This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

AHRQ is the lead Federal agency charged with supporting research designed to improve the quality of health care, reduce its cost, address patient safety and medical errors, and broaden access to essential services. AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes; quality; and cost, use, and access. The information helps health care decisionmakers—patients and clinicians, health system leaders, and policymakers—make more informed decisions and improve the quality of health care services.
Hormone Replacement Therapy and Osteoporosis

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
2101 East Jefferson Street
Rockville, MD 20852
http://www.ahrq.gov

Contract No. 290-97-0018
Task Order No. 2
Technical Support of the U.S. Preventive Services Task Force

Prepared by:
Oregon Health Sciences University
Evidence-based Practice Center, Portland, Oregon

Heidi D. Nelson, MD, MPH

August 2002
Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the “Methods” section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspsstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrq.gov/uspsstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

Carolyn M. Clancy, M.D.
Acting Director
Agency for Healthcare Research and Quality

Robert Graham, M.D.
Director, Center for Practice and Technology Assessment
Agency for Healthcare Research and Quality

* The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services—including screening, counseling, immunization, and chemoprevention—in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.
The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.
Structured Abstract

**Context:** Hormone replacement therapy (HRT) is widely used to prevent osteoporosis and fractures.

**Objective:** To systematically review and evaluate studies of the use of estrogen and selective estrogen receptor modulators (SERMs) to prevent bone loss and fractures in healthy postmenopausal women.

**Data Sources:** Studies with English language abstracts identified in MEDLINE, HealthSTAR, and Cochrane Library databases from 1994 to May 2001. Reference lists of key articles and meta-analyses were also reviewed.

**Study Selection:** Only randomized controlled trials and cohort studies were included.

**Data Extraction:** Studies meeting inclusion criteria were formally abstracted and quality was rated using criteria developed by the U.S. Preventive Services Task Force (USPSTF).

**Data Synthesis:** For bone density outcomes, randomized controlled trials consistently indicated improved bone density with estrogen use. These findings were similar between prevention and treatment trials, opposed and unopposed regimens, oral and transdermal forms of estrogen, and types of progestins. For fracture outcomes, 5 randomized controlled trials of estrogen were identified and none met criteria to be ranked as a good-quality study. A primary prevention trial indicated a significant decrease in risk of nonvertebral fractures in 1 of 2 estrogen arms. None of the other trials indicated a significant risk reduction with estrogen, but all had important methodologic limitations. A recent meta-analysis of 22 trials of estrogen, many with unpublished data, reported an overall 27% reduction in nonvertebral fractures (relative risk [RR], 0.73; confidence
interval [CI], 0.56-0.94). Six good-quality cohort studies were identified, and 3 of 4 studies reported 20% to 35% reductions in adjusted relative risks for hip fractures among ever users.

In randomized controlled trials, raloxifene increased bone density at lumbar spine, hip, and wrist sites, and tamoxifen modestly increased bone density at the hip and spine, although results were inconsistent between studies. The largest trial of raloxifene reported a protective effect for vertebral fractures (RR, 0.59; 95% CI, 0.05-0.70), but not for nonvertebral fractures. A large trial of tamoxifen indicated no statistically significant fracture benefit.

Conclusions. The results of these studies support a benefit for estrogen in improving bone density and protecting against fractures, although the evidence for fractures is based on one arm of one randomized controlled trial and good-quality cohort studies. Trials indicate that raloxifene increases bone density and protects against vertebral fractures.
Contents

Systematic Evidence Review

Chapter 1. Introduction .......................................................................................................1
  Burden of Suffering/Epidemiology ............................................................................2
  Healthcare Interventions ..................................................................................3
  Prior Recommendations ..................................................................................4
  Analytic Framework and Key Questions ..................................................4

Chapter 2. Methods .............................................................................................................5
  Literature Search Strategy ..................................................................................5
  Inclusion/Exclusion Criteria ..............................................................................5
  Literature Synthesis .........................................................................................7

Chapter 3. Results ...............................................................................................................8
  Arrow 1. Does hormone replacement therapy improve or stabilize bone density? ..............................................................8
  Summary ........................................................................................................10
  Arrow 2. Does hormone replacement therapy prevent osteoporotic fractures? ..........................................................10
  Randomized controlled trials ......................................................................11
  Cohort studies ...............................................................................................13
  Summary ........................................................................................................15
  Arrow 1. Does postmenopausal use of SERMs improve or stabilize bone density? ...............................................................15
  Summary ........................................................................................................17
  Arrow 2. Does postmenopausal use of SERMs prevent osteoporotic fractures? ...............................................................17
  Summary ........................................................................................................19

Chapter 4. Discussion .......................................................................................................20
  Conclusions ......................................................................................................20
  Limitations of the Literature ..........................................................................21
  Future Research ...............................................................................................22

Acknowledgements ........................................................................................................23

References .........................................................................................................................24

Appendix 1a. Search Strategy for Hormone Replacement Therapy with Bone Density or Fractures Outcomes ..........................................................44

Appendix 1b. Search Strategy for Randomized Controlled Trials of Estrogen and SERMs ..................................................................................45

Appendix 2. Criteria for Grading the Internal Validity of Individual Studies ...............46
Figures

Figure 1. Analytic Framework 1: Benefits of Hormone Replacement Therapy..............29
Figure 2. Analytic Framework 2: Adverse Effects of Hormone Replacement
Therapy ..............................................................................................................30

Tables

Table 1. Key Questions and Types of Studies Cited ....................................................31
Table 2. Combined Results of Randomized Controlled Trials of HRT with
Bone Density Outcomes ......................................................................................32
Table 3. Randomized Controlled Trials of HRT with Fracture Outcomes .................33
Table 4. Cohort Studies of HRT with Hip Fracture Outcomes.................................35
Table 5. Randomized Controlled Trials of SERMs with Bone Density Outcomes......39
Table 6. Randomized Controlled Trials of SERMs with Fracture Outcomes .............41
Table 7. Summary of Evidence ..............................................................................43
Chapter 1. Introduction

In this paper, we systematically review the medical literature and evaluate data on the use of hormone replacement therapy (HRT) to prevent osteoporosis in healthy postmenopausal women. Specifically, we focus on the effects of estrogen, with and without progestins, on fracture and bone density outcomes. We also review studies of selective estrogen receptor modulators (SERMs) because of their emerging role in preventing osteoporosis. This report is part of a larger project on the risks and benefits of HRT prepared for the U.S. Preventive Services Task Force (USPSTF) to assist them in making recommendations. A separate systematic evidence review on screening for osteoporosis contains more detailed information about other aspects of osteoporosis prevention.¹

The term osteoporosis describes both a process of decreasing bone density as well as the clinical outcome of fracture. Bone density can be measured by a number of techniques and at a number of anatomical sites, although the measures most often used in studies are dual energy x-ray absorptiometry (DXA) of the hip, spine, heel, or wrist. A World Health Organization (WHO) working group proposed that osteoporosis should be diagnosed when bone mineral density (BMD) is 2.5 standard deviations below the mean for healthy young adult women at the spine, hip, or wrist, or when a history of an atraumatic fracture is present.² The working group also proposed that low bone mass, or osteopenia, be diagnosed when bone density is between 1.0 to 2.5 standard deviations below the young healthy mean. The number of standard deviation units above or below the young healthy mean is called the T-score. This measure is often used in eligibility criteria for treatment trials and is used clinically to diagnose osteoporosis.
Burden of Suffering/Epidemiology

Osteoporosis affects a large proportion of American women over the age of 50. Estimates of rates of prevalence depend on the instrument used to measure bone density and on the characteristics, including ethnicity, of the population studied. The third National Health and Nutrition Examination Survey (NHANES III) reports prevalence rates for osteoporosis by race, adjusted for age and for census undercount estimates from 1990 and 1993. From these data, an estimated 12 million (41%) white women over age 50 met WHO criterion described above for osteopenia and 5 million (15%) met WHO criterion for osteoporosis. The prevalence of osteoporosis in Hispanic women is similar to white women, while rates in black women are approximately half that of the other groups (8%).

