

Postmenopausal Hormone Replacement Therapy

Scientific Review

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APPROXIMATELY 38% OF POSTMENOPAUSAL women in the United States in 1995 used hormone replacement therapy (HRT), estrogen with or without progestin, to treat symptoms of menopause and prevent chronic conditions such as cardiovascular disease and osteoporosis.¹ Although treatment of symptoms of menopause, such as hot flashes and urogenital atrophy, among others, is a common indication for short-term use, potential preventive effects of HRT on long-term health outcomes have become an increasingly important consideration.

In 1996, the second US Preventive Services Task Force (USPSTF) determined that there was insufficient evidence to recommend for or against HRT for all women but thought that individual decisions should be based on patient risk factors, an understanding of the probable benefits and harms, and personal preferences.² Many studies have been published since these recommendations were released, including the first report from the Women's Health Initiative (WHI),³ a large randomized primary prevention trial, and the Heart and Estrogen/progestin Replacement Study (HERS),⁴ a secondary prevention trial reporting multiple outcomes.⁴⁻⁶ This review was initiated to aid the current USPSTF in making new recommendations that will be

See also p 882 and Patient Page.

Context Although postmenopausal hormone replacement therapy (HRT) is widely used in the United States, new evidence about its benefits and harms requires reconsideration of its use for the primary prevention of chronic conditions.

Objective To assess the benefits and harms of HRT for the primary prevention of cardiovascular disease, thromboembolism, osteoporosis, cancer, dementia, and cholecystitis by reviewing the literature, conducting meta-analyses, and calculating outcome rates.

Data Sources All relevant English-language studies were identified in MEDLINE (1966-2001), HealthSTAR (1975-2001), Cochrane Library databases, and reference lists of key articles. Recent results of the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS) are included for reported outcomes.

Study Selection and Data Extraction We used all published studies of HRT if they contained a comparison group of HRT nonusers and reported data relating to HRT use and clinical outcomes of interest. Studies were excluded if the population was selected according to prior events or presence of conditions associated with higher risks for targeted outcomes.

Data Synthesis Meta-analyses of observational studies indicated summary relative risks (RRs) for coronary heart disease (CHD) incidence and mortality that were significantly reduced among current HRT users only, although risk for incidence was not reduced when only studies that controlled for socioeconomic status were included. The WHI reported increased CHD events (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.02-1.63). Stroke incidence but not mortality was significantly increased among HRT users in the meta-analysis and the WHI. The meta-analysis indicated that risk was significantly elevated for thromboembolic stroke (RR, 1.20; 95% CI, 1.01-1.40) but not subarachnoid or intracerebral stroke. Risk of venous thromboembolism among current HRT users was increased overall (RR, 2.14; 95% CI, 1.64-2.81) and was highest during the first year of use (RR, 3.49; 95% CI, 2.33-5.59) according to a meta-analysis of 12 studies. Protection against osteoporotic fractures is supported by a meta-analysis of 22 estrogen trials, cohort studies, results of the WHI, and trials with bone density outcomes. Current estrogen users have an increased risk of breast cancer that increases with duration of use. Endometrial cancer incidence, but not mortality, is increased with unopposed estrogen use but not with estrogen with progestin. A meta-analysis of 18 observational studies showed a 20% reduction in colon cancer incidence among women who had ever used HRT (RR, 0.80; 95% CI, 0.74-0.86), a finding supported by the WHI. Women symptomatic from menopause had improvement in certain aspects of cognition. Current studies of estrogen and dementia are not definitive. In a cohort study, current HRT users had an age-adjusted RR for cholecystitis of 1.8 (95% CI, 1.6-2.0), increasing to 2.5 (95% CI, 2.0-2.9) after 5 years of use.

Conclusions Benefits of HRT include prevention of osteoporotic fractures and colorectal cancer, while prevention of dementia is uncertain. Harms include CHD, stroke, thromboembolic events, breast cancer with 5 or more years of use, and cholecystitis.

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released this fall. The focus of the USPSTF is to develop recommendations on screening, counseling, and chemoprophylaxis for asymptomatic populations.

We conducted systematic searches of the literature on postmenopausal HRT use and its effectiveness for primary prevention of chronic conditions and its effects on harmful outcomes. Treatment of symptoms of menopause and use of HRT for treatment of a preexisting condition are outside the scope of the USPSTF recommendation, and this literature was not reviewed. We focused on primary outcomes such as myocardial infarction (MI) rather than intermediate outcomes such as lipid levels. To provide an overview of benefits and harms, we conducted several meta-analyses and used these results, as well as those from selected published articles, to calculate numbers of events prevented or caused by HRT in a hypothetical population of postmenopausal women.

