Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement

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Executive Summary: Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement

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A sound understanding of the actual benefits and risks of menopausal hormone therapy (MHT) requires interpretation of a complex body of existing data. The Endocrine Society commissioned a Scientific Statement designed to provide a comprehensive, objective evaluation of all available information and to judge the level of evidence with a validated method, the GRADE system. Because women might be expected to take MHT for approximately 5 yr, calculations framed that time period. Data were uniformly expressed as the number of women benefitted or harmed by MHT in excess of the expected number of women not using MHT. The precise term for this statistical measure is excess (or attributable) benefit and risk.

The Women's Health Initiative (WHI) Study provided a major source of data for this analysis. During the 1990s, MHT was being used increasingly to reduce heart disease risks, in addition to treating menopausal symptoms. This was based on evidence from large observational studies

that MHT provided cardioprotection. It was not clear whether MHT increased breast cancer risk. The WHI study was undertaken to determine, under the conditions of a randomized controlled trial, whether MHT truly protected against heart disease and whether or not it increased breast cancer risk. Funded by the National Institutes of Health in the United States, two large, randomized, placebo-controlled trials were undertaken: one trial of estrogen alone compared with placebo, and the second trial of estrogen plus a progestogen vs. placebo. The first results were published in 2002. This study exerted a large impact on decision-making by women and their health care providers and led to a marked reduction in MHT usage. Subsequent to its publication, controversy arose with respect to WHI's applicability to women just entering menopause. The average age of participants was 63, and only 3.5% of the women were 50–54 yr old, the age when women usually make a decision regarding initiation of MHT. In addition, the WHI did not address the major indication for MHT use, relief of symptoms. After publication of the WHI findings, a number of studies have examined the effects of MHT in 50- to 55-yr-old women more likely to consider starting MHT. This Scientific Statement was designed to integrate information from the WHI and subsequent studies in order to draw conclusions from the available data.

Conclusions are divided into those most likely to remain unchanged over time (level of evidence A), those likely to remain unchanged but with a lesser level of certainty (level of evidence B), and those that are tentative (levels of evidence C and D). Major conclusions are listed according to these categories, with benefits presented before risks.

Conclusions with Level of Evidence A

Hot flashes

- "Standard-dose" estrogen with or without a progestogen markedly lowers the frequency and severity of hot flashes, and lower doses of estrogen are also effective in many women.
- Tibolone (a hormonal alternative widely available worldwide but not in the United States) alleviates postmenopausal vasomotor symptoms.

Urogenital system

- Very low doses of vaginal estradiol relieve symptoms and normalize vaginal atrophy.
- Estrogen used vaginally or systemically reduces the symptoms of overactive bladder.
- Vaginal estrogen reduces the incidence of recurrent urinary tract infections.
- Tibolone improves urogenital atrophy.

Bone

- Estrogen with or without a progestogen prevents early postmenopausal bone loss and augments bone mass in late postmenopause as effectively as the bisphosphonates.
- Estrogen alone and estrogen plus a progestogen prevent hip and vertebral fractures.
- Tibolone significantly reduces vertebral and nonvertebral fractures in osteoporotic women over the age of 60 yr.
- Raloxifene, a selective estrogen receptor modulator, improves bone mineral density and reduces vertebral but not hip fractures.

Colon cancer

- MHT with estrogen plus a progestogen decreases colon cancer risk.

Breast

- Raloxifene decreases breast cancer risk.
- Estrogen and estrogen plus a progestogen increase mammographic density.
- Tibolone increases risk of breast cancer recurrence.

Sexual function

- Physiological amounts of transdermal testosterone increase the number of self-reported, sexually satisfying events per month as well as desire, arousal, responsiveness, and orgasm.
- DHEA does not significantly improve sexual function.

Venothrombotic episodes

- MHT increases the risk of venothrombotic episodes approximately 2-fold and is multiplicative with baseline risk factors including age, higher body mass index, thrombophilias, surgery, and immobilization.
- Raloxifene increases the incidence of venothrombotic episodes.

Stroke

- Tibolone increases risk of stroke in older but not in younger women.
- No increase in stroke occurs with raloxifene.
- Hormone use does not reduce stroke incidence in older women with preexisting vascular disease.

Endometrium

- Estrogen alone without a progestogen causes an increase in endometrial cancer.
- Continuous estrogen plus a progestogen does not cause endometrial cancer.

- Tibolone does not induce endometrial hyperplasia or carcinoma.

Gallbladder

- Estrogen alone and estrogen plus a progestogen increase the risk of gallbladder disease.

Cognition

- MHT initiated after age 60 yr does not improve memory.

Selected Conclusions with Level of Evidence B

Metabolism

- Use of estrogen alone and estrogen plus a progestogen in the WHI was associated with a decrease in the risk for type 2 diabetes.
- Initiation of MHT is associated with lesser accumulation of weight, fat mass, and/or centrally located fat mass.

Joints

- Estrogen exerts a protective effect on osteoarthritis.
- Estrogen alone reduces total arthroplasty rate.
- Addition of a progestogen to estrogen appears to counteract the beneficial effects of estrogen on arthroplasty rate.

Quality of life

- MHT produces an improvement in health-related quality of life through decreased symptoms, sleep enhancement, and, possibly, mood enhancement.

Sexual function

- Tibolone improves sexual well-being in postmenopausal women presenting with low libido, with greater improvements in desire, arousal, satisfaction, and receptiveness than seen with transdermal estrogen-progestogen therapy.

Endometrium

- Sequential estrogen plus a progestogen reduces the risk of endometrial carcinoma compared to estrogen but not as effectively as continuous estrogen plus a progestogen.
- Vaginal estrogen in doses of 7.5 to 25 μg twice weekly does not stimulate the endometrium.
- Raloxifene reduces the incidence of endometrial carcinoma.

Premature menopause

- Women with bilateral oophorectomy prior to age 45 are at increased risk of negative effects on the cardiovascular system, bone, cognition, mood, and sexuality.

Overall mortality

- MHT was associated with a 40% reduction in mortality in women in trials in which participants had a mean age below 60 yr or were within 10 yr of menopause onset.

Coronary heart disease (CHD)

- Basic science, animal models, and observational studies support the hypothesis that MHT may prevent atherosclerosis and reduce CHD events.
- Subgroup analyses suggest that the lack of benefit or increase in CHD risk observed in the overall analysis of the WHI resulted from harmful effects of MHT in older women starting therapy many years after onset of menopause.
- Tibolone does not increase the risk of CHD events.

Breast

- Use of estrogen alone for less than 5 yr may reduce the risk of breast cancer in patients starting therapy many years after the onset of menopause.
- Tibolone reduces the risk of developing breast cancer.
- Estrogens increase the risk of breast cancer after more than 5 yr of use, particularly in recently menopausal women.
- Combined estrogen and progestogen therapy increases the risk of invasive breast cancer, which may occur within 3 to 5 yr of initiation and rises progressively beyond that time.
- For the subgroup of first-time hormone users of estrogen plus a progestogen, the overall WHI data indicate no increased risk after 5.2 yr, particularly in those starting MHT several years after the onset of menopause.
- The risk of breast cancer in association with estrogens alone and estrogens plus a progestogen returns to approximately that of nonusers within 3–5 yr of cessation.
- Data suggest a rapid decline in incidence of estrogen receptor-positive breast cancer, which was temporally associated with a decline in use of MHT after the first reports of the WHI in 2002.
- Autopsy studies indicate that women between ages 50 and 80 yr have a 7% prevalence of undiagnosed breast cancer (6% in situ and 1% invasive).

Colorectal cancer

- Tibolone is associated with a reduction of colon cancer.

- Colorectal cancers diagnosed in women receiving estrogen plus a progestogen in the WHI tended to exhibit a higher percentage of local and metastatic spread.

Mood changes and cognition

- Estrogen therapy initiated at the time of surgical menopause benefits verbal memory over the short term.
- After menopause, MHT probably has no important effect on midlife cognitive function.
- MHT initiated after about age 65 yr increases risk of dementia.

Stroke

- Standard-dose oral MHT may increase stroke risk by about one third in generally healthy postmenopausal women.

Ovarian cancer

- Long-term therapy with estrogen alone is associated with a small risk of ovarian cancer.

Quality of evidence

- Evidence from the WHI trial is weighted less than that of a randomized controlled trial according to the GRADE system criteria because of mitigating factors: large dropout rate; lack of adequate representation of applicable group of women (i.e. those initiating therapy at the time of menopause); and modifying influence from prior hormone use. For this reason, many of the conclusions from the WHI are judged as level B evidence.

Selected Conclusions with Level of Evidence C

Gallbladder

- Observational studies report lower risks of gallbladder disease with transdermal and low-dose oral estrogen than with standard oral doses.

Venothrombotic episodes

- Transdermal estrogen does not increase venothrombotic episode risk.

Stroke

- Low-dose estrogen therapy does not increase stroke risk.

Breast

- Linear models suggest a 3% relative increase in breast cancer per year of exposure in thin women and a lesser risk in obese women.
- Emerging data, so far from two independent studies only, report that progesterone (and perhaps dydrogesterone) in combination with estrogen does not increase breast cancer risk if given for 5 yr or less.
- No single estimate of absolute risk can be provided for an individual woman because risk varies with time of initiation relative to final menses, duration of use, and body mass index and, possibly, with type of progestogen and family history of breast cancer.
- Women closer to menopause are emerging as the group at highest risk associated with some forms of MHT.

Mood and cognition

- Beneficial effects of estrogen or estrogen plus a progestogen on mood in postmenopausal women are minimal, and beneficial effects may be more likely in women with concurrent menopausal symptoms.

Selected Conclusions with Level of Evidence D

Breast

- Calculations from the placebo groups in the WHI study and from autopsy data regarding breast cancer prevalence suggest that only 30% of occult tumors progress to a size allowing clinical diagnosis in 5 to 6 yr.
- The decrease in breast cancer associated with use of estrogen alone in the overall WHI analysis could reflect a proapoptotic effect of estrogen in women starting therapy many years after the onset of menopause.
- The increase in breast cancer from estrogen plus a progestogen in the WHI could occur through an effect on occult undiagnosed breast cancer, rather than by the de novo development of new cancer.
- An effect of progestogens in combination with estrogens to increase the risk of breast cancer could be explained by an effect of estrogen plus a progestogen on existing occult tumor cells to enhance reprogramming into stem cells or to stimulate proliferation.
- Women receiving estrogen plus a progestogen exhibited a nonsignificant trend toward a higher incidence of lung cancer in the WHI, but this effect was limited to women more than 60 yr old.

- Whether standard MHT increases the recurrence risk in breast cancer survivors is unclear.

Benefits and Risks of MHT in Women Recently Menopausal (*i.e.* ages 50–59 or <10 yr postmenopausal)

Reanalyses of the WHI indicated the important influences of age and time since initiation of MHT on benefits and risks. Because most women start MHT shortly after menopause, available data regarding these women were specifically analyzed. Results are summarized as the excess number of women experiencing benefit or risk per 1000 women using MHT for 5 yr of more. Because no randomized controlled trials were available to determine these estimates, conclusions are tentative.

Benefits of Estrogen Alone (excess number of women per 1000 per 5 yr of use who experienced event attributable to use of MHT)

Excess number

0–1	None
1.1–5	Reduction in breast cancer, coronary heart disease
5.1–10	Reduction in fractures, overall mortality
>10	Reduction in type 2 diabetes

Benefits of Estrogen Plus a Progestogen

Excess number

0–1	Reduction in coronary heart disease (subgroup <10 yr postmenopausal), endometrial cancer
1.1–5	Reduction in fractures, colorectal cancer
5.1–10	Reduction in overall mortality
>10	Reduction in type 2 diabetes

Harm from Standard Oral Estrogen Alone

Excess number

0–1	Increase in colorectal cancer , ovarian cancer
1.1–5	Increase in venothrombotic episodes, stroke
5.1–10	None
>10	Increase in cholecystitis

Harm from Oral Estrogen Plus a Progestogen

Excess number

0–1	Increase in stroke
1.1–5	Increase in coronary heart disease (subgroup ages, 50–59 yr)
5.1–10	Increase in breast cancer, venothrombotic episodes, cholecystitis
>10	None

Issues Deemed Critical for the Future

- Disseminate literature to practitioners and postmenopausal women regarding the levels of benefit and risk associated with MHT as prescribed in currently used doses, in women close to menopause, and for periods of less than 3–5 yr.
- Continue research on lowest doses, optimal administration routes, and optimal products.
- Conduct research to identify women who may specifically benefit or be at risk from MHT.
- Develop new approaches to maximize benefit and minimize risk.
- Conduct randomized trials to examine rate of cardiovascular events, stroke, breast cancer, and carbohydrate intolerance as primary endpoints in women starting MHT for the first time between the ages of 50 and 55 yr.

Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement

Objective: Our objective was to provide a scholarly review of the published literature on menopausal hormonal therapy (MHT), make scientifically valid assessments of the available data, and grade the level of evidence available for each clinically important endpoint.

Participants in Development of Scientific Statement: The 12-member Scientific Statement Task Force of The Endocrine Society selected the leader of the statement development group (R.J.S.) and suggested experts with expertise in specific areas. In conjunction with the Task Force, lead authors (n = 25) and peer reviewers (n = 14) for each specific topic were selected. All discussions regarding content and grading of evidence occurred via teleconference or electronic and written correspondence. No funding was provided to any expert or peer reviewer, and all participants volunteered their time to prepare this Scientific Statement.

Evidence: Each expert conducted extensive literature searches of case control, cohort, and randomized controlled trials as well as meta-analyses, Cochrane reviews, and Position Statements from other professional societies in order to compile and evaluate available evidence. No unpublished data were used to draw conclusions from the evidence.

Consensus Process: A consensus was reached after several iterations. Each topic was considered separately, and a consensus was achieved as to content to be included and conclusions reached between the primary author and the peer reviewer specific to that topic. In a separate iteration, the quality of evidence was judged using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system in common use by The Endocrine Society for preparing clinical guidelines. The final iteration involved responses to four levels of additional review: 1) general comments offered by each of the 25 authors; 2) comments of the individual Task Force members; 3) critiques by the reviewers of the Journal of Clinical Endocrinology & Metabolism; and 4) suggestions offered by the Council and members of The Endocrine Society. The lead author compiled each individual topic into a coherent document and finalized the content for the final Statement. The writing process was analogous to preparation of a multiauthored textbook with input from individual authors and the textbook editors.

Conclusions: The major conclusions related to the overall benefits and risks of MHT expressed as the number of women per 1000 taking MHT for 5 yr who would experience benefit or harm. Primary areas of benefit included relief of hot flashes and symptoms of urogenital atrophy and prevention of fractures and diabetes. Risks included venothrombotic episodes, stroke, and cholecystitis. In the subgroup of women starting MHT between ages 50 and 59 or less than 10 yr after onset of menopause, congruent trends suggested additional benefit including reduction of overall mortality and coronary artery disease. In this subgroup, estrogen plus some progestogens increased the risk of breast cancer, whereas estrogen alone did not. Beneficial effects on colorectal and endometrial cancer and harmful effects on ovarian cancer occurred but affected only a small number of women. Data from the various Women's Health Initiative studies, which involved women of average age 63, cannot be appropriately applied to calculate risks and benefits of MHT in women starting shortly after menopause. At the present time, assessments of benefit and risk in these younger women are based on lower levels of evidence. (*J Clin Endocrinol Metab* 95: S7–S66, 2010)

A guiding principle underlying the practice of clinical endocrinology is the concept that hormones should be replaced after establishing a biologically important deficiency state. This rationale explained why many endocrinologists believed that long-term hormone replacement was indicated in menopausal women, a state of estrogen deficiency resulting from cessation of ovarian function. This postulate did not enter the crucible of a randomized clinical trial (RCT) in healthy women until the Women's Health Initiative (WHI) study examined the risks and benefits of menopausal hormone therapy (MHT). Publication of the WHI results caused initial consternation among women and their health care providers and raised critical questions regarding study design and clinical applicability. In response to the findings of the WHI trial, MHT usage declined by approximately 80%. The pendulum is now swinging back as a result of more careful assessment of the use of MHT shortly after menopause as a means to relieve symptoms due to vasomotor instability and urogenital atrophy. Since the original publication of the WHI study in 2002, a range of new studies has updated information on cardiovascular, cerebrovascular, and breast cancer risks with particular focus on the potential of timing of initiation of MHT to influence these risks. Additional studies have also been reported on the beneficial effects on bone, colon cancer, quality of life, and specific menopausal symptoms. This Scientific Statement provides a rigorous scientific critique of all relevant information on the use of MHT. Individual components emphasize the effects of age at initiation of therapy, timing of initiation relative to menopause, dosage, route of administration, type of estrogen or progestogen, cyclic *vs.* continuous regimen, duration of use, and genetic changes or single nucleotide polymorphisms (SNPs).

Approach

This Scientific Statement involved 25 leading experts in the field who reviewed the existing literature in their areas of expertise and prepared a summary of the evidence. Each summary was peer-reviewed by another expert and then revised. A task force of The Endocrine Society, its Council, Society Members, and journal peer reviewers reviewed the document in turn. Care was taken to minimize or eliminate bias, to use scientific evidence for all conclusions, and to grade the weight of the evidence. RCTs provided the most important evidence, followed in order of importance by meta-analyses, cohort studies, case-control studies, and collective wisdom (or observational studies). The level of evidence was graded according to the system called GRADE (Grading of Recommendations Assessment, Development and Evaluation), the method used previously by The Endo-

Detailed Explanations

Estrogen: a general term which refers to any substance that exerts estrogenic actions on tissues and includes conjugated equine estrogens, the human naturally occurring estrogens estrone, estradiol, and estriol and synthetic estrogens such as ethinyl estradiol. The specific term estradiol, when used, refers specifically to the chemical 17β-estradiol.

E: menopausal hormone therapy that consists of estrogen alone. This could reflect use of any type of estrogen. A commonly used synonym for this term is **ET** (estrogen therapy).

E+P: menopausal hormone therapy that consists of an estrogen plus a progestogen This could reflect use of any type of estrogen and any type of progestogen. A commonly used synonym for this is **EPT** (estrogen-plus-progestogen therapy). **E+P** is used as a generic term in describing studies where any type of estrogen or progestogen is used. **E+P** in the text might refer to conjugated equine estrogens plus medroxyprogesterone acetate or to other estrogen/progestogen combinations including those with progesterone itself.

MHT: menopausal hormone therapy. This is a generic term and refers to any type of hormone therapy used during menopause. When studies do not specifically stipulate estrogen alone or estrogen plus a progestogen, the term MHT is used. Synonyms for MHT include **HRT** (hormone replacement therapy) and **HT** (hormone therapy).

Progestogen: an umbrella term applied to any substance possessing progestational activity including synthetic steroid analogues or progesterone itself.

Relative risk: Studies in the literature use the terms **relative risk (RR)**, **hazard ratio (HR)**, and **odds ratio (OR)** to describe relationships between the frequency of an event or characteristic in a population treated with a particular agent to the frequency in a similar population not receiving that treatment. In general, these terms are broadly synonymous. To simplify the presentation of data in this Scientific Statement and achieve consistency, the terms used in the original publications have all been converted to **relative risk (RR)**.

Unopposed estrogen: This term refers to the use of estrogen alone which is not opposed by (or accompanied with) a progestogen, in order to neutralize (or oppose) the proliferative effect of E on the endometrium. This term, while still in common usage, is now considered outdated by some experts since the effects of progestogens on breast and other tissues may be additive to those of estrogens and not in opposition.

crine Society (1). Data on hazard ratios, relative risks (RRs), and odds ratios are uniformly expressed as RR, followed by a 95% confidence interval (CI). Summary data on risk are expressed on an absolute rather than relative basis and on a common statistic, the number of excess (or reduced) events attributed to taking MHT. Because women might be expected to use MHT for at least 5 yr, all data are expressed as the excess (attributable) risk per 1000 women per 5 yr of use. Benefit is expressed similarly. The conclusions drawn weigh heavily on the WHI estrogen-alone (E-alone) and estrogen-plus-progestogen (E+P) RCTs. The average age of the women in these two trials was 63 yr, whereas most women consider initiation of use of MHT at ages 50–55 yr. Accordingly, this Scientific Statement attempted to balance the WHI data with observational data on younger women to provide information that is more properly applicable to women at the age of decision-making for MHT.

The results discussed in this statement are largely based on studies involving 0.625 mg of conjugated equine estrogen (CEE) orally, 1–2 mg of estradiol orally, and 50 μg of estradiol delivered transdermally. It has become widespread current practice to start symptomatic women on lower doses (*e.g.* CEE, 0.3 or 0.45 mg orally; estradiol, 0.5 mg orally; and estradiol, 25 μg transdermally). Therefore, it may be necessary in the future to reassess risks and benefits for women treated with such lower doses.

Risks and Benefits

Cardiovascular and metabolic

Cardiovascular disease (CVD) is the leading cause of death in women and increases exponentially with aging. Considerable evidence suggests that endogenous estrogen contributes to delaying the onset of atherosclerotic CVD events in women. Basic science studies and numerous animal models provide biological plausibility for the concept that estrogens can exert atheroprotective effects via both systemic effects on circulating factors and direct effects on the heart and blood vessels (2, 3). These observations led to the hypothesis that estrogen-based MHT could reduce CVD risk in postmenopausal women.

Coronary heart disease and lipids

The concept that MHT could reduce CVD risk was based in part on a relatively large body of observational studies. In aggregate, these studies demonstrated a clinically meaningful reduction in CVD events of approximately 35% in postmenopausal women who chose to take MHT (4). In this context, the WHI was designed and conducted to test the hypothesis that MHT reduces CVD risk in a randomized, placebo-controlled clinical trial.

A recent analysis of the WHI reported findings from the entire group of women studied whose average age was 63 yr. The coronary heart disease (CHD) event rates were similar among women randomized to treatment with 0.625 mg/d of CEE *vs.* those randomized to placebo (RR, 0.95; CI, 0.78–1.16) (5). Women randomized to CEE combined with the progestogen medroxyprogesterone acetate (MPA; 2.5 mg/d) experienced a higher rate of CHD, although in the most recent analysis, this association did not reach formal statistical significance (RR, 1.23; CI, 0.99–1.53) (5). Expressed in terms of excess risk or benefit, 1.45 (CI, −6.6 to +4.2) fewer events occurred per 1000 women per 5 yr in the CEE arm and 3.9 (CI, 0.15–8.0) more events per 1000 patients per 5 yr in the CEE+MPA arm (5). Taken together, the results of the WHI study do not support the hypothesis that MHT reduces the risk of CHD in the population of postmenopausal women studied.

No single RCT can answer all questions about a given intervention, and thus many questions remained after the completion of the WHI. For example, it remains unclear what the cardiovascular effects of MHT would be if administered in lower doses, by transdermal rather than oral routes of delivery, by formulations containing different estrogens and/or progestogens, or with the progestogen given cyclically rather than continuously. The effect of duration of therapy also remains uncertain. In the CEE+MPA trial, the overall RR of 1.23 resulted from a significantly increased risk of CHD events in the first 2 yr of treatment (RR, 1.86; CI, 1.15–2.45) with a nonsignificant trend toward lower rates in subsequent years. There was no significant trend with duration of treatment in the CEE-alone study. The issue of route of administration is also an important (but unresolved) one because the effects of oral hormones differ from those of transdermal hormones on such potentially relevant parameters as circulating cholesterol levels and coagulation factors. Subgroup analyses of the WHI E alone and E+P trials do not show a statistically significant interaction between aspirin use and the effect of MHT on CHD or cerebrovascular accident outcomes (*P* values range from 0.22 to 0.71). Women who had undergone a total abdominal hysterectomy and bilateral salpingo-oophorectomy may also differ with respect to their underlying physiology when compared with women with spontaneous menopause. This concept should be taken into account when comparing the effects of E alone (women with total abdominal hysterectomy and bilateral salpingo-oophorectomy) with women receiving E+P (women with spontaneous menopause).

A central issue of discussion in interpreting the findings of the WHI study is the extent to which the effects of MHT are influenced by the timing of its initiation, in terms of

either the age of the recipient or the duration of estrogen deficiency (*i.e.* "time since menopause") (6). This "timing hypothesis," that MHT prevents CHD when administered soon after menopause or in younger women but not if initiated later in menopause or in older women, is supported by animal data and by some human studies (7). For example, Clarkson (8) and colleagues have repeatedly shown that MHT retards atherosclerosis progression in surgically menopausal monkeys when initiated early in menopause, but a similar approach failed to alter atherosclerotic burden when therapy was initiated late in menopause. Analyses comparing the results of the observational studies that demonstrate CVD risk reduction with MHT compared with the WHI are also consistent with this model. Women in the observational studies tended to be both younger and closer to the onset of menopause when they initiated MHT than those enrolled in the WHI (9). As an example, in the observational Nurses Health Study (NHS), participants were ages 30 to 55 yr on entry into the study, and it is estimated that about 80% of them initiated therapy within 2 or 3 yr of the onset of menopause. This is in contrast to the participants in the WHI who were, on average, age 63 yr at study entry and were more than 10 yr past the onset of menopause. Of course, such comparisons are limited by the potential biases inherent in nonrandomized population studies as well as by the stringent inclusion criteria that must be met for entry into randomized trials. The reduction in risk of coronary artery disease in younger women who underwent oophorectomy and received estrogens (discussed in *Use of hormones for premature menopause*) is also consistent with the timing hypothesis (10).