The prevalence of osteoporosis increases with age for all sites measured. By the WHO definition, up to 70% of women over age 80 have osteoporosis based on low measurements at the spine, hip or wrist. Age is an important factor in the relationship between bone density and the absolute risk of fracture. An increase in age of 13 years increases the risk of hip fracture by the same amount as a one standard deviation decrease in bone density. Older women have a much higher fracture rate than younger women with the same bone density because of increasing risk from other factors such as bone quality and tendency to fall.

Women with osteoporosis are more likely to have fractures, and demographic trends for hip fracture parallel those for osteoporosis. Hip fracture incidence in white women rises from 50 per 100,000 women at age 50 to 237 per 100,000 women at age 65. White women are generally 2 to 3 times more likely than non-white women to suffer a hip fracture. Wrist fracture incidence tends to increase at earlier ages than hip fractures, with 268 per 100,000 women at age
Sixteen percent of postmenopausal women have osteoporosis of the lumbar spine, and, among white women, 5% of 50-year-olds and 25% of 80-year-olds have had at least one vertebral fracture.

**Healthcare Interventions**

Estrogen has important effects on bone and estrogen deficiency is considered to be a major factor leading to bone loss in postmenopausal women. Estrogen inhibits bone loss by reducing bone resorption. Bone density decreases steadily after menopause, and supplementation with exogenous estrogen during the peri- and postmenopausal periods has been a common primary preventive approach.

A new class of agents, the SERMs, was developed in an effort to find a treatment for breast cancer and osteoporosis. The advantage of SERMs is that they bind to estrogen receptors competing with endogenous estrogens and may either activate or block estrogen action allowing tissue-selective effects. Raloxifene, for example, has estrogen-agonistic effects on bone and lipids, and estrogen-antagonistic effects on the breast and uterus and may be preferred by women at increased risk for breast cancer. Raloxifene has been approved for treatment of osteoporosis. Tamoxifen, a different kind of SERM primarily used for breast cancer prevention and treatment, is included in this review for completeness. It has not been approved for treatment of osteoporosis.
Prior Recommendations

The previous USPSTF thought that the evidence on the effects of HRT for improving or preserving bone density was good based on results of retrospective studies and a few clinical trials. Data on fracture reduction was based on epidemiologic and nonrandomized clinical trials, and the risk of hip fracture reduction was estimated as 25% among women who had used estrogens.

Analytic Frameworks and Key Questions

The analytic frameworks in Figures 1 and 2 show the target populations, interventions, and health outcome measures we examined for the overall question of the benefits and risks of postmenopausal HRT. Other benefits and risks of HRT are addressed in separate reports and will not be considered here. Arrows 1 and 2 in Figure 1 correspond to issues of HRT and osteoporosis specifically covered in this report. Key questions relating to the numbered arrows in the analytic framework guided our literature review. These include:

Arrow 1:  Does hormone replacement therapy improve or stabilize bone density?

Does postmenopausal use of SERMs improve or stabilize bone density?

Arrow 2:  Does hormone replacement therapy prevent osteoporotic fractures?

Does postmenopausal use of SERMs prevent osteoporotic fractures?

We were concerned with HRT as a primary preventive measure, and therefore focused on the use of either estrogen alone or estrogen combined with progestins in healthy, postmenopausal women without known secondary causes of osteoporosis. However, because osteoporosis is defined by both low bone density and fracture occurrence, we included studies of women with known low bone density. Results for HRT and SERMs are presented separately.
Chapter 2. Methods

Literature Search Strategy

We searched MEDLINE, HealthSTAR, and Cochrane Library databases for papers published between 1994 and May 2001 using the search strategies shown in Appendix 1. Separate searches were conducted to identify randomized controlled trials for estrogen and SERMs. Additional articles were obtained from reference lists of relevant papers including all studies of estrogen pre-dating the electronic search. Studies of raloxifene and tamoxifen, for purposes other than cancer treatment, were present only in the recent literature. A single reader reviewed all English abstracts. We also report the results of 2 recently conducted meta-analyses of HRT and bone density,12 and HRT and fractures.13 Only published studies were included in evidence tables; abstracts and other unpublished works were cited in the text if particularly pertinent.

Inclusion/Exclusion Criteria

In order to identify the most important studies for inclusion in this review, we used a “best evidence” approach.14 We first examined randomized, double-blind, placebo-controlled trials of estrogen, with and without progestins, and SERMs and fracture outcomes. Because very few such trials have been published, we next examined randomized controlled trials with bone density outcomes. However, these studies were limited because they report intermediate outcomes (bone density), provide only short-term exposure to treatment (1 to 4 years), and enroll subjects often using narrowly defined entry criteria that limit generalizability.
Cohort studies provide additional information about long-term estrogen use and fractures not yet available from randomized controlled trials. Therefore, we also included good-quality cohort studies of estrogen use and fractures acknowledging that these studies are subject to healthy user bias. Other studies have found that estrogen users are healthier, have healthier lifestyles and better mortality, and are more highly educated than nonusers. Nonetheless, a random sample of U.S. women aged 50 to 74 years old recently found that 38% currently use estrogen, and we felt that cohort studies may provide information useful to this high proportion of users in the population. Case-control and cross-sectional studies were excluded. Table 1 outlines the type and number of studies we reviewed for each key question.

Studies were included in this review if they enrolled postmenopausal women without secondary causes of osteoporosis; described the number of subjects and setting; and described characteristics of treatment and placebo groups including age, type of HRT, and duration of use. Study design factors that we recorded included exclusion/inclusion criteria, method of allocation, and compliance and follow-up rates. We abstracted comparable information from the cohort studies comparing HRT users and nonusers with the addition of how exposure status was determined. In both randomized controlled trials and cohort studies, we recorded the bone measurement tests that were used, how bone density or fracture outcomes were measured, and fracture rates or bone density outcomes of users and nonusers. All fractures had to be radiographically verified. The most adjusted values were recorded, and pertinent sub-group analyses were noted. Any trends in duration, currency of use, or dosage were also noted.
Literature Synthesis

We applied quality criteria developed by the methods workgroup for the USPSTF (Appendix 2). Most studies included in this report achieved a rating of good. The most common reason for a study not receiving a good rating was follow-up rates falling below 80%.
Chapter 3. Results

Arrow 1: Does hormone replacement therapy improve or stabilize bone density?

Many randomized controlled trials have been published indicating that estrogen, alone or in combination with progestin, improves bone density or prevents bone density loss compared to placebo. An unpublished Cochrane systematic review reported combined results of 57 randomized controlled trials at the NIH Consensus Development Conference on Osteoporosis in 2000. Eligible studies included randomized controlled trials enrolling postmenopausal women for more than one year in duration that compared HRT with placebo or calcium/vitamin D use. Studies were identified from MEDLINE (1966 to December 1998) and the Cochrane Library Controlled Clinical Trials Register. Additional methodology is described elsewhere. The Cochrane systematic review and meta-analysis met USPSTF criteria for high quality (comprehensive sources, standard appraisal, valid conclusions, recent and relevant).

The trials reported in the Cochrane systematic review are summarized in Table 2 with results expressed as weighted mean differences, calculated by using percent change from baseline and standard deviations. Combining 18 two-year prevention studies of opposed and unopposed HRT regimens, the increase in bone density at the lumbar spine was 6.98% (95% CI, 5.53-8.43). The 8 studies measuring femoral neck bone density indicated an increase of 4.07% (95% CI, 3.30-4.84), and the 14 studies measuring forearm bone density indicated an increase of 4.53% (95% CI, 3.68-5.36).

Results were similar when comparing prevention to treatment trials, opposed to unopposed HRT regimens, transdermal estrogen to oral estradiol and oral conjugated estrogen,
and types of progestins. Results differed, however, with different doses and duration of estrogen use. Use of usual doses (eg 0.625 mg of conjugated estrogen) resulted in larger increases at lumbar, femoral neck, and forearm sites than use of lower doses (0.3 mg). Two-year trials resulted in larger increases than one-year trials. The effect of using calcium and vitamin D in these trials rather than true placebo was not separately analyzed. Also, the proportion of nonresponders in these trials was not reported.