METHODS

Methods of searching the literature; selecting abstracts; reviewing, abstracting, and rating studies; and conducting meta-analyses were standardized for all topics. Because the literature for each topic varied, each review was also subject to topic-specific modifications in methods. Detailed methods for each topic are presented elsewhere.⁷⁻¹²

In conjunction with a medical librarian, we conducted topic-specific searches using MEDLINE (1966-2001), HealthSTAR (1975-2001), and the Cochrane Controlled Trials Register (<http://www.cochranelibrary.com>); dates of searches varied with some topics. Additional articles were obtained by reviewing reference lists of pertinent studies, reviews, and editorials and by consulting experts. We used only published data in meta-analyses.

Inclusion and exclusion criteria were developed by the investigators for each topic. In general, studies were included if they contained a comparison group of HRT nonusers and reported data relating to HRT use and clinical

outcomes of interest. Studies were excluded if the population was selected according to prior events or presence of conditions associated with higher risks for targeted outcomes.

Hormone replacement therapy use was classified as unopposed estrogen replacement (estrogen only) or combined (estrogen plus progestin) when specified. When data were available, we reported effects of formulation, dose, and duration. In studies with multiple publications from the same cohort or population, only data from the most recent publication were included in the meta-analyses. We used adjusted statistics when reported.

Two reviewers independently rated each study's quality by using criteria specific to different study designs developed by the USPSTF and categorized them as good, fair, or poor.¹³ When reviewers disagreed, a final score was reached through consensus.

In addition to the systematic literature review, we included 2 recently published randomized controlled trials (RCTs) with pertinent findings. The WHI reported results of 16 608 healthy postmenopausal women after 5.2 years of daily combined HRT or placebo.³ We also cite the noncardiac outcomes of the HERS follow-up (HERS II),^{5,6} a trial of daily combined HRT for 6.8 years in 2321 postmenopausal women with preexisting coronary heart disease (CHD).

Meta-analysis

Meta-analyses were conducted for some of the topics because either previous meta-analyses had not been published or they were outdated or inadequate.

We used adjusted relative risk (RR) estimates when available or calculated them when possible. Under the modeling assumptions made by each study, the logarithm of the RR (logRR) had a normal distribution. Standard errors for logRR were calculated from reported confidence intervals (CIs) or *P* values. The logRR and SEs provided the data points for the meta-analyses. Heterogeneity was assessed with study-level stratification factors in the regression models. Fixed and random-effects models

were fit on the data by using the Bayesian data analytic framework.¹⁴ We report only the random-effects model because the results of the 2 models were similar in all cases. Inference on the parameters was done via posterior probability distributions. The data were analyzed with WinBUGS software,¹⁵ which uses a method of Markov chain Monte Carlo called Gibbs sampling to simulate posterior probability distributions.

Sensitivity analysis was performed with different prior distributions, combining only studies with similar methods and excluding poor-quality studies and those with important biases or limitations. Sensitivity analysis varied according to the needs of each meta-analysis.

We also evaluated studies for selection bias by using funnel plots¹⁶ and investigated the sensitivity of the analysis to studies possibly missed because of publication bias by trim and fill.^{17,18} Results were unaffected, although this technique does not entirely rule out potential publication bias.

Estimates of Benefits and Harms

We calculated the number of events prevented or caused by HRT per year of use in 10 000 women by using RRs for clinical outcomes derived from the reviewed studies and meta-analyses and by using population-based estimates of incidence and mortality.¹⁹⁻²⁶ We stratified event rates by 10-year age intervals because incidence rates for some outcomes are strongly age-related. Data sources for incidence and mortality rates did not allow further breakdown by race, preexisting disease, risk factors, or other variables and varied in quality. These estimates, therefore, do not consider special subgroups and would be most applicable to the general population of postmenopausal women.

We used the best evidence available to determine the RR for each outcome.²⁷ Some estimates were derived from extensive literature reviews and meta-analysis; others, from a single study representing the only or best literature available. We sought data from randomized controlled trials (RCTs) when avail-

able. When evaluating observational studies, we looked carefully at the potential for confounding and took measures to reduce its influence by including only studies that controlled for important confounders, selecting outcomes less prone to confounding, or factoring it into our overall conclusions. In general, observational studies allowed examination of issues of duration and currency of use and examined end points that are difficult to study in random-

ized controlled trials because they are infrequent or develop slowly.

RESULTS

Cardiovascular Disease

Studies of HRT and the primary prevention of cardiovascular disease identified in our systematic review report various outcomes. Some studies examined CHD and stroke as separate categories, while others combined them into an overall cardiovascular disease

category. We describe these as they were reported in the original sources. We evaluated results by type of use as they were defined in each study. We also created a category, all use, that combined all mutually exclusive types of use (ever, past, and current).

