Does Counseling by Clinicians Improve Physical Activity? A Summary of the Evidence

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Epidemiology

Sedentary behavior (little to no recreational, household, or occupational physical activity) is one of the strongest risk factors for many chronic diseases and conditions, including cardiovascular disease, hypertension, diabetes, obesity, osteoporosis, colon cancer, and depression.[1,2] Only 25% of Americans achieve the level of physical activity recommended in *Healthy People 2010* guidelines, that is, 30 minutes of moderate activity on 5 or more days per week or 20 minutes of vigorous activity 3 or more times per week.[3] Twenty-nine percent report getting no regular physical activity. A recent review of observational studies reported that risk for all-cause mortality was 20% to 30% lower among adults who met the *Healthy People 2010* recommendation and somewhat lower for adults who exercised moderately or vigorously at least a few times per month or once per week.[4]

Despite inconclusive evidence that counseling by primary care clinicians improves patient activity levels, in 1996 the U.S. Preventive Services Task Force (USPSTF) recommended counseling to promote regular physical activity for all children and adults based on evidence of the benefits of increased physical activity. Surveys of patients suggest that a minority of clinicians follow this recommendation. In the 1997 Behavioral Risk Factor Surveillance System, 42% of adult respondents reported receiving clinician advice to increase physical activity levels.[5,6] Approximately three-fourths of the patients who reported receiving clinician advice also reported increasing physical activity levels, compared with only half of the patients who reported receiving no clinician advice.

Two recent systematic reviews came to different conclusions about the efficacy of counseling.[7,8] One review focused on 8 studies published between 1988 and 1998 in which primary care clinicians directly advised patients to increase physical activity.[8] The authors rated only 2 of these studies as good quality; in 4 studies, counseling led to small, short-term increases in self-reported activity levels. The other

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The USPSTF recommendations based on this evidence review can be found in Behavioral Counseling in Primary Care to Promote Physical Activity: Recommendations and Rationale (which precedes this chapter), available on the AHRQ Web site and through the AHRQ Publications Clearinghouse.

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review summarized 15 studies published between 1979 and 1999 of interventions initiated or conducted in the primary care setting, regardless of whether the primary care clinician played any role.[7] This review concluded that counseling was "moderately effective," but did not use study quality as a criterion for inclusion. Neither review sought evidence about the potential harms associated with increasing physical activity.

Since these reviews were published, results of several additional trials of counseling have been made available. In consultation with members of the USPSTF, we performed a new systematic review that focused on controlled trials published since the 1996 USPSTF guidelines and addressed these questions: (1) Do adults counseled by primary care clinicians improve or maintain physical activity behavior? (2) If so, what types of interventions are most effective? From the trials on physical activity counseling, we also assessed the harms associated with increased physical activity.

Methods

Search Strategy and Study Selection

The scope of the 2 previous systematic reviews[7,8] differed sharply: 1 included only studies of counseling by the clinician alone,[8] while the other included studies of interventions performed in the primary care setting even when clinicians did not interact with patients in any way.[7] In consultation with members of the USPSTF, we took the middle ground of including all controlled clinical trials in which some components of the intervention were performed by the patient's primary care clinician (nurse practitioner, nurse, physician, or physician assistant). To describe the clinician's role as well as other components of interventions consistently, we used an abstraction tool developed by the Behavioral Counseling Work Group of the current USPSTF.[9] The tool is based on a practical "5-A" framework (Assess, Advise, Agree, Assist, and Arrange/Adjust) originally developed to describe the elements of brief provider tobacco-cessation interventions.[10] We limited the review to trials that had been published since the last USPSTF review (1994 and later) and that reported behavioral outcomes of an intervention to increase physical activity.

We searched the Cochrane Database of Systematic Reviews and Registry of Controlled Trials through March 2002 using the term "physical activity" and found abstracts for 49 reviews and 966 controlled trials. We searched the MEDLINE and HealthStar databases from 1994 to March 2002, using the Medical Subject Headings "exercise," "physical fitness," "counseling," "patient education," and "health education," and found 549 abstracts. Experts and reference lists of pertinent articles provided an additional 145 references.

We excluded 2 randomized, controlled trials[11,12] that reported physical activity outcomes but did not mention counseling to increase physical activity. We excluded 1 ongoing trial that has not yet reported results for the physical activity intervention in the treatment groups.[13] We excluded 4 randomized, controlled trials[14-17] in which all components of the intervention were provided by a research staff member or exercise specialist. For example, in one study[15] a research associate recruited patients from waiting rooms or from lists provided by the general practitioners. The patients were mailed an invitation to participate in an intervention conducted by health educators at a fitness center. As a team, we reviewed this study and excluded it because no components of the intervention were performed by a primary care clinician.

Data Abstraction and Synthesis

A single reviewer abstracted information about setting, patient participants, providers, interventions, adherence, and outcomes. The outcome of primary interest was the proportion of patients who met the *Healthy People 2010* goal in the "long-term," which we defined as at least 6 months after randomization. When this outcome was not available, we recorded mean changes in activity levels. We also recorded short-term results if reported. At least 2 reviewers

summarized the quality of each study using criteria developed by the current USPSTF.[18] In applying the USPSTF criteria to trials that used randomization by practice rather than by individual patient, we placed particular importance on the methods used to create comparable groups, such as matching and stratification, and on whether the groups were similar at baseline. We also placed emphasis on whether the interventions were clearly described and whether most patients were retained throughout the study. The internal validity of each trial was rated "good," "fair," or "poor." A rating of good means that the trial met all criteria and was very likely to be valid. A fair rating means that the study was possibly or probably valid, depending on the nature or severity of its flaws. Poor studies have fatal flaws rendering the results invalid; such studies were excluded from further consideration.

We summarized the design, quality, and results of each included trial in an evidence table, focusing on the magnitude of change in and duration of physical activity. We examined the consistency of results among studies and the relationship between effects and specific components of the interventions, discussing separately studies that compared an intervention with usual care and those that compared 2 interventions.

Role of the Funding Source

This review was funded by the U.S Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Task Force members participated in the initial design of the review and reviewed interim summaries as well as the final manuscript. The funding source had no role in the study design, data collection, or synthesis; however, representatives of AHRQ reviewed interim summaries and copies of the manuscript. Since our report was prepared for the current USPSTF, it was distributed for review to 13 outside experts and representatives of professional societies and federal agencies.

Results

Seven randomized controlled trials[19-25] and 1 non-randomized controlled trial[26] met the inclusion criteria (Table 1). A pilot study for 1 of the trials[20] was excluded.[27] Five other trials[28-32] were excluded because they received a quality rating of poor according to criteria developed by the current USPSTF (Table 2).[18]

Most of the trials were conducted in typical primary care practices, and all included multiple sites. Clinicians delivered advice themselves, but usually did not perform the initial assessment. In some trials the patients completed a self-report tool on physical activity levels[20,22,26] or answered selected questions from larger validated health-assessment tools administered by telephone, in the office waiting area, or in the home.[19,21,23] Often, a nurse or research assistant conducted a baseline assessment and placed it on the medical chart for review during the clinician's visit.[20,22,26] The clinician used the assessment information to exclude patients for whom physical activity was contraindicated or to tailor the intervention to each patient's needs. In most trials, the clinician advised sedentary or minimally active patients to achieve regular, moderate-intensity physical activity; in some trials, clinicians recommended vigorous activity as an option.

Five studies[20,22,24-26] targeted physical activity alone, while 3[19,21,23] also had other behavioral targets (eg, diet change, smoking cessation). In 3 of the trials, the primary care clinicians condensed advice and counseling on behavior change into a single 3- to 5-minute encounter and, for some patients, a follow-up session with the clinician or another member of the health care team.[20,24,25] Five trials did not report the amount of time that the clinician spent with patients for the intervention.[19,21-23,26]

Two of the trials met all USPSTF criteria and were rated as good quality (Table 1).[20,25] The remaining trials were rated as fair quality because treatment and control groups differed significantly in physical activity levels at baseline,[22,26] the

Table 1. Summary of controlled trials for physical activity

Study, authors, year	Study design	Patients	Theory	Provider education and materials	Protocol
Counseling vs. usual care					
Physically Active for Life, Goldstein, 1999[20]	**RCT** of 24 community-based primary care practices matched by size (34 physicians). PA only.	Sedentary adults (not meeting HP) who were 50 years and older. Intervention: n=181; mean age, 65 years; baseline stages: 13% precontemplative, 31% contemplative, 56% preparation stage; 12% nonwhite. Control: n=174; mean age, 66 years; baseline stages: 17% precontemplative, 33% contemplative, 50% preparation stage; 20% nonwite.	Transtheoretical (5 stages), social cognitive theory, health education.	Training, pretested manual, and poster for patients.	5 min. stage-based advice on benefits; assisted with self-efficacy and barriers; community resources; written PA prescription; follow-up visit at 1 mo. for adjusted prescription.
Norris, 2000[22]	**RCT** of 32 primary care physicians in a staff-model HMO, stratified by clinic. PA only.	Adults over age 30 scheduled for well visits. Intervention: n=384 adults; mean age, 53; baseline stages: 2.6% precontemplative, 51.3% contemplative, 46.3% action; 11% nonwhite. Control: n=463; mean age, 57; baseline stages: 3.4% precontemplative, 46.8% contemplative, 49.8% action; 8% nonwhite.	Transtheoretical (3 stages).	1 hour training, follow-up calls with providers.	Stage-based advice on benefits; PA preferences; assisted with barriers, self-efficacy, and self-management. Gave stage-based hand-outs; agreed on written goal. Follow-up call at one month and mailed educational materials.
Smith , 2000[26]	**Non-randomized controlled trial** of patients in 27 general practices in Australia. Recruited controls first. PA only.	Active and inactive adults ages 25 to 65 years old. Prescription only intervention: n=380; mean age, 43 years; median total PA, 95 minutes; prescription and booklet intervention: n=376; mean age, 43 years; median total PA, 120 minutes; control: n=386, mean age, 42 years; total PA, 145 minutes.	Transtheoretical (5 stages).	20-30 mins of training.	Advice, provided PA prescription. Stage-based booklets sent to random sample.
Kerse, 1999[21]	RCT of 42 metropolitan general practices (42 physicians). PA, social activity.	Adults age 65 and older. Intervention: n= 135; mean age, 73 yrs; total activity, 281 minutes/ week. Control: n= 132; mean age, 74 years; total activity, 328 minutes/week.	Not reported	3 hour seminar with exercise physiologist, sociologist, and geriatrician; 15 minutes follow-up detailing; prompt card.	Counseling for PA and social activity. Other counseling techniques not reported.