A randomized controlled trial published in 1999 and not included in the Cochrane review found that a continuous low-dose HRT regimen given over 3.5 years resulted in increased bone density of the spine (mean percent change, 3.23; 95% CI, 1.64-4.82), nonsignificant increased bone density of the femoral neck (mean percent change, 1.79; 95% CI, 0.56-2.98), and no increase or decrease at the radius (P<0.01 compared with placebo who lost bone density). These results, using conjugated equine estrogen (0.3 mg/day) and oral medroxyprogesterone (2.5 mg/day) combined with calcium and vitamin D, are similar to the results of the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial that used a higher dose of estrogen (0.625 mg/day), various progestin regimens, and no calcium and vitamin D supplementation. The patients in these studies differed however. Women in PEPI were younger (aged 45 to 64 years) than those enrolled in this trial (age over 65, mean age 73), and had a wide range of T-scores, while women in this trial had T-scores of −1.226 or lower. Among subjects in the PEPI trial, older women and women with low initial bone density gained the most bone density with HRT use.

Another randomized controlled trial published in 1999 compared women aged 45 to 59 years, most not osteoporotic, who took alendronate, HRT, or placebo for 4-years. Two different doses of alendronate (5 mg/day and 2.5 mg/day) and 2 different forms of HRT (a cyclic regimen
of 2 mg of estradiol with 1 mg/day of norethisterone and a continuous regimen of 0.625 mg of conjugated equine estrogen with 5.0 mg of medroxyprogesterone) were used. Bone density decreased at all skeletal sites in the placebo group and increased or stayed the same at all sites except the forearm for the alendronate groups with the larger dose, demonstrating more benefit. Both HRT regimens resulted in statistically significantly greater increases in bone density at the spine, similar increases at the hip, and was significantly more effective in maintaining bone mass at the forearm than treatment with 5 mg of alendronate per day. A 5 mg dose of alendronate represents the dose used for prevention, 10 mg is used for treatment.

Summary

• Many randomized controlled trials have been conducted of HRT and bone density outcomes, and results consistently indicate improved bone density. These findings are similar between prevention and treatment trials, opposed and unopposed regimens, oral and transdermal forms of estrogen, and types of progestins.

• A meta-analysis of HRT randomized controlled trials indicated a better effect on bone density with usual compared to low dose regimens. However, a recent trial indicated similar results for a low dose regimen as previously reported for usual dose regimens, although patient populations differed between studies.

• A recent trial comparing bone density outcomes of HRT with alendronate found more benefit with HRT.

Arrow 2: Does hormone replacement therapy prevent osteoporotic fractures?
Randomized controlled trials

A recent meta-analysis of 22 trials of estrogen reported an overall 27% reduction in nonvertebral fractures (RR, 0.73; 95% CI, 0.56-0.94). Although the meta-analysis met USPSTF criteria for a good-quality rating, several trials included in the meta-analysis did not meet inclusion criteria for our review because they used unpublished data, did not verify fractures radiographically, included traumatic fractures, or included women who were hospitalized or had secondary causes of osteoporosis. Five randomized controlled trials of estrogen with vertebral or nonvertebral fracture outcomes met our inclusion criteria (Table 3).

Two trials evaluated the effect of HRT on preventing vertebral fractures in women with pre-existing osteoporosis. A trial of 78 postmenopausal women age 47 to 75 years with one or more pre-existing vertebral fractures recorded incident vertebral fractures. The treatment group was provided with a cyclic regimen of transdermal estrogen and progesterone for one year and was compared to an untreated placebo group. The estrogen group experienced 8 new vertebral fractures in 7 women, while the placebo group had 20 fractures in 12 women. Despite a lower vertebral fracture rate in the estrogen group (RR, 0.39; CI, 0.16-0.95), the number of women experiencing new vertebral fractures was not significantly different between groups. A smaller trial of 4 years duration comparing 18 women using a cyclic oral estrogen regimen to 18 women in a comparison group found no significant difference in vertebral fractures.

Three trials reported nonvertebral fracture outcomes. A primary prevention trial enrolled a subgroup of a large prospective osteoporosis study based in Finland. In this study, 464 early postmenopausal women without osteoporosis were randomly assigned to one of four
groups: cyclic oral estradiol with progestin, vitamin D alone, estradiol with progestin and vitamin D, or placebo. New, symptomatic, radiographically confirmed nonvertebral fractures were recorded during a mean 4.3 years of follow-up. The risk for fracture was significantly lower for the estrogen/progestin alone group (RR, 0.29; 95% CI, 0.10-0.90), but not for the estrogen/progestin and vitamin D group, or the vitamin D alone group, compared to placebo when adjusted for baseline bone density and prior fractures. Another primary prevention trial randomized 1,006 early postmenopausal women in Denmark to oral estradiol/norethisterone or placebo. After 5 years, the relative risk for all types of fractures was 0.82 (95% CI, 0.53-1.29), and for forearm fractures 0.40 (95% CI, 0.16-1.01).

The Heart and Estrogen/progestin Replacement Study (HERS) is a secondary prevention trial of the effects of estrogen on cardiovascular outcomes. This study enrolled 2,763 postmenopausal women with pre-existing coronary disease under 80 years old (mean 66.7 years). A subgroup of women underwent bone densitometry, and 15% of them had osteoporosis. Fractures at various sites were secondary outcomes. The treatment group was given a continuous combined regimen of conjugated estrogen with medroxyprogesterone per day and compared with an equal-sized placebo group. After 4 years, this study found no difference between groups for all fractures combined, or hip, wrist, spine, or other types of fractures specifically.

These trials did not meet USPSTF criteria to be ranked as good-quality studies because they did not assemble or maintain comparable groups, were not blinded, were small, or used inappropriate analyses. The largest trial, HERS, did not monitor for asymptomatic incident vertebral fractures, potentially missing as many as 2 out of 3 of vertebral fractures that would be diagnosed solely by radiographic morphometric criteria. Although
asymptomatic fractures may not be as important to patients as symptomatic fractures, patients with nontraumatic vertebral fractures meet diagnostic criteria for osteoporosis and are usually identified as such in trials.

Cohort studies

Several good-quality cohort studies that enrolled thousands of postmenopausal women and reported fracture outcomes have been published. These studies included more women, often recruited from community-based populations, and followed them for longer periods of time than the randomized controlled trials. In general, these studies determined estrogen use at baseline by interviewing subjects or reviewing prescription data. Use was usually defined as current, past, or ever use, and nonuse. However, type of HRT regimen including doses, concurrent use of progestins, and duration was not reported in all studies. Subjects were then followed over several years while investigators collected data on incident fractures. Fracture occurrence was determined by asking subjects directly or by reviewing hospital admission databases. In all studies included in this review, fractures were confirmed radiographically. Additional data was also collected, such as age, weight, history of previous fractures, and other known risk factors, in order to adjust for confounders and to examine subgroups. Most cohort studies adjusted for measurable confounders and reported adjusted results, although an important disadvantage of cohort studies is the inability to control for healthy user bias. Other studies have found that estrogen users are healthier and have healthier lifestyles\textsuperscript{19} which may influence health outcomes.

Table 4 outlines 6 good-quality cohort studies\textsuperscript{34-39} and the reported relative risks for hip fracture for each study based on ever or current use of estrogens. These studies include data from the Framingham Heart Study\textsuperscript{34}; pharmacy, questionnaire, and inpatient registry
information from the Uppsala health care region in Sweden\textsuperscript{35,36}; pharmacy and chart records from Kaiser\textsuperscript{37}; the Study of Osteoporotic Fractures (SOF)\textsuperscript{38}; and the Copenhagen Center for Prospective Population Studies.\textsuperscript{39} All studies, except the Kaiser study, include several thousand postmenopausal women. Follow-up times ranged from 4.5 years in SOF to up to 32 years in the Framingham study.

Three of the 4 studies of ever users of HRT reported significantly reduced adjusted relative risks for hip fractures ranging from 0.63 to 0.79.\textsuperscript{34-36} These studies also noted that those taking more potent forms of estrogen had even better risk reduction,\textsuperscript{35} the best results were found among those using estrogen for 7 or more years,\textsuperscript{36} and taking estrogen within 4 years of menopause was protective.\textsuperscript{34} No studies reported effects of progestins specifically. The only study not reporting a reduced relative risk for hip fracture was much smaller in size than the others, and reported significantly reduced relative risks for wrist and vertebral fractures.\textsuperscript{37} Hip fractures are less frequent outcomes than wrist or vertebral fractures in this relatively younger cohort.

