

# Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women

## US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**IMPORTANCE** Menopause occurs at a median age of 51.3 years, and the average US woman who reaches menopause is expected to live another 30 years. The prevalence and incidence of most chronic conditions, such as coronary heart disease, dementia, stroke, fractures, and breast cancer, increase with age; however, the excess risk for these conditions that can be attributed to menopause alone is uncertain. Since the publication of findings from the Women's Health Initiative that hormone therapy use is associated with serious adverse health effects in postmenopausal women, use of menopausal hormone therapy has declined.

**OBJECTIVE** To update the 2012 US Preventive Services Task Force (USPSTF) recommendation on the use of menopausal hormone therapy for the primary prevention of chronic conditions.

**EVIDENCE REVIEW** The USPSTF reviewed the evidence on the benefits and harms of systemic (ie, oral or transdermal) hormone therapy for the prevention of chronic conditions in postmenopausal women and whether outcomes vary among women in different subgroups or by timing of intervention after menopause. The review did not address hormone therapy for preventing or treating menopausal symptoms.

**FINDINGS** Although the use of hormone therapy to prevent chronic conditions in postmenopausal women is associated with some benefits, there are also well-documented harms. The USPSTF determined that the magnitude of both the benefits and the harms of hormone therapy in postmenopausal women is small to moderate. Therefore, the USPSTF concluded with moderate certainty that combined estrogen and progestin has no net benefit for the primary prevention of chronic conditions for most postmenopausal women with an intact uterus and that estrogen alone has no net benefit for the primary prevention of chronic conditions for most postmenopausal women who have had a hysterectomy.

**CONCLUSIONS AND RECOMMENDATION** The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women. (D recommendation) The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal women who have had a hysterectomy. (D recommendation)

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**Author/Group Information:** The USPSTF members are listed at the end of this article.

**Corresponding Author:** David C. Grossman, MD, MPH ([david.c.grossman@kp.org](mailto:david.c.grossman@kp.org)).

**T**he US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

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## Summary of Recommendations and Evidence

The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women. (D recommendation)

The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal women who have had a hysterectomy (D recommendation) (Figure 1).

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## Rationale

### Importance

Menopause is defined as the permanent cessation of a woman's menstrual cycle. It is typically defined in retrospect, 12 months after a woman's final menstrual period. Menopause occurs at a median age of 51.3 years, and the average US woman who reaches menopause is expected to live another 30 years. The prevalence and incidence of most chronic conditions, such as coronary heart disease, dementia, stroke, fractures, and breast cancer, increase with age; however, the excess risk for these conditions that can be attributed to menopause alone is uncertain. Since the publication of findings from the Women's Health Initiative (WHI) that hormone therapy use was associated with serious adverse health effects in postmenopausal women, use of menopausal hormone therapy has declined, from 44% of US women using or having used hormone therapy in 1988-1994 to 4.7% of women in 2010.<sup>1</sup>

### Benefits of Preventive Medication

#### Combined Estrogen and Progestin

Many health outcomes potentially associated with the use of hormone therapy in postmenopausal women have been examined. The USPSTF found convincing evidence that use of combined estrogen and progestin has a moderate benefit in reducing the risk of fractures in postmenopausal women and adequate evidence that it has a small benefit in reducing the risk of diabetes.

#### Estrogen Alone

The use of estrogen without progestin has generally been restricted to women who have had a hysterectomy, because unopposed estrogen use increases the risk of endometrial cancer in women with an intact uterus. The USPSTF found convincing evidence that use of estrogen alone has a moderate benefit in reducing the incidence of fractures in postmenopausal women. The

USPSTF found adequate evidence that the use of estrogen alone has a moderate benefit in reducing the risk of developing or dying of invasive breast cancer and a small benefit in reducing the risk of diabetes. The USPSTF found convincing evidence that estrogen use does not have a beneficial effect on risk of coronary heart disease.

### Harms of Preventive Medication

#### Combined Estrogen and Progestin

The USPSTF found convincing evidence that use of combined estrogen and progestin is associated with moderate harms, including increased risk of invasive breast cancer and venous thromboembolism, and a small to moderate harm of increased risk of coronary heart disease. The USPSTF also found adequate evidence of other moderate harms, such as increased risk of stroke, dementia, gallbladder disease, and urinary incontinence.

#### Estrogen Alone

The USPSTF found adequate evidence that use of estrogen alone is associated with moderate harms, including increased risk of stroke, dementia, gallbladder disease, urinary incontinence, and venous thromboembolism.

### USPSTF Assessment

The USPSTF concludes with moderate certainty that the use of combined estrogen and progestin has no net benefit for the primary prevention of chronic conditions in most postmenopausal women with an intact uterus.

The USPSTF concludes with moderate certainty that the use of estrogen alone has no net benefit for the primary prevention of chronic conditions in most postmenopausal women who have had a hysterectomy.

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## Clinical Considerations

### Patient Population Under Consideration

This recommendation statement applies to asymptomatic, postmenopausal women who are considering hormone therapy for the primary prevention of chronic medical conditions (Figure 2). It does not apply to women who are considering hormone therapy for the management of menopausal symptoms, such as hot flashes or vaginal dryness. It also does not apply to women who have had premature menopause (primary ovarian insufficiency) or surgical menopause.

