Original Research

Oophorectomy and Hysterectomy and Cancer Incidence in the Cancer Prevention Study-II Nutrition Cohort

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OBJECTIVE: To examine associations of simple hysterectomy and hysterectomy with bilateral salpingo-oophorectomy (BSO), relative to no surgery, with total and site-specific cancer risk in the Cancer Prevention Study-II Nutrition Cohort.

METHODS: We examined associations of hysterectomy with BSO and simple hysterectomy with total and site-specific cancer risk in 66,802 postmenopausal women from the Cancer Prevention Study-II Nutrition Cohort.

RESULTS: During a median follow-up of 13.9 years, 8,621 cancers were diagnosed. Hysterectomy with BSO performed at any age (1,892 cases), compared with no hysterectomy (n=5,586 cases), is associated with a 10% reduction in all cancers (relative risk [RR] 0.90, 95% confidence interval [CI] 0.85–0.96). This inverse association does not hold if the surgery occurred at ages 55 years or older (583 cases; RR 1.02, 95% CI 0.94–1.12). Hysterectomy with BSO (715 cases) was associated with a 20% reduction in breast cancer performed at any age (RR 0.80, 95% CI 0.73–0.88). Hysterectomy without BSO was associated with a deceased cancer risk only if performed at age 45 years or younger (541 cases; RR 0.88, 95% CI 0.80–0.97) and overall was associated with a decreased risk of breast cancer (419 cases; RR 0.86, 95% CI 0.76–0.96).

CONCLUSION: In a large prospective study, hysterectomy with BSO before age 55 years, relative to no surgery, is associated with a lower risk of total cancer. This information, particularly the lower risk in women younger than 45 years, should be considered in counseling women about ovarian management at the time of surgery.

(Obstet Gynecol 2014;123:1247–55)
DOI: 10.1097/AOG.0000000000000270

LEVEL OF EVIDENCE: II

Hysterectomy is the most common gynecologic surgery in the United States.[1] Women undergoing hysterectomy commonly are offered elective bilateral salpingo-oophorectomy (BSO) regardless of their ovarian cancer risk.[2] However, the ovarian hormone deprivation from BSO[3] might have detrimental effects on some health outcomes.[4] Data on cancer risks associated with BSO are needed to inform women at average risk of ovarian cancer of the risks and benefits of surgery.

The most comprehensive assessments of BSO and cancer risk identified lower risk of total cancer in one study[5] but not the other.[6] The former study[5] also found that hysterectomy with BSO was associated with lower breast cancer risk and higher lung cancer risk. However, the lung cancer analyses included smokers. Both studies used women with hysterectomy as the reference group, which allowed them to examine risks associated with elective BSO but limited their ability to separately evaluate the relative risks associated with simple hysterectomy. Associations with simple hysterectomy are plausible because the procedure could damage circulation to the ovaries.[7,8]

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The American Cancer Society (ACS) funds the creation, maintenance, and updating of the Cancer Prevention Study-II (CPS-II) cohort.

The authors thank the Cancer Prevention Study-II Nutrition Cohort participants and Study Management Group for their invaluable contributions to this research. The authors also acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries and cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program.

Presented at the12th Annual Frontiers in Cancer Prevention Research, American Association for Cancer Research, October 27–30, 2013, National Harbor, Maryland.

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/14

We examined associations of simple hysterectomy and hysterectomy with BSO, relative to no surgery, with total and site-specific cancer risk in the Cancer Prevention Study-II Nutrition Cohort. Lung cancer analyses were limited to women who were never or long-term former smokers. To compare our results with previous studies,[5,6] we also analyzed associations with hysterectomy with BSO using simple hysterectomy as the reference group.

