GYNECOLOGY

Excess morbidity and mortality associated with underuse of estrogen replacement therapy in premenopausal women who undergo surgical menopause

Jennifer S. Ferris, PhD; Yukio Suzuki, MD, PhD; Matthew T. Prest, MS; Ling Chen, MD; Elena B. Elkin, PhD; Chin Hur, MD; Dawn L. Hershman, MD; Jason D. Wright, MD

BACKGROUND: Contrary to clinical guidelines, there has been a decrease over time in estrogen therapy use in premenopausal women undergoing bilateral oophorectomy for benign indications.

OBJECTIVE: This study aimed to estimate the excess morbidity and mortality associated with current patterns of estrogen therapy use in women who undergo bilateral oophorectomy with hysterectomy for benign indications.

STUDY DESIGN: We developed 2 Bayesian sampling Markov state-transition models to estimate the excess disease incidence (incidence model) and mortality (mortality model). The starting cohort for both models were women who had undergone bilateral oophorectomy with hysterectomy for benign indications at the age of 45 to 49 years. The models tracked outcomes in 5-year intervals for 25 years. The incidence model estimated excess incidence of breast cancer, lung cancer, colorectal cancer, coronary heart disease, and stroke, whereas the mortality model estimated excess mortality due to breast cancer, lung cancer, coronary heart disease, and all-other-cause mortality. The models compared current rates of estrogen therapy use with optimal (100%) use and calculated the mean difference in each simulated outcome to determine excess disease incidence and death.

RESULTS: By 25 years after bilateral oophorectomy with hysterectomy, there were an estimated 94 (95% confidence interval, −158 to −23) fewer colorectal cancer cases, 658 (95% confidence interval, 339−1025) more coronary heart disease cases, and 881 (95% confidence interval, 402−1483) more stroke cases. By 25 years after bilateral oophorectomy with hysterectomy, there were an estimated 189 (95% confidence interval, 59−387) more breast cancer deaths, 380 (95% confidence interval, 114−792) more coronary heart disease deaths, and 759 (95% confidence interval, 307−1527) more all-other-cause deaths. In sensitivity analyses where we defined estrogen therapy use as a duration of >2 years of use, these differences increased >2-fold.

CONCLUSION: Underuse of estrogen therapy in premenopausal women who undergo oophorectomy is associated with substantial excess morbidity and mortality.

Key words: Bayesian, breast cancer, colorectal cancer, coronary heart disease, death, disease, lung cancer, Markov model, oophorectomy, stroke

Introduction

In the United States, it is estimated that >90,000 women per year undergo elective bilateral salpingo-oophorectomy (BSO) for benign indications.[1,2] More than half of these women are aged <50 years and will experience surgical menopause.[1] Although the removal of both ovaries reduces the risk of ovarian cancer, the abrupt deprivation of endogenous estrogen caused by bilateral oophorectomy (BO) in premenopausal women increases the risk of adverse events, including cardiovascular disease, metabolic disorders, cancer, and death.[3−7] A recent modeling study by Rush et al[8] found that in women aged <50 years, having BSO with hysterectomy (HYST) without the use of estrogen therapy (ET) was associated with worse survival compared with HYST alone.

To reduce the morbidity and mortality associated with surgical menopause, clinical guidelines recommend the use of ET immediately following surgery until at least the average age of natural menopause (ie, 52 years).[9−11] However, despite these guidelines, previous studies have shown that only approximately 50% of eligible women receive ET, and among those who do receive it, treatment duration is often short and does not last until the average age of menopause.[12−14] Specifically, using nationwide prescription data in the United States, the median duration of ET for women who had BO for benign indications was only 5.3 months.[12] These data suggest that most premenopausal women who have BO for benign indications are at risk of adverse events due to suboptimal use of ET.

Although research shows that a substantial number of women with surgical menopause are not receiving sufficient ET, the population-level health impact of these practice patterns on long-term health is unknown. Therefore, we developed Markov models to estimate the population-level number of adverse events associated with current patterns of ET use in premenopausal women who have BO with HYST (BO-HYST) for benign indications.

Materials and Methods

Model overview

We converted population-level data for age-specific incidence of breast cancer, lung cancer, colorectal cancer, coronary heart disease (CHD), and stroke (Supplemental Table 1), and cause-specific mortality from breast cancer,

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AJOG at a Glance

Why was this study conducted?

We conducted this study to estimate excess disease and death associated with current estrogen therapy trends in women undergoing surgical menopause for benign indications.

Key findings

Compared with optimal 100% use, current estrogen therapy use was associated with more coronary heart disease and stroke cases, fewer colorectal cancer cases, and more breast cancer, coronary heart disease, and all-other-cause death.

What does this add to what is known?

Research has shown that a lack of estrogen therapy use in premenopausal women who experience surgical menopause due to oophorectomy for benign indications is associated with negative outcomes. Further, research has shown a declining trend in estrogen therapy use in this group of women over time. Using this information, our study estimated the real-world impact of the documented underutilization of estrogen therapy in these women in terms of excess morbidity and mortality.

lung cancer, CHD, and all other causes to 5-year transition probabilities (Supplemental Table 2). From literature, we extracted 2 sets of data on the hazard ratios (HRs) and accompanying confidence intervals (CIs) of the same outcomes (Tables 1[15–18] and 2[4,19]). The first set of HRs compared the risks for each outcome between women who had a HYST and those who did not. The second set of HRs compared the risks for each outcome between women who had a BO-HYST and those who only had a HYST. The second set of HRs were further stratified according to whether ET was used.

Using these data, we created 2 Bayesian sampling Markov state-transition models: the incidence model (Figure 1, A) and the mortality model (Figure 1, B), based on a similar model developed by Rush et al.[8] These models simulated a cohort of healthy women having BO-HYST at the age of 45 to 49 years, and tracked health outcomes from the aforementioned conditions, which are potentially associated with estrogen deprivation, in 5-year time intervals up to 25 years after surgery. The output for both models was the excess numbers of each outcome that occurred when ET was not used (Figures 2, A and 3, A). To account for the uncertainty in the HR estimates, we used a technique known as Bayesian sampling. This involved taking 10,000 iterations of both models, each using values for the HRs that were randomly sampled from within the CIs. From the results of all iterations, we constructed CIs for the excess numbers of each outcome at 5-year intervals for 25 years of follow-up to reflect the uncertainty of our inputs. Additional uncertainty due to estimates in ET use and BO rates were explored in a series of sensitivity analyses (Tables 3 and 4).

Both models were constructed using R, version 4.2.2 (R Core Team, Vienna, Austria), only permitting age-dependent transitions from healthy to each outcome state subject to background mortality. Bayesian sampling for HRs was normal and independent. Outcome CIs were constructed nonparametrically by selecting the iteration results corresponding to the 2.5 and 97.5 percentiles of the outcome distributions.

Starting cohort

To determine our starting cohort for both models, we first estimated the base population using the Centers for Disease Control and Prevention WONDER[1–4] data.[20] The base population of women aged 45 to 49 years was 10,312,396. We then determined the BO rate using data from the Mayo Clinic Cohort Study of Oophorectomy and Aging. Erickson et al[21] published oophorectomy rates in women aged 18 to 49 years (most women who underwent BO [89.1%] had concurrent HYST). To represent more recent oophorectomy trends and maintain consistency with our model's age range, we calculated a weighted average of the oophorectomy rates for women aged 45 to 49 years for the years 2010–2014 and 2015–2018, which was 253.4 per 100,000. We then created our starting cohort of healthy women aged 45 to 49 years undergoing BO-HYST by multiplying the base population by the BO rate (n=26,134).

Exposure

Our group previously published findings using IBM Watson Health MarketScan Research Databases[22] on the percentage of ET use in premenopausal women who have had BO for benign indications, which was 64.5%.[12] From our starting cohort, we determined the number of women who received ET (n=16,856) by multiplying 64.5% by the cohort size. Sensitivity analyses described below address variable rates and durations of ET use.

