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Risk of *de novo* cancer after premenopausal bilateral oophorectomy

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SUPPLEMENTAL ONLINE MATERIAL
Supplementary material is available.

Abstract

BACKGROUND: Hysterectomy is one of the most frequent gynecologic surgeries in the United States. Women undergoing hysterectomy commonly are offered bilateral oophorectomy for ovarian and breast cancer prevention. Although bilateral oophorectomy may dramatically reduce the risk of gynecologic cancers, some studies suggested that bilateral oophorectomy may be associated with an increased risk of other types of cancer, such as lung cancer and colorectal cancer. However, the results are conflicted.

OBJECTIVE: To study the association between bilateral oophorectomy and the risk of subsequent cancer of any type.

STUDY DESIGN: This population-based cohort study included all premenopausal women who underwent bilateral oophorectomy for a nonmalignant indication before the age of 50 years between January 1, 1988 and December 31, 2007 in Olmsted County, Minnesota, and a random sample of age-matched (±1 year) referent women who did not undergo bilateral oophorectomy. Women with cancer before oophorectomy (or index date) or within 6 months after the index date were excluded. Time-to-event analyses were performed to assess the risk of *de novo* cancer. Cancer diagnosis and type were confirmed using medical record review.

RESULTS: Over a median follow-up of 18 years, the risk of any cancer did not significantly differ between 1562 women who underwent bilateral oophorectomy before natural menopause and 1610 referent women (adjusted hazard ratio (HR), 0.82, 95% CI, 0.66–1.03). However, women who underwent bilateral oophorectomy had a decreased risk of gynecologic cancers (HR, 0.15; 95% CI, 0.06–0.34) but not of non-gynecologic cancers (HR, 0.99; 95% CI, 0.78–1.26). In particular, the risk of breast cancer, gastrointestinal cancer, and lung cancer did not differ between these two cohorts. Use of estrogen therapy through the age of 50 years in women who underwent bilateral oophorectomy did not modify the results.

CONCLUSIONS: Women who underwent bilateral oophorectomy before menopause have a reduced risk of gynecologic cancer but not of other types of cancer including breast cancer. Women at average risk of ovarian cancer should not consider bilateral oophorectomy for the prevention of breast cancer or other non-gynecologic cancers.

Keywords

cancer; gynecologic cancer; breast cancer; bilateral oophorectomy; menopause; incidence; estrogen therapy

Introduction

Hysterectomy is one of the most frequent gynecologic surgeries in the United States.[1] Women undergoing hysterectomy commonly are offered bilateral oophorectomy for ovarian and breast cancer prevention.[1, 2] In addition, prophylactic bilateral oophorectomy is usually recommended for women with an inherited high risk variant in the *BRCA1* or *BRCA2* genes. As a result, it is estimated that one in eight US women have their ovaries removed before reaching natural menopause.[1] Indeed, premenopausal hysterectomy with bilateral oophorectomy may dramatically reduce the risk of gynecologic cancers, such as uterine, fallopian, and ovarian cancers.[3]

On the other hand, the effect of bilateral oophorectomy on the risk of breast cancer remains controversial. Previous studies have reported conflicting results, especially among women with *BRCA1* and *BRCA2* variants.[4–11] For example, findings from a large prospective study indicated that premenopausal bilateral oophorectomy was only associated with a reduced risk of breast cancer before age 50 years in *BRCA2* mutation carriers.[12] By contrast, a systematic review of the literature concluded that premenopausal bilateral oophorectomy was associated with a reduced risk of breast cancer in women with *BRCA1* mutations but not with *BRCA2* mutations.[13] Finally, a few observational studies suggested that bilateral oophorectomy may reduce the risk of breast cancer in the general population (in which most women do not carry the *BRCA1* or *BRCA2* pathogenic variants), only when performed at younger age.[14–17]

Some studies suggested that bilateral oophorectomy may be associated with an increased risk of other types of cancer. For example, one study reported that premenopausal bilateral oophorectomy was associated with an increased risk of lung cancer.[14] Studies examining the risk of colorectal cancer after bilateral oophorectomy have been inconsistent.[15, 18] In addition, increased attention has been directed at determining the risk-to-benefit ratio of prophylactic bilateral oophorectomy because of the increased risk of long-term non-cancer morbidity and mortality.[19–22] In this study, we investigated the association between premenopausal bilateral oophorectomy and the risk of subsequent cancer overall and by specific cancer type, using an established population-based cohort.

Materials and Methods

Data source and study population

The study design and clinical characteristics for women included in the Mayo Clinic Cohort Study of Oophorectomy and Aging-2 (MOA-2) have been previously described.[19, 20, 23, 24] Briefly, we included all premenopausal women who underwent bilateral oophorectomy between January 1, 1988 and December 31, 2007 in Olmsted County, Minnesota. We excluded women who underwent oophorectomy to treat ovarian cancer (primary or metastatic), to treat another estrogen-sensitive malignant disorder (usually breast cancer), or because they were considered at high risk of ovarian cancer (strong family history as judged by the gynecologist or carriers of *BRCA1* or *BRCA2* pathogenic variants). Bilateral oophorectomy was defined as the removal of both ovaries or as the removal of the remaining ovary for women who underwent two separate procedures. The date of the surgical procedure was considered the index date. Each woman who underwent bilateral oophorectomy was randomly matched to a referent woman of same age (±1 year) who had not undergone bilateral oophorectomy before the index date from the same Olmsted County population. Prior hysterectomy or unilateral oophorectomy were not exclusion criteria for referent women. Data were collected by abstracting medical records from the Rochester Epidemiology Project (REP) medical records-linkage system. Extensive details about the REP were published elsewhere.[25–28] All research activities were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Ascertainment of cancer

For all women, we extracted from the electronic indexes of the REP the International Classification of Diseases (ICD; eighth revision, ninth revision, or tenth revision) codes assigned for cancer at any time through December 31, 2018. ICD codes listed in any position on the death certificates were also obtained for deaths through December 31, 2018. We included all of the ICD codes for cancer recommended by the US Department of Health and Human Services (DHHS).[29] However, we removed the codes for secondary cancer or metastasis, recurrence of cancer, nonmelanoma skin cancer, male-specific cancer (eg, prostate cancer), carcinoma in situ, benign neoplasms, and for abnormal results of Papanicolaou smears.

