V. Epidemiology, Evidence, and Standards

A. Use of evidence in evaluating preventive reproductive screening
   1. Compare objectives of meta-analyses comparing treatment options with analyses of preventative screening
   2. Review the interaction of the epidemiology of a specific disease with the cost effectiveness of screening for it
   3. Note the relative paucity of studies which focus on cost effectiveness and preventive screening services

B. Standard setters for preventive reproductive health screening – sometimes in conflict with each other/evidence
   1. U.S. Preventive Services Task Force
   2. American Cancer Society
   3. American College of OB/GYN

C. Cost effectiveness and payers
   1. Historical conflict between reimbursement for acute vs. preventive services
   2. Role of federally funded programs such as Medicare and Medicaid in setting reimbursement levels
   3. Specific services covered and timing (Medicare Screening and Preventive Services)
      a. Medicare requires intervals based 12 month year
      b. Most other payers use a calendar year

D. Other U.S. Preventive Services Task Force recommendations related to reproductive health
   1. Hormone Replacement Therapy (HRT) – against routine use of HRT for prevention of chronic conditions
   2. ERT post hysterectomy – insufficient evidence
   3. Referral for BRCA testing in low-risk women – against
   4. Referral for BRCA testing in women at high-risk of mutations - for

Resources

Medicare Screening and Preventive Services

U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing. September, 2005.

U. S. Preventive Services Task Force. Hormone replacement therapy for primary prevention of chronic conditions. October, 2002.

Stewart et al

SCREENING PELVIC AND CLINICAL BREAST EXAMINATIONS AND SCREENING PAP SMEARS

SCREENING PELVIC AND CLINICAL BREAST EXAMINATIONS

Medicare Part B provides coverage of a screening pelvic and clinical breast examination for all female beneficiaries.

A screening pelvic examination should include at least seven of the following elements:

- Inspection and palpation of breasts for masses or lumps, tenderness, symmetry or nipple discharge.
- Digital rectal examination, including sphincter tone, presence of hemorrhoids and rectal masses.
- Pelvic examination (with or without specimen collection for smears and cultures) including:
  - Urethral meatus (for example, size, location, lesions or prolapse).
  - Urethra (for example, masses, tenderness or scarring).
  - Bladder (for example, fullness, masses or tenderness).
  - Vaginal (for example, general appearance, estrogen effect, discharge, lesions, pelvic support, cystocele or rectocele).
  - Cervix (for example, general appearance, lesions or discharge).
  - Uterus (for example, size, contour, position, mobility, tenderness, consistency, descent or support).
  - Adnexa/parametria (for example, masses, tenderness, or organomegaly or nodularity).
  - Anus and perineum.

Medicare Part B pays for a screening pelvic examination if it is performed by a doctor of medicine or osteopathy, a certified nurse midwife, a physician assistant, nurse practitioner or clinical nurse specialist who is authorized under state law to perform the examination.

The screening pelvic examination does not have to be ordered by a physician or practitioner.

HEALTHCARE COMMON PROCEDURE CODING SYSTEM (HCPCS) CODING

G0101	Cervical or vaginal cancer screening, pelvic and clinical breast examination

SCREENING PELVIC AND CLINICAL BREAST EXAMINATIONS AND SCREENING PAP SMEARS

REIMBURSEMENT

Screening pelvic exams are paid based on the Medicare Physician Fee Schedule. Coinsurance applies; however, Part B deductible does not apply.

LOW-RISK PATIENT

Medicare covers screening pelvic examinations for women who are asymptomatic once every two years.

Report the following ICD-9-CM codes:

V762	Cervix (routine cervical Papanicolaou smear)
V7647	Special screening for malignant neoplasm, vagina
V7649	Special screening for malignant neoplasm, other sites

Note: Providers use this diagnosis for women without a cervix.

Effective July 1, 2005.

V72.31	Routine gynecological examination

Note: Only use this diagnosis when the provider performs a full gynecological examination.

SCREENING PELVIC AND CLINICAL BREAST EXAMINATIONS AND SCREENING PAP SMEARS

PATIENTS AT HIGH RISK

Payment may be made for a screening pelvic exam performed once every 12 months if:

- There is evidence that the woman is at high risk (on the basis of her medical history and other findings) of developing cervical or vaginal cancer. The high-risk factors are:

Cervical Cancer High-Risk Factors:

- Early onset of sexual activity (under 16 years of age).
- Multiple sexual partners (five or more in a lifetime).
- History of a sexually transmitted disease (including HIV infection).
- Fewer than three negative Pap smears within the previous seven years.