MATERIALS AND METHODS

Women in this analysis were drawn from the 97,785 female participants in the Cancer Prevention Study-II Nutrition Cohort, a prospective study of cancer incidence and mortality established in 1992–1993 as a subgroup of a larger mortality study initiated in 1982.[9] The participants resided in 1 of 21 states, including California, Connecticut, Florida, Georgia, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Missouri, New Mexico, New Jersey, New York, North Carolina, Pennsylvania, Utah, Virginia, Washington, and Wisconsin. At enrollment in 1992–1993, all participants completed a mailed baseline questionnaire. At that time, most of the Cancer Prevention Study-II Nutrition Cohort members were 50–74 years old (mean 62.5, median 62.0 years). Follow-up questionnaires were sent to cohort members every 2 years starting in 1997 to update exposure information and ascertain newly diagnosed cancer outcomes. The response rate for each of these follow-up questionnaires through 2009 was at least 87%. Informed consent for participation was assumed based on completion and return of study questionnaires. The Emory University School of Medicine institutional review board approves all aspects of Cancer Prevention Study-II Nutrition Cohort.

Individuals were excluded from the analytical data set if they were alive at the time of the first survey mailing yet returned no surveys during follow-up (n=3,111), reported a history of cancer in 1992 (except nonmelanoma skin cancer, n=13,094), had incomplete data on oophorectomy or hysterectomy (n=3,170), reported an oophorectomy with one or unknown number of ovaries (n=5,073), reported a bilateral oophorectomy without hysterectomy (n=339), were premenopausal at baseline (n=5,384), did not complete the follow-up survey in 1997 (n=501), or had incomplete cancer diagnosis information (n=311). For lung cancer analyses, current smokers, former smokers who quit 20 years or less before baseline, and women with unknown smoking status also were excluded (n=18,404).

Incident cancer diagnoses were self-reported on follow-up questionnaires through June 30, 2009. In a substudy of the Cancer Prevention Study-II Nutrition Cohort, results showed that participants were able to accurately report a past diagnosis of cancer accurately.[10] The majority of the invasive cancer cases were verified through medical records or linkage with state registries or were identified during confirmation of other reported cancer diagnoses. A small percentage of cases (4.2%) were obtained through the National Death Index and were included if the death certificate listed invasive cancer as a cause of death.[11] In addition to examining total cancer cases, we individually examined associations with cancer sites that had at least 15 cases in the exposed categories, including invasive breast cancer, colorectal cancer, lung cancer, non-Hodgkin's lymphoma, melanoma, pancreatic cancer, kidney cancer, ovarian cancer, and all other cancers combined. We considered only first cancer diagnoses. "Other cancer" and "total cancer" outcomes did not include in situ breast cancer, endometrial cancer, and lung cancer diagnosed in current smokers and former smokers who quit less than 20 years before baseline.

Cancer Prevention Study-II Nutrition Cohort participants could report a hysterectomy and oophorectomy on the surveys from 1982 through the 2001 follow-up survey. The surveys from 1992 through the 2001 follow-up survey allowed participants to respond separately about the removal of their uterus, one ovary, or two ovaries. Exact age at oophorectomy and hysterectomy was captured only in the 1997 follow-up survey with a separate age field for removal of the uterus and removal of one or both ovaries. Primary exposure groups were women with a hysterectomy with BSO, simple hysterectomy with ovarian conservation, and women with intact ovaries and uteri. Because age at surgery was used as a categorical variable (younger than 45, 45–54, 55 years or older) in this analysis, we assigned an age category based on the questionnaire in which the surgery was first reported for women with missing age at surgery (22% for oophorectomy and 23% for hysterectomy surgeries). The age at surgery was assigned based on the age at the midpoint of the questionnaire with the first mention of surgery and the preceding questionnaire. For example, most women with missing age at surgery occurred between the 1982 and 1992 questionnaires; for these women, the midpoint age between the 1982 and 1992 questionnaires was assigned as the age at surgery.

Participants contributed person-time to the analysis from the return of the 1992 questionnaire until

they were censored at the date of diagnosis for their first cancer, date of death for those who died before the end of follow-up, date of last survey returned for those lost to follow-up before the end of follow-up, or June 30, 2009, for those who reached the end of the follow-up period. Extended Cox regression models[12] were used to calculate multivariable-adjusted hazard ratios (relative risk [RR]), 95% confidence intervals (CI), and the Wald *P* value. Models with lung cancer as the outcome were limited to women who never smoked and long-term former smokers.

