U.S. Preventive Services Task Force

Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: Recommendation Statement

▶ See related Putting Prevention into Practice on page 437.

This summary is one in a series excerpted from the Recommendation Statements released by the U.S. Preventive Services Task Force (USPSTF). These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and preventive medications.

The complete version of this statement, including supporting scientific evidence, evidence tables, grading system, members of the USPSTF at the time this recommendation was finalized, and references, is available on the USPSTF website at http://www.uspreventiveservicestaskforce.org/.

A collection of USPSTF recommendation statements reprinted in *AFP* is available at http://www.aafp.org/afp/uspstf.

Summary of Recommendations and Evidence

The U.S. Preventive Services Task Force (USPSTF) recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. **D recommendation.**

The USPSTF recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. **D recommendation.**

This recommendation applies only to postmenopausal women who are considering hormone therapy for the primary prevention of chronic medical conditions *(Table 1)*. This is not a recommendation about the use of hormone therapy to treat menopausal symptoms, such as hot flashes or vaginal dryness; the USPSTF did not review the evidence related to this possible indication because it falls outside of the mission and scope of the USPSTF. This recommendation also does not apply to women younger than 50 years who have had surgical menopause.

Rationale

IMPORTANCE

The average U.S. woman who reaches menopause is expected to live another 30 years. During her remaining life span, the estimated risk of a chronic medical condition is approximately 30 percent for coronary heart disease (CHD),[1] 22 percent for dementia,[2] 21 percent for stroke,[3] 15 percent for hip fracture,[4] and 11 percent for breast cancer.[5]

BENEFITS AND HARMS 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 estrogen and progestin therapy (specifically, oral conjugated equine estrogen, 0.625 mg per day, plus medroxyprogesterone acetate, 2.5 mg per day) is of moderate benefit in reducing the risk of fractures in postmenopausal women. However, the USPSTF found adequate evidence that its use is also associated with moderate harms, including an increase in the risk of stroke, dementia, gallbladder disease, and urinary incontinence. There is convincing evidence of a small increase in the incidence of invasive breast cancer and adequate evidence of a small increase in breast cancer deaths. There is also convincing evidence that estrogen and progestin therapy is associated with a small increased risk of deep venous thrombosis (DVT) and pulmonary embolism. Convincing evidence shows that the use of estrogen and progestin therapy does not have a beneficial effect on CHD, and probably increases the risk of its occurrence. *Table 2* provides absolute risk difference estimates for the benefits and harms of estrogen and progestin therapy.

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 estrogen (specifically, oral conjugated equine estrogen, 0.625 mg per day) is of moderate benefit in reducing the incidence of fractures. There is adequate evidence that the use of estrogen alone results in a small reduction in the risk of developing or dying of invasive breast cancer. However, the USPSTF found adequate evidence that its use is also associated with moderate harms, including increased risk of stroke, gallbladder disease,

Table 1. Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: Clinical Summary of the USPSTF Recommendation

Population	Postmenopausal women	Postmenopausal women who have had a hysterectomy
Recommendation	Do not prescribe combined estrogen and progestin for the prevention of chronic conditions. Grade: D	Do not prescribe estrogen for the prevention of chronic conditions. Grade: D
Risk assessment	This recommendation applies to the average-risk population. Risk factors for a specific chronic disease or individual characteristics that affect the likelihood of 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 medications	Although combined estrogen and progestin therapy (specifically, oral conjugated equine estrogen, 0.625 mg per day, plus medroxyprogesterone acetate, 2.5 mg per day) decreases the risk of fractures in postmenopausal women, there is an accompanying increased risk of serious adverse events, such as stroke, invasive breast cancer, dementia, gallbladder disease, deep venous thrombosis, and pulmonary embolism. Estrogen therapy (specifically, oral conjugated equine estrogen, 0.625 mg per day) decreases the risk of fractures and has a small effect on the risk of invasive breast cancer, but it is also associated with important harms, such as an increased likelihood of stroke, deep venous thrombosis, and gallbladder disease. Neither combined estrogen and progestin therapy nor estrogen alone reduces the risk of coronary heart disease in postmenopausal women.	
Balance of harms and benefits	The chronic disease prevention benefits of combined estrogen and progestin do not outweigh the harms in most postmenopausal women.	The chronic disease prevention benefits of estrogen are unlikely to outweigh the harms in most postmenopausal women who have had a hysterectomy.
Other relevant USPSTF recommendations	The USPSTF has made recommendations on screening for osteoporosis and the use of preventive medications for breast cancer, as well as other relevant interventions for the primary or secondary prevention of chronic diseases in women, such as medications for cardiovascular disease and screening for coronary heart disease, high blood pressure, lipid disorders, colorectal cancer, breast cancer, and dementia. These recommendations are available at http://www.uspreventiveservicestaskforce.org/.	

NOTE: *For the full recommendation statement and supporting documents, go to http://www.uspreventiveservicestaskforce.org/.*

USPSTF = U.S. Preventive Services Task Force.

and urinary incontinence, as well as a small increase in the risk of DVT. There is convincing evidence that estrogen does not have a beneficial effect on CHD. *Table 3* provides absolute risk difference estimates for the benefits and harms of estrogen therapy.

USPSTF ASSESSMENT

The USPSTF concludes with high certainty that the chronic disease prevention benefits of combined estrogen and progestin do not outweigh the harms in most postmenopausal women.

The USPSTF concludes with moderate certainty that the chronic disease prevention benefits of estrogen are unlikely to outweigh the harms in most postmenopausal women who have had a hysterectomy.