Vaginal Cancer High-Risk Factors

- DES (diethylstibestrol) – Exposed daughters of women who took DES during pregnancy.
- The woman is of childbearing age and has had such an examination that indicated the presence of cervical or vaginal cancer or other abnormality during any of the preceding three years. The term "woman of childbearing age" means a woman who is premenopausal and has been determined by a physician or qualified practitioner to be of childbearing age based on her medical history or other findings.

Report ICD-9-CM code V1589, other specified personal history presenting hazards to health.

U.S. Preventive Services Task Force

Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility

Release Date: September 2005

Summary of Recommendations / Supporting Documents

Summary of Recommendations

- **The U.S. Preventive Services Task Force (USPSTF) recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (*BRCA*) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*).**

  Rating: D Recommendation.

  Rationale: The USPSTF found fair evidence that women without certain specific family history patterns, termed here "increased risk family history" (go to Clinical Considerations for a definition), have a low risk for developing breast or ovarian cancer associated with *BRCA1* or *BRCA2* mutations. Thus, any benefit to routine screening of these women for *BRCA1* or *BRCA2* mutations, or routine referral for genetic counseling, would be small or zero.

  The USPSTF found fair evidence regarding important adverse ethical, legal, and social consequences that could result from routine referral and testing of these women. Interventions such as prophylactic surgery, chemoprevention, or intensive screening have known harms. The USPSTF estimated that the magnitude of these potential harms is small or greater. The USPSTF concluded that the potential harms of routine referral for genetic counseling or BRCA testing in these women outweigh the benefits.

- **The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for BRCA testing.**

  Rating: B Recommendation.

  Rationale: The USPSTF found fair evidence that women with certain specific family history patterns (increased-risk family history) have an increased risk for developing breast or ovarian cancer associated with *BRCA1* or *BRCA2* mutations. The USPSTF determined that these women would benefit from genetic counseling that allows informed decision making about testing and further prophylactic treatment. This counseling should be done by suitably trained health care providers. There is insufficient evidence to determine the benefits of chemoprevention or intensive screening in improving health outcomes in these women if they test positive for deleterious *BRCA1* or *BRCA2* mutations. However, there is fair evidence that prophylactic surgery for these women significantly decreases breast and ovarian cancer incidence. Thus, the potential benefits of referral and discussion of testing and prophylactic treatment for these women may be substantial.

  The USPSTF also found insufficient evidence regarding important adverse ethical, legal, and social consequences that could result from referral and testing of high-risk women. Prophylactic surgery is associated with known harms. The USPSTF estimated that the magnitude of these potential harms is small. The USPSTF concluded that the benefits of referring women with an increased-risk family history to suitably trained health care providers outweigh the harms.

Supporting Documents

Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility, 2005
- Recommendation Statement (PDF File, 220 KB)
- Evidence Review (PDF File, 885 KB)
- Evidence Synthesis (File Download, 3.6 MB)

Top of Page

Cancer Control PLANET Home

USPSTF Topic Index
USPSTF Clinical Categories
U.S. Preventive Services Task Force

Recommendations and Rationale

Hormone Replacement Therapy for Primary Prevention of Chronic Conditions

U.S. Preventive Services Task Force (USPSTF)

This statement summarizes the current U.S. Preventive Services Task Force (USPSTF) recommendation on hormone replacement therapy for primary prevention of chronic conditions, and updates the 1996 recommendation contained in the *Guide to Clinical Preventive Services*, Second Edition[1].

Summary of Recommendation

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

  Rating: D Recommendation.

  Rationale: The USPSTF found fair-to-good evidence that the combination of estrogen and progestin has both benefits and harms. Benefits include increased bone mineral density (good evidence), reduced risk for fracture (fair-to-good evidence), and reduced risk for colorectal cancer (fair evidence). Harms include increased risk for breast cancer (good evidence), venous thromboembolism (good evidence), coronary heart disease (CHD) (fair-to-good evidence), stroke (fair evidence), and cholecystitis (fair evidence). Evidence was insufficient to assess the effects of HRT on other important outcomes, such as dementia and cognitive function, ovarian cancer, mortality from breast cancer or cardiovascular disease, or all-cause mortality.

  The USPSTF concluded that the harmful effects of estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women. The USPSTF did not evaluate the use of HRT to treat symptoms of menopause, such as vasomotor symptoms (hot flashes) or urogenital symptoms. The balance of benefits and harms for an individual woman will be influenced by her personal preferences, individual risks for specific chronic diseases, and the presence of menopausal symptoms.

- **The USPSTF concludes that the evidence is insufficient to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.**

  Rating: I Recommendation.

