Clinical Perspective

Menopausal Estrogen Therapy and Risk of Breast Cancer

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Recent evidence suggests that use of menopausal estrogen-only therapy in patients who have undergone hysterectomy reduces breast cancer risk among patients at population risk for breast cancer as well as in those with pathogenic high-risk *BRCA* variants. A meta-analysis of 10 randomized trials of estrogen therapy compared with placebo among 14,282 participants at population risk noted that 3.6% those randomized to estrogen alone were diagnosed with breast cancer, compared with 4.7% of those randomized to placebo (relative risk 0.77; 95% CI, 0.65–0.91, *P*=.002). A matched prospective cohort study of 676 patients with *BRCA* mutations and intact breasts who used menopausal hormone therapy (MHT) found that the estimated 15-year cumulative incidence of breast cancer with estrogen alone compared with no MHT was 24.3%, compared with 47.3% in the matched nonusers of MHT (*P*<.0001). This evidence underscores the need for more data that specifically assess the effect of estradiol therapy among patients who have undergone hysterectomy. Until such data are available, counseling patients at risk for breast cancer who have completed childbearing and are planning surgery for benign gynecologic conditions should involve shared decision-making that addresses the future risk of breast and endometrial cancers, cardiovascular disease, as well as the morbidity associated with hysterectomy. When appropriate, such counseling should also describe the availability of uterine-sparing alternatives.

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Emerging data address the risk of breast cancer for women who underwent hysterectomy and are using menopausal estrogen-only therapy (Table 1). In this Clinical Perspective, we review recently published data that describe the association between estrogen-only therapy and risk of breast cancer in individuals at risk for breast cancer. We also review data that address a distinct population: those with pathogenic high-risk *BRCA1* and *BRCA2* variants. In addition, we describe associations between hysterectomy, bilateral salpingo-oophorectomy (BSO), and usage of estrogen-only therapy with respect to the risk of cardiovascular disease (CVD). Finally, we offer our perspective regarding how these data have the potential to change how we counsel patients regarding the benefits and risks of hysterectomy.

USE OF MENOPAUSAL ESTROGEN-ONLY THERAPY IN PATIENTS AT POPULATION RISK FOR BREAST CANCER

A number of recent reports from long-term randomized trials and observational cohorts have noted that estrogen in combination with progestogens may be a risk factor for breast cancer. In contrast, these studies have often noted a protective effect with estrogen alone.

The Women's Health Initiative (WHI), the largest randomized placebo-controlled trial examining menopausal hormone therapy (MHT), enrolled 16,608 individuals with an intact uterus and 10,739 individuals who had undergone hysterectomy. Women's Health Initiative participants with an intact uterus were randomized to conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) or placebo;

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Table 1. Studies That Assessed the Association Between Estrogen Use and Risk of Breast Cancer

Study	Population	Estrogen Formulation, Route	Comparator	Duration of Use (y)	Follow-Up (y)	Main Outcomes	Major Limitations
Chlebowski et al, 2020[2]	WHI participants (United States)	Oral conjugated equine	Visually matching oral placebo	Median 7	20+	22% reduction in breast cancer in the CEE arm (HR 0.78, 95% CI, 0.65–0.93, *P*=.005); 40% reduction in breast cancer mortality (HR 0.60, 95% CI, 0.37–0.97)	Estradiol not studied
Chlebowski et al, 2024[4,*]	Most participants from the United States, some from Denmark	Estradiol valerate, estradiol, ethinyl estradiol, CEE, estrone sulfate; all estrogens were oral	Placebos used in 8 trials; comparator was no treatment in 1 trial	1–10	12.6–16 (2 trials); not specified (7 trials)	35% reduction in breast cancer in the estrogen arm (RR 0.65, 95% CI, 0.38–1.11, *P*=.12)	Small trials, limited follow-up; small number of women randomized to estradiol
O'Brien et al 2025[5]	Pooled data from 13 cohorts in North America, Europe, Asia, and Australia; invasive and in situ cancer diagnosed before age 55 y	Information not available	No comparator; all studies were observational	Mean 4.7	Median 7.8	Estrogen-only use associated with HR 0.86, 95% CI, 0.75–0.98	No comparator; information on types of estrogen not available; no information on breast cancers diagnosed in participants aged 55 y or older
Kotsopoulos et al 2025[15]	All participants with *BRCA1/2* pathogenic variants; participants from numerous countries	Transdermal estradiol (most commonly used) and various oral estrogens	No comparator; not a clinical trial	Mean 5.7	6.6	Estrogen-only use associated with HR 0.37, 95% CI, 0.24–0.57; use of transdermal estradiol: HR 0.46, 95% CI, 0.25–0.82, *P*=.008	No comparator