In total, 43 observational studies of primary prevention of CHD or cardiovascular disease were reviewed. Characteristics of poor-quality studies included little or no control of confounding, non-representative cohorts, poor definition of outcomes, poor characterization of exposure, and bias in control selection. Our review and meta-analysis focuses on the good- or fair-quality studies, including 11 case-control²⁸⁻³⁸ and 10 cohort studies^{19,39-48} and 1 small trial.⁴⁹

For CHD outcomes, the summary RR for incidence was significantly reduced among current users (RR, 0.80; 95% CI, 0.68-0.95)^{19,30,32-35,37,47,49} but not among ever, past, or all use groups (TABLE 1). Similarly, when studies of CHD mortality were pooled, only current use was associated with reduced risk (RR, 0.62; 95% CI, 0.40-0.90),^{38,44,46,47} and no benefit was shown for ever, past, or all use groups. Combined estrogen and progestin therapy was evaluated specifically in 5 studies, with RRs ranging from 0.33 to 1.20.^{19,31,33,34,49}

Because of the marked variation in study results, we further examined the relationship between current use and CHD incidence with sensitivity analysis that included only studies that controlled for socioeconomic status by using measures of social class, education, or income.^{29,34,35,47} When these studies were combined, the summary RR became nonsignificant (RR, 0.97; 95% CI, 0.82-1.16), suggesting confounding. Further sensitivity analysis evaluating only studies that adjusted for alcohol use, exercise, or major cardiovascular risk factors confirmed this finding.^{34,35,43,47}

Among studies reporting results by using an overall cardiovascular disease outcome, only 3 contributed to our meta-analysis of cardiovascular disease incidence. Risk of cardiovascular disease was not significantly related to any use group.^{31,43,47} In the analysis of

Table 1. Hormone Replacement Therapy (HRT) and Cardiovascular Disease and Thromboembolism Studies

Outcome by HRT Use	Relative Risk (95% Confidence Interval)*	Type of Study†	Quality‡
Coronary heart disease			
Incidence			
Current ^{19,30,32-35,37,47,49}	0.80 (0.68-0.95)	RCT, cohort	Fair-good
Current adjusted for socioeconomic status ^{29,34,35,47}	0.97 (0.82-1.16)		
Ever ^{28,29,34,43}	0.91 (0.67-1.33)	Cohort, case control	Fair-good
Past ^{19,30,32,34-36,47}	0.89 (0.75-1.05)	Cohort, case control	Fair-good
All groups ^{19,28-30,32-37,43,47,49}	0.88 (0.64-1.21)	RCT, cohort	Fair-good
Mortality			
Current ^{38,44,46,47}	0.62 (0.40-0.90)	Cohort, case control	Fair-good
Ever ⁴⁵	0.81 (0.37-1.60)	Cohort	Fair-good
Past ^{38,44,46,47}	0.76 (0.53-1.02)	Cohort, case control	Fair-good
All groups ^{37,44-47}	0.74 (0.36-1.45)	Cohort	Fair-good
Cardiovascular disease§			
Incidence			
Current ⁴⁷	1.27 (0.80-2.00)	Cohort	Fair
Ever ^{31,43}	1.35 (0.92-2.00)	Cohort, case control	Good
Past ⁴⁷	1.26 (0.79-2.08)	Cohort	Fair
All groups ^{31,43,47}	1.28 (0.86-2.00)	Cohort	Fair-good
Mortality			
Current ^{38,40,44,47}	0.64 (0.44-0.93)	Cohort, case control	Fair-good
Ever ^{41,43,45,48}	0.81 (0.58-1.13)	Cohort	Fair-good
Past ^{44,47}	0.79 (0.52-1.09)	Cohort	Fair-good
All groups ^{38,40,41,43-45,47,48}	0.75 (0.42-1.23)	Cohort	Fair-good
Stroke			
Incidence, ever			
Overall stroke ^{19,31,43,47,50-54}	1.12 (1.01-1.23)	Cohort	Fair-good
Thromboembolic ^{19,43,50,53}	1.20 (1.01-1.40)	Cohort	Fair-good
Subarachnoid ^{19,53,55}	0.80 (0.57-1.04)	Cohort	Fair-good
Intracerebral ^{50,53,54,56}	0.71 (0.25-1.29)	Cohort	Fair-good
Mortality, ever ^{19,40,41,44,46,47,51,52,57}			
Thromboembolism			
Overall, current ^{4,58-68}	2.14 (1.64-2.81)	RCT, case control, cohort	Poor-good
During first year only ^{4,61,63-66}	3.49 (2.33-5.59)	RCT, case control	Poor-good
After the first year ^{4,61,63-66}	1.91 (1.18-3.52)	RCT, case control	Poor-good

*Based on meta-analyses conducted by the authors or individual studies as indicated.

†RCT indicates randomized controlled trial.

