

Oophorectomy vs Ovarian Conservation With Hysterectomy

Cardiovascular Disease, Hip Fracture, and Cancer in the Women's Health Initiative Observational Study

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Background: Elective bilateral salpingo-oophorectomy (BSO) is routinely performed with hysterectomy for benign conditions despite conflicting data on long-term outcomes.

Methods: This is a prospective cohort of 25 448 postmenopausal women aged 50 to 79 years enrolled in the Women's Health Initiative Observational Study who had a history of hysterectomy and BSO (n=14 254 [56.0%]) or hysterectomy with ovarian conservation (n=11 194 [44.0%]) and no family history of ovarian cancer. Multivariable Cox proportional hazards regression models were used to examine the effect of BSO on incident cardiovascular disease, hip fracture, cancer, and death.

Results: Current or past use of estrogen and/or progestin was common irrespective of BSO status (78.6% of cohort). In multivariable analyses, BSO was not associated with an increased risk of fatal and nonfatal coronary heart disease (hazard ratio, 1.00 [95% confidence interval, 0.85-

1.18]), coronary artery bypass graft/percutaneous transluminal coronary angioplasty (0.95 [0.82-1.10]), stroke (1.04 [0.87-1.24]), total cardiovascular disease (0.99 [0.91-1.09]), hip fracture (0.83 [0.63-1.10]), or death (0.98 [0.87-1.10]). Bilateral salpingo-oophorectomy decreased incident ovarian cancer (0.02% in the BSO group; 0.33% in the ovarian conservation group; number needed to treat, 323) during a mean (SD) follow-up of 7.6 (1.6) years, but there were no significant associations for breast, colorectal, or lung cancer.

Conclusions: In this large prospective cohort study, BSO decreased the risk of ovarian cancer compared with hysterectomy and ovarian conservation, but incident ovarian cancer was rare in both groups. Our findings suggest that BSO may not have an adverse effect on cardiovascular health, hip fracture, cancer, or total mortality compared with hysterectomy and ovarian conservation.

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HYSTERECTOMY IS THE MOST common nonobstetric major surgery among women in the United States, with approximately 600 000 procedures each year.¹⁻³ Ninety percent of hysterectomies are for benign gynecologic conditions, such as

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symptomatic uterine fibroids or abnormal uterine bleeding.^{3,4} Elective bilateral salpingo-oophorectomy (BSO) is routinely offered to women 40 years or older at the time of hysterectomy to prevent the development of ovarian cancer, a rare but highly morbid disease with a 1.4% lifetime risk.⁵ Bilateral salpingo-oophorectomy is performed in 40% of benign hysterectomies

among women aged 40 to 44 years; 60%, among women aged 45 to 50 years; and 78%, among women aged 50 to 55 years.^{1,6}

The decision to perform an elective BSO is complex and controversial. Most hysterectomies are performed in premenopausal women, when BSO causes an abrupt decline in ovarian hormone levels that may result in menopausal symptoms. Historically, estrogen was commonly prescribed after BSO to treat these symptoms and substitute for the loss of endogenous ovarian hormones. However, since the Women's Health Initiative (WHI) randomized trials demonstrated more harm than benefit associated with postmenopausal hormone therapy (HT), there has been a dramatic decline in the use of HT.⁷⁻¹⁰ As a result, the practice of performing elective BSO with hysterectomy has become more controversial.¹¹

Although the benefit of BSO for ovarian cancer prevention is well established,^{12,13}

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studies on the potential risks associated with BSO have had conflicting results. Some observational studies have found an increased rate of fatal and/or nonfatal coronary heart disease (CHD) after BSO,¹⁴⁻¹⁸ whereas others have reported no association between BSO and CHD.¹⁹⁻²² Several studies have reported an increased risk of fracture after BSO due to the protective effect of endogenous estrogen and androgens on bone health,^{23,24} but other investigations have not confirmed this risk.^{25,26} These conflicting data are due to methodologic and statistical limitations in much of the current literature, including small sample sizes, lack of multivariable models, comparison groups of women who did not undergo hysterectomy, and inattention to use of HT among participants.

In this study, we used data from the WHI Observational Study to examine the effect of BSO on the development of cardiovascular disease (CVD), hip fracture, and cancer. Our aim was to overcome the limitations of prior studies by using data from a large prospective cohort of diverse women who all underwent hysterectomy and reported detailed histories of HT use. These results may inform preoperative counseling for the thousands of women who undergo benign hysterectomy every year and are offered an elective BSO.

METHODS

STUDY POPULATION

The WHI Observational Study is a prospective cohort study of 93 676 postmenopausal women aged 50 to 79 years at enrollment. Women were recruited at 40 clinical centers in the United States from September 1, 1993, through December 31, 1998. These women were initially invited to participate in a randomized trial of either dietary modification or exogenous hormone use. After a screening examination, they were found to be ineligible or not interested in trial participation but agreed to participate in an observational study. For the observational study, major exclusion criteria were the expectation of not residing in the area for at least 3 years, a medical condition associated with predicted survival of less than 3 years, or inability to provide informed consent. The study was approved by each clinical center's institutional review board. All women provided signed informed consent.