### Assessment of Risk

This recommendation statement applies to an average-risk population. Risk factors for a specific chronic condition or individual characteristics that affect the likelihood of experiencing a specific therapy-associated adverse event may cause a woman's net balance of benefits and harms to differ from that of the average population.

### Treatment and Intervention

Menopausal hormone therapy refers to the use of combined estrogen and progestin in women with an intact uterus, or estrogen alone in women who have had a hysterectomy, taken at or after the time of menopause. For this recommendation, the USPSTF considered evidence on the benefits and harms of systemic (ie, oral or transdermal) menopausal hormone therapy but not local formulations

Figure 1. US Preventive Services Task Force (USPSTF) Grades and Levels of Certainty

What the USPSTF Grades Mean and Suggestions for Practice		
Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit	
Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
The USPSTF defines certainty as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

(eg, creams or rings) of hormone therapy, because these are not generally used for the primary prevention of chronic conditions.

Indications for hormone therapy approved by the US Food and Drug Administration (FDA) in menopausal women are limited to the treatment of menopausal symptoms and the prevention of postmenopausal osteoporosis. An FDA-issued black box warning indicates that estrogen therapy, with or without progestin, should be prescribed at the lowest effective dose and for the shortest duration consistent with the patient’s treatment goals and risks.<sup>2</sup>

Several different formulations of menopausal hormone therapy are approved by the FDA for use in the United States; the specific formulation used in the WHI trial, the largest trial reviewed by the USPSTF, was 0.625 mg/d of oral conjugated equine estrogens, with

or without 2.5 mg/d of medroxyprogesterone acetate. Currently, evidence to determine whether different types, doses, or modes of delivery of hormone therapy affect its benefit-to-harm profile for the prevention of chronic conditions is limited.<sup>1</sup>

The use of menopausal hormone therapy is associated with both benefits and harms. Combined estrogen and progestin use is associated with a decreased risk of fractures, diabetes, and colorectal cancer; however, it is also associated with an increased risk of invasive breast cancer, coronary heart disease, thromboembolic events, stroke, dementia, gallbladder disease, and self-reported urinary incontinence. Estrogen use alone is associated with a decreased risk of fractures, invasive breast cancer, and diabetes; however, it is also associated with an increased risk of thromboembolic events, stroke, dementia, gallbladder disease,

Figure 2. Clinical Summary: Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women

Population	Postmenopausal women	Postmenopausal women who have had a hysterectomy
Recommendation	Do not use combined estrogen and progestin for the primary prevention of chronic conditions. Grade: D	Do not use estrogen alone for the primary prevention of chronic conditions. Grade: D
	This recommendation statement applies to postmenopausal women who are considering hormone therapy for the primary prevention of chronic medical conditions. It does not apply to women who are considering hormone therapy for the management of menopausal symptoms, or to women who have had premature menopause (primary ovarian insufficiency) or surgical menopause.	
Risk Assessment	These recommendations apply to an average-risk population. Risk factors for a specific chronic condition or individual characteristics that affect the likelihood of experiencing a specific therapy-associated adverse event may cause a woman's net balance of benefits and harms to differ from that of the average population.	
Preventive Medication	Hormone therapy refers to the use of combined estrogen and progestin in women with an intact uterus, or estrogen alone in women who have had a hysterectomy, taken at or after the time of menopause. For this recommendation, the USPSTF considered evidence on systemic (ie, oral or transdermal) menopausal hormone therapy but not local formulations (ie, creams or rings), since they are not generally used for primary prevention. Several different formulations of menopausal hormone therapy are approved by the US Food and Drug Administration for use in the United States; the specific formulation used in the Women's Health Initiative, the largest trial, was 0.625 mg/d of oral conjugated equine estrogens, with or without 2.5 mg/d of medroxyprogesterone acetate.	
Other Relevant USPSTF Recommendations	The USPSTF recommends behavioral counseling interventions to promote a healthful diet and physical activity for the prevention of cardiovascular disease in women who are overweight or obese and have additional cardiovascular disease risk factors. The USPSTF recommends daily low-dose aspirin use to decrease the risk of colorectal cancer and cardiovascular disease in appropriate candidates. The USPSTF recommends offering medications such as tamoxifen and raloxifene to women at increased risk of breast cancer who do not have contraindications and are at low risk of adverse medication effects to decrease the risk of breast cancer.	

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to <https://www.uspreventiveservicestaskforce.org>.



and self-reported urinary incontinence. The reason for the discordant effect of estrogen alone compared with combined estrogen and progestin on the risk of invasive breast cancer is unclear. Table 1 and Table 2 show the estimated absolute event rate differences associated with the use of combined estrogen and progestin and estrogen alone, compared with placebo, for these health outcomes.<sup>1</sup>

### Other Approaches to Prevention

Several interventions and preventive medications to reduce the risk of chronic conditions in women have been studied. For example, the use of medications such as tamoxifen and raloxifene in women at increased risk of breast cancer who do not have contraindications and are at low risk of adverse medication effects is a potential strategy to reduce risk of breast cancer.<sup>3</sup> The USPSTF recommends behavioral counseling interventions to promote a healthful diet and physical activity for the prevention of cardiovascular disease in adults who are overweight or obese and have additional cardiovascular disease risk factors.<sup>4</sup> The USPSTF also recommends daily use of low-dose aspirin to decrease the risk of colorectal cancer and cardiovascular disease in appropriate candidates.<sup>5</sup>