Multivariable-adjusted models included race, education, parity, age at first birth, age at menopause, active smoking, alcohol consumption, family history of site-specific cancer, recreational physical activity, body mass index (calculated as weight (kg)/[height (m)]^2), use of postmenopausal hormones as well as use of mammography screening in models with breast cancer as the outcome, diabetes, nonsteroidal anti-inflammatory drugs, and recent colonoscopy in models with colorectal cancer as the outcome and diabetes and nonsteroidal anti-inflammatory drugs in models with lung cancer as the outcome. Body mass index, use of postmenopausal hormones, and screening behaviors were treated as time-dependent covariates (ie, updated over the follow-up period). All Cox models were stratified on year of age at enrollment.

We stratified analyses by age at the surgery (younger than 45, 45–54, and 55 years or older). In sensitivity analysis, the influence of oophorectomies performed because of a strong family history of breast cancer was examined by excluding women with one or more first-degree family members with breast or ovarian cancer. We also examined the influence of the proportion of women with missing age at surgery by performing all analyses in women with exact age at oophorectomy and hysterectomy. To compare our results with those from the Nurses' Health Study[5] and Women's Health Initiative,[6] we also estimated the multivariable-adjusted association of cancer risk with hysterectomy with BSO compared with simple hysterectomy. Reported *P* values were two-sided and were considered statistically significant if $<.05$. The number of women needed to treat for benefit or harm, rounded up to the nearest whole number, was determined based on the adjusted RR and the unexposed event proportion using the calculation described by Bender et al.[13] All analyses were performed in SAS 9.3.

RESULTS

In the 66,802 postmenopausal women followed for a median of 13.9 years (range 0.01–16.72 years) with a total of 778,305 person-years, a total of 8,621 cancers were diagnosed of which 3,401 were invasive breast cancers, 958 were colorectal cancers, 752 were non-Hodgkin's lymphoma, 586 were melanoma, 403 were ovarian cancers, 256 were pancreatic cancers, and 138 were kidney cancers. Additionally, 484 lung cancers occurred in the 48,398 never and long-term former smokers. A total of 15,750 (23.6%) women had a hysterectomy with BSO and 9,655 (14.4%) women had a simple hysterectomy. Women who had a simple hysterectomy or hysterectomy with BSO, compared with women with no surgery, tended to be less educated, use postmenopausal hormones, participate in screening for breast or colon cancer, be heavier, have diabetes, and use nonsteroidal anti-inflammatory drugs (Table 1). Women who had no surgery or who had a hysterectomy with BSO were more likely to be nulliparous than women with a simple hysterectomy; however, women with surgery tended to have children at an earlier age. There was little difference in the proportion of women with a family history of breast and ovarian cancers in first-degree family members by type of surgery.

Overall, there was a 10% lower risk of total cancer (number needed to treat for benefit 85) associated with hysterectomy with BSO (Table 2) compared with women without surgery, and the RR was lowest for women who had the surgery before age 45 (RR 0.79, 95% CI 0.71–0.87, number needed to treat for benefit 40). Simple hysterectomy was associated with lower risk of total cancer only if it was performed before age 45 years (RR 0.88, 95% CI 0.80–0.97, number needed to treat for benefit 71).

Overall, breast cancer was the most commonly diagnosed cancer (437 cases/100,000 person-years). Compared with no surgery, hysterectomy with BSO before age 45 years was associated with a 27% reduction in risk of breast cancer (Table 2; number needed to treat for benefit 333). Similarly, simple hysterectomy before age 45 years was associated with a 20% lower risk of breast cancer (number needed to treat for benefit 450). These inverse associations were similar when women with a first-degree family history of breast or ovarian cancer were excluded (data not shown).