For the current analysis, we included women from the WHI Observational Study who reported a history of hysterectomy (n=39 149 [41.8% of the study population]). These participants completed questionnaires that queried whether they had undergone a unilateral oophorectomy or BSO. We classified women who reported prior BSO as the BSO group and women who did not report removal of any ovaries as the hysterectomy-only group. Women who underwent unilateral oophorectomy, "partial removal" of an ovary, or removal of an unknown number or who had an unknown history of ovarian removal were excluded, leaving 32 235 participants for analysis. In the primary analysis, we excluded women with an incident BSO during the study (n=234) and those with a personal history of cancer (n=5868) or a family history of ovarian cancer (n=943) because our focus was on women at low risk for ovarian cancer when BSO is an elective procedure. After these exclusions, there remained 25 448 women in the analysis of whom 14 254 (56.0%) reported a prior BSO.

OUTCOME MEASURES

Detailed explanations of all outcomes and methods for ascertainment and classification have been published.²⁷ In brief, participants completed baseline questionnaires on demographic information, reproductive history, and medical and family history. Surgical histories of hysterectomy and oophorectomy and age at surgery were obtained through these self-reported questionnaires. Body mass index was calculated using height and weight measured at a clinical visit. Smoking status (never, past, or current) was determined from lifetime smoking of at least 100 cigarettes, current daily cigarette smoking, and self-report of smoking cessation. Physical activity was categorized by the number of weekly episodes of mild, moderate, or strenuous recreational physical activity.

Prevalent medical conditions, such as diabetes mellitus, hypertension, hypercholesterolemia, angina, prior myocardial infarction (MI), fracture, or cancer were based on self-report at baseline. Family history of premature CHD was defined as an MI in a first-degree male relative before 55 years of age or a first-degree female relative before 65 years of age. Hormone therapy use was classified as never, past, or current use of estrogen or estrogen with progestin delivered through pills or patches. Participants were asked to estimate the number of years they had been using HT.

The primary outcome measures were incident cardiovascular events, including fatal and nonfatal CHD; coronary revascularization (coronary artery bypass graft [CABG] or percutaneous transluminal coronary angioplasty [PTCA]); stroke defined as the rapid onset of neurological deficit that lasted more than 24 hours, required hospitalization, and was supported by imaging studies when available; and total CVD (fatal and nonfatal MI, CHD death, angina, congestive heart failure, CABG/PTCA, carotid endarterectomy, peripheral vascular disease, stroke, definite and possible silent MI, and cardiovascular death). Secondary outcomes were hip fracture confirmed by radiographic findings and/or surgical report; ovarian, breast, or colorectal cancer confirmed by pathology report; and death confirmed by death certificate. Participants were contacted once a year and asked to report any hospitalizations or events suggestive of study outcomes of interest. Medical records for all participant responses indicating a possible study outcome were reviewed and abstracted. Hip fracture and ovarian, breast, and colorectal cancer outcomes were adjudicated centrally by WHI physician adjudicators (including M.A.A.) for hip fracture or trained SEER (Surveillance, Epidemiology, and End Results) coders for cancer outcomes. Coronary heart disease, stroke, and total cardiovascular and lung cancer outcomes were adjudicated by local WHI physicians at each site.

STATISTICAL METHODS

Differences in baseline characteristics by oophorectomy status were compared using χ^2 tests of association for categorical variables and 2-sample *t* tests for continuous variables. Incidence rates per 100 000 person-years were reported for all outcome variables. Incident follow-up time was defined as the number of days from enrollment to the first outcome event. For women who did not have an event, follow-up time was censored at last contact if lost to follow-up (4.8% of the study population) or at study termination (March 31, 2005).

Multivariable Cox proportional hazards regression analyses were used to assess the association between BSO and all outcomes of interest. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the entire cohort. Age was used as the time variable in all Cox models because HRs for BSO outcomes may differ by age at enrollment. In addition, overall models for each end point used age at hysterectomy as a strata variable. The proportional hazards assumption was tested by

Table 1. Baseline Demographic and Clinical Characteristics of Women With a History of Hysterectomy With or Without BSO^a

