Menopausal hormone therapy and the risk of breast cancer

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INTRODUCTION

We consider the initiation of menopausal hormone therapy (MHT) to be a safe option for healthy, symptomatic women who are within 10 years of menopause or younger than age 60 years and who do not have contraindications to MHT (such as a history of breast cancer, coronary heart disease [CHD], a previous venous thromboembolic event or stroke, or active liver disease). Long-term use of MHT for prevention of disease is not currently recommended.

One of the greatest concerns of women who are considering MHT is the relationship between hormone use and breast cancer. Data from the WHI suggest a small increase in risk with combined estrogen-progestin therapy, but a reduction in risk with short-term unopposed estrogen therapy. (See 'Women's Health Initiative' below.)

The impact of exogenous estrogen, alone or combined with a progestin, on breast cancer risk will be reviewed here. The relationship between endogenous hormones and breast cancer, a general discussion of the risks and benefits of MHT, and an overview of menopausal symptom management are discussed separately. (See "Factors that modify breast cancer risk in women" and "Menopausal hormone therapy: Benefits and risks" and "Treatment of menopausal symptoms with hormone therapy".)

ENDOGENOUS HORMONES

Support for the association of menopausal hormone therapy (MHT) with breast cancer is derived from studies that suggest that prolonged exposure to higher concentrations of endogenous estrogen increases the risk of breast cancer. These risk factors include:

- Reproductive factors, including age at menarche, age at first live birth, age at menopause, parity, and breastfeeding. (See "Factors that modify breast cancer risk in women", section on 'Reproductive factors'.)
- High endogenous estrogen levels increase the risk of breast cancer (particularly hormone receptor-positive breast cancer) in both post- and premenopausal women. (See "Factors that modify breast cancer risk in women".)
- Bone mineral density (BMD) is considered a surrogate marker for long-term exposure to endogenous and exogenous estrogen; women with higher bone density have a higher breast cancer risk. (See "Factors that modify breast cancer risk in women", section on 'Bone mineral density'.)
- Higher weight/body mass index (BMI) and postmenopausal weight gain have been associated with a higher risk of postmenopausal breast cancer in multiple studies. The association between a higher BMI and postmenopausal breast cancer risk may be explained by higher estrogen levels resulting from the peripheral conversion of estrogen precursors (from adipose tissue) to estrogen. (See "Factors that modify breast cancer risk in women", section on 'Weight and body fat in postmenopausal women'.)

EXOGENOUS HORMONE THERAPY

Epidemiologic data — Multiple observational studies have shown an increased risk of breast cancer with multiyear use of menopausal hormone therapy (MHT), which includes unopposed estrogen therapy and combined estrogen-progestin therapy [1,2]. A 1997 meta-analysis of 51 epidemiologic studies comprising 52,705 women with and 108,411 women without breast cancer found that for each year a woman uses MHT, her risk of breast cancer increases by 2.3 percent [1]. However, many, if not most, women at that time were using conjugated estrogens and medroxyprogesterone acetate. Current MHT regimens typically include lower doses of estrogen (often transdermal 17-beta estradiol) with micronized progesterone (which may be associated with lower breast cancer risk than medroxyprogesterone acetate, although this is not yet proven). (See 'Type of progestin' below.)

Women's Health Initiative — The limitations of observational studies were overcome in the randomized, placebo-controlled Women's Health Initiative (WHI) trial [3]. However, the

population studied in the WHI was considerably older than the typical, recently menopausal woman who starts taking MHT for symptoms such as hot flashes (see "Clinical manifestations and diagnosis of menopause", section on 'Symptoms'). The overall results of this trial (which was stopped early because of excess breast cancer risk), adverse cardiovascular effects, and no evidence of overall health benefit [3] are discussed in detail elsewhere. (See "Menopausal hormone therapy: Benefits and risks".)

Combination therapy — In the WHI combination estrogen-progestin (conjugated equine estrogens [CEE] 0.625 mg/day and medroxyprogesterone acetate [MPA] 2.5 mg/day) arm, the risk of invasive breast cancer was increased at an average follow-up of 5.6 years (hazard ratio [HR] 1.2) compared with placebo (figure 1) [4]. The increase in risk was first seen in year 3 in women who had previously used menopausal hormones, but not until year 4 in women with no previous use.