There have been several subgroup analyses and one surrogate endpoint study from the WHI aimed at exploring the timing hypothesis. These analyses are complicated by the fact that timing can be assessed by chronological age and/or by time since menopause, and event rates can be examined in relative terms and/or in absolute terms. Despite this complexity, a pattern has emerged from these subgroup studies that, taken together, indicate that the effects of MHT on CHD are indeed modified by the timing of initiation. In the surrogate endpoint study, the Coronary Artery Calcium Study, women in their 50s at study entry had lower coronary artery calcium scores at follow-up if they had been randomized to the CEE-alone arm in the WHI, compared with those in the placebo arm (11). This finding is consistent with subgroup analyses of clinical events in the women younger than age 60 in the CEE-alone arm who experienced significant reductions in selected CHD endpoints, including revascularization (RR, 0.55; CI, 0.35–0.86) and the composite of CHD death,

myocardial infarction, and revascularization (RR, 0.66; CI, 0.44–0.97) (5).

A comprehensive subgroup analysis of the WHI focused on these issues and provides some support for the timing hypothesis (5). Another reanalysis from the same group excluded nonadhering patients (12). Examining RRs first, in the CEE-alone arm, a nonsignificant ($P = 0.12$) trend toward a reduction in CHD in women younger than age 60 yr was observed that was not evident in the women older than 60 yr (*i.e.* RR, 0.63; CI, 0.36–1.09 for ages 50–59 yr; RR, 0.94; CI, 0.71–1.24 for ages 60–69 yr; and RR, 1.13; CI, 0.82–1.54 for ages 70–79 yr). This trend was not apparent ($P = 0.70$) in the CEE +MPA study (*i.e.* RR, 1.29; CI, 0.79–2.12 for ages 50–59 yr; RR, 1.03; CI, 0.74–1.43 for ages 60–69 yr; and RR, 1.48; CI, 1.04–2.11 for ages 70–79 yr). A similar nonsignificant ($P = 0.15$) trend toward a reduction in the RR of CHD only in the women less than 10 yr since menopause also was observed in the CEE-alone arm (Table 1). However, a significant increase in the RR of CHD with greater time since menopause was observed in the CEE plus MPA arm ($P = 0.05$), with the RR reaching 1.66 (CI, 1.14–2.41) in the women more than 20 yr since menopause. Turning to absolute event rate analyses, a significant increase in the number of CHD events per 1000 women per 5 yr with increasing age was noted in the CEE plus MPA arm, although no such trend was observed in the CEE-alone arm. Similarly, a significant increase in the number of CHD events per 1000 women per 5 yr was also observed with greater time since menopause in the CEE plus MPA study, with no significant effect in the CEE-alone arm.

Currently, the majority of women who initiate MHT do so within 10 yr of onset of menopause and, thus, it is important for clinical decision-making to examine this subgroup specifically. In the WHI, no statistically significant increase or decrease risk of CHD from CEE or CEE

TABLE 1.   RR (CI) for CHD events by age and time since menopause in the WHI studies (5)

	CEE	CEE/MPA
Age (yr)		
50–59	0.63 (CI 0.36–1.09)	1.29 (CI 0.79–2.12)
60–69	0.94 (CI 0.71–1.24)	1.03 (CI 0.74–1.43)
70–79	1.13 (CI 0.82–1.54)	1.48 (CI 1.04–2.11)
P value for trend	0.12	0.70
Time since menopause (yr)		
<10	0.48 (CI 0.20–1.17)	0.88 (CI 0.54–1.43)
10–19	0.96 (CI 0.64–1.44)	1.23 (CI 0.85–1.77)
≥20	1.12 (CI 0.86–1.46)	1.66 (CI 1.14–2.41)
P value for trend	0.15	0.05

plus MPA was observed in this subgroup of women. Estimates of the attributable benefit in this subgroup were 7.0 per 1000 women for 5 yr in the CEE group and 2.0 per 1000 women per 5 yr in the CEE plus MPA group.

Taken together, these subgroup analyses support the hypothesis that timing of initiation can influence the effects of MHT with either beneficial or neutral effects in younger, more recently menopausal women or harmful effects in older women with longer duration of menopause. These findings are also consistent with meta-analyses of the broader MHT literature and with subgroup analysis of the Raloxifene Use for The Heart (RUTH) trial (13).

In summary, basic science, animal models, and observational studies support the hypothesis that MHT may prevent atherosclerosis and reduce CHD events. Overall, the WHI and other RCTs do not support this hypothesis. However, more recent subgroup analyses suggest that the lack of benefit or increase in CHD risk observed in the WHI resulted from harmful effects of MHT in older women further from menopause, a subgroup that contributed a large percentage of the events recorded in the WHI and other trials. The major clinical implication of these findings is that whereas MHT is not recommended for CHD risk reduction, its use for other indications should not be hampered by fear of increasing CHD in younger, newly menopausal women.

Venothromboembolism (VTE)

VTE represents an important factor in the benefit-to-risk equation for MHT use. Both observational and interventional trials have shown significant increases in VTE risk among current MHT users (14). Based on the WHI trials, oral CEE and 2.5 mg MPA increased VTE compared with placebo (RR, 2.06; CI, 1.57–2.70) (15, 16). However, high dropout rates may have underestimated risk. With CEE only, adjusted VTE risk was also only marginally increased (RR, 1.32; CI, 0.99–1.75) (15). The estimated excess MHT-related VTE events in 1000 women of all ages approximated 4 per 1000 per 5 yr with use of CEE and 9 per 1000 per 5 yr with CEE plus MPA. The estimated excess MHT-related VTE events in women ages 50 to 59 yr approximated 2 per 1000 per 5 yr with use of CEE and 5 per 1000 per 5 yr with CEE+MPA.

The route of administration of estrogen and the dosage and type of progestogen used may impact thrombosis risk. With route of administration, based on case-control studies, adjusted RRs for VTE with oral or transdermal estrogen compared with nonusers are 4.2 (CI, 1.5–11.6) and 0.9 (CI, 0.4–2.1), respectively (17). This is consistent with mechanistic data showing that oral MHT increases clotting protein production via a first-pass hepatic effect, which is not replicated with transdermal therapy (17, 18). These findings require confirmation in RCTs. There are limited data on estrogen dose; however, the literature does suggest that the type of progestogen impacts VTE risk. A case-control study of idiopathic VTE has noted no association with micronized progesterone and pregnane derivatives, including MPA (19). However, relatively few women were receiving MPA, and these results contrast with WHI data on combined MPA and VTE risk. In contrast, case-control data suggest that nonpregnane-derived progestogens (*i.e.* nomegestrol and promegestone) are associated with a 4-fold increased VTE risk (RR, 3.9; CI, 1.5–10.0) (19, 20); yet again, these findings need to be explored in RCTs for confirmation.

Increasing age and obesity are major risk factors for VTE, with this risk, in turn, multiplied approximately 2-fold with MHT use. This translated to a higher absolute VTE risk with increasing age and body mass index (BMI), but the RR associated with MHT did not increase according to age or BMI. The interaction between MHT, age, and obesity was highlighted in the WHI study. In obese women ages 70 to 79 yr, approximately 45 VTE events per 1000 women per 5 yr occurred with combined oral MHT compared with 23 with placebo (14). In comparison, nine VTE events per 1000 women ages 50 to 59 yr with normal weight per 5 yr would be expected on oral combined MHT, compared with four with placebo (note that excess risk is 5, as described in the first paragraph above).

Of the thrombophilias that predispose to thrombosis, factor V Leiden (FVL) is the primary one that interacts mechanistically with MHT (21), due to estrogenic aggravation of underlying FVL mutation-related activated protein C resistance. The risk of VTE in FVL heterozygotes on combined oral MHT is approximately 7-fold higher than those on placebo. In high-risk women with a personal or family history of VTE, thrombophilia screening should be completed before MHT; however, routine screening is not recommended. Observational studies suggest that transdermal estrogen does not increase VTE with FVL mutation (22). Surgery, fractures, and immobilization also predispose to VTE: lower limb fractures (RR, 18.1; CI, 5.4–60.4), recent inpatient surgery (RR, 4.9; CI, 2.4–9.8), and recent nonsurgical hospitalization (RR, 5.7; CI, 3.0–10.8). The risk is aggravated an additional 2-fold by oral combined MHT. "There is no specific evidence that suspension of MHT reduces VTE risk at the time of a procedure, however oral combined MHT doubles VTE risk and up to 30% of VTEs occurred in WHI in relation to procedures. It is recommended that oral MHT be suspended around the time of surgery and/or that VTE prophylaxis is

used" (23). Further studies of this issue are required before more specific recommendations are possible. Overall, baseline risk assessment encompassing weight, age, and other risk factors is critical in assessment of the MHT impact on absolute increase in VTE events.

Stroke

Over 5 million Americans have suffered a stroke (24), the leading cause of prolonged adult disability and the third leading cause of death among women. Stroke incidence increases steeply with age (25), and early natural menopause may be associated with elevated risk of ischemic stroke later in life (26). The age-specific incidence is lower for women than men until late old age (27). However, because of longer life expectancy, a woman's lifetime risk of stroke—about one in five—is higher than that of men (27, 28). In addition, approaches to treatment may differ by gender (29).

A leading biological rationale for possible gender differences in stroke risk factors pertains to estrogen exposure. Estrogens exert various effects on brain, vascular endothelium and smooth muscle, blood elements, lipids, and inflammatory pathways. These effects could modify stroke risk and outcomes as supported by experimental and clinical data. After ovariectomy, cynomolgus monkeys develop less arterial atherosclerosis—a recognized risk factor for stroke (30)—if treatment with an estrogen is initiated at the time of surgery (8). In middle-aged ovariectomized rats, cerebral infarct volume after acute middle cerebral artery occlusion is reduced by physiological levels of estradiol initiated at the time of ovariectomy (31).

Clinical trials of MHT have generally focused on stroke prevention rather than treatment in the acute setting. In the WHI trials of community-dwelling women ages 50 to 79 yr, conjugated estrogens with or without MPA increased stroke risk by about one third (RR, 1.31; CI, 1.02–1.68 with MPA; RR, 1.37; CI, 1.09–1.73 without MPA) (32, 33). This effect appeared confined to ischemic stroke, although the study had reduced power to address other stroke types. The absolute excess risk approximated 4.5 additional cases per 1000 women per 5 yr of use (5). For women who had a stroke, severity at the time of hospital discharge did not differ by treatment assignment (32, 33), and excess stroke risk declined after the WHI trial was terminated (34). In trials of older women with elevated stroke risk due to coronary or cerebral vascular disease, MHT did not reduce stroke incidence (35, 36). Findings in other studies are consistent. A meta-analysis of 28 trials suggested a 29% increase (RR, 1.29; CI, 1.13–1.47) (37) in stroke due to hormone use. As in the WHI, risk was confined to ischemic stroke, with no indication that risk was modified by hormone preparation (E alone *vs.* E+P)

or type of estrogen (conjugated estrogens *vs.* estradiol) (37). Poor stroke outcomes were more common among hormone users (37).

Whether cerebrovascular effects of MHT are modified by age, timing of menopause, estrogen or progestogen dose, or route of administration (*i.e.* oral *vs.* transdermal) are questions of considerable interest (38, 39). In the WHI, the relative stroke risk from MHT was elevated for postmenopausal women regardless of age (5). Whereas the WHI was not designed to detect modest age-related differences, similar findings are reported from the larger NHS. In this prospective observational study, the RR of stroke was increased by about one third among current users of E alone or E+P, regardless of age at initiation (39). Because stroke incidence increases with age but RR from MHT remains constant, the attributable risk also appears to increase with age. Accordingly, among women ages 50 to 59 yr, excess risk attributed to MHT approximated one case per 1000 per 5 yr *vs.* 4.5 in the overall group with a mean age of 63 yr. Risk was not increased in nurses taking low-dose oral estrogen (0.3 mg Premarin), suggesting that risk might be dose dependent.

Diabetes and carbohydrate intolerance

Type 2 diabetes (T2D) risk increases at midlife in women. Likely associated factors include advancing age, increased total and central adiposity, and decreased physical activity. Decline in ovarian hormone levels at the time of menopause may play a role. However, this possibility has not yet been established, and existing literature is conflicting. Positive associations of endogenous estrogen concentration with diabetes and inverse associations with insulin sensitivity suggest an adverse effect of estrogen (40–43). Whether or not MHT can mitigate increased risk for T2D with age and menopause remains an open question. Data regarding MHT and T2D primarily relate to use of CEE and MPA because insufficient data are available regarding other types of MHT to draw conclusions.

Critical evaluation and insightful interpretation of the existing literature regarding T2D and MHT require several important considerations: 1) effects of MHT may be direct (*e.g.* on pancreas or skeletal muscle) or indirect (*e.g.* on reducing total or visceral fat accumulation) and may exert opposing actions on various tissues; 2) effects of MHT may differ from those of endogenous ovarian hormones; 3) discrepancies among studies may be due to population-specific or study-specific differences or to direct *vs.* indirect effects of MHT on diabetes risk; and 4) studies to date have not been designed specifically to address the role of MHT on diabetes prevention; thus, existing data, while informative, are less than optimal.

The WHI provides the most recent data from a large RCT (44) that addresses the issue of MHT and diabetes. This study indicated a lower rate of incident, self-reported, treated T2D among women randomized to the combined MHT arm (277 women; 0.61% annualized incidence) in comparison with the placebo group (324 women; 0.76% annualized incidence). These effects were independent of the slight reduction in BMI and waist circumference also noted in the MHT group. The protective effect of MHT on diabetes risk was less apparent among women with smaller waist circumferences ($P = 0.06$), suggesting that abdominally obese women may benefit more from MHT use, or that baseline metabolic status may influence response to MHT. This represented an absolute reduction of 7.5 cases per 1000 women per 5 yr of use and a relative reduction of 21%. Expressed differently, prevention of one new case of diabetes over 5 yr would require treating 133 women with MHT.

Among women who used estrogen without a progestogen, the protective effect of CEE on diabetes incidence was slightly attenuated, an outcome that may have been related to characteristics of the subject population (45). Data from the Heart and Estrogen/Progestin Replacement Study (HERS) (46) and the NHS (47) likewise revealed a slight but significant reduction in incidence of T2D in combined MHT users. One obvious mechanism through which MHT may reduce risk for T2D is by improving insulin sensitivity. However, existing studies using robust measures of insulin sensitivity have indicated the opposite. Two randomized, placebo-controlled clinical trials indicated that CEE plus MPA had an adverse effect on insulin sensitivity among normal-weight postmenopausal women (48). Similarly, cross-sectional data suggest an adverse effect of MHT on insulin sensitivity among women with relatively low visceral adiposity (49). The effect of MHT on insulin sensitivity among obese and/or viscerally obese women has not been documented using robust methodology in combination with sufficient sample size and duration of treatment. The effects of MHT on other outcomes related to diabetes risk (*e.g.* insulin secretion and clearance and glucose tolerance) are inconsistent and have been summarized in an excellent and comprehensive review (50). Endogenous estrogen, in contrast to MHT, is invariably associated with increased diabetes risk, an effect that may be due to the inverse association between endogenous estrogen and insulin sensitivity (40–43).

Taken together, data indicate that CEE with or without MPA may be associated with a slight decrease in the risk for T2D, independent of its effects on BMI. This protective effect is not via insulin sensitivity. Results may not be generalizable to other MHT preparations.

Change in body weight or BMI

Women perceive that initiation of MHT causes "weight gain." However, the majority of studies (but not all) suggest the opposite, that MHT users gain less weight or body fat than do nonusers.

Data compiled in 1999. A comprehensive review of randomized, placebo or no-treatment controlled trials published in 1999 concluded that "There is no evidence of an effect of estrogen alone or estrogen combined with a progestogen on body weight and on the BMI increase normally experienced at the time of menopause. Insufficient evidence currently exists to enable examination of the effect of MHT on waist-hip ratio, fat mass, or skin-fold thickness" (51). Interpreted from the perspective of 2010, several factors confounded interpretation of these earlier data. Large trials and meta-analyses may mask individual variability in response to MHT. "Weight" may not be the most appropriate term. Changes in the hormonal environment may cause shifts in body fat distribution or changes in the relative proportions of fat and nonfat mass gained or lost, changes that are not necessarily reflected in weight. Discrepancies among studies are likely due to differences in study populations, subject number, study design, and MHT preparations used. Small sample sizes combined with subject heterogeneity may exacerbate discordance among results. Because both age and proximity to menopause may affect energy balance, energy partitioning, and fat distribution, it is important that studies include appropriately matched control groups.

More recent studies. Results from numerous [but not all (52)] studies suggest that MHT is associated with lower adiposity (53–59) and a lesser central fat distribution (54, 59–66). In general, women in the early postmenopausal period gain fat mass and lose lean mass (52). Thus, effects of MHT require interpretation in the context of this changing baseline condition. Use of dual-energy x-ray absorptiometry (DXA) for assessing changes in total and regional body composition has become more common in recent years. However, this technique cannot distinguish water mass from other soft lean-tissue mass. Thus, it is not clear how to interpret lean-mass data reported in conjunction with hormone intervention studies, such as in the large WHI study, which showed a preservation of non-bone lean mass in MHT users (63). MHT may have beneficial effects on skeletal muscle mass and function (53), but data are limited and inconsistent (67). Although most studies suggest an adiposity-minimizing effect of MHT, therapy type may affect results. One crossover study noted greater fat gain with oral *vs.* transdermal estrogen (68), results that are supported by clinical data (69). Based on limited

TABLE 2. MHT and body composition/fat distribution

Method	Outcome (MHT effect *vs.* control)	Study design	MHT type	No. of subjects; mean age; mean BMI; country	Refs.
CT, BIA	Lower proportion thigh fat, greater proportion muscle; less fat infiltration of muscle; E users: lower % body fat	Cross-sectional; observational; twin pairs discordant for MHT use	Multiple; estrogen-containing; tibolone	n = 30; 57 yr; 25 kg/m^2; Finland	53
DXA	Less total and central fat in current estrogen users; effect on central fat independent of total fat	Cross-sectional; observational; twin pairs discordant for MHT use	Multiple; estrogen-containing	n = 712; 59 yr; 24 kg/m^2; United Kingdom	54
DXA	Oral E2: decrease in central fat; tibolone: preservation of lean; td E2: preservation of lean	Intervention over 2 yr	Oral E2+dydrogesterone; td E2; tibolone	n = 100; 52 yr; 24 kg/m^2; Switzerland	61
DXA	No change in abdominal fat % (*vs.* increase in controls)	Prospective, randomized, placebo-controlled over 2 yr	EV+CPA or LNG	n = 62; 45–55 yr; 24 kg/m^2; Denmark	62
DXA	Less lean loss; less trunk, leg fat gain	Prospective, randomized, placebo-controlled, over 3 yr (WHI)	CEE+MPA	n = 835; 63 yr; 28 kg/m^2; United States	63
DXA	Less fat gain; more pronounced in nonobese women	Intervention and observation over 5 yr	Trisequens; E2	n = 595; 50 yr; 24 kg/m^2; Denmark	55
DXA	No change (*vs.* increased total and % fat mass, decreased total lean in placebo)	Cross-over; 10 wk	E2+NETA	n = 16; 55 ± 3 yr; 27 ± 5 kg/m^2; Denmark	56
DXA	Lesser gain in total fat; greater gain in leg fat	Intervention over 36 months; calcium (used as equivalent to placebo)	EV+CPA	n = 31; 50 yr; 25 kg/m^2; Italy	57
DXA	Less increase in weight and fat mass	Intervention and observation over 5 yr	E2+NETA	n = 2016; 50 yr; 25 kg/m^2; Denmark	58
Weight, waist	Less increase in weight and waist circumference	Placebo-controlled intervention over 3 yr	CEE; CEE+MPA; CEE+progesterone	n = 875; 41%, 45–54 yr, and 59%, 55–65 yr; 26 kg/m^2; United States	64
DXA, CT	Less visceral fat	Observational; longitudinal over 2 yr	Multiple; mainly CEE+MPA	n = 50; 50 yr; 25 kg/m^2; United States	60
CT	Less visceral fat	Cross-sectional	Multiple	n = 45; 57 yr; 35 kg/m^2; United States	66
CT	Decrease in total and visceral fat	Prospective, randomized over 1 yr	EV+MPA	n = 51; 52 yr; 26–27 kg/m^2; Sweden	59
CT	No change in visceral fat (*vs.* increase in controls)	Prospective; over 1 yr	CEE+MPA	n = 61; 53 yr; 24 kg/m^2; Japan	65

CT, Computed tomography; BIA, bioimpedance analysis; CPA, cyproterone acetate; td, transdermal; E2, estradiol; EV, estradiol valerate; trisequens, triphasic hormone therapy with estradiol and norethisterone acetate.

data, it appears possible that some women respond uniquely to oral MHT with weight and fat gain, perhaps based on their metabolic condition (55, 69, 70). Although few studies have examined abdominal fat distribution, those that have reported on this measure indicated less visceral and intraabdominal fat in women using MHT (59, 60, 65, 66).

Table 2 summarizes results from large placebo-controlled intervention trials, studies using robust methodol-
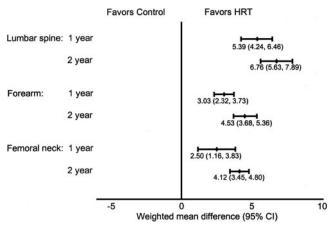
FIG. 1. Improvement in BMD with E+P therapy: a meta-analysis of 57 studies. The *bars and numbers* on the *right* indicate aspects that are improved by MHT. Illustrated on the bar is the mean of the RR (*middle portion of the bar*) with the CI limits indicated by the numbers at the *end of the bar*. None of the bars are on the left, which would indicate that the placebo was favored. Data from women receiving MHT or placebo for 1 or 2 yr are indicated. [Data were reproduced with permission from G. Wells *et al.*: *Endocr Rev* 23:529–539, 2002 (74).]

ogy to assess body composition and fat distribution, and other studies that provide unique insight into this question. Most of these studies have involved nonoverweight or nonobese subjects with an average BMI less than 30 kg/m^2 [*e.g.* Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, mean BMI, 26 ± 4.5 kg/m^2; WHI, mean BMI, ~28 ± 5 kg/m^2]. Thus, generalizations can be made only regarding women in these weight ranges.

Musculoskeletal

Osteoporosis and fractures

Early studies. Reifenstein and Albright (71) first commented on the association between declining estrogen levels at menopause and rapid bone loss, osteoporosis, and associated fragility fractures six decades ago. Many studies documented that E alone or E+P prevent menopausal bone loss when begun early in menopause. Independent studies in the 1970s by Lindsay and colleagues (72) and by Christiansen *et al.* (73) first quantified the effects of E+P on bone mass. Both studies concluded that early intervention, at the time of menopause, prevented accelerated bone loss. A delay of 3 to 4 yr also halted and, to some extent, reversed bone loss. Further delay also prevented bone loss but did not result in any restoration of bone mass.

Meta-analyses. A meta-analysis published in 2002 included 57 randomized, placebo-controlled trials of E+P in postmenopausal women (74). The trials were 1 yr or more in duration, and seven of them included fracture as an end-point. The studies were conducted and reported between 1977 and 1998, during which time there were substantial changes in the methods available for measurement of bone mineral density (BMD) and in the available preparations of estrogen with or without progestogens. Despite important shortcomings, these studies demonstrated that estrogen was significantly more effective than placebo in preserving and increasing BMD (Fig. 1). Subsequent studies have also demonstrated significant improvement in bone mass when estrogen therapy was started in late postmenopause (75). Importantly, the improvement was similar to that seen with alendronate. In addition, the combination of estrogen plus alendronate had an additive positive effect on bone mass (Fig. 2). Discontinuation of estrogen resulted in bone loss at a rate similar to that seen in early menopause (76, 77), but gains in bone mass induced by alendronate (with or without estrogen) were sustained for at least 1 yr after all therapy was discontinued (78). These data underscore the different mechanisms by which bisphosphonates and estrogen affect bone remodeling.