Characteristic	Study Group, No. (%) ^b		P Value
	Hysterectomy-Alone (n=11 194)	BSO (n=14 254)	
Demographic			
Race/ethnicity			
White	9068 (81.0)	11 677 (81.9)	<.001
Black	1102 (9.8)	1365 (9.6)	
Hispanic	602 (5.4)	509 (3.6)	
Native American	63 (0.6)	61 (0.4)	
Asian/Pacific Islander	217 (1.9)	431 (3.0)	
Unknown	142 (1.3)	211 (1.5)	
Annual income, \$			
<20 000	1788 (17.1)	2076 (15.7)	.01
20 000-49 999	4674 (44.6)	5944 (44.8)	
≥50 000	4008 (38.3)	5238 (39.5)	
Educational level			
<High school diploma/GED	694 (6.3)	729 (5.2)	<.001
High school diploma/GED	6522 (58.8)	7969 (56.4)	
College degree or higher	3883 (35.0)	5438 (38.5)	
Any medical insurance			
Private insurance	10 672 (96.3)	13 699 (96.1)	.001
Medicare	4993 (45.1)	6643 (47.0)	.002
Medicaid	4289 (38.7)	5670 (40.2)	.02
	172 (1.6)	192 (1.4)	.20
Clinical			
Age at hysterectomy, y			
<40	4499 (40.4)	3084 (21.7)	<.001
40-49	4714 (42.3)	6683 (47.0)	
50-54	927 (8.3)	2624 (18.5)	
≥55	1007 (9.0)	1823 (12.8)	
Parity			
Never pregnant	539 (4.8)	1506 (10.6)	<.001
Never had term pregnancy	199 (1.8)	392 (2.8)	
≥1 Term pregnancy	10 401 (93.4)	12 305 (86.6)	
Smoking			
Never	5837 (52.8)	7304 (51.9)	.05
Past	4521 (40.9)	5956 (42.3)	
Current	689 (6.2)	812 (5.8)	
Exercise, No. of episodes/wk			
None	1580 (14.3)	2153 (15.2)	.20
≤3	2601 (23.5)	3258 (23.0)	
>3-6.5	3390 (30.6)	4318 (30.5)	
>6.5	3497 (31.6)	4416 (31.2)	

Abbreviations: BSO, bilateral salpingo-oophorectomy; GED, General Educational Development test.

^aMean (SD) age at screening was 63.3 (7.4) years in the hysterectomy-alone group compared with 63.5 (7.3) years in the BSO group ($P=.02$). Among the 11 071 patients in the hysterectomy-only group in whom body mass index (BMI, calculated as the weight in kilograms divided by height in meters squared) was calculated, mean (SD) BMI was 27.6 (5.7) compared with 27.7 (6.0) in 14 120 patients in the BSO group ($P=.44$).

^bPercentages have been rounded and might not total 100. Denominators may vary because of missing data.

incorporating an interaction term of BSO status with the log of follow-up time for each outcome in a Cox model with the main effect of BSO status and testing for a deviation from unity. P values for all end points other than total cardiovascular outcomes and death ranged from .12 to .81. Although the P values for the total cardiovascular and death end points were moderately significant, plots of the Kaplan-Meier survival vs survival time and $\log(-\log[\text{survival}])$ vs $\log(\text{survival time})$ did not show a violation of the assumption. Similar results were obtained when the Cox regression analyses were performed with time to event as the time variable. A multivariable model was constructed that

controlled for race/ethnicity, education, medical insurance, current health care provider, parity, body mass index, and type and duration of HT use. In addition, other covariates unique to each outcome variable were included in the model as follows: (1) cardiovascular outcomes were adjusted for smoking, alcohol use, exercise, treatment for hypertension, diabetes mellitus ever, high cholesterol levels requiring medication therapy, history of angina, personal or family history of MI (for CHD and total CVD), CABG/PTCA (for CABG/PTCA and total CVD), or stroke (for stroke and total CVD); (2) hip fracture was adjusted for smoking, alcohol use, exercise, or personal or family history of fracture; (3) cancer outcomes were adjusted for smoking, alcohol use, exercise, diabetes ever, family history of breast cancer (for breast cancer), colorectal cancer (for colorectal cancer), or any cancer (for total cancer); and (4) death was adjusted for smoking, alcohol use, exercise, hypertension, diabetes ever, high cholesterol levels requiring medication therapy, personal history of angina, MI, CABG/PTCA, stroke, or family history of MI or stroke.

Tests for interaction of BSO status with age at hysterectomy and HT use were performed for all outcomes using a Wald χ^2 test. Although none of these tests were statistically significant at the .05 level, we present results by age at hysterectomy and among women who never used HT because of the clinical relevance of evaluating these groups separately. We also conducted a subgroup analysis of women with a family history of breast and/or ovarian cancer to gain insight into counseling these patients at high risk for ovarian cancer. All analyses were conducted using commercially available software (SAS for Windows, version 9; SAS Institute, Inc, Cary, North Carolina).

RESULTS

Table 1 demonstrates the demographic and clinical characteristics of the 25 448 women in our analysis who underwent hysterectomy with or without BSO. The mean age at enrollment was approximately 63 years for the BSO and hysterectomy-only groups. Most of the women in both groups were white and had an annual income of more than \$20 000 with at least a high school diploma or equivalent. Women who underwent BSO were more likely to undergo hysterectomy at 40 years or older compared with women who underwent hysterectomy only ($P<.001$). There were no statistically significant differences between the study groups in body mass index, smoking, or exercise. The mean (SD) follow-up time for participants was 7.6 (1.6) years.