‡Defined in Harris et al.¹³

§Includes multiple cardiovascular outcomes such as coronary heart disease, stroke, sudden cardiac death, and congestive heart failure.

||Includes deep vein thrombosis, pulmonary embolism, or both.

mortality, only current use was associated with reduced risk (RR, 0.64; 95% CI, 0.44-0.93),^{38,40,44,47} and risks for ever, past, or all use groups were not significantly reduced (Table 1).^{38,40,41,43-45,47,48}

Our findings differ from those of prior meta-analyses indicating cardiovascular protection⁶⁹⁻⁷¹ because we excluded poor-quality studies, cross-sectional studies, and secondary prevention studies, conducted separate analyses for mortality and incidence outcomes, and assessed effects of risk factors such as socioeconomic status. Nearly all of the studies we excluded because of poor quality or cross-sectional design suggested benefit with HRT use. The WHI provides additional evidence for lack of CHD protection, reporting an increased risk for nonfatal MI (HR, 1.32; 95% CI, 1.02-1.72) but no increased risk for CHD death or coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty among estrogen users.³

Our meta-analysis of 9 observational studies indicated that stroke incidence was significantly increased among ever users (RR, 1.12; 95% CI, 1.01-1.23) (Table 1).^{19,31,43,47,50-54} No differences were shown between current, ever, or past users. On subanalyses, risk was significantly elevated for thromboembolic stroke (RR, 1.20; 95% CI, 1.01-1.40)^{19,43,50,53} but not subarachnoid^{19,53,55} or intracerebral stroke.^{50,53,54,56} Our meta-analysis of 9 observational studies indicated that overall stroke mortality among ever users was marginally reduced.⁶ The WHI indicated an increased risk for nonfatal stroke and no increase for fatal stroke among HRT users.³ The HERS reported no increase in strokes.⁶

Thromboembolism

Results of our meta-analysis, WHI, and HERS consistently report a statistically significant 2-fold increase in risk for thromboembolic events (deep vein thrombosis and pulmonary embolism) among estrogen users, with the highest risks occurring in the first year of use.^{3,5,9}

*References 19, 40, 41, 44, 46, 47, 51, 52, 57.

Table 2. Hormone Replacement Therapy (HRT) and Osteoporosis Studies

Outcome by HRT Use	Relative Risk or Change From Baseline (95% Confidence Interval)*	Type of Study	Quality†
Nonvertebral fractures			
Current ⁷³	0.73 (0.56-0.94)	Meta-analysis (22 trials)	Good
Hip fractures			
Current ^{74,75,79}	0.64 (0.32-1.04)	Cohort	Good
Ever ⁷⁵⁻⁷⁸	0.76 (0.56-1.01)	Cohort	Good
Wrist fractures			
Current ⁷⁴	0.39 (0.24-0.64)	Cohort	Good
Ever ⁷⁶	0.44 (0.23-0.84)	Cohort	Good
Vertebral fractures			
Ever ⁷⁶	0.60 (0.36-0.99)	Cohort	Good
Bone density change, %			
Lumbar spine ⁸⁰	6.98 (5.53-8.43)	Meta-analysis (18 trials)	Good
Femoral neck ⁸⁰	4.07 (3.30-4.84)	Meta-analysis (8 trials)	Good
Forearm ⁸⁰	4.53 (3.68-5.36)	Meta-analysis (14 trials)	Good

*Relative risks for fractures are based on meta-analyses conducted by the authors, published meta-analyses, or individual studies as indicated. The change from baseline is from a Cochrane meta-analysis of 2-year prevention trials and is expressed as a weighted mean difference calculated by using the percentage of change from baseline and SDs.

†Defined in Harris et al.¹³

Twelve studies, including 3 RCTs,^{4,58,59} 8 case-control studies,⁶⁰⁻⁶⁷ and 1 cohort study,⁶⁸ met inclusion criteria for the meta-analysis. Despite differences in design and quality, the studies had consistent results, with 11 of 12 reporting RR point estimates above 1.0 and 6 of these with CIs above 1.0.

When studies were combined by meta-analysis, current use of HRT was associated with an increased risk of venous thromboembolism (RR, 2.14; 95% CI, 1.64-2.81) (Table 1). Estimates did not significantly change when studies were pooled by study design, quality rating, or whether subjects had preexisting CHD. The absolute rate increase was 1.5 venous thromboembolic events per 10000 women in 1 year. Five of 6 studies that reported the timing of thromboembolic events indicated that risk was higher during the first year of use than after the first year (RR, 3.49; 95% CI, 2.33-5.59).^{4,61,63-66} Three studies reported a higher risk with increased estrogen dose (>0.625 mg of conjugated estrogen).^{61,63,64} Three studies reported a higher risk for use of estrogen combined with a progestin compared with use of estrogen alone (OR, 2.2-5.3).^{61,64,65}