The medical records for all women with at least one diagnostic code for cancer were manually reviewed by a physician (N.H.) to confirm the presence of a primary cancer, the date of diagnosis, and the type of primary cancer. Cancers were categorized as gynecologic (ie, ovaries, fallopian tubes, uterus, cervix, vagina, and vulva), breast, gastrointestinal (ie, esophagus, stomach, colon, rectum and anus, liver and intrahepatic bile duct, pancreas, etc.), lung (including bronchus and intrathoracic), head and neck, bone and connective tissue, melanomas of skin, urinary (ie, bladder, kidney and renal pelvis, etc.), brain and nervous system, thyroid, hematologic (ie, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, and multiple myeloma), and other primary cancer. If a woman had two or more primary cancers, they were considered separately in analyses by type.

Other variables

Demographic and clinical characteristics at the index date were manually abstracted for all women from the medical records, and included age, education, race, ethnicity, household income, body mass index (BMI), smoking status, reproductive characteristics, and systemic estrogen therapy after the index date. The indication and the pathology results for each bilateral oophorectomy were defined by the gynecologist and pathologist at the time of surgery.[23, 24] In addition, we considered 16 of the 20 chronic conditions used by the DHHS to define multi-morbidity plus anxiety that were present at the index date (total of 17 conditions): depression, anxiety, substance abuse disorders, dementia, schizophrenia or psychosis, hyperlipidemia, hypertension, diabetes, cardiac arrhythmias, coronary artery disease, stroke, congestive heart failure, arthritis, asthma, chronic obstructive pulmonary disease, osteoporosis, and chronic kidney disease.[29] From the DHHS list we excluded: cancer (study outcome), human immunodeficiency virus infection (HIV), autism spectrum disorder, and hepatitis. All chronic conditions were assessed by extracting ICD diagnostic codes from the REP diagnostic indexes at any time before the index date. Women needed to have at least two diagnostic codes in a given category separated by >30 days to reduce false positive diagnoses.[23, 30]

Statistical analyses

All women who were diagnosed with any type of cancer before the index date or within 6 months after the index date were excluded from the primary analyses. Each woman was followed from 6 months after the index date to the first cancer diagnosis or was censored at the earliest occurring of three end-points: date of death, last visit with a REP provider,

or the end of the study (December 31, 2018). Inverse probability weights (IPW) derived from a logistic regression model were used to adjust for age at index date (continuous), calendar year (continuous), race (white versus nonwhite), BMI (<30 versus ≥30 kg/m^2), years of education (≤12, 13–16, or >16), quartiles of household income (<$42,000, $42,000–56,999, $57,000–71,999, or ≥$72,000), smoking status (current or former vs never), and 17 chronic conditions at baseline. These adjustments were done overall and separately in each stratum to maximize the balance at the index date. After the IPW adjustment, the standardized differences for all of the conditions or characteristics considered were below the recommended threshold of 0.10 (ie, negligible imbalance between the two cohorts).

Cox proportional hazards regression models using age as the time scale and IPW adjustment were used to calculate the hazard ratios (HR) and 95% confidence intervals. The proportional hazards assumptions were checked using time-dependent covariates and with graphical methods; the assumptions were satisfied.[31] Differences between the two cohorts were also measured using the absolute risk increase (ARI) or absolute risk reduction (ARR) obtained by subtracting the two absolute risks at 25 years of follow-up. The analyses were conducted in the overall sample and stratified by age at index date (≤45 vs 46–49 years), ovarian indication (benign vs none), and estrogen therapy within each age stratum (estrogen therapy continued to the 50th birth date vs otherwise). We also conducted a further stratification of the age group ≤45 years at index date into <40 and 40–45 years; however, the numbers were small for some specific types of cancer. Finally, we conducted stratified analyses by decade of the index date (1988–1997 vs 1998–2007). The analyses for gastrointestinal and lung cancer were only stratified by age at index date because of the small number of outcomes.

We performed four sets of sensitivity analysis. First, we considered each type of cancer separately, and we excluded only the women who had that type of cancer before the index date or within the 6 months after the index date. Second, we censored at the date of surgery those referent women who underwent bilateral oophorectomy after the index date and before age 50 years. Third, we excluded from analyses all women who had any of the 17 DHHS chronic conditions at the index date. Fourth, we repeated the primary analyses using the traditional multivariable adjustment method rather than the inverse probability weighting method. In the last three sets of sensitivity analyses, women with any type of cancer before the index date or within 6 months of follow-up were excluded. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC), and tests of statistical significance were conducted at the two-tailed α-level of 0.05.

Results

Characteristics at the index date

Figure 1 shows detailed flowcharts for the two cohorts. Women who underwent bilateral oophorectomy were more likely to have diagnoses of gynecologic cancer before the index date or within 6 months after the index date (Supplemental Figure 1). After excluding women with any type of cancer before the index date or within 6 months after the index date, there were 1562 women who underwent bilateral oophorectomy and 1610 age-matched referent women (Table 1). Most women in both cohorts were white. At the index date,

women who underwent bilateral oophorectomy had a greater number of chronic conditions, were more likely to be overweight or obese, and were more likely to be former or current smokers compared with referent women (Table 1).

Risk of cancer

Starting at 6 months after the index date, the median follow-up was 18.0 years (interquartile interval 13.6–22.5) for the 1562 women who underwent bilateral oophorectomy. A total of 143 women had a *de novo* diagnosis of cancer (6 women had 2 types of cancer). The median follow-up was 17.8 years (interquartile interval 13.5–22.6) for the 1610 referent women. A total of 174 women had a *de novo* diagnosis of cancer (10 women had 2 types of cancer).

After adjustment using IPW, the overall risk of cancer was not significantly different between the two cohorts (HR, 0.82; 95% CI, 0.66–1.03, ARR 3.6%, Table 2, Figure 2). The risk of cancer was significantly lower in women who underwent bilateral oophorectomy before age 46 years (HR, 0.69; 95% CI, 0.51–0.94; ARR, 3.9%), but not in women who underwent bilateral oophorectomy at 46–49 years (HR, 1.03; 95% CI, 0.74–1.45; ARR, 2.6%). However, the HRs did not differ significantly across the two age strata, or in strata by estrogen therapy or by ovarian indication (Table 2, footnote b).

Women who underwent premenopausal bilateral oophorectomy had a reduced risk of gynecologic cancer compared to referent women overall (HR, 0.15; 95% CI, 0.06–0.34; ARR, 3.6%, Table 2, Figure 3), and in strata by age and ovarian indication. However, there was no significant interaction by estrogen therapy. Details about the gynecologic cancers experienced by the two cohorts are provided in Table 2 (footnote g). In particular, ovarian cancer developed in 2 women in the bilateral oophorectomy cohort vs 7 women in the referent cohort.