Outcomes

We focused on diseases associated with abrupt estrogen deprivation due to surgical menopause,[23] and that were included in the Rush model.[8] Specifically, we examined breast cancer, colorectal cancer, lung cancer, CHD, and stroke. We estimated the 2019 female population level incidence rates of breast, lung, and colorectal cancer using SEER (Surveillance, Epidemiology, and End Results) 17 and the ICD-10 (International Classification of Diseases, Tenth Revision) codes C50, C34, and C18, respectively.[24] Because there are limited US population-level data on the incidence of CHD and stroke in this cohort, we used 2017 data from the British Heart Foundation using ICD-10 codes I60-I69 and I20-I25, respectively.[25] The female population-level mortality rates for each disease and for all-other-cause mortality were determined using the WONDER[1–4] data.[20] Both population incidence and mortality rates were estimated in 5-year age groups from 45 to 49 years through 70 to 74 years,

TABLE 1
Inputs for select outcomes in women aged <50 years with bilateral oophorectomy with hysterectomy compared with hysterectomy only, stratified by estrogen use, and with hysterectomy only compared with no surgery

	Bilateral oophorectomy with hysterectomy vs hysterectomy only				Hysterectomy only vs no surgery	
	No estrogen		Estrogen			
Condition	HR (95% CI)	Reference	HR (95% CI)	Reference	HR (95% CI)	Reference
Coronary heart disease	1.98 (1.18–3.32)	Parker et al,[15] 2009	1.26 (1.04–1.54)	Parker et al,[15] 2009	1.34 (1.07–1.68)	Laughlin-Tommaso et al,[16] 2018
Stroke	2.19 (1.16–4.14)	Parker et al,[15] 2009	1.19 (0.96–1.49)	Parker et al,[15] 2009	1.22 (0.88–1.67)	Laughlin-Tommaso et al,[16] 2018
Breast cancer	0.66 (0.43–1.03)	Parker et al,[15] 2009	0.62 (0.53–0.74)	Parker et al,[15] 2009	0.80 (0.69–0.94)	Gaudet et al,[17] 2014
Lung cancer	2.36 (0.78–7.17)	Parker et al,[15] 2009	1.21 (0.91–1.61)	Parker et al,[15] 2009	0.80 (0.53–1.19)	Gaudet et al,[17] 2014
Colorectal cancer	0.94 (0.45–1.96)	Jacoby et al,[18] 2011	1.36 (0.98–1.89)	Parker et al,[15] 2009	0.84 (0.62–1.15)	Gaudet et al,[17] 2014

HRs and 95% CIs from the literature for incidence.

CI, confidence interval; *HR*, hazard ratio.

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when available. For data provided in larger age categories, we used the same estimate for each 5-year age group within the larger age category (Supplemental Tables 1 and 2).

Literature review

To determine our model inputs, we conducted a comprehensive literature review. We identified studies comparing HYST and no surgery, and BO-HYST and HYST, stratified by ET use, in women undergoing BO for benign indications, and incidence and mortality rates for the diseases of interest. Two independent reviewers conducted the search in PubMed on February 5, 2023. The search was conducted using ("hysterectomy [MeSH]" or "salpingo-oophorectomy [MeSH]") and ("incidence" or "mortality") and ("cardiovascular diseases [MeSH]" or "stroke [MeSH]" or "breast neoplasms [MeSH]" or "lung neoplasms [MeSH]" or "colorectal neoplasms [MeSH]" or "coronary heart disease" or "cancer"). In addition to the strategic search, we performed manual searches through PubMed and other online public resources, and through review of manuscript citations.[8] When we identified >1 relevant input in the literature, we gave priority to articles that reported HRs, were US-based cohort studies, and had larger sample sizes.

For HYST compared with no surgery, we included data for women aged 36 to 50 years from an Olmsted County cohort study to estimate the incidence of CHD and stroke,[16] and data for women aged <45 years from the Cancer Prevention Study-II Nutrition Cohort study for the incidence of breast, lung, and colorectal cancer.[17] For BO-HYST compared with HYST, we included data for women aged <45 years who did not receive ET from the Nurses' Health Study[15] to estimate the incidence of breast cancer, lung cancer, CHD, and stroke, and for women aged 40 to 49 years from the Women's Health Initiative Observational Study[18] to estimate the incidence of colorectal

TABLE 2
Inputs for mortality of select outcomes in women aged <50 years with bilateral oophorectomy with hysterectomy compared with hysterectomy only, stratified by estrogen use, and with hysterectomy only compared with no surgery

	Bilateral oophorectomy with hysterectomy vs hysterectomy only				Hysterectomy only vs no surgery	
	No estrogen		Estrogen			
Condition	HR (95% CI)	Reference	HR (95% CI)	Reference	HR (95% CI)	Reference
Coronary heart disease	2.35 (0.76–7.26)	Parker et al,[4] 2013	0.91 (0.63–1.31)	Parker et al,[4] 2013	1.11 (0.01–1.22)	Gierach et al,[19] 2014
Breast cancer	2.41 (0.75–7.73)	Parker et al,[4] 2013	0.78 (0.49–1.24)	Parker et al,[4] 2013	0.96 (0.78–1.19)	Gierach et al,[19] 2014
Lung cancer	1.44 (0.17–12.2)	Parker et al,[4] 2013	0.80 (0.58–1.12)	Parker et al,[4] 2013	0.92 (0.76–1.11)	Gierach et al,[19] 2014

CI, confidence interval; *HR*, hazard ratio.

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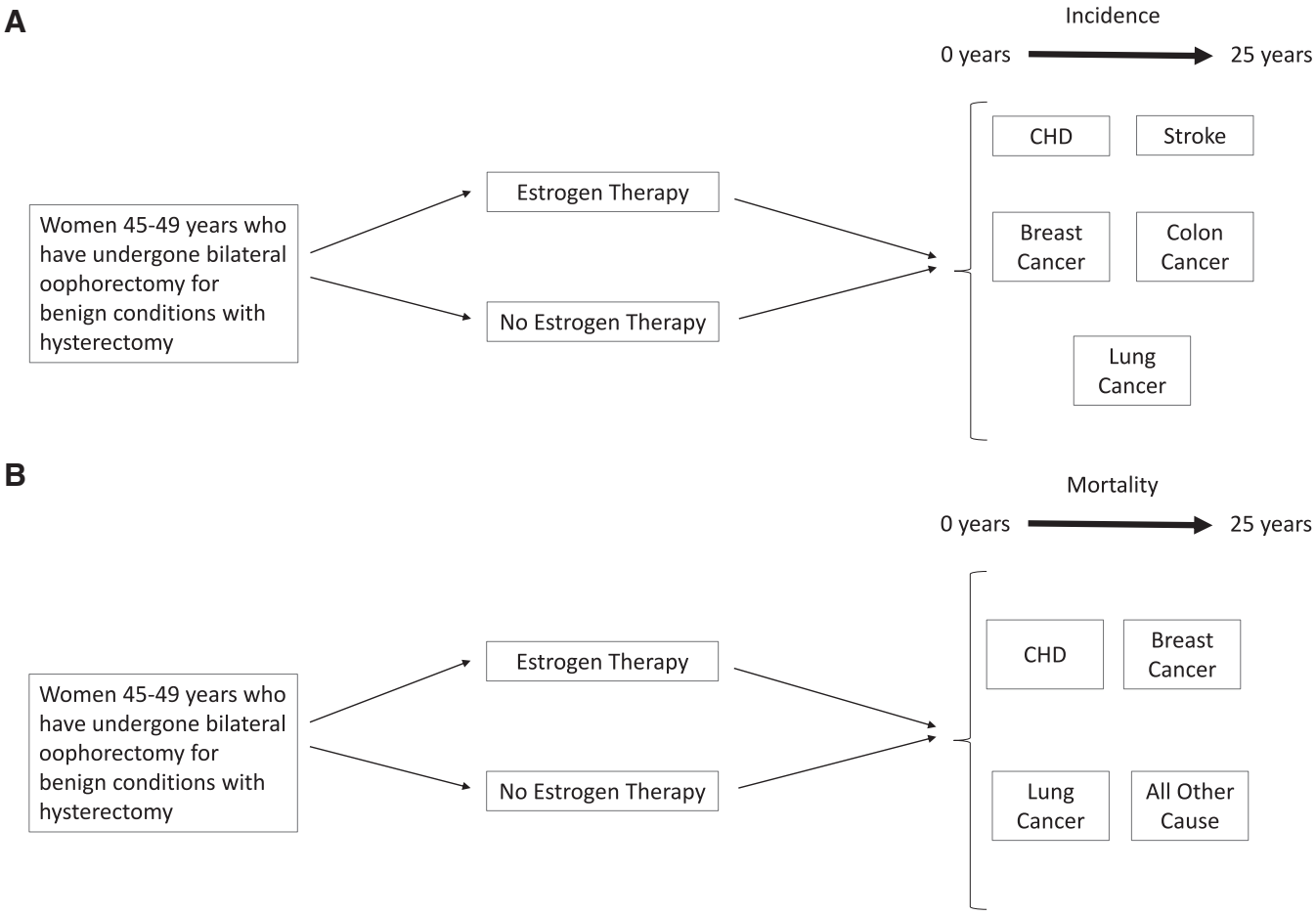
FIGURE 1
Decision tree for bilateral oophorectomy and hysterectomy by estrogen therapy status



A, We incorporated hazard ratios for the incidence of select outcomes and then estimated differences in the average number of cases between estrogen groups. **B,** We incorporated hazard ratios for cause-specific mortality of select outcomes and all-other-cause mortality and then estimated differences in the average number of deaths between estrogen groups.