Excluding invasive breast cancers from the total cancer cases (resultant total N=5,220) eliminated the association of total cancers with hysterectomy with BSO (RR 0.97, 95% CI 0.90–1.05) and simple hysterectomy (RR 1.04, 95% CI 0.95–1.13). A similar lack of association was observed for simple hysterectomy performed before age 45 years (RR 0.94, 95% CI 0.83–1.06), yet a statistically significant association

Table 1. Relationship of Type of Surgery With Cancer Risk Factors at Baseline, Cancer Prevention Study-II Nutrition Cohort (1992–2009)

Risk Factor	Surgery Type		
	No Surgery	Hysterectomy Only	Hysterectomy +Oophorectomy
Total	41,397 (62.0)	9,655 (14.4)	15,750 (23.6)
Age at baseline (y)			
Younger than 55	3,163 (7.6)	1,007 (10.4)	1,581 (10.0)
55–59	10,157 (24.5)	2,214 (22.9)	3,660 (23.2)
60–64	12,067 (29.2)	2,743 (28.4)	4,462 (28.3)
65–69	9,499 (23.0)	2,154 (22.3)	3,664 (23.3)
70–74	5,655 (13.7)	1,321 (13.7)	2,056 (13.1)
75 or older	856 (2.1)	216 (2.2)	327 (2.1)
Race			
White	40,476 (97.8)	9,359 (96.9)	15,319 (97.3)
Black	458 (1.1)	171 (1.8)	256 (1.6)
Other or missing	463 (1.1)	125 (1.3)	175 (1.1)
Education			
High school graduate or less	14,866 (35.9)	3,710 (38.4)	6,225 (39.6)
Some college	12,464 (30.1)	3,252 (33.6)	5,124 (32.5)
College graduate or more	13,786 (33.3)	2,641 (27.4)	4,291 (27.2)
Missing	281 (0.7)	52 (0.5)	110 (0.7)
Age at first birth (y)			
Nulliparous	3,196 (7.7)	375 (3.9)	1,332 (8.4)
Younger than 20	2,971 (7.2)	1,193 (12.2)	1,773 (11.2)
20–24	18,505 (44.7)	4,973 (51.6)	7,672 (48.7)
25–29	12,125 (29.2)	2,346 (24.4)	3,674 (23.4)
30 or older	3,656 (8.8)	590 (6.1)	954 (6.1)
Missing	944 (2.3)	178 (1.8)	345 (2.2)
No. of live births			
Nulliparous	3,194 (7.7)	375 (3.9)	1,332 (8.4)
1	2,964 (7.2)	523 (5.4)	1,236 (7.8)
2	10,667 (25.8)	2,342 (24.1)	4,258 (27.0)
3 or more	23,780 (57.3)	6,275 (65.2)	8,625 (54.9)
Missing	790 (1.9)	140 (1.4)	299 (1.9)
Hormone use for postmenopausal replacement therapy			
Never	22,596 (54.5)	2,963 (30.6)	2,455 (15.7)
Current estrogen only	1,292 (3.1)	3,947 (40.9)	7,825 (49.5)
Current estrogen+progesterone	6,857 (16.7)	305 (3.1)	728 (4.6)
Current but unknown hormones	612 (1.5)	84 (0.9)	188 (1.2)
Former	7,556 (18.2)	1,887 (19.6)	3,844 (24.6)
Ever or other hormones	1,570 (3.8)	376 (3.9)	581 (3.7)
Missing	914 (2.2)	93 (1.0)	129 (0.8)
Age at menopause (y)			
Younger than 50	13,076 (31.7)	7,551 (78.1)	10,754 (68.1)
50–54	21,956 (53.0)	1,561 (16.3)	3,906 (24.9)
55 or older	6,365 (15.2)	543 (5.6)	1,090 (7.0)
Active smoking			
Never	22,288 (53.8)	5,577 (57.8)	8,682 (55.2)
Current	3,655 (8.9)	721 (7.4)	1,120 (7.1)
Former	14,792 (35.7)	3,212 (33.3)	5,683 (36.1)
Unknown or unclassifiable	662 (1.6)	145 (1.5)	265 (1.7)
Alcohol consumption			
Noncurrent drinker	18,120 (43.8)	4,738 (49.0)	7,710 (48.9)
Fewer than 1 drink/wk	4,817 (11.6)	1,145 (11.9)	1,799 (11.4)
Fewer than 1–6 drinks/wk	11,230 (27.1)	2,372 (24.5)	3,899 (24.7)
1 drink/d	3,423 (8.3)	624 (6.5)	1,074 (6.8)
2 or more drinks/d	2,109 (5.1)	370 (3.8)	622 (4.0)
Missing	1,698 (4.1)	406 (4.2)	646 (4.1)