### Other Considerations

#### Research Needs and Gaps

Evidence is limited whether the benefits and harms of menopausal hormone therapy vary by age, race/ethnicity, or timing of initiation

after menopause. In the WHI trial, the test for trend by age group showed a statistically significant trend toward lower all-cause mortality among younger women (aged 50 to 59 years at time of randomization) assigned to estrogen alone but not women assigned to combined estrogen and progestin. There is no evidence that women of different races/ethnicities experience a different balance of benefits and harms with menopausal hormone therapy; however, the majority (approximately 80%) of women in the largest trial (WHI) were white, so these analyses may be underpowered to detect such differences. Data regarding whether the timing of initiation of hormone therapy after menopause affects the balance of benefits and harms are conflicting. A meta-analysis of individual-patient data may be helpful to determine whether the balance of benefits and harms of hormone therapy is different in any of these subgroups.

### Discussion

#### Burden of Disease

Natural menopause occurs at a median age of 51.3 years.<sup>6</sup> The prevalence and incidence of most chronic conditions increase with age, and the average US woman who reaches menopause is expected to live another 30 years.<sup>7</sup> However, the excess risk for these conditions that can be attributed to menopause alone is uncertain. The evidence supporting menopause as a risk factor for chronic disease is strongest for cardiovascular disease and osteoporosis. According to the National Center for Health Statistics, heart disease is the

**Table 1. Estimated Event Rate Difference Associated With Combined Estrogen and Progestin Use vs Placebo in Postmenopausal Women**

Outcome	Absolute Event Rate Difference per 10 000 Woman-Years (95% CI)
<b>Harms</b>	
Breast cancer (invasive)	9 (1 to 19)
Coronary heart disease	8 (0 to 18)
Dementia (probable) <sup>a</sup>	22 (4 to 53)
Gallbladder disease	21 (10 to 34)
Stroke	9 (2 to 19)
Venous thromboembolism <sup>b</sup>	21 (12 to 33)
Urinary incontinence	876 (606 to 1168)
<b>Benefits</b>	
Diabetes	-14 (-24 to -3)
All fractures	-44 (-71 to -13)
Colorectal cancer	-6 (-9 to -1)

<sup>a</sup> Women aged 65 years and older.

<sup>b</sup> Includes deep vein thrombosis and pulmonary embolism.

leading cause of death among women in the United States; in 2013, 289 758 women died from the disease.<sup>8</sup> In 2014, there were more than 267 000 hospitalizations for hip fractures among persons 65 years and older, and overall, 69% of hip fractures occur in women.<sup>9</sup> By 2025, the estimated annual incidence and costs of fractures in the United States will increase by 50%.<sup>10</sup>

### Scope of Review

To update its 2012 recommendation, the USPSTF reviewed evidence about the benefits and harms of systemic (ie, oral or transdermal) hormone therapy for the prevention of chronic conditions in postmenopausal women and whether outcomes vary among women in different subgroups or by timing of intervention after menopause. The use of hormone therapy, whether administered orally, transdermally, or locally for the treatment of menopausal symptoms (eg, vasomotor hot flashes or vulvovaginal symptoms) or for other indications is outside the scope of this recommendation.

### Benefits and Harms of Preventive Medication

The USPSTF found 18 fair- or good-quality trials comparing the effects of combined estrogen and progestin or estrogen alone vs placebo on the prevention of chronic conditions in postmenopausal women.<sup>1</sup> Of these trials, the WHI trial was the largest and was the only trial designed and sufficiently powered to evaluate the effectiveness of hormone therapy for primary prevention of the multiple conditions that are the focus of this recommendation statement.

The WHI trial compared 0.625 mg/d of oral conjugated equine estrogens, both with and without 2.5 mg/d of medroxyprogesterone acetate, vs placebo. Other trials used a variety of estrogenic agents (conjugated equine estrogens, estradiol, or transdermal estradiol) and progestogens (medroxyprogesterone acetate, norethindrone, or micronized progesterone) as active study agents. The WHI trial enrolled women aged 50 to 79 years; the mean age was 63 years.

The WHI trial provided most of the estimates used to assess the benefits and harms of menopausal hormone therapy. Including the posttrial phases, the WHI trial had up to 13 years of follow-up to assess how risks for chronic conditions changed after women stopped

**Table 2. Estimated Event Rate Difference Associated With Estrogen Use Alone vs Placebo in Postmenopausal Women**

Outcome	Absolute Event Rate Difference per 10 000 Woman-Years (95% CI)
<b>Harms</b>	
Dementia (probable) <sup>a</sup>	12 (-4 to 41)
Gallbladder disease	30 (16 to 48)
Stroke	11 (2 to 23)
Venous thromboembolism <sup>b</sup>	11 (3 to 22)
Urinary incontinence	1261 (880 to 1689)
<b>Benefits</b>	
Breast cancer (invasive)	-7 (-14 to 0.4)
All fractures	-53 (-69 to -39)
Diabetes	-19 (-34 to -3)

<sup>a</sup> Women aged 65 years and older.