By contrast, there was no association between bilateral oophorectomy and non-gynecologic cancers overall (HR, 0.99; 95% CI, 0.78–1.26, ARR, 0.6%, Table 2), or in strata by age and ovarian indication. There was no significant interaction by estrogen therapy. In particular, women with or without bilateral oophorectomy before natural menopause had a similar risk of breast cancer (HR, 0.87; 95% CI, 0.61–1.24; ARR, 1.9%), gastrointestinal cancer (HR, 1.07; 95% CI, 0.56–2.03; ARI, 0.7%), and lung cancer (HR, 0.84; 95% CI, 0.39–1.82; ARR, 0.1%) (Table 2).

Sensitivity analyses

In our four sets of sensitivity analyses, the results were similar to the primary analyses. The results for the first set of sensitivity analyses are reported in Supplemental Table 1. The results of the remaining three sets of sensitivity analyses are not shown.

Comment

Principal findings

In this population-based cohort study, women who underwent bilateral oophorectomy before spontaneous menopause had a significantly reduced risk of gynecologic cancer compared to age-matched referent women. However, there were no significant differences for all types

of cancer, all non-gynecological cancers, or specifically for breast cancer, gastrointestinal cancer, or lung cancer. The results remained similar when the analyses were stratified by age, use of estrogen therapy, or by ovarian indication for bilateral oophorectomy.

Results and comparison with other studies

Our finding of a lower risk of all types of gynecological cancers, including ovarian cancer, among women who underwent bilateral oophorectomy is consistent with previous studies.[3, 14, 15, 32] Ovarian cancer is the fifth most common cause of cancer death, and the most common cause of gynecologic cancer death in women, with an estimated 22,240 new diagnoses and 14,070 deaths each year in the United States.[33] Unfortunately, our numbers were small to consider each one of the gynecological cancers separately. Because almost all women underwent concurrent or prior hysterectomy (98.7%), the difference was driven by the dramatic reduction in ovarian and uterine cancer.

By contrast, the risk of breast cancer was not significantly different in our study. Accumulating evidence suggests that sex hormones may play an important role in the development of breast cancer, and that bilateral oophorectomy before natural menopause may reduce the risk, especially among *BRCA2* mutation carriers. For example, Kauff and colleagues reported a 72% decrease in breast cancer risk among *BRCA2* mutation carriers after bilateral oophorectomy.[7] Another study from the Hereditary Breast Cancer Clinical Study Group reported a significantly reduced risk of breast cancer diagnosed before age 50 years among *BRCA2* mutation carriers, but not among *BRCA1* mutation carriers.[12] However, a 2018 systematic review of the literature concluded that the association is more certain for *BRCA1* mutation carriers than for *BRCA2* mutation carriers.[13]

The association between premenopausal bilateral oophorectomy and breast cancer risk among women in the general population (ie, in women at average risk of ovarian cancer) is less clear and may vary by age at the time of oophorectomy.[14–17] For example, a study using the Cancer Prevention Study-II Nutrition Cohort showed a 20% reduction in breast cancer risk in women who underwent bilateral oophorectomy with hysterectomy at any age compared with no surgery.[15] However, the Nurses' Health Study showed a significant reduction in the risk of breast cancer only for women who underwent bilateral oophorectomy with hysterectomy at ages younger than 45 years compared with women who underwent hysterectomy alone. The risk was not decreased for women who underwent oophorectomy at ages 45–54 or 55 years or older.[14]

Similarly, a recent study from Australia reported a significant difference in the risk of breast cancer only for women who underwent bilateral oophorectomy with hysterectomy at ages younger than 45 years, but not at ages 45–54 or 55+ years compared to women with no surgery.[17] A large case-control study showed reduced odds of breast cancer with hysterectomy and bilateral oophorectomy performed at age ≤40 years but not at age older than 40 years.[16] We did not find a significant reduction in risk both at ages ≤45 years or at ages 46–49 years. When we further stratified the age group ≤45 years, there was a trend toward more reduced risk in women with age <40 years compared to age 40–45 years; however, our numbers were too small and we did not have adequate power to test the association restricted to women age <40 years. Therefore, we did not observe a reduced risk

of breast cancer; however, we cannot exclude a reduction in risk restricted to women with very early oophorectomy.

We did not observe an increased risk of gastrointestinal cancer after bilateral oophorectomy. Similarly, a recent study from Australia did not report an increased risk of colorectal cancer in women who underwent hysterectomy with bilateral oophorectomy vs no surgery.[17] These results contrast with findings from a previous study by Segelman and colleagues.[34] Possible reasons for the discrepancy are the small number of events or the frequent use of estrogen therapy among women who underwent bilateral oophorectomy in our study. The use of oral contraceptives or menopausal hormone therapy has been associated with a lower risk of developing colorectal cancer,[35, 36] which is the second most common type of cancer and the third leading cause of cancer deaths in women.[37] Estrogen receptors are present in the human colorectal tissues, and physiological levels of estrogen stimulate humoral and cell-mediated immune response.[38] These observations suggest that estrogen may reduce the risk of colorectal cancer risk in women; however, the studies are inconsistent.[39]

We did not observe an increased risk of lung cancer. Previous studies have examined multiple sex-specific risk factors for lung cancer (eg, age at menarche, age at first pregnancy, age at first live birth, parity, and lactation), with mixed results.[40–43] A study showed that early menopause or oophorectomy were associated with an increased risk of lung cancer.[43] However, the investigators did not control for smoking, one of the strongest risk factors for lung cancer. Higher risk after bilateral oophorectomy was also reported from the Nurses' Health Study.[14]

In our study, the use of estrogen therapy after bilateral oophorectomy did not significantly modify the risk of any cancer types, including gynecological cancers and breast cancer. Several previous studies suggested that estrogen therapy may increase the risk of breast cancer.[44, 45] However, the impact of estrogen therapy on breast cancer risk after bilateral oophorectomy remains unclear.[46–48] In addition, it remains unknown whether the increased risk of breast cancer is associated with an increased duration of estrogen use, time since menopause, and with estrogen receptor-positive disease.[49, 50] For example, a meta-analysis, showed a progressively greater risk with longer use, and a greater risk for estrogen receptor-positive cancers.[50]

Implications

In this population-based study, we did not observe an association between premenopausal bilateral oophorectomy and risk of non-gynecological cancers, including breast cancer, among women at average risk of ovarian cancer. Thus, for the general population of women at average risk of ovarian cancer, these results suggest that the ovaries should not be removed prior to spontaneous menopause to reduce the risk of non-gynecological cancers including breast cancer. Considering the additional increased risk for long-term morbidity and mortality not related to cancer after premenopausal bilateral oophorectomy, the benefits of undergoing the surgery may not outweigh possible risk for women in whom the absolute risk for developing ovarian cancer or breast cancer is low.[19–22]