  Rationale: The USPSTF found fair-to-good evidence that the use of unopposed estrogen has both benefits and harms. Although most current data come from observational studies, likely benefits include increased bone mineral density, reduced fracture risk, and reduced risk for colorectal cancer. Likely harms include increased risk for venous thromboembolism, cholecystitis, and stroke; in women who have not had a hysterectomy, unopposed estrogen increases the risk for endometrial cancer. Evidence is insufficient to determine the effects of unopposed estrogen on the risk for breast and ovarian cancer, CHD, dementia and cognitive function, or mortality. As a result, the USPSTF could not determine whether the benefits of unopposed estrogen outweigh the harms for women who have had a hysterectomy.

  Better data on benefits and harms are expected from ongoing randomized trials, including the Women's Health Initiative (WHI) study of unopposed estrogen in women who have had a hysterectomy.[3]

Contents

Clinical Considerations

- Although the USPSTF concludes that the harms of estrogen-progestin therapy are likely to outweigh the chronic disease prevention benefits for most women, the absolute increase in risk from HRT is modest. Some women, depending on their risk characteristics and personal preferences, might decide that the benefits of taking HRT outweigh the potential harms. Based on results reported from the WHI study[3] for women aged 50 to 79 years (average age, 63 years), 10,000 women taking estrogen and progestin for 1 year might experience 7 additional CHD events, 8 more strokes, 8 more pulmonary emboli, and 8 more invasive breast cancers, but would also have 6 fewer cases of colorectal cancer and 5 fewer hip fractures.

- Clinicians should develop a shared decisionmaking approach to preventing chronic diseases in perimenopausal and postmenopausal women. This approach should consider individual risk factors and preferences in selecting effective interventions for reducing the risks for fracture, heart disease, and cancer. Clinicians should discuss with patients other effective strategies for preventing osteoporosis and fractures. See other USPSTF recommendations:

    - Screening for Postmenopausal Osteoporosis.
    - Screening for High Blood Pressure.
    - Screening Adults for Lipid Disorders.
    - Counseling to Prevent Tobacco Use.
    - Counseling to Promote a Healthy Diet.
    - Counseling to Promote Physical Activity.
    - Screening for Breast Cancer.
    - Screening for Colorectal Cancer.

- The USPSTF did not consider the use of HRT for the management of menopausal symptoms. Decisions to initiate or continue HRT for menopausal symptoms should be made on the basis of discussions between a woman and her clinician. Women should be informed that there are some risks (such as the risk for venous thromboembolism, CHD, and stroke) within the first 1 to 2 years of therapy, whereas other risks (such as the risk

for breast cancer) appear to increase with longer-term HRT. Other expert groups have recommended that women who decide to take HRT for the relief of menopausal symptoms use the lowest effective dose for the shortest possible time.

- The quality of evidence on the benefits and harms of HRT varies for different hormone regimens. Other than the two large randomized controlled trials of daily conjugated equine estrogen (CEE) and medroxyprogestrone acetate (MPA), most of the evidence on HRT comes from observational studies that did not differentiate among the effects of specific hormone preparations.[3,4] Until data indicate that other HRT regimens have a favorable balance of benefits to harms, a cautious approach would be to avoid using HRT routinely for the specific purpose of preventing chronic disease in women.

- Evidence is inconclusive to determine whether phytoestrogens (isoflavones such as iproflavone, which are found in soy milk, soy flour, tofu, and other soy products) are effective for reducing the risk for osteoporosis or cardiovascular disease (USPSTF, unpublished data, 2002).

Return to Contents

Scientific Evidence

Epidemiology and Clinical Consequences

Hormone replacement therapy is one of the most commonly prescribed drug regimens for postmenopausal women in the United States. Many women use HRT to treat symptoms of menopause, but publicity about the possible ability of HRT to prevent chronic conditions, such as osteoporosis, CHD, Alzheimer's disease, and colorectal cancer, has also contributed to the increase in HRT use over the past decade.

The median age of menopause in women in the United States is 51 years (range, 41 to 59 years), but ovarian production of estrogen and progestin begins to decrease years before the complete cessation of menses. Lower levels of circulating estrogen contribute to the accelerated bone loss and increased low-density lipoprotein levels that occur around menopause. The average woman in the U.S. who reaches menopause has a life expectancy of nearly 30 years. The probability that a menopausal woman will develop various chronic diseases over her lifetime has been estimated to be 46 percent for CHD, 20 percent for stroke, 15 percent for hip fracture, 10 percent for breast cancer, and 2.6 percent for endometrial cancer.[4] In North America, an estimated 7-8 percent of people 75 to 84 years of age have dementia, and postmenopausal women have a 1.4- to 3.0-fold higher risk for Alzheimer's disease than do men. The lifetime risk for developing colorectal cancer for a woman in the United States is 6 percent, with more than 90 percent of cases occurring after 50 years of age.[5] Many of these causes of morbidity in older women appear to be influenced by estrogen or progestin.