From an individual perspective, a critical issue is the **absolute risk** of developing breast cancer. In the combined estrogen-progestin WHI trial, there were eight excess cases per 10,000 person-years at an average of 5.2 years [3].

After the active intervention arms were stopped in the WHI, several updates with longer follow-up have been published [5,6]. During the intervention phase, there were 206 and 155 cases of invasive breast cancer in the combined hormone therapy and placebo groups, respectively (HR 1.24, 95% CI 1.01-1.53) [5]. Most risks and benefits decreased postintervention, but some excess breast cancer risk persisted during 13 years of cumulative follow-up (434 cases for CEE plus MPA versus 323 for placebo; HR 1.28, 95% CI 1.11-1.48).

The attributable risk of breast cancer in women in their 50s, the group most likely to take hormone therapy for menopausal symptoms, is very low [7]. In the Endocrine Society Clinical Practice Guideline, the estimated additional risk of breast cancer based upon WHI data was three additional cases per 1000 women for five years of combined conjugated estrogen-MPA use (figure 2) [8]. (See "Menopausal hormone therapy: Benefits and risks", section on 'Estimates of risk in women 50 to 59 years'.)

Unopposed estrogen — During the active intervention phase (median duration 5.9 years), there was a nonsignificant lower risk of breast cancer (104 versus 135 cases in the estrogen and placebo groups, respectively (HR 0.79, 95% CI 0.61-1.02) [6]. With median follow-up of 13 years, there were 168 versus 216 cases of breast cancer, respectively (HR 0.79, 95% CI 0.65-0.97).

The attributable risk of breast cancer for women in their 50s taking unopposed estrogen is also very low. As noted above, the Endocrine Society Clinical Practice Guideline, using WHI data, estimated the excess risk of breast cancer related to hormone use. For unopposed conjugated

estrogen, they estimated there would be 2.5 fewer cases of breast cancer per 1000 women (in their 50s) taking hormones for five years (figure 2). (See "Menopausal hormone therapy: Benefits and risks", section on 'Estimates of risk in women 50 to 59 years'.)

These data provide reassurance for postmenopausal women who have had a hysterectomy and would like to take estrogen for symptoms. We do not propose that unopposed estrogen therapy be used for breast cancer risk reduction, as there are abundant observational data that estrogen is eventually associated with excess risk.

Mammographic density — Data from a subset of the WHI trial showed that mammographic density increased with both combined estrogen-progestin and unopposed estrogen therapy. For combined therapy, breast density increased 4.9 percent at year 2 compared with a 0.8 percent decrease in the placebo group [9].

In the unopposed estrogen arm, estrogen use was associated with a smaller but still significant increase in breast density compared with placebo (absolute difference 2.9 percent at two years) [10]. (See "Screening for breast cancer: Strategies and recommendations" and 'Exogenous hormone therapy' above.)

Abnormal mammography — Both combined estrogen-progestin and unopposed estrogen therapy increased the rate of mammograms with short-interval follow-up recommendations, but only combined therapy increased the likelihood of an abnormal mammogram (defined as suggestive of or highly suggestive of malignancy). By the end of the follow-up period, combined therapy, when compared with placebo, significantly increased both the cumulative frequency of abnormal mammograms (35 versus 23 percent, respectively) and the need for breast biopsies (10 versus 6.1 percent) [11].

In contrast, the use of unopposed estrogen increased the rate of mammograms requiring short-interval follow-up (cumulative rate by the end of the trial 39.2 versus 29.6 percent for unopposed estrogen therapy versus placebo) [12], but not abnormal mammograms.

Stopping MHT (either combined therapy or unopposed estrogen) short term does **not** reduce the rate of abnormal mammograms. In a separate, randomized trial of 1704 postmenopausal women taking MHT who were due for an annual mammogram, suspending MHT for one to two months reduced breast density slightly, but it did not significantly reduce mammography recall rates [13].

Duration of use — In most studies, the risk of breast cancer does not appear to be increased in women who take combined estrogen-progestin therapy for less than four or five years, but then increases with longer duration of use [1,14]. The analysis of epidemiologic studies cited above

found that the relative risk (RR) of developing cancer was 1.35 for women who were current hormone users and had taken hormones for five years or longer compared with never users (figure 3) [1]. A similar timeframe was noted in the WHI (figure 1), although the increase in risk was seen after only three years in women who had previously used menopausal hormones [4].

Of note, most available data, including the WHI, are based upon oral conjugated estrogens. It is not known if different types of estrogens or different routes of estrogen administration would be associated with different risk profiles.