The 3 studies of effects for current estrogen users, a subgroup of ever users, reported nonsignificant reduced relative risks for hip fracture.\textsuperscript{34,38,39} Although data from the Copenhagen Center for Prospective Population Studies included over 6,000 women and followed them for 7 years, current users had a mean age of only 55 years at baseline and accrued only 37 fractures. Incident hip fracture rates for all user groups would be expected to rise as this cohort ages.

The Study of Osteoporotic Fractures is primarily designed to prospectively measure fracture outcomes in a cohort of 9,704 community-dwelling postmenopausal women residing in 4 areas of the U.S. Although the effect of HRT on hip fracture outcomes was not statistically
significant after 4.5 years of follow-up, SOF reported significant risk reduction for wrist (RR, 0.39; 95% CI, 0.24-0.64) and all nonvertebral fractures (RR, 0.66; 95% CI, 0.54-0.80) after adjustment for several other variables. Subgroup analyses within SOF also indicated that estrogen was most effective in preventing hip fractures for those over 75 years old, and for current users who started estrogen within 5 years of menopause. Previous use of estrogen, however, had no effect on fracture outcomes, implying a transient protective effect. Additional data from SOF expands the follow-up time to 10 years. These results indicate that current users have significantly reduced probabilities of hip, wrist, and nonvertebral fractures at 10 years compared to never users in age and weight adjusted models.

Summary

- Only 5 randomized controlled trials report the effects of HRT on fracture outcomes, and they are methodologically limited.
- Good-quality cohort studies indicate 20% to 35% reduction in relative risks for hip fracture and reduced risks for other types of fractures. Subgroup analyses indicate that certain users may have additional benefits such as older women, long-term users, and those who initiate use at or near menopause.
- Cohort studies of estrogen users, even when well-designed and controlled for measurable confounders, are subject to healthy user bias making it difficult to determine if beneficial effects are due to HRT or bias.

Arrow 1: Does postmenopausal use of SERMs improve or stabilize bone density?
Five randomized controlled trials\textsuperscript{41-45} reporting the effect of raloxifene on bone density have been published (Table 5). Three studies were rated good\textsuperscript{41-43} and 2 were rated fair.\textsuperscript{44, 45}

The largest study, the Multiple Outcomes of Raloxifene Evaluation (MORE) study, included 7,705 postmenopausal women aged 31 to 80 years (mean age 67 years) and followed them for 3 years.\textsuperscript{43} These women met WHO criteria for osteoporosis based on low bone density or presence of vertebral fractures. Two doses of raloxifene (60 or 120 mg/day) were compared with placebo, and all subjects received calcium and vitamin D. Both raloxifene treatment groups experienced significant increases in bone density, with the largest gains reported as 2.4\% at the femoral neck and 2.7\% at the lumbar spine for the 120 mg dose. It is important to note that 60 mg of raloxifene is the FDA approved dose.

A smaller randomized controlled trial of one year duration also evaluated the effects of raloxifene.\textsuperscript{41} The trial included 143 postmenopausal women, mean age 68 years, with at least one prevalent vertebral fracture and low bone density. Two doses of raloxifene (60 and 120 mg/day) were compared to placebo, and all groups took calcium and vitamin D. Results included significant increases at the total hip (1.7\% for 60 mg dose) and radius (2.9\% for 60 mg, 2.5\% for 120 mg), and nonsignificant increases in the lumbar spine.

Another trial of 601 postmenopausal women recruited from the community in Europe and the United Kingdom with a range of initial bone densities also compared various doses of raloxifene (30, 60, or 150 mg/day) with placebo.\textsuperscript{45} After 2 years, there were significant increases in bone density with the 60 mg/day dose at the lumbar spine (1.6\%), hip (1.6\%), and femoral neck (1.2\%). All of the raloxifene doses resulted in significant increases, although the higher doses generally had more effect. Two other small studies also reported gains at the lumbar spine and hip.\textsuperscript{42, 44} One of these trials compared raloxifene with conjugated equine
estrogen and noted higher gains at the lumbar spine for the estrogen group.\textsuperscript{44} Some of these raloxifene trials, however, had dropout rates exceeding 20\%.\textsuperscript{43-45}

Only 2 small randomized controlled trials\textsuperscript{46,47} of postmenopausal women without breast cancer reported effects of tamoxifen on bone density (Table 5). One reported a 1.4\% increase at the lumbar spine\textsuperscript{46} and the other 1.8\% at the hip.\textsuperscript{47} These studies were limited by either high dropout rates\textsuperscript{47} or lack of intention-to-treat analysis\textsuperscript{46} and were rated poor.

Summary

- The 2 larger randomized controlled trials of raloxifene indicated significant increases in bone density at the lumbar spine, hip, and wrist. These ranged from 2.1\% in the femoral neck to 2.7\% in the spine measured from baseline after 3 years of treatment in the MORE study. The smaller randomized controlled trials reported increases in most of the sites tested.
- Randomized controlled trials of tamoxifen reported modest, inconsistent increases in bone density at the spine and hip, however these trials have important methodologic limitations.

Arrow 2: Does postmenopausal use of SERMs prevent osteoporotic fractures?

Two good-quality randomized controlled trials of raloxifene with fracture outcomes have been published (Table 6). The MORE study,\textsuperscript{43} described above, evaluated incident vertebral fractures using radiographic criteria at the 24- and 36- month visits and at other times if new
symptoms of vertebral fractures developed. Nonvertebral fractures were determined by interviewing subjects at 6-month visits. After 3 years of treatment, women in the raloxifene group had a significantly reduced risk for vertebral fractures compared with women in the placebo group (RR, 0.59; 95% CI, 0.50-0.70). The risk for nonvertebral fractures was not significantly reduced.

A smaller randomized controlled trial, also described above, evaluated the effects of raloxifene after one year of use and found no significant reductions in risk for vertebral or nonvertebral fractures in the treatment groups compared to the control group. When the outcomes were re-analyzed using more stringent radiographic criteria for vertebral fractures (30% or more reduction in vertebral height rather than 15%), there were significantly fewer vertebral fractures among raloxifene users than placebo (P=0.047; RR not given). These results were not calculated using the fracture criteria of the MORE study (20% or more reduction of vertebral height), precluding direct comparison of the 2 studies.

Women enrolled in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P-1) of tamoxifen were also monitored for fractures, although this was a secondary outcome. In this study, 13,388 women were randomized to tamoxifen or placebo and followed for 5 years. Incident fractures of the hip, wrist, and spine were confirmed by x-rays. Relative risks for total fractures, hip, wrist, and spine were not significantly reduced. This study, however, has important methodologic limitations and was rated fair. Since this trial was designed to determine tamoxifen's role in breast cancer prevention, the inclusion criteria were based on breast cancer risk not osteoporosis risk. As such, it is not known if the treatment and placebo groups have comparably distributed osteoporosis risk factors. These were not controlled for in the analysis and could have biased the results. Also, vertebral fractures were
diagnosed only if reported by participants who may have missed asymptomatic fractures.

Undercounting of fractures would compromise estimation of relative risks.

**Summary**

- The largest trial of raloxifene, the MORE study, reported a protective effect for vertebral fractures, but not for nonvertebral fractures.
- The subgroup of women in this study with low bone density and pre-existing fractures demonstrated additional benefit with the 120 mg/day dose compared to the 60 mg/day dose.
- A smaller trial with short duration of follow-up indicated no fracture benefit when using less stringent vertebral fracture criteria, but some benefit when using more stringent criteria (15% compared to 30% or more loss of vertebral height).
- A large trial of tamoxifen, designed for breast cancer prevention indicated no statistically significant effect.
Chapter 4. Discussion

Conclusions

Table 7 summarizes the type and quality of evidence for each of the 4 key questions. For bone density outcomes, randomized controlled trials consistently indicated improved bone density with estrogen use. These findings were similar between prevention and treatment trials, opposed and unopposed regimens, oral and transdermal forms of estrogen, and types of progestins. Most studies support a dose-response effect, and higher doses of estrogen and longer duration of use tend to be associated with greater benefit on bone density. This is not true with all studies, however, and significant bone density effects have been demonstrated with lower doses of estrogen. Estrogen appears to have a stronger effect on bone density than raloxifene, and the effect of tamoxifen is much weaker than either.