Osteoporosis affects a large proportion of postmenopausal women in the United States, and the prevalence of osteoporosis increases steadily with age. In the postmenopausal period, decline of estrogen production is associated with reduction of bone mineral density. Bone density is estimated to decrease by 2 percent each year during the first 5 years after menopause, followed by an annual loss of approximately 1 percent for the rest of a woman's life. On the basis of commonly used criteria, up to 70 percent of women older than 80 years of

age have osteoporosis.

Benefits of Hormone Replacement Therapy

Osteoporosis and Fractures

Low bone density is associated with an increased risk for osteoporotic fractures. Good evidence from observational studies and randomized clinical trials demonstrate that estrogen therapy increases bone density and reduces risk for fractures. Good evidence from many randomized clinical trials has demonstrated that HRT increases bone density at the hip, the lumbar spine, and peripheral sites.

A meta-analysis of 22 trials of estrogen reported an overall 27 percent reduction in nonvertebral fractures (relative risk [RR], 0.73; 95 percent CI, 0.56 to 0.94), although the quality of individual studies varied.[6] Observational studies have also demonstrated reductions in fractures of the vertebrae (RR for ever use, 0.6; 95 percent CI, 0.36 to 0.99), wrist (RR for current use, 0.39; 95 percent CI, 0.24 to 0.64), and possibly hip (RR for current use, 0.64; 95 percent CI, 0.32 to 1.04) among women taking HRT.

The Heart and Estrogen/Progestin Replacement Study (HERS and its unblinded followup study, HERS II),[7] a trial of combined estrogen and progestin (CEE/MPA) for the secondary prevention of heart disease that reported many other outcomes, found no reduction in hip, wrist, vertebral, or total fractures with hormone therapy (relative hazard [RH] for total fractures, 1.04; 95 percent CI, 0.87 to 1.25).

The WHI[3] found significant reductions in total fracture risk (RH, 0.76; 95 percent CI, 0.63 to 0.92) among healthy women taking estrogen and progestin. The WHI also reported reductions for hip (RH, 0.66; 95 percent CI, 0.33 to 1.33) and vertebral fracture (RH, 0.66; 95 percent CI, 0.32 to 1.34), although these did not achieve statistical significance in adjusted analyses.[3] The WHI reported both nominal and adjusted confidence intervals. The USPSTF relied on nominal confidence intervals for the primary outcomes of breast cancer and CHD and adjusted confidence intervals for other secondary outcomes. The USPSTF concluded that there was good evidence that HRT increases bone mineral density and fair-to-good evidence that it reduces fractures.

Colorectal Cancer

A meta-analysis of 18 observational studies of postmenopausal women reported a 20 percent reduction in cancer of the colon (RR, 0.80; 95 percent CI, 0.74 to 0.86) and a 19 percent reduction in cancer of the rectum (RR, 0.81; 95 percent CI, 0.72 to 0.92) among women who had ever used HRT.[8] This decrease in risk was more apparent when current users were compared with those who had never used HRT (RR, 0.66; 95 percent CI, 0.59 to 0.74). Comparable results from the WHI study were reported for women taking CEE/MPA (RH, 0.63; 95 percent CI, 0.32 to 1.24), and the HERS studies also found reduced incidence of colon cancer (RH, 0.8; 95 percent CI, 0.46 to 1.45). The USPSTF concluded that there was fair evidence that HRT reduces colorectal cancer incidence.

Uncertain Benefits or Harms of Hormone Replacement Therapy

Cognition and Dementia

Nine randomized controlled trials examining the effect of HRT on cognition showed improvement in verbal memory, vigilance, reasoning, and motor speed among women who had menopausal symptoms but not among women who were asymptomatic at baseline. Because of heterogeneity and variation in assessment of outcomes among studies, meta-analysis of these studies was not performed for the USPSTF.[2] A meta-analysis of 12 observational studies (1 of good quality, 3 of fair quality, and 8 of poor quality) showed a reduction in the risk for dementia among postmenopausal women taking HRT (RR, 0.66; 95 percent CI, 0.53 to 0.82).[9] Neither the WHI nor HERS has yet reported effects of HRT on cognition and dementia, but other ongoing trials are examining the effects of HRT on these endpoints. Given the methodologic limitations of the available studies and the potential for confounding or selection bias, the USPSTF concluded that there is insufficient evidence to determine whether HRT reduces the risk for dementia or cognitive dysfunction in otherwise healthy women.