Fractures. As noted previously, the meta-analysis by Wells *et al.* (74) included several studies with fracture as an endpoint (in addition to changes in BMD). With one notable exception, there were fewer fractures in the women receiving estrogens, but in neither the individual studies nor the pooled data analysis did the reduction in fractures reach statistical significance (Fig. 3). Another meta-analysis, reporting exclusively on fracture by Torgerson and Bell-Syer (79), included 22 fracture trials, only two of which were published before 1990. Their analysis concluded that E+P significantly reduced nonvertebral fractures (RR, 0.73; CI, 0.56–0.94), but the effect was attenuated and not statistically significant in women older than age 60 yr. Limited data are available regarding dose-response effects. A recent study examined the doses of estrogen required and demonstrated that 17β-estradiol in amounts as low as 0.25 mg/d preserves bone mass (80). An important caveat associated with cessation of estrogen therapy was the observation from the National Osteoporosis Risk Assessment observational study (81), which reported rapid bone loss and 70% more hip fractures in women who had discontinued estrogen within the preceding 5 yr.

The HERS trial, restricted to nonhysterectomized women with known coronary artery disease, was larger and of longer duration than most of the studies included in the above meta-analyses, but it, too, failed to demonstrate a significant reduction in fractures with E+P (82). The WHI studies (CEE plus MPA in nonhysterectomized women or CEE alone in women with surgical menopause) (83, 84) were different from any of the earlier trials in two important respects—the study subjects were not specifically selected on the basis of a known history of osteoporosis (with or without prior fracture), and fracture was the
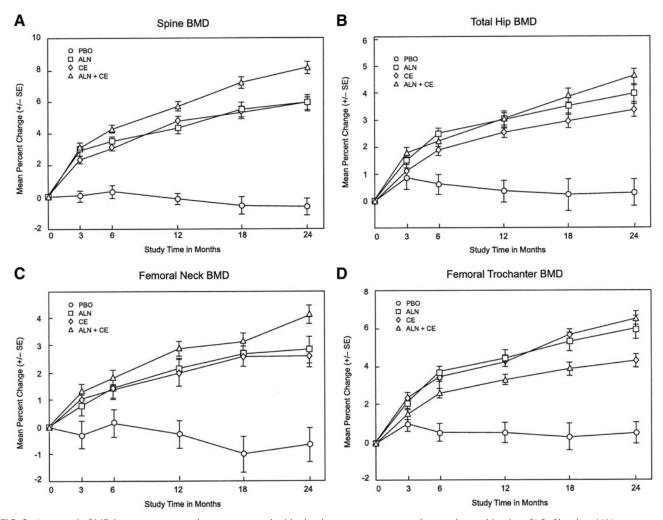
FIG. 2. Increase in BMD in postmenopausal women treated with alendronate or estrogen, alone or in combination. PLO, Placebo; ALN, alendronate; CE, conjugated estrogen. [Reproduced with permission from H. G. Bone *et al. J Clin Endocrinol Metab* 85:720–726, 2000 (75). © The Endocrine Society.]

primary (skeletal) outcome with only a subset of the women having BMD measured as part of the study. In the subset of women who had BMD tested during these studies, fewer than 10% had a hip T-score lower than −2.5. All fractures referred to hip, vertebral, and other osteoporotic fractures except those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae. The fracture data were reported both by decade of age and by decade after menopause (Table 3). In the CEE+MPA study, active therapy reduced all fractures significantly by 24% (RR, 0.76; CI, 0.69–0.83) and hip fractures by 33% (CI, 47–96). In the CEE-alone study, all fractures were reduced by 29% (RR, 0.71; CI, 0.45–0.94) and hip fractures by 29% (RR, 0.71; CI, 0.64–0.80). Not surprisingly, the effect of CEE plus MPA on hip fractures was only apparent in women older than age 70 yr or more than 20 yr after menopause, consistent with the epidemiological data concerning hip fracture. In the CEE-only arm, the effect on hip fractures was only significant in those women who were more than 20 yr after menopause. Regarding the effect of

therapy on all fractures in the CEE+MPA trial, a beneficial effect was seen in groups categorized by decade after menopause. The stratification by age in the publication was in 5-yr increments, and there was no apparent age effect on this outcome. In the CEE-only arm, in which the published data were by age decade, a significant antifracture effect was not demonstrated in women ages 50 to 59 yr. The numbers of women on CEE alone or CEE+MPA in the WHI trials can be expressed as number of women whose fractures were prevented over a 5-yr period of use. For CEE alone, this represents 27.1 women per 1000 per 5 yr, and for CEE+MPA, 21.8.

Degenerative arthritis

Progressive degradation of articular cartilage and the overall joint structure characterizes osteoarthritis and leads to joint stiffness, pain, disability, and loss in quality of life. Estrogen receptors (ERs) have been identified in articular chondrocytes in animals and humans, and estrogen can elicit genomic and nongenomic effects on the regulation of carti-
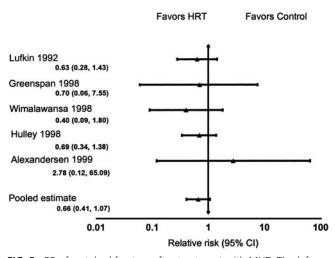
FIG. 3. RR of vertebral fracture after treatment with MHT. The *left side of the vertical bar* indicates that the therapy favors MHT. The *right side* represents data favoring controls. The *horizontal bars* represent the mean (middle portion of bar), and the ends of each bar represent the CIs. The studies included are Lufkin, Greenespan, Winalawansa, Alexandersen, and a pooled estimate. [Data were reproduced from G. Wells *et al.*: *Endocr Rev* 23:529–539, 2002 (74). © The Endocrine Society.]

lage metabolism (85, 86). The effects of estrogen administration on the development and severity of osteoarthritis remain controversial, despite multiple epidemiological, clinical, and experimental studies (87–90). The evaluation of this possible relationship might take into account not only the aging process, individual susceptibility, and SNPs but also methodological issues, such as heterogeneity in measurements, population evaluated, and age at menopause as well as the types and doses used and timing of initiation of hormones after menopause. These factors may partially explain inconsistencies among reported studies.

After menopause, the reduction in estrogen levels is associated with rapid changes in intervertebral discs that can be considered an *in vivo* measurable marker of fibrocartilage condition (91–93). These changes occur almost entirely in the first 5 yr after menopause (92). Early hormone initiation can avoid the deleterious effects of estrogen deprivation on intervertebral discs (91, 94). At present, there is evidence of a protective effect of estrogen alone on osteoarthritis. The WHI demonstrated that the women treated with CEE alone had significantly lower rates (RR, 0.84; CI, 0.70–1.00; $P = 0.05$) of arthroplasty than those in the placebo group (93). Considering only adherent women, the protective effect of estrogen was strengthened: RR became 0.73 (CI, 0.58–0.93). However, these benefits on arthroplasty were not evident in the WHI CEE+MPA arm (RR, 0.99; CI, 0.82–1.20; $P = 0.92$), suggesting that continuous combined progestogen administration might counteract the beneficial effects of estrogen (93). Censoring for adherence had little effect on estimates or significance in the E+P trial. Thus, progestogens seem to neutralize the chondropro-

tective actions of estrogen. Further studies are needed on the possible role of different progestogen type, doses, and routes of administration.

Cancer

Effect of MHT on breast tissue and breast cancer
Mammographic density. Percentage mammographic density (PMD) is a strong risk factor for breast cancer and is influenced by some forms of MHT that also influence risk of breast cancer. In Table 4, the results of RCTs on the effects of hormonal therapies on PMD assessed using quantitative methods are summarized. Freedman *et al.* (95) showed that E alone increased PMD slightly, but statistically significantly (1.2%), over 1 yr compared with a reduction with placebo (1.3%). Greendale *et al.* (96) reported that administration of E alone for 2 yr resulted in a nonsignificant increase in PMD. In contrast, E+P increased PMD by about 3 to 5%, a change that was significantly different from placebo and E-alone use. Mc-Tiernan *et al.* (97) reported similar findings for combined MHT in the WHI study. A testosterone patch did not increase PMD compared with placebo in women receiving combined MHT (98). Tibolone, a form of hormone replacement, did not increase PMD, whereas combined MHT resulted in a significant increase in PMD (99). Observational studies have shown that combined MHT use may have a greater effect on PMD than E alone (100, 101).

Intervention studies have shown that administration of tamoxifen substantially reduces PMD (102, 103). In the International Breast Cancer Intervention Study (IBIS) of tamoxifen for the prevention of breast cancer, Cuzick *et al.* (102) showed that PMD was reduced by 13.7% in the tamoxifen arm compared with 7.3% in the placebo arm over 4.5 yr. Data from the same trial recently reported in abstract form (104) that a decrease in PMD was significantly associated with the reduction in breast cancer risk in the women taking tamoxifen. For women who experienced a reduction of 10% or greater in PMD, the risk of breast cancer was reduced by 52% relative to the control group ($P = 0.01$), whereas for women who experienced a reduction of less than 10% in PMD, there was only a nonsignificant 8% reduction in breast cancer risk.

Combined MHT but not E alone appears to increase both risk of breast cancer and PMD, a risk factor for the disease that reflects stroma and epithelium in the breast. The effect of combined MHT on PMD is modest, with a reported 5% average increase in PMD after 1 yr of therapy. It is, however, unclear whether the effects of MHT and tamoxifen on breast cancer risk are causally mediated by their effect on PMD.

TABLE 3.   Antifracture effects of estrogen by age and time since menopause

	E+P			
	E+P	**PBO**	**RR (CI)**	**Duration of follow-up (yr)**
No. of subjects	8506	8102		5.6
No. with fracture (%)[a,b]	733 (1.52)	896 (1.99)	0.76 (0.69–0.83)	
Years since menopause				
<10	187 (1.17)	221 (1.44)	0.80 (0.66–0.98)	
10–19	255 (1.55)	327 (2.03)	0.75 (0.64–0.89)	
≥20	200 (2.03)	257 (2.69)	0.74 (0.61–0.89)	
No. with hip fracture (%)	52 (0.11)	73 (0.16)	0.67 (0.47–0.96)	

PBO, Placebo.

[a] Fractures refer to hip, vertebral, and other osteoporotic fractures except those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae.

[b] Annualized percent shown in parentheses.

Effects of E alone on breast cancer risk. **Pre-WHI studies.** Until the late 1980s, postmenopausal women with a uterus received E alone as MHT. After the relationship between E alone and uterine cancer became generally accepted, a progestogen was added to the regimen to prevent uterine cancer. For this reason, substantial epidemiological data before the mid-1980s are available regarding E alone and breast cancer. A collaborative meta-analysis published in 1997 (105) pooled data from 51 studies involving 67,370 women and examined the role of MHT on breast cancer risk. In the 4460 women in whom data on the hormonal constituents of the treatment used were available, 80% had received E alone, and 12% had received combinations of E+P. Thus, the data largely represent the use of E alone.

Risk increased linearly by 2.3% per year (RR, 1.023; CI, 1.011–1.036 per year) (105). Notably, this per-year increase paralleled that observed for each year of delay of menopause [2.8% per year (RR, 1.028; CI, 1.021–1.034)]. When limiting data to the subgroup receiving only estrogens (*i.e.* omitting the 12% receiving E+P), no increase in risk occurred for use less than 5 yr (RR, 0.99 ± 0.08 SEM), but with use for more than 5 yr, RR increased to 1.34 ± 0.09. By years of use in all patients, RR was 1.31 ± 0.079 for 5 to 9.9 yr, 1.24 ± 0.18 for 10 to 14.9 yr, and 1.56 ± 0.145 for more than 15 yr.

Increased risk was confined to thin women (BMI < 25 kg/m^2, RR, 1.52 ± 0.83; and BMI > 25 kg/m^2, RR, 1.02 ± 0.107) (105). The linear increase in risk per year was also confined to thin women with a 3% increase (CI, 0.01–0.06) per year *vs.* −0.01% (CI, −0.02 to 0.10) in women with a BMI of more than 24.4 kg/m^2 (105, 106). Risk largely dissipated 5 yr after stopping therapy with a RR of 1.10 ± 0.063 at 1 to 4 yr after cessation and 1.01 ± 0.068 at 5 to 9 yr (105). Furthermore, no apparent differences in risk were observed among the various dosages or types of estrogen (105).

Recent cohort studies. Eleven cohort studies published later (Table 5) generally confirmed the collaborative pooled analysis (106–117). Five of nine studies reporting overall risk (not taking into account duration) found statistically significant increments in women using E alone *vs.* nonusers (108, 112, 114–118). With longer duration of use, more consistent increases in risk were reported, as best exemplified by the NHS (109), Lyytinen *et al.* (110), Epic (113), and Million Women Study (MWS) studies (112). A comprehensive meta-analysis including all prior studies from 1989–2004 reported overall RRs of 1.27 (CI, 1.19–1.35) and a 3.1% increase per year of use [RR, 1.031 (CI, 1.23–1.039)] (107). Available data are insufficient to indicate differences in risk related to dose or type of estrogen (105, 110, 112).

Further analysis indicated that E alone was associated with nonstatistically significant trends toward higher breast cancer risk in those with a higher Gail model risk score (RR, 1.28; CI, 0.83–1.97) (119), benign breast disease with one (RR, 1.60; CI, 0.82–3.14) or two biopsies (RR, 2.54; CI, 0.73–8.66) (119), and those with a first-degree relative with breast cancer (RR, 1.75; CI, 0.95–3.22) (119).

Because risk increases linearly with time, the minimal duration of use associated with an increase in breast cancer is difficult to define precisely. Evaluation of data in Table 5 suggests that use for less than 5 yr would be without substantial risk, but a statistically significant increase in risk is likely with use for more than 5 yr. These cohort studies also confirmed the duration-BMI association reported previously (105). As best exemplified in the NHS, RRs for thin women increased to a greater extent than those for obese women (Fig. 4).

Recent RCTs. Although four RCTs [WHI, WEST (Women's Estrogen for Stroke Trial), ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial), and EPAT (Estrogen in the Prevention of Atherosclerosis Trial)] have been reported, the WHI trial represents the largest and, therefore, most heavily weighted

E alone				
E	**PBO**	**RR (CI)**	**Duration of follow-up (yr)**	**Refs.**
5310	5429		7.1	83, 84
540 (1.44)	761 (1.97)	0.71 (0.64–0.80)		83, 84
5 (0.08)	1 (0.02)	5.38 (0.61–47.37		83, 84
9 (0.09)	10 (0.09)	0.91 (0.37–2.25)		83, 84
24 (0.16)	48 (0.30)	0.52 (0.32–0.86)		83, 84
46 (0.12)	73 (0.19)	0.65 (0.45–0.94)		83, 84

(108, 119). Data pooled from the four RCTs reported a RR of 0.79 (CI, 0.61–1.01), which approached statistical significance and represented a paradoxical reduction in breast cancer risk (120). In a *post hoc* WHI analysis, statistically significant reductions were reported in women actually taking study medications per protocol [sensitivity analysis (RR, 0.67; CI, 0.47–0.97)], in those with localized cancer (RR, 0.69; CI, 0.51–0.95), and in those with ductal tumors (RR, 0.71; CI, 0.52–0.99) (119).

The reduced risk of breast cancer in the WHI E-alone RCT appeared initially to represent an "outlier finding" because earlier studies had reported an increase in risk. The outlier hypothesis was strengthened by findings in the WHI observational arm (17,437 subjects), which reported an increased risk of breast cancer with the use of E alone reported in a similar group of patients (RR, 1.28) (108). A plausible explanation for this discrepancy is the "gap time," the duration between onset of menopause and start of MHT [short gap time is 5 yr or less, whereas long gap time is more than 5 yr]. Prentice *et al.* (108) reanalyzed the WHI-RCT and WHI-observational data and provided evidence (reviewed below) that gap time provided the major reason for the discrepancy among studies.

Gap time. Starting E alone more than 5 yr after onset of menopause (long gap time) was associated with a significant reduction in breast cancer risk (RR, 0.58; CI, 0.36–0.93), whereas starting immediately after menopause (short gap time) was not (RR, 1.12; CI, 0.39–3.21) in patients who had not received prior MHT (108). This advantageous effect of a long *vs.* short gap time was observed in groups with each duration interval of estrogen use (*e.g.* <2 yr of use, RR 0.70 *vs.* 1.28; 2–5 yr of use, RR 0.68 *vs.* 1.53; and >5 yr of use, RR 0.79 *vs.* 0.97) (108). In the WHI RCT, prior use of estrogens with a washout period upon study entry mimicked the effects of a short gap time (119). These women experienced no reduction of breast cancer risk (RR, 1.02; CI, 0.70–1.50), whereas patients with no prior use of MHT did (RR, 0.58; CI, 0.36–0.93) (108). Regarding the discrepancy between the WHI RCT and observational study findings, it should be noted that the gap time in the WHI observational study was

very short on average in contrast to the long gap time in the WHI RCT (108). Prentice *et al.* (108) reconciled the WHI RCT and observational study findings based on two factors. Adjusting for mammographic screening patterns reduced the discrepancy between studies to 43%, and further correction for gap time narrowed the difference to only 7%.

The French E3N observational study (433,647 person-years of follow-up) provides additional support for the importance of gap time. This study involved many more women starting MHT at the time of menopause, *i.e.* short gap time (121). In this study, both the E alone and E+P groups with a short gap time experienced a greater increase in risk of breast cancer than those with a long gap time.

Other data supporting beneficial effects of estrogens. Whereas the paradoxical findings from the WHI RCT on the beneficial effects on breast cancer risk were surprising, careful study of other reports uncovered trends that would support the WHI RCT results. As shown on Table 5 and in references 122 and 123, seven other studies reported trends toward breast cancer reduction in subsets of women receiving E alone (109–112, 116, 122, 123). Based on these findings, it is clear that prospective studies of the role of gap time are needed.

Effects of estradiol on type of breast cancer. A summary of four studies found that the RR of ER-positive tumors was 1.14 (CI, 0.95–1.37), and the RR of ER-negative tumors was 0.92 (CI, 0.71–1.19) in women using E alone ($P = 0.06$) (120). A meta-analysis of 11 studies reported that E alone is associated with a greater increase in lobular tumors (RR, 1.42; CI, 1.27–1.57) than in ductal tumors (RR, 1.10; CI, 1.05–1.15) (124). The WHI reported larger tumors (1.8 *vs.* 1.5 cm) and greater node positivity (35.5 *vs.* 23.3%) in the women receiving E alone, contrary to the findings of the collaborative reanalysis (105). No consistent systematic data are available to determine whether tumor aggressiveness or long-term outcome is affected (120).

Possible mechanisms to explain findings. One potential explanation of the possible reduction in breast cancer risk in long gap time patients is estrogen-induced apoptosis. Breast cancer cells deprived of estrogen long term in cell

TABLE 4.   Summary of effects of hormonal interventions on quantitative measures of mammographic density from randomized trials

First author, publication year (Ref.)	Intervention	Subjects	Mean change in PMD[a]	Duration
Freedman, 2001 (95)	Estrogen	36	+1.2% (*P* < 0.01)	2 yr
	Raloxifene (60 mg)	45	−1.5%	
	Raloxifene (150 mg)	42	−1.7%	
	Placebo	45	−1.3%	
Greendale, 2003 (96)	CEE	99	+1.2% (*P* = 0.24)	1 yr
	CEE+progestogen[b]	306	+3–5% (*P* = 0.002 to < 0.001)	
	Placebo	93	−0.1%	
McTiernan, 2005 (97)	CEE+progestogen	202	+4.9%	2 yr
	Placebo	211	−0.8% (*P* < 0.001)	
Hofling, 2007 (98)	Testosterone patch[c]	46	+5.4%	6 months
	Placebo patch	41	+7.4% (ns)	
Eilertsen, 2008 (99)	Tibolone	47	+0.8 (*P* < 0.01)[d]	12 wk
	Raloxifene	49	+0.4 (*P* < 0.001)	
	Estrogen+NETA, usual dose	49	+2.3 (ns)	
	Estrogen+NETA, low dose	48	+2.6	
Vachon, 2002 (101)	Letrozole	35	−0.3	1 yr
	Placebo	33	−1.0 (*P* = 0.58)	
Brisson, 2000 (103)	Tamoxifen	36	−9.4%	3.3 yr
	Placebo	33	−3.6% (*P* = 0.01)	
Cuzick, 2009 (104)	Tamoxifen	388	−13.7%	4.5 yr
	Placebo	430	−7.3% (*P* < 0.001)	

ns, Nonsignificant.

[a] Measured using a computer-assisted method, except for Brisson and Cuzick, which used visual estimation of percentage density. *P* value is for comparison between treatment and placebo, except for Freedman, in which *P* value is for comparison of estrogen with all other groups, and for Eilertsen, in which *P* values are for comparison of each group with low-dose estrogen+NETA. Change in PMD shown is adjusted for covariates where available.

[b] Three types of progestogen treatment were tested: cyclic MPA, continuous MPA, and micronized progesterone. Results were similar and are combined for the table.

[c] Subjects in both groups received continuous oral estrogen+NETA.

[d] Results shown are for difference in mean PMD between baseline and follow-up, but *P* values refer to comparison of median percentage change in PMD.

culture (analogous to a long gap time) (125–128) adapt and become sensitized to the proapoptotic effects of estradiol. In women, this paradoxical proapoptotic effect could shrink the size of occult preexisting tumors (see *Reservoir of occult or undiagnosed breast cancer*) and reduce the rate of clinical cancer detection later.

Why might a long duration of estrogen exposure enhance breast cancer risk? Two mechanisms alone or in combination have been suggested. One is that estrogens stimulate cell proliferation and thereby increase the number of DNA replicative errors (mutations or SNPs) and promote their propagation (129). Over a long period, a sufficient number of mutations could be present to transform benign cells into cancer. Another is that estradiol can be metabolized to directly genotoxic derivatives or can induce mutations through oxidative damage resulting from redox cycling, a process requiring long-term exposure to produce detrimental effects (130). Although plausible, these various mechanisms require further study and a greater degree of evidence and should be considered speculative at present.

Conclusions. Existing data suggest no increased risk of breast cancer (and likely a reduction in risk) when E alone is used for less than 5 yr in women starting MHT several

years after onset of menopause (*i.e.* long gap time). Those with a short gap time experience a 3% increase in RR of breast cancer per year of use (107, 108). From SEER (Surveillance, Epidemiology and End Results) data, a woman between ages 50 and 54 yr has a 13.0 per 1000 chance of developing breast cancer over 5 yr. Therefore, in women starting estrogen within 5 yr of menopause (*i.e.* short gap time), attributable risk would represent 2.59 per 1000 per 5 yr (if the WHI RCT is used for calculations) (108), a relatively small excess risk.

Effects of E+P on breast cancer risk. **Pre-WHI studies.** As noted for E alone, the major database before the WHI was the collaborative reanalysis published in 1997 (105). Only 12% of women used combined preparations, making conclusions regarding combined therapy unreliable. RR for E+P or progestogens alone was 1.15 (CI, 0.78–1.52) for less than 5 yr of use and 1.53 (CI, 0.88–2.18) for 5 yr or more. The numbers were too small to derive definitive data in the latter group with only 58 cancers and 86 controls. A qualitative review (131) later included articles accessed from Medline and Dialog-web published from 1975 to 2000. The authors concluded that, "The evidence did not support

the hypotheses that estrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more than estrogen alone." This review focused largely on differences between "ever use" and "never use." Because the risk of breast cancer returns to baseline within 4 to 5 yr of discontinuation and duration of use was not accounted for, the ever-use exposure would tend to mask associations observed among current users only. Because of this and the potential of other confounding factors to influence the results, heterogeneity of the data would be expected and was, indeed, present.

The WHI RCT. In July 2002, the first results of the WHI RCT of continuous or combined MHT with CEE 0.625 mg and MPA 2.5 mg daily were published. The overall RR for breast cancer was 1.26 (CI, 1.00–1.59), later revised to 1.24 (CI, 1.01–1.54) (132). Absolute excess (attributable) risks per 1000 women taking combined MHT for 5 yr were 4 per 1000. Among the women randomized in the age range of 50 to 79 yr, 76% were women who had never used MHT ("non-prior users"). In them, the RR was 1.09 (CI, 0.86–1.39), indicating no significant increase in risk after a mean of 5.2 yr of follow-up. Women enrolled in the trial were not representative of the symptomatic perimenopausal women for whom MHT is generally prescribed. Only 574 [of a total of 16,608 (3.5%)] were women in the 50- to 54-yr age group, with moderate to severe symptoms, typical of women normally presenting for consideration of MHT. Thus, the overall results are not applicable to women in the 50- to 55-yr-old usual target age group, who tend to start their treatment soon after menopause if not perimenopausally. By the end of the trial, 42% of the combined-hormone users had stopped taking study drugs, as had 38% of the placebo group, an element reducing the power of the study as a true randomized trial.