The baseline medical history of study participants and use of HT are shown in **Table 2**. Women who underwent a BSO had a slightly higher prevalence of treated hypertension (31.0% vs 28.3%; $P<.001$) and angina (7.3% vs 6.6%; $P=.03$). However, at baseline, the BSO group did not report a greater number of past cardiovascular events, including MI, stroke, and deep vein thrombosis or pulmonary embolus, compared with the hysterectomy-only group. There were no statistically significant differences between the groups for a family history of MI, breast or colorectal cancer, or fracture (data not shown). Most of the women (78.6%) had used HT. Women who underwent BSO were more likely to have used HT in the past (15.8% vs 12.9%), at study enrollment (68.0% vs 59.3%), and for at least 10 years (50.4% vs 35.3%). Most of the women who reported prior or current HT use had used estrogen alone, not estrogen and a progestin.

Overall, there were no statistically significant increased risks of CVD among women in the BSO group compared with the hysterectomy-only group (**Table 3**). In a multivariable model that controlled for multiple cardiovascular risk factors as well as current and prior hormone use, the BSO group did not demonstrate an increased risk of fatal and nonfatal CHD (380 vs 353 events per 100 000 person-years, BSO vs hysterectomy-only groups; HR, 1.00 [95% CI, 0.85-1.18]), CABG/PTCA (0.95 [0.82-1.10]), stroke (1.04 [0.87-1.24]), or total CVD (0.99 [0.91-1.09]). These negative findings were similar for the BSO group regardless of age at hysterectomy. The BSO group did not have an increased risk of hip fracture compared with the hysterectomy-only group (HR, 0.83 [95% CI, 0.63-1.10]).

Ovarian cancer was rare in both groups, although far less common among women who underwent BSO compared with ovarian conservation (Table 3). In the hysterectomy-only group, 0.33% of the women developed ovarian cancer compared with 0.02% of the women in the BSO group (number needed to treat, 323). There were no statistically significant differences between the groups for incident breast, colorectal, lung, or total cancer. Total mortality was equivalent for the BSO and hysterectomy-only groups (797 vs 791 deaths per 100 000 person-years; HR, 0.98 [95% CI, 0.87-1.10]).

In a subgroup of women who never used HT (**Table 4**), BSO was not associated with a statistically significant increased risk of CHD (HR, 1.24 [95% CI, 0.92-1.68]), stroke (1.31 [0.92-1.87]), or death (0.99 [0.80-1.23]) in multivariable models. In these analyses, there was 90% power to detect HRs of at least 1.6 for CHD, 1.8 for stroke, and 1.4 for death. The percentage of women with ovarian cancer was greatly reduced in the BSO group (0.04% vs 0.23% for the hysterectomy-only group). There were no overall statistically significant differences between groups for breast, colorectal, lung, or total cancer, but women younger than 40 years at hysterectomy had a decreased risk of breast cancer (HR, 0.36 [95% CI, 0.14-0.95]). In the subgroup analysis of women with a family history of breast or ovarian cancer (n = 5270), there were no statistically significant adverse outcomes after BSO (data not shown).

COMMENT

In this observational cohort study of more than 25 000 postmenopausal women with a history of hysterectomy, there were no statistically significant risks associated with BSO for incident CVD, hip fracture, or total mortality. As expected, women who underwent BSO were far less likely to develop ovarian cancer compared with women who retained their ovaries. However, incident ovarian cancer was rare, irrespective of BSO status (0.33% vs 0.02%). There were no significant associations of BSO with other cancer outcomes, including breast, colorectal, lung, or total cancer in the overall analysis.

Our negative findings for BSO risk do not indicate that ovarian hormones lack an important role in the pathogenesis of CVD, fractures, cancer, or death. Rather, our results suggest that, compared with women who undergo hysterectomy alone, concomitant BSO may not incur additional

Table 2. Medical History and HT Use of Women With a History of Hysterectomy With or Without BSO