Harms of Hormone Replacement Therapy

Breast Cancer

Because breast tissue is sensitive to reproductive hormones, there has been long-standing concern about breast cancer risk among women who take HRT. The estrogen and progestin arm of the WHI study was recently terminated because of an increased breast cancer incidence (RH, 1.26; 95 percent CI, 1.00 to 1.59).[3] However, no effect on breast cancer mortality was observed. Comparable increases in breast cancer incidence were observed among women taking estrogen and progestin over 6.8 years of followup in the HERS studies (RH, 1.27; 95 percent CI, 0.84 to 1.94).[7] Although many good observational studies on breast cancer and meta-analyses of these studies have been conducted, the conclusions are limited by:

- Healthy-user bias.
- Variations in specific preparations, dose, and duration of estrogen and progestin therapy.
- Differences in the ways in which breast cancer end points were ascertained.

In the aggregate, breast cancer incidence is slightly increased for current (RR, 1.21 to 1.40) or long-term (>5 years) users (RR, 1.23 to 1.35) compared with nonusers.[2,10,11] However, there seems to be no effect on or decreased breast cancer mortality in ever- or short-term users (RR, 0.5 to 1.0).[11] The effects of long-term HRT use on breast cancer mortality in two good-quality cohort studies are conflicting.[12,13] Whether the combination of estrogen and progestin confers a greater risk than estrogen alone is unknown; WHI investigators have reported that no increase in breast cancer has been observed after 5 years of followup in the ongoing study of unopposed estrogen in women who have had a hysterectomy.

The USPSTF concluded that there was fair-to-good evidence that HRT increases the incidence of breast cancer (with best evidence for estrogen plus progestin), but its effects on breast cancer mortality are uncertain.

Coronary Heart Disease

Coronary heart disease remains the leading cause of death among women. Hormone replacement therapy has diverse effects on lipid levels, endothelial wall function, blood pressure, coagulation factors, weight, and inflammation (for example, C-reactive protein). In

the WHI study, women who took CEE/MPA daily had an increased risk for CHD (fatal and non-fatal myocardial infarctions), which was evident shortly after initiation of the study (RH, 1.29; 95 percent CI, 1.02 to 1.63). Coronary heart disease mortality was not significantly increased (RH, 1.18; 95 percent CI, 0.70 to 1.97). Meta-analysis of observational studies showed a statistically significant reduction in CHD (RR, 0.80; 95 percent CI, 0.68 to 0.95) among current HRT users, but not among ever or past users, compared with women who had never taken HRT (nonusers).[2,14] However, among studies that controlled for socioeconomic status (social class, education, or income), no benefit was seen among current HRT users (RH, 0.97; 95 percent CI, 0.82 to 1.16), suggesting that the observed difference may be due to confounding by socioeconomic status and other lifestyle factors (e.g., exercise, alcohol use) rather than use of HRT. Coronary heart disease mortality in observational studies is reduced among current HRT users (RR, 0.62; 95 percent CI, 0.40 to 0.90) but is not reduced among ever, past, or all users. Thus, selection bias (the tendency of healthier women to use HRT) appears to explain the apparent protective effect of estrogen on CHD seen in observational studies.

The USPSTF concluded that HRT does not decrease, and may in fact increase, the incidence of CHD. The effects of HRT on CHD mortality, however, are less certain.

Stroke

A meta-analysis of nine observational primary prevention studies suggests that HRT use is associated with a small increase in stroke incidence (RR, 1.12; 95 percent CI, 1.01 to 1.23), due primarily to an increase in thromboembolic stroke (RR, 1.20; 95 percent CI, 1.01 to 1.40).[14,15] The risk for subarachnoid bleeding and hemorrhagic stroke was not increased, and the overall stroke mortality was marginally reduced (RR, 0.81; 95 percent CI, 0.71 to 0.92). These results are consistent with findings from the estrogen and progestin arm of the WHI, which reported increased incidence of stroke in women taking CEE/MPA daily (RH, 1.41; 95 percent CI, 0.86 to 2.31). Two secondary prevention trials,[16,17] which were not included in the USPSTF review of HRT for primary prevention, reported no clear effect of HRT on stroke incidence, but stroke mortality was increased in women with a previous stroke.[17]

The USPSTF concluded that there is fair evidence that HRT increases the risk for stroke.

Venous Thromboembolism (Deep Venous Thrombosis and Pulmonary Embolism)

In a meta-analysis of 12 studies (3 randomized, controlled trials; 8 case-control studies; and 1 cohort study), HRT was associated with an increased risk for venous thromboembolism (RR, 2.14; 95 percent CI, 1.64 to 2.81).[18,19] Five of six studies that examined the effects of HRT over time reported that the risk was highest within the first year of use (RR, 3.49; 95 percent CI, 2.33 to 5.59). These results are consistent with the findings in the estrogen and progestin arm of the WHI, which reported a 2-fold increased rate of venous thromboembolic disease (RH, 2.11; 95 percent CI, 1.26 to 3.55), including deep venous thrombosis and pulmonary embolism, in women taking CEE/MPA daily.