For unopposed estrogen, there did not appear to be increased risk of breast cancer in the WHI. However, in an updated report from the Nurses' Health Study of 28,835 women who had undergone hysterectomy, long-term, but not shorter-term, use of unopposed estrogen was associated with a statistically significant increase in breast cancer risk (RR for current use >20 years = 1.42, 95% CI 1.13-1.77) [15]. The risk of estrogen receptor-positive/progesterone receptor-positive (ER+/PR+) cancers became statistically significant after 15 years of unopposed use (RR 1.48, 95% CI 1.05-2.07). Similar results were noted in another prospective cohort study, the Million Women Study (MWS) [16]. However, the MWS also observed an increased risk of breast cancer with less than five years of use, which is in contrast to the WHI and many other studies.

For past users, duration of use does not appear to be strongly related to breast cancer risk. In the combined analysis of epidemiologic studies, women who had stopped MHT more than five years previously were not at increased risk compared with never users, regardless of the duration of previous use [1]. However, there have not been enough data on long-term past users; there may still be a risk associated with past use if the duration was long enough.

Effect of progestins — The randomized WHI study showed that conjugated estrogen plus MPA modestly increased breast cancer risk, compared with estrogen alone. Many of the earlier epidemiologic studies have grouped together unopposed estrogen and combined estrogen-progestin users. The majority of studies that have distinguished between these groups have reported a greater risk of breast cancer in those receiving combined therapy compared with unopposed estrogen [1,2,14,17-21].

There has also been a suggestion that progestin given continuously with estrogen may be associated with higher risk than regimens in which the progestin is given in a cyclic fashion [22,23], but this has not been reported in all studies [2,18]. The WHI used the continuous schedule.

Progestins may cause an increase in cell division in mammary tissue, thereby leading to an accumulation of DNA errors that eventually result in breast cancer or in a greater proliferation of malignant cells [24]. Support for this hypothesis is derived from the observation that the proliferative activity of the breast in premenopausal women is highest during the luteal phase of the menstrual cycle, a time of increasing progesterone secretion (figure 4) [25]. In addition, women treated with combined estrogen-progestin therapy have greater increases in mammographic density and more cell proliferation in benign breast biopsies than those taking unopposed estrogen therapy [26]. However, in vivo [27] and in vitro studies [28] have found differing effects of progesterone on breast cell proliferation.

Type of progestin — The type of progestin may also affect breast cancer risk. A synthetic progestin, MPA, was used in the WHI trial and was associated with excess breast cancer risk. Limited observational data suggest that natural micronized progesterone may not be associated with additional risk. In a prospective cohort study of approximately 80,000 women, menopausal hormone regimens containing estrogen plus a synthetic progestin were associated with an excess breast cancer risk, while regimens containing estrogen plus natural progesterone were not [29]. (See "Preparations for menopausal hormone therapy", section on 'Progestin preparations'.)

Prognosis and tumor characteristics — The impact of MHT on breast cancer tumor characteristics is unclear. Epidemiologic studies have suggested that breast cancer in women taking MHT (unopposed estrogen or combined estrogen-progestin) has a relatively good prognosis and improved survival when compared with breast cancer that develops in women not taking MHT [30-34]. However, women who take MHT may be more compliant with mammography than non-MHT users.

In the 2015 update of the WHI trials, the authors provided numbers for the tumor characteristics across intervention and placebo but only reported on the differences between tumors that developed during the intervention and post-intervention phases [5]. Overall, in both hormone therapy groups, there was no significant difference in the types of tumors that developed during the intervention and postintervention across a variety of characteristics, including ER, PR, HER2, nodal status, and tumor size. Breast cancer mortality is described in the next section.

Mortality — In a 2017 WHI report on mortality based upon a cumulative follow-up of 18 years, there was a nonsignificant increase in breast cancer mortality in the combined therapy group and a significant decrease in the unopposed estrogen group (HR 1.44, 95% CI 0.97-2.15 [p = 0.07] and HR 0.55, 95% CI 0.33-0.92 [p = 0.02], respectively) [35]. There was no excess risk of all-

cause, cardiovascular, or cancer mortality with either regimen. (See "Menopausal hormone therapy: Benefits and risks", section on 'Mortality'.)