	Study Group, No. (%) ^a		P Value
	Hysterectomy-Only	BSO	
Medical history			
Hypertension or BP > 140/90 mm Hg			
Never hypertensive	6983 (63.4)	8482 (60.3)	<.001
Untreated hypertension	920 (8.3)	1222 (8.7)	
Treated hypertension	3115 (28.3)	4353 (31.0)	
High cholesterol level requiring medication	1694 (15.1)	2289 (16.1)	.07
Diabetes mellitus ever	720 (6.4)	874 (6.1)	.33
History of angina	735 (6.6)	1036 (7.3)	.03
History of MI	299 (2.7)	383 (2.7)	.94
History of CABG/PTCA	245 (2.2)	312 (2.2)	>.99
History of stroke	183 (1.6)	245 (1.7)	.61
History of DVT/PE	589 (5.3)	728 (5.1)	.58
History of fracture	4228 (37.8)	5430 (38.1)	.75
HT use			
None	3106 (27.8)	2312 (16.2)	<.001
Past	1448 (12.9)	2242 (15.8)	
Current estrogen only	6410 (57.3)	9363 (65.8)	
Current estrogen and progestin	223 (2.0)	315 (2.2)	
Prior HT use duration, y			
None	3106 (27.7)	2312 (16.2)	<.001
<5	2396 (21.4)	2491 (17.5)	
5 to <10	1741 (15.6)	2266 (15.9)	
≥10	3951 (35.3)	7185 (50.4)	
Estrogen-only use			
Never	3378 (30.2)	2697 (19.0)	<.001
Past	1399 (12.5)	2171 (15.3)	
Current	6410 (57.3)	9363 (65.8)	
Estrogen-only use duration, y			
None	3378 (30.2)	2697 (18.9)	<.001
<5	2445 (21.8)	2722 (19.1)	
5 to <10	1766 (15.8)	2245 (15.7)	
≥10	3605 (32.2)	6590 (46.2)	
Estrogen and progestin use			
Never	10267 (91.7)	12501 (87.7)	<.001
Past	703 (6.3)	1436 (10.1)	
Current	223 (2.0)	315 (2.2)	
Estrogen and progestin use, y			
None	10267 (91.7)	12501 (87.7)	<.001
<5	473 (4.2)	916 (6.4)	
5 to <10	212 (1.9)	442 (3.1)	
≥10	242 (2.2)	395 (2.8)	

Abbreviations: BP, blood pressure; BSO, bilateral salpingo-oophorectomy; CABG, coronary artery bypass graft; DVT, deep vein thrombosis; HT, hormone therapy; MI, myocardial infarction; PE, pulmonary embolism; PTCA, percutaneous transluminal coronary angioplasty.

^aPercentages have been rounded and may not total 100.

risks. Women who undergo hysterectomy, with or without BSO, may have more risk factors for CVD compared with women who do not undergo hysterectomy.¹⁷ In addition, hysterectomy alone with ovarian preservation has been found to compromise ovarian function, likely because of disruption of the ovarian blood supply during hysterectomy.^{28,29} Premenopausal women who undergo hysterectomy with ovarian preservation have higher follicle-stimulating hormone levels, lower ovarian sex steroid levels, decreased ovarian blood flow, and earlier menopause compared with similarly aged women who do not undergo hysterectomy.³⁰⁻³³ Even among postmenopausal women, ovarian androgen levels are decreased in women

Table 3. Incident Clinical Outcomes Among Women With Hysterectomy vs Hysterectomy and BSO

Outcome by Age at Hysterectomy, y	Study Group				Multivariable Model HR (95% CI) ^a
	Hysterectomy-Only (n=11 194)		BSO (n=14 254)		
	No. of Patients	No. of Cases/100 000 PYE	No. of Patients	No. of Cases/100 000 PYE	
CVD					
Total CHD (fatal and nonfatal)	298	353	405	380	1.00 (0.85-1.18)
<40	105	311	98	429	0.98 (0.72-1.35)
40-49	121	338	169	338	0.99 (0.76-1.29)
≥50	72	499	137	411	1.02 (0.74-1.41)
CABG/PTCA	397	478	512	488	0.95 (0.82-1.10)
<40	158	476	125	557	0.93 (0.72-1.22)
40-49	152	431	215	436	0.97 (0.77-1.22)
≥50	86	606	171	522	0.95 (0.72-1.27)
Stroke	263	311	341	320	1.04 (0.87-1.24)
<40	93	275	85	372	1.13 (0.81-1.58)
40-49	110	307	153	305	1.09 (0.83-1.43)
≥50	57	393	103	309	0.98 (0.68-1.41)
Total CVD	1171	1439	1513	1475	0.99 (0.91-1.09)
<40	443	1358	383	1752	0.98 (0.83-1.15)
40-49	461	1331	637	1316	1.00 (0.87-1.14)
≥50	263	1905	490	1529	1.03 (0.86-1.23)
Hip fracture					
<40	131	155	131	122	0.83 (0.63-1.10)
40-49	38	112	26	113	0.74 (0.41-1.34)
≥50	55	153	59	117	0.94 (0.61-1.43)
>=50	38	262	46	137	0.80 (0.48-1.32)
Cancer					
Ovarian cancer^b					
<40	37	44	3	3	
40-49	12	35	1	4	
≥50	17	47	2	4	
>=50	8	55	0	0	
Invasive breast cancer					
<40	309	368	430	406	0.96 (0.81-1.13)
40-49	116	345	78	342	0.72 (0.51-1.02)
≥50	133	374	196	394	0.95 (0.74-1.21)
>=50	59	409	155	469	1.11 (0.80-1.55)
Colorectal cancer					
<40	89	105	126	118	1.19 (0.88-1.62)
40-49	31	91	22	96	1.13 (0.60-2.12)
≥50	44	122	68	135	1.08 (0.71-1.67)
>=50	14	96	36	107	1.38 (0.69-2.75)
Lung cancer					
<40	99	117	129	120	0.96 (0.72-1.27)
40-49	44	129	37	161	0.80 (0.49-1.32)
≥50	41	114	58	115	1.08 (0.71-1.64)
>=50	14	96	34	101	0.98 (0.50-1.93)
Total cancer					
<40	951	1155	1205	1161	0.96 (0.87-1.05)
40-49	348	1054	250	1119	0.97 (0.81-1.17)
≥50	436	1252	552	1131	0.89 (0.77-1.02)
>=50	162	1143	399	1233	1.08 (0.89-1.32)
Death					
<40	673	791	857	797	0.98 (0.87-1.10)
40-49	240	705	206	894	0.90 (0.72-1.13)
≥50	292	809	369	731	1.00 (0.84-1.19)
>=50	139	951	278	826	1.07 (0.84-1.35)