For fracture outcomes, 5 randomized controlled trials\textsuperscript{27-31} of estrogen were identified and none met criteria to be ranked as a good-quality study. A primary prevention trial indicated a significant decrease in risk of nonvertebral fractures in 1 of 2 estrogen arms.\textsuperscript{29} None of the other trials indicated a significant risk reduction with estrogen, but all had important methodologic limitations. A recent meta-analysis of 22 trials of estrogen, many with unpublished data, reported an overall 27\% reduction in nonvertebral fractures (RR, 0.73; 95\% CI, 0.56-0.94).\textsuperscript{13} Six good-quality cohort studies\textsuperscript{34-39} were identified, and 3 of 4 studies reported 20\% to 35\% reductions in adjusted relative risks for hip fractures among ever users.\textsuperscript{34-36}

In randomized controlled trials, raloxifene increased bone density at lumbar spine, hip, and wrist sites, and tamoxifen modestly increased bone density at the hip and spine, although results were inconsistent between studies. The largest trial of raloxifene reported a protective
effect for vertebral fractures (RR, 0.59; 95% CI, 0.05-0.70), but not for nonvertebral fractures.\textsuperscript{43} A large trial of tamoxifen indicated no statistically significant fracture benefit.\textsuperscript{48}

**Limitations of the Literature**

Although randomized controlled trials are available for all of the key questions, they are limited in important ways. Except for trials of estrogen and bone density, there are very few trials available upon which to make treatment decisions, and the results are sometimes conflicting. This is particularly true for studies of estrogen and fracture outcomes. Fracture benefits would be expected from randomized controlled trials based on results reported in the cohort studies supporting a 20% to 35% reduction in fractures, and on randomized controlled trials consistently demonstrating improved bone density at lumbar spine, hip, and wrist sites. Although an intermediate outcome, bone density is an important risk factor for fracture. Too few trials with fracture outcomes have been performed, however, and they have not been sufficiently large or long enough to measure a treatment effect. The largest trial\textsuperscript{31} was designed as a secondary prevention trial for cardiac disease, did not monitor for asymptomatic incident vertebral fractures, and did not provide information on osteoporotic confounders to assure comparability of treatment groups.

The MORE study of raloxifene, however, provides good evidence of benefit for vertebral fractures.\textsuperscript{43} It is possible that similar effects for estrogen could be detected if subjected to a study as large and comprehensive as the MORE trial. The tamoxifen trial did not measure vertebral fracture outcomes as precisely as the MORE trial, was designed as a breast cancer prevention study, and could have missed a potential effect.\textsuperscript{48}
Future Research

Additional trials are needed to more accurately weigh the benefits and harms of HRT. Results of the Women’s Health Initiative will add this type of information. As SERMs and other estrogen-like agents are developed, direct comparisons with estrogen in addition to placebo during trials will be important. Careful monitoring and reporting of adverse events would contribute additional knowledge of the consequences of HRT use.

Many gaps exist in current understanding of estrogen’s effect on bone. It is not clear how age affects the impact of estrogen, and it would be valuable to know if it is as effective in an 80-year-old woman as in a 50-year-old woman. Similarly, understanding the optimal duration of effect would allow targeting of estrogen use to specific times of a woman’s life. Despite the overall effect on increasing bone density described in treatment trials, some women do not experience this benefit. These women could be spared prolonged estrogen exposure if adequately identified. There is also little understanding of potential harms of long-term HRT on bone.
Acknowledgements

This systematic evidence review was prepared for the Agency for Healthcare Research and Quality (contract #290-97-0018, task order no. 2) to be used by the U.S. Preventive Services Task Force. Task Force members Janet Allen, PhD, RN, and Steven Teutsch, MD, MPH, served as liaisons. Oregon Health & Science University, Evidence-based Practice Center staff who contributed to this project included Peggy Nygren, MA, research associate, and Patty Davies, MA, librarian.
References


Postmenopausal women

HRT
• estrogen
• estrogen/progestin
• SERMs
• alternative forms

Improvement/stabilization of bone density

Reduction of fractures

Reduction of coronary artery disease/myocardial infarction

Reduction of stroke

Improvement/stabilization of cognitive function

Reduction of dementia

Other benefits

Adverse effects (Analytic Framework 2)

Reduction in morbidity and mortality

Note: SERMs indicates Selective estrogen receptor modulators
Figure 2. Adverse Effects of Hormone Replacement Therapy

Analytic Framework 2

Note: DVT indicates Deep-vein thrombosis; PE, pulmonary embolus; SERMs, Selective estrogen receptor modulators
Appendix 1a: Search Strategy for Hormone Replacement Therapy with Bone Density or Fracture Outcomes

The topic of HRT and osteoporosis and fractures was searched in the MEDLINE database including 1994 to May 2001.

1 exp hormone replacement therapy
   estrogen replacement therapy
2 hormone replacement.tw. (text word taken from title and abstract of article)
3 estrogen replacement.tw.
4 exp estrogens/ad,tu (ad = administration & dosage; tu = therapeutic use)
   equilenin            estrogens, catechol
   equilin             estrogens, conjugated
   estradiol        estrogens, non-steroidal
   estriol              estrone
5 exp estrogens, synthetic/ad,tu
   estrogens, non-steroidal      epimestrol
   chlorotrianisene        ethinyl estradiol
   coumestrol             mestranol
   dienestrol              quinestrol
   diethylstilbestrol     hexestrol
   zearalenone            zeranol
6 1 or 2 or 3 or 4 or 5
7 exp osteoporosis
   osteoporosis, postmenopausal
8 exp fractures
   femoral fractures         fractures, closed
   fractures, comminuted     fractures, malunited
   fractures, open           fractures, spontaneous
   fractures, stress         fractures, ununited
   humeral fractures         radius fractures
   rib fractures             shoulder fractures
   skull fractures            spinal fractures
   tibial fractures          ulna fractures
9 fracture$.tw.
10 bone density
11 7 or 8 or 9 or 10
12 6 and 11
13 limit 12 to human
14 limit 13 to english language
15 looked at english abstracts of foreign articles
Appendix 1b: Search Strategy for Randomized Controlled Trials of Estrogen and SERMs

The topic of randomized controlled trials of estrogen with bone density or fracture outcomes was searched in the MEDLINE database including 1994 to May 2001. A similar search was also conducted for the SERMs raloxifene and tamoxifen.

Estrogen

1 exp hormone replacement therapy
   estrogen replacement therapy
2 hormone replacement.tw. (text word taken from title and abstract of article)
3 estrogen replacement.tw.
4 exp estrogens/ad, tu (ad = administration & dosage;  tu = therapeutic use)
   equilenin                  estrogens, catechol
   equilin                   estrogens, conjugated
   estradiol                 estrogens, non-steroidal
   estriol                   estrone
5 exp estrogens, synthetic/ad, tu
   estrogens, non-steroidal  epimestrol
   chlorotrianisene          ethinyl estradiol
   coumestrol                mestranol
   dienestrol                quinestrol
   diethylstilbestrol         hexestrol
   zearalenone                zeranol
6 1 or 2 or 3 or 4 or 5
7 limit 6 to randomized controlled trials (check for document type)
8 randomized controlled trials
9 randomized.tw.
10 8 or 9
11 6 and 10
12 7 or 11
13 limit 12 to human
14 limit 13 to english language
15 looked at english abstracts of foreign articles

Tamoxifen and raloxifene

1 (tamoxifen or raloxifene).mp.
2 Bone density/ or "bone density".mp
3 exp osteoporosis/ or "osteoporosis".mp
4 exp fractures/ or fracture$.mp.
5 exp hormone replacement therapy
6 estrogen replacement.mp.
7 2 or 3 or 4 or 5 or 6
8 1 and 7
9 limit 8 to (human and english language)
10 exp breast neoplasms/
11 9 not 10
12 from 11 keep 1-145
Presented below is a set of minimal criteria for each study design and then a general definition of three categories—“good,” “fair,” and “poor”—based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a “good” study is one that meets all criteria well. A “fair” study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known important limitations. “Poor” studies have at least one important limitation.