A further analysis of the data was published in 2006 (133), providing adjusted RRs of 1.85 (CI, 1.18–2.90) for the prior users (n = 4,311) and 1.09 (CI, 0.86–1.39) among 12,297 non-prior users. For non-prior users, annualized percentage incidence rates were 0.40 and 0.36% per year for E+P and placebo, respectively, whereas for prior users the rates were 0.46 and 0.25%. It should be noted that these were unadjusted rates, and women with prior use were younger and leaner. These data suggested that the increased RR may be attributable largely to the lower incidence rates in women assigned to placebo, who were technically discontinuers of MHT, being prior-users now assigned to placebo. In these women, previously elevated risks resulting from long-term therapy would have returned to baseline within 3 to 4 yr of stopping. This return to baseline was seen in that group, whose rate remained the same as the active group for 3 yr and then began to fall. Among the non-prior users, the Kaplan-Meier curves indicated that the breast cancer risk was actually lower for the first 4 yr of therapy, after which the lines crossed, and risk among the active treatment group was then higher than in the placebo group. As discussed below, observational data also suggest that the risk may increase after 3 to 5 yr of combined therapy.

The overall applicability of the WHI results to estimation of the risks of breast cancer associated with MHT for all women is questionable, with the important (and potentially misleading) finding that risk was not increased in non-prior users after an average of 5.2 yr of follow-up.

Another analysis of the data was published in 2008 (134), as noted above, in which the effect of time from menopause to first use of MHT (gap time) was explored both for the RCT and for the WHI observational study. This further underlined the lack of applicability of the RCT findings to women who usually use MHT. Only 17% (n = 952) of women in the RCT commenced MHT within 5 yr of final menses, and 22 breast cancers were observed, giving a RR of 1.77 (CI, 1.07–2.93) for gap times of less than 5 yr. In contrast, the RR was 0.99 (CI, 0.74–1.31) for gap times of 5 or more years according to data based on 92 breast cancers in a total of 4498 women with gap times of 5 yr to more than 15 yr. The above considerations seriously undermine the use of the RCT data to make valid estimates of risk in the applicable group of women (*i.e.* recently menopausal women who were not prior users). It should be noted, however, that the RR of 1.77 in the women with a gap of less than 5 yr suggests the possibility that the risk with E+P is actually higher than initially reported in the WHI (*i.e.* 1.26).

Post-WHI studies. A comprehensive review of existing evidence regarding E+P and breast cancer risk was published in 2005 by Collins *et al.* (120) (Table 6).[14] Data from four randomized trials (including WHI) and 18 epidemiological studies published subsequent to the collaborative reanalysis were included (105). Age ranges varied from 20 to 79 yr and duration of follow-up from 2.6 to 10.2 yr. For 248 cases from the RCTs, the largest of which was the WHI study described above, the RR was 1.24 (CI, 1.03–1.50) with a higher estimate for adherent women (RR, 1.49; CI, 1.13–1.96). The number of cancers was regarded as too small to provide a precise estimate of risk. From the epidemiological studies, which largely include women who started MHT for symptoms close to the time of menopause, the RR for current use (3455 cases) was 1.70 (CI, 1.36–2.13), comparable to Prentice's finding in the women with a gap time of less than 5 yr. Past use was not associated with increased risk. In terms of absolute risks, assuming a population incidence for Western coun-

TABLE 5. RR of breast cancer in users of estrogen in comparison with nonusers

Study name	Type	No. of subjects	Av age	Av/median BMI	RR Overall	RR <2 yr	RR >2 yr, <5 yr
WHI	RCT	10,739	63	NA	0.80 (0.62–1.04)	NA	NA
WHI, observational and RCT combined	Cohort[a]	10,658	64	30.1	NA	1.24 (0.57–2.68)	0.72 (0.42–1.24)
WHI, observational and RCT combined	Cohort[a]	15,790	64	30.1	NA	0.72 (0.30–1.70)	0.75 (0.46–1.21)
WHI, observational and RCT	Cohort	10,658	64	30.1	NA	1.63 (0.68–3.91)	0.82 (0.42–1.57)
WHI, observational and RCT	Cohort	15,790	64	30.1	NA	1.44 (0.54–3.84)	1.15 (0.57–2.32)
NHS	Cohort	16,041	59.3	25	NA	NA	0.96 (0.75–1.22)
Lyytinen	Cohort	110,984	60	NA	NA	NA	0.93 (0.73–1.12)
Kerlikowske	Cohort	292,876	60	NA	NA	NA	0.86 (0.71–1.03)
MWS	Cohort	508,140	60	NA	1.30 (1.22–1.38)	0.81 (0.55–1.20)	1.25 (1.10–1.41)
EPIC-E3N	Cohort	42,148	53	22.5	1.29 (1.02–1.65)	1.26 (0.83–1.89)	1.13 (0.70–1.81)
Multi-Ethnic	Cohort	43,472	61	25	1.10 (1.05–0.16)	NA	NA
NIH-AARP	Cohort	124,687	62.6	25	1.15 (1.04–1.27)	NA	1.16 (1.02–1.33)
Mission	Cohort	2,355	62	24.5	0.40	NA	NA
Calle	Cohort	41,094	63	25.8	0.99 (0.87–1.12)	NA	0.91 (0.68–1.21)
Schairer	Cohort	36,806	58	NA	1.10 (1.00–1.30)		
EPAT	RCT	199	61	29	Too small	NA	NA
WEST	RCT	664	72	28	1.00 (0.3–3.5)	NA	NA
ESPRIT	RCT	1,017	63	NA	0.98 (0.25–3.91)	NA	NA
Reeves	Meta-analysis	NA	NA	NA	1.27 (1.19–1.35)	NA	NA
Greiser	Meta-analysis	NA	NA	NA	NA	NA	NA
Collins	Meta-analysis	NA	NA	NA	0.79 (0.61–1.01)	NA	NA

NA, Not available; Av, average; EPIC, Evaluation of 7E3 for the Prevention of Ischemic Complications; EPAC, Estrogen in the Prevention of Atherosclerosis Trial.

tries of approximately 300 per 100,000 per year (135), the excess cases with a RR of 1.70 would be approximately 10.5 per 1000 women over 5 yr. From the RCTs, the excess cases would be about 5 per 1000 per 5 yr, and from the epidemiological studies 10 per 1000 per 5 yr. A precise estimate of risk by duration of current use varies among studies, but risk appears to increase as a function of duration of use (Table 6).

Several epidemiological studies published since the Collins review have confirmed its estimates of risk with E+P (Table 6). For example, Lyytinen *et al.* (136) reported a RR of 1.31 (CI, 1.20–1.42) for users of E+P with estradiol as the estrogen for 3 to 5 yr, rising to 2.07 (CI, 1.84–2.30) with 10 or more years of use. Risks with norethindrone acetate (NETA) as the progestogen (RR, 2.03; CI, 1.88–2.18) were higher than for MPA (RR, 1.64; CI, 1.49–1.70) used for more than 5 yr. Calle *et al.* (117) reported similar results, indicating that, particularly for lobular histology, risk began to increase within 3 yr of initiation, although lobular tumors represent only about 20% of breast cancers. Whether the risk varies with the type of progestogen has also been questioned recently by Fournier *et al.* (118), who reported differences between micronized progesterone and dydrogesterone. Over a mean follow-up period of 8.1 yr, 2,354 cases of invasive breast cancer were observed among 59,216 French postmenopausal women. RR was 1.08 (CI, 0.89–1.31) for estradiol combined with micronized progesterone and 1.18 (CI, 0.95–1.48; not significant) for estrogen and dydrogesterone (as confirmed in the Lyytinen study) (136).

This contrasted with a RR of 1.69 (CI, 1.50–1.91) for other synthetic progestogens, similar to the risks reported in other epidemiological studies. Risk with dydrogesterone was also not statistically significantly increased after 3 to 5 yr (RR, 1.22; CI, 0.83–1.72) or after 5 yr (RR, 1.13; CI, 0.49–2.22) in another study, although numbers in the latter group were very small (136).

It should be noted that risks reported from the majority of European studies are somewhat higher than those from U.S. studies, one explanation being the average lower BMI of European women. Data from the MWS suggested that risk was higher in women whose BMI was less than 25 kg/m^2 (RR, 2.31; CI, 2.12–2.53) than in women with a BMI of more than 25 kg/m^2 (RR, 1.78; CI, 1.64–1.94) (112). Other considerations might be the preponderance of estradiol use in Europe rather than conjugated estrogens. For example, in Scandinavian countries, doses of 2 and 4 mg of estradiol are commonly used in continuous combined regimens containing synthetic progestogen. In addition, the progestogen commonly used is norethisterone, which could have a different impact on the breast than MPA. Lifestyle variables, such as more liberal alcohol consumption, might be another contributory factor.

In nearly all studies to date (Table 6), the risk of breast cancer in women receiving E+P has been higher than in those receiving E alone, suggesting a direct role for progestogens (in addition to estrogen) in breast cancer development. The likely mechanistic explanation is that pro-

	RR					
5–9.9 yr	10–14.9 yr	>15 yr	>20 yr	Subset	Comments	Refs.
NA	NA	NA		WHI	Invasive breast cancer only	119
>5 yr, 0.83 (0.52–1.35)	NA	NA	NA	Prior MHT	Overall RR 1.02; (0.70–1.50) in RCT	108, 119
>5 yr, 0.71 (0.45–1.12)	NA	NA	NA	No prior MHT	Overall RR 0.65; (0.46–0.92) in RCT	108, 119
>5 yr, 0.91 (0.49–1.69)	NA	NA	NA	Prior MHT 0 gap time		108
>5 yr, 1.00 (0.54–1.84)	NA	NA	NA	No Prior MHT 0 Gap time		108
0.90 (0.73–1.12)	1.06 (0.87–1.3)	1.18 (0.95–1.48)	1.42 (1.13–1.77)		Current	109
>5 yr, 1.44 (1.29–1.59)	NA	NA	NA		Not stated; all were hormone naive	110
>5 yr, 0.92 (0.84–1.00)	NA	NA	NA		Current	111
1.32 (1.20–1.46)	>10 yr, 1.37 (1.22–1.54)	NA	NA	RR <2 yr is <1 yr	Current	112
>6 yr, 1.32 (0.76–2.28)	NA	NA	NA	2–4 yr, 1.13 (0.70–1.81); 4–6 yr, 1.50 (0.88–2.56)	Majority current users; some past users	113, 118
NA	NA	NA	NA		Current	114
1.09 (0.90–1.31)	1.16 (1.02–1.31)	1.25 (1.01–1.55)	1.16 (0.98–1.37)		Current and past users	115
NA	NA	NA	NA		Current and past	116
1.18 (0.99–1.49)	0.94 (0.78–1.12)	NA	0.97 (0.78–1.2)	Ductal only	Current	117
1.00 (0.8–6.3) < 8 yr	0.94 (0.78–1.12); 8–16 yr	1.6 (1.2–2.2)	NA		Current and past	106
NA	NA	NA	NA			509
NA	NA	NA	NA			36
NA	NA	NA	NA			510
NA	NA	NA	NA			124
NA	NA	NA	NA	1.031 (1.023–1.039) per yr		107
NA	NA	NA	NA	RCTs only		120

[a] This study combines the WHI RCT with the WHI observational study and analyzes subgroups into those receiving prior hormonal therapy and those who did not.

gestogens are mitogens. A general theory of carcinogenesis holds that agents that increase the rate of cell proliferation enhance the development of new mutations (129, 137). Whether progestogens are mitogens or antimitogens has represented a major area of prior controversy (138). Reports of experiments involving benign and malignant breast cells in two- and three-dimensional culture *in vitro*, in rats and mice *in vivo*, and with progesterone knockout studies have been conflicting (139–153). In cultured breast cancer cells, acute progestogen exposure stimulates proliferation for one to two cell cycles but then inhibits DNA synthesis (154). Certain progestogens stimulate proliferation and others inhibit cell growth (149). It is important to note, however, that *in vivo* studies on normal human breast tissue strongly support a mitogenic effect of progestogens. Proliferation is greatest during the luteal phase of the menstrual cycle, a time when progesterone is at its highest level (155, 156). Exogenous E+P stimulates terminal duct lobular units (thought to be the site of cancer initiation) to a greater extent than E alone (157). Breast density increases to a greater extent with E+P than with E alone (100, 158, 159). Three-dimensional cultures of normal human breast tissue respond to progestogens with increased proliferation (150). This promitotic effect of progestogens in women may serve as one mechanism to explain the increased risk of breast cancer, when comparing E alone and E+P (160–162). Another mechanism has been the subject of a recent hypothesis. Progestogens can reactivate cancer stem cells, a mechanism that might ex-

plain a rapid increase in breast cancer diagnosis in women with occult, undiagnosed breast cancer (162).

Effects of estrogen plus testosterone on breast cancer risk. Physiological data regarding androgen effects on the breast and epidemiological data relating to breast cancer risk with E+T lead to conflicting conclusions. In a
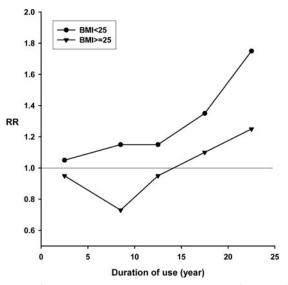

FIG. 4. RR of breast cancer as observed in the NHS as a function of BMI. One line represents women with a BMI of less than 25 kg/m² and the other, 25 kg/m² or greater. Each point on the line represents the mean RR of breast cancer for women taking E alone as MHT for 2 yr to more than 20 yr. Figure was constructed from the data reported in the study of Chen *et al.* (109).

TABLE 6. RR of breast cancer in users of E+P in comparison with nonusers

Study name	Type	No. of subjects	Av age (yr)	Av/ median BMI	RR Overall	RR <2 yr	RR >2 yr, <5 yr
WHI	RCT	16,608	63[a]	28.5	1.26 (1.00–1.59)	NA	NA
WHI	RCT, subset analysis	4311	63.0	27.8	1.85 (1.18–2.90)	1.10 (0.47–2.61)	NA
WHI	RCT, subset analysis	12,297	63.5	28.7	1.09 (0.86–1.39)	0.65 (0.34–1.25)	NA
WHI, observational and RCT combined	Cohort, subset analysis[b]	11,017	64	30.1	NA	1.28 (0.66–2.51)	2.56 (1.54–4.24)
WHI, observational and RCT combined	Cohort subset analysis[b]	37,675	63	30.1	NA	0.98 (0.56–1.72)	2.01 (1.41–2.86)
NHS	Cohort	4,177	61.7	25[a]	1.41 (1.15–1.74)	NA	NA
Lyytinen	Cohort	136,213	<60	NA	1.31 (1.20–1.42)	1.05 (0.97–1.11)	1.31 (1.20–1.42)
Kerlikowske	Cohort	295,249	~60	NA	1.39 (1.31–1.47)	NA	0.85 (0.73–0.98)
MWS	Cohort	142,870	56	NA	2.00 (1.88–2.12)	NA	1.74 (1.60–1.89)
EPIC-E3N	Cohort	96,900	53	22.5[a]	1.69 (1.50–1.91)	1.36 (1.07–1.72)	1.59 (1.30–1.94)
Multi-ethnic	Cohort	55,371	61	25[a]	1.29 (1.23–1.35)	NA	1.62 (1.38–1.90)
NIH-AARP	Cohort	73,986	62.6	25[a]	1.82 (1.65–2.01)	NA	1.39 (1.22–1.59)
Mission	Cohort	5967	61	24	1.34	NA	NA
Calle	Cohort	4,194	61	25	1.75 (1.53–2.01)	NA	1.49 (1.21–1.82)
Schairer	Cohort	20,859	58	NA	1.40 (1.10–1.90)	1.20 (0.6–2.4)	1.20 (0.50–2.50)
Reeves	Meta-analysis	NA	NA	NA	1.76 (1.68–1.85)	NA	NA
Greiser	Meta-analysis	NA	NA	NA	NA	NA	NA
Collins	Meta-analysis	NA	NA	NA	1.24 (1.03–1.50)	NA	1.15 (0.78–1.52)
EPIC-E3N	Cohort	59,216	53	22.5	1.08 (0.89–1.31)	0.71 (0.44–1.14)	0.95 (0.67–1.36)
EPIC-E3N	Cohort	52,325	53	22.5	1.18 (0.95–1.48)	0.84 (0.51–1.38)	1.16 (0.79–1.71)

Av, Average; NA, not available.

[a] Estimates calculated from published data.

6-month prospective, placebo-controlled trial, testosterone administration significantly counteracted breast cell proliferation induced by E+P therapy in postmenopausal women, suggesting that the addition of testosterone to estrogen or E+P therapy would decrease the risk of breast cancer (163). On the other hand, nine studies examined the relationship between plasma testosterone concentration and the ensuing risk of breast cancer over the following 5 to 15 yr in postmenopausal women. Some studies (but not all) found a significant association between endogenous testosterone levels and the risk of

breast cancer. However, in many of these studies, the statistical significance of the association was diminished, or it disappeared when the independent effects of estrogen were removed.

In clinical trials, four case-control studies and four cohort studies (two concurrent and two nonconcurrent) reported retrospective analyses on populations receiving an androgen alone, estrogen plus an androgen, and estrogen-progestogen-androgen combinations (Tables 7 and 8). Two of these studies (164, 165) found a significantly increased risk of breast cancer, whereas the other six (166–

| | RR | | | | | | |
5–9.9 yr	10–14.9 yr	>15 yr	>20 yr	Comments	Comments	Refs.
>6 yr, 3.56 (0.52–7.60)	NA	NA	NA		IBC only	172
>6 yr, 1.24 (0.75–2.05)	NA	NA	NA	Prior MHT		133
NA	NA	NA		No prior MHT		133
3.30 (1.90–5.73)	NA	NA	NA	Prior MHT, gap time 0	Current	134
2.85 (2.29–3.54)	NA	NA	NA	No prior MHT, gap time 0	Current	134
NA	NA	NA	NA		Current	511
	>10 yr, 2.07 (1.84–2.30)				Not stated; all were hormone naive	136
>5 yr, 1.49 (1.36–1.63)	NA	NA	NA		Current	111
2.17 (2.03–2.33)	2.31 (2.08–2.86)	NA	NA	>6 yr, 1.95 (1.66–2.35)	Current	112
>6 yr, 1.95 (1.66–2.35)	NA	NA	NA	Excludes use of progesterone and dydrogesterone	Majority current users; some past users	118
2.07 (1.68–2.55)	2.73 (2.21–3.36)	NA	NA		Current	114
1.91 (1.67–2.19)	2.25 (1.94–2.62)	NA	2.48 (1.71–3.59)		Current and past users	115
NA	NA	NA	NA		Current and past	116
1.76 (1.45–2.44)	>10 yr, 2.02 (1.67–2.45)	NA	NA	Ductal only	Current	117
0.6 (0.30–1.60)	NA	NA	NA		Current and past	106
NA	NA	NA	NA			124
NA	NA	NA	NA	1.09 (1.09–1.10), RR per year of use		107
>5 yr, 1.53 (0.88–2.18)	NA	NA	NA			120
>6 yr, 1.22 (0.89–1.67)	NA	NA	NA	Progesterone		118
>6 yr, 1.32 (0.93–1.86)	NA	NA	NA	Dydrogesterone		118

[b] This study combines the WHI RCT with the WHI observational study and analyzes subgroups into those receiving prior HT and those who did not.

171) did not. In addition, none of the five studies that sought a relationship between duration of testosterone use and risk of breast cancer showed a significantly increased risk with longer duration of treatment (165–167, 169–171). Several of these studies had important methodological problems which included: 1) potential recall bias on questionnaires (165, 167); 2) differences between the cases and controls for other risk factors for breast cancer, such as benign breast disease and prior exposure to estrogen or E+P (165, 167, 168); 3) use of nonconcurrent, historical controls (169); 4) lack of adjustment for other risk factors (170, 171); 5) small numbers of women receiving andro-

gens; and 6) control groups not uniformly concurrent, although quite large.

Decline in incidence of breast cancer in various countries.
Adverse effects of MHT reported in the first WHI study led to the termination of that trial in mid-2002 (172). Widespread media coverage of results of this trial led to a marked decline in sales and use of postmenopausal hormones (173). The first reports of a subsequent rapid decline in breast cancer incidence were published by Clarke *et al.* (174) and by Ravdin *et al.* (175). Between 2002 and 2004, Clarke *et al.* (174) noted a 68% drop in the use of

TABLE 7. Breast cancer risk in postmenopausal women receiving testosterone with or without estrogen or E+P: case-control studies

| First author | Study design | Cases/controls | No. of breast cancers | |
			T+E	C
Brinton	Population-based case control	1960/2258	25	29
Ewertz	Population-based case control	1484/1334	56	21
			16 (E+P+T)	11
Jick	Observational case control	4,515/18,058	98	380
			22 (E+P+T)	55
van Staa	Observational case control[b]	2,103 T/6,309 no T	16	52

O, Oral; ND, not determined; T, testosterone; E, estrogen; P, progestogen; C, control.

[a] RR when E+T preparation was used the longest of all HT.

[b] Included premenopausal, menopausal, and postmenopausal women.

combination E+P and a 10% decline in breast cancer incidence in Kaiser Permanente's northern California (Oakland, CA) region (174). This finding was subsequently confirmed in the broader SEER data (175). Glass *et al.* (176) subsequently reported data from the Kaiser Permanente northern California regional patient population, which tracks the use of postmenopausal hormones. Although concerns persisted that changing mammography use may have contributed to the decrease in incidence, Kerlikowske *et al.* (177) removed any such bias by limiting their analysis to over 600,000 women who had undergone mammography. They observed a decline in the use of MHT of 34%, a 5% decline in incidence of breast cancer, and a 13% decline in invasive ER-positive breast cancer (177). It should be noted that Kerlikowske *et al.* (177) also noted a lesser decline from 2000–2002, concordant with a decline in MHT use during that period as well (177). Subsequent analysis of data from the WHI showed a similar decline in incidence, although numbers of cases are much smaller in the trial population, limiting evaluation of receptor status (178). An analysis by regions in California also reported declines in breast cancer incidence that related to decreases in MHT usage (179). Similar declines in incidence (around 10%) have been observed in numerous other countries, including Australia (180), New Zealand (181), Germany (182), and France (183). The decrease in incidence appears to involve predominantly ER-positive as opposed to ER-negative breast cancers (175, 177). For example, Ravdin *et al.* (175) noted a 14.7% (CI, 11.6–17.4%) decrease in ER-positive breast cancer and only a 1.7% (CI, −4.6 to 8.0%) decrease for ER-negative. Other countries, such as Norway, Sweden, the United Kingdom, and The Netherlands apparently did not observe a decline in breast cancer incidence (184–188). A careful review of the existing data suggests that factors such as time of onset of screening in a population and changes in risk factors might partially explain the reported declines. Because several studies reported a decline before publication of the WHI, caution has been raised regarding interpretation of these data (187). Nonetheless, together they support a rapid decline in incidence of breast cancer, which was temporally associated with a decline in the use of MHT. As discussed below, in *Reservoir of occult or undiagnosed breast cancer*, this effect is consistent with the late-promoter effect of combination MHT (189). The differences among countries may reflect time of introduction of screening programs, frequency of breast cancer screening, prevalence of use of MHT in a given country, and the

TABLE 8. Breast cancer risk in postmenopausal women receiving testosterone with or without E alone or E+P: cohort studies

| First author | Study design | No. taking MHT | |
		E+T	No MHT
Dimitrakakis	Retrospective observational nonconcurrent controls	508	392,757[d]
Tamimi	Retrospective review of prospective cohort—concurrent controls	550, 37 (T only)	18,754
Ness	Observational cohort concurrent controls	1,705	30,137
Davis	Retrospective cohort—nonconcurrent controls	599	419,853[e]

O, Oral; E, estrogen; T, testosterone; P, progestogen; TD, transdermal; IRR, age-standardized incidence rate ratio.

[a] Breast cancer incidence rate expressed as number of cases per 100,000 woman-years. These rates were compared to the rates published for E+P use in the WHI study (380 per 100,000) [Rossouw *et al.* (172)] and the MWS E+P arm (521 per 100,000) and never-user arm (283 per 100,000) [Beral (112)].

[b] Adjusted for age at menopause, type of menopause, family history of breast cancer, personal history of benign breast disease, BMI at age 18 yr, weight change since 18 yr, age at menarche, parity and age of first birth, and alcohol consumption.