<sup>b</sup> Includes deep vein thrombosis and pulmonary embolism.

hormone therapy. Data on the effects of menopausal hormone therapy on the risk of chronic conditions for all relevant studies are presented below. Where possible, trial data were combined in a meta-analysis. If this was not possible, trial data are discussed separately.

### Coronary Heart Disease

Observational evidence has suggested that there might be a protective effect of menopausal hormone therapy on coronary heart disease; however, the WHI and other trials have not demonstrated such an effect. Pooled results of 3 trials reporting on the risk of coronary heart disease in women randomized to combined estrogen and progestin vs placebo (N = 18 081) showed a higher risk of coronary events in women who took hormone therapy (relative risk [RR], 1.23 [95% CI, 1.00-1.52]) during a mean follow-up of 5 years<sup>1</sup>; however, this difference did not reach statistical significance.

Postintervention follow-up of women in the WHI trial showed that 2.4 years after stopping combined estrogen and progestin, risk of coronary heart disease was not significantly different between women who took hormone therapy during the trial and those who received placebo (hazard ratio [HR], 1.04 [95% CI, 0.89-1.21]).<sup>11</sup>

Pooled results of 3 trials reporting on the risk of coronary heart disease in women randomized to estrogen alone vs placebo (N = 11 310) showed no statistically significant difference in risk of coronary events between women who took estrogen therapy and those who received placebo (RR, 0.95 [95% CI, 0.79-1.14]).<sup>1</sup>

Postintervention follow-up of women in the WHI trial showed that 3.9 years after stopping estrogen alone, risk of coronary heart disease was not significantly different between women who took hormone therapy during the trial and those who received placebo (HR, 0.97 [95% CI, 0.75-1.25]).<sup>12</sup>

### Breast Cancer

Because estrogen generally stimulates breast cell proliferation, trials of menopausal hormone therapy have reported on the risk of breast cancer as one of the primary adverse outcomes of treatment. Six trials comparing combined estrogen and progestin vs placebo reported on breast cancer incidence. However, only 2 of these trials followed up women for more than 4 years, and only the WHI trial reported on the risk of invasive breast cancer (vs any breast cancer).



During the intervention phase of the WHI trial (median duration, 5.6 years), women assigned to combined estrogen and progestin had a significantly increased risk of invasive breast cancer vs women assigned to placebo (HR, 1.24 [95% CI, 1.01-1.53]). The risk remained significantly increased during a median postintervention follow-up of 8.2 years (HR, 1.32 [95% CI, 1.08-1.61]).<sup>13</sup> In the Heart and Estrogen/Progestin Replacement Study (HERS), more women randomized to combined estrogen and progestin developed breast cancer during the 4.1-year intervention phase than did women who received placebo, but the results were not statistically significant (HR, 1.38 [95% CI, 0.82-2.31]).<sup>14</sup>

In 3 smaller trials (the Estrogen Replacement and Atherosclerosis [ERA],<sup>15</sup> Postmenopausal Estrogen/Progestin Interventions [PEPI],<sup>16</sup> and Estonian Postmenopausal Hormone Therapy [EPHT]<sup>17</sup> trials), the risk of breast cancer incidence was not significantly different between women randomized to receive combined estrogen and progestin and those who received placebo over 3 to 4 years; however, few cases occurred overall. The fourth trial, the Women's International Study of Long Duration Estrogen After Menopause (WISDOM), was stopped after 1 year because of the WHI results indicating excess breast cancer risk in women receiving combined estrogen and progestin; breast cancer incidence was not significantly different between groups at 1 year.<sup>18</sup>

Five trials comparing estrogen alone vs placebo reported on breast cancer incidence; however, only the WHI trial reported on risk of invasive breast cancer. In the WHI trial, women assigned to estrogen alone had a nonsignificant decrease in risk of invasive breast cancer vs women assigned to placebo during the median 7.2-year intervention phase (HR, 0.79 [95% CI, 0.61-1.02]).<sup>12,13</sup> The risk remained lower during the median 6.6-year postintervention phase after the trial had been stopped. The difference between groups was statistically significant during cumulative follow-up (includes trial and postintervention phase; median duration, 13 years) (HR, 0.79 [95% CI, 0.65-0.97]).<sup>13</sup>

In the Estrogen for the Prevention of Re-Infarction Trial (ESPRIT), the risk of breast cancer was not significantly different between women randomized to estrogen alone and those receiving placebo during the 2-year intervention period (RR, 0.98 [95% CI, 0.25-3.91]).<sup>19</sup> In the ERA trial,<sup>15</sup> PEPI trial,<sup>16</sup> and Estrogen in the Prevention of Atherosclerosis Trial (EPAT),<sup>20</sup> there were few cases of breast cancer, and the results were inconclusive.