CHD, coronary heart disease

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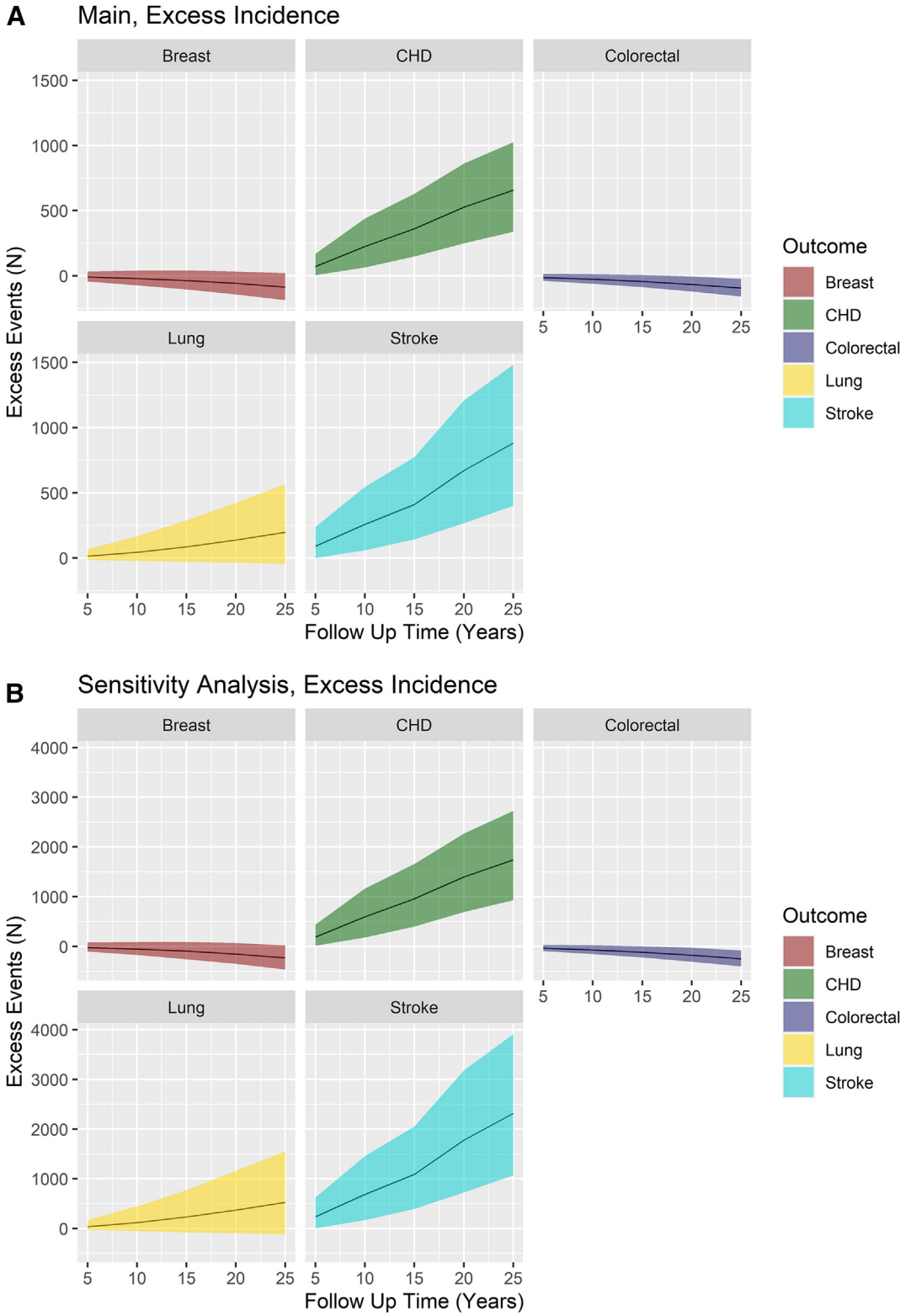
cancer. However, neither of these studies examined these associations while restricting the analysis to women who received ET. Therefore, we included data from Parker et al[15] on all women who had BO-HYST regardless of ET use (78.3% of the BO-HYST group used ET and 36.0% of the HYST group used ET) (Table 1[15–18]).

For mortality, we did not identify studies that examined stroke and colorectal cancer in premenopausal women who had BO-HYST for benign indications and did not receive ET. Thus, we were unable to include these outcomes in our mortality model. For HYST compared with no surgery, we included data for women aged ≤50 years from the Breast Cancer Detection Demonstration Project follow-up study[19] to estimate CHD, breast cancer, and lung cancer mortality. For BO-HYST compared with HYST, we included data for women aged <50 years from the Nurses' Health Study[4] to estimate CHD, breast cancer, and lung cancer mortality for both the no-ET and ET groups (Table 2[4,19]).

Sensitivity analyses

We conducted sensitivity analyses that varied the population BO rate, the rate of ET use, and the duration of ET use assumed to offer a protective effect for the diseases of interest. Scenarios evaluated included the following: (1) 10% lower BO rate, (2) 10% higher BO rate, (3) 10% lower ET use rate, (4) ET use defined as >180 days of use, (5) ET use defined as >1 year of use, (6) ET use defined as >2 years of use, (7) 10% lower ET use rate and ET use defined as >180 days of use, (8) 10% ET use rate and ET

FIGURE 2
Mean excess cases with 95% confidence intervals for current versus optimal (100%) ET use



A, Main analysis: defining ET use as any use (64.5% ET users). **B,** Sensitivity analysis: defining ET use as >2 years of use (6.1% ET users).

CHD, coronary heart disease, *ET*, estrogen therapy.

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use defined as >1 year of use, and (9) 10% ET use rate and ET use defined as >2 years of use.

Because we only used deidentified publicly available data and information already published in the literature, our institutional review board considered this nonhuman subjects research.

Results

Current practice patterns of ET use compared with optimal (100%) ET use result in an estimated 72 (95% CI, 5−169) more CHD cases and 91 (95% CI, 1−240) more stroke cases after 5 years of follow-up. However, after 25 years of follow-up, there are an estimated 658 (95% CI, 339−1025) more CHD cases, 881 (95% CI, 402−1483) more stroke cases, and 94 (95% CI, −158 to −23) fewer colorectal cancer cases (Table 3) (Figure 2, A). In a sensitivity analysis in which ET use was limited to only those who used hormonal therapy for >2 years (sensitivity analysis 5), there was an estimated 1742 (95% CI, 929−2726) more CHD cases, 2319 (95% CI, 1071−3913) more stroke cases, and 248 (95% CI, −400 to −78) fewer colorectal cancer cases after 25 years of follow-up (Table 3) (Figure 2, B).

For mortality, current practice patterns of ET use compared with optimal (100%) ET use result in an estimated 189 (95% CI, 59−387) more breast cancer deaths, 380 (95% CI, 114−792) more CHD deaths, and 759 (95% CI, 307−1527) more all-other-cause deaths at 25 years following oophorectomy (Table 4) (Figure 3, A). In a sensitivity analysis where ET use was defined as >2 years of use (sensitivity analysis 5), there were an estimated 503 (95% CI, 164−1034) more breast cancer deaths, 1007 (95% CI, 330−2142) more CHD deaths, and 2015 (95% CI, 853−4052) more all-other-cause deaths at 25 years following oophorectomy (Table 4) (Figure 3, B).

In our sensitivity analysis where we increased the oophorectomy rate by 10% (Sensitivity 2), there were minor increases in the excess cases of CHD and stroke, and a minor reduction in cases of colorectal cancer. We observed a similar pattern in our mortality model where the 10% higher oophorectomy rate increased the excess deaths from breast cancer, CHD, and all-other-cause mortality (Table 4).

Comment

Principal findings

Based on current practice patterns of women who have oophorectomy for benign indications and experience surgical menopause, underuse of ET results in a substantial increase in the number of excess cases and deaths from lung cancer, CHD, and stroke. When we defined ET use as having used hormonal therapy for >2 years, which approximates recommended clinical guidelines, morbidity and mortality further increased approximately 2-fold.