Principle type/route	Duration of usage	Risk (CI)	Duration effect	Refs.
Methyltestosterone (O)	Median, 5–9 yr	RR 1.05 (0.6–1.8)[a]	No	166
Testosterone (im)	Median, 6–9 yr	RR 2.31 (1.37–3.88), E+T	No	164
		RR 1.26 (0.96–2.24), E+P+T		
Methyltestosterone (O)	Median, 2.83 yr	RR 1.08 (0.86–1.36), E+T	No	171
		RR 1.69 (1.03–2.79), E+P+T		
Mostly T (72% sc; 18.4% O; 7.9% im)	Mean, 4.4 yr	RR 0.78 (0.44–13.7)[c]	No	168

[c] Adjusted for database source, BMI, smoking, alcohol use, history of early or late menopause, dysplasia or benign neoplasm of the breast, recent use of hormone therapy, and use of nonsteroidal antiinflammatory drugs.

masking effect of MHT on ability to diagnose breast cancer by mammography (186, 187, 190, 191).

Biological concepts influencing breast cancer risk from MHT. The actual concentrations of estradiol in breast tissue likely influence the development and growth of breast cancer in women (129, 130). Several investigators have suggested that local synthesis of estrogen via the aromatase enzyme in the breast provides the major source of breast tissue estradiol in postmenopausal women. If use of exogenous estrogens as MHT were to increase the risk of breast cancer, uptake into the breast from plasma, rather than local synthesis, must represent a significant contributor to breast tissue estrogen levels. Existing studies, however, suggest that both local synthesis and uptake contribute to breast tissue estradiol levels in postmenopausal women. Substantial levels of aromatase are present in the breast as demonstrated by immunohistochemistry, enzyme assays, and quantitation of aromatase message by PCR (192). Eleven studies reported mean estradiol levels of 46 to 480 pg/g in breast cancer tissue from postmenopausal women, levels substantially higher than plasma estrogen levels of 2 to 10 pg/ml (193). In contrast, plasma and breast tissue estradiol levels are similar in premenopausal women. These findings have been cited as inferential evidence that local synthesis predominates over uptake from plasma in postmenopausal women (194). However, the issue of uptake *vs.* local synthesis has been controversial. Other investigators suggest that the maintenance of higher tissue than plasma levels following menopause could also reflect enhanced uptake against a gradient mediated by high-affinity estrogen receptors (195).

Several direct studies have attempted to resolve the tissue synthesis *vs.* uptake controversy. Administration of radio-labeled estradiol to nude mice, oophorectomized to mimic the menopausal state, demonstrated that components of both uptake and local synthesis contribute equally to breast tissue estradiol levels (196). In postmenopausal women with breast cancer, direct determination of the proportion of estrogen synthesized *in situ vs.* uptake involved infusion of ^{3}H-androstenedione and ^{14}C-estrone with quantitation of radioisotope ratios in plasma and breast tissue. These studies indicated that 50–70% of estrogen in the breast resulted from local synthesis and the remainder from uptake (197, 198). Two other studies correlated plasma estradiol levels with ERα levels, estradiol-metabolizing enzymes, and estrogen-responsive gene expression in breast tumors in women (199, 200). These two studies suggested that 37 to 70% of the vari-

No. of breast cancers		Principle testosterone type/route	Duration of usage (yr)	Risk (CI)	Refs.
E+T	**No MHT**				
7	2,883[f]	Testosterone (sc)	Mean, 5.8	115/100,000 E+T[a], 293/100,000 E+P+T	169
29, 3 (T only)	1,647	Methyltestosterone (O)	Up to 24	RR 1.77 (1.22–2.56)[b], E+T; RR 2.52 (0.80–7.94), T only	165
35	558	Methyltestosterone (O)	Mean, 4.6	RR 1.42 (0.95–2.11)[c]	167
12	1,333	Testosterone (sc or TD)	Median, 1.3	299/100,000 E+T+P[a], RR 1.35 (0.76–2.38)	170

[c] Adjusted for BMI, age at menopause, history of breast cancer in a first-degree relative, number of mammograms in the 5 yr before study enrollment, and prior hormone therapy use.

[d] No MHT group taken from MWS.

[e] No MHT group taken from State of Victoria, Australia population data.

[f] Number estimated from MWS by multiplying person-years times duration of follow-up (2.6 yr).

TABLE 9.   Incidence of breast cancer in autopsy studies of women not known to have breast cancer

Author	No. of cases	Autopsy setting	% Occult DCIS (all ages)	% Occult IBC (all ages)	% Occult DCIS or IBC (age ≥40 yr)	Refs.
Ryan	200	Hospital	0	0	0% (40–100 yr)	214
Kramer	70	Hospital	4.3	1.4	4.3% (DCIS), 1.4% (IBC) (all >70 yr)	211
Wellings	67	Hospital	4.5	0	10% (DCIS) (50–70 yr)	206
Nielsen	77	Hospital	14.3	1.3	Not available	212
Alpers	101	Hospital	8.9	0	13% (DCIS) (40–70 yr)	208
Bhathal	207	Forensic	12.1	1.4	Not available	210
Bartow	221	Forensic	0	1.8	7% (IBC) (45–54 yr)	209
Nielsen	109	Forensic	14.7	0.9	39% (DCIS) (40–49 yr)	213

ability in breast tissue estradiol levels were the result of uptake from plasma, with tissue ERα levels serving as a major modulator of uptake (199, 200).

These experimental data, taken together, suggest that exogenous estrogens as MHT should increase breast tissue estradiol levels substantially. However, obesity might favor local synthesis over uptake. Obesity possibly enhances the proportion of locally synthesized estradiol because aromatase expression in adipocytes is increased in obese patients (201). Although speculative, these findings could explain why the increased risk of breast cancer from MHT appears less significant in obese than in thin women (Fig. 4). Specifically, the proportion of estrogen in the breast coming from the peripheral circulation, as opposed to local synthesis, might be less in obese women. In contrast, MHT would increase the risk in thin women whose breast tissue estradiol levels might reflect predominantly uptake. Furthermore, the relative contribution of uptake *vs.* local synthesis might also influence risk in nonobese women. Additional studies are required to prove or disprove these hypotheses.

Reservoir of occult or undiagnosed breast cancer. At the time of initiation of MHT, a proportion of women harbor occult or undiagnosed breast cancer. The concept of a "reservoir" of occult tumors is important in interpreting data regarding MHT and its effects on breast cancer. The promotional effects of MHT on occult tumors would likely accelerate the growth of these lesions sufficiently to allow detection by mammography or clinical examination. These occult breast cancers might then be detected earlier than those in women not receiving MHT. If sufficiently large, this reservoir of occult tumors would be expected to contribute substantially to the RR of breast cancer observed in the RCTs. It is important to recognize that newly detected cancers could represent either *de novo* tumors initiated by MHT or occult tumors promoted by MHT to grow to a size sufficient for clinical detection. The majority of invasive breast cancers (IBCs) in women are the end result of a decades-long evolution of increasingly abnormal premalignant stages, ranging from hyperpla-

sias, to atypical hyperplasias, to *in situ* carcinomas (202). Ductal carcinoma *in situ* (DCIS) accounts for the vast majority of *in situ* disease and is the immediate precursor of most IBCs (203–205). The size of this reservoir is, therefore, an important consideration for analysis of whether MHT causes breast cancer *de novo* or promotes the growth of preexisting occult tumors.

The exact prevalence of occult tumors in the otherwise normal population is unknown. However, estimates are available from several types of pathology studies evaluating presumed noncancerous breasts. Tissues for these studies were obtained from autopsies of women not known to have breast cancer and from reduction mammoplasties, prophylactic mastectomies in high-risk women, and contralateral mastectomies in women with breast cancer performed for prevention and for cosmetic reasons. Autopsy is probably the best context because it most closely reflects the general population. There have been at least eight autopsy studies during the past 40 or more years addressing this issue (Table 9), and the majority involved far more comprehensive pathological evaluation of the breast than occurs in routine autopsy (206–214).

Combined results from these studies in women of all ages indicated a range of 0 to 14.7% for occult DCIS and 0 to 1.8% for occult IBC. Among women older than age 40 yr (*i.e.* the age for beginning routine mammographic screening), from 0 to 39% had occult DCIS, and 0 to 7% had occult IBC. The large variations in these studies are probably due primarily to differences in methodology, such as the technique used to decide which areas of the breast to sample; the number of histological sections examined; and the pathological criteria used to define breast cancer, especially DCIS (which can be problematic) (207). The studies span an era in which the rate of diagnosed breast cancer increased more than 2-fold (215). Accordingly, some of the variation may reflect true differences insofar as data suggest possible increasing incidence over this period of time. The studies also span a period before and soon after the introduction of routine screening

mammography, which should reduce the incidence of occult disease. However, the suggestion of increasing frequency of occult tumors argues against this possibility (208, 209, 213).

The best estimates of the size of the reservoir involve determination of the mean prevalence rates from the 1052 patients studied at autopsy. These data indicate a 6% prevalence of occult DCIS and a 1% prevalence of occult IBC, for a total of 7%. The prevalence is probably similar or even somewhat higher today.

Two recent studies suggested that some occult breast tumors in the reservoir remain dormant and do not progress over time (184, 216, 217). From this perspective, it is enlightening to compare the prevalence of occult tumors at autopsy (Table 9) with the incidence of newly diagnosed tumors over a 6-yr period in placebo arms of the WHI studies (E alone and E+P). In the E-alone study, 2.96% of women (161 of 5310) were diagnosed with *in situ* or IBC over a period of 7 yr and 1.85% (150 of 8102) in the placebo arm of the E+P group in 6 yr of follow-up (119, 132). Assuming that 7% of the WHI population harbored occult or undiagnosed breast cancer at study entry, only one third (*i.e.* 1.85–2.97%) progressed to a size sufficient for diagnosis over the 6 to 7 yr of the study.

These data support the concept that two thirds of tumors remain relatively dormant. Older data estimate an average doubling time of 50 to 100 d for breast tumors. An average of 10 yr is required from onset of the tumor to the time necessary to reach the size of detection (*i.e.* 1 billion cells) (218). Taken together, these data suggest that E+P might only exert a promotional effect on existing occult tumors, causing them to grow to a sufficient size to allow diagnosis. In the E+P group of the WHI study, there was an excess of only 0.49% of patients with diagnosed breast tumors. There were 150 tumors detected in the placebo group and 199 in the E+P group out of 8102 patients on placebo and 8506 on E+P. If the total reservoir of tumors were 7% in this population, only one tenth of existing occult tumors (0.49% of 7%) would have grown to the size of detection to explain the WHI results. On the basis of this analysis, it would appear much more likely that a promotional, rather than an initiation effect is operative to explain the WHI results of E+P. Put simply, E+P causes preexisting tumors to grow, rather than initiating the onset of de novo tumors.

The nonstatistically significant 20% reduction of diagnosed breast cancer in the E-alone arm (161 cancers in the 5429-member placebo group; 129 cancers in the 5310-member E-alone group) could also represent an effect on occult or undiagnosed tumors (119). E alone causes apoptosis in breast tumors exposed to low-estrogen conditions long term (127, 128). Only the patients without prior MHT exposure in the E-alone arm experienced a reduction in breast cancer over the period of 6 yr of follow-up. This could have represented a proapoptotic effect of estrogen (127). As discussed above, there was an apparent decline in breast cancer incidence after publication of the WHI. This finding could also represent a reduction in growth of occult breast cancers upon cessation of MHT and, therefore, a reduction in their rate of detection. At the present time, this interpretation is considered plausible, but definitive proof requires further study. The correlations of autopsy prevalence of breast cancer with incidence in RCTs are indirect, and the concepts regarding promotion and apoptosis of occult tumors must remain hypothetical until direct evidence is obtained.

Endometrial cancer (EC)

EC is diagnosed in approximately 40,000 women annually in the United States, and 7,000 of these women are expected to die from the disease. A woman's lifetime risk of EC is 2.6 per 100 women, with 90% diagnosed after the age of 50 yr and a median age at diagnosis of 63 yr. Type I or endometrioid EC comprises 80% of all ECs and is usually well differentiated and hormonally responsive (219). Type II tumors (papillary, serous, and other rarer cancers such as clear cell) are poorly differentiated, often diagnosed at a later stage, are not hormonally responsive, and commonly arise in an atrophic endometrium. Type II ECs are often associated with aberrancies in the tumor-suppressor gene P53, or inactivation of p16 and/or over-expression of HER-2/neu, whereas type I cancers most commonly are associated with mutations in another tumor-suppressor gene, PTEN (220), and less commonly with PI3CA, K-ras, and β-catenin.

The major risk factors for type I EC are obesity, diabetes mellitus, and increased endogenous or exogenous estrogen. The expected scenario in type I EC is the progression from a normal endometrium to endometrial hyperplasia (simple or complex). Estrogen without progestogen after menopause has been well established to increase the risk of endometrial hyperplasia as well as type I EC. In a meta-analysis, E alone was found to increase the risk of EC 2-fold (RR, 2.3; CI, 2.1–2.5) (221). The risk was related to dose and duration, with E alone for 10 or more years increasing the risk by 9.5 times. Although the risk is lowered by approximately one half with doses less than 0.625 mg of CEE, this risk of long-term therapy is still 3-fold increased with E alone (222). Data suggest a persistence of the risk after cessation of E-alone therapy, with a risk as high as 1.9 even 12 yr after cessation (223). RCT data from the PEPI trial provide additional information on the biological effects of E alone (224). Women receiving 0.625

mg of CEE daily for 3 yr without a progestogen experienced an incidence of simple, complex, and atypical endometrial hyperplasia of 27.7, 22.7, and 11.8%, respectively.

Compared with women receiving E alone who develop EC, those women who develop EC who were not taking estrogen have a mortality rate 4.8 times higher (CI, 2.2–10.3) (225). All-cause mortality was also 2.4 times higher in nonusers of estrogen (CI, 1.4–4.0) (226). These data reflect the better prognosis of well-differentiated type I cancers, which is the type of cancer increased in estrogen users.

Studies have examined the effects on endometrial hyperplasia and EC of progestogens given in various different regimens along with estrogen. The addition of progestogens to estrogen decreases the risk of endometrial hyperplasia and EC, and data are consistent for various types of progestogens and regimens (224). The most commonly used regimens include: 1) combined continuous, in which the E+P is taken daily; 2) combined cyclic, in which the E+P is given together in a cyclic fashion, usually with 3 wk on and 1 wk off; and 3) sequential cyclic, in which the progestogen is given for 5 to 15 d per month, the estrogen (usually) for 3 wk, and no hormone administration for 1 wk. The data are most consistent for use of combined-continuous therapy (daily E+P), which results in either no increased risk or a significantly decreased risk of EC. Whereas sequential cyclic therapy has been shown to reduce risk compared with E alone, the risk remained increased in those using progestogens for less than 10 d per month.

Substantial RCT and observational data confirm the endometrial safety of combined-continuous and combined-cyclic therapy. In the WHI study (227), the RR for EC in women receiving combined-continuous CEE 0.625 mg and MPA 2.5 mg was 0.81 (CI, 0.48–1.06). In the MWS (228), the RR was 0.71 (CI, 0.56–0.90). In the latter study, combined-cyclic therapy was associated with an RR of 1.05 (CI, 0.91–1.21). With respect to sequential-cyclic therapy, a trend was observed toward a decreasing risk with increasing days of progestogen with a RR of 0.75 (CI, 0.43–1.30) for 13 to 14 d per month. However, in a case-control study, long-term (more than 6 yr) sequential-cyclic therapy has been reported to be associated with increased risk of 2.0 (CI, 1.2–3.5) (229).

Although obesity is a risk factor for EC, lean women had a higher risk of EC with sequential-cyclic therapy. In lean women (BMI < 25 kg/m^2), the RR was 1.54 (CI, 1.20–1.99) in women receiving sequential-cyclic therapy and 1.07 (CI, 0.73–1.56) for combined-continuous therapy. In obese women (BMI > 30 kg/m^2), however, the risk was lower with both sequential-cyclic (RR, 0.67; CI, 0.49–0.91) and combined-continuous therapy (RR, 0.28;

CI, 0.14–0.55) (228). Progestogens are considered to be unnecessary in women using small doses of local or vaginal estrogen therapy.

Use of different types of progestogens might be expected to alter rates of endometrial hyperplasia. Whereas use of more potent progestogens, such as 19-nor-progestogens, should have a greater protective effect on the endometrium, this expectation is not supported by current data (228). "Bioidentical" hormones (see *Bioidentical HT*) have been suggested by some advocates to be a "safer" form of therapy. However, EC has been reported with such use (230).

MHT has been prescribed for women after treatment of early-stage EC. In several retrospective trials (231, 232) and one prospective trial (which was not fully enrolled) (233), there was no evidence for an increase in the risk of recurrence in EC (stages 1 and 2) when adequately treated initially.

MHT and ovarian cancer

Ovarian cancer ranks as the ninth most common cancer diagnosed in Western populations, with an age-standardized incidence rate of 12 per 100,000 women per year (0.6 per 1000 per 5 yr). In Western women older than age 50 yr, the rate was 27 per 100,000 per year (1.35 per 1000 per 5 yr), as observed, for example, in the WHI RCT of combined E+P therapy. The median age of diagnosis approximates 64 yr, and 80% of cancers occur in women older than age 50 yr.

Observational studies. Case-control and cohort epidemiological studies have reported ovarian cancer risks in users of E alone, E+P, and MHT (type not specified) (234). In 2002, Lacey *et al.* (234) studied 44,241 postmenopausal women who were former participants in the Breast Cancer Detection Demonstration Project (BCDDP). With follow-up starting at a mean age of 56.6 yr, they observed that 329 were diagnosed with ovarian cancer. Use of E alone resulted in a RR of 1.6 (CI, 1.2–2.0) with a 7% increase per year of use. For 10 to 19 yr of use, RR was 1.8 (CI, 1.1–3.0) and for more than 20 yr of use, 3.2 (CI, 1.7–5.7). Combined estrogen and progestogen use was associated with a RR of 1.1 (CI, 0.64–1.7) with no evidence of a duration effect. Similar findings were reported in 19 case-control studies (235). For specified durations of MHT of less than 5 yr, 6 to 10 yr, and more than 10 yr of use, RR was 1.03, 1.07, and 1.21, respectively—none of which is statistically significant.

A recent population-wide study in Denmark (236) provided data from 909,946 perimenopausal and postmenopausal women followed for an average of 8 yr. Compared with women who never took MHT, current users had incidence ratios of 1.38 (CI, 1.26–1.51) for all ovarian

tumors and 1.44 (CI, 1.30–1.58) for epithelial ovarian cancer. Risk declined to 0.98 (CI, 0.75–1.28) 2 to 4 yr after cessation of therapy. The risks did not differ with respect to type of hormone therapy (HT). Excess (attributable) risk was calculated to be 0.6 women per 1000 per 5 yr.

Meta-analyses. Greiser *et al.* (237) reported that annual risk was increased 1.28 times by E alone (CI, 1.18–1.40) and 1.11 times (CI, 1.02–1.21) by E+P. Risks were greater in European than American women. Zhou *et al.* (238) gave summary estimates for eight prospective cohort studies in which any use of MHT was associated with a RR of 1.24 (CI, 1.15–1.34). Current users for less than 5 yr had no significant increase in risk (RR, 1.04; CI, 0.91–1.20) compared with more than 5 yr of use (RR, 1.47; CI, 1.12–1.92), with higher risks for E alone than for combined therapy.

RCTs. The WHI trial (227) represents the only RCT examining the effect of MHT on ovarian cancer. During an average of 5.6 yr of follow-up, 20 cases of invasive ovarian cancer were diagnosed in women receiving continuous E+P and 12 cases in the placebo arm for a RR of 1.58 (CI, 0.77–3.24; *i.e.* not significant). The study involved 16,608 women; annualized rates were 42 per 100,000 and 27 per 100,000 per year, respectively. The excess (attributable) risk was not statistically significant and represented 0.75 women per 1000 per 5 yr of use, a rare outcome but similar to that in the large Danish study (236) quoted above. E-alone therapy for ovarian cancer survivors did not appear to affect outcome in a 4-yr follow-up on 130 women (239).

MHT and colon cancer
Observational studies. In the BCDDP, Johnson *et al.* (240) identified 960 women with colorectal cancer ascertained by self-reports in the total population of 56,733 women followed for 15 yr. Trends suggested that reductions in risk occurred in users of E+P (RR, 0.78; CI, 0.66–1.02) and among past (more than 5 yr prior) users of E+P (RR, 0.55; CI, 0.32–0.99). Sequential E+P regimen users had a larger reduction in risk at 36% compared with continuous users at 25%. Among E+P users, women who had stopped for more than 5 yr and women who had used E+P for 2 to 5 yr had the largest reduction in colorectal cancer risk. Reductions in risk occurred with ever-users of E alone (RR, 0.83; CI, 0.70–0.99). Trends suggested that reductions in risk occurred among current users of E alone (RR, 0.75; CI, 0.54–1.05) and long-term (RR, 0.74; CI, 0.56–0.96) users of E alone. An overall dose-response pattern was not evident for duration of use among E+P users.

Meta-analyses. Three meta-analyses (241–243) reported that colon cancer was decreased in ever-users of MHT, with a persistent reduction for up to 4 yr after cessation of therapy. The meta-analysis by Grodstein *et al.* (241) of 18 observational studies reported a 20% reduction in colon cancer incidence in ever-users of MHT (RR, 0.80; CI, 0.74–0.86) and a 34% reduction in current users of MHT compared with never-users.

RCTs. The HERS I and II trials (244) of postmenopausal women with CHD reported on colorectal cancer but were underpowered to detect significant differences (*i.e.* 21 cancers in the MHT group and 26 in the placebo arm—RR, 0.81; CI, 0.46–1.45). The WHI E+P trial reported 43 cases of invasive colorectal cancer in the E+P group and 72 in the placebo group (RR, 0.56; CI, 0.38–0.81; $P = 0.003$). Specifically for colon cancer, the RR was 0.54 (CI, 0.36–0.82; $P = 0.004$), and for rectal cancer, the RR was 0.66 (CI, 0.26–1.64; $P = 0.37$). A more detailed analysis by Chlebowski *et al.* (246) revealed that the invasive colorectal cancers were similar for both E+P and placebo groups in location, tumor grade, and histological features. However, there was more lymph node involvement in the E+P cancers than in placebo cancers (59.0 *vs.* 29.4%; $P = 0.003$), with a higher number of positive nodes in the E+P group compared with the placebo group (3.2 ± 4.1 *vs.* 0.8 ± 1.7; $P = 0.002$). A more advanced stage at diagnosis was observed in the E+P group (rate of regional or metastatic disease was 76.2 *vs.* 48.5% in the placebo group; $P = 0.004$). From this analysis, it appeared that local colorectal cancers were decreased in the E+P group, but the E+P group had more advanced cancers with regional or metastatic disease or positive nodes (RR for local disease, 0.26; CI, 0.13–0.53; $P < 0.001$; RR for regional or metastatic disease, 0.87; CI, 0.54–1.41; $P = 0.57$). Few patients (nine in HT, eight in placebo group) died from colon cancer, and mortality effects could not be adequately assessed.

Ritenbaugh *et al.* (245) reported the results of the WHI CEE-alone RCT. After a median 7.1 yr, there were 58 invasive colorectal cancers in the HT group and 53 in the placebo group (RR, 1.12; CI, 0.77–1.63). Tumor size, stage, and grade were comparable. The cumulative mortality after colorectal cancer diagnosis among women in the CEE-alone group was 34%, compared with 30% in the placebo group (RR, 1.34; CI, 0.58–3.19). The WHI E+P study (246), when taken together with the WHI E-alone trial, suggested that the effect on colorectal risk might be related to the type of MHT, with reductions with E+P and no effect with E alone.

Possible mechanisms to explain findings. Observational studies appeared to indicate that both E+P and E alone reduce the risk of colon cancer, whereas the WHI trial only reported a reduction with E+P. The average age of women in the WHI was 63 yr, whereas observational studies usually

involve younger women. Hypothetically, estrogens may have a different effect on the colon in younger women than in older women. Further data are required to assess this possibility.

The mechanism of action of MHT on colorectal cancer is not known, although several observations suggest that colonic tissue is hormonally influenced. Estrogen decreases concentrations of bile acids (247), which are thought to promote malignant change within the colon. Progestogens are hypothesized to work through antiproliferative effects on colonic cell cycle proteins (248). A significant decrease in a type of estrogen receptor, ERβ, has been found in colonic tumors (249), hypothesized by Di Leo *et al.* (250) to play a pivotal role in the organization and architecture of the colon with a potential role in the regulation of colon tumor growth. The loss of ERβ receptor leads to hyperproliferation, loss of differentiation, and decreased apoptosis in the epithelium of the colon. This latter observation appears counterintuitive with respect to hormones and colon cancer and highlights the lack of understanding of the hormonal pathophysiology of colon cancer.