Abbreviations: BSO, bilateral salpingo-oophorectomy; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; PTCA, percutaneous transluminal coronary angioplasty; PYE, person-years of exposure.

^aAll outcomes are controlled for age, race/ethnicity, educational level, medical insurance, current health care provider, parity, body mass index, hormone therapy (HT) use and duration of use, and HT type. In addition, other variables included in the model were unique to each outcome as follows: (1) for CVD outcomes, smoking, alcohol use, exercise, treatment for hypertension, diabetes mellitus ever, high cholesterol levels requiring medication, history of angina, personal or family history of myocardial infarction, CABG/PTCA, or stroke; (2) for hip fracture, smoking, alcohol use, exercise, or personal or family history of fracture; (3) for cancer outcomes, smoking, alcohol use, exercise, diabetes ever, or family history of breast cancer (for breast cancer), colorectal cancer (for colorectal cancer), or any cancer (for total cancer); and (4) for death, smoking, alcohol use, exercise, hypertension, diabetes ever, high cholesterol levels requiring medication, personal history of myocardial infarction, CABG/PTCA, stroke, or family history of myocardial infarction or stroke.

^bUnable to conduct multivariable analysis owing to small number of outcomes (n=3).

with a history of hysterectomy alone compared with those who experience natural menopause.³⁴ Therefore, the absolute difference in hormone levels between women who

undergo hysterectomy with or without BSO and the duration of these differences may not be sufficient to demonstrate a significant effect on health outcomes.

Table 4. Incident Clinical Outcomes Among Women With Hysterectomy vs Hysterectomy and BSO and No History of Hormone Use

Outcome by Age at Hysterectomy, y	Study Groups				Multivariable Model HR (95% CI) ^a
	Hysterectomy-Only (n=3106)		BSO (n=2312)		
	No. of Patients	No. of Cases/100 000 PYE	No. of Patients	No. of Cases/100 000 PYE	
CVD					
Total CHD (fatal and nonfatal)	104	452	117	706	1.24 (0.92-1.68)
<40	33	364	32	817	1.33 (0.77-2.30)
40-49	43	440	46	642	1.33 (0.82-2.16)
≥50	28	685	39	719	1.00 (0.56-1.78)
CABG/PTCA	108	476	94	574	1.07 (0.79-1.44)
<40	40	449	28	727	1.43 (0.85-2.41)
40-49	45	468	41	580	1.02 (0.64-1.63)
≥50	23	568	25	463	0.80 (0.41-1.56)
Stroke	72	312	74	444	1.31 (0.92-1.87)
<40	29	321	24	609	1.44 (0.78-2.65)
40-49	29	296	31	429	1.35 (0.78-2.33)
≥50	14	338	19	348	1.37 (0.62-3.00)
Total CVD	379	1719	340	2144	1.05 (0.89-1.25)
<40	141	1627	101	2738	1.25 (0.93-1.70)
40-49	155	1652	134	1940	1.01 (0.78-1.32)
≥50	83	2132	104	2000	1.03 (0.73-1.47)
Hip fracture	57	247	35	209	0.67 (0.42-1.08)
<40	18	198	6	151	0.39 (0.12-1.22)
40-49	25	255	15	207	0.91 (0.45-1.86)
≥50	14	339	14	257	0.84 (0.35-2.04)
Cancer					
Ovarian cancer ^b	7	30	1	6	
<40	3	33	0	0	
40-49	4	41	1	14	
≥50	0	0	0	0	
Invasive breast cancer	90	392	59	354	0.72 (0.49-1.05)
<40	35	388	10	252	0.36 (0.14-0.95)
40-49	31	319	26	361	0.93 (0.51-1.67)
≥50	23	561	22	407	0.77 (0.41-1.45)
Colorectal cancer	37	160	30	179	1.06 (0.62-1.81)
<40	11	121	4	101	1.31 (0.37-4.71)
40-49	21	214	16	221	0.94 (0.45-1.96)
≥50	5	120	10	183	2.05 (0.60-7.04)
Lung cancer	26	112	36	214	1.31 (0.77-2.23)
<40	9	99	6	150	0.42 (0.11-1.58)
40-49	14	142	17	234	1.40 (0.67-2.92)
≥50	3	72	13	237	2.11 (0.56-7.94)
Total cancer	288	1285	211	1300	0.90 (0.74-1.10)
<40	96	1087	43	1101	0.93 (0.62-1.39)
40-49	133	1406	91	1300	0.88 (0.65-1.18)
≥50	56	1392	76	1443	0.92 (0.63-1.33)
Death	237	1019	216	1282	0.99 (0.80-1.23)
<40	79	865	63	1579	1.15 (0.78-1.70)
40-49	109	1107	80	1097	0.95 (0.67-1.32)
≥50	49	1176	71	1290	0.97 (0.62-1.52)