#### Thromboembolic Events

In the WHI trial, women randomized to combined estrogen and progestin had an increased risk of pulmonary embolism (HR, 1.98 [95% CI, 1.36-2.87]) and deep vein thrombosis (HR, 1.87 [95% CI, 1.37-2.54]) vs women randomized to placebo over a median follow-up of 5.6 years.<sup>13</sup> There was no significant difference between groups in risk of deep vein thrombosis or pulmonary embolism during the 2.4-year postintervention period.<sup>11</sup> Women randomized to estrogen alone had an increased risk of deep vein thrombosis during the mean 7.1-year intervention phase (HR, 1.48 [95% CI, 1.06-2.07]); the risk of pulmonary embolism was not significantly higher than in the placebo group (HR, 1.35 [95% CI, 0.89-2.05]).<sup>13</sup> There was no significant difference between groups in risk of deep vein thrombosis or pulmonary embolism during the 3.9-year postintervention period.<sup>12</sup>

In 3 smaller trials (ERA,<sup>15</sup> EPHT,<sup>17</sup> and the Estrogen Memory Study [EMS]<sup>21</sup>) of combined estrogen and progestin, which varied

in study duration and outcome measures, there was no significant difference in risk of venous thromboembolism between women randomized to hormone therapy vs placebo over 2 to 3 years; however, the number of events was small. One trial of estrogen alone (EPAT<sup>20</sup>) reported no venous thromboembolic events in either group during 2 years of follow-up.

#### Stroke

In the WHI trial, women who took combined estrogen and progestin had a significantly higher risk of stroke vs those who received placebo during the intervention phase (median duration, 5.6 years; HR, 1.37 [95% CI, 1.07-1.76]); during postintervention follow-up, stroke risk was not significantly different between the 2 groups (HR, 1.04 [95% CI, 0.86-1.26]).<sup>13</sup>

Two other trials comparing combined estrogen and progestin vs placebo reported on the incidence of various cerebrovascular events. In the EPHT trial, women randomized to combined estrogen and progestin had an increased risk of any cerebrovascular event vs those randomized to placebo (HR, 2.46 [95% CI, 1.14-5.34]).<sup>17</sup> In EMS, few events occurred over 2 years, and the results were inconclusive.<sup>21</sup>

In the WHI trial, women who took estrogen alone had a statistically significantly higher risk of stroke vs those who received placebo during the intervention phase (median duration, 7.2 years; HR, 1.35 [95% CI, 1.07-1.70]). During postintervention follow-up, the risk of stroke was not significantly different between the 2 groups (HR, 0.92 [95% CI, 0.71-1.19]).<sup>13</sup> In the smaller EPAT<sup>20</sup> and the ERA<sup>15</sup> trial, few events occurred, and the results were inconclusive.

#### Cognitive Impairment

Observational evidence has suggested that menopausal hormone therapy might be associated with a protective effect against dementia or cognitive impairment; however, the WHI Memory Study (WHIMS) did not confirm such an effect. WHIMS and the WHIMS estrogen-only trial evaluated the risk of probable dementia or mild cognitive impairment in women taking combined estrogen and progestin or estrogen alone vs placebo. Both studies were subsets of the WHI trial and were limited to women aged 65 to 79 years at baseline who were free of probable dementia. Women who took combined estrogen and progestin had a higher risk of probable dementia than those who received placebo (HR, 2.05 [95% CI, 1.21-3.48]) but not mild cognitive impairment.<sup>22</sup> Women who took estrogen alone had a higher risk of the composite outcome measure (probable dementia or mild cognitive impairment) (HR, 1.38 [95% CI, 1.01-1.89]) but not probable dementia alone.<sup>23</sup>

#### Gallbladder Disease

In the WHI trial, women randomized to combined estrogen and progestin or estrogen alone had an increased risk of gallbladder disease (HR, 1.59 [95% CI, 1.28-1.97] and HR, 1.67 [95% CI, 1.35-2.06], respectively).<sup>24</sup> Risk of gallbladder disease in the combined estrogen and progestin group decreased postintervention but continued to be greater in the hormone therapy group than in the placebo group (median duration, 8.2 years; HR, 1.24 [95% CI, 1.01-1.52]); the risk of gallbladder disease was no longer significantly different at 6.6 years postintervention in the estrogen-alone group (HR, 0.98 [95% CI, 0.68-1.41]).<sup>13</sup>

### Urinary Incontinence

Both the WHI trial and HERS showed a consistently higher risk of self-reported incident urinary incontinence at all time points in women who took combined estrogen and progestin vs placebo. In the WHI trial, women who took combined estrogen and progestin had a higher risk of incontinence at 1 year (RR, 1.39 [95% CI, 1.27-1.52]) and at 3 years (RR, 1.81 [95% CI, 1.16-2.84]).<sup>25</sup> In HERS, women who took combined estrogen and progestin had a higher risk of incontinence at the 4.2-year follow-up (odds ratio, 1.6 [95% CI, 1.3-1.9]).<sup>26</sup>

Two trials, WHI<sup>25</sup> and Ultra Low Dose Transdermal Estrogen Assessment (ULTRA),<sup>27</sup> provided data on self-reported incident urinary incontinence in women who took estrogen alone vs placebo. In the WHI trial, women who took estrogen alone had an increased risk of urinary incontinence vs those who received placebo at 1 year (RR, 1.53 [95% CI, 1.37-1.71]); results based on smaller samples at 2 (ULTRA) and 3 (WHI) years of treatment did not show any significant differences in incident urinary incontinence.