(*continued*)

Table 1. Relationship of Type of Surgery With Cancer Risk Factors at Baseline, Cancer Prevention Study-II Nutrition Cohort (1992–2009) (*continued*)

Risk Factor	Surgery Type		
	No Surgery	Hysterectomy Only	Hysterectomy +Oophorectomy
Family history of breast cancer			
Yes	5,721 (13.8)	1,367 (14.2)	2,317 (14.7)
No	35,676 (86.2)	8,288 (85.8)	13,433 (85.3)
Family history of colorectal cancer			
Yes	2,412 (5.8)	613 (6.4)	1,012 (6.5)
No	38,985 (94.2)	9,042 (93.6)	14,738 (93.5)
Family history of lung cancer			
Yes	2,226 (5.4)	526 (5.5)	882 (5.6)
No	39,171 (94.6)	9,129 (94.5)	14,868 (94.4)
Mammogram screening			
Never or not recent	14,635 (35.3)	2,998 (31.0)	4,759 (30.3)
Within 2 y	26,423 (63.8)	6,634 (68.7)	10,944 (69.4)
Unknown	339 (0.8)	23 (0.2)	47 (0.3)
Colon screening (1997 survey)			
Never or not recent	17,260 (42.9)	3,222 (34.1)	5,520 (35.7)
Within 2 y	17,792 (44.1)	4,966 (52.9)	8,189 (53.2)
Unknown	5,254 (13.0)	1,227 (13.1)	1,725 (11.2)
BMI (kg/m^2)			
Less than 18.5	900 (2.2)	139 (1.4)	245 (1.6)
18.5–22.4	11,199 (27.1)	2,196 (22.7)	3,689 (23.4)
22.5–24.9	10,397 (25.1)	2,353 (24.4)	3,740 (23.7)
25.0–29.9	12,293 (29.7)	3,296 (34.2)	5,203 (33.1)
30.0 or greater	5,952 (14.4)	1,538 (15.9)	2,645 (16.7)
Missing	656 (1.6)	133 (1.4)	228 (1.5)
Recreation physical activity (metabolic equivalent h/wk)			
0	3,680 (8.9)	860 (8.9)	1,411 (8.9)
0.1–6.9	12,872 (31.1)	3,090 (32.0)	4,845 (30.8)
7.0–17.5	14,270 (34.5)	3,303 (34.2)	5,410 (34.4)
17.6–24.4	3,439 (8.3)	810 (8.4)	1,313 (8.3)
24.5 or greater	6,546 (15.8)	1,457 (15.1)	2,513 (16.0)
Missing	590 (1.4)	135 (1.4)	258 (1.6)
Diabetes			
Yes	2,467 (6.0)	717 (7.5)	1,085 (6.9)
No	38,930 (94.0)	8,938 (92.5)	14,665 (93.1)
Nonsteroidal anti-inflammatory drug use (pills/mo)			
Nonuser	18,800 (45.4)	3,895 (40.3)	6,413 (40.7)
1–14	6,570 (15.9)	1,393 (14.4)	2,330 (14.7)
15–29	3,778 (9.1)	860 (8.9)	1,419 (9.0)
30–59	5,961 (14.4)	1,502 (15.6)	2,489 (15.8)
60 or more	4,690 (11.3)	1,562 (16.2)	2,377 (15.1)
Missing	1,598 (3.9)	443 (4.6)	722 (4.6)

BMI, body mass index.
Data are n (%).

still remained for hysterectomy with BSO performed before age 45 years (RR 0.83, 95% CI 0.73–0.94, number needed to treat for benefit 80; results not otherwise shown).