MHT and lung cancer

Preclinical evidence suggests that non-small-cell lung cancers can be ER-positive and respond to estradiol with increased gene transcription and growth (251). Aromatase, the rate-limiting enzyme for estrogen synthesis, and ERs are present in human non-small-cell lung cancers, and high estrogen levels in women correlate with higher mortality from this tumor. Based upon these data, the WHI investigators assessed the incidence of non-small-cell lung cancer in women receiving E+P *vs.* those receiving placebo. The RR for those receiving E+P exhibited a trend toward a higher incidence (RR, 1.23; CI, 0.92–1.63) but did not reach statistical significance ($P = 0.16$). In those aged 60–69 yr, the difference was statistically significant (RR, 2.00; CI, 1.11–3.62). The absolute attributable risk would represent 1.8 women per 1000 taking E+P for 5 yr. More women died from non-small-cell lung cancer in the E+P group than in the placebo group (HR, 1.87; CI, 1.22–2.88; $P = 0.004$), although all-cause mortality did not differ. The absolute increase in risk of death from lung cancer in women receiving E+P compared with controls was higher in current smokers than in never-smokers (251). In women ages 50 to 59 yr, no increase in risk of lung cancer was observed (RR, 1.02; CI, 0.47–2.24).

Another study (the Vitamin and Lifestyle Study) reported a RR of 1.27 (CI, 0.91–1.78) for women taking MHT for 9 yr or less and 1.48 (CI, 1.03–2.12) for more than 10 yr (252). Those receiving MHT experienced a more advanced stage at diagnosis (RR, 1.52; CI, 1.06–

2.19). E alone as MHT was associated with no increased risk in this study and in the recently presented WHI data on E alone (253). These findings should be considered preliminary and will require validation in additional studies. This conclusion is particularly important in light of the fact that large observational studies have reported protective effects of oral contraception and MHT on lung cancer risk (254–257).

Genitourinary system

Overactive bladder (OAB), stress urinary incontinence (SUI), and recurrent urinary tract infection (RUTI)

OAB affects more than 50 million people in the developed world (258). Symptoms of OAB are diurnal, consisting of nocturnal frequency, with or without urgency and urge incontinence. OAB can be diagnosed without the need for formal urodynamic studies (259); however, two objective urodynamic evaluations are available for use in the diagnosis—first sensation to void, and bladder capacity (260). The roles of E alone or E+P, the route of administration, and dosage are not fully defined. Reported results are mixed, which probably reflects several problems including: 1) the small number of participants in the clinical trials; 2) lack of consistency in criteria for entry; 3) differences in estrogen route of administration and dose; and 4) limited follow-up, to name a few of the problems (258, 260, 261).

Three published meta-analyses of prospective randomized, placebo-controlled trials and one review serve as the primary basis for our current knowledge of this problem (260–263). The most recent meta-analysis includes 11 publications that met the criteria of estrogen use in randomized, placebo-controlled trials of OAB (260). Estrogen improved all six outcome measures to a greater extent than did placebo. Diurnal frequency diminished with estrogen in eight of 10 studies compared with placebo ($P = 0.0011$) (260). Systemic estrogen reduced nocturnal frequency ($P = 0.0371$) (260) and urgency ($P = 0.0425$) in four of six study groups. Local estrogen provided greater benefit than did systemic (260). Systemic estrogen reduced the number of incontinence episodes ($P = 0.0002$), decreased the first sensation to void ($P = 0.0018$), and increased bladder capacity ($P = 0.0018$) compared with placebo (260). All of the meta-analyses and the review found that estrogen improved OAB symptoms and that the participants perceived greater improvement with local than with systemic therapy (260–263). The Cochrane review group concluded that estrogen improved urge incontinence (261).

SUI reflects a decrease in pelvic tone compared with an alteration in bladder contractility (260). In the eval-

uation of estrogen as a treatment for SUI, investigators reported variable results without evidence of consistent improvement for this condition (261, 263, 264). In one study, E+P appeared to increase the incidence of SUI (261).

The criteria for making a diagnosis of RUTI require three episodes of UTI within 12 months or two episodes within 6 months (265). The prevalence rate for UTI in 1 yr is 8 to 10% in postmenopausal women (265). Five percent of the postmenopausal women experiencing a UTI will have a recurrence within 1 yr (265). A Cochrane review identified nine appropriate studies involving 3345 postmenopausal women and evaluated the evidence for efficacy of estrogen on RUTI. These studies (265) suggested no apparent benefit of oral estrogen *vs.* placebo on RUTI (RR, 1.08; CI, 0.88–1.33). Two studies investigated vaginal estrogen *vs.* placebo, both using different vaginal estrogen preparations that precluded any meta-analysis. Use of an estrogen cream resulted in a RR of 0.25 (CI, 0.13–0.50) compared with placebo for RUTI, whereas an estrogen-releasing vaginal ring reported a RR of 0.64 (CI, 0.47–0.86) compared with placebo (266, 267). The conclusion was that local estrogen delivered vaginally reduced RUTI.

Vaginal atrophy

Estrogen therapy (268) promotes vaginal cell growth and cellular maturation (269), fosters recolonization with lactobacilli, enhances vaginal blood flow, decreases vaginal pH to premenopausal levels, improves vaginal thickness and elasticity (270), and improves sexual response (271, 272). Three meta-analyses showed that estrogen also consistently relieved vulvovaginal symptoms. All formulations of topical vaginal therapies resulted in better symptom relief and greater improvement in cytological findings than oral estrogen (272). Systemic adverse effects were muted with the vaginal preparations (272, 273). Treatment usually consists of a daily "priming" dose followed by a reduction to the lowest dose that maintains vaginal integrity. Doses as low as 10 μg/d of estradiol cream (274) or 10 and 25 μg in tablet form for vaginal use have been found effective (275, 276).

Systemic effects of vaginal estrogens. Low-dose vaginal estradiol tablets and rings result in lower serum estradiol concentrations than occurs with standard doses of vaginal estrogen cream (277). Some absorption into the systemic circulation results, but not in amounts sufficient to relieve hot flashes. In an atrophic vagina, estrogen is rapidly absorbed through a thin, vascularized vaginal mucosa (278). Once vaginal maturation and thickening have occurred, absorption is reduced (279).

The vaginal estrogen 2-mg ring releases 7.5 μg/d of 17β-estradiol for up to 90 d. A "burst" effect occurs with peak levels of plasma estradiol of 63 and 44 pg/ml at 3 h for the first and second ring insertions, then decreases rapidly to a low steady state of 7 to 8 pg/ml (278). Serum estradiol increased 5.4 times from 3 to 17 pg/ml during a 24-h period after daily 25 μg estradiol tablets or 1 g (0.625 mg) CEE cream, whereas serum estrone levels increased 150% with estradiol tablets and 500% with CEE cream (280). In one trial, estradiol appeared to diffuse preferentially to nearby sites, such as the uterus, based on its location. Distribution to the uterus predominated if tablets were placed in the upper third of the vagina and to the periurethral area if placed in the lower third of the vagina. Slightly elevated serum estradiol levels were detected 3 h after placement, regardless of delivery location (280, 281).

Endometrial effects. Based on available clinical data, low-dose (*i.e.* 7.5–25 μg) vaginal estrogen preparations appear to stimulate the endometrium minimally. However, concern remains that higher amounts (50–100 μg of estradiol or CEE cream) could lead to endometrial proliferation (282). In the Cochrane review, no cases of EC were reported, with rare cases of endometrial hyperplasia with low-dose estrogen (272). There are no evidence-based recommendations for endometrial monitoring or progestogen dosing with low-dose vaginal estrogen alone therapy. Postmenopausal bleeding on topical vaginal estrogen therapy warrants full evaluation.

Quality of life

The World Health Organization defined health as "complete physical, mental, and emotional well-being" and quality of life (QOL) as "an individual's perceptions of their position of life in the context of the culture and value systems in which they live and in relation to their goals, standards, and concerns." QOL is subclassified into health-related QOL (HRQOL) and global QOL (GQOL). HRQOL can be conceptualized as patients' perceptions of their physical, cognitive, and mental health. GQOL is a broader measure and can be defined as a reflection of a person's beliefs about his or her functioning and achievements in various aspects of life, that is, an overall sense of life satisfaction and well-being.

Overall indices

Several contemporary instruments have been validated to measure HRQOL and one to specifically measure GQOL in menopause-related populations (283–286). These instruments have been used neither in large population-based studies to determine the impact of the menopause itself on domains of QOL nor in long-term, randomized, placebo-controlled trials of MHT in symptomatic postmenopausal women. The WHI attempted to

determine the impact of MHT on HRQOL by using surrogate parameters such as single questions to determine level of sexual satisfaction. It should be noted that the average age of subjects was 63 yr, and these women endorsed only limited menopause symptoms (287–289). Results were mixed, with significant improvement in domains such as sleep, but no impact on other domains of HRQOL. Short-term drug studies (*i.e.* usually of 12-wk duration) in younger perimenopausal symptomatic populations have incorporated these instruments with mixed results. The majority show improvement in some domains of HRQOL and, to a lesser extent, in some domains of GQOL (290–293).

Vasomotor instability: hot flashes

Hot flashes are the most common menopausal symptom, affecting as many as 60 to 80% of women. For many women, vasomotor symptoms are mild, but for a substantial percentage of women, they are severe enough to interfere with QOL (294). For these women, estrogen therapy can be considered. For hormone users, the Cochrane review calculated a 75% (CI, 64–82%) reduction in the frequency of hot flashes and 87% reduction in severity (RR, 0.13; CI, 0.06–0.27) (295). In another systematic review and meta-analysis of 12 placebo-controlled estrogen trials of at least 3-month duration, the pooled weighted-mean difference in number of hot flashes per week compared with placebo was -16.8 (CI, -23.4 to -10.2) for oral 17β-estradiol, -22.4 (CI, -35.9 to -10.4) for transdermal estradiol, and -19.1 (CI, -33 to -5.1) for conjugated estrogen (296). The addition of a progestogen to estrogen did not affect results, and there were no significant differences observed between various types of estrogens. Similar results were seen in a second meta-analysis of 24 trials of MHT (295). Weekly hot-flash frequency decreased significantly compared with placebo (weighted-mean difference, -17.92; CI, -22.86 to 12.99), equivalent to a 75% reduction in frequency when compared with placebo (CI, 64.3–82.3%).

Most available data on MHT and hot flashes are based upon "standard-dose" estrogen (conjugated estrogen, 0.625 mg; oral micronized 17β-estradiol, 1 mg; transdermal 17β-estradiol, 50 μg/d) (295, 296). However, lower doses of estrogen are also effective for relief of hot flashes in many women and are associated with less vaginal bleeding and breast tenderness (269). Examples include conjugated estrogen (0.3 mg), micronized oral 17β-estradiol (0.5 mg), and transdermal 17β-estradiol (0.025 mg). An even lower dose of estrogen (transdermal 17β-estradiol, 0.014 mg) is effective for hot flashes in some women (297). Nonhormonal alternatives for hot flashes include newer antidepressants and gabapentin. Although these agents are not as effective as estrogen for hot flashes, they are significantly better than placebo (298).

Female sexual function

Systemic E or E+P therapy, even at very low doses, improves dyspareunia associated with vulvovaginal atrophy in postmenopausal women (299). Vaginal estrogen preparations appear to be as effective as systemic therapy (273). Minimal data are available to support a significant benefit of estrogen therapy on sexual function in women lacking vaginal atrophy or in women with hypoactive sexual desire disorder (HSDD). Tibolone, a synthetic compound with estrogenic, progestogenic, and androgenic actions, improves sexual function, as measured by the Female Sexual Function Index, to a greater extent than transdermal estradiol-NETA in postmenopausal women presenting with low libido (300). Combined oral methyltestosterone (2.5 or 1.25 mg/d) and esterified estradiol (0.625 mg/d) therapy improves sexual desire in naturally and surgically postmenopausal women presenting with low libido (301, 302).

Large RCTs in both surgically and naturally menopausal (303, 304) women demonstrate that treatment with a transdermal testosterone patch, which delivers 300 μg of testosterone per day, significantly increases the number of self-reported sexually satisfying events per month when compared with placebo. These studies also demonstrated significant improvements in desire, arousal, responsiveness, orgasm, pleasure, and satisfaction (305).

An analysis of data from a number of these studies combined indicates that women with a SHBG level above 160 nmol/liter or women taking concurrent CEE are unlikely to benefit from testosterone therapy (see http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4082B1_01_A-P&G-Intrinsa.pdf).

Transdermal testosterone at a dose of 300 μg/d has been shown to improve all domains of sexual function previously mentioned in naturally and surgically menopausal women not using concurrent estrogen therapy (306). The baseline mean frequency of total sexual activity across the various testosterone patch studies was five to six events per month. These women reported that, on average, they experienced satisfying experiences two to three times per month. With the 300-μg testosterone patch, the mean increase in satisfying sexual events per month over baseline was 2 to 2.5 times *vs.* 0.5 to one time with placebo.

Dehydroepiandrosterone (DHEA) at an oral dose of 50 mg/d does not significantly improve sexual function in postmenopausal women with HSDD who are not using concurrent estrogen (307). The effects of systemic DHEA in combination with estrogen for the treatment of HSDD are not known.

Mood and depression

Depression has a lifetime prevalence of 18% and is predicted to be second only to heart disease as a source of morbidity both in the United States and worldwide by 2020. Reports of increased mood symptoms and depressive disorders during perimenopause and postmenopause date back more than 150 yr and generated the belief that reversal of these symptoms could be achieved with ovarian hormone replacement. Controversy regarding the antidepressant efficacy of hormone replacement stems almost from its inception (308, 309). This problem reflects the same methodological inconsistencies that have compromised efforts to determine whether perimenopause and postmenopause are accompanied by an increase in mood symptoms or depression. Methodological differences of note (other than study design) include menopausal state (perimenopause *vs.* postmenopause), determination of state (earlier studies used age as a proxy measure), baseline symptomatology (asymptomatic *vs.* depressive symptoms *vs.* "syndromal" or clinical depression), and symptom or syndrome measure.

Meta-analyses

A meta-analysis of 26 studies of the effects of MHT on depressive symptoms in perimenopausal and postmenopausal women revealed a moderate-to-large-effect size of 0.68, showing lower ratings of depressed mood in treated patients compared with controls (310). Baseline symptom rating scores were suggestive of clinically significant depression in only two of these studies. Twenty-two additional studies have been published since this earlier meta-analysis, nine of which are double-blind and placebo-controlled.

RCTs

Nondepressed patients. Among the double-blind, placebo-controlled studies, two had large sample sizes and showed no effect of CEE on affective symptoms in postmenopausal women. However, subjects in both studies were affectively asymptomatic at baseline or discouraged from participating if menopausal symptoms were present (288, 292). An additional trial of estrogen in significantly older women (older than age 70 yr) showed no improvement in mood compared with placebo (311). These studies, then, provide moderate to strong evidence for a statement of limited clinical value: estrogen does not prevent or remedy symptoms of depression in an asymptomatic, postmenopausal population. Nonetheless, data from the HERS study suggested that among postmenopausal women, those with menopausal symptoms showed lower depressive symptoms on MHT than did those lacking menopausal symptoms (312).

Depressed patients. Two small randomized, placebo-controlled trials demonstrated the antidepressant efficacy of transdermal estradiol in depressed, perimenopausal women. Selected subjects met diagnostic criteria for depression and were followed with standard syndrome-rating scales (313, 314). A study employing similar methodology failed to show antidepressant efficacy of transdermal estradiol in a postmenopausal sample (315). One study did demonstrate antidepressant efficacy of a continuous-combined E+P preparation in postmenopausal women selected with diagnostic criteria for the presence of mild to moderate depression. This study was performed by the makers of the E+P preparation and, while methodologically sound, showed a very high dropout rate (316). Remaining studies provide less compelling evidence regarding the antidepressant efficacy of estrogen or E+P consequent to methodological concerns.

Observational or flawed RCTs. 1) Three noninterventional survey studies showed either no effect of MHT on mood symptoms or effect only in white women with menopausal symptoms (317–319). 2) Two RCTs showed improvement in mood symptoms in postmenopausal women with mild to moderate depression, albeit with unblinded assignment to and lack of baseline depression matching for the active placebo group (320, 321). 3) Five open-label studies showed mixed results (314, 322–325). 4) Three randomized studies (one single blind) lack placebo controls and showed either no effect (326, 327) or positive effect (328) of MHT on mood symptoms in nondepressed perimenopausal or postmenopausal women. 5) One double-blind, placebo-controlled trial of estradiol implants presents multiple methodological confounds (329).

Other changes

MHT and skin aging

Assessing the benefits of MHT on skin is complicated due to the combined effects of intrinsic aging (including estrogen loss) and extrinsic aging (UV radiation, smoking, *etc.*). Reduced estrogen levels associated with menopause have been linked to age-related changes in the skin, such as coarse and fine wrinkling, skin laxity, and rough or dry skin texture. Biopsies of skin from postmenopausal women are most notable for a loss of skin collagen content, which is sometimes taken as a marker for skin wrinkling (330). Several bodies of evidence point to the potential benefit of estrogen therapy or E+P in the treatment of skin changes associated with menopause. Studies in rodents suggest a benefit of estrogen on skin vascularization (331). Several observational studies suggest a benefit of

MHT on parameters such as wrinkling, facial laxity, and wound healing.

A limited number of RCTs examined the effects of oral MHT on the skin of postmenopausal women (332–334). In three of these studies, improvement in skin thickness or collagen content was noted when subjects in the MHT group were compared with their baseline (but not to the placebo group). Phillips *et al.* (335) noted improvements in the global assessment of coarse and fine wrinkling over time in women treated for 48 wk with NETA or ethinyl estradiol. However, they noted no statistical differences in those scores *vs.* subjects in the placebo group and concluded that low-dose MHT did not significantly alter mild-to-moderate, age-related facial skin changes in postmenopausal women (335). Studies of topical estrogen applied to human skin indicate an increase in collagen in sun-protected skin but not in sun-exposed skin (336).

MHT and immune disorders

Autoimmune diseases are a diverse group of disorders that may be systemic, such as systemic lupus erythematosus (SLE), or organ specific, such as thyroiditis. Most autoimmune diseases have a predilection for women, especially women of child-bearing age. The basis for this predilection remains controversial but suggests a role for estrogen. The specific effects of estrogen on the immune system are complex and include some responses that may be classified as antiinflammatory, whereas others are proinflammatory (337). Animal models and human studies have shown that multiple factors appear to play a role in defining the clinical effect of estrogen. These include: 1) the dose of estrogen and whether it is given in conjunction with progestogens; 2) the specific estrogen receptor expressed; 3) the time of administration in the inflammatory process (prodromal phase, which can last several years, or the symptomatic phase); and 4) the specific immune cell-type involved (B cells are stimulated, whereas T cells are inhibited by estrogen). MHT causes several changes in the immune system in experimental subjects, such as decreased levels of natural killer cells, CD4+, CD8+, CD11b+, and memory T cells, and increased CD19+ B cells (338–341).

For most autoimmune diseases, there are as yet no large RCTs examining the effects of MHT on the risk of development of the disease or disease activity. The NHS demonstrated that MHT increased the risk of development of SLE (RR, 1.9; CI, 1.2–3.1) (342), but a smaller population-based study found no association between incidence of SLE and current or prior MHT use (343). The SELENA-SLEDAI RCT (344) assessed SLE flares during 12 months of treatment with E+P (0.625 mg CEE + 5 mg MPA 12 d per month) *vs.* placebo in women with SLE. The use of

E+P was associated with mild or moderate flares (RR, 1.34; CI, 1.07–1.66) (344), but not severe flares (RR, 1.75; CI, 0.73–4.22).

MHT does not increase the risk of development of rheumatoid arthritis (RA) as shown by a *post hoc* analysis of the WHI cohort, which demonstrated a nonsignificant reduction in self-reported incidents of RA among combined MHT users (RR, 0.76; CI, 0.51–1.12) and E-only users (RR, 0.69; CI, 0.41–1.14) (345). Small studies have suggested that MHT (using a variety of preparations) has either a neutral or beneficial effect on RA disease activity (343, 346–349).

The data regarding other autoimmune diseases are more limited, but one report suggests that MHT increases the risks of mixed connective tissue disease and scleroderma (350). Additionally, there appears to be an increased prevalence of Raynaud's syndrome and in the severity and incidence of asthma with the use of MHT (351, 352). Finally, in multiple sclerosis, some data suggest that menopause is associated with worsening symptoms; however, a beneficial effect of MHT has not been consistently demonstrated (353, 354). Limited information is available concerning MHT use in Sjögren's syndrome and autoimmune polyglandular syndrome (355–358).

MHT and gallbladder disease risk

Treatment with oral estrogen or E+P increases the risk of cholecystitis, cholelithiasis, and cholecystectomy. In two U.S. RCTs (HERS and WHI), administration of E+P (CEE 0.625 mg, and MPA 2.5 mg daily) to women of average age of 68 yr (359) and 63 yr (360) was associated with an increased risk of gallbladder disease (both cholecystitis and cholelithiasis). The increase in rate of cholecystectomy in women with known coronary disease in the HERS trial just reached statistical significance ($P = 0.05$). Excess (attributable) risk represented 27 women per 1000 taking E+P for 5 yr. In the WHI RCT (360), there were 55 gallbladder events (cholecystectomy, cholelithiasis, and cholecystitis) per 10,000 person-years in the active E+P arm, compared with 35 per 10,000 in the placebo arm. Both studies reported that the risk increased with duration of use. Women treated with estrogen in the WHI RCT (360) had an incidence rate of 15.5 per 1000 per 5 yr of use attributable to the MHT. Increases in risk for cholecystitis and cholelithiasis were seen in both trials. The risks for combined E+P were similar to risks for E alone. The majority of participants in all three of these RCTs were older than women who are conventionally prescribed MHT, and most were overweight or obese, increasing their absolute risks of disease.

A large cohort study of women ages 50 to 69 yr studied in the United Kingdom (361) in the MWS showed that in nonusers of MHT, 26 per 10,000 per year were admitted

to hospital with gallbladder disease and 22 for cholecystectomy. For current users of transdermal estrogen, the rates were 30 and 26, respectively, representing an excess (attributable) risk of 2 per 1000 for 5 yr. For oral therapy, the excess (attributable) risks were 10 per 1000 women for 5 yr and 9 per 1000 per 5 yr, respectively. Oral estrogen was thus associated with higher risks than transdermal estrogen, and absolute risks in the UK study were somewhat lower than those in the RCTs in the United States, almost certainly reflecting a leaner population in the United Kingdom. The UK study also reported on type and dose of estrogen, showing that equine estrogen conferred slightly higher risks than estradiol and that higher doses were associated with somewhat higher risk than lower doses. Risk dissipated over 10 yr from cessation ($P = 0.004$ for trend), but minimal increased risk persisted. Similar findings were reported in the NHS in the United States (362).

Minimal data exist regarding gallbladder cancer. One case-control study was conducted in Italy between 1985 and 1997 on 31 incident, histologically confirmed cases of gallbladder cancer (363). This study reported an increased risk for MHT users with a trend toward increasing risk with longer duration of use. However, no gallbladder cancers were reported in the largest RCTs and cohort studies (359–362).

Geriatric considerations

Macular degeneration

Nearly 1.7 million people in the United States have either early or late macular degeneration, a leading cause of blindness (364). Although pathogenesis is poorly understood, higher rates in women than in men suggest the possibility of a hormonal link. One RCT, two cohort studies, three cross-sectional, and one case-control study have examined the effect of MHT on macular degeneration (364–369). For purposes of analysis, lesions can be divided into: 1) drusen; 2) early age-related macular degeneration (AMD); and 3) neovascular AMD. Minimal data are available regarding the effects of MHT on drusen, and the results are conflicting with trends toward improvement in the Salisbury Eye Project (368) and the E+P arm of the WHI study (364). No change was observed in the E-alone arm of the WHI study (364). For early AMD, the NHS reported a trend toward an increase in these lesions with E alone (RR, 1.27; CI, 0.97–1.66) and a statistically significant increase with E+P (RR, 1.45; CI, 1.07–1.96), whereas the WHI and the Study of Fractures (SOF) detected no differences (364–366). For neovascular AMD, the NHS (364), SOF (366), Eye Disease Case-Control (370), and Snow *et al.* (369) studies reported reductions, but this was not uniform among all studies (Table 10).

Data are not sufficient to determine whether the effects of E alone differed from those of E+P for all categories.

Cognitive aging: decline and dementia

The usual aging process is often accompanied by mild cognitive decline. Not all cognitive skills show change, and occupational and social activities are typically unaffected. The concept of cognitive aging excludes the severe decrements characteristic of dementia and cognitive impairment (371) believed to presage overt dementia. Loss of ovarian hormone production after menopause is speculated to be a potential contributor to cognitive aging and dementia (372). An assortment of tests has been used to assess cognition in relation to menopause and MHT. Most studies include a memory measure, but other cognitive functions have been less thoroughly examined.