### Fractures

Pooled results of 5 trials (N = 20 499) showed a significantly reduced risk of fractures in women randomized to combined estrogen and progestin vs placebo (RR, 0.80 [95% CI, 0.68-0.94]).<sup>1</sup>

The WHI trial showed a significantly reduced risk of total osteoporotic fractures in women randomized to estrogen alone vs placebo (HR, 0.72 [95% CI, 0.64-0.80]).<sup>13</sup> The difference was no longer statistically significant in the postintervention phase (duration, 10.7 years); however, this study reported only on hip fractures.<sup>12</sup> The ERA trial found fewer fractures of any type in women who took estrogen alone vs placebo, but the finding was not statistically significant (RR, 0.42 [95% CI, 0.17-1.04]).<sup>15</sup>

### Diabetes

Two trials provided information about the risk of developing diabetes with combined estrogen and progestin (N = 17 903) in women without diabetes or not receiving treatment for diabetes at baseline. Combined estrogen and progestin reduced the risk of incident diabetes in HERS (mean follow-up, 4.1 years; HR, 0.65 [95% CI, 0.48-0.89])<sup>28</sup> and self-reported incident diabetes in the WHI trial (mean follow-up, 5.6 years; HR, 0.81 [95% CI, 0.70-0.94]). This risk reduction was no longer observed 8.2 years postintervention in the WHI trial (HR, 1.19 [95% CI, 1.05-1.34]).<sup>13</sup>

The WHI trial was the only trial to provide information about the risk of self-reported incident diabetes with use of estrogen alone. During a median follow-up of 7.2 years, fewer women who took estrogen alone vs placebo reported a new diabetes diagnosis (HR, 0.86 [95% CI, 0.76-0.98]). The overall reduction in diabetes risk was no longer observed 6.6 years postintervention (HR, 1.07 [95% CI, 0.92-1.25]).<sup>13</sup>

### Colorectal Cancer

Four trials reported on the incidence of colorectal cancer in women receiving combined estrogen and progestin vs placebo. In the WHI intervention phase, women who received combined estrogen and progestin vs placebo were less likely to develop colorectal cancer (HR, 0.62 [95% CI, 0.43-0.89]). Over the median 13.2-year cumulative follow-up period, the risk of colorectal cancer remained numerically lower in the hormone therapy group, but this difference did not reach statistical significance (HR, 0.80 [95% CI,

0.63-1.01]).<sup>13</sup> In HERS, there were fewer cases of colorectal cancer in women randomized to combined estrogen and progestin (vs placebo) over a mean duration of 4.1 years, but the results were not statistically significant (HR, 0.69 [95% CI, 0.32-1.49]).<sup>14</sup> EMS<sup>21</sup> and the WISDOM<sup>18</sup> trial reported no statistically significant differences in risk of colorectal cancer. However, event rates in these studies were low, and the length of follow-up was short (<2 years), which precluded these studies from being combined with the WHI trial and HERS in a meta-analysis.

The WHI trial reported no significant difference in the incidence of colorectal cancer between women randomized to estrogen alone vs placebo during the intervention phase (HR, 1.15 [95% CI, 0.81-1.64]) or the cumulative follow-up period (HR, 1.13 [95% CI, 0.85-1.51]).<sup>13</sup>

### Other Types of Cancer

Both the WHI trial<sup>13</sup> and HERS<sup>14</sup> showed no significant difference in the incidence of lung cancer in women who received combined estrogen and progestin vs placebo during the intervention phase and postintervention follow-up. EMS<sup>21</sup> reported only 1 case of lung cancer, in the hormone therapy group, and its short trial period precluded it from being combined with the WHI trial and HERS in a meta-analysis.

The WHI trial reported no significant difference in lung cancer incidence between women who received estrogen alone and women who received placebo, both during the intervention phase and postintervention follow-up.<sup>13</sup>

In the WHI trial<sup>13</sup> and HERS,<sup>14</sup> the incidence of endometrial cancer during the intervention phase did not differ significantly between women who received combined estrogen and progestin vs placebo. During the WHI postintervention period, statistically significantly fewer women randomized to hormone therapy during the trial phase developed endometrial cancer (HR, 0.58 [95% CI, 0.40-0.86]) than did women who received placebo.<sup>13</sup> Two additional trials, ERA<sup>15</sup> and PEPI,<sup>16</sup> reported no cases of endometrial cancer; however, the trials were too short to be combined with the WHI trial and HERS in a meta-analysis.

In the WHI trial, there was no significant difference in the incidence of invasive ovarian cancer between women who received combined estrogen and progestin vs placebo, both during the intervention phase and postintervention follow-up.<sup>13</sup>

ESPRIT<sup>29</sup> reported no significant difference in the incidence of ovarian cancer between women who received estrogen alone vs placebo during long-term follow-up (which included a 2-year intervention phase and a posttrial observational phase, for an average of 12.6 years).