Results in the context of what is known

Most bilateral oophorectomies performed in premenopausal women occur at the time of HYST.[1,21,26] The decision to perform oophorectomy in premenopausal women is likely driven by a number of clinical factors, including the underlying gynecologic pathology and severity of disease, and influenced by nonclinical factors such as age, race and ethnicity, insurance status, and geographic location.[23,27] Premenopausal women who undergo oophorectomy will experience surgical menopause. Abrupt estrogen cessation due to surgical menopause has been associated with more severe negative health outcomes compared with natural menopause, including increased rates of lung cancer, cardiovascular disease, cognitive impairment, osteoporosis, sexual dysfunction, and overall mortality.[3,5,23] Many of these sequelae can be mitigated with exogenous estrogen replacement therapy. Current national recommendations advocate exogenous estrogen replacement therapy in premenopausal women who undergo surgical menopause until the age of natural menopause.[9−11] Although we compared real-world ET use rates with a counterfactual best-case scenario of 100% ET use, we recognize that whether a woman uses ET is influenced by several factors including overall health, patient preference, and patient−physician decision-making.[28]

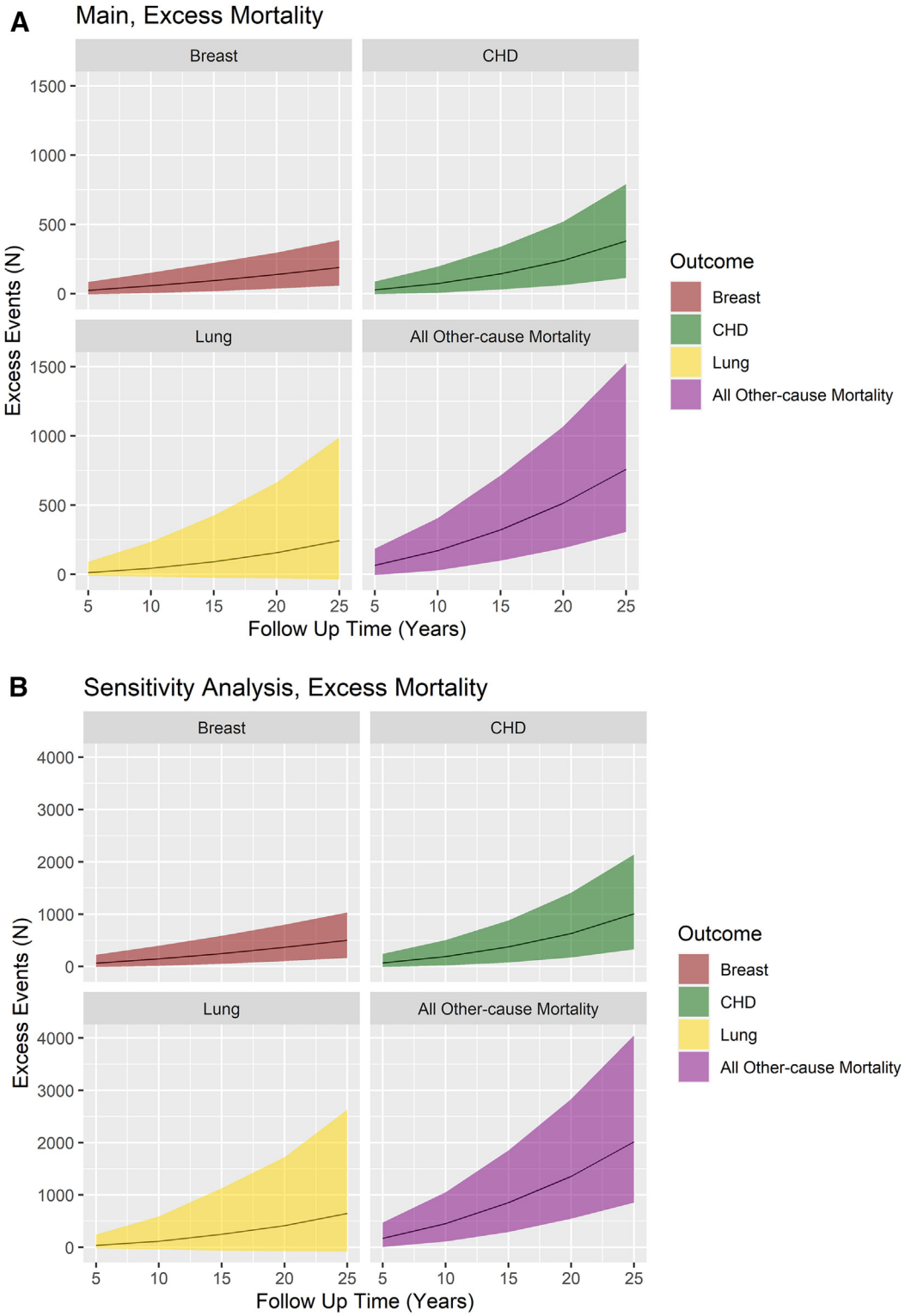
Despite the benefits of ET use in premenopausal women who undergo oophorectomy, several previous studies in the United States and Canada have demonstrated that utilization of ET is suboptimal, the duration of use is often short, and the overall rate of use is decreasing.[12−14,29] It is unlikely that women treated with ET for a short duration will experience the beneficial effects on long-term health. To account for suboptimal ET use, we modeled several scenarios in which we required 1 or 2 years of ET use to achieve the benefits of therapy. Unsurprisingly, our findings were even more pronounced in these analyses.

A variety of factors likely contribute to the underuse of ET in the United States. The early closure of the Women's Health Initiative study due to safety concerns has undoubtedly played a role in the overall decline in menopausal hormone therapy (MHT) use, and influenced perceptions of the safety of hormonal therapy, including in premenopausal women undergoing BO.[11] Importantly, the Women's Health Initiative study was conducted in postmenopausal women, whereas the potential benefits of hormonal therapy are much greater in premenopausal women who undergo surgical menopause.[3] In addition to perceptions by both patients and providers, there is likely a lack of recognition of the beneficial effects of ET in this population.[12]

Clinical implications

To contextualize our findings, the overall perioperative mortality rate among premenopausal women who undergo oophorectomy for benign indications is approximately 0.1%.[30] Thus, for our main cohort of 26,134 women aged 45 to 49 years who underwent BO for benign indications, there would be approximately 26 perioperative deaths, as opposed to our estimated 1572 deaths from all causes due to a lack of ET use. Although great efforts have been made to reduce perioperative morbidity, including the prevention of

FIGURE 3
Mean excess deaths with 95% confidence intervals for current versus optimal (100%) ET use



A, Main analysis: defining ET use as any use (64.5% ET users). **B,** Sensitivity analysis: defining ET use as >2 years of use (6.1% ET users).

CHD, coronary heart disease; *ET*, estrogen therapy.

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TABLE 3
Estimated mean number of excess cases with 95% confidence intervals of select outcomes for women aged 45 to 49 years who underwent bilateral oophorectomy with hysterectomy for benign indications, comparing current ET use versus optimal (100%) ET use, at 5, 15, and 25 years after surgery

		Mean (95% CI)		
Scenario[a]	Follow-up y	5	15	25
Main	Breast cancer incidence	−9 (−44 to 33)	−36 (−104 to 42)	−88 (−186 to 21)
	Lung cancer incidence	14 (−13 to 68)	87 (−29 to 288)	197 (−45 to 567)
	CHD incidence	72 (5−169)[b]	361 (149−630)[b]	658 (339−1025)[b]
	Stroke incidence	91 (1−240)[b]	410 (144−774)[b]	881 (402−1483)[b]
	CRC incidence	−14 (−38 to 16)	−44 (−88 to 7)	−94 (−158 to −23)[b]
Sensitivity 1: 10% lower BO rate	Breast cancer incidence	−8 (−40 to 30)	−32 (−94 to 37)	−79 (−170 to 16)
	Lung cancer incidence	13 (−12 to 62)	78 (−28 to 263)	178 (−42 to 530)
	CHD incidence	65 (3−152)[b]	326 (128−572)[b]	596 (309−934)[b]
	Stroke incidence	81 (−1 to 208)[b]	372 (129−707)[b]	793 (368−1337)[b]
	CRC incidence	−12 (−34 to 15)	−40 (−80 to 6)	−84 (−144 to −19)[b]
Sensitivity 2: 10% higher BO rate	Breast cancer incidence	−10 (−48 to 35)	−39 (−113 to 42)	−96 (−200 to 19)
	Lung cancer incidence	16 (−15 to 75)	94 (−35 to 317)	214 (−54 to 626)
	CHD incidence	80 (5−186)[b]	398 (161−698)[b]	727 (376−1138)[b]
	Stroke incidence	99 (0−260)[b]	452 (153−856)[b]	969 (436−1632)[b]
	CRC incidence	−15 (−42 to 17)	−48 (−97 to 6)	−103 (−175 to −26)[b]
Sensitivity 3: 10% lower ET rate	Breast cancer incidence	−10 (−51 to 39)	−42 (−123 to 47)	−103 (−221 to 21)
	Lung cancer incidence	17 (−15 to 79)	105 (−35 to 355)	235 (−50 to 691)
	CHD incidence	85 (5−198)[b]	427 (172−742)[b]	782 (413−1225)[b]
	Stroke incidence	107 (0−280)[b]	486 (169−912)[b]	1041 (470−1744)[b]
	CRC incidence	−16 (−44 to 18)	−52 (−103 to 5)	−111 (−186 to −28)[b]
Sensitivity 4: ET use defined as >180 d of use	Breast cancer incidence	−17 (−79 to 61)	−69 (−193 to 69)	−171 (−347 to 23)
	Lung cancer incidence	29 (−22 to 134)	175 (−56 to 584)	395 (−85 to 1165)
	CHD incidence	142 (16−325)[b]	711 (297−1236)[b]	1302 (702−2023)[b]
	Stroke incidence	181 (6−461)[b]	817 (290−1539)[b]	1746 (809−2921)[b]
	CRC incidence	−27 (−71 to 27)	−88 (−166 to 6)	−185 (−303 to −52)[b]
Sensitivity 5: ET use defined as >1 y of use	Breast cancer incidence	−20 (−94 to 67)	−82 (−228 to 79)	−204 (−416 to 29)
	Lung cancer incidence	33 (−27 to 157)	203 (−67 to 678)	462 (−96 to 1320)
	CHD incidence	170 (19−392)[b]	846 (358−1465)[b]	1548 (826−2404)[b]
	Stroke incidence	214 (5−541)[b]	964 (334−1838)[b]	2061 (930−3487)[b]
	CRC incidence	−32 (−83 to 32)	−103 (−194 to 4)	−220 (−357 to −67)[b]
Sensitivity 6: ET use defined as >2 y of use	Breast cancer incidence	−23 (−104 to 79)	−94 (−256 to 89)	−229 (−462 to 21)
	Lung cancer incidence	37 (−28 to 174)	231 (−76 to 773)	524 (−112 to 1553)
	CHD incidence	191 (18−442)[b]	958 (400−1657)[b]	1742 (929−2726)[b]
	Stroke incidence	239 (6−626)[b]	1089 (392−2053)[b]	2319 (1071−3913)[b]
	CRC incidence	−36 (−92 to 36)	−117 (−220 to 5)	−248 (−400 to −78)[b]