Strengths and limitations

This study has several strengths. First, the bilateral oophorectomy cohort and the referent cohort were representative of a well-defined population with up to 30 years of follow-up.[23] Second, details about the bilateral oophorectomy, baseline characteristics, estrogen therapy, and cancer were confirmed through abstraction of medical records from a medical records-linkage system, thus limiting recall bias.[23]

However, limitations also warrant consideration. First, participants were predominantly white, and all women resided in Olmsted County, Minnesota. Thus, results may not be generalizable to other populations with different racial, ethnic, or socioeconomic characteristics.[25] Second, the observational nature of our study limits causal inference. For example, women with multiple clinically recognized chronic conditions may be more likely to undergo a bilateral oophorectomy. However, we performed a sensitivity analysis that excluded all women with a documented history of chronic conditions before the index date, and the results did not change noticeably. Third, the majority of women in our study were not tested for *BRCA1* or *BRCA2* variants. In the study time frame (1988–2007), genetic testing was seldom performed even in women judged by the gynecologist to be at high genetic risk (strong family history). Fourth, the study had limited power to study specific types of cancer such as gastrointestinal and lung cancer. On the other hand, the sample size was dictated by the geographically-defined population and by the study time frame rather than by a power calculation conducted during the design of the study. Fifth, the median length of follow-up was 18.0 years in women who underwent bilateral oophorectomy, and 17.8 years in the referent cohort. Therefore, women in our study were still relatively young at the end of follow-up (median age of 62 years). It is possible that we would observe additional significant associations if the women were followed for a longer time. Therefore, we remain cautious in our interpretations until these findings can be replicated elsewhere. We also plan to continue to follow our cohorts. Sixth, the two cohorts were balanced for several possible confounders present at the index date using inverse probability weights. In particular, balancing for 17 chronic conditions present at baseline should have balanced indirectly also for several other possible variables that were not directly measured. The results did not vary using traditional multivariable adjustments. However, some residual confounding is possible. Finally, surgical and medical practices may have changed over the 20-year study time frame. However, analyses stratified in two decades did not show significant differences (data not shown).

Conclusion

This large cohort study showed that the risk of non-gynecologic cancers, including breast cancer, was similar for women with premenopausal bilateral oophorectomy and referent women. Thus, bilateral oophorectomy should not be considered for the prevention of non-gynecological cancers, including breast cancer, in the general population. These findings, in conjunction with the results of other studies showing the increased risk of multiple chronic conditions after premenopausal bilateral oophorectomy, may help women to better evaluate the risk-to-benefit ratio of undergoing bilateral oophorectomy before natural menopause for the prevention of ovarian and other cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AJOG at a Glance

Why was this study conducted?

- Some studies suggest that premenopausal bilateral oophorectomy may be associated with an increased risk of lung or colon cancer and a decreased risk of breast cancer. However, evidence in the general population is lacking.

What are the key findings

- In this population-based cohort study, women who underwent premenopausal bilateral oophorectomy had a reduced risk of gynecologic cancers, but not of other types of cancer including breast cancer.

What does this study add to what is already known?

- Premenopausal bilateral oophorectomy among women at average risk of ovarian cancer (ie, without a strong family history or a high risk genetic variant) does not reduce the risk of non-gynecological cancers including breast cancer and should not be utilized for the prevention of these cancers.

Condensation

Premenopausal bilateral oophorectomy in the general population does not reduce the risk of non-gynecologic cancers including breast cancer and should not be utilized for the prevention of these cancers.

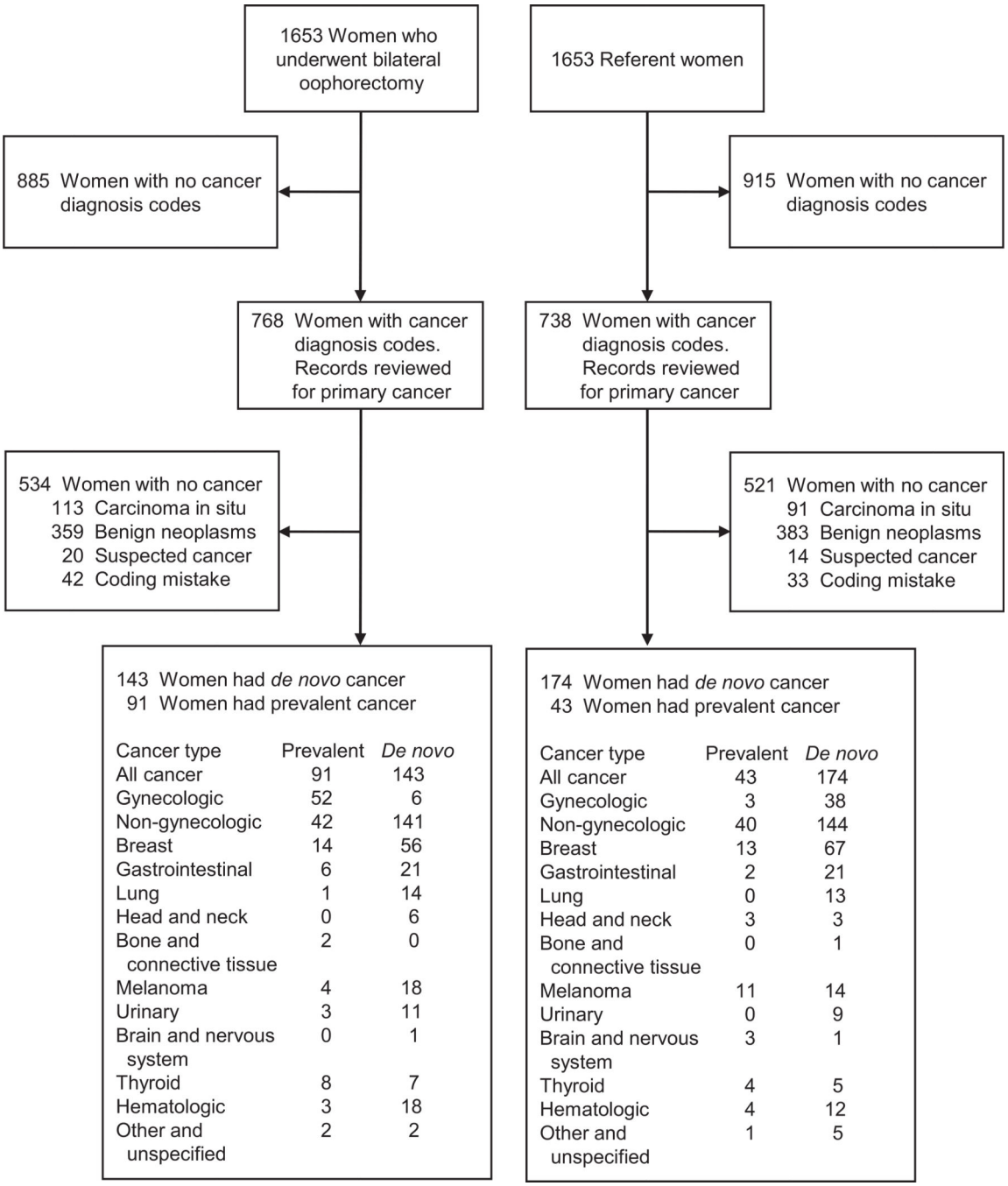

FIGURE 1.