Osteoporosis

The WHI is the first RCT to demonstrate reduction of hip fracture risk with

estrogen use.³ Risk reductions were also reported for vertebral and other osteoporotic fractures. No risk reduction for hip or other types of fractures was evident in HERS.^{5,72} A recently published meta-analysis of 22 trials of estrogen reported an overall 27% reduction in nonvertebral fractures (RR, 0.73; 95% CI, 0.56-0.94) (TABLE 2).⁷³ Although the meta-analysis itself met USPSTF criteria for a good-quality rating, 21 trials included in the meta-analysis did not meet inclusion criteria for our review because they used unpublished data, did not verify fractures radiographically, or included traumatic fractures, women with preexisting osteoporosis, or those who were hospitalized or had secondary causes of osteoporosis.

Two trials identified in our review met inclusion criteria. A primary prevention trial of early postmenopausal women without osteoporosis showed that the adjusted risk for fracture after 4.3 years of follow-up was significantly lower for the group taking HRT (RR, 0.29; 95% CI, 0.10-0.90) but not for the group taking HRT with vitamin D compared with placebo.⁸¹ Another trial identified no differences between HRT and placebo groups for various types of fractures.⁸²

Six cohort studies of HRT and fractures met criteria for good quality.⁷⁴⁻⁷⁹ These studies included large numbers

of women, often recruited from community-based populations, and followed them up for longer periods than did the RCTs.

Three of 4 studies reported 20% to 35% statistically significant reductions in adjusted RRs for hip fractures among ever users.^{75,77,78} The one study indicating no benefit differed from the others by its retrospective design and much smaller size.⁷⁶ Significant reductions in wrist fractures,^{74,76} vertebral fractures,⁷⁶ and nonvertebral fractures⁷⁴ were also reported in some studies (Table 2).

An unpublished Cochrane review and meta-analysis of RCTs of HRT and bone density outcomes indicated significant improvements in bone density from baseline at multiple anatomic sites (Table 2).⁸⁰ These findings were similar among prevention and treatment trials, opposed and unopposed estrogen regimens, oral and transdermal forms of estrogen, and types of progestins.

Breast Cancer

Fourteen of 18 observational studies and 7 of 8 meta-analyses reported no

increase in risk of breast cancer with ever use of estrogen (RRs, 0.85-1.14 from 8 meta-analyses) (TABLE 3).^{70,83-89}

However, current use of estrogen is associated with an increased breast cancer risk according to 3 meta-analyses (RRs, 1.21-1.40).⁸³⁻⁸⁵ Risk increases with longer duration of use in all the meta-analyses that evaluated this relationship (RRs, 1.23-1.35).^{70,83-85,89} The WHI results indicate increased breast cancer risk (HR, 1.26; 95% CI, 1.00-1.59) for women using estrogen combined with progesterone after 5.2 years.³ Trend data indicate increasing risk with increasing duration of use. Breast cancer risk was not elevated in HERS.³

No meta-analyses have evaluated breast cancer mortality. Five recent cohort studies showed no effect or decreased mortality with ever or short-term HRT use (RRs, 0.5-1.0).⁹¹⁻⁹⁵ Risk by duration of use was assessed in 5 studies that evaluated mortality in different ways, including by tumor node status and family history.^{90-92,94,95} Two good-quality studies that reported results for use longer than 5 years have conflicting results.^{89,93}

Endometrial Cancer

For this review, we used a meta-analysis of 29 observational studies of unopposed estrogen and incidence of endometrial cancer.⁹⁶ The combined RR for endometrial cancer incidence was significantly elevated for unopposed estrogen users compared with nonusers (RR, 2.3; 95% CI, 2.1-2.5) (Table 3). Increased risk was associated with increasing duration of use, and risk remained elevated 5 or more years after discontinuation of unopposed estrogen therapy. Users of unopposed conjugated estrogen had a greater increase in risk than users of synthetic estrogens. Mortality from endometrial cancer was not significantly elevated (RR, 2.7; 95% CI, 0.9-8.0).

A meta-analysis of 7 studies evaluating the effects of combined regimens (estrogen with progestin) on endometrial cancer incidence reported an RR of 0.8 (95% CI, 0.6-1.2).⁹⁶ Three cohort studies indicated a decreased risk of endometrial cancer (RR, 0.4; 95% CI, 0.2-0.6), whereas 3 case-control studies showed an increase in risk (RR, 1.8; 95% CI, 1.1-3.1). Neither the WHI nor