Systematic Reviews

Criteria:
- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important for systematic reviews

Definition of ratings from above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.
Appendix 2: Criteria for Grading the Internal Validity of Individual Studies (continued)

Randomized Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups
  - for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

Definition of ratings based on above criteria:

**Good:** Meets all criteria: comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

**Fair:** Studies will be graded “fair” if any or all of the following problems occur, without the fatal flaws noted in the “poor” category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for RCTS.

**Poor:** Studies will be graded “poor” if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.
Table 1. Key Questions and Types of Studies Cited

<table>
<thead>
<tr>
<th>Key Questions</th>
<th>Type of Study</th>
<th>RCT</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does HRT improve or stabilize bone density?</td>
<td></td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Does HRT prevent fractures?</td>
<td></td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td><strong>SERMs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does postmenopausal use of SERMs improve or stabilize bone density?</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Does postmenopausal use of SERMs prevent fractures?</td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Note: RCT indicates randomized controlled trial; SERMs, selective estrogen receptor modulators
Table 2. Combined Results of Randomized Controlled Trials of HRT with Bone Density Outcomes*

<table>
<thead>
<tr>
<th>BMD Site</th>
<th>Types of studies</th>
<th>Number of studies</th>
<th>Weighted Mean Difference (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (1-year)</td>
<td>Treatment and prevention opposed and unopposed</td>
<td>25</td>
<td>5.39 (4.24-6.46)</td>
</tr>
<tr>
<td>Lumbar spine (2-years)</td>
<td>Treatment and prevention opposed and unopposed</td>
<td>21</td>
<td>6.76 (5.63-7.89)</td>
</tr>
<tr>
<td>Femoral neck (1-year)</td>
<td>Treatment and prevention opposed and unopposed</td>
<td>7</td>
<td>2.50 (1.16-3.83)</td>
</tr>
<tr>
<td>Femoral neck (2-years)</td>
<td>Treatment and prevention opposed and unopposed</td>
<td>9</td>
<td>4.12 (3.45-4.80)</td>
</tr>
<tr>
<td>Lumbar spine (2-year prevention)</td>
<td>opposed and unopposed</td>
<td>18</td>
<td>6.98 (5.53-8.43)</td>
</tr>
<tr>
<td>Femoral neck (2-year prevention)</td>
<td>opposed and unopposed</td>
<td>8</td>
<td>4.07 (3.30-4.84)</td>
</tr>
<tr>
<td>Forearm (2-year prevention)</td>
<td>opposed and unopposed</td>
<td>14</td>
<td>4.53 (3.68-5.36)</td>
</tr>
</tbody>
</table>

*Data from a Cochrane systematic review presented at the NIH Consensus Development Conference on Osteoporosis, March 2000³³

**Weighted mean difference is calculated by using percent change from baseline and standard deviations.

Note: CI indicates confidence interval
<table>
<thead>
<tr>
<th>Author/year</th>
<th>N</th>
<th>Duration (years)</th>
<th>Population</th>
<th>Drug/dose</th>
<th>Assessment of fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lufkin, 1992</td>
<td>78</td>
<td>1</td>
<td>Age 47 to 75 years with 1 or more vertebral fractures enrolled at the Mayo Clinic, Minnesota.</td>
<td>Cyclic transdermal patch with 0.1 mg estradiol / 10 mg oral medroxyprogesterone compared to placebo.</td>
<td>At least 1 of 3 measurements on lateral x-ray of spine was decreased by more than 15% compared with baseline.</td>
</tr>
<tr>
<td>Wimalawansa, 1998</td>
<td>36</td>
<td>4</td>
<td>Women with mean age 65 years attending metabolic bone disease outpatient clinics with established osteoporosis.</td>
<td>Cyclic premarin 0.625 mg/day with norgestrel 150 micorg/12 days each month compared with placebo; all subjects received calcium and vitamin D.</td>
<td>Reduction of 20% or more on 1 of 3 measurements with reduction of 15% or more in area in a previously unaffected vertebra on lateral x-ray of spine compared to baseline.</td>
</tr>
</tbody>
</table>
| Komulainen, 1998 | 464| 4.3              | Early postmenopausal women without osteoporosis, a subgroup of the Kuopio Osteoporosis Studv (n=13,100) based in Finland.                     | 1. Sequential estradiol (2 mg/day) / cyproterone acetate (1 mg/day)  
2. Vitamin D (300 IU/day)  
3. HRT & vitamin D  
4. Placebo                                                                 | New, symptomatic radiographically defined nonvertebral fractures.                                                                            |
<p>| Cauley, 2001     | 2,763| 4.1          | Heart and Estrogen/progestin Replacement Study (HERS), postmenopausal women with coronary disease under 80 years (mean 67 years) with an intact uterus, fractures were a secondary outcome. | Continuous combined regimen of 0.625 mg/day conjugated equine estrogen with 2.5 mg/day medroxyprogesterone or placebo.                        | New fractures were reviewed by coordinating center physicians blinded to treatment assignment.               |
| Mosekilde, 2000  | 1,006| 5             | Postmenopausal Danish women ages 45 to 52 years recruited by mailed questionnaire.                                                            | Sequential estradiol (1-2 mg/day) with norethisterone acetate (1 mg/day for 10 days each month); continuous estradiol (2 mg/day) if hysterectomy; or nonuse. | Not well described.                                                                                         |</p>
<table>
<thead>
<tr>
<th>Author/year</th>
<th>relative risk (95% CI) for fractures</th>
<th>USPSTF Quality Rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td>----------------</td>
<td>--------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Lufkin, 1992</td>
<td>0.39 (0.16-0.95)</td>
<td>Fair: 77% follow-up in HRT group, 82% placebo; inappropriate analysis.</td>
</tr>
<tr>
<td>Wimalawansa, 1998</td>
<td>HRT: 33.3/1,000 patient-yrs; calcium/vitamin D: 89.3/1,000 patient-yrs; no difference between groups</td>
<td>Poor: 83% follow-up in HRT group, 77% calcium/vitamin D; inappropriate analysis; under powered for fracture outcomes.</td>
</tr>
<tr>
<td>Komulainen, 1998</td>
<td>NA</td>
<td>Fair: 79% completed study; randomized open trial.</td>
</tr>
<tr>
<td>Cauley, 2001</td>
<td>Any fracture: 0.95 (0.75-1.21); Hip fracture: 1.10 (0.49-2.50)</td>
<td>Fair: fractures are secondary outcomes, inclusion criteria was based on cardiac risk, not known if treatment groups have comparably distributed osteoporosis risk factors; asymptomatic vertebral fractures not included.</td>
</tr>
<tr>
<td>Mosekilde, 2000</td>
<td>2.0 (0.62-6.49)</td>
<td>Poor: 83% follow-up in HRT group, 77% calcium/vitamin D; inappropriate analysis; under powered for fracture outcomes.</td>
</tr>
</tbody>
</table>

*See appendix 2 for quality criteria

Note: CI indicates confidence interval
Table 4. Cohort Studies of HRT with Hip Fracture Outcomes