Diagnostic codes for cancer were obtained electronically from the diagnostic indexes of the Rochester Epidemiology Project for all women in the bilateral oophorectomy and the referent cohorts. Medical record review was used to confirm cancer status, diagnosis date, and type of cancer for all women who received at least one diagnostic code for cancer. Women with cancer diagnosed before the index date (date of oophorectomy) or within 6 months after the index date were considered to have prevalent cancer and were excluded. Women with cancer diagnosed more than 6 months after the index date were considered to

have *de novo* cancer. Some women (18 who underwent bilateral oophorectomy, 15 referent women) had two or more types of primary cancer. Gynecologic cancer includes cancer of the ovaries, fallopian tubes, uterus, cervix, vagina, and vulva. Non-gynecologic cancer includes all remaining types of cancer.

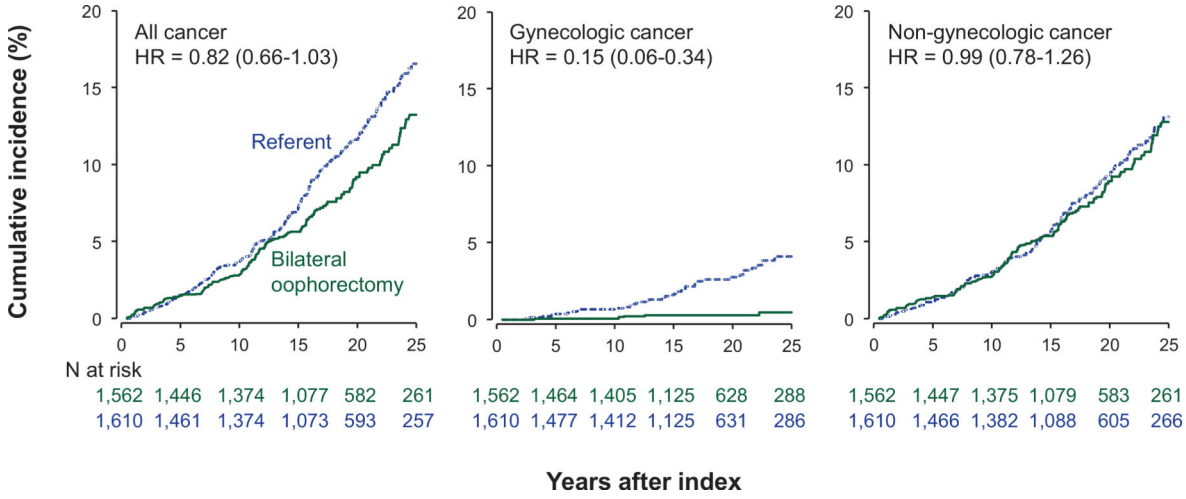

FIGURE 2.

Cumulative incidence curves for cancer overall, gynecologic cancer, and non-gynecologic cancer in women who underwent bilateral oophorectomy compared with referent women. The curves were adjusted using inverse probability weights derived from a logistic regression model including 17 chronic conditions present at baseline (list provided in text), years of education, quartiles of household income, race, body mass index, cigarette smoking, and age and calendar year at the index date.

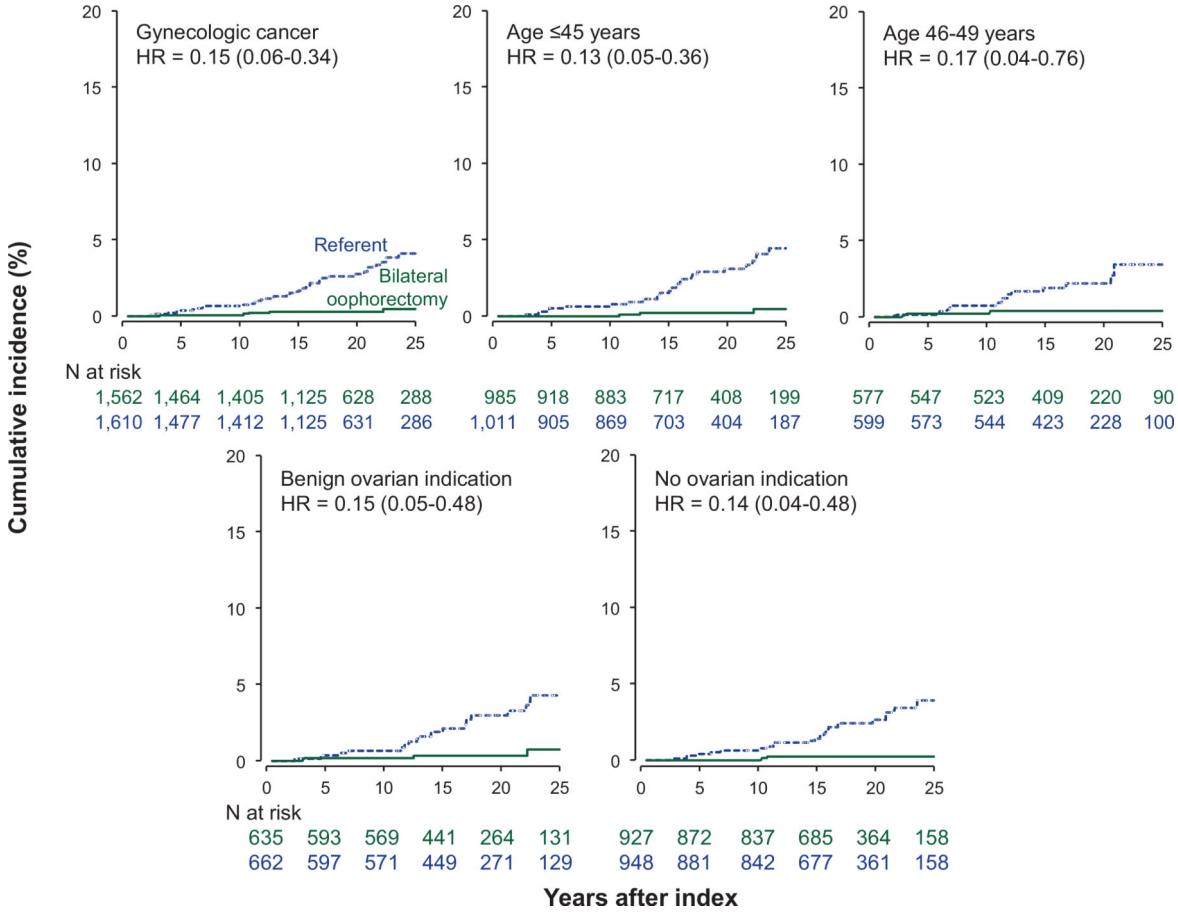

FIGURE 3.