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Table 1. Summary of controlled trials for physical activity *(cont.)*

Study, authors, year	Study design	Patients	Theory	Provider education and materials	Protocol
Counseling vs. usual care					
Change of Heart, Steptoe, 1999[23]	**RCT** of 20 general practices (20 nurse practitioners), minimization technique. PA, smoking, diet.	Adults 18-69 years with 1or more CHD risk. Intervention: n=316; mean age, 48; 80% BMI >25 kg/m2 plus sedentary. Control: n=567; mean age, 46; 79% BMI > 25 kg/m2 plus sedentary.	Transtheoretical (5 stages).	3 day training with refresher day at 6 months.	Stage-based advice on benefits and attitudes; assisted with incentives, self monitoring, relapse prevention, barriers. Telephoned patients between counseling sessions. Mailed educational materials.
Burton, 1995[19]	**RCT** of 4,195 Medicare patients in 119 practices. PA, immunization, smoking, drinking.	Sedentary Medicare beneficiaries. 61% age 65 to 74 years; 33% age 75 to 84 years; 6% age 85+ years. Intervention:n=2,105; Control: n=2,090.	Suggested but not directed.	Continuing medical education credits on preventive and counseling visits. Educational materials.	Feedback and advice from pre-visit risk screen, assisted with community resources. 20 minute follow-up counseling sessions as needed. Most counseling details not reported.
Comparison of different interventions (no usual care)					
Activity Counseling Trial, 2001[25,33,34]	RCT of 874 adult patients from 11 primary care settings (51 physicians, 2 physician assistants, 1 nurse practitioner). PA only.	Inactive adults (ages 35 to 75 years) in stable health. Intervention: Advised group: n=292; avg age, 51 years; Assisted group: n=293; avg age 52 years; Counseled group: n=289; avg age 52 years.	Social cognitive theory.	Clinicians received advice training; health educators received assist and behavioral counseling training.	3 minutes of initial advice (Advised Group); initial advice and 30-40 minutes of behavioral counseling plus telephone follow-up (Assissted Group); initial advice, behavioral counseling, and biweekly telephone counseling for first 6 weeks, monthly calls thereafter, weekly class offerings (Counseled Group).
Swinburn, 1998[24]	RCT of 491 patients of 37 providers in 2 New Zealand urban centers. PA only.	Sedentary adults. 50% had at least one coronary heart risk factor. Intervention: n=239; Control: 252.	Self-management (goal setting).	1 training session on assessing and prescribing physical activity.	Advice (avg. 5 minutes) and written PA prescription. Stage-based booklets sent to random sample. Control group received advice only.

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Table 1. Summary of controlled trials for physical activity *(cont.)*

Study, authors, year	Provider adherence	Short-term: less than 6 months	Long-term: 6 months or more	Quality comments
Counseling vs. usual care				
Physically Active for Life, Goldstein, 1999[20]	Intervention: 99% received PA prescription, 77% received follow-up prescription. Control: 1% received PA prescription.	At 6 weeks, 28% of intervention patients met HP goal vs 21% of controls (difference of 7%; CI, -3% to 15%).	At 8 months, 28% of intervention patients met HP goal vs 23% of controls (difference of 5%; CI, -6% to 14%).	Good quality Met all criteria. Follow-up: 95% at 6 weeks, 88% at 8 months.
Norris, 2000[22]	Intervention: 94% were counseled, 90% of these received PA prescription. Control: 65% were counseled, 81% of these received a PA prescription.			Fair quality Follow-up: 93% at 6 weeks, 97% at 6 months. Baseline differences in preveious PA counseling. During the trial, control clinicians increased PA counseling rate.
Smith , 2000[26]	Intervention: 62% received PA prescription. Inferred 468 of 471 sedentary patients for 99% adherence. Control: Not reported.	Among inactive patients at 6-10 weeks in the prescription plus booklet vs control: 31% met HP goal vs. 27% control (difference of 4%; CI, -5% to 12%); 46% increased 60 minute weekly vs. 35% control (difference of 11%; CI, 2% to 20%; *P*=0.02). In the prescription only vs control: 26% met HP goal vs. 27% (difference of -1%; CI, -10% to 7%); 41% increased 60 minutes weekly vs 35% control (difference of 6%; CI, -3% to 15%).	Among inactive patients at 7-8 months in the prescription plus booklet vs control: 24% met HP goal vs 17% (difference of 8%; CI, 0% to 15%; *P*=0.053); 36% increased 60 minute weekly vs 27% control (difference of 9%; CI, 0% to 17%; *P*=0.06). In the prescription only vs control: 22% met HP goal vs 17% (difference of 5%; CI, -3% to 12%); 32% increased 60 minutes weekly vs 27% control (difference of 4%; CI, -4% to 13%).	Fair quality Follow-up: 92% at 6-10 week, 83% at 7-8 months. Baseline differences in PA levels.
Kerse, 1999[21]	Intervention: 32% of patients reported discussing PA with physician. Control: 21% reported discussing PA with physician.		At 1 year, intervention patients increased walking 44 min/week more than control patients (CI, 4 to 84 min/week; *P*=0.03.	Fair quality Follow-up: intervention, 90% at 1 year; control, 85% at 1 year. Counseling interventions not clearly defined, low provider adherence.

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Table 1. Summary of controlled trials for physical activity *(cont.)*

Study, authors, year	Provider adherence	Short-term: less than 6 months	Long-term: 6 months or more	Quality comments
Counseling vs. usual care				
Change of Heart, Steptoe, 1999[23]	Not reported.	At 4 months, intervention patients had 13 (20-minute) activity sessions/4 weeks vs 9 sessions/ 4 weeks in controls (difference of 3.7; CI, 1.3 to 6.3 sessions/4 weeks; $P<0.05$).	At 1 year, intervention patients performed 14 sessions/4 weeks vs 9 sessions/4 weeks in controls (difference of 3.9; CI, 1.0 to 6.8 sessions/4 weeks; $P<0.05$).	Fair quality Follow-up: intervention, 65% at 4 months, 54% at 1 year; control, 74% at 4 months, 62% at 1 year.
Burton, 1995[19]	Intervention: 89% of physician encounter forms contained PA discussion note. Inferred that up to 39% of patients attended follow-up counseling visit that included PA.		At 2 years, 42% of intervention patients in good health vs 42% control group patients in good health increased PA. 20% of intervention patients in poor health increased PA vs 18% of control patients in poor health (difference of 3%; CI, -4% to 9%).	Fair quality Follow-up: intervention, 75% at 2 years; control, 73% at 2 years. Counseling interventions not clearly defined.
Comparison of different interventions (no usual care)				
Activity Counseling Trial, 2001[25,33,34]	99% received initial 3 minutes of advice; documented for 97%. Avg contact time: Advised Group: 18 minutes over 24 month study; Assisted Group: 2.7 hours; Counseled Group: 8.9 hours for women, 5.6 hours.		At 6, 12, and 24 months, no difference in total energy expenditure for male or female patients with one exception.Women in the counseled group had an average total energy expenditure of 33.3 kcal*kg-1*day-1 at 6 months vs 32.7 kcal*kg-1*day-1 for women in the assisted group (difference of 0.54 kcal*kg-1*day-1; CI, 0.07 to 1.0; adjusted P=0.01).	Good quality Follow-up: 91% at 24 months, 78% completed fitness test (Vo2 max) at 24 months Met all criteria.
Swinburn, 1998[24]	Not reported.	More patients receiving advice and a written PA prescription performed any activity (51% to 86%, an increase of 35%) at 6 weeks vs patients who received only advice (56% to 77%, an increase of 21%) (difference of 14%; CI, 6% to 22%; P=0.004). No difference in the number of ncreased minutes spent in PA for ithe groups, 156 minutes per 2 weeks.		Fair quality. Follow-up: Intervention: 91% at 6 weeks; Control: 94% at 6 weeks. Intervention not well defined. Adherence not reported.

Note: HP indicates Healthy People 2010 recommendation (30 minutes of moderate physical activity on at least 5 days per week or 20 minutes of vigorous activity on at least 3 days per week); PA, physical activity.

counseling intervention was not clearly defined,[19,21,24] attrition was high.[19,23]

Efficacy of Counseling

Interventions Compared with a Usual Care Control

In 6 controlled trials that contained a usual care control group,[19,23,26] the effects of counseling on physical activity after 6 to 24 months were mixed (Table 1). Only 1 of the trials[20] met all of our criteria for a good quality rating. In this trial, clinicians provided sedentary patients with a brief (5-minute) message, a prescription for exercise, and a follow-up visit to adjust the prescription 1 month later. After 8 months, 28% of 181 intervention patients met the Healthy People 2010 goal compared with 23% of 174 patients who received usual care (difference of 5%; 95% CI, -6% to 14%).

Of the 5 fair-quality trials, 2 showed no effect of counseling on physical activity levels after 6 or more months[19,22] and 3 showed statistically significant increases in activity.[21,23,26] In the latter 3 trials, 2 randomized trials reported increases in the average number of exercise sessions[23] or in time spent walking[21] but did not report the proportion of patients who increased physical activity. The third trial, which was non-randomized, reported that an increased proportion of inactive patients added 60 minutes or more of physical activity per week.[26]

Among the studies we rated as fair quality, 2 had relatively serious threats to validity. One was a non-randomized trial in which a significantly greater proportion of the intervention patients (62%) were inactive at baseline compared with the usual care group (54%) ($P<0.05$).[26] In the other, a randomized trial in which counseling was ineffective, more control patients (55%) than intervention patients (42%) reported receiving physical activity counseling in the 6 months before the trial began ($P=0.02$).[22] Although the groups were otherwise similar, this inequality raises the possibility that randomization was not conducted properly.[22] Also, control physicians counseled 81% of their patients, greatly reducing the trial's ability to show a difference between groups.