Timing of hormone therapy — Whether the benefits and risks of MHT vary with age of initiation relative to women's age at menopause is controversial. For cardiovascular disease, some data suggest that women who start closer to the time of natural menopause may derive more benefit than those who start later. However, limited data on breast cancer suggest that women who start MHT around the time of menopause may be at greater risk of developing breast cancer than those who start later after menopause [36-38]. However, all of the studies to date that have evaluated time since menopause have not been able to fully adjust for the fact that women who start closer to age at menopause generally have longer durations of use, so the increased risk may be due to duration rather than age at menopause.

OTHER ISSUES

Women with a family history of cancer — Overall, the available epidemiologic evidence suggests that the magnitude of risk conferred by menopausal hormone therapy (MHT) in women with and without a family history of breast cancer is similar [39,40]. However, women with a positive family history already have a higher baseline risk than women without a family history and may also be more concerned about behaviors that would modify their breast cancer risk. Some experts suggest calculating overall breast cancer risk before initiating MHT [8]. (See "Treatment of menopausal symptoms with hormone therapy", section on 'Calculating risks'.)

Effect of testosterone — Although data are limited, the addition of exogenous testosterone therapy to MHT does not appear to impact breast cancer risk [41,42].

Effect of alcohol — Menopausal women on MHT who also drink alcohol may be at considerably higher risk for breast cancer than women who take MHT alone or who drink alcohol alone. As an example, in the prospective Nurses' Health Study, the risk of breast cancer was significantly increased in women who took MHT for more than five years but did not consume alcohol (relative risk [RR] 1.32) and for those who drank at least 1.5 to 2 drinks per day but did not take MHT (RR 1.28) [43]. For women who used MHT for more than five years **and** drank at least 1.5 to 2 drinks daily, the RR was even higher at 1.99. Thus, postmenopausal women on MHT should be cautioned about the added risk of alcohol.

Women with primary ovarian insufficiency — Data from the Women's Health Initiative (WHI) should not be extrapolated to women with primary ovarian insufficiency (premature ovarian failure; menopause before age 40 years) in whom MHT is generally initiated at a much younger

age. Issues in these women are discussed in detail elsewhere. (See "Management of primary ovarian insufficiency (premature ovarian failure)".)

Effect of race on risk — The increase in risk of breast cancer associated with MHT appears to be similar in Black and White women as illustrated by data from the WHI and the Black Women's Health Study [44].

Personal history of breast cancer — We recommend that MHT **not** be given to women with a personal history of breast cancer, although menopausal symptoms (hot flashes) are an important issue for breast cancer survivors.

Multiple observational studies [45-50] and a systematic review of four studies [51] suggested that MHT in women with treated breast cancer did not increase the risk of recurrence [45-51] and may even be beneficial [52], but there was considerable selection bias regarding which breast cancer survivors took MHT. It is likely that these observational studies did not account completely for residual confounding, with hormone users being overall healthier and at lower risk of recurrence than nonusers.

Two randomized, clinical trials have been conducted among breast cancer survivors, and the results are conflicting. The larger study was the Hormonal Replacement Therapy After Breast Cancer - Is It Safe? (HABITS) trial with follow-up data on 442 women randomized to either MHT (the majority used estradiol with or without norethisterone acetate depending upon the presence of a uterus) versus nonhormonal symptom management. The HABITS trial was stopped early due to an increase in breast cancer events in the MHT arm.

With median follow-up of four years, new breast cancer events occurred almost twice as often in the hormone group compared with the nonhormone group (39 of 221 versus 17 of 221, hazard ratio [HR] 2.4) [53]. The cumulative incidence of a breast cancer event in the hormone and nonhormone groups at five years was estimated at 22 and 8 percent, respectively.

A similar trial in Stockholm was started at the same time as HABITS and also terminated early based upon the results of the HABITS trial and difficulties in recruitment. Unlike the HABITS trial, after 10.8 years of follow-up, there was no significant difference in new breast cancer events overall, with 60 in the MHT group and 48 in the controls (HR 1.3, 95% CI 0.9-1.9), but there **was** an increased risk of contralateral breast cancer with MHT (RR 3.6) [54].