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Exposure</th>
<th>N</th>
<th>Duration</th>
<th>Population</th>
<th>Assessment of fracture</th>
<th>RR (95% CI) for fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiel, 1987</td>
<td>Ever use</td>
<td>2,873</td>
<td>Up to 32 years</td>
<td>Women in the Framingham Heart Study.</td>
<td>Hip fractures confirmed by hospital discharge summary, review of hospital admission diagnoses, subject interview, and/or routine contact during study asking about hospitalizations.</td>
<td>0.63 (0.42-0.95)</td>
</tr>
<tr>
<td>Naessen, 1990</td>
<td>Ever use</td>
<td>23,246</td>
<td>5.7 years</td>
<td>All women age 35 and older (mean age 53.7 years) who received noncontraceptive estrogens from 1977-80 compared to nonusers based on prescription data in the Uppsala health care region in Sweden.</td>
<td>Follow-up through 1983 for hospital admissions for first hip fracture.</td>
<td>0.79 (0.68-0.93)</td>
</tr>
<tr>
<td>Maxim, 1995</td>
<td>Ever use for at least 5 years</td>
<td>490</td>
<td>Approx. 25 years</td>
<td>Retrospective review of computerized pharmacy records at Kaiser of postmenopausal women who began using estrogen between 1968-1971 and used it regularly for at least 5 years (n=245) compared with age matched nonusers.</td>
<td>Nontraumatic fractures based on x-ray reports and chart review.</td>
<td>1.31 (0.55-3.12) wrist 0.44 (0.23-0.84); vertebral 0.60 (0.36-0.99)</td>
</tr>
<tr>
<td>Grodstein, 1999</td>
<td>Ever use</td>
<td>9,236</td>
<td>8 years</td>
<td>Women in the Uppsala health care region in Sweden who had received at least one prescription for postmenopausal hormones from 1977-1980 and responded to a mailed questionnaire about estrogen use in 1987-88 (response rate 66%).</td>
<td>National Swedish Inpatient Registry to confirm hip fractures.</td>
<td>0.65 (0.45-0.95)</td>
</tr>
</tbody>
</table>

Note: CI indicates confidence interval
Table 4. Cohort Studies of HRT with Hip Fracture Outcomes

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Exposure</th>
<th>N</th>
<th>Duration</th>
<th>Population</th>
<th>Assessment of fracture</th>
<th>RR (95% CI) for fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiel, 1987</td>
<td>Current user</td>
<td>2,873</td>
<td>Up to 32 years</td>
<td>Women in the Framingham Heart Study.</td>
<td>Hip fractures confirmed by hospital discharge summary, review of hospital admission diagnoses, subject interview, and/or routine contact during study asking about hospitalizations.</td>
<td>0.34 (0.11-1.09)</td>
</tr>
<tr>
<td>Cauley, 1995</td>
<td>Current user</td>
<td>9,704</td>
<td>4.5 years</td>
<td>Women in the Study of Osteoporotic Fractures (community dwelling, ambulatory women age 65 and above, predominantly white); mean age at baseline 72 years.</td>
<td>Incident fractures validated by radiographic report.</td>
<td>0.60 (0.36-1.02)</td>
</tr>
<tr>
<td>Hoidrup, 1999</td>
<td>Current user</td>
<td>6,159</td>
<td>Approx. 7 years</td>
<td>Postmenopausal women from the Copenhagen Center for Prospective Population Studies, Denmark; mean age at baseline 55 for users, 60 for nonusers.</td>
<td>National Register of Hospital Discharges and review of hospital records for hip fracture.</td>
<td>0.71 (0.50-1.01)</td>
</tr>
</tbody>
</table>

Note: CI indicates confidence interval
Table 4. Cohort Studies of HRT with Hip Fracture Outcomes

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Ever Use</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiel, 1987</td>
<td></td>
<td>Results adjusted for age, weight, age at menopause, smoking, alcohol consumption; 28 fractures for users, 135 for non users; taking estrogen within 4 years of menopause also protected against fracture.</td>
</tr>
<tr>
<td>Naessen, 1990</td>
<td></td>
<td>Observed number of cases was compared with that expected based on incidence rates in the background population; type of estrogen, age at and period of the first recorded prescription, and follow-up period were included in multivariate model; for those taking more potent estrogens RR=0.37 (0.13-0.79).</td>
</tr>
<tr>
<td>Maxim, 1995</td>
<td></td>
<td>Results adjusted for age at menopause, body mass index, smoking.</td>
</tr>
<tr>
<td>Grodstein, 1999</td>
<td></td>
<td>Results adjusted for age; best results found for those using estrogen for 7 or more years.</td>
</tr>
</tbody>
</table>

**USPSTF Quality Rating*** 

- Good

*See appendix 2 for quality criteria; few studies reported loss to follow-up or cross-over.
Table 4. Cohort Studies of HRT with Hip Fracture Outcomes

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Current Use</th>
<th>Other</th>
<th>USPSTF Quality Rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiel, 1987</td>
<td>Defined as use within 2 years; adjusted for age, weight, age at menopause, smoking, alcohol consumption; 3 fractures for users, 135 for nonusers.</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Cauley, 1995</td>
<td>Adjusted for multiple confounders (age, physical activity, calcium intake, body mass index, surgical menopause, health status, use of thiazide diuretics, poor cognition, alcohol intake, recent fall, use of sedatives or anxiolytics, smoking, thyroid supplements); estrogen use was most effective in preventing hip fracture for those over 75 years old and current users who started within 5 years of menopause, previous use had no effect; number of fractures for current users included 134 hip, 200 wrist, 824 total nonvertebral.</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Hoidrup, 1999</td>
<td>Adjusted for multiple confounders (age, body mass index, physical activity, smoking, alcohol intake, cohabitation, marital status, school education, age at menopause, and parity); 326 hip fractures for nonusers, 37 for current users.</td>
<td>Good</td>
<td></td>
</tr>
</tbody>
</table>

*See appendix 2 for quality criteria; few studies reported loss to follow-up or cross-over
Table 5. Randomized Controlled Trials of SERMs with Bone Density Outcomes

<table>
<thead>
<tr>
<th>Author/year</th>
<th>N</th>
<th>Duration</th>
<th>Population</th>
<th>Drug/dose</th>
<th>Significant Increases in BMD (mean % from baseline)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lumbar spine</td>
</tr>
<tr>
<td>Prestwood,</td>
<td>51</td>
<td>6 months</td>
<td>Postmenopausal women age 55 to 85 with low bone density in Connecticut.</td>
<td>Raloxifene 60 mg/day compared to conjugated equine estrogen (0.625 mg/day).</td>
<td>1.3</td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>femoral neck 3.0; trochanter 4.0; Ward's triangle 5.0</td>
</tr>
<tr>
<td>Lufkin,</td>
<td>143</td>
<td>1 year</td>
<td>Postmenopausal women age 45 to 75 (mean age 68 years) with at least 1 prevalent vertebral fracture and low BMD, recruited at the Mayo Clinic, Minnesota and Arizona.</td>
<td>Raloxifene 60 or 120 mg/day or placebo; all received calcium and vitamin D.</td>
<td>1.7 (60 mg); NS (120 mg)</td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.9 (60 mg); 2.5 (120 mg)</td>
</tr>
<tr>
<td>Delmas,</td>
<td>601</td>
<td>2 years</td>
<td>Postmenopausal women age 45 to 60 (mean age 55 years) recruited from the community in Europe and UK with a range of BMD values.</td>
<td>Raloxifene 30, 60, or 150 mg/day or placebo; all received calcium.</td>
<td>1.6 (60 mg)</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>total hip 1.6 (60 mg); femoral neck 1.2 (60 mg)</td>
</tr>
<tr>
<td>Meunier,</td>
<td>129</td>
<td>2 years</td>
<td>Postmenopausal women age 50 to 75 years (mean age 60 years) with low bone density, a third had prior nonvertebral fractures, recruited at 8 clinic sites in France.</td>
<td>Raloxifene 60 or 150 mg/day or placebo; all received calcium and vitamin D.</td>
<td>3.3 (60 and 150 mg combined)</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>trochanter 3.0 (combined); femoral neck 2.1 (60 mg); total hip 1.6 (60 mg), 2.4 (150 mg) femoral neck 2.1 (60 mg); 2.4 (120 mg)</td>
</tr>
<tr>
<td>Ettinger,</td>
<td>7,705</td>
<td>3 years</td>
<td>Multiple Outcomes of Raloxifene Evaluation (MORE) study of women aged 31 to 80 years (mean 67 years) in 25 countries who had been postmenopausal for at least 2 years and met WHO criteria for osteoporosis.</td>
<td>Raloxifene 60 or 120 mg/day or placebo; all received calcium and vitamin D.</td>
<td>2.6 (60 mg); 2.7 (120 mg)</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifien</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grey,</td>
<td>57</td>
<td>2 years</td>
<td>Postmenopausal women with mean age 58 to 60, not with low bone density or breast cancer, in New Zealand.</td>
<td>Tamoxifen 20 mg/day compared to placebo.</td>
<td>1.4</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>proximal femur NS</td>
</tr>
<tr>
<td>Powles,</td>
<td>54</td>
<td>3 years</td>
<td>Postmenopausal women (mean age 57 to 59) enrolled in a breast cancer prevention trial in the UK.</td>
<td>Tamoxifen 20 mg/day compared to placebo.</td>
<td>NS</td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hip 1.8</td>
</tr>
</tbody>
</table>

*Meunier, 1999 expressed this as mean % difference compared to placebo rather than baseline.