Cumulative incidence curves for gynecologic cancer in women who underwent bilateral oophorectomy compared with referent women, overall and in strata by age at the index date and indication for the oophorectomy. The curves were adjusted using inverse probability weights derived from a logistic regression model including 17 chronic conditions present at baseline (list provided in text), years of education, quartiles of household income, race, body mass index, cigarette smoking, and age and calendar year at the index date.

TABLE 1

Baseline sociodemographic and clinical characteristics of women who underwent bilateral oophorectomy and referent women, excluding women with cancer of any type before the index date or within 6 months of follow-up

Characteristics	Bilateral oophorectomy (n=1562)		Referent women (n=1610)		
	N	%	N	%	*P* value[a]
Age at index date (years)					.88
≤45	985	63.1	1011	62.8	
46–49	577	36.9	599	37.2	
Index year					.72
1988–1997	679	43.5	710	44.1	
1998–2007	883	56.5	900	55.9	
Race					<.001
White	1523	97.5	1528	94.9	
Black	17	1.1	29	1.8	
Asian	16	1.0	48	3.0	
Other	6	0.4	5	0.3	
Hispanic ethnicity	17	1.1	23	1.4	.39
Years of education					.01
≤12	499	32.0	461	29.3	
13–16	846	54.3	840	53.3	
>16	214	13.7	275	17.4	
Missing[b]	3	--	34	--	
Income quartiles					.36
<$42,000	394	25.3	397	24.7	
$42,000–56,999	417	26.8	405	25.2	
$57,000–71,999	393	25.3	400	24.9	
≥$72,000	352	22.6	406	25.2	
Missing[b]	6	--	2	--	
Body mass index (kg/m^2)					<.001
<25.0	564	36.1	679	42.8	
25.0–29.9	460	29.4	479	30.2	
≥30.0	538	34.4	430	27.1	
Missing[b]	0	--	22	--	
Smoking					.13
Never	848	54.3	927	57.6	
Former	371	23.8	369	22.9	
Current	343	22.0	314	19.5	
Number of chronic conditions[c]					<.001
0	650	41.6	908	56.4	

Characteristics	Bilateral oophorectomy (n=1562)		Referent women (n=1610)		
	N	%	N	%	*P* value[a]
1	402	25.7	374	23.2	
2	245	15.7	171	10.6	
≥3	265	17.0	157	9.8	
Hysterectomy status					<.001
None	21	1.3	1453	90.2	
Before	149	9.5	157	9.8	
Concurrent	1392	89.1	0	0.0	
Prior unilateral oophorectomy	139	8.9	51	3.2	<.001
Indication for oophorectomy[d]					--
Benign ovarian condition	635	40.7	--	--	
No ovarian condition	927	59.3	--	--	

[a] The *P* values were calculated using chi-squared tests.

[b] In the logistic regression models used to derive the inverse probability weights, women with unknown education were assigned to the ≤12 years group, women with unknown household income were assigned to the $42,000–56,999 quartile, and women with unknown body mass index were assigned to the <30 kg/m^2 group.

[c] A total of 17 chronic conditions defined by the US Department of Health and Human Services (DHHS) were considered, including depression, anxiety, substance abuse disorders, dementia, schizophrenia or psychosis, hyperlipidemia, hypertension, diabetes mellitus, cardiac arrhythmias, coronary artery disease, stroke, congestive heart failure, arthritis, asthma, chronic obstructive pulmonary disease, osteoporosis, and chronic kidney disease. Cancer was excluded from the DHHS list because it was an exclusion criterion for our study.

[d] The indication was listed by the gynecologist in the medical record at the time of oophorectomy.

TABLE 2

De novo cancer outcomes after bilateral oophorectomy, overall and in strata by age at oophorectomy, estrogen therapy, and surgical indication; excluding women with cancer of any type before the index date or within 6 months of follow-up

Cancer type and strata	Bilateral oophorectomy				Referent women				Unweighted models[a]		Weighted models[b]	
	N at risk	Person-years	N of events	Absolute risk[c] (95% CI)	N at risk	Person-years	N of events	Absolute risk[c] (95% CI)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
All cancer	1562	26,786	143	13.2% (10.9–16.0)	1610	26,928	174	16.8% (14.3–19.8)	0.84 (0.67–1.04)	.11	0.82 (0.66–1.03)	.09
Age ≤45 y	985	17,173	75	11.4% (8.7–14.8)	1011	16,758	102	15.3% (12.3–18.9)	0.73 (0.54–0.97)	.03	0.69 (0.51–0.94)	.02
Age <40 y	332	5961	18	5.6% (2.9–10.5)	340	5544	27	11.5% (7.2–18.2)	0.62 (0.35–1.12)	.11	0.57 (0.31–1.06)	.07
Age 40–45 y	653	11,212	57	14.2% (10.4–19.2)	671	11,214	75	17.2% (13.3–22.0)	0.76 (0.54–1.07)	.12	0.74 (0.52–1.04)	.08
ET >49[d]	507	6246	46	22.4% (15.2–32.4)	446	5617	45	18.0% (13.1–24.5)	0.92 (0.61–1.39)	.71	0.87 (0.57–1.32)	.52
No ET or ≤49	322	3057	16	25.5% (8.9–60.4)	281	2820	17	26.2% (11.9–51.7)	0.86 (0.45–1.66)	.65	0.78 (0.39–1.55)	.47
Age 46–49 y	577	9614	68	17.1% (13.0–22.4)	599	10,170	72	19.7% (15.3–25.0)	1.00 (0.72–1.38)	.98	1.03 (0.74–1.45)	.84
ET >49[d]	393	6222	47	21.4% (15.0–30.1)	373	6087	49	20.1% (14.7–27.2)	0.94 (0.63–1.40)	.75	0.96 (0.64–1.45)	.86
No ET or ≤49	107	1396	6	5.3% (2.1–13.0)	127	1729	12	14.3% (7.6–25.9)	0.61 (0.23–1.61)	.32	0.59 (0.22–1.60)	.30
Benign indication[e]	635	10,987	53	12.1% (8.9–16.3)	662	11,040	72	15.5% (12.1–19.8)	0.76 (0.54–1.08)	.13	0.71 (0.49–1.01)	.06
No indication[f]	927	15,800	90	14.2% (11.0–18.2)	948	15,888	102	18.4% (14.8–22.7)	0.89 (0.67–1.18)	.42	0.89 (0.67–1.19)	.43
Gynecologic cancer[g]	1562	27,718	6	0.5% (0.2–1.3)	1610	27,865	37	4.1% (2.9–5.8)	0.17 (0.07–0.38)	<.001	0.15 (0.06–0.34)	<.001
Age ≤45 y	985	17,604	4	0.5% (0.1–2.0)	1011	17,309	25	4.5% (2.9–6.8)	0.16 (0.06–0.45)	<.001	0.13 (0.05–0.36)	<.001
Age <40 y	332	6060	2	0.8% (0.1–5.6)	340	5685	7	5.4% (2.5–11.8)	0.28 (0.07–1.14)	.08	0.16 (0.05–0.54)	.003
Age 40–45 y	653	11,544	2	0.1% (0.0–1.3)	671	11,624	18	3.9% (2.4–6.4)	0.11 (0.03–0.49)	.003	0.10 (0.02–0.42)	.002
ET >49[d]	512	6540	2	2.4% (0.3–16.8)	462	5963	14	8.6% (2.8–24.8)	0.13 (0.03–0.58)	.008	0.11 (0.03–0.50)	.004