Possible explanations include the use of different progestins (norethisterone acetate in HABITS, medroxyprogesterone acetate [MPA] in Stockholm study), the small number of events in both trials, and a lower-risk patient population with greater use of tamoxifen in the Stockholm trial compared with HABITS. Although the data are not entirely consistent, the increase in risk

observed in the HABITS trial is of great concern [55]. Thus, we agree with expert guidelines that recommend the use of nonestrogen therapies for controlling symptoms before considering MHT in these women [56]. Local therapies with low systemic absorption such as vaginal estrogen preparations would also be reasonable to use in breast cancer survivors. (See "Menopausal hot flashes", section on 'Nonhormonal pharmacotherapy'.)

For *BRCA1/2* carriers who have undergone risk-reducing bilateral salpingo-oophorectomy, a shared decision-making process must include counseling women about nonhormonal options and the lack of population-specific data regarding hormone therapy. Nonhormonal options are considered to be first-line therapy for these women. This is discussed in detail separately. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Hormone therapy'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Menopause".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Menopause (The Basics)")
- Beyond the Basics topics (see "Patient education: Menopause (Beyond the Basics)")

SUMMARY

- The available evidence supports a causal relationship between menopausal hormone therapy (MHT) and breast cancer. (See 'Epidemiologic data' above.)
- On the other hand, short-term use of combined estrogen-progestin therapy (less than four years if no prior use of estrogen) appears not to increase the risk of breast cancer significantly, although it may make mammographic detection more difficult. (See 'Combination therapy' above and 'Mammographic density' above.)
- Unopposed estrogen did not increase the risk of breast cancer in the randomized Women's Health Initiative (WHI) (median duration of use 5.9 years). However, observational studies suggest increased risk with longer-term use >10 years. (See 'Unopposed estrogen' above and 'Duration of use' above.)
- The attributable risks of breast cancer for women in their 50s, the group most likely to take hormone therapy for menopausal symptoms, are very low. In the Endocrine Society Clinical Practice Guideline, the estimated additional risk of breast cancer based upon WHI data was three additional cases per 1000 women for five years of combined conjugated estrogen-medroxyprogesterone acetate [MPA] use. For five years of unopposed conjugated estrogen use, the estimated risk was 2.5 fewer cases. (See 'Combination therapy' above and 'Unopposed estrogen' above.)
- Data on the prognosis of breast cancers that develop in women taking MHT have been somewhat inconsistent. However, in a 2015 update of both WHI hormone therapy trials, there was no significant difference in the types of tumors that developed during the intervention and postintervention phases across a variety of characteristics, including ER, PR, HER2, nodal status, and tumor size. (See 'Prognosis and tumor characteristics' above.)
- The type of progestin may affect breast cancer risk. A synthetic progestin, MPA, was used in the WHI trial and was associated with excess breast cancer risk. Limited observational data suggest that natural micronized progesterone may not be associated with additional risk. (See 'Type of progestin' above.)
- The WHI used oral conjugated estrogens. The effects of other types of estrogens or lower estrogen doses on breast cancer risk are currently unknown. (See 'Women's Health Initiative' above.)

- We recommend **not** using MHT for breast cancer survivors. Local vaginal estrogen preparations could be considered. (See 'Personal history of breast cancer' above.)

- The risks and benefits of MHT and practical aspects of menopausal symptom management use are discussed separately. (See "Menopausal hormone therapy: Benefits and risks" and "Treatment of menopausal symptoms with hormone therapy".)