Components of the interventions included advice,[20,22,26] assistance with perceived self-efficacy[20] and barriers,[20,22] mailed educational materials,[22,26] referral to community resources,[20] and written exercise prescriptions.[20,22,26] There were too few studies and too few details to discern any relationship between the components of the interventions and the reported efficacy. None of the fair-quality trials reported the time the clinician spent with the patient. The 4 studies that applied the "stages of change" (transtheoretical) model of behavior change had mixed results.[20,22,23,26]

Three of the trials addressed physical activity only,[20,22,26] while the other 3 addressed multiple behavior changes.[19,21,23] Within each of these categories, results of the trials were mixed. The trials addressing multiple behavior changes reported few details about the intervention components and either did not report adherence[19,23] or reported poor adherence to the physical activity component (39%).[21]

Interventions Compared with Other Interventions

We identified 2 trials that compared the efficacy of different interventions and had no usual care group (Table 1).[24,25,33,34] The results of these trials suggested that a written prescription was more effective than advice alone[24] and that women may need more intensive counseling interventions (that is, more contact and time with the clinician) than men to increase physical activity in the long term.[25]

In the larger, methodologically stronger study, the Activity Counseling Trial,[25] more intense counseling programs were better than brief advice for women, but not for men. In this trial, 874 sedentary adults in stable health were randomly assigned to 1 of 3 interventions: clinician advice and educational materials (advice group); clinician advice, educational materials, and 30 to 40 minutes of behavioral counseling and interactive mail (assistance group); or all of the above plus counseling telephone calls and class offerings (counseling group).[25] At 6, 12, and 24 months, men in all groups did not differ in expended energy or fitness levels.[25] After 6 months, women in the counseling group had

Table 2. Studies rated as poor quality*

Study	Reasons for poor rating *	Result
Bull and Jamrozik, 1998[31]	Maintenance of comparison groups in question. Nonrandomized trial design (same providers for control and intervention patients based on days of the week during 3 week recruitment) had high potential for contamination. Fair to poor rates of follow-up assessments (70% at 1 month, 57% at 6 months, 56% at 12 months).	Increased proportion of active intervention patients (40%) at 1 month compared with 31% of control patients (a difference of 9%). Increased proportion of active intervention patients (38%) at 6 months compared with 30% of control patients (a difference of 8%). No difference in the active proportion at 1 year, 36% intervention patients compared with 31% control patients (a difference of 5%).
Calfas et al, 1996[30]	Establishment and maintenance of comparison groups in question. Nonrandomized trial design with intervention physicians selected based on personal interest in physical activity. Suggests that control physicians had less interest in physical activity and may have had lower than expected usual care counseling rates at baseline. Trial lost 17% of intervention physicians and 30% of control physicians during study.	Increased proportion of intervention patients (52%) achieved PACE active stage (meets HP) at 4-6 weeks compared with 12% of control patients (a difference of 40%; CI, 28% to 52%).
Elder et al, 1995[28]	High loss to follow-up. 45% of intervention patients responded at 4 years compared with 44% of control patients. Patients who did not complete the follow-up assessment were excluded from the analysis.	Intervention patients reported increased metabolic rate (432) at 4 years compared with 388 for control patients (*P*=0.0006).
Graham-Clarke and Oldenburg, 1994[29]	Unclear whether randomization was adequate because a greater proportion of intervention patients were at "intended to change" stage (53% compared with 37% of control patients; a difference of 16%; CI, 13% to 19%). Achieved poor rates of follow-up assessments (44% at 4 months and 50% at 12 months). Paper didn't give sufficient results to abstract needed results relative to randomization.	Not reported based on randomization.
Kreuter et al, 2000[32]	Unclear whether randomization was adequate because no baseline demographic characteristics were provided. The analysis made no mention of an intention-to-treat analysis. Used a new PA tool with no validity.	Intervention patients who received physician advice to exercise before receiving education materials were more likely to change behavior than patients who received no advice (OR, 1.51; CI, 0.95 to 2.4).

*These studies were rated poor using the USPSTF quality criteria.[18] Poor quality studies have fatal flaws rendering the studies invalid.

Note: CI indicates 95% confidence interval; HP, Healthy People 2010 recommendation: Moderate activity 30 min./5 times/week (or) vigorous activity 20 min./3 times/week; OR, odds ratio; PA, physical activity; PACE, Physician-based Assessment and Counseling on Exercise.

increased self-reported physical activity compared with women in the assistance group. At 6 months, women in the counseling group achieved a total energy expenditure of 33.3 kcal*kg-1*day-1 compared with 32.7 kcal*kg-1*day-1 for women in the assistance group (difference of 0.54 kcal*kg-1*day 1; 95% CI, 0.07 to 1.0; adjusted *P*=0.01). For a woman weighing 50 to 55 kg, this difference corresponds to walking an extra 2 miles per week. At 12 and 24 months, women in the different intervention groups did not differ significantly in total energy expenditure. At the 24 month examination, women in the counseling and assistance groups were more fit than women in the advice group. For counseling compared with advice, difference in maximal oxygen uptake (Vo_2max) was 73.9 mL/min (99.2% CI, 0.9 to 147.0 mL/min; *P*=0.046). For assistance compared with advice, the difference in Vo_2max was 80.7 mL/min (99.2% CI, 8.1 to 153.2 mL/min; *P*=0.02).

Potential Harms of Counseling

Potential harms of physical activity counseling have not been well defined. Harms of physical activity probably include musculoskeletal injuries, fall-related injuries, and cardiovascular events. Whether counseling decreases or increases such events is not clear. Only the Activity Counseling Trial reported rates of physical harm in the 2 years following counseling.[25] Although patients were instructed to gradually increase physical activity, approximately 60% of all patients reported musculoskeletal events, and 3% of all patients required hospitalization during the study. Twenty-nine percent of patients reported potential cardiovascular events during the 2 years. Nineteen percent of all patients saw a physician about these events and 5% required hospitalization. Since there was no usual care group in this trial, it is difficult to know whether or how much the interventions contributed to the harms. Although patients with preexisting heart disease or a positive result on a submaximal treadmill test were excluded from the trial before randomization, the sample included patients taking medication for chronic conditions, including hypertension. Many patients were overweight (average body mass index, 29.5 kg/m2) and 9% smoked.[34]

To avoid injury, most trials excluded patients at risk or offered moderate rather than vigorous activity. Five of the 8 trials specifically stated that patients were excluded for medical reasons.[20,22,23,25,26] Six of the 8 trials offered a moderate activity option.[20-25] However, these trials did not provide sufficient detail about harms to judge the efficacy of these precautions.

Feasibility and Costs

Assessment and counseling take patient and staff time, which may explain why only 3 trials reported that more than 90% of patients received the intended intervention.[20,22,23] Some of the counseling efficacy studies used additional staffing for assessments.[20,21,23] One trial reported that a research staff member spent 5.8 minutes assessing each patient using the Physical Activity Scale for the Elderly (PASE) assessment tool.[20]

The Activity Counseling Trial reported that patients who received both advice and counseling (the assistance group) spent an average of an extra 2.7 hours with a clinician or health educator over 2 years compared with patients who were simply advised to increase physical activity (18 minutes of contact time over 2 years).[25] Women who received advice, counseling, follow-up counseling telephone calls, and classes (the counseling group) spent 9 more hours with a clinician or educator than women who received only advice. Similarly, men in the counseling group spent an extra 5 hours with a clinician or educator over 2 years.

Discussion

We performed this review to determine whether adults who receive counseling in primary care settings improve and maintain physical activity behavior. Several recent good- and fair-quality trials on efficacy of counseling for physical activity in primary care demonstrated modest or no increases in physical activity; these trials were extremely heterogeneous. Previous reviews[7,8] found that

interventions targeting physical activity were effective in the short-term. However, we found mixed, inconclusive evidence to support this finding. Two of 3 trials in our review that addressed multiple behaviors reported increased activity in the short and long term.

Most trials in our review provided limited details on the counseling intervention and had only fair follow-up rates; highly motivated providers; differences in physical activity levels at baseline between intervention and control groups; uncertain or low provider adherence; or inadequate power to detect differences because of high baseline activity levels, small numbers of participants (patients and physicians), or inclusion of some counseling advice in usual care control groups. In several trials, it was difficult to assess whether patients had actually received a physical activity behavioral intervention.

Many people move between being sedentary and being active at different times in their lives.[35] Since most physical activity interventions in primary care focus on changing sedentary behavior to active behavior, studies with very long follow-up periods are needed to evaluate which strategies best encourage maintenance of physical activity.[36] These long-term interventions may be more feasible for clinicians and more effective if the larger health systems provide support for initiation and maintenance, such as telephone-based interventions and mailed support. For example, a recent trial of health-system sponsored telephone support by trained health educators reported increased physical activity in patients committed to increasing physical activity.[37] Clinical interventions may also be more effective if patients are referred to community programs that provide ongoing social support, such as established walking groups.[38]

Only 1 trial in this review reported harms.[25] Understanding the potential harms and revising future interventions to reduce them may improve patient adherence. We need large prospective studies that report type of intervention, including the recommended intensity of physical activity, and also report injuries in the long term (eg, more than 2 years). Such trials should document the reasons why patients drop out of studies. It is possible that some nonresponders stop exercising because they experience harm.

Because of the methodological limitations described earlier, we found it difficult to assess the efficacy or effectiveness of the interventions examined. Although research suggests that counseling can be effective in some specific situations, the evidence is insufficient to generally conclude that counseling is effective. Existing studies do not provide a clear picture of the specific features of counseling that relate to its effectiveness.

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Postmenopausal Hormone Replacement Therapy for the Primary Prevention of Chronic Conditons

Recommendations and Rationale

U.S. Preventive Services Task Force

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations for use of hormone replacement therapy (HRT) for the primary prevention of chronic conditions in postmenopausal women, and it updates the 1996 recommendations contained in the *Guide to Clinical Preventive Services*, second edition.[1] Explanations of the ratings and of the strength of overall evidence are given in Appendix A and Appendix B, respectively. The complete information on which this statement is based, including evidence tables and references, is available in the summary of the evidence, "Postmenopausal Hormone Replacement Therapy for the Primary Prevention of Chronic Conditions."[2] The USPSTF recommendations and individual reports on hormone replacement therapy and specific disease outcomes are available on the USPSTF Web site (www.preventiveservices.ahrq.gov) and through the National Guideline Clearinghouse (www.guideline.gov).