Cognitive decline. Complaints of memory loss are common around the time of menopause. However, cross-sectional and longitudinal findings from midlife cohorts suggest that the natural menopausal transition is not associated with important objective changes in memory or other cognitive skills (373–377). This inference is supported by results from clinical trials of MHT in middle-age women (378). Thus, in a trial of 180 naturally menopausal women, there were no significant cognitive differences between groups after 4 months, when MHT (CEE plus MPA) was compared with placebo (379). Reports from other trials in this age group are generally consistent, but numbers of participants in those trials were smaller, interventions were of even shorter duration, and the trials lacked statistical power to detect moderate effects of MHT (378).

Findings from large observational studies of older women vary. In Cache County, Utah, for example, ever-use of MHT was associated with slower rates of cognitive decline (380). In contrast, long-term MHT use (E alone or E+P) in the NHS was associated with increased risk of cognitive decline, especially for use initiated at older ages (381). More consistent results come from relatively large RCTs of women ages 60 yr and older without identified cognitive impairment. In the WHI Memory Study (WHIMS) of women 65 to 79 yr of age, the active intervention arm with CEE was compared with the placebo arm. Women with a uterus were randomized to CEE plus MPA or placebo in a continuous-combined formulation. After average follow-up periods of 4 to 5 yr, mean scores on a test of global cognitive ability were very slightly lower among women in the hormone groups than among women receiving placebo (382). A WHIMS ancillary study found that the combined CEE-MPA formulation was associated with small deleterious effects on verbal memory and a small beneficial effect on nonverbal memory (383). In

TABLE 10.   MHT: drusen, early AMD, and neovascular AMD

| Study | Type | Drusen | | |
		T	E	E+P
NHS	Cohort			
WHI	RCT		1.05 (0.84–1.30)	0.83 (0.68–1.00)
SOF	Cohort			
Eye disease	Case control			
Salisbury eye project	Cross-sectional	0.5 (0.3–1.1)		
Snow *et al.*	Cross-sectional			

Data are expressed as RR (CI). T, All patients regardless of receiving E or E+P.

women with underlying vascular disease, CEE plus MPA (384) and oral estradiol (385) had little effect on most cognitive measures. In other trials of older healthy post-menopausal women, 20 wk of oral estradiol (311) and 2 yr of very-low-dose transdermal estradiol (386) did not affect cognitive outcomes. Smaller trials in this age group generally failed to show an effect of hormone treatment (378).

Surgical menopause occurs at an earlier mean age than natural menopause and involves the abrupt loss of hormones produced by ovarian follicles (*i.e.* estradiol, progesterone) and stroma (*i.e.* androgen precursors). Cognitive outcomes after surgical menopause have been infrequently examined. In a study in Rancho Bernardo, California, surgical menopause was not associated with cognitive deficits later in life (387), but in Olmsted County, Minnesota, oophorectomy was associated with increased risk of cognitive impairment or dementia (388). Small, short-term clinical trial data suggest that estrogen treatment begun at the time of oophorectomy can enhance verbal memory (389, 390). Trials in which surgical menopause was defined by hysterectomy rather than oophorectomy and in which interventions did not begin at the time of surgery failed to show significant effects of treatment (378).

Dementia. Alzheimer's disease is the most common cause of dementia in most countries, and the incidence of dementia in general and Alzheimer's disease in particular climbs steeply with age (391, 392). Whether Alzheimer's disease incidence varies by sex is controversial (391, 392), but more women than men suffer from this disorder, in large part because of greater longevity and longer survival after diagnosis.

Clinical trials of MHT for Alzheimer's disease have been small and of relatively short duration. Several smaller trials suggested benefits on a subset of cognitive outcomes (393), but other trials report no differences between groups (394–397). The largest of these trials randomized 120 women without a uterus to conjugated estrogens or placebo. At 12 months, there were no differences between estrogen and placebo groups on most cognitive outcomes (396).

Dementia outcomes have been examined in only one clinical trial (*i.e.* WHIMS), in which incident dementia was identified in 108 women (398, 399). In half, the diagnosis was Alzheimer's disease. Dementia incidence was greater in hormone groups compared with placebo (RR, 2.05; CI, 1.21–3.48, for women with a uterus; and RR, 1.49; CI, 0.83–2.60, for women without a uterus) (399). Associations between MHT and Alzheimer's disease risk have been considered in a number of observational studies, including Leisure World (400), Northern Manhattan (401), the Baltimore Longitudinal Study on Aging (402), and Cache County (403). Although dementia risk was increased in the WHIMS trials (398, 399), meta-analyses of observational studies imply reductions in Alzheimer's disease risk of about one third (404, 405). The apparent discrepancy is not fully understood. Unrecognized confounding is a concern for the observational studies, as are both recall bias in studies of older women asked to report hormone use many years before enrollment and the healthy-user bias (406). Differences in study populations are another concern (373). Much of the hormone exposure in observational studies is presumed to have occurred during midlife (407); randomized exposures in WHIMS began at age 65 yr or older. It is speculated that MHT effects on dementia risk may differ based on age of exposure or timing of exposure in relation to menopause, although supporting evidence in humans is indirect.

In a large clinical trial of older postmenopausal women with osteoporosis, the selective ER modulator (SERM) raloxifene had no effect on memory or other cognitive test scores after 3 yr (408). High-dose raloxifene, however, reduced the risk of incident cognitive impairment in this trial (409).

Special Considerations

Use of hormones for premature menopause

Shuster *et al.* (410) reported that premature loss of ovarian function due to bilateral oophorectomy before natural menopause was associated with an increased risk

Early AMD			Neovascular AMD			
T	E	E+P	T	E	E+P	Refs.
1.34 (1.06–1.68)	1.27 (0.97–1.66)	1.45 (1.07–1.96)	0.52 (0.38–0.71)	0.49 (0.34–0.72)	0.48 (0.28–0.80)	364
	0.98 (0.78–1.25)	0.84 (0.68–1.04)		1.15 (0.45–2.98)	0.57 (0.25–1.35)	365
	1.01 (0.77–1.34)	0.85 (0.55–1.30)				366
			0.3 (0.1–0.6)			370
0.8 (0.4–1.6)			1.1 (0.3–3.7)			368
				0.62 (0.39–0.96)	0.60 (0.29–1.24)	369

of premature death, CVD, cognitive impairment and dementia, Parkinsonism, osteoporosis and bone fractures, and declines in psychological well-being and sexual function (Table 11). Estrogen treatment is usually recommended to provide cardiac and bone protection and maintain healthy sexual function in such patients. However, a paucity of large RCTs is available to guide decision-making, and evidence from studies of older women (172, 411) likely does not apply. In women with ovarian failure or surgical menopause before the age of 40 yr, risk-*vs.*-benefit data must rely on observational studies and small RCTs (412).

Observational data on surgical menopause

Mortality. Parker *et al.* (10) recently reported data from the NHS on women who underwent bilateral hysterectomy for benign disease with either conservation or removal of ovaries. Ovarian removal was associated with a decreased risk of breast cancer (RR, 0.75; CI, 0.68–0.84) and ovarian cancer (RR, 0.04; CI, 0.01–0.09) but an in-

creased risk of total mortality (RR, 1.12; CI, 1.03–1.21), fatal and nonfatal CHD (RR, 1.17; CI, 1.02–1.35), stroke (RR, 1.14; CI, 0.98–1.33; not formally statistically significant), and lung cancer (RR, 1.26; CI, 1.02–1.56). Based on an approximate 35-yr life span after surgery, Parker and Manson (413) calculated one additional death for every nine oophorectomies performed. It was surprising that the reduction in breast, ovarian, and total cancers did not outweigh other effects associated with increased overall mortality. Notably, prophylactic oophorectomy did not improve survival at any age.

Parker *et al.* (10) also reported on a subset of 10,094 women with either bilateral oophorectomy at younger than age 50 yr or ovarian conservation who had never used estrogen. Those having undergone bilateral oophorectomy experienced an increased risk of all-cause mortality (RR, 1.54; CI, 1.17–2.02), fatal and nonfatal CHD (RR, 1.73; CI, 1.17–2.57), and stroke (RR, 1.88; CI, 1.18–3.02) with no difference in total cancer risk. Similar results of an increased mortality with bilateral oophorectomy before age 45 yr (RR, 1.67; CI, 1.16–2.40; $P = 0.006$) were seen in the Mayo Cohort Study (414), mostly in nonusers up to age 45 yr (RR, 1.93; CI, 1.25–2.96).

Using a Markov decision analysis model of mortality attributable to oophorectomy at hysterectomy, Parker *et al.* (415) predicted 8.6% excess mortality by age 80 yr. Ovarian conservation between ages 50 and 54 yr led to an 8% increased survival rate due to fewer deaths from CVD and hip fracture. Between ages 55 and 59 yr, a 4% survival advantage occurred with no difference in survival after age 64. Women with hysterectomy for benign disease at average risk of ovarian cancer were calculated to benefit from ovarian conservation until at least age 65 yr (416).

Cardiovascular risk. The "timing" hypothesis (discussed previously), suggests that earlier menopause and fewer years from menopause might be stronger risk factors for CHD events than age (417). A meta-analysis of 11 observational studies found that bilateral oophorectomy doubled the RR of CVD (RR, 2.62; CI, 2.05–3.35) (418) com-

TABLE 11. Hysterectomized women and bilateral oophorectomy

	RR (CI)
Increased risks with bilateral oophorectomy	
Total mortality	1.12 (1.03–1.21)
Fatal plus nonfatal CHD	1.17 (1.02–1.35)
Stroke	1.14 (0.98–1.33)
Lung cancer	1.26 (1.02–1.56; NNH [harm] = 190)
Total cancer mortality	1.17 (1.04–1.32)
Decreased risks with bilateral oophorectomy	
Breast cancer	0.75 (0.68–0.84)
Ovarian	0.04 (0.01–0.09; NNT [treatment] = 220)
Total cancers	0.90 (0.84–0.96)

NNH, Number needed to harm; NNT, number needed to treat.

pared with natural menopause or premenopausal status. Bilateral oophorectomy at ages younger than 50 yr compared with older than 50 yr was associated with a RR of 4.55 (CI, 2.56–8.01). Natural menopause at ages younger than 50 yr compared with older than age 50 yr was associated with a RR of 1.27 (CI, 1.14–1.43). Hysterectomy with oophorectomy was an independent predictor of risk from myocardial infarction or coronary death using the Framingham scoring system (419). More severe coronary atherosclerosis has been found at autopsy in women with prior bilateral oophorectomy (420).

The effect of estrogen use on CVD events and mortality in women not prematurely menopausal remains inconclusive (see *Coronary heart disease and lipids*) (413). However, data from the Danish Nurse Cohort Study of younger women who had undergone bilateral oophorectomy and were given estrogen provide suggestive evidence of a protective effect (421). The adjusted risk of CVD with bilateral oophorectomy at ages younger than 40 yr compared with older than age 45 yr was 8.7 (CI, 2.0–38.1) after 5 yr of follow-up (421). After bilateral oophorectomy, estrogen provided significant protection against CVD (RR, 5.5 among ever-users *vs.* 16.2 among never-users), with most pronounced benefits for current users or those who started MHT within 1 yr after surgical menopause.

Additional evidence suggesting protection comes from the Mayo Clinic Cohort Study (422). Whereas bilateral oophorectomy was associated with increased cardiovascular-related mortality (RR, 1.44; CI, 1.01–2.05), this risk fell with use of estrogen. Specifically, in women undergoing oophorectomy before age 45 yr not taking estrogen, total cardiovascular-related mortality was significantly increased (RR, 1.84; CI, 1.27–2.68) compared with that of users of estrogen (RR, 0.65; CI 0.30–1.41).

Cognition. Observational and small RCTs suggest that cognitive impairment occurs with surgical menopause, primarily affecting verbal episodic memory (378), but evidence is conflicting. Vearncombe's analysis of recent trials (423) did not find an effect of surgical menopause on cognitive functioning. Substantial methodological problems, including lack of long-term follow-up and limited assessment of cognitive domains, could have confounded the interpretation of these studies. Bilateral oophorectomy before natural menopause in the Mayo Cohort Study was associated with an increased risk of Parkinsonism, cognitive impairment, dementia, depression, and anxiety (388, 424). The increased risk of dementia was seen in those younger than age 43 yr, specifically those younger at the time of surgery and those who discontinued estrogen therapy before age 50 yr (RR, 1.74; CI, 0.97–3.14; $P = 0.06$).

The trend toward increasing risk with younger age at oophorectomy was significant ($P = 0.01$) for those who underwent oophorectomy before age 49 yr and were not treated with estrogen until at least age 50 yr (RR, 1.89; CI, 1.27–2.83; $P = 0.002$).

The results of studies of the effects of estrogens on cognition have been conflicting (382, 398). As a possible explanation, Henderson and Sherwin (378) suggested that estrogen might have an age-dependent neuroprotective effect on the brain (378, 425). They proposed the "critical window" or "timing" hypothesis, which suggests that estrogen begun later in menopause does not benefit cognitive outcome and, instead, is detrimental, whereas early initiation of estrogen might reduce dementia risk (378, 382, 425–427).

Bone. Women with declining ovarian reserve and those with premenopausal vasomotor symptoms have shown increased bone turnover and bone loss (428, 429). Guthrie *et al.* (430) found that this correlated best with plasma estradiol levels, whereas Sowers *et al.* (429) found the best correlation with FSH and suggested direct effects of FSH on bone. Early menopause and oophorectomy before age 45 yr are associated with lower BMD and higher osteoporotic fracture rate (431–433), which is reduced with estrogen (434–436). In a systematic review of RCTs (437), estrogen for an average of 6.2 yr reduced incident fractures by 52% (CI, 18–64%). Lower than standard doses of estrogen and E+P prevent bone loss with milder effect on BMD (438, 439). Discontinuation of MHT leads to rapid bone loss of 3 to 6% during the first year and consequent loss of fracture protection (34).

Mood disorders. Limited RCT data have shown an association between depression or sexual problems before oophorectomy and increased risk for negative mood and libido effects postoperatively (440, 441). Oophorectomy and hysterectomy have been associated with significantly greater anxiety and depression, with a less positive sense of well-being compared with ovarian conservation. Oophorectomized women on estrogen reported less anxiety and depression, however, similar to women with ovarian conservation (442). Bilateral oophorectomy in the observational Mayo Study was associated with an increased risk of developing *de novo* depressive symptoms (RR, 1.54; CI, 1.04–2.26) and *de novo* anxiety symptoms (RR, 2.29; CI, 1.33–3.95) compared with referent women. This effect occurred in women who did not suffer these symptoms before the surgery with persistence after surgery (424).

Sexuality. Cross-sectional and longitudinal studies suggest that bilateral oophorectomy has a greater negative

impact on sexual functioning than hysterectomy, due to combined loss of estradiol and testosterone. Surgical menopause (bilateral oophorectomy) either premenopausally or postmenopausally is associated with a rapid decline (up to 50%) in testosterone (443). Hysterectomized women with oophorectomy reported greater loss of libido than those with ovarian conservation. Compared with hysterectomized women, bilateral oophorectomy was associated with anorgasmia 12 months postoperatively (444). These women experienced overall worsening of sex life postoperatively, with lower coital frequency (442), lower libido, less lubrication, and less coital pleasure than those who retained their ovaries (445). Similarly, Dennerstein *et al.* (446), in a cross-sectional survey, found surgically menopausal women more likely to have low sexual desire and more likely to have HSDD (RR, 2.1; CI, 1.4–3.4; $P = 0.001$) compared with premenopausal or naturally menopausal women (RR, 1.4; CI, 1.1–1.9; $P = 0.02$).

Possible mechanisms to explain findings. Estrogen levels are higher in women with intact ovaries than in women after bilateral oophorectomy, even among older women. Oophorectomy before menopause leads to an abrupt reduction in endogenous estrogen, progesterone, and androgen production with disruption of the hypothalamic-pituitary-ovarian axis, which causes an increase in gonadotropins. Surgical and chemical menopause with abrupt withdrawal of estrogen has the potential to exert different neurobiological effects than those occurring with natural menopause (447, 448). The responses to estrogen in women with premature menopause (natural or surgical) may be different than those in older menopausal women.

MHT in breast cancer survivors

Women treated for breast cancer continue to seek advice about MHT for the relief of estrogen-deficiency symptoms when nonhormonal alternatives are not sufficiently effective. Whether occurring as a consequence of natural or iatrogenic menopause, these symptoms can significantly impair QOL and present a clinical dilemma (449). The use of MHT in breast cancer survivors has been controversial (450–452). Some investigators suggest that MHT might have an adverse effect on occult lesions not cured by previous treatment in women with ER-positive disease. A reduction in the therapeutic benefit of aromatase inhibitors would be anticipated with use of exogenous MHT in such patients. However, concomitantly prescribed tamoxifen would be predicted to prevent any growth-promoting effect of MHT because it blocks the ER in the presence of endogenous estrogen. Most assume that MHT will be safe in ER-negative disease. However, if exogenous E+P is associated with an increased risk of new breast cancer primaries, its use in breast cancer survivors might likewise be detrimental.

Observational data comparing breast cancer survivors who are MHT users or nonusers may be flawed due to an underlying bias in patient selection, although the summary data suggested decreased recurrence rates and mortality in the MHT-treated survivors across several observational studies (453–456). Three large randomized trials established to answer whether MHT is safe in breast cancer survivors have all been closed prematurely by trial safety-monitoring boards due to concern regarding increased risk of recurrence (451, 457). Two of these studies published initial reports [the HABITS, Hormonal replacement therapy After Breast cancer—Is iT Safe? (457), and the Stockholm trials (456)]. One of these extended the follow-up period and published an update (451). The third, the LIBERATE (Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints) trial with tibolone, is summarized in Table 12. Preliminary analyses of the two Scandinavian studies (HABITS and Stockholm) were conflicting, with HABITS reporting an increased risk and Stockholm reporting no effect of MHT on recurrence. The adverse outcome in HABITS has been attributed to greater progestogen exposure (long-cycle combined therapy was used preferentially by the Stockholm investigators) and less tamoxifen use, and commentators noted that indirect evidence for a breast-protective effect of tamoxifen is provided by data from the European tamoxifen chemoprevention trials (458, 459). The most recent publication from the HABITS study does not support this finding regarding tamoxifen, but, as with previous analyses, the number of breast cancer events is too small for reliable interpretation of subgroup outcomes (451). The placebo-controlled LIBERATE study has shown an increased risk of distant metastases in women allocated to tibolone that appears to be restricted to those with ER-positive cancer (460) and was seen particularly in women treated with aromatase inhibitors (Table 12). Again, whereas events are small in number, tibolone would appear to negate any benefit of concomitantly prescribed aromatase inhibitors (460, 461).

It is not possible to determine whether there is a "breast neutral" MHT option for breast cancer survivors from published data. The HABITS investigators found no differences in risk across the main categories of MHT use, but events were few (451). Interest in minimizing progestogen exposure by using the levonorgestrel-releasing intrauterine system (LNG-IUS) combined with an estrogen remains unproven. A small cohort study of the LNG-IUS alone suggests that a longer duration of exposure may be associated with increased recurrence, but

TABLE 12. Outcomes of randomized MHT and tibolone trials in women treated for breast cancer

	HABITS 2004[a]	HABITS 2008[a]	Stockholm 2005[a]	LIBERATE 2009[b]
Baseline characteristics (%)				
n	345/457	447/451	378/456	3148/460
Lymph node+ ve	26/21	19.7/20	18/18.8	57.7/58
ER+ ve	56/48	62.3/56	65/54.5	71.5/69.6
Tamoxifen	21/21	33.6/53	52/33.5	66.6/66.9
Aromatase inhibitor				6.6/6.4
Breast cancer events, RR (CI)				
All women	3.5 (1.5–8.1)	2.2 (1.0–5.1)	0.82 (0.35–1.90)	1.39 (1.14–1.70)
ER+ ve	4.8 (1.1–21.4)	2.6 (1.3–5.4)		1.56 (1.22–2.01)
ER− ve	1.9 (0.4–9.6)	1.8 (0.7–4.8)		1.15 (0.73–1.80)
Lymph node+ ve		2.3 (0.8–6.4)		1.85 (1.14–2.99)
Lymph node− ve		2.4 (1.1–5.4)		1.36 (1.09–1.69)
Current tamoxifen	2.8 (0.3–27.4)	4.7 (1.4–16.2)		
No tamoxifen	3.7 (1.5–9.0)	1.9 (1.0–3.6)		1.69 (1.14–2.49)
Tamoxifen at baseline				1.25 (0.98–1.59)
Aromatase inhibitor at baseline				2.42 (1.01–5.79)
Recurrence				
Locoregional	11 *vs.* 2	17 *vs.* 4	5 *vs.* 5	48 *vs.* 33; 1.412 (0.91–2.21)
Contralateral cancer	5 *vs.* 1	11 *vs.* 4	3 *vs.* 3	25 *vs.* 17; 1.39 (0.74–2.59)
Distant	10 *vs.* 5	10 *vs.* 8	3 *vs.* 8	171 *vs.* 121; 1.38 (1.09–1.74)
Mortality				
Breast cancer	3 *vs.* 4	0 *vs.* 0	2 *vs.* 4	54 *vs.* 49
Nonbreast cancer	2 *vs.* 0	3 *vs.* 0	2 *vs.* 5	72 *vs.* 63; 1.12 (0.80–1.6)

[a] Data represent MHT/no MHT for basic characteristics and MHT vs. no MHT for breast cancer events, recurrence, and mortality.

[b] Data represent tibolone/placebo for basic characteristics and tibolone *vs.* placebo number of events for breast cancer events, recurrence, and mortality.

affected breast cancer patients had worse disease prognosis at diagnosis (462). A recent larger cohort study in healthy women, however, has shown an increased risk with the LNG-IUS, irrespective of the concomitant prescription of estrogen (463). There is no published clinical evidence to support the concern that serum estrogen levels attained with vaginal estrogens will increase recurrence in women using aromatase inhibitors, but caution has been advised (464).

Retrospective analysis from the UK IBIS-I tamoxifen chemoprevention trial and a cohort study have concluded that, in the presence of tamoxifen, MHT is ineffective at ameliorating estrogen deficiency symptoms (465, 466). However, this was an *a priori* hypothesis in the randomized UK trial of MHT, in which significant symptom relief was achieved with MHT, irrespective of tamoxifen exposure.

The conflicting results from the Stockholm and HABITS RCTs make it impossible to draw firm conclusions regarding the possible risks of MHT in breast cancer survivors (451, 456), and the use of tibolone must be viewed with great caution. Current cancer position statements and clinical guidelines advise that MHT should be contraindicated or discouraged (467–469). Nonetheless, impaired QOL will outweigh recurrence and survival issues for some women.

MHT and total mortality

In the WHI, the RRs for all-cause mortality were 1.04 (CI, 0.88–1.22) in the CEE-alone trial and 1.00 (CI, 0.83–1.19) in the CEE plus MPA trial (5). Age appeared to modulate the effect of MHT on total mortality, however. In an analysis that pooled data from both trials, MHT was associated with a significant reduction in mortality (RR, 0.70; CI, 0.51–0.96) among women ages 50 to 59 yr. This would represent five fewer deaths per 1000 women per 5 yr of therapy. A Bayesian meta-analysis from 19 randomized trials reported similar data with a RR of mortality of 0.73 (CI, 0.52–0.96) for women younger than age 60 yr (470). However, MHT had minimal effect among those between 60 and 69 yr of age (RR, 1.05; CI, 0.87–1.26) and was associated with a borderline significant increase in mortality among those ages 70 to 79 yr (RR, 1.14; CI, 0.94–1.37; P for trend = 0.06) (133). This pattern was observed in both trials when examined separately. Similarly, in the HERS trial comprising participants with a mean age of 66.7 yr, MHT was not associated with any reduction in total mortality (RR, 1.08; CI, 0.84–1.38) (471). In a 2003 meta-analysis of 30 randomized trials of MHT in relation to mortality, MHT was associated with a nearly 40% reduction in mortality in trials in which participants had a mean age of less than 60 yr or were within 10 yr of menopause onset but was unrelated to mortality in the other trials (472). The findings in the younger age groups were similar to those in the observational NHS (RR for mortality, 0.63; CI, 0.56–0.70) (473).

Alternative Forms of MHT

Tibolone as MHT

Tibolone is a synthetic steroid that is approved for use to treat menopausal symptoms in Europe and Australia but not in the United States. This compound is metabolized to two estrogenic metabolites, 3α and 3β, which then circulate predominantly in their sulfated inactive forms (474). These metabolites become estrogenically active only when the sulfate group is cleaved by the sulfatase enzyme in target tissues. Tibolone itself and its 3β metabolite may be converted to a $\Delta4$-isomer, which can bind and transactivate the progesterone and androgen receptors. Tibolone also significantly lowers SHBG and increases circulating free testosterone, further adding to its androgenicity (475).