Abbreviations: See Table 3.

^aAll outcomes controlled for are described in Table 3.

^bUnable to conduct multivariable analysis owing to small number of outcomes (n=3).

The primary goal of performing elective BSO is ovarian cancer prevention. Currently, there is no validated screening test for ovarian cancer in low-risk populations. Most patients present with advanced disease, for which the 5-year survival is 28%.³⁵ Although BSO nearly eliminates the risk of developing ovarian cancer, hysterectomy alone with ovarian preservation may also have a protective effect. In our analysis, the rate of ovarian can-

cer in the hysterectomy-only group (0.33%) is consistent with reports of lower rates of ovarian cancer in studies of women who undergo hysterectomy compared with women who do not.³⁶⁻³⁸ Several mechanisms have been proposed to explain this decreased rate of ovarian cancer after hysterectomy, including intraoperative inspection of the ovaries, common preoperative use of oral contraceptives among women who undergo hysterectomy,

and prevention of exposure to carcinogens from the lower genital tract.³⁹⁻⁴¹ Given the very low rate of ovarian cancer after hysterectomy with ovarian preservation, BSO may provide minimal additional benefit.

The findings in our subgroup analyses are of interest, although smaller sample sizes make the results less robust than the primary analysis, particularly for models that stratify by age at hysterectomy. Many women are hesitant to use HT because of the risks reported in the WHI randomized trials of estrogen alone and estrogen plus progesterone.^{42,43} In this context, women may forego BSO because they believe postoperative HT is necessary to prevent adverse consequences of BSO. However, in our overall analysis of 5418 women who never used HT, BSO was not associated with statistically significant increased risks for CVD, hip fracture, or mortality. This subgroup sample size provided 90% power to detect HRs of at least 1.60 for fatal and nonfatal coronary heart and 1.40 for death. This leaves open the possibility that we were unable to identify statistically significant small differences between groups for the outcomes of interest given the point estimate of 1.24 for CHD. There was less power to detect differences between groups in models stratified by age at hysterectomy, including those for women younger than 40 years at hysterectomy, for whom some HRs were greater than 1.00 (HR, 1.33 [95% CI, 0.77-2.30] for CHD, 1.44 [0.78- 2.65] for stroke, and 1.15 [0.78-1.70] for death).

Our findings differ from results of the Nurses' Health Study (NHS), the only other large prospective cohort study to evaluate the risks of BSO compared with hysterectomy and ovarian conservation.¹³ In the NHS, BSO was associated with an increased risk of CHD, death from lung cancer or any cancer, and total mortality, with HRs ranging from 1.17 to 1.31.¹³ In the NHS and the WHI, most of the women underwent hysterectomy in their fifth decade of life, but the WHI was an older cohort at study enrollment (mean age, 63 vs 51 years). Our findings may therefore differ if BSO increases the risk of adverse outcomes among women in their sixth decade of life, closer to the time of hysterectomy. Follow-up time was also longer in the NHS compared with our study (≤ 24 vs nearly 8 years), which may explain some of the variation in our findings. Finally, we selected different cut points for age at hysterectomy than the NHS. To facilitate direct comparisons, we repeated our analyses using the NHS categories for age at hysterectomy (<45 , 45-54, and ≥ 55 years for Table 3, and <50 or ≥ 50 years for Table 4). However, there were no substantial quantitative or qualitative differences in our results using these new cut points (data not shown). Therefore, we present our initial age-at-hysterectomy groupings because we believe these are clinically meaningful categories to distinguish the effect of BSO on premenopausal women (aged 40-49 years) compared with postmenopausal women (aged ≥ 50 years).