The USPSTF reviewed the evidence on the use of postmenopausal HRT and the following outcomes: cardiovascular disease, including coronary heart disease and stroke; osteoporosis and fractures; thromboembolism; dementia and cognitive function; breast, colon, ovarian, and endometrial cancer; and cholecystitis. The USPSTF also reviewed evidence of the effects of HRT on phytoestrogens and osteoporosis and CVD. The use of HRT for relieving active symptoms of menopause, such as hot flashes, urogenital symptoms, and mood and sleep disturbances, among others, is outside the scope of these USPSTF recommendations, and literature on this topic was not reviewed. Sources for estimates of benefits and harms cited in this Recommendation statement are described in the summary of the evidence.[2]

This recommendation statement first appeared on the AHRQ Web site Ocotber 15, 2002 (www.preventiveservices.ahrq.gov).

Summary of Recommendations

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

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

The USPSTF concluded that the harmful effects of estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women. The USPSTF did not evaluate the use of HRT to treat symptoms of menopause, such as vasomotor symptoms

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(hot flashes) or urogenital symptoms. The balance of benefits and harms for an individual woman will be influenced by her personal preferences, individual risks for specific chronic diseases, and the presence of menopausal symptoms.

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

The USPSTF found fair to good evidence that the use of unopposed estrogen has both benefits and harms. Although most current data come from observational studies, likely benefits include increased bone mineral density, reduced fracture risk, and reduced risk for colorectal cancer. Likely harms include increased risk for venous thromboembolism, cholecystitis, and stroke; in women who have not had a hysterectomy, unopposed estrogen increases the risk for endometrial cancer. Evidence is insufficient to determine the effects of unopposed estrogen on the risk for breast and ovarian cancer, CHD, dementia and cognitive function, or mortality. As a result, the USPSTF could not determine whether the benefits of unopposed estrogen outweigh the harms for women who have had a hysterectomy. Better data on benefits and harms are expected from ongoing randomized trials, including the Women's Health Initiative (WHI) study of unopposed estrogen in women who have had a hysterectomy.[3]

Clinical Considerations

- **Although the USPSTF concludes that the harms of estrogen-progestin therapy are likely to outweigh the chronic disease prevention benefits for most women, the absolute increase in risk from HRT is modest.** Some women, depending on their risk characteristics and personal preferences, might decide that the benefits of taking HRT outweigh the potential harms. Based on results reported from the WHI study[3] for women aged 50 to 79 years (average age 63 years), 10,000 women taking estrogen and progestin for 1 year might experience 7 additional CHD events, 8 more strokes, 8 more pulmonary emboli, and 8 more invasive breast cancers, but would also have 6 fewer cases of colorectal cancer and 5 fewer hip fractures.
- **Clinicians should develop a shared decision-making approach to preventing chronic diseases in perimenopausal and postmenopausal women.** This approach should consider individual risk factors and preferences in selecting effective interventions for reducing the risks for fracture, heart disease, and cancer. Clinicians should discuss with patients other effective strategies for preventing osteoporosis and fractures (see other USPSTF recommendations available on the USPSTF Web site [www.preventive services.ahrq.gov]: *Screening for Postmenopausal Osteoporosis, Screening for Hypertension, Screening Adults for Lipid Disorders, Counseling To Prevent Tobacco Use, Counseling To Promote a Healthy Diet, Counseling to Promote Physical Activity, Screening for Breast Cancer, and Screening for Colorectal Cancer*).
- **The USPSTF did not consider the use of HRT for the management of menopausal symptoms.** Decisions to initiate or continue HRT for menopausal symptoms should be made on the basis of discussions between a woman and her clinician. Women should be informed that there are some risks (such as the risk for venous thromboembolism, CHD, and stroke) within the first 1 to 2 years of therapy, whereas other risks (such as the risk for breast cancer) appear to increase with longer-term HRT. Other expert groups have recommended that women who decide to take HRT for the relief of menopausal symptoms use the lowest effective dose for the shortest possible time.
- **The quality of evidence on the benefits and harms of HRT varies for different hormone regimens.** Other than the 2 large randomized controlled trials of daily conjugated equine estrogen (CEE) and medroxyprogestrone acetate (MPA), most of the evidence on HRT comes from observational studies that did not differentiate among the effects of specific hormone preparations.[3,4] Until data indicate that

other HRT regimens have a favorable balance of benefits to harms, a cautious approach would be to avoid using HRT routinely for the specific purpose of preventing chronic disease in women.

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

Scientific Evidence

Epidemiology and Clinical Consequences

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

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

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

Benefits of Hormone Replacement Therapy

Osteoporosis and Fractures

Low bone density is associated with an increased risk for osteoporotic fractures. Good evidence from observational studies and randomized clinical trials demonstrate that estrogen therapy increases bone density and reduces risk for fractures. Good evidence from many randomized clinical trials has demonstrated that HRT increases bone density at the hip, the lumbar spine, and peripheral sites. A meta-analysis of 22 trials of estrogen reported an overall 27% reduction in nonvertebral fractures (relative risk [RR], 0.73; 95% CI, 0.56 to 0.94), although the quality of individual studies varied.[6] Observational studies have also demonstrated reductions in fractures of the vertebrae (RR for ever use, 0.6; 95% CI, 0.36 to 0.99), wrist (RR for current use, 0.39; 95% CI, 0.24 to 0.64), and possibly hip (RR for current use, 0.64; 95% CI, 0.32 to 1.04) among women taking HRT. The Heart and Estrogen/Progestin Replacement Study (HERS and its unblinded follow-up study, HERS II),[7] a trial of combined estrogen and progestin (CEE/MPA) for the secondary prevention of heart disease that reported many other outcomes, found no reduction in hip, wrist, vertebral, or total fractures with hormone therapy (relative hazard [RH] for total fractures, 1.04; 95% CI, 0.87 to 1.25). The WHI[3] found significant reductions in total fracture risk (RH, 0.76; 95% CI, 0.63 to 0.92)

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

Colorectal Cancer

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

Uncertain Benefits or Harms of Hormone Replacement Therapy

Cognition and Dementia

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

Harms of Hormone Replacement Therapy

Breast Cancer

Because breast tissue is sensitive to reproductive hormones, there has been long-standing concern about breast cancer risk among women who take HRT. The estrogen and progestin arm of the WHI study was recently terminated because of an increased breast cancer incidence (RH, 1.26; 95% CI, 1.00 to 1.59).[3] However, no effect on breast cancer mortality was observed. Comparable increases in breast cancer incidence were observed among women taking estrogen and progestin over 6.8 years of follow-up in the HERS studies (RH, 1.27; 95% CI, 0.84 to 1.94).[7] Although many good observational studies on breast cancer and meta-analyses of these studies have been conducted, the conclusions are limited by healthy-user bias; variations in specific preparations, dose, and duration of estrogen and progestin therapy; and differences in the ways in which breast cancer end points were ascertained. In the aggregate, breast cancer incidence is slightly increased for current (RR, 1.21 to 1.40) or long-term (>5 years) users (RR, 1.23 to 1.35) compared with nonusers.[2,10,11] However, there seems to be no effect on or decreased breast cancer mortality in ever- or short-term users (RR, 0.5 to 1.0).[11] The effects of long-term HRT use on breast cancer mortality in 2 good-quality cohort studies are conflicting.[12,13] Whether the

combination of estrogen and progestin confers a greater risk than estrogen alone is unknown; WHI investigators have reported that no increase in breast cancer has been observed after 5 years of follow-up in the ongoing study of unopposed estrogen in women who have had a hysterectomy. The USPSTF concluded that there was fair to good evidence that HRT increases the incidence of breast cancer (with best evidence for estrogen plus progestin), but its effects on breast cancer mortality are uncertain.

Coronary Heart Disease

Coronary heart disease remains the leading cause of death among women. Hormone replacement therapy has diverse effects on lipid levels, endothelial wall function, blood pressure, coagulation factors, weight, and inflammation (for example, C-reactive protein). In the WHI study, women who took CEE/MPA daily had an increased risk for CHD (fatal and non-fatal myocardial infarctions), which was evident shortly after initiation of the study (RH, 1.29; 95% CI, 1.02 to 1.63). Coronary heart disease mortality was not significantly increased (RH, 1.18; 95% CI, 0.70 to 1.97). Meta-analysis of observational studies showed a statistically significant reduction in CHD (RR, 0.80; 95% CI, 0.68 to 0.95) among current HRT users, but not among ever or past users, compared with women who had never taken HRT (nonusers).[2,14] However, among studies that controlled for socioeconomic status (social class, education, or income), no benefit was seen among current HRT users (RH, 0.97; 95% CI, 0.82 to 1.16), suggesting that the observed difference may be due to confounding by socioeconomic status and other lifestyle factors (eg, exercise, alcohol use) rather than use of HRT. Coronary heart disease mortality in observational studies is reduced among current HRT users (RR, 0.62; 95% CI, 0.40 to 0.90) but is not reduced among ever, past, or all users. Thus, selection bias (the tendency of healthier women to use HRT) appears to explain the apparent protective effect of estrogen on CHD seen in observational studies. The USPSTF concluded that HRT does not decrease, and may in fact increase, the incidence of CHD. The effects of HRT on CHD mortality, however, are less certain.

Stroke

A meta-analysis of 9 observational primary prevention studies suggests that HRT use is associated with a small increase in stroke incidence (RR, 1.12; 95% CI, 1.01 to 1.23), due primarily to an increase in thromboembolic stroke (RR, 1.20; 95% CI, 1.01 to 1.40).[14,15] The risk for subarachnoid bleeding and hemorrhagic stroke was not increased, and the overall stroke mortality was marginally reduced (RR, 0.81; 95% CI, 0.71 to 0.92). These results are consistent with findings from the estrogen and progestin arm of the WHI, which reported increased incidence of stroke in women taking CEE/MPA daily (RH, 1.41; 95% CI, 0.86 to 2.31). Two secondary prevention trials,[16,17] which were not included in the USPSTF review of HRT for primary prevention, reported no clear effect of HRT on stroke incidence, but stroke mortality was increased in women with a previous stroke.[17] The USPSTF concluded that there is fair evidence that HRT increases the risk for stroke.