There was no significant difference in the incidence of cervical cancer among women with an intact uterus who received either combined estrogen and progestin or placebo in the WHI trial.<sup>30</sup>

### All-Cause Mortality

Pooled results of 3 trials (N = 19 580) showed no significant difference in all-cause mortality between women receiving combined estrogen and progestin and those receiving placebo (RR, 1.01 [95% CI, 0.88-1.17]) during a mean follow-up of 5.2 years. Similarly, pooled results of 3 trials reporting all-cause mortality in women randomized to estrogen alone vs placebo (N = 11 961) showed no significant difference between the 2 groups (RR, 1.01 [95% CI, 0.88-1.17])

during a mean follow-up of 6.8 years.<sup>1</sup> A recent WHI analysis showed no significant difference in all-cause mortality between women randomized to combined estrogen and progestin (HR, 1.02 [95% CI, 0.96-1.08]) or estrogen alone (HR, 0.94 [95% CI, 0.88-1.01]) vs placebo during 18 years of cumulative follow-up.<sup>31</sup>

### Subgroups of Interest

Subgroups of interest for this recommendation statement include women grouped according to race/ethnicity; age; duration of hormone therapy use; type, dose, and mode of delivery of hormone therapy; and presence of comorbid conditions.

Trials did not report results for most of these subgroups. Subgroup analyses were limited to those based on race/ethnicity, age, and a small number of comorbid conditions or risk factors. For most outcomes, there were no statistically significant subgroup effects; however, studies may have been underpowered to detect such effects.

In the WHI estrogen-alone trial, statistically significant interactions between age and the risk of all-cause mortality, colorectal cancer, and myocardial infarction, though not total coronary heart disease events, were detected. There were significant trends toward lower risks of these outcomes in younger women (50-59 years) and higher risks in older women (70-79 years) randomized to estrogen alone relative to placebo.<sup>13</sup> However, the multiplicity of outcomes and subgroup comparisons conducted (in these analyses, *P* values for trend by age group were not adjusted for the large number of tests conducted), as well as the small number of events that occurred for some of these outcomes in the estrogen-alone trial subgroups, limit the strength of these findings. These limitations, along with the absence of significant subgroup effects for most outcomes, led the USPSTF to conclude that the evidence was inadequate to determine that any subgroup had a different balance of benefits and harms.

To date, evidence to determine whether different types, doses, or modes of delivery of hormone therapy have a different balance of benefits and harms is limited.

### Timing of Preventive Medication

It has been proposed that hormone therapy initiated closer to the time of menopause may have a more beneficial, or less deleterious, effect on risk of coronary heart disease (and possibly other health outcomes) than hormone therapy initiated later; this proposal has been termed the timing hypothesis. Findings from post hoc subgroup analyses of the WHI trial regarding the effect of timing of hormone therapy initiation on the risk of coronary events are conflicting. In 1 subgroup analysis, women randomized to combined estrogen and progestin within 10 years of menopause did not have the increased risk of coronary heart disease observed in women randomized to hormone therapy more than 20 years postmenopause; however, there was also no beneficial effect in the former group. In contrast, a second subgroup analysis that considered prior hormone therapy use (ie, before trial enrollment), which provides a more accurate assessment of the time between menopause and initiation of hormone therapy, found no difference in coronary risk between early (<5 years) vs late (≥5 years) initiation of hormone therapy. It is important to note that all such post hoc analyses should be considered exploratory (hypothesis forming) and not confirmatory in nature, and are also subject to potential bias.

To date, no good-quality randomized trials have prospectively evaluated the effect of timing of hormone therapy initiation relative to the onset of menopause on associated benefits and harms.

### Estimate of Magnitude of Net Benefit

Although the use of hormone therapy to prevent chronic conditions in postmenopausal women is associated with some benefits, there are also well-documented harms. The USPSTF determined that the magnitude of both the benefits and the harms of hormone therapy in postmenopausal women is small to moderate. Therefore, the USPSTF concludes with moderate certainty that combined estrogen and progestin has no net benefit for the primary prevention of chronic conditions in most postmenopausal women with an intact uterus and that estrogen alone has no net benefit for the primary prevention of chronic conditions in most postmenopausal women who have had a hysterectomy.

### How Does Evidence Fit With Biological Understanding?

Traditionally, estrogen has been viewed as having cardioprotective effects. The incidence of coronary heart disease in premenopausal women is lower than in men of the same age; this difference decreases as women age past menopause. Estrogen decreases levels of low-density lipoprotein cholesterol, increases levels of high-density lipoprotein cholesterol, and has a vasodilator effect. Despite these observations, data from randomized clinical trials show a lack of benefit, or even a harmful effect, of hormone therapy on risk of coronary heart disease in postmenopausal women. Several potential factors, including timing of initiation of hormone therapy with respect to menopause, older age, and presence of atheroma, have been proposed to account for these discrepant findings. Nonetheless, the underlying causes of this lack of benefit are uncertain.

Another discrepant finding is that combined estrogen and progestin is associated with a small increase in the risk of breast cancer, while estrogen alone appears to slightly reduce this risk. Although estrogen generally stimulates breast cell proliferation, some preclinical studies have shown that estrogen can induce breast cell apoptosis if administered under conditions of estrogen deprivation, and that progestin can stimulate breast cell proliferation and formation of new blood vessels. These findings have been proposed as a possible explanation for the apparent discrepant effects of combined estrogen and progestin and estrogen alone on breast cancer risk.<sup>32</sup>

### Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from May 16 to June 12, 2017. In response to public comment, the USPSTF modified the title of the recommendation statement to clarify that the patient population under consideration consists of postmenopausal women. The USPSTF clarified that it reviewed the evidence on the benefits and harms of systemic menopausal hormone therapy (ie, administered orally or transdermally), not local hormone therapy (eg, creams or rings). The USPSTF also provided additional details about the WHI trial, specifying the formulation of hormone therapy used and the average age of women enrolled in the trial. The USPSTF added 2 tables showing the absolute risk increase or decrease of various health outcomes in women receiving combined estrogen and progestin or estrogen alone (Table 1 and Table 2).