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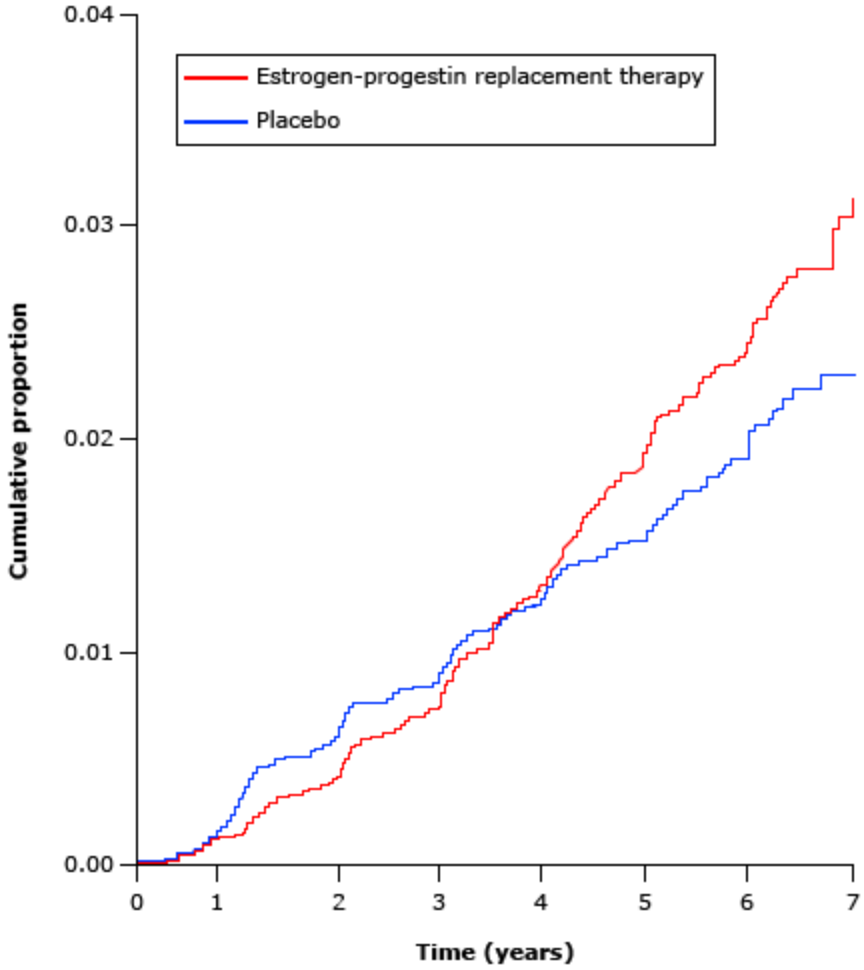
Topic 7392 Version 22.0

GRAPHICS

MHT increases invasive breast cancer



No. at risk								
Estrogen + progestin	8506	8396	8303	8194	7943	5751	3013	1302
Placebo	8102	8002	7895	7793	7581	5430	2696	977

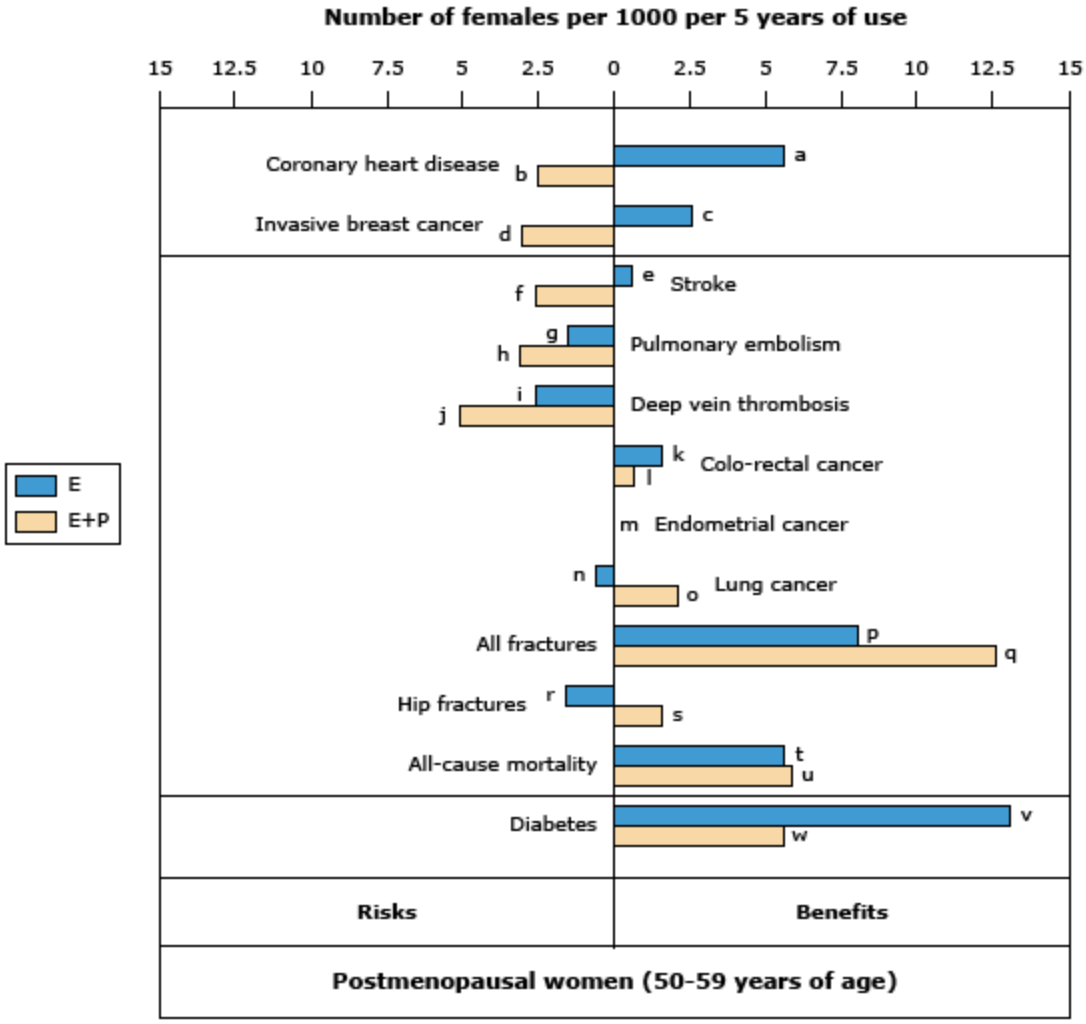
In the Women's Health Initiative (WHI), combined estrogen-progestin replacement therapy was associated with a significant increase in invasive breast cancer (unadjusted HR 1.24, 95% CI 1.01-1.54) when compared with placebo.