Cancer type and strata	Bilateral oophorectomy				Referent women				Unweighted models[a]		Weighted models[b]	
	N at risk	Person-years	N of events	Absolute risk[c] (95% CI)	N at risk	Person-years	N of events	Absolute risk[c] (95% CI)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
No ET or ≤49	327	3159	1	0.3% (0.0–3.4)	285	2905	5	3.4% (1.3–8.5)	0.19 (0.02–1.60)	.13	0.10 (0.01–0.92)	.04
Age 46–49 y	577	10,114	2	0.4% (0.1–1.6)	599	10,556	12	3.4% (1.9–6.1)	0.17 (0.04–0.78)	.02	0.17 (0.04–0.76)	.02
ET >49[d]	394	6562	1	0.3% (0.0–2.1)	373	6374	8	3.6% (1.7–7.5)	0.12 (0.02–0.98)	.047	0.11 (0.01–0.91)	.04
No ET or ≤49	114	1510	1	0.8% (0.1–7.5)	127	1775	2	1.9% (0.5–7.3)	0.55 (0.05–6.09)	.63	0.43 (0.04–4.80)	.49
Benign indication[e]	635	11,279	3	0.7% (0.2–3.0)	662	11,396	18	4.3% (2.6–7.1)	0.17 (0.05–0.56)	.003	0.15 (0.05–0.48)	.002
No indication[f]	927	16,439	3	0.2% (0.1–1.0)	948	16,469	19	3.9% (2.4–6.3)	0.16 (0.05–0.54)	.003	0.14 (0.04–0.48)	.002
Non-gynecologic cancer[h]	1562	26,815	137	12.8% (10.5–15.5)	1610	27,184	143	13.4% (11.1–16.1)	0.99 (0.78–1.24)	.92	0.99 (0.78–1.26)	.95
Age ≤45 y	985	17,189	71	10.9% (8.3–14.3)	1011	16,918	82	11.6% (8.9–14.9)	0.87 (0.63–1.19)	.38	0.85 (0.61–1.17)	.32
Age <40 y	332	5974	16	4.8% (2.4–9.3)	340	5584	21	6.2% (3.5–10.8)	0.71 (0.37–1.36)	.30	0.72 (0.37–1.43)	.35
Age 40–45 y	653	11,215	55	14.1% (10.3–19.1)	671	11,334	61	14.3% (10.6–19.1)	0.92 (0.64–1.32)	.65	0.90 (0.62–1.30)	.58
ET >49[d]	507	6249	44	20.3% (13.9–29.0)	447	5678	34	14.4% (9.8–20.8)	1.19 (0.76–1.85)	.45	1.15 (0.73–1.82)	.55
No ET or ≤49	323	3067	15	25.3% (8.8–60.4)	283	2875	14	37.4% (15.8–72.1)	1.02 (0.51–2.05)	.96	0.87 (0.41–1.83)	.71
Age 46–49 y	577	9626	66	16.8% (12.6–22.1)	599	10,266	61	16.9% (12.8–22.1)	1.15 (0.82–1.63)	.42	1.22 (0.86–1.73)	.27
ET >49[d]	393	6222	46	21.2% (14.8–29.9)	373	6149	41	16.7% (11.7–23.5)	1.11 (0.73–1.69)	.63	1.16 (0.75–1.78)	.51
No ET or ≤49	107	1409	5	4.5% (1.6–12.1)	127	1746	11	15.5% (8.0–28.9)	0.57 (0.20–1.62)	.29	0.58 (0.20–1.70)	.32
Benign indication[e]	635	11,013	50	11.4% (8.3–15.5)	662	11,171	58	12.1% (9.0–16.2)	0.91 (0.63–1.32)	.62	0.85 (0.58–1.25)	.42
No indication[f]	927	15,802	87	14.0% (10.8–18.0)	948	16,012	85	14.9% (11.6–18.9)	1.04 (0.78–1.41)	.78	1.07 (0.79–1.45)	.66
Breast cancer	1562	27,282	54	5.0% (3.6–6.8)	1610	27,673	67	6.9% (5.2–9.1)	0.83 (0.58–1.18)	.30	0.87 (0.61–1.24)	.44