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TABLE 3
Estimated mean number of excess cases with 95% confidence intervals of select outcomes for women aged 45 to 49 years who underwent bilateral oophorectomy with hysterectomy for benign indications, comparing current ET use versus optimal (100%) ET use, at 5, 15, and 25 years after surgery *(continued)*

		Mean (95% CI)		
Sensitivity 7: 10% lower BO rate and ET use defined as >180 d of use	Breast cancer incidence	−16 (−74 to 54)	−64 (−175 to 64)	−157 (−318 to 21)
	Lung cancer incidence	25 (−21 to 123)	159 (−49 to 534)	358 (−74 to 1047)
	CHD incidence	129 (12−299)[b]	648 (267−1133)[b]	1180 (616−1847)[b]
	Stroke incidence	161 (4−415)[b]	735 (264−1380)[b]	1572 (707−2661)[b]
	CRC incidence	−24 (−64 to 25)	−78 (−150 to 8)	−166 (−274 to −47)[b]
Sensitivity 8: 10% lower BO rate and ET use defined as >1 y of use	Breast cancer incidence	−19 (−86 to 65)	−75 (−205 to 75)	−185 (−378 to 25)
	Lung cancer incidence	30 (−24 to 148)	185 (−59 to 609)	422 (−85 to 1246)
	CHD incidence	151 (16−352)[b]	765 (321−1320)[b]	1394 (738−2173)[b]
	Stroke incidence	195 (7−508)[b]	867 (313−1622)[b]	1857 (861−3075)[b]
	CRC incidence	−28 (−75 to 29)	−93 (−178 to 4)	−198 (−322 to −59)[b]
Sensitivity 9: 10% lower BO rate and ET use defined as >2 y of use	Breast cancer incidence	−21 (−94 to 72)	−84 (−230 to 81)	−209 (−419 to 24)
	Lung cancer incidence	34 (−27 to 165)	205 (−66 to 695)	468 (−105 to 1359)
	CHD incidence	172 (20−399)[b]	859 (356−1496)[b]	1566 (827−2432)[b]
	Stroke incidence	218 (7−561)[b]	975 (345−1797)[b]	2097 (974−3519)[b]
	CRC incidence	−32 (−85 to 32)	−105 (−201 to 7)	−223 (−365 to −63)[b]

BO, bilateral oophorectomy; *CHD*, coronary heart disease; *CI*, confidence interval; *CRC*, colorectal cancer; *ET*, estrogen therapy.

[a] Main: main analysis defining ET use as any use (64.5% ET users); Sensitivity 1: 10% lower BO rate; Sensitivity 2: 10% higher BO rate; Sensitivity 3: 10% lower ET use rate; Scenario 4: ET use defined as >180 days of use; Scenario 5: ET use defined as >1 year of use; Scenario 6: ET use defined as >2 years of use; Scenario 7: 10% lower BO rate and ET use defined as >180 days of use; Scenario 8: 10% lower BO rate and ET use defined as >1 year of use; Scenario 9: 10% lower BO rate and ET use defined as >2 years of use; [b] Statistically significant 95% confidence interval.

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thromboembolic disease and other perioperative morbidity, we found that lack of ET would lead to approximately 60-fold excess deaths compared with perioperative death.

In our cohort of premenopausal women undergoing BO-HYST for benign indications, some of them may be having their ovaries removed for ovarian cancer prevention. With recent research showing the safety and effectiveness of opportunistic salpingectomy for ovarian cancer prevention, it is possible that the rates of surgical menopause in premenopausal women will decrease.[31] However, our results still highlight the importance of using ET in women undergoing surgical menopause.

Research implications

Given the impact of current ET use trends on disease morbidity and mortality among premenopausal women who experience surgical menopause due to oophorectomy for benign indications, it is critical that future work identify barriers to ET use and educate providers and patients on the importance of ET use until the average age of natural menopause.[28] Recent research has shown that only 30% of obstetrics and gynecology residency programs have a formal menopause education curriculum, highlighting an area for targeted interventions to enhance provider education on this topic.[32]

Strengths and limitations

Our study has several strengths and limitations of note. Given the reduction in ET use over time in this population, our study highlights the impact that this may have on excess disease and death. In addition, we used a previously published model and conducted a thorough literature review to identify the most relevant model inputs. We also recognize a number of important limitations. One of the main limitations of all modeling studies is the quality of model inputs. Some of the HR inputs for our incidence and mortality outcomes were not statistically significant; however, this uncertainty was fully contained within the Bayesian framework of our models. In addition, although the HR inputs were derived from large, well-established US cohort studies (ie, the Nurses' Health Study[4,15] and Women's Health Initiative[18]), observational studies are subject to confounding and information and selection bias. Specifically, there may be underlying differences between premenopausal women undergoing surgical menopause who receive ET and who do not receive ET, that are associated with morbidity and mortality risk. Although we conducted a thorough literature search, we were unable to find some

TABLE 4
Estimated mean number of excess deaths with 95% confidence intervals from select outcomes for women aged 45 to 49 years who underwent bilateral oophorectomy for benign indications, comparing current ET use versus optimal (100%) ET use, at 5, 15, and 25 years after surgery