Table 3. Hormone Replacement Therapy (HRT) and Cancer Studies

Outcome by HRT Use	Relative Risk (95% Confidence Interval)*	Type of Study	Quality†	Comments
Breast cancer incidence				
Current ⁸³⁻⁸⁵	1.21-1.40	Meta-analysis	Fair-good	3 Meta-analyses of observational data with studies of poor to good quality
Ever ^{70,83-89}	0.85-1.14	Meta-analysis	Fair-good	7 Meta-analyses of observational data with studies of poor to good quality and 1 meta-analysis of 9 clinical trials
Ever, ≥5 years ^{70,83-85,89}	1.23-1.35	Meta-analysis	Fair-good	6 Meta-analyses of observational data with studies of poor to good quality
Mortality				
Current ⁹⁰	1.14	Cohort	Good	Evaluated only in the Nurses' Health Study and not statistically significant
Ever, <5 years ⁹¹⁻⁹⁵	0.5-1.0	Cohort	Good	
Ever, ≥5 years‡ ^{89,93}	0.55-1.45	Cohort	Good	
Endometrial cancer				
Incidence, ever ⁹⁶ §	2.3 (2.1-2.5)	Meta-analysis	Good	29 Observational studies of poor to good quality
Incidence, ever	0.8 (0.6-1.2)	Meta-analysis	Good	6 Observational studies and 1 trial; results of cohort studies show no risk; case-control studies show slight increased risk
Mortality, ever§	2.7 (0.9-8.0)	Meta-analysis	Good	4 Observational studies
Colon cancer				
Incidence, current ⁹⁷	0.66 (0.59-0.74)	Meta-analysis	Good	18 Observational studies of poor to good quality
Incidence, ever	0.80 (0.74-0.86)	Meta-analysis	Good	18 Observational studies of poor to good quality

*Based on published meta-analyses or individual studies as indicated. For breast cancer, numbers represent the range of results.

†Defined in Harris et al.¹³

‡Long-term use is described differently in these studies but generally relates to at least 5 to 12 years of use.

§Estrogen-only regimen.

||Estrogen and progestin combined regimen.¹¹

HERS reported an increase in endometrial cancer when a daily combined regimen was used.^{3,5}

Colon Cancer

A published meta-analysis of 18 observational studies of colorectal cancer and HRT indicated a 20% reduction in colon cancer among ever users compared with never users (RR, 0.80; 95% CI, 0.74-0.86) and a 34% reduction among current users (RR, 0.66; 95% CI, 0.59-0.74) (Table 3).⁹⁷ Duration of HRT use did not influence risk estimates. The WHI is the first RCT to report similar outcomes.³ Risk was not reduced among HRT users in HERS.⁵

Cognition and Dementia

Nine RCTs used formal testing to measure the effects of estrogen on cognition of women without preexisting dementia.⁹⁸⁻¹⁰⁶ Nonstandardized testing and other important differences between studies did not allow pooling of results. Our review indicated that women symptomatic from menopause had improvement in certain aspects of cognition such as verbal memory, vigilance, reasoning, and mo-

tor speed but not in other areas. Generally, no benefits were observed in asymptomatic women.

Twelve studies of HRT and Alzheimer disease met inclusion criteria, including 2 fair-quality cohort studies^{107,108} and 10 case-control studies, 1 rated good,¹⁰⁹ 1 fair,¹¹⁰ and 8 poor.¹¹¹⁻¹¹⁸ The most important limitations of these studies were using self-reported outcomes for controls and proxy for cases, using interviewers who were not blinded to the outcome, not controlling for education, and including only current estrogen users. Eight studies reported point estimates below 1.0; 4, above 1.0.

When results were combined by meta-analysis, HRT was associated with a decreased risk of dementia (RR, 0.66; 95% CI, 0.53-0.82) (TABLE 4). Results were similar when studies were pooled by study design, quality rating, use of proxy responders, or definition of dementia and in other ways. Possible biases and lack of control for other potential confounders limit interpretation of these studies. Adequate assessment of the effects of progestin use, estrogen preparations or doses, or duration of therapy were not possible. Neither the WHI nor

HERS has reported effects of HRT on cognition and dementia.

Cholecystitis

The most detailed report of the relationship between HRT and cholecystitis is from the Nurses' Health Study, a good-quality cohort study.²⁵ When compared with never users, current short-term users had an age-adjusted RR for cholecystitis of 1.8 (95% CI, 1.6-2.0) (Table 4). This risk increased after 5 years of use and remained elevated at this rate for women with 10 or more years of use. Among past users, the risk decreased to between 1.4 and 1.7 but remained significantly elevated for all past durations of use.