The USPSTF concluded that there is good evidence that HRT increases the risk for venous thromboembolism.

Endometrial and Ovarian Cancer

Results of a previously published meta-analysis of 29 good-quality observational studies of

endometrial cancer reported a relative risk of 2.3 (95 percent CI, 2.1 to 2.5) for users of unopposed estrogen compared with nonusers.[20] Risks increased with increasing duration of use (RR, 9.5 for 10 years of use). The risk for endometrial cancer remained elevated 5 or more years after discontinuation of unopposed estrogen therapy in these studies. With combined estrogen-progestin regimens, cohort studies showed a decreased risk for endometrial cancer (RR, 0.4; 95 percent CI, 0.2 to 0.6) compared with nonusers, but case-control studies showed an increase in risk (odds ratio [OR], 1.8; 95 percent CI, 1.1 to 3.1). Estrogen and progestin did not increase the risk for endometrial cancer in HERS (RH, 0.25; 95 percent CI, 0.05 to 1.18)[6] or in the WHI (RH, 0.83; 95 percent CI, 0.29 to 2.32).

The USPSTF concluded that unopposed estrogen, but not combined estrogen-progestin therapy, increases risk for endometrial cancer.

Data on the association between the use of HRT and the risk for ovarian cancer are inconsistent. Results of case-control studies have been mixed, but two good-quality cohort studies reported increased risks (RR, 1.8 to 2.2) for ovarian cancer or ovarian cancer mortality among women who had taken HRT for 10 years or more[21,22]. A third study found no effect of HRT on ovarian cancer mortality.[23] One study suggested higher risk with unopposed estrogen than with estrogen-progestin therapy,[21] but data are insufficient to resolve the effects of different formulations or doses of HRT on ovarian cancer risk. Neither the WHI nor HERS has reported risk for ovarian cancer.

The USPSTF concluded that evidence was insufficient to determine the effect of HRT on ovarian cancer.

Cholecystitis

Many but not all studies have reported an association between HRT and gallbladder disease. Results from a good-quality cohort study, the Nurses' Health Study, reported an increase in risk for cholecystitis among current HRT users (RR, 1.8; 95 percent CI, 1.6 to 2.0) and long-term users (>5 years) (RR, 2.5; 95 percent CI, 2.0 to 2.9) compared with nonusers.[24] Risk for cholecystitis remained elevated among past users. An increase in biliary tract surgery during 6.8 years of followup was reported among women taking estrogen plus progestin compared with those taking placebo (RR, 1.48; 95 percent CI, 1.12 to 1.95) in HERS[7,25]; the WHI has not reported biliary tract outcomes.

The USPSTF concluded that there is fair evidence that HRT increases the risk for cholecystitis.

Return to Contents

Discussion

Most women begin HRT to relieve symptoms of menopause. Many women, however, have continued to take HRT because earlier studies indicated that HRT could prevent osteoporosis, heart disease, and possibly other chronic diseases. More recent, higher quality studies have confirmed the benefits of HRT in preventing osteoporosis and fractures. These studies, however, demonstrated that HRT does not reduce, and may actually increase, the risk for CHD, and they confirmed previously suspected harms of HRT. Therefore, the calculus of benefits and harms has changed. Important questions about the effects of dose, duration, and specific preparations of hormone therapy remain. For an individual woman, the balance of

benefits and harms may vary. Women considering taking HRT for prevention should make that decision with their clinician in the context of a discussion of benefits and harms of HRT and alternatives to HRT for the prevention of chronic diseases.

Return to Contents

Recommendations of Others

Most organizations with guidelines on postmenopausal HRT have revised or are revising their recommendations in light of the findings of recently reported clinical trials. The American College of Obstetricians and Gynecologists[26] and the North American Menopause Society[27] recommend against the use of HRT for the primary or secondary prevention of cardiovascular disease. Both organizations recommend caution in using HRT solely to prevent osteoporosis and suggest that alternative therapies should also be considered. Both organizations consider HRT an acceptable treatment option for menopausal symptoms but advise caution about the prolonged use of HRT for the relief of symptoms. The American Heart Association now recommends against the use of HRT for primary or secondary prevention of cardiovascular disease.[28]

The American College of Preventive Medicine,[29] the American Association of Clinical Endocrinologists,[30] and the American Academy of Family Physicians[31] have previously recommended counseling perimenopausal and menopausal patients about the benefits and harms of HRT based on the individual risks for a particular patient, but these organizations have not yet revised their recommendations in light of the findings of recently reported trials. The Canadian Task Force on Preventive Health Care is updating its assessment of the effect of HRT on cardiovascular disease and cancer.[32]

Return to Contents

References

1. U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services*, 2nd edition. Washington, DC: Office of Disease Prevention and Health Promotion; 1996.