		Mean (95% CI)		
Scenario[a]	Follow-up y	5	15	25
Main	Breast cancer death	25 (−5 to 85)	94 (17−223)[b]	189 (59−387)[b]
	Lung cancer death	14 (−9 to 91)	92 (−25 to 426)	244 (−36 to 989)
	CHD death	26 (−4 to 88)	143 (30−339)[b]	380 (114−792)[b]
	All-other-cause death	65 (−5 to 187)	322 (99−716)[b]	759 (307−1527)[b]
Sensitivity 1: 10% lower BO rate	Breast cancer death	22 (−5 to 78)	85 (15−200)[b]	171 (54−346)[b]
	Lung cancer death	13 (−8 to 85)	83 (−23 to 397)	221 (−30 to 870)
	CHD death	24 (−4 to 80)	128 (25−299)[b]	345 (110−737)[b]
	All-other-cause death	58 (−7 to 164)	290 (88−638)[b]	688 (287−1390)[b]
Sensitivity 2: 10% higher BO rate	Breast cancer death	26 (−5 to 92)	104 (18−243)[b]	209 (66−426)[b]
	Lung cancer death	15 (−9 to 102)	106 (−27 to 506)	272 (−35−1056)
	CHD death	29 (−5 to 96)	156 (30−374)[b]	417 (129−885)[b]
	All-other-cause death	70 (−5 to 199)	359 (112−799)[b]	839 (354−1677)[b]
Sensitivity 3: 10% lower ET rate	Breast cancer death	29 (−4 to 99)	112 (21−262)[b]	224 (72−458)[b]
	Lung cancer death	17 (−10 to 111)	109 (−29 to 509)	287 (−41 to 1118)
	CHD death	31 (−5 to 110)	166 (32−400)[b]	449 (139−935)[b]
	All-other-cause death	76 (−4 to 212)	380 (119−840)[b]	896 (371−1772)[b]
Sensitivity 4: ET use defined as >180 d of use	Breast cancer death	47 (−6 to 160)	186 (37−430)[b]	377 (127−764)[b]
	Lung cancer death	27 (−15 to 181)	181 (−48 to 836)	477 (−69 to 1854)
	CHD death	52 (−5 to 177)	284 (56−663)[b]	756 (239−1579)[b]
	All-other-cause death	126 (1−345)[b]	638 (206−1399)[b]	1505 (646−2993)[b]
Sensitivity 5: ET use defined as >1 y of use	Breast cancer death	56 (−7 to 190)	221 (44−519)[b]	445 (150−916)[b]
	Lung cancer death	33 (−17 to 220)	220 (−56 to 1012)	572 (−77 to 2287)
	CHD death	62 (−6 to 210)	335 (73−784)[b]	894 (286−1903)[b]
	All-other-cause death	150 (4−422)[b]	762 (250−1671)[b]	1785 (762−3565)[b]
Sensitivity 6: ET use defined as >2 y of use	Breast cancer death	66 (−8 to 227)	249 (52−590)[b]	503 (164−1034)[b]
	Lung cancer death	36 (−19 to 245)	247 (−61 to 1130)	646 (−84 to 2632)
	CHD death	70 (−7 to 241)	375 (81−882)[b]	1007 (330−2142)[b]
	All-other-cause death	172 (9−472)[b]	854 (292−1854)[b]	2015 (853−4052)[b]
Sensitivity 7: 10% lower BO rate and ET use defined as >180 d of use	Breast cancer death	43 (−7 to 148)	168 (34−401)[b]	339 (109−696)[b]
	Lung cancer death	26 (−14 to 171)	168 (−42 to 795)	430 (−60 to 1720)
	CHD death	47 (−6 to 158)	256 (53−598)[b]	677 (218−1427)[b]
	All-other-cause death	116 (0−317)	580 (188−1286)[b]	1351 (561−2726)[b]
Sensitivity 8: 10% lower BO rate and ET use defined as >1 y of use	Breast cancer death	51 (−6 to 174)	200 (42−469)[b]	399 (137−799)[b]
	Lung cancer death	29 (−16 to 191)	193 (−50 to 896)	506 (−72 to 1995)
	CHD death	56 (−6 to 190)	300 (64−713)[b]	805 (260−1706)[b]
	All-other-cause death	135 (1−376)[b]	678 (223−1468)[b]	1596 (681−3230)[b]

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TABLE 4
Estimated mean number of excess deaths with 95% confidence intervals from select outcomes for women aged 45 to 49 years who underwent bilateral oophorectomy for benign indications, comparing current ET use versus optimal (100%) ET use, at 5, 15, and 25 years after surgery *(continued)*

		Mean (95% CI)		
Sensitivity 9: 10% lower BO rate and ET use defined as >2 y of use	Breast cancer death	58 (−7 to 202)	227 (43−541)[b]	453 (150−920)[b]
	Lung cancer death	32 (−17 to 215)	221 (−55 to 1049)	571 (−76 to 2224)
	CHD death	64 (−7 to 214)	340 (72−814)[b]	905 (289−1906)[b]
	All-other-cause death	153 (4−421)[b]	772 (268−1702)[b]	1802 (780−3532)[b]

BO, bilateral oophorectomy; *CHD*, coronary heart disease; *CI*, confidence interval; *CRC*, colorectal cancer; *ET*, estrogen therapy.

[a] Main: main analysis defining ET use as any use (64.5% ET users); Sensitivity 1: 10% lower BO rate; Sensitivity 2: 10% higher BO rate; Sensitivity 3: 10% lower ET use rate; Scenario 4: ET use defined as >180 days of use; Scenario 5: ET use defined as >1 year of use; Scenario 6: ET use defined as >2 years of use; Scenario 7: 10% lower BO rate and ET use defined as >180 days of use; Scenario 8: 10% lower BO rate and ET use defined as >1 year of use; Scenario 9: 10% lower BO rate and ET use defined as >2 years of use; [b] Statistically significant 95% confidence interval.

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relevant inputs for our model. For incidence, all of our inputs for the BO-HYST ET arm included women who did and did not use ET (78.3% used ET). However, including women who did not use ET in the ET arm would have attenuated our results, suggesting that the true estimates would be larger. For mortality, we were unable to identify inputs for stroke and colorectal cancer for women with BO-HYST who did not use ET. Therefore, we were unable to examine these cause-specific deaths; however, they are included in the all-other-cause death outcome. We were unable to identify any population-level US data for the BO rate for women aged 45 to 49 years, or for the CHD and stroke incidence rates in women aged 45 to 79 years. Thus, we used regional data for the BO rate[21] and data from the United Kingdom for CHD and stroke.[25] In addition, the BO rate is for all women and not restricted to those undergoing the surgery for benign indications. The cohort studies used for the model inputs consisted of predominantly non-Hispanic White women; thus, our results may not apply to other racial and ethnic groups. Data from one study in North Carolina showed that non-Hispanic Black women had a higher premenopausal BO rate than non-Hispanic White women in 2014 (284 vs 248 per 100,000, respectively).[33] To address this, we conducted a sensitivity analysis (Sensitivity 2) to examine our results with a higher BO rate. We observed increases in excess cases of CHD and stroke, a greater reduction in colorectal cancer cases, and increases in excess breast, CHD, and all-other-cause deaths. Lastly, although some studies did not specify whether estrogen treatment included combined progestin, Jacoby et al[18] collected data on estrogen use with or without progestin and stated that most women used estrogen only.

Conclusions

Our findings provide further evidence of the harms associated with both a lack of ET use and an insufficient duration of ET in premenopausal women undergoing BO for benign indications. Given the population-level decrease in ET use, these results suggest that there will be increases in cancer and cardiovascular cases and deaths and in all-other-cause deaths. Although the optimal scenario would be for all women experiencing surgical menopause due to oophorectomy for benign indications to receive ET, given the decline in ET use over time in this population, ovarian conservation must also be addressed. ■

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Author and article information

From the Department of Obstetrics and Gynecology, (Drs Ferris and Suzuki, Mr Prest, and Drs Chen, and Wright); Department of Medicine (Drs Hur, and Hershman), Columbia University Vagelos College of Physicians and Surgeons, New York, NY; Joseph L. Mailman School of Public Health, Columbia University, New York, NY (Dr Elkin); Department of Medicine, Joseph L. Mailman School of Public Health, Columbia University, New York, NY (Dr Hershman); Herbert Irving Comprehensive Cancer Center, New York, NY (Dr Elkin); Department of Medicine (Drs Hur, and Hershman), Department of Obstetrics and Gynecology, (Dr Wright), Herbert Irving Comprehensive Cancer Center, New York, NY; and Department of Medicine (Drs Hur, and Hershman), Department of Obstetrics and Gynecology, (Dr Wright), NewYork-Presbyterian Hospital, New York, NY.

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Corresponding author: Jason D. Wright, MD. jw2459@columbia.edu

SUPPLEMENTAL TABLE 1
Population-level cause-specific incidence rates by age group

Cause	Age (y)						
	45–49	50–54	55–59	60–64	65–69	70–74	75–79
Breast cancer[a]	202	240.2	272.2	339.2	424.9	475.2	449.9
Lung cancer[a]	12.9	29.5	66.3	110.4	158.6	227.4	283.9
Colorectal cancer[a]	32.7	56.2	55.3	70	90.1	110.4	131.9
Coronary heart disease[b]	104	104	236	236	332.7	332.7	561.3
Stroke[b]	119.5	119.5	235.4	235.4	466.1	466.1	1275.8

Rates per 100,000 population.

[a] SEER (Surveillance, Epidemiology, and End Results) 19, 2019, females; [b] British Heart Foundation data for 2017 in 10-year age groups (45–54, 55–64, 65–74, ≥75); assuming same rate across the two 5-year age groups.

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SUPPLEMENTAL TABLE 2
Population-level cause-specific mortality rates by age group

Cause	Age (y)						
	45–49	50–54	55–59	60–64	65–69	70–74	75–79
Breast cancer[a]	17.8	26.6	35.4	45.7	55.4	70.4	85.4
Lung cancer[b]	7.3	18.5	42.1	70.3	96.9	146.7	203.5
Coronary heart disease[c]	14.5	26.4	47	75.7	112.6	179.4	302.1
All other causes[d]	196.8	286.2	421.9	607.3	853.2	1354.7	2277.2

Rates per 100,000 population.