WHI, Women's Health Initiative; CEE, conjugated equine estrogen; HR, hazard ratio; RR, relative risk.
[*] Meta-analysis of nine trials. The Women's Health Initiative was not included because it is described in Chlebowski et al, 2020[2].

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these participants took study medications for a median of 5.6 years. Participants who had undergone hysterectomy were randomized to CEE or placebo; these participants took study medications for a median of 7.2 years. The WHI MHT trials excluded women with a personal history of breast cancer. With a 13-year follow-up, a small, but statistically significant, elevated risk of invasive breast cancer was noted among individuals who were randomized to CEE and MPA (hazard ratio [HR] 1.28; 95% CI, 1.11–1.48). In contrast, a significant reduction in breast cancer risk was noted among individuals randomized to CEE alone (HR 0.79; 95% CI, 0.65–0.97).[1]

With more than 20 years of follow-up, the small, but statistically significant, elevated risk of breast cancer persisted among participants randomized to CEE and MPA (HR 1.28; 95% CI, 1.13–1.45). An elevated risk of mortality from breast cancer was also noted with CEE and MPA; however, this elevated risk did not achieve statistical significance. In contrast, among the WHI participants randomized to CEE alone, the previously observed significant reduction in the risk of breast cancer persisted (HR 0.78; 95% CI, 0.65–0.93). The annualized incidence of breast cancer was 30 per 10,000 for women randomized to CEE compared with 37 per 10,000 for women randomized to placebo. In addition, a statistically significant 40% reduction in breast cancer mortality was noted among those randomized to CEE alone (HR 0.60; 95% CI, 0.37–0.97).[2]

It is notable that CEE is the only medication that has been shown to reduce breast cancer mortality. Chemoprevention trials of tamoxifen and aromatase inhibitors have not demonstrated reduced mortality from breast cancer.[3]

OTHER DATA REGARDING ESTROGEN-ONLY THERAPY AND RISK OF BREAST CANCER

To assess whether findings that CEE alone reduced the risk of breast cancer were limited only to the WHI or only to CEE use, the WHI investigators performed a meta-analysis that aggregated findings from the WHI trial of CEE alone with data from nine smaller randomized trials of menopausal estrogen-alone therapy. The duration of estrogen usage in these trials ranged from 1 to 10 years, and the aggregate number of participants was 14,282; 5,605 individuals used CEE and 543 used estrogen only. In the pooled analysis, this 2024 report noted that estrogen-only therapy significantly reduced risk of breast cancer by 23% (relative risk [RR] 0.77; 95% CI, 0.65–0.91), with a 3.6% risk for individuals randomized to estrogen alone compared with 4.7% for those randomized placebo. In an analysis that aggregated the findings of five small trials that assessed estradiol use, the investigators noted a similar degree of protection from breast cancer as observed with CEE; however, this comparison did not achieve statistical significance (RR 0.63; 95% CI, 0.34–1.16). In their concluding comments, the authors of the meta-analysis stated, "The totality of randomized clinical trial evidence supports that estrogen alone use significantly reduces breast cancer incidence."[4]