2. Nelson H, Humphrey L, LeBlanc E, et al. Postmenopausal hormone replacement therapy for the primary prevention of chronic conditions: a summary of the evidence for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality. AHRQ Pub. No. 03-513A. On the AHRQ Web site at: www.ahrq.gov/clinic/3rduspstf/hrt/hrtsum1.htm

3. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321-33.

4. Grady D, Rubin S, Petitti D, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016-37.

5. *Cancer Facts & Figures 2002: Special section: Colorectal Cancer and Early Detection*. Atlanta, GA: American Cancer Society. Available at: www.cancer.org. Accessed June 5, 2002.

6. Torgerson D, Bell-Syer S. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001;285(22):2891-7.

7. Hulley S, Furberg C, Barrett-Conner E, et al. Non-cardiovascular disease outcomes during 6.8 years of hormone

therapy. *JAMA* 2002;288:58-66.

8. Grodstein F, Newcomb P, Stampfer M. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999;106(5):574-82

9. LeBlanc E, Chan B, Nelson H. *Hormone Replacement Therapy and Cognition.* Systematic Evidence Review No. 13 (Prepared by the Oregon Health & Science Evidence-based Practice Center under Contract No. 290-97-0018). Rockville, MD: Agency for Healthcare Research and Quality. August 2002. Available on the AHRQ Web site at: www.ahrq.gov/clinic/serfiles.htm.

10. Steinberg K, Smith S, Thacker S, Stroup D. Breast cancer risk and duration of estrogen use: the role of study design in meta-analysis. *Epidemiology* 1994;5:415-21.

11. Humphrey LL. *Hormone Replacement Therapy and Breast Cancer.* Systematic Evidence Review No. 14 (Prepared by the Oregon Health & Science Evidence-based Practice Center under Contract No. 290-97-0018). Rockville, MD: Agency for Healthcare Research and Quality. August 2002. Available on the AHRQ Web site at: www.ahrq.gov/clinic/serfiles.htm.

12. Colditz G, Hankinson S, Hunter D, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332(24):1589-93.

13. Sellers TA, Mink PJ, Cerhan JR, et al. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Ann Intern Med* 1997;127(11):973-80.

14. Humphrey LL, Takano L, Chan B. *Hormone Replacement Therapy and Cardiovascular Disease.* Systematic Evidence Review No.10 (Prepared by the Oregon Health &Science Evidence-based Practice Center under Contract No. 290-97-0018). Rockville, MD: Agency for Healthcare Research and Quality. August 2002. Available on the AHRQ Web site at: www.ahrq.gov/clinic/serfiles.htm.

15. Humphrey LL, Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. *Ann Intern Med* 2002;137:273-84.

16. Simon J, Hsia J, Cauley J, et al. Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001;103(5):638-42.

17. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345(17):1243-1249.

18. Miller J, Chan B, Nelson H. *Hormone Replacement Therapy and Risk of Venous Thromboembolism.* Systematic Evidence Review No.11 (Prepared by the Oregon Health &Science Evidence-based Practice Center under contract No. 290-97-0018). Rockville, MD: Agency for Healthcare Research and Quality. August 2002. Available on the AHRQ Web site at: www.ahrq.gov/clinic/serfiles.htm.

19.Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136:680-90.

20. Grady D, Gebretsadik T, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;85:304-313.

21.. Lacey JJ, Mink P, Lubin J, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002;288(3):334-341.

22. Rodriguez C, Patel A, Calle E, Jacob E, Thun M. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001;285(11):1460-1465.

23. Persson I, Yuen J, Bergkvist L, Schairer C. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy—long-term followup of a Swedish cohort. *Int J Cancer* 1996;67(3):327-332.

24. Grodstein F, Colditz G, Stampfer M. Postmenopausal hormone use and cholecystectomy in a large prospective study. *Obstet Gynecol* 1994;83(1):5-11.

25. Simon J, Hunninghake D, Agarwal S, et al. Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2001;135:493-501.

26. American College of Obstetricians and Gynecologists. Response to Women's Health Initiative Study Results by the American College of Obstetricians and Gynecologists. August 9, 2002.

27. The North American Menopause Society. *Report from the NAMS Advisory Panel on Postmenopausal Hormone Therapy*. Available at: www.menopause.org/news.html#advisory. Accessed October 8, 2002.

28. American Heart Association. *Q & A About Hormone Replacement Therapy*. Available at: http://216.185.112.5/presenter.jhtml?identifier=3004068. Accessed October 7, 2002.