[a] Centers for Disease Control and Prevention (CDC) WONDER, C50, females, 2019; [b] CDC WONDER, C34, females, 2019; [c] CDC WONDER, I20-I25, females, 2019; [d] CDC WONDER, all codes not listed above, females, 2019.

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SUPPLEMENTAL TABLE 3

Estimated mean number of excess cases with 95% confidence intervals of select outcomes for women aged 45 to 49 years who underwent bilateral oophorectomy with hysterectomy for benign indications and did not use estrogen therapy compared with if they had used estrogen therapy at 5-year intervals after surgery

		Mean (95% CI)				
Scenario[a]	Follow-up y	5	10	15	20	25
Main	Breast cancer incidence	−9 (−44 to 33)	−20 (−73 to 40)	−36 (−104 to 42)	−58 (−143 to 34)	−88 (−186 to 21)
	Lung cancer incidence	14 (−13 to 68)	44 (−22 to 168)	87 (−29 to 288)	139 (−34 to 425)	197 (−45 to 567)
	CHD incidence	72 (5−169)	225 (65−440)	361 (149−630)	527 (250−862)	658 (339−1025)
	Stroke incidence	91 (1−240)	260 (60−547)	410 (144−774)	672 (268−1209)	881 (402−1483)
	CRC incidence	−14 (−38 to 16)	−27 (−61 to 13)	−44 (−88 to 7)	−66 (−120 to −6)	−94 (−158 to −23)
Sensitivity 1: 10% lower BO rate	Breast cancer incidence	−8 (−40 to 30)	−17 (−66 to 38)	−32 (−94 to 37)	−53 (−130 to 33)	−80 (−170 to 16)
	Lung cancer incidence	13 (−12 to 62)	40 (−21 to 151)	78 (−28 to 263)	127 (−32 to 398)	178 (−42 to 530)
	CHD incidence	65 (3−152)	203 (56−400)	326 (128−572)	478 (223−787)	596 (309−934)
	Stroke incidence	81 (−1 to 208)	236 (52−502)	372 (129−707)	606 (253−1087)	793 (368−1337)
	CRC incidence	−12 (−34 to 15)	−24 (−56 to 13)	−40 (−80 to 6)	−60 (−110 to −4)	−84 (−144 to −19)
Sensitivity 2: 10% higher BO rate	Breast cancer incidence	−10 (−48 to 35)	−21 (−80 to 44)	−39 (−113 to 42)	−63 (−153 to 39)	−96 (−200 to 19)
	Lung cancer incidence	16 (−15 to 75)	47 (−26 to 185)	94 (−35 to 317)	151 (−43 to 476)	214 (−54 to 626)
	CHD incidence	80 (5−186)	249 (73−489)	398 (161−698)	582 (275−959)	727 (376−1138)
	Stroke incidence	99 (0−260)	286 (63−612)	452 (153−856)	741 (288−1330)	969 (436−1632)
	CRC incidence	−15 (−42 to 17)	−30 (−67 to 14)	−48 (−97 to 6)	−73 (−134 to −8)	−103 (−175 to −26)
Sensitivity 3: 10% lower ET rate	Breast cancer incidence	−10 (−51 to 39)	−23 (−84 to 47)	−42 (−123 to 47)	−68 (−167 to 39)	−103 (−221 to 21)
	Lung cancer incidence	17 (−15 to 79)	52 (−27 to 208)	105 (−35 to 355)	168 (−39 to 532)	235 (−50 to 691)
	CHD incidence	85 (5−198)	267 (78−525)	427 (172−742)	627 (301−1029)	782 (413−1225)
	Stroke incidence	107 (0−280)	309 (71−656)	486 (169−912)	795 (324−1432)	1041 (470−1744)
	CRC incidence	−16 (−44 to 18)	−32 (−71 to 14)	−52 (−103 to 5)	−79 (−142 to −7)	−111 (−186 to −28)
Sensitivity 4: ET use defined as >180 d of use	Breast cancer incidence	−17 (−79 to 61)	−37 (−131 to 72)	−69 (−193 to 69)	−113 (−266 to 60)	−171 (−347 to 23)
	Lung cancer incidence	29 (−22 to 134)	88 (−40 to 340)	175 (−56 to 584)	281 (−64 to 858)	395 (−85 to 1165)
	CHD incidence	142 (16−325)	445 (137−867)	711 (297−1236)	1044 (502−1691)	1302 (702−2023)
	Stroke incidence	181 (6−461)	519 (116−1109)	817 (290−1539)	1333 (548−2362)	1746 (809−2921)
	CRC incidence	−27 (−71 to 27)	−54 (−115 to 18)	−88 (−166 to 6)	−131 (−232 to −18)	−185 (−303 to −52)
Sensitivity 5: ET use defined as >1 y of use	Breast cancer incidence	−20 (−94 to 67)	−45 (−158 to 83)	−82 (−228 to 79)	−135 (−317 to 66)	−204 (−416 to 29)
	Lung cancer incidence	33 (−27 to 157)	104 (−48 to 395)	203 (−67 to 678)	327 (−84 to 1015)	462 (−96 to 1320)
	CHD incidence	170 (19−392)	527 (158−1030)	846 (358−1465)	1239 (600−2015)	1548 (826−2404)
	Stroke incidence	214 (5−541)	609 (139−1280)	964 (334−1838)	1579 (621−2820)	2061 (930−3487)
	CRC incidence	−32 (−83 to 32)	−63 (−135 to 23)	−103 (−194 to 4)	−155 (−270 to −26)	−220 (−357 to −67)
Sensitivity 6: ET use defined as >2 y of use	Breast cancer incidence	−23 (−104 to 79)	−52 (−173 to 91)	−94 (−256 to 89)	−152 (−350 to 73)	−230 (−462 to 21)
	Lung cancer incidence	37 (−28 to 174)	118 (−52 to 445)	231 (−76 to 773)	370 (−95 to 1162)	524 (−112 to 1553)
	CHD incidence	191 (18−442)	599 (181−1165)	958 (400−1657)	1397 (691−2271)	1742 (929−2726)
	Stroke incidence	239 (6−626)	688 (170−1459)	1089 (392−2053)	1779 (728−3181)	2319 (1071−3913)
	CRC incidence	−36 (−92 to 36)	−71 (−151 to 24)	−117 (−220 to 5)	−175 (−306 to −24)	−248 (−400 to −78)
Sensitivity 7: 10% lower BO rate and ET use defined as >180 d of use	Breast cancer incidence	−16 (−74 to 54)	−36 (−121 to 62)	−64 (−175 to 64)	−104 (−242 to 51)	−157 (−318 to 21)
	Lung cancer incidence	25 (−21 to 123)	79 (−36 to 299)	159 (−49 to 534)	253 (−62 to 757)	358 (−74 to 1047)
	CHD incidence	129 (12−299)	404 (121−793)	648 (267−1133)	946 (452−1550)	1180 (616−1847)
	Stroke incidence	161 (4−415)	464 (102−968)	735 (264−1380)	1202 (479−2179)	1572 (707−2661)
	CRC incidence	−24 (−64 to 25)	−48 (−103 to 21)	−78 (−150 to 8)	−117 (−209 to −14)	−166 (−274 to −47)

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SUPPLEMENTAL TABLE 3

Estimated mean number of excess cases with 95% confidence intervals of select outcomes for women aged 45 to 49 years who underwent bilateral oophorectomy with hysterectomy for benign indications and did not use estrogen therapy compared with if they had used estrogen therapy at 5-year intervals after surgery *(continued)*

		Mean (95% CI)				
Sensitivity 8: 10% lower BO rate and ET use defined as >1 y of use	Breast cancer incidence	−19 (−86 to 65)	−42 (−142 to 74)	−75 (−205 to 75)	−122 (−287 to 62)	−185 (−378 to 25)
	Lung cancer incidence	30 (−24 to 148)	94 (−42 to 362)	185 (−59 to 609)	297 (−69 to 908)	422 (−85 to 1246)
	CHD incidence	151 (16−352)	479 (149−942)	765 (321−1320)	1116 (533−1828)	1394 (738−2173)
	Stroke incidence	195 (7−508)	551 (128−1173)	867 (313−1622)	1417 (588−2529)	1857 (861−3075)
	CRC incidence	−28 (−75 to 29)	−57 (−123 to 22)	−93 (−178 to 4)	−140 (−245 to −22)	−198 (−322 to −59)
Sensitivity 9: 10% lower BO rate and ET use defined as >2 y of use	Breast cancer incidence	−21 (−94 to 72)	−46 (−160 to 84)	−84 (−230 to 81)	−138 (−321 to 66)	−209 (−419 to 24)
	Lung cancer incidence	34 (−27 to 165)	105 (−48 to 401)	205 (−66 to 695)	331 (−87 to 1036)	468 (−105 to 1359)
	CHD incidence	172 (20−399)	536 (159−1048)	859 (356−1496)	1255 (597−2032)	1566 (827−2432)
	Stroke incidence	218 (7−561)	616 (152−1297)	975 (345−1797)	1602 (652−2863)	2097 (974−3519)
	CRC incidence	−32 (−85 to 32)	−64 (−138 to 21)	−105 (−201 to 7)	−158 (−276 to −17)	−223 (−365 to −63)

BO, bilateral oophorectomy; *CHD*, coronary heart disease; *CI*, confidence interval; *CRC*, colorectal cancer; *ET*, estrogen therapy.