To assess the effect of hormone therapy on risk of breast cancer in younger women, National Institutes of Health–based investigators pooled data from 10 prospective (observational) cohort studies that assessed the risk of invasive breast cancer or ductal carcinoma in situ diagnosed in individuals younger than age 55 years. Among 459,476 individuals diagnosed with breast cancer or ductal carcinoma in situ during a median follow-up of 7.8 years, 6% used estrogen–progestin therapy and 5% used estrogen-only therapy. Compared with no use of hormone therapy, a small, nonsignificant elevated risk of breast cancer (HR 1.10; 95% CI, 0.98–1.24) was noted among those who used estrogen–progestin. In contrast, use of estrogen-only therapy was associated with a significantly reduced risk of breast cancer (HR 0.86; 95% CI, 0.75–0.98). Unfortunately, this 2025 report did not include data on which estrogen formulations were used.[5]

Conjugated equine estrogen, a complex mixture of equine estrogens, may well be a selective estrogen receptor modulator, which could explain why its use reduces breast cancer incidence. Most of the data that demonstrates reduced breast cancer incidence with estrogen-only therapy relates to CEE. Accordingly, more studies, preferably randomized trials, are needed to more definitively assess the effect of estradiol on risk of breast cancer.

MENOPAUSAL HORMONE THERAPY IN SURGICALLY MENOPAUSAL PATIENTS

Individuals with surgical menopause (prior BSO) experience more severe menopausal symptoms than those who have natural menopause.[6,7] In addition, observational studies suggest that estrogen deficiency in those with surgical menopause is associated with an increased risk for CVD, other chronic diseases, and all-cause mortality and that many of these adverse outcomes can be mitigated by use of MHT.[8–10]

USE OF MENOPAUSAL HORMONE THERAPY IN PATIENTS WITH PATHOGENIC *BRCA1/2* VARIANTS WITH INTACT BREASTS WHO

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Box 1. Examples of Individuals Who Have Completed Their Reproductive Plans and Are Considering Gynecologic Surgery Include Those:

- considering surgery for benign adnexal disease (eg, ovarian cyst or endometriosis) or cervical intraepithelial neoplasia
- considering medical (eg, intrauterine or oral progestin therapy, or tranexamic acid) vs surgical management of abnormal uterine bleeding
- weighing the pros and cons of endometrial ablation vs hysterectomy for abnormal uterine bleeding
- with symptomatic uterine fibroids and are making decisions regarding uterine-sparing treatments such as myomectomy and uterine artery embolization vs hysterectomy

HAVE UNDERGONE RISK-REDUCING BILATERAL SALPINGO-OOPHORECTOMY

As awareness of hereditary breast and ovarian cancer has increased among clinicians and our patients, the costs of genetic testing have decreased and more people are being diagnosed with *BRCA1*and *BRCA2* mutations. These pathogenic variants, which are associated with an elevated lifetime risk of breast cancer, occur in approximately 1 in 280 (0.35%) individuals.[11] To decrease future risk of tubal, ovarian and peritoneal cancers, the National Comprehensive Cancer Network recommends that individuals with *BRCA1* and *BRCA2* mutations undergo risk-reducing BSO at age 35–40 years and age 40–45 years, respectively.[12]

Since initial publication of the WHI's findings from the trial of estrogen–progestin therapy in 2002, a profound and persistent decline in use of MHT has occurred, reflecting safety concerns regarding use of MHT among patients and clinicians.[13] Given these safety concerns, it is not surprising that patients with *BRCA* mutations with no personal history of breast cancer may be apprehensive about the safety of MHT. Although randomized trials that address the safety of MHT in those with *BRCA* mutations are not available, observational studies have addressed the risk of breast cancer among women with *BRCA* mutations and intact breasts who use systemic MHT. These studies have not observed a higher risk of breast cancer in patients with pathogenic variants and intact breasts who use MHT.[14]

