annual physical or Papanicolaou smear and chose not to include the menopause code. Despite these shortcomings, we would not expect precision to be related to OS status; thus, any coding errors are unlikely to be a source of significant bias. Also, if women were experiencing menopausal symptoms but chose not to seek care, then they would not be captured in our outcomes. We cannot rule out that differences in menopausal symptoms between the OS and comparator groups were not captured in our measured outcomes of physician visits for menopause and the initiation of HRT. However, the fact that we consistently reported large and significant differences among women who underwent hysterectomy with BSO suggests that any substantive differences in the OS and comparator groups would likely have been reflected in our outcome measures. Most importantly, we have studied a relatively young cohort, in which many women have not reached the natural age of menopause (approximately 51 years old). Although our subgroup analysis of women who had reached 50 years old by the end of follow up revealed consistent results, this research should be updated when more of these women have reached the age of natural menopause. This limitation is particularly relevant in the OS for sterilization group, where we had very few women who had reached 50 years old by the end of follow up.

Research implications

Although a large prospective study of the effectiveness of OS is needed urgently, historic studies lead us to hypothesize that OS will be effective in the prevention of high-grade serous ovarian cancer.[40–43] The findings that there are no indications of earlier onset of menopause in women who underwent OS are reassuring and consistent with our body of safety research from British Columbia, Canada, and from the United States. We previously reported no difference in major surgical outcomes, which included overall hospital readmission rates, blood transfusions, and postoperative complications,[18,20] and no difference in minor complications, except for a small increased likelihood of filling a prescription analgesic medication in the immediate 2 weeks after discharge, which disappears by 1 month after discharge.[22] However, we recommend that future research investigate this issue with the use of menopause (defined as a 12-month period of amenorrhea) as the outcome. Reassuringly, we see an increased likelihood of women having a hysterectomy with BSO seeking care for menopause if they had their hysterectomy with BSO at <40 years old. This is appropriate, because these women should be treated for surgical menopause to avoid adverse effects of an early age of onset of menopause.[30–32] We also see that the HR for women who have hysterectomy with OS is slightly elevated and approaching significance; thus, future research will be done to extend follow up in that group.

Conclusion

Our findings are reassuring, given that earlier age at menopause is associated with increased mortality rates, particularly from cardiovascular disease.[30–32] We recommend future research to address whether OS reduces the age at menopause, because this reduction may offset the protection against ovarian cancer.

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