Note: BMD indicates bone mass density; NS, not significant.
Table 5. Randomized Controlled Trials of SERMs with Bone Density Outcomes

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Other</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Raloxifene</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prestwood, 2000</td>
<td>Numbers estimated from graph; estrogen had a greater effect than raloxifene for lumbar spine.</td>
<td>Fair: estrogen group had more dropouts than raloxifene group (23% vs 4%); follow up shorter than other trials, significance of bone density changes after only 6 months questionable.</td>
</tr>
<tr>
<td>Lufkin, 1998</td>
<td>120 mg dose did not significantly increase bone density at the total hip.</td>
<td>Good: 9% dropped out of study.</td>
</tr>
<tr>
<td>Delmas, 1997</td>
<td>All raloxifene doses resulted in significant increases; higher doses generally had more effect although this was not seen at the hip; placebo group lost bone at all sites and comparisons with placebo rather than baseline indicate greater effect; increases in bone density in the lumbar spine and hip were similar regardless of initial BMD.</td>
<td>Fair: 25% of subjects dropped out of the study although there were no differences among therapy groups with respect to the number who dropped out.</td>
</tr>
<tr>
<td>Meunier, 1999</td>
<td>Mean % differences compared to placebo, pooled results for both doses unless indicated.</td>
<td>Good: 16% dropped out of study.</td>
</tr>
<tr>
<td>Ettinger, 1999</td>
<td>Bone density of hip peaked at 24 months, spinal density remained constant between 2 and 3 years; 24% of subjects had adverse effects regardless of treatment group.</td>
<td>Good: 18% of placebo, 17% of treatment groups dropped out at 2 years; 25% of placebo and 22% of treatment groups at 3 years.</td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grey, 1995</td>
<td>Effect of tamoxifen was maximal after 1 year.</td>
<td>Poor: intention-to-treat analysis not used; 19% dropout rate.</td>
</tr>
<tr>
<td>Powles, 1996</td>
<td>Expressed as mean annual %; numbers estimated from graph.</td>
<td>Poor: high dropout rates, 28% after 2 years, 48% after 3 years.</td>
</tr>
</tbody>
</table>

**See appendix 2 for quality criteria

Note: BMD indicate bone mass density
<table>
<thead>
<tr>
<th>Author/year</th>
<th>N</th>
<th>Duration</th>
<th>Population</th>
<th>Drug/dose</th>
<th>Assessment of fracture</th>
<th>RR (95% CI) for fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luufkin,</td>
<td>143</td>
<td>1 year</td>
<td>Postmenopausal women age 45 to 75 (mean age 68 years) with at least 1 prevalent vertebral fracture and low BMD, recruited at the Mayo Clinic, Minnesota and Arizona.</td>
<td>Raloxifene 60 or 120 mg/day or placebo; all received calcium and vitamin D.</td>
<td>Vertebral fractures determined by lateral spine x-rays with incident fractures defined as 15% or more decrease in vertebral height at specific points.</td>
<td>1.15 (0.75-1.75) 0.51 (0.12-2.16)</td>
</tr>
<tr>
<td>Ettinger,</td>
<td>7,705</td>
<td>3 years</td>
<td>Multiple Outcomes of Raloxifene Evaluation (MORE) study of women aged 31 to 80 years (mean 67 years) in 25 countries who had been postmenopausal for at least 2 years and met WHO criteria for osteoporosis; 2 treatment groups studied 1.) BMD t-score &lt;2.5; 2.) low BMD and previous vertebral or other fracture.</td>
<td>Raloxifene 60 or 120 mg/day or placebo; all received calcium and vitamin D.</td>
<td>Incident vertebral fractures determined radiographically as a 20% reduction in vertebral height at 24- and 36-month visits and if new symptoms; nonvertebral fractures determined by interview at 6-month visits.</td>
<td>0.59 (0.05-0.70) 0.91 (0.79-1.06)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher,</td>
<td>13,388</td>
<td>5 years</td>
<td>Women enrolled in National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P-1), high risk for breast cancer, age 35 and over (61% age 50 and over), in U.S. and Canada; fractures were secondary outcome measures.</td>
<td>Tamoxifen 20 mg/day or placebo.</td>
<td>Radiographically confirmed incident fractures of hip, wrist, and vertebra (criteria for vertebral fracture not provided).</td>
<td>0.74 (0.41-1.32) Hip: 0.55 (0.25-1.15); Colles' 0.61 (0.29-1.23)</td>
</tr>
</tbody>
</table>

Note: BMD indicates bone mass density; CI, confidence interval; WHO, World Health Organization
Table 6. Randomized Controlled Trials of SERMs with Fracture Outcomes

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Other</th>
<th>USPSTF Quality Rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Raloxifene</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lufkin, 1998</td>
<td>41</td>
<td>No differences with dose; when vertebral fracture criteria changed to 30% or more reduction in vertebral height, fracture reduction was significant ( P=0.047; ) RR not given.</td>
</tr>
<tr>
<td>Ettinger, 1999</td>
<td>43</td>
<td>Results similar for both doses except for significantly fewer vertebral fractures for subgroup 2 (with pre-existing fractures) who took 120 mg compared with 60 mg.</td>
</tr>
</tbody>
</table>

| **Tamoxifen** |       |                        |
| Fisher, 1998 | 48    | All fractures RR= 0.81 (0.63-1.05); overall reduction greater in women 50 or older at entry RR= 0.79 (0.60-1.05). | Fair: fractures are secondary endpoints, inclusion criteria was based on breast cancer risk, not known if treatment groups have comparably distributed osteoporosis risk factors; vertebral fractures diagnosed only if reported by patient, asymptomatic fractures would be missed; 74% followed for more than 3 years, 37% for more than 5 years. |

*See appendix 2 for quality criteria.*
Table 7. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Questions</th>
<th>Evidence Codes*</th>
<th>Quality of Evidence**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arrow 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does HRT improve or stabilize bone density?</td>
<td>I</td>
<td>Good: many good-quality RCTs of HRT and bone density are consistent and demonstrate benefit; limited by short duration of trials; BMD is an intermediate outcome.</td>
</tr>
<tr>
<td>Does postmenopausal use of SERMs improve or stabilize bone density?</td>
<td>I</td>
<td>Few trials available but are good-quality; larger studies with at least 2-year follow-up indicate benefit; limited by short duration and small numbers of trials; BMD is an intermediate outcome.</td>
</tr>
<tr>
<td><strong>Arrow 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does HRT prevent fractures?</td>
<td>I, II-2</td>
<td>RCTs: only 5 studies available that are limited methodologically; lack of hip fracture outcomes. Cohort studies: Good: several good-quality cohort studies are consistent and demonstrate benefit; limited by healthy user bias.</td>
</tr>
<tr>
<td>Does postmenopausal use of SERMS prevent fractures?</td>
<td>I</td>
<td>One large good-quality RCT demonstrates benefit for vertebral fractures, one small RCT shows no benefit; limited by short duration of trials and small numbers of trials. No studies yet.</td>
</tr>
</tbody>
</table>

*Study Design Categories  
I: Randomized, controlled trials  
II-1: Controlled trials without randomization  
II-2: Cohort or case-control analytic studies  
II-3: Multiple time series, dramatic uncontrolled experiments  
III: Opinions of respected authorities, descriptive epidemiology

**Quality of evidence ratings based on criteria developed by the U.S. Preventive Services Task Force (Harris, 2001)**

22