A matched prospective analysis published in 2025 compared the risk of incident breast cancer in 676 patients who had *BRCA* mutations (35 patients used estrogen therapy; of those, 30 used oral or transdermal estradiol) and intact breasts who used MHT (mean duration of therapy almost 5 years) with the breast cancer risk in an identical number of mutation carriers who did not use MHT. Overall, 95% of these mutation carriers had undergone bilateral oophorectomy. During follow-up, almost one-quarter of participants underwent bilateral mastectomy (18.6% of MHT users and 28.7% of nonusers). The investigators discontinued follow-up of participants at the time of bilateral mastectomy, thereby avoiding confounding related to mastectomy status. After a mean follow-up of almost 6 years, the incident breast cancer rate was lower among pathogenic variant carriers who used MHT (12.9% vs 18.9%; P=.002). The estimated 15-year cumulative incidence of breast cancer with estrogen alone compared with no MHT was 24.3%, compared with 47.3% in the matched control group (P<.0001). These findings suggest that usage of MHT is safe for *BRCA* mutation carriers. With respect to usage of estrogen–progestogen MHT, risk of breast cancer was similar in users and nonusers. Compared with patients in the matched control group who had not used MHT, the risk of incident breast cancer was 63% lower (HR 0.37; 95%: CI, 0.24–0.57) among individuals who used estrogen-only therapy.[15] Among *BRCA* carriers who used estrogen-only therapy, the most common route and type of estrogen was transdermal estradiol, which was associated with a 54% lower risk of breast cancer (HR 0.46; P=.008). The HRs for the use of oral estradiol or CEE suggested a similar degree of protection from breast cancer as transdermal estradiol, but due to small numbers, these comparisons did not achieve statistical significance. In this report, the authors, who have specific expertise in caring for women with hereditary breast cancer, did not recommend changes in screening mammography or magnetic resonance imaging for variant carriers who have intact breasts and use MHT. In their conclusion, the authors of this report, which represents the largest analysis of the safety of MHT in *BRCA* carriers, stated "The observed protective effect of E alone on breast cancer risk suggests that a hysterectomy might be considered at the time of oophorectomy so that women can avail themselves of the potential benefit of unopposed estrogen."[15] We agree with this conclusion and note that breast cancer prevention along with traditional reasons to consider hysterectomy when performing risk-reducing BSO in mutation carriers–the small, elevated risk of endometrial cancer in this population and the elevated risk of bleeding, endometrial polyps, and endometrial cancer

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with tamoxifen use—collectively make a case for considering hysterectomy in this setting.

HOW MIGHT ESTROGENS REDUCE RISK OF BREAST CANCER?

Unanswered questions remain regarding the association between estrogen-only therapy and risk of breast cancer. By blocking estrogen receptors, tamoxifen prevents recurrence of estrogen receptor-positive breast cancers. By diminishing endogenous production of estrone, aromatase inhibitors reduce risk of recurrent estrogen receptor-positive tumors in menopausal women. Accordingly, it appears counterintuitive that CEE and estradiol prevent incident breast malignancies. In preclinical studies, CEE and estradiol demonstrate pro-apoptotic properties,[16,17] and the sensitivity of breast tumor cells to the apoptotic properties of estrogen increases when estrogen deprivation precedes exposure to estrogen.[18]In the WHI trial of participants who underwent hysterectomy, the reduction of breast cancer risk with use of CEE initially was greater among participants with a gap time (time from menopause to initiation of estrogen-only therapy) of 5 or more years. However, over follow-up, the association between gap time and the prevention of breast cancer diminished. Accordingly, the protection menopausal estrogen-only therapy offers against time-associated tumor cell apoptosis are not limited to sensitivity of tumor cells to gap time-related apoptosis.[4]

COMPARED WITH CONJUGATED EQUINE ESTROGEN, LESS DATA ADDRESS RISK OF BREAST CANCER WITH ESTRADIOL

Since the publication of the initial WHI findings, U.S. clinicians have been moving away from CEE in favor of prescribing estradiol, including transdermal formulations. It is important to recognize that most available data that address estradiol use and risk of breast cancer are observational and, thus, subject to bias. Might women who undergo hysterectomy process estrogen differently from other women, leading to different breast cancer outcomes among women who have surgery? Concerns regarding this and other potential sources of bias underscore the importance of future randomized trials of estradiol and the risk of breast cancer in patients after hysterectomy.

HYSTERECTOMY AND CARDIOVASCULAR DISEASE

In premenopausal patients, hysterectomy with ovarian conservation is associated with an approximately twofold risk of ovarian failure.[19] Menopause before age 40 years in individuals with intact ovaries is associated with a 54% elevated risk of CVD.[20] Cardiovascular disease, not breast cancer, represents the leading cause of death in U.S. women. Accordingly, when making decisions regarding hysterectomy, the potential effect of this surgery with respect to risk of CVD merits consideration.