Other studies support these findings,^{60,119-122} although some do not.¹²³⁻¹²⁷ The HERS trial reported an increase in biliary tract surgery among HRT users compared with placebo during 6.8 years of follow-up (RR, 1.44; 95% CI, 1.10-1.90).⁵ This outcome has not yet been reported by the WHI. Another study evaluated data from 800 000 women in Canada to explore the relationship of a variety of medications and gallbladder and other

Table 4. Hormone Replacement Therapy Use in 10 000 Women: Benefits and Harms per Year

	Relative Risk (95% Confidence Interval [CI]) From Review and Meta-analysis	Hazard Ratio (95% CI) From WHI*	Events Prevented or Caused per Year, No.					
			Aged 55-64 Years		Aged 65-74 Years		Aged 75-84 Years	
			Review	WHI	Review	WHI	Review	WHI
Benefits (prevention)								
Hip fractures	0.76 (0.56-1.01)	0.66 (0.33-1.33)	3	4	9	13	33	47
Wrist fractures	0.44 (0.23-0.84)	NA	34	...	37.5	...	45	...
Vertebral fractures	0.60 (0.36-0.99)	0.66 (0.32-1.34)	32	27	57	49	91	78
Cases of colon cancer	0.80 (0.74-0.86)	0.63 (0.32-1.24)	2	3	4	7	7	12.5
Uncertain benefits								
Cases of dementia prevented	0.66 (0.53-0.82)	NA	17†	...	34	...	68†	...
Harms (caused)								
Coronary heart disease events	0.91 (0.67-1.33)	1.29 (1.02-1.63)	0	6	0	9	0	11.5
Strokes	1.12 (1.01-1.23)	1.41 (0.86-2.31)	1†	4†	3	9	6†	19†
Thromboembolic events	2.14 (1.64-2.81)	2.11 (1.26-3.55)	1.5	1.4	1.5	1.4	1.5	1.4
Thromboembolic events during first year	3.49 (2.33-5.59)	NA	3	...	3	...	3	...
Breast cancer cases (<5 years' use)	1.0 to 1.14	NA	0 to 2.5	...	0 to 6	...	0 to 7	...
Breast cancer cases (≥5 years' use)	1.23 to 1.35	1.26 (1.00-1.59)	7 to 11	8	10 to 15	11	11 to 17	12
Cholecystitis cases (<5 years' use)	1.8 (1.6-2.0)	NA	25	...	25	...	25	...
Cholecystitis cases (≥5 years' use)	2.5 (2.0-2.9)	NA	53.5	...	53.5	...	53.5	...

*WHI indicates Women's Health Initiative; NA, not applicable; and ellipses, data not computed. Nominal CIs are indicated for main outcomes of the trial (breast cancer and coronary heart disease); adjusted CIs, for secondary outcomes.
†Estimates are based on extrapolations.

diseases.¹²⁸ In this study, estrogen users were significantly more likely to have cholecystectomy and primary appendectomy than users of other medications.

Benefits and Harms

To calculate the number of events prevented or caused by HRT per year in 10000 postmenopausal women, we selected RRs for clinical outcomes according to our review of evidence and results of our meta-analyses and incidence and mortality rates from population-based sources. We calculated outcomes twice, once using results of the literature review and meta-analysis and once using recent results of the WHI. We predominantly used incidence rates because our review of evidence indicated that either HRT did not significantly affect mortality for specific outcomes (breast cancer) or mortality outcomes were not studied (fractures, colon cancer, and thromboembolism).

For most clinical outcomes, we used RR estimates from ever users as opposed to current or past users. This user group was the most consistently reported across studies and would be expected to have less healthy-user bias than the current users group. Cholecystitis and thromboembolism are associated with current use, however, and rates for ever use were not provided, so the risk for current users was used.

For some outcomes, such as cholecystitis and breast cancer, risk increases with duration of use. To reflect these changing risks, we calculated events for short-term (<5 years) and long-term (≥5 years) users. Data support an increased risk of thromboembolic events in the first year of use, but because many HRT users have a longer course, we calculated first-year and overall event rates.

We did not calculate endometrial cancer outcomes, because the association between unopposed estrogen and endometrial cancer is well known, and the standard of care is to provide combined therapy for women who have not had a hysterectomy. Combined therapy is not associated with increased risks of endometrial cancer.

Eight published meta-analyses of breast cancer incidence provided different risk estimates. To reflect this range of risk, we calculated a potential range of cases caused.

Table 4 summarizes these results by 10-year age groups for women aged 55 to 84 years. For example, according to results based on the review and meta-analysis, among 10000 women aged 65 to 74 years and using HRT for 1 year, 9 hip fractures, 37.5 wrist fractures, and 57 vertebral fractures would be prevented. Other benefits include preventing 4 cases of colorectal cancer and 34 cases of dementia. Harms include causing 3 strokes, 1.5 thromboembolic events, 0 to 6 cases of breast cancer with short-term use and 10 to 15 cases with long-term use, 25 cases of cholecystitis with short-term use, and 53.5 cases of cholecystitis with long-term use. Data from our meta-analysis indicated no CHD benefit or harm, although results of the WHI indicated a potential for 9 cases of CHD among women aged 65 to 74 years. Event rates for benefits and harms are generally lower in younger women and higher in older women (Table 4). Except for CHD, rates are similar when WHI HRs rather than RR from our review are used.