MHT: menopausal hormone therapy; HR: hazard ratio.

Data from: Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative randomized trial. JAMA 2003; 289:3243.

Graphic 69819 Version 4.0

Risks and benefits of menopausal hormone therapy (MHT)



Updated summary of the effects of orally administered CEE alone or combined with MPA in females ages 50 to 59 years during intervention phase of WHI. One set of analyses examined the risks and benefits of these agents in females ages 50 to 59 years. This figure plots these data, which are expressed here as excess risks and benefits per 1000 females using MHT for 5 years. Because females deciding to use MHT are more likely to continue this for a period of years rather than 1 year, this figure is constructed according to that assumption. WHI studies were not powered for age-related subset analyses, and none of the data presented in the figure are statistically significant. Nonetheless, this figure represents the best estimates that are available at the present time and are likely more reliable than similar estimates based on observational studies as reported previously in The Endocrine Society Scientific Statement.

The HR (95% CI) values for the bars in the figure are listed here with reference to the alphabetical designations shown next to the bars: (a) HR 0.60 (0.35-1.04); (b) HR 1.34 (0.82-2.19); (c) HR 0.82 (0.50-1.34); (d) HR 1.21 (0.81-1.80); (e) HR 0.99 (0.53-1.85); (f) HR 1.51 (0.81-2.82); (g) HR 1.53 (0.63-3.75); (h) HR 2.05 (0.89-4.71); (i) HR 1.66 (0.76-3.67); (j) HR 3.01 (1.36-6.66); (k) HR 0.71 (0.30-1.67); (l) HR 0.79 (0.29-2.18); (m) HR

1.00 (ns-ns); (n) HR 1.12 (0.45-2.75); (o) HR 0.62 (0.30-1.29); (p) HR 0.90 (0.72-1.11); (q) HR 0.82 (0.68-1.00); (r) HR 5.01 (0.59-42.9); (s) HR 0.17 (0.02-1.45); (t) HR 0.70 (0.46-1.09); (u) HR 0.67 (0.43-1.04); (v) HR 0.83 (0.67-1.04); and (w) HR 0.85 (0.66-1.09).[1]