Venous Thromboembolism (Deep Venous Thrombosis and Pulmonary Embolism)

In a meta-analysis of 12 studies (3 randomized, controlled trials; 8 case-control studies; and 1 cohort study), HRT was associated with an increased risk for venous thromboembolism (RR, 2.14; 95% CI, 1.64 to 2.81).[18,19] Five of 6 studies that examined the effects of HRT over time reported that the risk was highest within the first year of use (RR, 3.49; 95% CI, 2.33 to 5.59). These results are consistent with the findings in the estrogen and progestin arm of the WHI, which reported a 2-fold increased rate of venous thromboembolic disease (RH, 2.11; 95% CI, 1.26 to 3.55), including deep venous thrombosis and pulmonary embolism, in women taking CEE/MPA daily. The USPSTF concluded that there is good evidence that HRT increases the risk for venous thromboembolism.

Endometrial and Ovarian Cancer

Results of a previously published meta-analysis of 29 good-quality observational studies of endometrial cancer reported a relative risk of 2.3 (95% CI, 2.1 to 2.5) for users of unopposed estrogen compared with

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

Data on the association between the use of HRT and the risk for ovarian cancer are inconsistent. Results of case-control studies have been mixed, but 2 good-quality cohort studies reported increased risks (RR, 1.8 to 2.2) for ovarian cancer or ovarian cancer mortality among women who had taken HRT for 10 years or more[21,22]; a third study found no effect of HRT on ovarian cancer mortality.[23] One study suggested higher risk with unopposed estrogen than with estrogen-progestin therapy,[21] but data are insufficient to resolve the effects of different formulations or doses of HRT on ovarian cancer risk. Neither the WHI nor HERS has reported risk for ovarian cancer. The USPSTF concluded that evidence was insufficient to determine the effect of HRT on ovarian cancer.

Cholecystitis

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

Discussion

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

Recommendations of Others

Most organizations with guidelines on postmenopausal HRT have revised or are revising their recommendations in light of the findings of recently reported clinical trials. The American College of Obstetricians and Gynecologists[26] and the North American Menopause Society[27] recommend against the use of HRT for the primary or secondary prevention of cardiovascular disease. Both organizations recommend caution in using HRT solely to prevent osteoporosis and suggest that alternative therapies should also be considered. Both organizations consider HRT an acceptable treatment option for menopausal symptoms but advise caution about the prolonged use of HRT for the relief of symptoms. The American Heart Association now recommends against the use of HRT for primary or secondary prevention of cardiovascular disease.[28] The American College of Preventive Medicine,[29] the American Association of Clinical Endocrinologists,[30]

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

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Appendix A
U.S. Preventive Services Task Force - Recommendations and Ratings

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

Appendix B
U.S. Preventive Services Task Force - Strength of Overall Evidence

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

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Postmenopausal Hormone Replacement Therapy for the Primary Prevention of Chronic Conditions: A Summary of the Evidence for the U.S. Preventive Services Task Force

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Epidemiology

Hormone replacement therapy (HRT), either estrogen alone or estrogen combined with progestin, is used in the United States and worldwide to treat symptoms of menopause and to prevent chronic conditions such as osteoporosis. It is one of the most commonly prescribed drugs in the United States. A survey conducted in 1995 of postmenopausal women aged 50 to 75 showed that nearly 38% of women were using HRT at the time of the survey.[1] Recently published studies, however, suggest that HRT use is associated with potential harms that were not previously appreciated, causing

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The USPSTF recommendations based on this evidence review can be found in Postmenopausal Hormone Replacement Therapy—Primary Prevention of Chronic Conditions: Recommendations and Rationale, which is available on the AHRQ Web site.

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many to reconsider the appropriateness of its use for prevention.

To determine the current status of benefits and harms of HRT use, we conducted systematic searches of the literature on HRT use among postmenopausal women, its effectiveness for the primary prevention of chronic conditions, and its association with harmful outcomes. Several reports and publications provide additional details of these reviews on the effects of HRT on cardiovascular disease,[2,3] thromboembolism,[4,5] breast cancer,[6] osteoporosis,[7] cognition and dementia,[8,9] as well as overall benefits and harms.[10] This report serves as a summary of the evidence with the objective of aiding the U.S. Preventive Services Task Force (USPSTF) in updating its recommendations on HRT scheduled for release in October 2002.

Use of HRT for the treatment of symptoms of menopause and for the treatment of preexisting conditions are outside the scope of the USPSTF recommendation, and this literature was not reviewed. All papers included in this review met inclusion criteria and were rated for quality (See "Inclusion/Exclusion Criteria" below). We focused on health outcomes such as myocardial infarction 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 papers, to calculate numbers of events prevented or caused by HRT for specific outcomes in a hypothetical population of postmenopausal women.

Prior Recommendations

In 1996, the USPSTF recommended counseling all perimenopausal and postmenopausal women about the potential benefits and harms of HRT.[11] They 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 (for example, the prevention of myocardial infarction or fracture) and harms (for example, endometrial cancer with unopposed estrogen or breast cancer), and personal preferences.

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 harms of HRT used by postmenopausal women to prevent chronic conditions. Numbered arrows in the figures correspond to key questions specifically covered in this report (Figure 3). We were concerned with HRT as chemoprevention for primary prevention and therefore focused on the use of either estrogen alone (unopposed) or estrogen combined with progestins (combined) in healthy, postmenopausal women.

Methods

Literature Search Strategy

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.[2-10]

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 consulting experts and by reviewing reference lists of pertinent studies, reviews, and editorials. We used only published data in meta-analyses.

Inclusion/Exclusion Criteria

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

Figure 1. Potential benefits of Hormone Replacement Therapy Analytic Framework 1

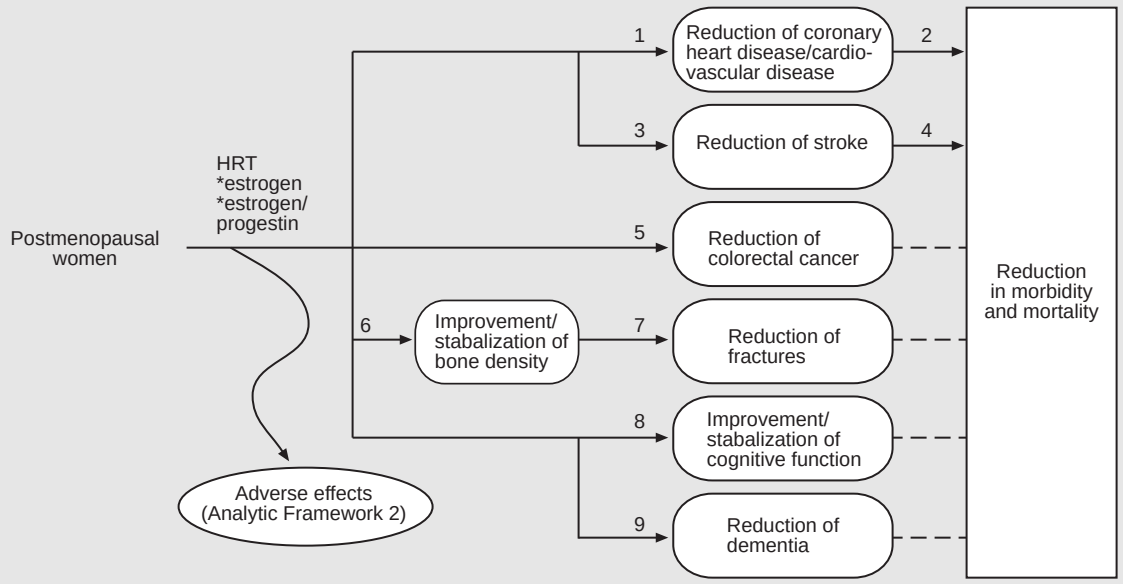
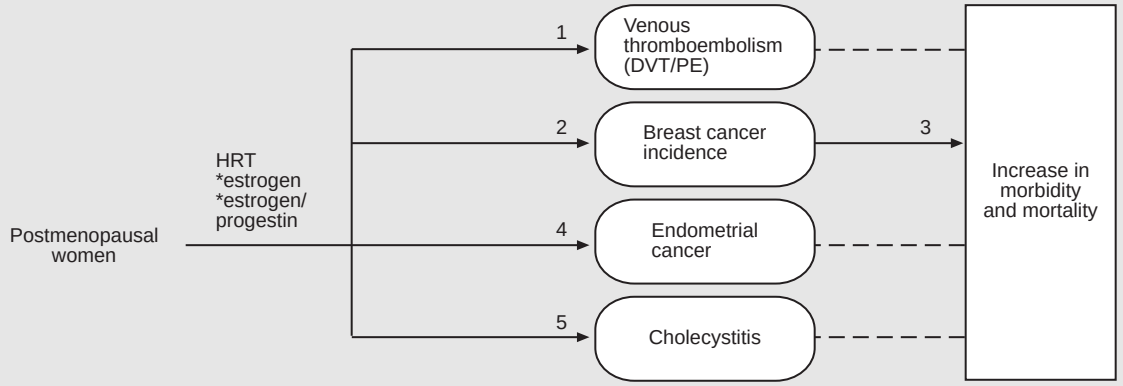


Figure 2. Potential harms of Hormone Replacement Therapy Analytic Framework 2



Note: DVT indicates deep-vein thrombosis; PE, pulmonary embolus.

Figure 3. Key Questions

Potential benefits

Does HRT reduce risks for:

1. Coronary heart disease and cardiovascular disease incidence?
2. Coronary heart disease and cardiovascular disease mortality?
3. Stroke incidence?
4. Stroke mortality?
5. Colorectal cancer?
6. Low bone density?
7. Fractures?
8. Decline in cognitive function?
9. Dementia?

Potential harms

Does HRT increase risks for:

1. Venous thromboembolism (deep vein thrombosis and pulmonary embolism)?
2. Breast cancer incidence?
3. Breast cancer mortality?
4. Endometrial cancer?
5. Cholecystitis?

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.[12] When reviewers disagreed, a final rating was reached through consensus.