Clinical Considerations

PATIENT POPULATION

This recommendation applies only 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, such as hot flashes or vaginal dryness. It also does not apply to women younger than 50 years who have had surgical menopause.

ASSESSMENT OF RISK

This recommendation applies to the average-risk population. Risk factors for a specific chronic disease or individual characteristics that affect the likelihood of having 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.

USE OF PREVENTIVE MEDICATION

Although combined estrogen and progestin therapy decreases the risk of fractures in postmenopausal women (about 46 fractures of any type prevented per 10,000 person-years), there is an accompanying increased risk of

serious adverse events, such as stroke, invasive breast cancer, dementia, gallbladder disease, DVT, and pulmonary embolism *(Table 2)*. It does not decrease a woman's risk of CHD, and results from the Women's Health Initiative randomized controlled trial show a trend toward an increased likelihood of having a cardiac event (hazard ratio = 1.22; 95% confidence interval, 0.99 to 1.51).[6,7]

Estrogen-only therapy is associated with a reduction in the risk of fractures (about 56 fractures of any type prevented per 10,000 person-years), as well as a small reduction in the risk of invasive breast cancer (about eight fewer cases per 10,000 person-years) and of dying of the disease (about two fewer deaths per 10,000 person-years; *Table 3*). The biological mechanism underlying the apparent protective effect of estrogen alone, compared with the harmful effect of estrogen and progestin combined, on the development of invasive breast cancer in postmenopausal women is unclear. However, estrogen-only therapy is also associated with important harms, such as an increased likelihood of stroke, DVT, and gallbladder disease. It does not reduce the risk of CHD (Women's Health Initiative results: hazard ratio = 0.95; 95% confidence interval, 0.78 to 1.15).[6,7]

In addition to other harms, combined oral estrogen and progestin and oral estrogen-only therapy have both been shown to be associated with an increased incidence of stress, mixed, or any urinary incontinence in previously asymptomatic women after one year.[8] This outcome was measured by a self-administered questionnaire; additional randomized trials that focus on urinary incontinence as a primary study end point and use urodynamic testing as part of the assessment strategy would be useful to further clarify the effect of hormone therapy on urinary symptoms.

U.S. Food and Drug Administration–approved indications for hormone therapy in postmenopausal women are limited to the treatment of menopausal symptoms and the prevention of osteoporosis. A boxed warning indicates that estrogen with or without progestin should be prescribed at the lowest effective dose and for the shortest duration of use consistent with treatment goals and risks of the individual woman.[9]

Table 2. Estimated Event Rate Differences Associated with the Use of Oral Estrogen and Progestin in Postmenopausal Women Compared with No Treatment

	Event rate difference per 10,000 person-years	
Outcome	*Events prevented (95% CI)*	*Events caused (95% CI)*
Benefits		
Total fractures	46 (29 to 63)	—
Hip fracture	6 (1 to 10)	—
Harms		
Invasive breast cancer incidence	—	8 (3 to 14)
Pulmonary embolism	—	9 (4 to 14)
Stroke	—	9 (2 to 15)
Deep venous thrombosis	—	12 (6 to 17)
Gallbladder disease	—	20 (11 to 29)
Dementia	—	22 (5 to 39)
Self-reported urinary incontinence	—	872 (591 to 1,153)

CI = confidence interval.

Table 3. Estimated Event Rate Differences Associated with the Use of Unopposed Oral Estrogen in Postmenopausal Women Without a Uterus Compared with No Treatment

	Event rate difference per 10,000 person-years	
Outcome	*Events prevented (95% CI)*	*Events caused (95% CI)*
Benefits		
Total fractures	56 (37 to 75)	—
Invasive breast cancer incidence	8 (1 to 14)	—
Hip fracture	7 (1 to 12)	—
Breast cancer deaths	2 (1 to 3)	—
Harms		
Deep venous thrombosis	—	7 (1 to 14)
Stroke	—	11 (2 to 20)
Gallbladder disease	—	33 (20 to 45)
Self-reported urinary incontinence	—	1,271 (883 to 1,660)

CI = confidence interval.

TIMING OF INTERVENTION

No randomized trials have prospectively evaluated the effect of the timing of initiation of hormone therapy relative to menopause onset on associated benefits and harms. Post hoc subgroup analyses suggest an increased probability of harm with increasing age at initiation and longer

duration of use, but these findings are not consistent across all trials and generally do not reach statistical significance.[6,7]

OTHER APPROACHES TO PREVENTION

Women have different characteristics and risk factors, such as age, family history, and comorbid medical conditions, that affect their likelihood of developing a given chronic disease; they may also differentially value preventing specific outcomes. As such, any choice of therapy should be based on the intersection of a woman's clinical situation, preferences, and values to maximize benefits over harms.

In the case of fractures, other effective interventions for treating women with low bone density include weight-bearing exercise, bisphosphonates, and calcitonin (the USPSTF addressed screening for osteoporosis in 2011[10]). In women at high risk of breast cancer, the use of tamoxifen or raloxifene could potentially be a preventive strategy in selected situations, depending on the woman's underlying risk of stroke and thrombolic events.[11] In addition to breast cancer chemoprevention and screening for osteoporosis, the USPSTF has issued recommendations on other relevant interventions for the primary or secondary prevention of chronic diseases in women, including medications for cardiovascular disease and screening for CHD, high blood pressure, lipid disorders, colorectal cancer, breast cancer, and dementia. All are available at http://www.uspreventiveservicestaskforce.org.

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The "Other Considerations," "Discussion," and "Recommendations of Others" sections of this recommendation statement are available at http://www.uspreventiveservicestaskforce.org/uspstf/uspspmho.htm.

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