COMMENT

Prevention of osteoporotic fractures is supported by results of the WHI and several consistent, good-quality observational studies of fractures and RCTs of bone density, an important intermediate outcome and risk factor for fracture. Prevention of colon cancer is also supported by the WHI and observational studies. Effects on dementia are supported only by observational studies with important methodological limitations. Prevention of CHD, previously believed to be an important indication for long-term HRT, is not supported by our analysis of observational studies and is contradicted by results from the WHI.

Several additional harms of HRT use are supported by an increasingly strong body of evidence, including stroke, thromboembolic events, breast can-

cer, and cholecystitis. Risk for thromboembolic events is highest in the first year of use; risks for breast cancer and cholecystitis increase with time. Current data indicate that mortality from these events, as well as overall mortality, is not increased in HRT users.

Previous understandings of the relationship of HRT and prevention of chronic conditions have been challenged by the first report from the WHI. Serious harms, including breast cancer and cardiovascular disease, appear to outweigh measurable benefits such as prevention of fractures, leading many to reconsider HRT as a preventive approach. Although these data provide a new standard of evidence, questions remain. Several findings of the WHI are based on the unadjusted HRs. When HRs are adjusted for multiple comparisons, the CIs shift and cross 1.0 for most of the secondary outcomes, including stroke, colon cancer, hip and vertebral fractures, and a global index of harm. This evidence does not appear as definitive when adjusted results are used. Confidence in the results is strengthened, however, by their consistency with the overall body of evidence.

Results of the WHI were based on the use of a daily combined regimen of conjugated equine estrogen and medroxyprogesterone acetate in women with an intact uterus. A smaller arm of the study consisting of women with hysterectomies and using estrogen alone is continuing and apparently has not experienced statistically significant adverse outcomes. The roles of progestins and types and doses of estrogen on outcomes are alluded to in other studies in the literature but are unresolved. Additional studies may find that women taking unopposed estrogen have reduced risks for some outcomes but increased risks for others, such as ovarian cancer.^{129,130} Also, the data in the WHI are not stratified by age or other important risk factors. Although this makes no difference when well-matched HRT and placebo groups are compared, it could affect practice if women who experience thromboembolic events, for example, are different from those who do

not. Future reports from the WHI may resolve these issues.

We encountered difficulties in assessing other HRT studies because most are observational and subject to several sources of bias.

Women who take HRT differ from those who do not in many ways that are known or believed to alter risk. Hormone replacement therapy users tend to be more affluent, leaner, and more educated, and they exercise more often and drink alcohol more frequently.^{43,90,131} These factors are associated with increased risk for breast cancer and decreased risk for cardiovascular disease.^{43,131-133} Also, by definition, women who take HRT have access to health care and have a greater likelihood of being treated for other comorbid conditions that may also decrease their risks for certain clinical outcomes. Long-term users are compliant, itself a factor associated with better health.^{134,135} Women often quit HRT when they become ill, a tendency that would bias studies that evaluate recent or current use by underestimating use in ill patients. Hormone replacement therapy is more often used by women who have undergone hysterectomy and oophorectomy, a condition associated with decreased risks for breast cancer and increased risks for osteoporosis.

There have been significant secular changes in the use of estrogen, including type, administration, and dose, as well as the relatively recent practice of adding progestins to estrogen therapy. For many of the years represented in these studies, hypertension, diabetes, and heart disease were considered contraindications to the use of HRT. Practicing physicians may have been more likely to offer and prescribe HRT to women for whom the physicians' sense of overall health was higher. This type of selection bias is difficult to measure and may have led to systematic overestimates of the benefit of HRT. Also, most studies measured estrogen use only at one point or asked women if they had ever used estrogen. Thus, ever and current use could include both long- and short-term exposures.

Our review is also limited by assumptions made when we calculated results for Table 4. In many cases, a variety of RRs was available for certain outcomes, and we selected a value according to our judgment of the best evidence. This judgment may differ from that of other reviewers of the evidence. Sources for population incidence and mortality rates for health outcomes varied in their reliability and may not be directly comparable. The applicability of population estimates when risks are determined for individuals is unknown. Our estimates do not account for racial and ethnic differences or important risk factors. These estimates are most valuable when relative magnitudes of benefits and harms are compared in conjunction with patient preferences, individual risk factors, and other concerns.

Although many gaps exist in the understanding of the effects of postmenopausal HRT on health and illness, current evidence supports prevention of osteoporotic fractures and colorectal cancer, as well as increased harms for cardiovascular disease, breast cancer, and cholecystitis.

With the addition of new data to the body of evidence, use of HRT for primary prevention of chronic conditions requires reevaluation by postmenopausal women and their physicians.

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