In addition to the systematic literature review, we included 2 recently published randomized controlled trials (RCTs) with pertinent findings. The Women's Health Initiative (WHI), a primary prevention trial, reported results of 16,608 healthy postmenopausal women after 5.2 years of daily combined HRT or placebo.[13] We also cite the noncardiac outcomes of the Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II),[14] a trial of daily combined HRT in 2,321 postmenopausal women with preexisting coronary heart disease after 6.8 years.[15,16]

Data Extraction and Synthesis

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 relative risk (logRR) had a normal distribution. Standard errors (SEs) for logRR were calculated from reported confidence intervals (CIs) or *P* values. The logRR and standard errors 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.[17] 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,[18] 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 plots[19] and investigated the sensitivity of the analysis to studies possibly missed because of publication bias by trim and fill.[20,21] 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 relative risks for clinical outcomes derived from the reviewed studies and meta-analyses. We also used population-based estimates of incidence and mortality.[22-29] 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 relative risk for each outcome.[30] 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 RCTs when available. 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 the potential for confounding 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 RCTs because they are infrequent or develop slowly.

Results

Cardiovascular Disease

Studies of HRT and the primary prevention of cardiovascular disease (CVD) report various outcomes. Some studies examined coronary heart disease (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: current users are those using estrogen at the time of assessment, past users are those who used estrogen previously but not at the time of assessment, ever users include those who used estrogen both at the time of assessment and previously, and never users have not used estrogen at any time. We also created a category, all use, that combined all mutually exclusive types of use (ever, past, and current) for purposes of pooling studies in the meta-analysis. Our review and meta-analysis focuses on the studies we rated good or fair-quality using USPSTF criteria. Characteristics of poor-quality studies included little or no control for confounding, nonrepresentative cohorts, poor definition of outcomes, poor characterization of exposure, and bias in control selection.

Overall Cardiovascular Disease

Eight observational studies evaluated overall CVD mortality.[31-38] The summary relative risk for CVD mortality was significantly reduced among those using HRT at the time of assessment (RR, 0.64; 95% CI, 0.44-0.93) but not among ever, past, or any users (Table 1). Two cohort studies,[31,32] 1 case-control study,[39] and data from a published meta-analysis[40] reported CVD incidence. The summary relative risk with any use was 1.28 (95% CI, 0.86-2.00) (Table 1). Results were similar for those who were using estrogen at the time of assessment, those who used estrogen previously but not at the time of assessment, and those who had ever used estrogen.

Coronary Heart Disease

Five studies evaluated the risk for CHD mortality.[32,34,35,41,42] Combined data from these studies indicated that mortality was significantly reduced among those using HRT at the time of assessment (RR, 0.62; 95% CI, 0.40-0.90), but not among any, past, or ever users (Table 1).

The association between HRT use and CHD incidence was evaluated in 3 cohort studies[22,31,32]; 9 case-control studies[43-51]; and 1 small randomized, controlled trial.[33] Combined data indicated that CHD incidence was also reduced among those using HRT at the time of assessment (RR, 0.80; 95% CI, 0.68-0.95), but not among any, past, or ever users (Table 1). Further analysis of studies adjusting for

Table 1. Summary of cardiovascular disease meta-analyses

	Relative Risk According to Use of Hormone Replacement Therapy (95% CI)*			
	Current	Past	Ever	Any
Mortality				
Total cardiovascular disease†	0.64 (0.44-0.93)	0.79 (0.52-1.09)	0.81 (0.58-1.13)	0.75 (0.42-1.23)
Coronary heart disease	0.62 (0.40-0.90)	0.76 (0.53-1.02)	0.81 (0.37-1.60)	0.74 (0.36-1.45)
Stroke			0.81 (0.71-0.92)	
Incidence				
Total cardiovascular disease	1.27 (0.80-2.00)	1.26 (0.79-2.08)	1.35 (0.92-2.00)	1.28 (0.86-2.00)
Coronary heart disease	0.80 (0.68-0.95)	0.89 (0.75-1.05)	0.91 (0.67-1.33)	0.88 (0.64-1.21)
Coronary heart disease adjusted for socioeconomic status	0.97 (0.82-1.16)	1.07 (0.90-1.27)	1.11 (0.84-1.53)	1.04 (0.79-1.44)
Overall stroke			1.12 (1.01-1.23)	
Thromboembolic stroke			1.20 (1.01-1.40)	
Subarachnoid stroke			0.80 (0.57-1.04)	
Intracerebral stroke			0.71 (0.25-1.29)	

*Current users are those using estrogen at the time of assessment, past users are those who used estrogen previously but not at the time of assessment, ever users includes current and past users, and never users have not used estrogen at any time. We also created a category, all use, that combines all mutually exclusive types of use (ever, past, and current) for purposes of pooling studies in the meta-analysis.

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

socioeconomic status by using measures of social class such as education or income indicated no significant reductions in risk for any of the groups who used HRT (Table 1). Similar results were found when the analysis was stratified by studies adjusting for alcohol consumption and/or exercise, in addition to other major risk factors, suggesting confounding by these factors.

The WHI reported an increased risk for CHD events (hazard ratio [HR], 1.29; 95% CI, 1.02-1.63), including nonfatal myocardial infarction (HR, 1.32; 95% CI, 1.02-1.72) among estrogen users.[13] Coronary heart disease mortality and rates of coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty were not increased. Results from HERS II indicated no significant decreases in rates of primary or secondary CHD events among estrogen users.[16]

Stroke

Hormone replacement therapy and stroke mortality were evaluated in 8 cohort studies and 1 case control study.[32,34,36,37,41,42,52-54] After combining data from these studies, the summary relative risk for stroke mortality was 0.81 (95% CI, 0.71-0.92) among HRT users (Table 1). Two cohort studies, each of good quality, evaluated long-term use of estrogen and risk for stroke mortality and identified no significant association.[41,42] The majority of studies did not differentiate between unopposed and combined estrogen regimens.

Combining 9 studies of stroke incidence resulted in a summary relative risk of 1.12 (95% CI, 1.01-1.23), indicating a small increase in stroke in association with HRT use (Table 1).[22,31,32,39,50,52,53,55-57] Results of a sub-analysis indicate a significant increase in risk for thromboembolic stroke (RR, 1.20; 95% CI,1.01-1.40)[54,55,57,58] but not

subarachnoid hemorrhage (RR, 0.80; 95% CI, 0.57-1.04)[57,59,60] or intracerebral hemorrhage (RR, 0.71; 95% CI, 0.25-1.29)[50,55,57,61] among women who had ever taken HRT.

One cohort and 1 case-control study evaluated the effect of long-term use (≥5 years) of estrogen and the risk for stroke and neither showed an association.[22,57] The Nurses Health Study reported a significant dose-response relationship between stroke and HRT use, with graded risks of 0.54 (95% CI, 0.28-1.06), 1.35 (95% CI, 1.08-1.68), and 1.63 (95% CI, 1.18-2.26) for estrogen doses of 0.3 mg, 0.625 mg, and 1.25 mg or more, respectively.[22] A 45% higher risk for stroke among women taking combined regimens compared with women who had never used HRT was also shown in the Nurses Health Study (RR, 1.45; 95% CI, 1.10-1.92)[22]; the association between stroke and unopposed estrogen use also was increased (RR, 1.18; 95% CI, 0.95-1.46), though was not statistically significant.

The WHI reported an increased risk for nonfatal strokes, although the confidence interval crossed 1.0 in adjusted analysis (HR, 1.50; 95% CI, 0.83-2.70).[13] HERS II reported no increase in stroke or transient ischemic attacks.[16]

Thromboembolism

Twelve abstracts met inclusion criteria and contained primary data (3 randomized controlled trials,[15,62,63] 8 case-control studies,[29,64-70] and 1 cohort study[60]). No studies were designed to report venous thromboembolic events (ie, deep vein thrombosis and/or pulmonary embolism) as primary outcomes. Studies varied in quality with the most important limitations including lack of controlling for key confounders such as smoking, not reporting dose or duration of estrogen use, differences in characteristics of patients and controls, small numbers of cases, and variation in outcome assessment. Despite differences in design and quality, the studies had consistent results, with 11 of 12 reporting relative risk point estimates above 1.0, and 6 of these with confidence intervals above 1.0.

When studies were combined by meta-analysis, results indicated that use of HRT at the time of the studies was associated with an increased risk for venous thromboembolism (RR, 2.14; 95% CI, 1.64-2.81). Estimates did not significantly change when pooling studies by type of study design, quality rating, or whether subjects had preexisting coronary artery disease. Using a baseline risk of 1.3 events per 10,000 woman-years based on a study with 10,000 controls, an additional 1.5 events per 10,000 women each year would be expected.[29] Six studies that reported risk according to duration of use found the highest risks in the first 1 to 2 years (combined RR for first year was 3.49; 95% CI, 2.[15,29,65,67-69]

Some studies reported the effects of dose and regimen, although the numbers of study participants were small. Three studies reported a higher risk for increased doses of estrogen (>0.625 mg conjugated) compared with lower doses.[29,65,67] A higher risk (odds ratio [OR], 2.2-5.3) for estrogen combined with progestin compared with estrogen alone was reported by 3 studies.[29,65,68] A comparison of oral (OR, 4.6; 95% CI, 2.1-10.1) and transdermal (OR, 2.0; 95% CI, 0.5-7.6) estrogen was reported by only 1 study.[65]

Both the WHI and HERS II reported statistically significant 2-fold increases in thromboembolic events among estrogen users with trends toward higher rates early in the course of use.[13,15]

Breast Cancer

Our search identified studies that evaluated breast cancer incidence or mortality as primary or secondary outcomes in association with HRT use. Those meeting inclusion criteria included 8 meta-analyses,[71-78] 15 case-control studies,[79-93] and 15 cohort studies.[94-109]

The WHI results indicated increased breast cancer risk for women using estrogen combined with progestin after 5.2 years of use (HR, 1.26; 95% CI, 1.00-1.59).[13] Trend data indicated increasing risk for breast cancer with increasing duration of use. Studies identified by our literature search support these findings. Current estrogen users have an increased risk for breast cancer according to most recent good-quality studies including 3 meta-analyses (relative risks range from 1.21 to 1.40).[71-73] Risk increases with longer duration of use (relative risks range from 1.23 to 1.35 based on all 6 meta-

analyses that evaluated this relationship).[71-77] Few studies and no meta-analyses specifically evaluated estrogen combined with progestin, although some recent studies suggest increased risk above that of unopposed estrogen,[78-81,94] while others do not.[82-85]