Overall, hysterectomy with BSO was strongly associated with a lower risk of ovarian cancer (RR 0.12, 95% CI 0.07–0.21, number needed to treat for benefit 156). There was a higher risk of ovarian cancer associated with simple hysterectomy performed at any age (RR 1.36, 95% CI 1.03–1.78, number needed to treat for harm 383).

Compared with women who had no surgery, hysterectomy with and without BSO was not associated with risk of colorectal cancer, lung cancer for never smokers and long-term former smokers, non-Hodgkin's lymphoma, kidney cancer, and all other cancers combined (Table 2). However, hysterectomy with BSO was associated with a higher risk of

Table 2. Associations of Cancer Incidence With Simple Hysterectomy (Ovarian Conservation) and Hysterectomy With Bilateral Salpingo-oophorectomy Relative to No Surgery, Cancer Prevention Study-II Nutrition Cohort (1992–2009)

	No Surgery (Reference, n=41,397)		Simple Hysterectomy (Ovarian Conservation, n=9,655) Relative to No Surgery (n=41,397)	
Event/Age at Hysterectomy (y)	Case (n)	Incidence Rate/100,000 Patient-Years	Case (n)	Incidence Rate/100,000 Patient-Years
Total cancer[†]				
Younger than 45			541	1,005
45–54			314	1,142
55 or older			288	1,263
All	5,586	1,181	1,143	1,089
Breast cancer				
Younger than 45			201	345
45–54			124	436
55 or older			94	417
All	2,267	465	419	385
Ovarian cancer				
Younger than 45			39	67
45–54			26	93
55+ or older			21	95
All	303	64	86	80
Lung cancer (in never smokers and former smokers who quit 20 or more y ago)				
Younger than 45			29	79
45–54			12	68
55 or older			17	97
All	315	92	58	76
Colorectal cancer				
Younger than 45			48	98
45–54			32	118
55 or older			36	160
All	623	134	116	116
Non-Hodgkin's lymphoma				
Younger than 45			46	93
45–54			38	145
55 or older			29	120
All	438	95	113	112
Melanoma cancer				
Younger than 45			48	87
45–54			23	74
55 or older			16	69
All	329	70	87	80
Pancreatic cancer				
All	157	36	45	46
Kidney cancer				
All	85	18	22	22
All other cancers[†]				
Younger than 45			98	185
45–54			45	166
55 or older			54	241
All	1,069	230	197	189

BSO, bilateral salpingo-oophorectomy; RR, relative risk; CI, confidence interval.

* Multivariable-adjusted models controlled for attained age, race, education, alcohol consumption, smoking, parity, age at first birth, use of hormone replacement therapy, physical activity, age at menopause, and body mass index. Models with breast cancer as the outcome were further adjusted for first-degree family history of breast cancer and recent mammogram; colorectal cancer for first-degree family history of colorectal cancer, diabetes, nonsteroidal anti-inflammatory drug use, and recent colonoscopy; and lung cancer for family history of lung cancer, diabetes, and nonsteroidal anti-inflammatory drug use.

† "Total cancer" and "other cancer" outcomes did not include in situ breast cancer, endometrial cancer, and lung cancer diagnosed in current smokers, former smokers who quit less than 20 years before baseline, and women with unknown smoking status.