When performed in premenopausal patients, bilateral oophorectomy with or without hysterectomy results in surgical menopause. Compared with individuals experiencing natural or spontaneous menopause, patients with surgical menopause experience an abrupt decline in serum estradiol levels, resulting in more severe menopausal symptoms. Observational studies suggest that, in addition, estrogen declines associated with surgical menopause increase risk for chronic diseases, including coronary heart disease.[9,21]

The Nurses' Health Study is a large survey-based prospective cohort study of U.S. nurses, with long-term follow-up. In a 2013 report based on nurses in the original Nurses' Health Study cohort, among individuals younger than 50 at the time of hysterectomy, bilateral oophorectomy was associated with significantly increased risk of all-cause mortality as well as mortality from coronary heart disease in nurses who had never used estrogen-only therapy, but not among women who were past or current estrogen-only therapy users.[8]

In a 2025 publication, investigators pooled data obtained from the original Nurses' Health Study (initiated in 1976) as well as the Nurses' Health Study II (initiated in 1989) to assess the association between hysterectomy with or without bilateral oophorectomy and risk of CVD (myocardial infarction, coronary artery bypass graft, or stroke). When the original Nurses' Health Study and Nurses' Health Study II data are pooled, the risk of CVD overall was higher among nurses who underwent hysterectomy before age 50 years. Compared with those not having surgery, nurses who underwent hysterectomy without oophorectomy at any age and used estrogen had a similar risk of CVD as women not having surgery. In the pooled analysis of Nurses' Health Study and Nurses' Health Study II data, nurses who underwent hysterectomy without BSO before age 46 years and did not use estrogen had a 21.0% increased risk of CVD. Compared with those who did not have surgery, nurses younger than age 46 years who underwent hysterectomy with bilateral oophorectomy and used estrogen had a 26% increased risk of CVD; nurses aged 46–50 years had an 11% increased risk of CVD.[22] An important caveat when interpreting these findings is that details regarding duration of estrogen use are not available. Women in Nurses' Health Study

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II were substantially less likely to have used estrogen than those in the original Nurses' Health Study.[21] This likely reflects the precipitous decline in use of MHT after the publication of the initial WHI findings in 2002.[13] Furthermore, and likely reflecting post-WHI concerns, the median duration of estrogen-only therapy use among U.S. patients with private insurance after BSO from 2008 to 2016 was only 5.3 months.[23] Accordingly, hesitancy to use MHT after the WHI study may explain why a history of estrogen use was found to be protective against CVD in surgically menopausal individuals in the 2013 Nurses' Health Study report, but not in the 2025 report.

HELPING OUR PATIENTS MAKE SOUND, EVIDENCE-BASED DECISIONS REGARDING HYSTERECTOMY

With multiple lines of evidence noting a lower risk of breast cancer with estrogen-only therapy, how should we counsel patients at risk for breast cancer who have completed childbearing and are planning gynecologic surgery (Box 1)?

Currently, we encourage many patients with the clinical scenarios detailed in Box 1 to consider uterine conservation. However, should future high-quality data support that estradiol therapy reduces breast cancer risks among patients who have undergone hysterectomy, such evidence would change how we counsel such patients about surgery. Until then, counseling regarding the pros and cons of hysterectomy in this clinical context should involve shared decision-making that addresses the future risk of breast and endometrial cancer, CVD as well as the morbidity associated with hysterectomy. Such counseling should also describe the availability of uterine-sparing alternatives, as the previous examples detail.

Clinicians who caring for patients who undergo hysterectomy with ovarian conservation in their premenopausal years should be alert to the possibility of early menopause, checking estradiol and follicle stimulating hormone levels if such patients report menopausal symptoms such as hot flashes. If the laboratory assessment suggests menopause, clinicians should recommend estrogen-only therapy in the absence of contraindications. In such patients, the use of estrogen-only therapy at least until the normal age of menopause (51–52 years) should be encouraged.[24]

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