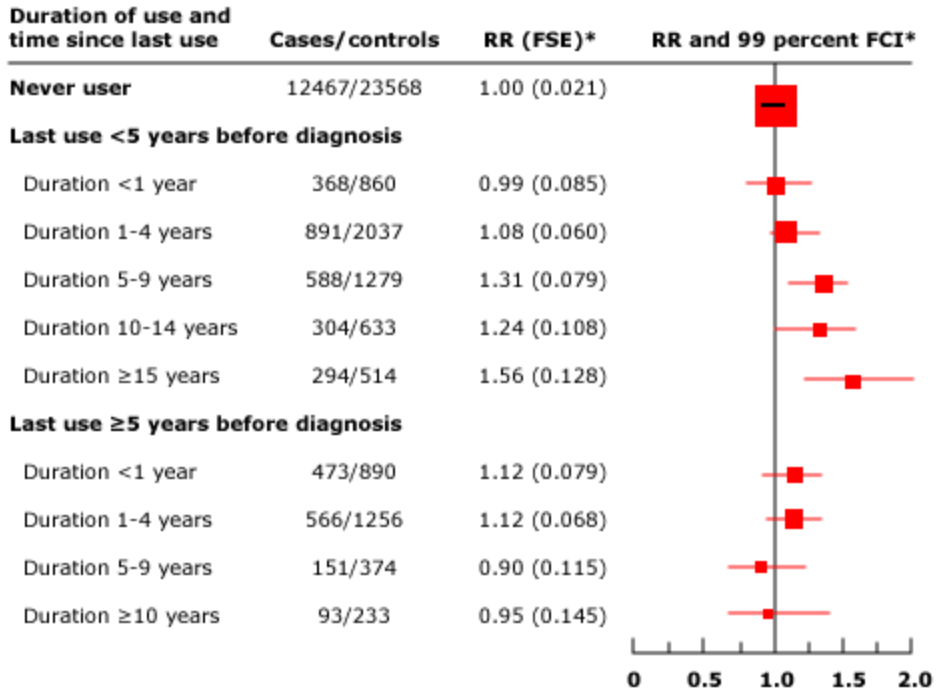
CEE: conjugated equine estrogen; E: estrogen; E+P: estrogen-progestin; HR: hazard ratio; MHT: menopausal hormone therapy; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative.

Reference:

1. *Santen RJ, Stuenkel CA, Burger HG, Manson JE. Competency in menopause management: whither goest the internist? J Womens Health (Larchmt) 2014; 23:281.*

Graphic 87938 Version 6.0

Breast cancer risk and hormone replacement therapy



RR of breast cancer according to the duration of use within categories of time since the last use of hormone replacement therapy. The RR of breast cancer in this analysis of data from 51 epidemiologic studies was highest among women who were current or recent (within five years) users of ERT and had the longest duration of use compared with never users. The RR of developing cancer was 1.35 for women who were current ERT users and had taken hormones for five years or longer.

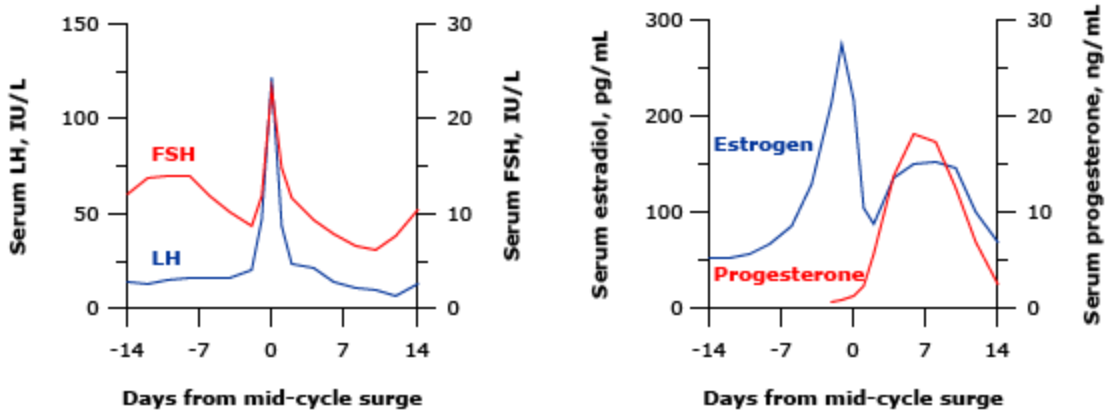
ERT: estrogen replacement therapy; RR: relative risk.

* Relative to never-users, stratified by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born.

"Last use <5 years before diagnosis" includes current users.

Graphic 63013 Version 3.0

Hormonal changes during normal menstrual cycle



Sequential changes in the serum concentrations of the hormones released from the pituitary gland (FSH and LH; left panel) and from the ovaries (estrogen and progesterone; right panel) during the normal menstrual cycle. By convention, the first day of menses is day 1 of the cycle (shown here as day -14). The cycle is then divided into two phases: the follicular phase is from the onset of menses until ovulation, and the luteal phase is from ovulation until the next menses. To convert serum estradiol values to pmol/L, multiply by 3.67, and to convert serum progesterone values to nmol/L, multiply by 3.18.

LH: luteinizing hormone; IU: international units; FSH: follicle-stimulating hormone.

Graphic 72415 Version 5.0

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Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

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