Simple Hysterectomy (Ovarian Conservation, n=9,655) Relative to No Surgery (n=41,397)	Hysterectomy With BSO (n=15,750) Relative to No Surgery (n=41,397)			Hysterectomy With BSO (n=15,750) Relative to Simple Hysterectomy (n=9,655)
Multivariable-Adjusted* RR (95% CI)	Case (n)	Incidence Rate/100,000 Patient-Years	Multivariable-Adjusted* RR (95% CI)	Multivariable-Adjusted* RR (95% CI)
0.88 (0.80–0.97)	502	961	0.79 (0.71–0.87)	0.91 (0.81–1.04)
0.99 (0.88–1.12)	807	1,065	0.88 (0.81–0.95)	0.86 (0.76–0.99)
1.04 (0.93–1.18)	583	1,244	1.02 (0.94–1.12)	1.00 (0.86–1.16)
0.96 (0.90–1.03)	1,892	1,077	0.90 (0.85–0.96)	0.95 (0.88–1.02)
0.80 (0.69–0.94)	189	350	0.73 (0.62–0.86)	0.93 (0.75–1.14)
0.93 (0.77–1.12)	326	417	0.81 (0.72–0.92)	0.89 (0.72–1.11)
0.85 (0.69–1.04)	200	432	0.85 (0.73–0.98)	0.99 (0.76–1.27)
0.86 (0.76–0.96)	715	399	0.80 (0.73–0.88)	0.95 (0.84–1.08)
1.18 (0.81–1.72)				
1.53 (1.01–2.33)				
1.41 (0.89–2.21)				
1.36 (1.03–1.78)	14	8	0.12 (0.07–0.21)	
0.80 (0.53–1.19)	31	93	0.80 (0.54–1.19)	0.92 (0.54–1.59)
0.68 (0.38–1.23)	42	78	0.85 (0.60–1.19)	1.16 (0.58–2.29)
1.12 (0.68–1.85)	38	99	1.13 (0.80–1.60)	1.23 (0.67–2.26)
0.85 (0.63–1.15)	111	88	0.92 (0.72–1.18)	1.09 (0.78–1.52)
0.84 (0.62–1.15)	56	114	0.96 (0.71–1.29)	1.23 (0.82–1.86)
1.02 (0.71–1.47)	80	108	0.96 (0.75–1.22)	0.86 (0.56–1.31)
1.14 (0.81–1.61)	83	176	1.46 (1.15–1.86)	1.28 (0.85–1.93)
0.99 (0.80–1.23)	219	128	1.12 (0.94–1.34)	1.12 (0.89–1.42)
0.97 (0.70–1.34)	57	108	1.09 (0.80–1.48)	1.21 (0.81–1.83)
1.53 (1.08–2.15)	95	130	1.28 (1.01–1.63)	0.78 (0.53–1.15)
1.28 (0.88–1.88)	49	102	1.05 (0.77–1.42)	0.79 (0.49–1.29)
1.20 (0.96–1.51)	201	115	1.17 (0.97–1.41)	0.98 (0.77–1.24)
1.12 (0.80–1.56)	45	77	1.13 (0.80–1.60)	1.05 (0.69–1.62)
1.16 (0.75–1.79)	80	101	1.39 (1.07–1.81)	1.28 (0.79–2.07)
1.07 (0.64–1.78)	45	92	1.40 (1.01–1.93)	1.23 (0.68–2.23)
1.13 (0.87–1.47)	170	94	1.32 (1.07–1.64)	1.23 (0.94–1.61)
1.48 (1.03–2.14)	54	32	0.97 (0.69–1.37)	0.66 (0.44–0.99)
1.43 (0.85–2.40)	31	18	1.17 (0.74–1.85)	0.75 (0.42–1.34)
0.82 (0.66–1.02)	103	204	0.82 (0.66–1.02)	1.02 (0.76–1.36)
0.76 (0.56–1.04)	154	206	0.91 (0.76–1.09)	1.14 (0.81–1.60)
1.01 (0.77–1.33)	120	259	1.10 (0.91–1.34)	1.18 (0.85–1.65)
0.86 (0.73–1.02)	377	216	0.95 (0.83–1.08)	1.12 (0.94–1.34)

melanoma (RR 1.32, 95% CI 1.07–1.64, number needed to treat for harm 398), and simple hysterectomy was associated with a higher risk of pancreatic cancer (RR 1.48, 95% CI 1.03–2.14, number needed to treat for benefit 553).

Using a referent group of women with simple hysterectomy, hysterectomy with BSO performed was not associated with total cancer or any site-specific cancer with the exception of the lower risk observed for pancreatic cancer. In particular, associations of

hysterectomies with BSO performed before age 45 years also were null (Table 2).