Cancer type and strata	Bilateral oophorectomy				Referent women				Unweighted models[a]		Weighted models[b]	
	N at risk	Person-years	N of events	Absolute risk[c] (95% CI)	N at risk	Person-years	N of events	Absolute risk[c] (95% CI)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age ≤45 y	985	17,368	32	5.3% (3.5–7.8)	1011	17,217	37	5.3% (3.7–7.7)	0.87 (0.55–1.39)	.57	0.86 (0.54–1.39)	.54
Age <40 y	332	6015	6	2.7% (1.0–7.2)	340	5679	10	4.0% (1.9–8.4)	0.58 (0.21–1.58)	.29	0.65 (0.23–1.84)	.42
Age 40–45 y	653	11,353	26	6.5% (4.1–10.2)	671	11,538	27	6.0% (3.8–9.3)	0.99 (0.58–1.70)	.96	0.95 (0.55–1.63)	.84
ET >49[d]	512	6399	20	10.3% (5.5–19.0)	454	5865	13	5.0% (2.5–10.0)	1.43 (0.71–2.88)	.32	1.48 (0.71–3.05)	.29
No ET or ≤49	324	3082	7	6.1% (2.7–13.4)	286	2919	8	16.5% (6.4–38.6)	0.84 (0.33–2.16)	.72	0.71 (0.26–1.96)	.51
Age 46–49 y	577	9914	22	4.3% (2.7–7.0)	599	10,455	30	10.2% (6.8–15.2)	0.77 (0.45–1.33)	.35	0.83 (0.47–1.45)	.50
ET >49[d]	394	6450	15	9.1% (4.5–18.0)	373	6302	19	9.6% (5.6–16.0)	0.77 (0.39–1.50)	.44	0.79 (0.40–1.57)	.51
No ET or ≤49	108	1432	0	0.0% (0.0–0.0)	127	1752	8	12.0% (5.2–26.4)	--	--	--	--
Benign indication[e]	635	11,141	22	6.0% (3.8–9.6)	662	11,345	31	6.8% (4.6–10.0)	0.75 (0.44–1.29)	.30	0.76 (0.44–1.31)	.32
No indication[f]	927	16,141	32	4.3% (2.8–6.6)	948	16,327	36	7.4% (5.0–10.8)	0.90 (0.56–1.45)	.68	0.95 (0.59–1.55)	.85
Gastrointestinal cancer[i]	1562	27,667	19	2.4% (1.4–4.0)	1610	28,031	20	1.7% (1.0–2.9)	0.98 (0.52–1.83)	.94	1.07 (0.56–2.03)	.83
Age ≤45 y	985	17,590	11	2.3% (1.2–4.5)	1011	17,416	15	2.1% (1.1–4.0)	0.74 (0.34–1.61)	.44	0.78 (0.35–1.72)	.53
Age <40 y	332	6073	1	0.0% (0.0–0.0)	340	5723	3	0.3% (0.0–3.2)	0.30 (0.03–2.54)	.27	0.35 (0.04–3.21)	.35
Age 40–45 y	653	11,517	10	3.6% (1.8–7.1)	671	11,693	12	3.0% (1.5–5.9)	0.85 (0.37–1.97)	.71	0.87 (0.37–2.03)	.75
Age 46–49 y	577	10,077	8	2.5% (1.1–5.5)	599	10,615	5	1.0% (0.4–2.6)	1.67 (0.55–5.10)	.37	2.07 (0.65–6.55)	.22
Lung cancer	1562	27,705	12	1.0% (0.5–1.9)	1610	28,105	13	1.1% (0.6–1.9)	0.96 (0.45–2.03)	.91	0.84 (0.39–1.82)	.65
Age ≤45 y	985	17,608	4	0.3% (0.1–1.0)	1011	17,463	5	0.7% (0.3–1.8)	0.82 (0.22–3.06)	.76	0.57 (0.15–2.21)	.42
Age <40 y	332	6072	1	0.0% (0.0–0.0)	340	5726	1	0.0% (0.0–0.0)	0.91 (0.06–13.9)	.95	0.92 (0.06–14.2)	.95

Cancer type and strata	Bilateral oophorectomy				Referent women				Unweighted models[a]		Weighted models[b]	
	N at risk	Person-years	N of events	Absolute risk[c] (95% CI)	N at risk	Person-years	N of events	Absolute risk[c] (95% CI)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age 40–45 y	653	11,535	3	0.4% (0.1–1.5)	671	11,738	4	0.8% (0.3–2.3)	0.77 (0.17–3.47)	.74	0.60 (0.13–2.73)	.51
Age 46–49 y	577	10,097	8	2.4% (1.1–5.1)	599	10,642	8	1.6% (0.8–3.5)	1.05 (0.42–2.63)	.91	1.14 (0.45–2.89)	.78

CI, confidence interval; *ET*, estrogen therapy.

[a] Hazard ratios were calculated using Cox proportional hazards models with age as the time scale. Follow-up for these analyses was started at 6 months after index date.

[b] Hazard ratios were calculated using Cox proportional hazards models with age as the time scale and adjusted using inverse probability weights derived from a logistic regression model including 17 chronic conditions present at baseline, years of education (≤12, 13–16, >16), quartiles of household income (<$42,000, $42,000–56,999, $57,000–71,999, ≥$72,000), race (white vs non-white), body mass index (<30 vs ≥30 kg/m^2), cigarette smoking (current or former vs never), age at index date (continuous), and calendar year at index date (continuous). These adjustments were done separately in each stratum to maximize the balance at index date. Follow-up for these analyses was started at 6 months after index date. No significant interactions by age (≤45 y vs 46–49 y), estrogen therapy, or surgical indication were found.

[c] Absolute cumulative risk at 25 years after bilateral oophorectomy (or index) calculated using the Kaplan-Meier method. The estimates were adjusted using inverse probability weights (see details in footnote b). These adjustments were done separately in each stratum to maximize the balance at index date.

[d] Women who were taking systemic ET (only oral or transdermal) on their 50^{th} birth date, after bilateral oophorectomy. Women who died or were lost to follow-up prior to their 50^{th} birth date, had reached age 50 years within 6 months after index date, or had not reached age 50 years as of December 31, 2018 were not included in this analysis. Follow-up for these analyses was started at age 50 years.

[e] The benign condition (eg, benign tumors, cysts, endometriomas) was listed by the gynecologist as the surgical indication in the medical record at the time of oophorectomy, but may not have been the sole indication for the surgery.

[f] Women without a benign ovarian condition. Historically, the terms “prophylactic”, “elective”, or “incidental” oophorectomy we re used; however, we prefer to avoid these terms.

[g] Includes cancer of the ovaries, fallopian tubes, uterus, cervix, vagina, and vulva. Six women had gynecologic cancer after bilateral oophorectomy (2 ovaries, 1 uterus, 1 vagina, and 2 vulva), and 37 referent women had gynecologic cancer after index date (7 ovaries, 26 uterus, 2 cervix, 1 vulva, and 1 unspecified uterine adnexa).

[h] Includes all types of cancer other than cancer of the ovaries, fallopian tubes, uterus, cervix, vagina, and vulva.

[i] Includes cancer of the esophagus, stomach, colon, rectum, liver, pancreas, peritoneum, duodenum, etc. There were 19 women who developed gastrointestinal cancer after bilateral oophorectomy (1 esophagus, 4 stomach, 3 colon, 1 rectum, 4 liver, 3 pancreas, 1 peritoneum, 1 gallbladder, 1 bile duct) and 20 referent women who developed gastrointestinal cancer after index date (10 colon, 4 rectum, 1 liver, 3 pancreas, 1 peritoneum, 1 bile duct).