In contrast to studies of current users, the majority of studies of women who have ever used HRT, including 14 of 18 observational studies and 7 of 8 meta-analyses, reported no increase in risk for breast cancer (relative risks range from 0.85 to 1.14 from 8 meta-analyses).[40,71-77]

No meta-analyses have evaluated breast cancer mortality. All 6 recent cohort studies that evaluated breast cancer mortality showed either no effect or decreased mortality among those who had ever used HRT, or among those who used HRT in the short-term (<5 years) (relative risks ranging from 0.5 to 1.0).[78,95-99] Risk by duration of use was evaluated in 5 studies of mixed quality that evaluated mortality in different ways, including by tumor node status and family history.[78,95,96,98,99] Two good-quality studies that reported results for use longer than 5 years have conflicting results.[78,98]

Colon Cancer

A published meta-analysis of 18 observational studies of colorectal cancer and HRT indicated a 20% reduction in colon cancer among those who had ever used HRT compared with those who had never used HRT (RR, 0.80; 95% CI, 0.74-0.86) and a 34% reduction among those using HRT at the time of assessment (RR, 0.66; 95% CI, 0.59-0.74).[110] Duration of HRT use did not influence risk estimates. Results were similar for rectal cancer. These results were based entirely on observational studies that included estrogen users who were healthier, less obese, more physically active, and had healthier diets than nonusers, and who may have been at a lower risk for developing colorectal cancer based on these factors.

The WHI is the first RCT to report similar outcomes, although results were not significant when adjusted analysis was used.[13] Risk was not reduced among HRT users in HERS II.[14]

Endometrial Cancer

A meta-analysis of 29 observational studies reported a significantly elevated relative risk for endometrial cancer for unopposed estrogen users compared with nonusers (RR, 2.3; 95% CI, 2.1-2.5).[111] 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 HRT regimens (estrogen with progestin) on endometrial cancer incidence reported a relative risk of 0.8 (95% CI, 0.6-1.2).[111] Three cohort studies indicated a decreased risk for endometrial cancer (RR, 0.4; 95% CI, 0.2-0.6),[112-114] and 3 case-control studies showed an increase in risk (RR, 1.8; 95% CI, 1.1-3.1).[115-117] Neither the WHI nor HERS II reported an increase in endometrial cancer when a daily combined HRT regimen was used.[13,14]

Osteoporosis

For bone density outcomes, RCTs consistently indicated improved bone density with estrogen use. A published Cochrane systematic review reported combined results of 57 RCTs enrolling postmenopausal women for more than 1 year that compared HRT with placebo or calcium/vitamin D use.[118] Findings were similar between prevention and treatment trials, opposed and unopposed regimens, oral and transdermal forms of 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 greater bone density increases at lumbar, femoral neck, and forearm sites than use of lower doses (0.3 mg). Two-year trials resulted in greater increases than 1-year trials.

For fracture outcomes, a meta-analysis of 22 trials of estrogen reported an overall 27% reduction in nonvertebral fractures (RR, 0.73; 95% CI, 0.56-0.94).[119] 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.

We identified 4 trials[13,14,120-122] that met inclusion criteria and reported fracture outcomes. A primary prevention trial enrolled a subgroup of a large prospective osteoporosis study based in Finland.[120] In this study, early postmenopausal women without osteoporosis were randomly assigned to 1 of 4 treatment groups. New, symptomatic, radiographically confirmed nonvertebral fractures were recorded during a mean 4.3 years of follow-up. Compared with the groups given placebo, the risk for fracture was significantly lower for the group using estrogen/progestin alone (RR, 0.29; 95% CI, 0.10-0.90), but not for the group using estrogen/progestin and vitamin D, or the group using vitamin D alone when adjusted for baseline bone density and prior fractures. Another primary prevention trial randomized early postmenopausal women in Denmark to oral HRT 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 it was 0.40 (95% CI, 0.16-1.01).[121] The WHI is the first RCT to demonstrate reduction of hip fracture risk with estrogen use, although the confidence interval crosses 1.0 when adjusted analysis is used.[13] Risk for other osteoporotic fractures was significantly reduced (HR, 0.77; 95% CI, 0.63-0.94). No risk reduction for hip or other types of fractures was evident in HERS[122] or HERS II.[14]

Six good-quality cohort studies were also identified,[123-128] and 3 of 4 studies reported 20% to 35% reductions in adjusted relative risks for hip fractures among those who had ever used HRT (combined RR for 4 studies, 0.76; 95% CI, 0.56-1.01).[124-127] Cohort studies also reported reduced risks for wrist (RR, 0.44; 95% CI, 0.23-0.84),[123,125] vertebral (RR, 0.60; 95% CI, 0.74-0.86),[125] and nonvertebral fractures.[123] Cohort studies included large numbers of women, often recruited from community-based populations, and followed them for longer periods than did the RCTs.

Cognitive Function and Dementia

Twenty-nine studies met inclusion criteria, including 9 RCTs[129-137] and 8 cohort studies[138-145] describing the effects of HRT on cognitive decline and 2 cohort[146,147] and 10 case-control studies[148-157] providing estimates for dementia risk.

Studies measuring the effects of estrogen on cognition in women without preexisting dementia were not combined quantitatively because of their heterogeneity. These studies used more than 40 different tests among them and administered these tests in nonstandardized ways. They also differed in their study design and patient populations. Results indicated that women with menopausal symptoms experienced improved verbal memory, vigilance, reasoning, and motor speed, but no enhancement of other cognitive functions. Generally, no benefits were observed in asymptomatic women.

Our meta-analysis of 12 observational studies with dementia outcomes[146-157] suggested that HRT was associated with a decreased risk for dementia (summary OR, 0.66; 95% CI, 0.53-0.82). However, these studies commonly used self-reported outcomes for controls and proxy for cases, used interviewers who were not blinded to the outcome, did not control for education, and included only those using estrogen at the time of assessment. Possible biases and lack of control for potential confounders limit interpretation of these studies. Studies did not contain enough information to adequately assess the effects of progestin use, various estrogen preparations or doses, or duration of therapy.

Neither the WHI nor HERS II reported effects of HRT on cognition and dementia.[13,14] We considered the relationship between HRT and dementia to be an uncertain benefit because of lack of RCT evidence and the methodologic limitations and inconsistencies among observational studies.

Cholecystitis

The relationship between HRT and cholecystitis is well-described in a publication from the Nurses Health Study, a good-quality cohort study.[28] When compared with those who had never used HRT, those who were using HRT for the short-term at the time of assessment had an age-adjusted relative risk for cholecystitis of 1.8 (95% CI, 1.6-2.0). This risk increased after 5 years of use and remained elevated at this rate for women who had used HRT for 10 years or more. Among those who used HRT in the past, the risk decreased to between 1.4 and 1.7 but still remained significantly elevated as compared with those who had never used HRT.

Other studies support these findings,[64,79,158-160] although some do not.[161-165] The HERS II trial reported an increase in biliary tract surgery among HRT users compared with those receiving placebo during 6.8 years of follow-up (RR, 1.44; 95% CI, 1.10-1.90).[14] 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 with gallbladder and other diseases.[166] In this study, estrogen users were significantly more likely than users of other medications to have cholecystectomy and primary appendectomy.

Benefits and Harms Outcomes Table

Our review of the evidence and the results of our meta-analyses, as well as recent results from the WHI, provided risk estimate assumptions for a table summarizing the benefits and harms of HRT (Table 2). We obtained incidence rates for target conditions from population-based sources and calculated the number of events prevented or caused by HRT per year in 10,000 postmenopausal women. We calculated outcomes twice, once using results of this 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 protect against mortality for specific outcomes (stroke and breast cancer) or mortality outcomes were not studied (fractures, colon cancer, and thromboembolism).

For most clinical outcomes, we used relative risk estimates from those who had ever used HRT as opposed to those who were using HRT at the time of assessment or those who had used HRT in the past. The groups who had ever used HRT were the most consistently reported across studies and would be expected to bias results less than those who were using HRT at the time of assessment. Cholecystitis and thromboembolism were associated with HRT use at the time of assessment; rates for those who had ever used HRT were not provided, the relative risk estimates for those who were taking HRT at the time of assessment 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 for thromboembolic events in the first year of use, but because most HRT users intend a longer course to prevent chronic conditions, 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 risk for endometrial cancer. Eight published meta-analyses[71-78] of breast cancer incidence provided different risk estimates. To reflect this range of risk, we calculated a potential range of cases of endometrial cancer caused by HRT use.

Table 3 summarizes these results by 10-year age groups for women aged 55 to 84. Event rates for benefits and harms are generally lower in younger women and higher in older women. Except for CHD, rates are similar when WHI hazard ratios rather than relative risks from our review are used.

Table 2. Outcomes table assumptions

			Incidence or mortality rates by age group					
	This review	Results of WHI*	55-64		65-74		75-84	
Condition (reference)	RR or OR (95% CI)	HR (95% CI)	55-59	60-64	65-69	70-74	75-79	80-84
Benefits								
Hip fracture (23)	0.76 (0.56-1.01)	0.66 (0.33-1.33)	0.00089	0.001528	0.002372	0.005305	0.010184	0.017315
Wrist fracture (24)	0.44 (0.23-0.84)	NA	0.006053		0.00671		0.008113	
Vertebral fracture (25)	0.60 (0.36-0.99)	0.66 (0.32-1.34)	0.0068	0.0093	0.0123	0.0161	0.0205	0.0252
Colorectal cancer (27)	0.80 (0.74-0.86)	0.63 (0.32-1.24)	0.000712	0.001121	0.001568	0.002274	0.002951	0.003838
Uncertain Benefits								
Dementia incidence (26)	0.66 (0.53-0.82)	NA	0.005**		0.01		0.02**	
Harms								
Coronary heart disease incidence (22)	0.91 (0.67-1.33)	1.29 (1.02-1.63)	0.00174	0.00264	0.00308	0.00398†		
Overall stroke incidence (22)	1.12 (1.01-1.23)	1.41 (0.66-2.31)	0.00064*	0.00121		0.00229	0.00469†	
Thromboembolism incidence (≤1 year) (29)	3.49 (2.33-5.59)	NA	NA	NA	NA	NA	NA	NA
Thromboembolism incidence (overall) (29)	2.14 (1.64-2.81)	2.11 (1.26-3.55)	0.00013	0.00013	0.00013			
Breast cancer incidence (<5 years) (27)	1.0 - 1.14	NA	0.002963	0.003473	0.004044	0.004555	0.004833	0.004681
Breast cancer incidence (≥5 years) (27)	1.23 - 1.35	1.26 (1.00-1.59)	0.002963	0.003473	0.004044	0.004555	0.004833	0.004681
Cholecystitis (<5 years) (28)	1.8 (1.6-2.0)	NA	0.00357		0.00357		0.00357	
Cholecystitis (≥5 years) (28)	2.5 (2.0-2.9)	NA	0.00357		0.00357		0.00357	

*Nominal CIs are indicated for main outcomes of the trial (breast cancer, CHD), adjusted CIs for secondary outcomes.