There are several limitations to our study. First, incorrect self-report of oophorectomy status can result in misclassification of the predictor groups. In the NHS, self-report of oophorectomy was nearly perfect compared with adjudication of the surgical record,⁴⁴ but other studies have found lower accuracy rates.^{33,45} Second, we were un-

able to determine whether women who reported prior hysterectomy and BSO underwent these surgeries concomitantly or at different times. However, most women likely underwent BSO at the time of hysterectomy because the incidence of BSO after hysterectomy is 0.89% to 5.5%.⁴⁶⁻⁵² Our analyses may also be affected by survivor bias because WHI participants began follow-up many years after they underwent hysterectomy. Although we included many confounding factors in our multivariable Cox models, residual confounding or confounding by unknown variables may also have influenced our results. Finally, our primary analysis had 90% power to detect HRs of at least 1.10 to 1.30 for cardiovascular outcomes, 1.50 for hip fracture, 1.10 to 1.60 for cancer, and 1.20 for death. Therefore, despite a large sample size, it is possible that we were unable to detect small differences between groups in some outcome measures.

To date, there are no randomized trials of BSO, although a pilot study is under way (clinicaltrials.gov identifier NCT01007305). Women who plan to undergo hysterectomy must weigh the risks and benefits of elective BSO on the basis of the current observational literature, which is inherently prone to bias and confounding. Some women may highly value BSO for ovarian cancer prevention, although the absolute benefit beyond hysterectomy alone is small. In our study with an average of 7.6 years of follow-up, 1 case of ovarian cancer was prevented for every 323 BSOs performed. Cardiovascular disease is the most important potentially adverse outcome of BSO because it is the primary cause of mortality among women, resulting in 454 613 deaths per year compared with 14 857 deaths due to ovarian cancer.⁵³ In our analysis, BSO was not associated with statistically significant increased risks of any cardiovascular outcome compared with hysterectomy and ovarian conservation despite a sample size with 90% power to detect HRs of at least 1.30 for fatal and nonfatal CHD. We did not evaluate some possible outcomes of BSO that have been examined in prior studies and may influence patient preferences, including menopausal symptoms, sexual function, mental health, and cognitive function. Overall, our findings in this large cohort of postmenopausal women demonstrate a benefit of BSO for ovarian cancer prevention beyond that of hysterectomy alone and suggest that there may not be significant long-term harms after BSO on cardiovascular health, hip fractures, or cancer.

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INVITED COMMENTARY

Hysterectomy With Oophorectomy: Implications for Clinical Decision Making

Despite small but significant decreases in the incidence of hysterectomy in recent years,¹ approximately 600 000 women undergo the procedure each year in the United States. After cesarean delivery, hysterectomy is the second most common surgery performed on women of child-bearing age.² Because elective BSO reduces the risk of ovarian cancer,³ the procedure is performed in conjunction with more than half of all hysterectomies; incidence trends for the dual surgery vary by age, with higher proportions of older women undergoing concomitant BSO.²

The benefit of BSO is well established for those with a known genetic risk for ovarian and breast cancer (eg, *BRCA1* [GenBank U14680] and *BRCA2* [GenBank U43746] carriers).^{3,4} However, there is a lack of consistent scientific evidence in support of (or against) prophylactic ovarian removal in all other women. The reduction in ovarian estrogen and androgen levels that follows BSO raises concern about additional risks for short- and long-term health consequences, namely osteoporosis, CVD, menopausal symptoms, and quality of life.³ Recognizing this, guidelines from the American Congress of Obstetricians and Gynecologists⁵ recommend BSO for postmenopausal women who have a known risk for ovarian cancer and/or women with chronic gynecologic conditions that might affect any risks associated with subsequent ovarian surgery. The American Congress of Obstetricians and Gynecologists specifically advocates for ovarian conservation in premenopausal women with no known genetic risk for ovarian can-

cer. New high-quality, large-scale studies that examine the risks and benefits of BSO vs ovarian conservation during hysterectomy provide a valuable addition to the discussion on this clinical issue. However, it is important for clinicians to keep in mind the principles of evidence-based medicine and informed decision making (by the patient) when deciding how to counsel women about their surgical options.

One area of discrepancy that may confuse the physician and patient alike is the effect of combined BSO-hysterectomy on CVD. A review of the literature underscores the importance of looking at this relation on a more detailed level, taking into account factors such as HT use, age at which BSO-hysterectomy is performed, and subtypes of CVD. For example, although a meta-analysis⁶ failed to find a convincing association between menopausal status and CVD, it was noted that early menopause, and surgical menopause in particular, increased the risk of CVD even after controlling for the effects of smoking and age. A subsequent cohort study⁷ with 38-year follow-up data found increased mortality from CVD in women who underwent BSO-hysterectomy before age 45 years; this risk was further magnified when stroke was excluded. Analysis of the NHS data⁸ examined stroke and CHD separately and noted increased CHD mortality in women who underwent BSO-hysterectomy before age 50 years. This was further elevated in the subgroup of women younger than 50 years without a history of estrogen use. With 24 years of follow-up data and inclusion of 29 380