29. Nawaz H, Katz DL. American College of Preventive Medicine Practice Policy Statement: perimenopausal and postmenopausal hormone replacement therapy. *Am J Prev Med* 1999;17:250-254.

30. The American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for management of menopause. *Endocr Pract* 1999;5:355-366.

31. Sadovsky R. *Recent analysis of hormone replacement therapy*. Available at: www.aafp.org/afp/20000101/tips/17.html. Accessed June 5, 2002.

32. Canadian Task Force on the Periodic Health Examination. Ottawa (Canada): Health Canada. Updates available at: http://www.ctfphc.org/index.html.

Return to Contents

Members of the Task Force

Members of the U.S. Preventive Services Task Force are: Alfred O. Berg, M.D., M.P.H., Chair, USPSTF (Professor and Chair, Department of Family Medicine, University of Washington, Seattle, WA); Janet D. Allan, Ph.D., R.N., C.S., Vice-chair, USPSTF (Dean and Professor, School of Nursing, University of Texas Health Science Center, San Antonio, TX); Paul S. Frame, M.D. (Tri-County Family Medicine, Cohocton, NY, and Clinical Professor of Family Medicine, University of Rochester, Rochester, NY); Charles J. Homer, M.D., M.P.H. (Executive Director, National Initiative for Children's Healthcare Quality, Boston, MA); Mark S. Johnson, M.D., M.P.H. (Associate Professor of Clinical Family Medicine and Chairman Department of Family Medicine, University of Medicine and Dentistry of New Jersey-New Jersey Medical School); Jonathan D. Klein, M.D., M.P.H. (Associate Professor of Pediatrics and of Community and Preventive Medicine, University of Rochester School of Medicine); Tracy A. Lieu, M.D., M.P.H. (Associate Professor, Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care and Harvard Medical School, Boston, MA); Cynthia D. Mulrow, M.D., M.Sc. (Professor of Medicine, University of Texas Health Science Center, Audie L. Murphy Memorial Veterans Hospital, San Antonio, TX); C. Tracy Orleans, Ph.D. (Senior Scientist, The Robert Wood Johnson Foundation, Princeton, NJ); Jeffrey F. Peipert, M.D., M.P.H. (Director of Research, Women and Infants' Hospital, Providence, RI); Nola J. Pender, Ph.D., R.N. (Professor and Associate Dean for Research, School of Nursing, University of Michigan, Ann Arbor, MI); Albert L. Siu, M.D., M.S.P.H. (Professor of Medicine, Chief of Division of General Internal Medicine, and Medical Director of the Primary Care and Medical Services Care Center, Mount Sinai School of Medicine and The Mount Sinai Medical Center); Steven M.

Teutsch, M.D., M.P.H. (Senior Director, Outcomes Research and Management, Merck & Company, Inc., West Point, PA); Carolyn Westhoff, M.D., M.Sc. (Associate Professor of Obstetrics, Gynecology and Public Health, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY); and Steven H. Woolf, M.D., M.P.H. (Professor of Family Medicine, Department of Family Medicine, Medical College of Virginia, Fairfax, VA).

Return to Contents

Contact the Task Force

Address correspondence to: Chair, U.S. Preventive Services Task Force; c/o Project Director, USPSTF; 540 Gaither Road; Rockville, MD 20850; E-mail: uspstf@ahrq.gov.

Return to Contents

Available Products

This recommendation and rationale statement, plus complete information on which this statement is based, including evidence tables and references, are available on the USPSTF Web site at www.preventiveservices.ahrq.gov.

Individual copies of this statement are available online through the National Guideline Clearinghouse™ at: www.guideline.gov; or may be obtained in print from the AHRQ Publications Clearinghouse: Phone Toll-Free 1-800-358-9295; E-mail ahrqpubs@ahrq.gov.

The summary of the evidence and the recommendation statement are also available in print by subscription to the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates*. Contact the AHRQ Publications Clearinghouse (call 1-800-358-9295 or E-mail ahrqpubs@ahrq.gov).

Recommendations made by the USPSTF are independent of the U.S. Government. They should not be construed as an official position of AHRQ or the U.S. Department of Health and Human Services.

Source: This recommendation first appeared in *Ann Intern Med* 2002;137(10):834-9.

Return to Contents

Current as of October 2002

Internet Citation:

U.S. Preventive Services Task Force. *Hormone Replacement Therapy for Primary Prevention of Chronic Conditions: Recommendations and Rationale*. October 2002. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/clinic/3rduspstf/hrt/hrtrr.htm

---

USPSTF Topic Index
USPSTF Clinical Categories
U.S. Preventive Services Task Force (USPSTF)
Clinical Information
AHRQ Home Page