†Data based on extrapolated values.

Note: NA indicates not available; WHI, Women's Health Initiative.

Table 3. Outcomes table: hormone replacement therapy use in 10,000 women—benefits and harms per year

	Number of events prevented or caused per year					
	Age 55-64		Age 65-74		Age 75-84	
	This review	WHI	This review	WHI	This review	WHI
Benefits (prevention)						
Hip fractures	3	4	9	13	33	47
Wrist fractures	34	_	37.5	_	45	_
Vertebral fractures	32	27	57	49	91	78
Cases of colon cancer	2	3	4	7	7	12.5
Uncertain Benefits						
Cases of dementia	17*	_	34	_	68*	_
Harms (caused)						
Coronary heart disease events	0	6	0	9	0	11.5
Strokes	1*	4*	3	9	6*	19*
Thromboembolic events during first year	3	_	3	_	3	_
Thromboembolic events overall	1.5	1.4	1.5	1.4	1.5	1.4
Breast cancer cases (<5 years' use)	0 to 2.5	_	0 to 6	_	0 to 7	_
Breast cancer cases (≥5 years' use)	7 to 11	8	10 to 15	11	11 to 17	12
Cholecystitis cases (<5 years' use)	25	_	25	_	25	_
Cholecystitis cases (≥5 years' use)	53.5	_	53.5	_	53.5	_

*Estimates based on extrapolations.

Note: WHI indicates Women's Health Initiative.

Discussion

Conclusions

Table 4 summarizes the quality of evidence for each key question addressed in this review. According to our analysis of observational studies and results of the WHI, using HRT to prevent CHD and CVD does not reduce these events. However, HRT use does not increase mortality from CHD and CVD based on these studies. Stroke incidence, specifically thromboembolic stroke—but not stroke mortality—is increased with HRT use according to our meta-analysis and results of the WHI. Prevention of colorectal cancer is also supported by the WHI and observational studies, although this evidence is weaker because WHI findings are not significant when the analysis is adjusted and observational studies are biased. 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. HRT effects on cognition were reported only in women with symptoms of menopause. Prevention of dementia is supported only by observational studies with important methodological limitations.

Several harms of HRT use are supported by an increasingly strong body of evidence. Our meta-analysis, the WHI, and HERS II are consistent in reporting a 2-fold increase in thromboembolic events with HRT use. Risk is highest in the first year of use. Observational studies support the WHI

Table 4. Summary of evidence

Key questions	Evidence codes*	Quality of evidence†
Potential benefits		
Does HRT reduce risks for:		
1. CHD and CVD incidence?	I, II-2	Fair-good: most studies are observational and have important biases; when confounders are considered, apparent benefits for current users are not supported; trial data from WHI indicates increased risk further undermining validity of observational studies.
2. CHD and CVD mortality?	I, II-2	Fair-good: results based on observational studies with biases; both observational and trial data indicate no increase or decrease in risk.
3. Stroke incidence?	I, II-2	Fair-good: results based on observational studies with biases; observational and trial data suggest increased risk.
4. Stroke mortality?	I, II-2	Fair-good: observational studies indicated reduced risk for stroke mortality, although trial data did not support this finding.
5. Colorectal cancer?	I, II-2	Poor-good: results are based on observational studies that were primarily designed for other outcomes; findings from the WHI are not significant when the analysis is adjusted.
6. Low bone density?	I	Good: many good-quality RCTs are consistent and demonstrate benefit; limited by short duration of trials, bone density is an intermediate outcome.
7. Fractures?	I, II-2	Fair-good: RCTs- few trials available, none is definitive because of limitations of methods although benefit is supported. Cohort studies- several good-quality cohort studies are consistent and demonstrate benefit; limited by healthy user bias.
8. Decline in cognitive function?	I, II-2	Fair-poor: studies enlist different patient populations and measure many different outcomes; results for symptomatic women are different from asymptomatic women. Duration of studies is too short to be meaningful. Difficult to draw any conclusions because outcome measures are so diverse.
9. Dementia?	II-2	Fair-poor: although the meta-analysis supports a protective effect, methodologic limitations and biases exist in individual studies (e.g., healthy user effect, use of proxy interviews, historical data obtained from subjects with dementia).
Potential Harms		
Does HRT increase risks for:		
1. Venous thromboembolism?	I, II-2	Poor-good: RCTs- venous thromboembolism is a secondary outcome, groups were randomized for cardiac outcomes, method of outcome assessment was not reported. Case-control- quality ratings range from poor to good; analysis based on small numbers of cases, important confounders such as smoking not considered in some studies. The consistency of the findings for an increased risk support the relationship.

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Table 4. Summary of evidence *(continued)*

2. Breast cancer incidence?	I, II-2	Poor-good: increased risk with current use of long duration was supported by observational data and WHI trial; despite biases of the observational studies, the consistency of this finding provides stronger evidence for an association.
3. Breast cancer mortality?	II-2	Poor-good: observational and trial data indicate that mortality is not increased.
4. Endometrial cancer?	II-2	Poor-good: results are based on observational studies only, although results are consistent and demonstrated dose-response relationships.
5. Cholecystitis?	I, II-2	Poor-good: increased risk was reported from RCTs and observational studies, but was not a finding in every study; results demonstrated dose-response relationships.

*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[21]

finding that breast cancer incidence was increased in those using HRT at the time of assessment after 5 or more years of use. Our review indicated that those who used estrogen previously but not at the time of assessment and short-term users were not at increased risk for breast cancer, and mortality was not increased for any group. Risks for endometrial cancer are increased with unopposed estrogen use but not with combined regimens. Studies are consistent in reporting increased risk for cholecystitis among those using HRT at the time of assessment which appears to increase with time.

New studies reporting associations between HRT use and ovarian cancer have been recently reported since this review was completed. Results indicate that women using unopposed estrogen for prolonged durations may have an increased risk for ovarian cancer.[167-169]

Limitations of the Literature

Studies of HRT, particularly observational studies, have many limitations. 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 tend to exercise more often and drink alcohol more frequently than those who do not use HRT.[31,78,170] These lifestyle factors are associated with increased risk for breast cancer and decreased risk for cardiovascular disease.[31,170-172] 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 HRT users are treatment-compliant, itself a factor associated with better health.[173,174] Women often stop HRT when they become ill, a tendency that would bias studies evaluating recent or current use by underestimating HRT use in ill patients. Hormone replacement therapy is used more often by women who have undergone hysterectomy and oophorectomy, conditions associated with decreased risks for breast cancer and increased risks for osteoporosis.

There have been significant changes in clinical practice regarding 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 at one point only or asked women if they had ever used estrogen. Thus, those who had ever used HRT and those who used HRT at the time of assessment could have used HRT for either long or short periods of time.

Our review is also limited by assumptions in Table 2 that lead to the estimated cases in Table 3. In many cases, a variety of relative risks 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.

Future Research

Additional evidence from RCTs is needed to more accurately weigh the benefits and harms of HRT. Areas of future research could include the following:

- The roles of progestins and types and doses of estrogen on outcomes are alluded to in the literature but are unresolved. Results of the WHI were based on use of a daily combined regimen 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. Additional studies may find that women taking unopposed estrogen have reduced risks for some outcomes, but increased risk for others.
- As selective estrogen receptor modulators (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.
- Effects of HRT may differ by age or other important risk factors. Practice could be influenced if women who experience thromboembolic events, for example, are different from those who do not and could be identified prior to initiating HRT. Results from other studies indicate that women with a prior history of venous thromboembolism while taking HRT, those with the Factor V Leiden mutation, or those with hip or lower extremity fracture, cancer, hospitalization, or surgery are at increased risk for thromboembolism.
- It is unclear how age modifies the impact of estrogen. Understanding the optimal duration of effect would allow targeting of estrogen use to enhance beneficial effects and avoid harms.
- Although our review supports an association between HRT and increased risk for venous thromboembolism, as well as HRT and reduced risk for colorectal cancer, the pathophysiology of these relationships is not well understood.
- Clarification of potential increased risk for breast cancer with HRT use among subpopulations of women already considered at high-risk would help these women make decisions about HRT use.
- Studies can be designed to evaluate whether HRT has different effects in women with BRCA 1 and/or BRCA 2 tumor suppressor gene mutations. Are women with these mutations at any higher risk for breast cancer if they use HRT?
- Research on the effects of HRT on cognitive performance should focus on older, asymptomatic women instead of perimenopausal women.
- Studies of cognition need to use standardized outcome measures. The tests should not have

ceiling values and need to be sensitive to very small differences because the effects of estrogen on cognition may be subtle. These tests should examine particular cognitive domains because the evidence indicates that estrogen may have neural and cognitive specificity. Future studies should include measures of the ability to care for oneself, live independently, and complete activities of daily living.

- Estrogen's cognitive and neural specificity should also be considered when interpreting the results of future research studies, including the 2 ongoing primary prevention trials of HRT and cognition, the Women's Health Initiative Study of Cognitive Aging (WHISCA)[175] and the Women's International Study of Long Duration Oestrogen after Menopause in the United Kingdom.[176]

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