In sensitivity analyses excluding women with assigned age at surgery, results (data not shown) were similar to those in Table 2.

DISCUSSION

In an analysis of 66,802 postmenopausal women with medical histories collected before health outcomes, we found that hysterectomy with BSO performed at age 54 years or younger was associated with lower cancer risk. Hysterectomy with BSO was associated with a reduction in breast cancer performed at any age. The inverse association for simple hysterectomy without BSO performed at age 45 years or younger was driven by the lower risk of breast cancer. We also found that simple hysterectomy was associated with higher risk of ovarian and pancreatic cancer, and hysterectomy with BSO was associated with higher risk of melanoma.

Women with known deleterious genetic mutations for breast and ovarian cancer are advised to have a prophylactic BSO after childbearing to remove the ovaries and to minimize lifetime exposure to ovarian hormones.[14] Results from the Nurses' Health Study and Women's Health Initiative cohorts showed that the addition of BSO with hysterectomy at older ages (45 years or older and 40 years or older, respectively), compared with simple hysterectomy, was not associated with lower risk of breast cancer.[5,6] In our analyses that used simple hysterectomy as the reference group, we also found no association between hysterectomy with BSO and breast cancer because there were inverse associations with both simple hysterectomy and hysterectomy with BSO compared with women who retained their uterus and ovaries. Indeed, hysterectomy with ovarian conservation has the potential to damage ovarian function, as shown in prospective studies of women before and after simple hysterectomy.[15,16] The reduction in sex steroid hormones likely contributes to the lower breast cancer risk associated with hysterectomy regardless of ovarian conservation.

The higher risk of ovarian cancer for women with simple hysterectomy observed in this study has been shown in other studies.[17] However, it is likely that these results are confounded by indication for hysterectomy. For instance, endometriosis is a common reason for hysterectomy,[1] and endometrioid and clear cell ovarian tumors are hypothesized to develop from atypical endometriosis.[18] In our study, we did not have information on the reason for removal of the organs.

Our results for melanoma and pancreatic cancer need to be replicated in other large cohorts. There is some prior evidence for both cancers that supports a possible role for endogenous hormones in the etiology of these cancers.[19,20] One cohort study found hysterectomy and BSO (examined separately) were associated with higher risk of pancreatic cancer.[21]

Our conclusions are strengthened by the large, prospective design, updated exposure information on oophorectomy and hysterectomy and postmenopausal hormone use, and detailed data on important confounders, like family history of cancer and cancer screening behaviors, from our study. Although surgery type was self-reported by study participants, older women from a managed care plan were shown to accurately report removal of their uterus, but not removal of their ovaries, as the cause of the menstrual cessation.[22] Exposure misclassification of BSO could have biased our results for simple hysterectomy away from the null. However, we are reassured that reporting bias of BSO had minimal influence on our results, because we did not detect an inverse association of ovarian cancer with simple hysterectomy. We assigned the age range at surgery for nearly one-fourth of the women with missing data. It is unlikely this led to significant misclassification because results from the sensitivity analysis that included only women with the exact age at surgery were not significantly different from the reported results. Like in nearly all observational studies, selective survival bias might have influenced our results, especially because the exposure of interest occurred before the start of follow-up for some women; interpretation of our results is based on adult women who lived to participate in our study. For some of the rare cancer outcomes, power might have been insufficient to detect weak RRs.

Hysterectomy with BSO performed before age 45 years was associated with a lower risk of total cancer even after accounting for the lower risk of breast cancer. On average, 71 women with a similar age distribution of the Cancer Prevention Study-II participants with no surgery would have to have hysterectomy with BSO before age 45 years to prevent one woman from being diagnosed with cancer. These results provide suggestive evidence for a hormonal etiology of some cancers; for breast and ovarian cancer, this is well documented, but our findings for lung cancer and melanoma deserve further study. The possible cancer benefits and risks of hysterectomy later in life with elective BSO performed at a young age need to be considered with other health consequences by the patient with her surgeon before surgery.[23]

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