In response to comments that some subgroups of women (eg, women aged 50 to 59 years taking estrogen alone) experience a more beneficial balance of benefits and harms than the overall group of women in the WHI trial, the USPSTF expanded its discussion on the interaction between age and health outcomes in the WHI trial in the "Discussion" section. The USPSTF also clarified that the WHI analyses that assessed whether time between menopause and initiation of hormone therapy affects the benefits and harms of hormone therapy were conducted post hoc.

The USPSTF added the word "primary" to the recommendation summary to further highlight that this recommendation statement focuses on the use of hormone therapy for the primary prevention of chronic conditions in postmenopausal women, not on its use for the treatment of vasomotor, vulvovaginal, or other symptoms. The USPSTF is tasked with evaluating the benefits and harms of clinical preventive services in generally asymptomatic populations; therefore, the treatment of symptoms is outside of its purview.

The USPSTF agrees with comments regarding the importance of individualized and shared decision making, and states so in the preamble to each recommendation statement. Last, the USPSTF clarified the definition of menopause in the "Rationale" section and added a reference to the Endocrine Society's guidelines on hormone therapy in the "Recommendations of Others" section.

## Update of Previous USPSTF Recommendation

As in its 2012 recommendation on the use of menopausal hormone therapy for the primary prevention of chronic conditions, the USPSTF continues to recommend against the use of combined estrogen and

progestin for the primary prevention of chronic conditions in postmenopausal women and against the use of estrogen alone in postmenopausal women who have had a hysterectomy.

## Recommendations of Others

The American Heart Association<sup>33</sup> and the American College of Obstetricians and Gynecologists<sup>34</sup> recommend against the use of hormone therapy for the primary or secondary prevention of coronary heart disease, and most clinical guidelines, including those of the Canadian Task Force on Preventive Health Care<sup>35</sup> and the American Academy of Family Physicians,<sup>36</sup> recommend against the use of hormone therapy for prevention of any chronic conditions. The American Association of Clinical Endocrinologists<sup>37,38</sup> recommends that cardiovascular risk, age, and time from menopause be considered when using hormone therapy in symptomatic postmenopausal women and notes that hormone therapy is approved by the FDA for use in women at increased risk of osteoporosis and fractures. The American College of Obstetricians and Gynecologists mentions that the effect of hormone therapy on risk of cardiovascular disease may differ based on early vs late initiation of hormone therapy with respect to onset of menopause. The North American Menopause Society<sup>39</sup> focuses primarily on considerations for women with symptoms; it notes that hormone therapy has been shown to prevent fractures and that treatment should be individualized to balance the potential health benefits and risks for each woman. The Endocrine Society<sup>40</sup> also focuses primarily on the use of hormone therapy for the treatment of symptoms of menopause.

### ARTICLE INFORMATION

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#### The US Preventive Services Task Force (USPSTF)

**Members:** David C. Grossman, MD, MPH; Susan J. Curry, PhD; Douglas K. Owens, MD, MS; Michael J. Barry, MD; Karina W. Davidson, PhD, MASc; Chyke A. Doubeni, MD, MPH; John W. Epling Jr, MD, MSED; Alex R. Kemper, MD, MPH, MS; Alex H. Krist, MD, MPH; Ann E. Kurth, PhD, RN, MSN, MPH; C. Seth Landefeld, MD; Carol M. Mangione, MD, MSPH; Maureen G. Phipps, MD, MPH; Michael Silverstein, MD, MPH; Melissa A. Simon, MD, MPH; Chien-Wen Tseng, MD, MPH, MSEE.

#### Affiliations of The US Preventive Services Task Force (USPSTF) Members:

Kaiser Permanente Washington Health Research Institute, Seattle (Grossman); University of Iowa, Iowa City (Curry); Veterans Affairs Palo Alto Health Care System, Palo Alto, California (Owens); Stanford University, Stanford, California (Owens); Harvard Medical School, Boston, Massachusetts (Barry); Columbia University, New York, New York (Davidson); University of Pennsylvania, Philadelphia (Doubeni); Virginia Tech Carilion School of Medicine, Roanoke (Epling); Nationwide Children's Hospital, Columbus, Ohio (Kemper); Fairfax Family Practice Residency, Fairfax, Virginia (Krist); Virginia Commonwealth University, Richmond (Krist); Yale University, New Haven, Connecticut (Kurth); University of Alabama at Birmingham (Landefeld); University of California, Los Angeles (Mangione); Brown University, Providence, Rhode Island (Phipps);

Boston University, Boston, Massachusetts (Silverstein); Northwestern University, Evanston, Illinois (Simon); University of Hawaii, Honolulu (Tseng); Pacific Health Research and Education Institute, Honolulu, Hawaii (Tseng).

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