[a] Main: main analysis defining ET use as any use (64.5% ET users); Sensitivity 1: 10% lower BO rate; Sensitivity 2: 10% higher BO rate; Sensitivity 3: 10% lower ET use rate; Scenario 4: ET use defined as >180 days of use; Scenario 5: ET use defined as >1 year of use; Scenario 6: ET use defined as >2 years of use; Scenario 7: 10% lower BO rate and ET use defined as >180 days of use; Scenario 8: 10% lower BO rate and ET use defined as >1 year of use; Scenario 9: 10% lower BO rate and ET use defined as >2 years of use.

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SUPPLEMENTAL TABLE 4

Estimated mean number of excess deaths with 95% confidence intervals of select outcomes for women aged 45 to 49 years who underwent bilateral oophorectomy with hysterectomy for benign indications and did not use estrogen therapy compared with if they had used estrogen therapy at 5-year intervals after surgery

		Mean (95% CI)				
Scenario[a]	Follow-up y	5	10	15	20	25
Main	Breast cancer death	25 (−5 to 85)	56 (4−152)	94 (17−223)	138 (37−297)	189 (59−387)
	Lung cancer death	14 (−9 to 91)	44 (−17 to 235)	92 (−25 to 426)	157 (−30 to 665)	244 (−36 to 989)
	CHD death	27 (−4 to 88)	72 (6−195)	143 (30−339)	240 (62−521)	380 (114−792)
	All-other-cause death	65 (−5 to 187)	171 (30−406)	322 (99−716)	514 (189−1068)	759 (307−1527)
Sensitivity 1: 10% lower BO rate	Breast cancer death	22 (−5 to 78)	50 (1−136)	85 (15−200)	124 (32−268)	171 (54−346)
	Lung cancer death	13 (−8 to 85)	40 (−16 to 212)	83 (−23 to 397)	141 (−27 to 610)	221 (−30 to 870)
	CHD death	24 (−4 to 80)	65 (4−173)	128 (25−299)	216 (59−477)	345 (110−737)
	All-other-cause death	58 (−7 to 164)	154 (26−363)	290 (88−638)	464 (173−971)	688 (287−1390)
Sensitivity 2: 10% higher BO rate	Breast cancer death	26 (−5 to 92)	61 (3−168)	104 (18−243)	153 (39−332)	209 (66−426)
	Lung cancer death	15 (−9 to 102)	49 (−18 to 264)	106 (−27 to 506)	175 (−34 to 731)	272 (−35 to 1056)
	CHD death	29 (−5 to 96)	79 (6−214)	156 (30−374)	263 (69−578)	417 (129−885)
	All-other-cause death	70 (−5 to 199)	188 (38−447)	359 (112−799)	569 (221−1179)	839 (354−1677)
Sensitivity 3: 10% lower ET rate	Breast cancer death	29 (−4 to 99)	66 (5−174)	112 (21−262)	164 (42−355)	224 (72−458)
	Lung cancer death	17 (−10 to 111)	52 (−20 to 272)	109 (−29 to 509)	183 (−37 to 756)	287 (−41 to 1118)
	CHD death	31 (−5 to 110)	85 (7−227)	167 (32−400)	283 (74−627)	449 (139−935)
	All-other-cause death	76 (−4 to 212)	201 (43−467)	380 (119−840)	606 (225−1245)	896 (371−1772)
Sensitivity 4: ET use defined as >180 d of use	Breast cancer death	47 (−6 to 160)	109 (10−283)	186 (37−430)	275 (78−596)	377 (127−764)
	Lung cancer death	27 (−15 to 181)	87 (−31 to 471)	181 (−48 to 836)	303 (−59 to 1244)	477 (−69 to 1854)
	CHD death	52 (−5 to 177)	144 (16−388)	284 (56−663)	476 (131−1036)	756 (239−1579)
	All-other-cause death	126 (1−345)	337 (75−799)	638 (206−1399)	1015 (396−2086)	1505 (646−2993)
Sensitivity 5: ET use defined as >1 y of use	Breast cancer death	56 (−7 to 190)	129 (12−341)	221 (44−519)	325 (90−706)	445 (150−916)
	Lung cancer death	33 (−17 to 220)	104 (−37 to 555)	220 (−56 to 1012)	371 (−71 to 1582)	572 (−77 to 2287)
	CHD death	62 (−6 to 210)	170 (16−451)	336 (73−784)	562 (153−1251)	894 (286−1903)
	All-other-cause death	150 (4−422)	400 (97−946)	762 (250−1671)	1210 (468−2476)	1785 (762−3565)
Sensitivity 6: ET use defined as >2 y of use	Breast cancer death	66 (−8 to 227)	148 (14−397)	249 (52−590)	367 (104−799)	503 (164−1034)
	Lung cancer death	36 (−19 to 245)	116 (−41 to 592)	247 (−61 to 1130)	412 (−75 to 1724)	646 (−84 to 2632)
	CHD death	70 (−7 to 241)	191 (21−505)	375 (81−882)	630 (173−1408)	1008 (330−2142)
	All-other-cause death	172 (9−472)	451 (111−1052)	855 (292−1854)	1355 (549−2835)	2015 (853−4052)
Sensitivity 7: 10% lower BO rate and ET use defined as >180 d of use	Breast cancer death	43 (−7 to 148)	99 (8−267)	168 (34−401)	247 (66−543)	339 (109−696)
	Lung cancer death	26 (−14 to 171)	80 (−28 to 423)	168 (−42 to 795)	277 (−55 to 1194)	430 (−60 to 1720)
	CHD death	47 (−6 to 158)	129 (13−335)	256 (53−598)	429 (118−933)	677 (218−1427)
	All-other-cause death	116 (0−317)	305 (69−722)	580 (188−1286)	917 (347−1886)	1351 (561−2726)
Sensitivity 8: 10% lower BO rate and ET use defined as >1 y of use	Breast cancer death	51 (−6 to 174)	117 (9−315)	200 (42−469)	292 (82−629)	399 (137−799)
	Lung cancer death	29 (−16 to 191)	92 (−33 to 497)	193 (−50 to 896)	327 (−62 to 1360)	506 (−72 to 1995)
	CHD death	56 (−6 to 190)	151 (14−400)	300 (64−713)	505 (140−1108)	805 (260−1706)
	All-other-cause death	135 (1−376)	357 (84−843)	678 (223−1468)	1081 (431−2212)	1596 (681−3230)

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SUPPLEMENTAL TABLE 4

Estimated mean number of excess deaths with 95% confidence intervals of select outcomes for women aged 45 to 49 years who underwent bilateral oophorectomy with hysterectomy for benign indications and did not use estrogen therapy compared with if they had used estrogen therapy at 5-year intervals after surgery *(continued)*

		Mean (95% CI)				
Sensitivity 9: 10% lower BO rate and ET use defined as >2 y of use	Breast cancer death	58 (−7 to 202)	133 (11−361)	227 (43−541)	330 (90−714)	453 (150−920)
	Lung cancer death	32 (−17 to 215)	106 (−36 to 573)	221 (−55 to 1049)	367 (−66 to 1523)	571 (−76 to 2224)
	CHD death	64 (−7 to 214)	174 (20−465)	340 (72−814)	568 (165−1229)	905 (289−1906)
	All-other-cause death	153 (4−421)	410 (96−971)	772 (268−1702)	1217 (481−2477)	1802 (780−3532)

BO, bilateral oophorectomy; *CHD*, coronary heart disease; *CI*, confidence interval; *CRC*, colorectal cancer; *ET*, estrogen therapy.

[a] Main: main analysis defining ET use as any use (64.5% ET users); Sensitivity 1: 10% lower BO rate; Sensitivity 2: 10% higher BO rate; Sensitivity 3: 10% lower ET use rate; Scenario 4: ET use defined as >180 days of use; Scenario 5: ET use defined as >1 year of use; Scenario 6: ET use defined as >2 years of use; Scenario 7: 10% lower BO rate and ET use defined as >180 days of use; Scenario 8: 10% lower BO rate and ET use defined as >1 year of use; Scenario 9: 10% lower BO rate and ET use defined as >2 years of use.

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