Tibolone alleviates postmenopausal vasomotor symptoms and improves urogenital atrophy (476, 477). At a dosage of 1.25 mg/d for 2 yr, tibolone prevents postmenopausal bone loss in older women and results in a larger increase of BMD at both the lumbar spine and hip than does raloxifene 60 mg/d (478). In osteoporotic women over the age of 60 yr who were studied for 3 yr, tibolone significantly reduced the incidence of vertebral and non-vertebral fractures (RR, 0.55; CI, 0.41–0.74; $P = <0.001$; and RR, 0.74; CI, 0.58–0.93; $P = 0.01$, respectively) and was associated with a reduced risk of breast cancer (RR, 0.32; CI, 0.13–0.80; $P = 0.02$) and colon cancer (RR, 0.31; CI, 0.10–0.96; $P = 0.04$) (479, 480). These breast cancer data conflict with a reported increase in breast cancer risk in the MWS (112). However, randomized, controlled trial data support a beneficial effect and outweigh the observational data from the MWS that could be confounded by biases inherent in an observational study (480). The incidence of breast tenderness with tibolone is low, and mammographic density does not generally increase (99, 481). Of interest is the fact that tibolone increases the risk of breast cancer recurrence in breast cancer survivors (460).

Tibolone has been associated with an increased risk of stroke in older women, but this has not been observed in multiple RCTs of younger women (481). Tibolone also does not increase the risk of VTE disease or CHD events (479). There have been conflicting reports in the literature about the endometrial safety of tibolone. In a large RCT comparing tibolone 1.25 and 2.5 mg to CEE plus MPA, tibolone did not induce endometrial hyperplasia or carcinoma in postmenopausal women, and it was associated with a better vaginal bleeding profile than that of CEE plus MPA (481). In addition, rates of breakthrough bleeding after commencement of tibolone are low (300). Tibolone improves sexual well-being in postmenopausal women presenting with low libido, with greater improvements in desire, arousal, satisfaction, and receptiveness than that seen with transdermal estrogen-progestogen therapy (482). Recent composite tibolone data from phase 2–4 studies in 7904 women showed no increase in VTE with tibolone compared with 3527 women on placebo. Mechanistically, tibolone does not activate the coagulation cascade (483).

Raloxifene as MHT

The SERM raloxifene, although known to exert estrogenic effects on bone, clotting factors, and lipids, exerts antiestrogenic actions on breast, uterus, vaginal tissues, and brain centers controlling hot flashes. As a result of its estrogenic actions, raloxifene at 60 mg/d improves BMD (lumbar spine, 2.6%; femoral neck, 2.1% at 4 yr) (478) and reduces vertebral fractures but not hip fractures (RR, 0.63; CI, 0.52–0.77) (484). The incidence of VTE episodes is significantly enhanced (RR, 2.76; CI, 1.30–5.86) (484), although no increase in CHD (RR, 0.95; CI, 0.84–1.07) (13) or stroke (RR, 0.91; CI, 0.58–1.41) has been observed (13, 485). An increased mortality from stroke (RR, 1.75; CI, 1.01–3.02) was observed only in women with a high risk of stroke based on the Framingham Risk Score, but not in those at low risk (RR, 1.08; CI, 0.47–2.37) (486). As a result of its antiestrogenic actions, raloxifene reduced breast cancer in women treated for osteoporosis in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial (RR, 0.28; CI, 0.17–0.46) (487). This effect was observed in subgroups both at low risk (RR, 0.67; CI, 0.23–1.92) and at high risk (RR, 0.33; CI, 0.16–0.67) as reported in the CORE (*i.e.* Continuing Outcomes Relevant to Evista) trial (488). The reduction in risk of invasive breast cancer was similar with raloxifene and tamoxifen in the STAR trial (489), but tamoxifen reduced *in situ* cancer (*i.e.* DCIS) to a greater extent. A reduction of endometrial carcinoma (RR, 0.50; CI, 0.29–0.85) has been observed with raloxifene in a case-control study (490). The frequency of hot flashes is increased (491).

Bioidentical HT

"Bioidentical HT" is used to describe medication containing estrogen, progesterone, or other hormones that are chemically similar or exact duplicates of hormones secreted by the ovary or adrenal or synthesized in extraglandular tissues (Table 13). The term "bioidentical" is a lay literature term that generally refers to estradiol, estrone, estriol, progesterone, DHEA, and testosterone.

A common misconception is that bioidentical hormones can be obtained only from compounding pharmacies and that they are safer than the MHT typically prescribed (Table 13). There are Food and Drug Ad-

TABLE 13.   Comparison of traditional HT with "bioidentical hormone" therapy

Characteristics	Traditional hormones	Many "bioidentical hormones"
Molecular structure	Similar or identical to human	Identical to human
FDA oversight	Yes	No
Dosage	Monitored; accurate and consistent	Not monitored; may be inaccurate or inconsistent
Purity	Monitored; pure	Not monitored; may be impure
Safety	Tested; risks known	Not FDA tested; risks unknown
Efficacy	Tested and proven	Not FDA tested; unproven
Scientific evidence	Existent; conclusive	Insufficient

ministration (FDA)-approved bioidentical estradiol preparations, including transdermal and oral once-or-twice-per-week patches, gels, and vaginal rings, available in lotion, cream, or spray form. FDA-approved micronized progesterone is available in oral or vaginal (inserts and creams) forms.

All bioidentical hormones are synthesized from similar precursor compounds. They are not "bioengineered" to contain the same chemical structures as natural female sex hormones. There are no published studies in peer-reviewed literature that show: 1) that non-FDA-approved compounded bioidentical MHT preparations are safer or more effective than the FDA-approved formulations that are the standard of care; 2) that they carry less risk than FDA-approved products; 3) that salivary testing is a reliable measure on which to safely and effectively base dosing; or 4) that they prevent or do not cause breast or uterine cancer. In addition, there are safety concerns about custom-compounded bioidentical hormones due to the paucity of safety and efficacy data available in the literature as well as quality control concerns about purity, predictable blood and tissue levels, and batch-to-batch consistency.

Although bioidentical compounded MHT is often prescribed on the basis of salivary hormone testing, there is neither scientific evidence of a correlation between symptoms and measured salivary hormones, nor a correlation between salivary hormone testing and hormone tissue levels. Therefore, for all MHT, dosing should be based on symptom relief at the lowest effective dose.

A potential advantage of using FDA-approved bioidentical hormones, such as estradiol and progesterone, is the ability to measure them in blood, but no clearly established target ranges have been established for postmenopausal women. One observational study reported that progesterone, in combination with an estrogen, was associated with a lesser risk of breast cancer than some synthetic progestogens, but this finding requires confirmation in additional studies (113).

In the absence of more data about compounded bioidentical hormones, their risks and benefits should be assumed to be similar to FDA-approved MHT—with the caveats that there is uncertainty from batch to batch about what a woman is receiving, there are no safety or efficacy data, and there is no FDA monitoring for quality. For The Endocrine Society Position Statement on Bioidentical Hormones, see http://www.endo-society.org/advocacy/policy/upload/BH_Position_Statement_final_10_25_06_w_Header.pdf.

The Future of MHT

Publication of the first results of the WHI trial of combined-continuous MHT in July 2002 (172) was followed rapidly by a substantial fall in the prescriptions for and use of MHT worldwide. This decline occurred despite the fact that the study investigators stated that the trial addressed chronic disease prevention in older women (average age, 63 yr) but not symptomatic menopause management in younger women. Several issues regarding this study raised concern. The breast cancer risk as first described in the original publication was not formally statistically significant (RR, 1.26; CI, 1.00–1.59) (172), and the increase in cardiovascular risk, initially stated to apply across age strata, was subsequently reported (5) 5 yr later as occurring only in the participants older than age 70 yr. Critical *post hoc* analyses of the WHI and subsequent cohort studies have identified several aspects requiring further study. The most important are the benefits and risks of MHT in women who are the most likely candidates to initiate this therapy. Specifically, this group would include women ages 50 to 55 yr with symptoms related to menopause and who would be starting MHT for the first time and planning to continue use for at least 5 yr. Before RCTs addressing these issues are completed, moderate or low levels of evidence must be used to draw reasonable conclusions (Fig. 5, A and B). Five examples of needed actions and trials and interim conclusions include:

1. Literature dissemination among practitioners and postmenopausal women of the levels of benefit and risk associated with MHT as prescribed in currently used low doses, in women close to menopause, and for periods of less than 3 to 5 yr. A key component is to
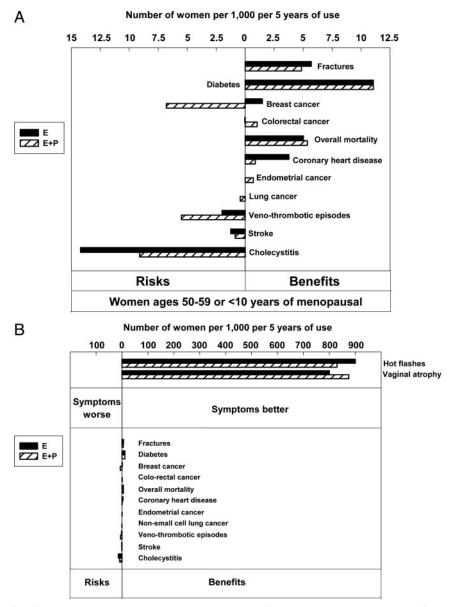
FIG. 5. A, Risks and benefits of MHT in women starting MHT between the ages of 50 and 59 yr or less than 10 yr after the start of menopause. Data are expressed as the attributable (excess) risk or benefit for a woman taking E alone as MHT for 5 yr. B, Number of women per 1000 taking MHT for 5 yr who are expected to have improvement of symptoms of vaginal atrophy or hot flashes. Design of panels A and B is the same. Note that the data regarding risks and benefits in the bottom of panel B represent those illustrated in panel A, where they are illustrated in expanded form so that they can be clearly seen. The purpose of reproducing these data in the bottom of panel B is to compare the number of women benefiting from relief of symptoms of hot flashes and vaginal atrophy with the number of women experiencing other risks and benefits. Fig. 5B is based on data in Refs. 270, 295, and 508. *Solid black bars*, E alone; *hatched bars*, E+P.

inform these groups about which conclusions are supported by a high level of evidence and which are currently based on moderate and low evidence levels that ultimately require RCTs to finally resolve. Conclusions based on moderate or low levels of evidence should be accepted as a working construct until RCTs are completed.

Statements from organizations such as the International Menopause Society (492) and the North American Menopause Society (412) and publications such as those of Birkhäuser *et al.* (493) have been disseminated to some degree, but widespread and often unwarranted anxiety among women persists. Specific practical issues for women include addressing the fact that women with symptoms adversely impacting their QOL are not receiving appropriate treatment and that women discontinuing therapy prematurely as a result of the WHI announcements may now be experiencing unwanted consequences, such as increased rates of fracture (34, 494) and loss of prior protection against colorectal cancer (34).

2. Continued research on the lowest doses, optimal routes of administration, and optimal products (*i.e.*

type of estrogen, type of progestogen, possible use of testosterone) is necessary.

Until RCTs are completed, several interim conclusions are warranted. Since the WHI trials were conducted, it has been recognized both that lower doses of estrogen than those used in the trials are often effective for symptom management and bone density maintenance (269, 438) and that low doses of other combinations (*e.g.* estradiol and NETA) (495) are also effective and do not increase mastalgia or breast density over at least 6 months of administration. Recent publications suggest that up to 5 yr of use of progesterone or dydrogesterone as the progestin may not increase breast cancer risk significantly (113, 121). Transdermal estradiol may not increase thromboembolic risk (20) in contrast to estrogens administered orally. Furthermore, standard or low-dose therapy given to healthy postmenopausal women does not increase cardiovascular events significantly (496).

  3. Research should be directed toward identifying women who may specifically benefit or be at risk from MHT.

ER polymorphisms have been associated with annual changes in BMD and estrogen responsiveness (497) and with the cardiovascular effects of MHT (498, 499). It may thus be possible to select for or against treatment in patients particularly likely to achieve benefit or to experience risks greater than the norm.

  4. New approaches should be developed to maximize benefit and minimize risk.

The combination of low-dose CEEs with a SERM might be used to provide tissue-selective estrogen complexes (500). Early clinical trial data (501–503) suggest that tissue-selective estrogen complexes are effective in reducing symptoms, increasing bone density, having favorable lipid effects, and causing no significant endometrial stimulation. Clinical trials are in progress with recent publication of promising reports (501–503).

The discovery in the mid-1990s of ERβ (504) has stimulated the pharmaceutical industry to synthesize compounds relatively selective for ERβ. These agents are in preclinical or clinical trials for treatment of hot flushes, depression, and interstitial cystitis among others. An underlying concept is that ERβ appears to be antiproliferative, whereas ERα is proproliferative and that the two ERs often modulate their respective activities in a "yin-yang" fashion. These mechanisms underlie the possibility that MHT regimens based on ERβ agonists may lack several of the drawbacks of agents currently available that activate ERα and pose a risk for breast cancer with long-term use (505).

  5. Future randomized trials are needed to examine the rates of cardiovascular events, stroke, breast cancer,

and carbohydrate intolerance as primary endpoints in women starting MHT for the first time between ages 50 and 55 yr.

Data that we have in this area are of moderate to low levels of evidence because the WHI data only provide *post hoc* analyses on these issues. Because the average age of women in the WHI studies was 63 yr, evidence regarding younger women must be interpreted currently as having lower levels of reliability. Two randomized trials that are now fully enrolled may provide important information within a few years: the Kronos Early Estrogen Prevention Study (KEEPS) and the Early *vs.* Late Intervention Trial with Estradiol (ELITE) (506).

Conclusions and Grading of Evidence

For the reader's convenience, the salient points of the MHT studies presented here are summarized as "bullet" points. Data are also assigned a grade according to validity, including such aspects as number of trial subjects, soundness of trial methodology, and absence or presence of confounding factors. The GRADE system (Table 14) is used for assessing level of evidence (1, 507).

Cardiovascular and metabolic effects

Coronary heart disease

- Basic science, animal models, and observational studies support the hypothesis that MHT may prevent atherosclerosis and reduce CHD events. Level of evidence: **B**
- More recent subgroup analyses suggest that the lack of benefit or increase in CHD risk observed in the overall analysis of the WHI resulted from harmful effects of MHT in older women starting therapy many years after onset from menopause, a subgroup that contributed to a large percentage of events recorded in the WHI. Level of evidence: **B**

VTE

- MHT increases VTE risk approximately 2-fold. The VTE risk with MHT is multiplicative with baseline risk factors including age, higher BMI, thrombophilias, surgery, and immobilization. Level of evidence: **A**
- Based on observational, but not RCT, data, transdermal estrogen does not increase VTE risk. Level of evidence: **C**

Stroke

- Standard-dose oral MHT may increase stroke risk by about one third in generally healthy postmenopausal women. Level of evidence: **B**

TABLE 14.   GRADE system for level of evidence[a,b,c]

Grade	Description of supporting evidence	Clarity of risk/benefit	Implications
A: high-quality evidence	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies.[d]	Benefits clearly outweigh harms and burdens or vice versa.	Applies to most patients in most circumstances. Further research is unlikely to change our confidence in the estimation of effect.
B: moderate-quality evidence	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence) or unusually strong evidence from unbiased observational studies.	Benefits clearly outweigh harms and burdens or vice versa.	Applies to most patients in most circumstances. Further research (if performed) is likely to have an impact on our confidence in the estimation of effect and may change the estimate.
C: low-quality evidence	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence.	Benefits clearly outweigh harms and burdens or vice versa.	Conclusions may change when higher quality evidence becomes available. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
D: very-low-quality evidence	Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence.	Benefits clearly outweigh harms and burdens or vice versa.	Conclusions may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.

[a] Factors that may decrease the quality of evidence include: 1) poor quality of planning and implementation of the available RCTs, 2) high likelihood of bias; 3) inconsistency of results; 4) indirectness of evidence; 5) lack of precision; 6) sparse evidence; and 7) reporting bias (including publication bias).

[b] Factors that may increase the quality of evidence based on observational studies include: 1) large magnitude of effect; 2) all plausible confounding would reduce a demonstrated effect; and 3) dose-response gradient.

[c] See www.gradeworkinggroup.org for background of evidence development by the GRADE working group (1).

[d] Exceptionally strong evidence from unbiased observational studies includes: 1) evidence from studies that yield estimates of the treatment effect that are large and consistent; 2) evidence in which all potential biases may be working to underestimate an apparent treatment effect, and therefore, the actual treatment effect is likely to be larger than that suggested by the study data; and 3) evidence in which a dose-response gradient exists.

- Hormone use does not reduce stroke incidence in older women with preexisting vascular disease. Level of evidence: **A**
- Low-dose estrogen therapy may not increase stroke risk. Level of evidence: **C**

Diabetes and carbohydrate intolerance

- CEE (±MPA), independent of its effects on BMI, was associated with a decrease in the risk for T2D. Level of evidence: **B**
- This protective effect is not predominantly via insulin sensitivity. Level of evidence: **C**.
- Results may not be generalizable to other MHT preparations. Level of evidence: **C**

Changes in body weight or BMI

- Initiation of MHT is associated with lesser accumulation of weight, fat mass, and/or centrally located fat mass. Level of evidence: **B**

- The most consistent finding is the minimizing effect of MHT on central fat accumulation. Level of evidence: **B**

Musculoskeletal

Bone and fractures

- Estrogen with or without a progestogen is as effective as bisphosphonates in preventing early postmenopausal bone loss and augmenting bone mass in late postmenopause. Level of evidence: **A**
- The WHI studies have demonstrated that E alone and E+P prevent hip and vertebral fractures in an unselected population of women. Level of evidence: **A**

Degenerative arthritis

- Evidence suggests a protective effect of endogenous and exogenous estrogen on osteoarthritis. Level of evidence: **B**
- E alone as MHT reduces total arthroplasty rate. Level of evidence: **B**

- Benefits on arthroplasty were not evident in the WHI E+P arm, suggesting that continuous-combined progestogen administration might counteract the beneficial effects of estrogen (93). Level of evidence: **B**

Breast cancer

Mammographic density

- E alone and E+P increase mammographic density. Level of evidence: **A**
- Tamoxifen reduces mammographic density. Level of evidence: **B**

E alone and breast cancer

- Use of E alone for less than 5 yr may reduce the risk of breast cancer in patients starting therapy many years after the onset of menopause. Level of evidence: **B**
- Estrogens increase the risk of breast cancer after more than 5 yr of use, particularly in recently postmenopausal women. Level of evidence: **B**
- The precise duration of exposure needed to exert this effect is not clear, but linear models suggest a 3% relative increase in breast cancer per year of exposure in thin women and a lesser risk in obese women. Level of evidence: **C**
- Increased risk dissipates within 5 yr of discontinuing estrogens as MHT. Level of evidence: **B**
- Short-term use may reduce the risk of breast cancer being diagnosed in "long gap-time patients." Level of evidence: **B**
- Tumors arising in women receiving E alone are more likely to be ER-positive and lobular in type. Level of evidence: **C**
- The attributable or "excess" risk from E alone used for 5 yr is minimal, ranging from 0 per 1000 (most optimistic estimate) to 2.59 per 1000 in women starting E alone within 5 yr of menopause (most pessimistic estimate). Level of evidence: **C**

E+P and breast cancer

- Combined E+P therapy, particularly with synthetic progestogens, is associated with an increased risk of IBC, which may occur within 3 to 5 yr of initiation and increases progressively beyond that time. Level of evidence: **B**
- The risk returns to approximately that of nonusers within 3 yr of cessation and is thus associated with current but not past use. Level of evidence: **B**
- Emerging data, so far from two independent studies only, report that progesterone (and perhaps dydrogesterone) in combination with estrogen does not increase breast cancer risk if given for 5 yr or less. Level of evidence: **C**
- The WHI data, which cite an overall RR of 1.26, perhaps should not be used to form estimates of risk in non-prior hormone users early in menopause who are the main candidates for MHT and in whom risk estimates are most clinically useful. Level of evidence: **B**
- The WHI data indicate no increased risk after 5.2 yr for first-time hormone users of E+P, possibly attributable to the fact that the majority started MHT more than 5 yr after final menses. Level of evidence: **B**
- No single estimate of absolute risk can be provided for an individual woman because risk varies with time of initiation relative to final menses, duration of use, and BMI and, possibly, with type of progestogen and family history of breast cancer.
- Women closer to menopause are emerging as the group at highest risk associated with some forms of MHT. Level of evidence: **C**

Androgens and breast cancer

- Available data are of low quality and conflict regarding the risk for breast cancer relating to use of androgens. Level of evidence: **D**
- An adequately powered, prospective, randomized and blinded study of adequate duration is required to more fully assess the risk. Level of evidence: **D**

Declining incidence of breast cancer

- Data suggest a rapid decline in incidence of ER-positive diagnosed breast cancer, which was temporally associated with a decline in use of MHT after the first reports of the WHI in 2002. Level of evidence: **B**
- This effect is consistent with the late-promoter effect of combination MHT. Level of evidence: **D**

Sources of breast tissue estradiol

- Breast tissue levels represent locally synthesized estrogen as well as that taken up from plasma via receptor-mediated mechanisms. Level of evidence: **B**
- Obesity might favor local estrogen synthesis in the breast. Level of evidence: **D**
- These findings could explain the reduced risk of breast cancer with MHT in obese women in whom local estrogen synthesis from aromatase might predominate. In contrast, MHT would increase the risk in thin women whose breast tissue estradiol levels might reflect predominantly uptake. Level of evidence: **D**

Quality of evidence

- Evidence from the WHI trial is weighted less than that of a randomized controlled trial according to the

GRADE system criteria because of mitigating factors: large dropout rate; lack of adequate representation of applicable group of women (*i.e.* those initiating therapy at the time of menopause); and modifying influence from prior hormone use. For this reason, many of the conclusions from the WHI are judged as level B evidence.

Reservoir of undiagnosed breast cancer

- Autopsy studies indicate that women between ages 50 and 80 yr have a 7% prevalence of undiagnosed breast cancer (6% *in situ* and 1% invasive). Level of evidence: **B**
- Calculations from the placebo groups in the WHI study suggest that only 30% of occult tumors progress to a size allowing clinical diagnosis in 5 to 6 yr. Level of evidence: **D**
- The increase in diagnosis of breast cancer from E+P in the WHI could be explained by an effect on occult undiagnosed breast cancer, rather than by the *de novo* development of new cancer. Level of evidence: **D**
- The possible decrease in diagnosis of breast cancer from estrogen in the WHI could reflect a proapoptotic effect of estrogen in women in the "long gap-time" group. Level of evidence: **D**
- An effect of progestogens in combination with estrogens to increase the risk of breast cancer could be explained by an effect of estrogen plus a progestogen to enhance reprogramming into stem cells or to stimulate proliferation. Level of evidence: **D**

EC

- E alone without a progestogen causes an increase in EC. Level of evidence: **A**
- Continuous E+P abrogates the effect of estrogen and does not cause an increase in EC. Level of evidence: **A**
- Sequential E+P reduces the risk of EC compared with estrogen but not as effectively as continuous E+P. Level of evidence: **B**

Ovarian cancer risk

- Long-term E-alone therapy is associated with a small attributable risk of ovarian cancer of 0.7 per 1000 women per 5 yr of use. Level of evidence: **B**
- Either no risk or a significantly smaller risk occurs with combined estrogen and progestogen therapy. Level of evidence: **C**

Colorectal cancer risk

- RCT data indicate that MHT with E+P decreases colon cancer risk. Level of evidence: **A**

- Data regarding E alone are conflicting with observational data suggesting protection against colon cancer and RCT data demonstrating no effect. Level of evidence: **C**
- Based on RCT data, the colorectal cancers diagnosed in women on E+P tended to be more advanced with more likelihood of lymphatic or metastatic involvement. Level of evidence: **B**

Lung cancer risk

- Women receiving E+P exhibited a nonsignificant trend toward a higher incidence of lung cancer, but this effect was limited to women aged more than 60 yr. Level of evidence: **D**

Genitourinary system

OAB, stress incontinence, and RUTIs

- Estrogen used locally or systemically reduces the symptoms of OAB, with a better outcome using vaginal estrogen. Level of evidence: **A**
- No conclusive evidence suggests efficacy of systemic estrogen for RUTIs. Level of evidence: **D**
- Local (vaginal) estrogen reduces the incidence of RUTIs in postmenopausal women, and evidence is based on two RCTs. Level of evidence: **A**

Vaginal atrophy

- Vaginal doses as low as 10 μg of estrogen inserted into the vagina twice weekly or 7.5 μg daily by vaginal ring normalize vaginal atrophy assessed histologically and relieve symptoms of vaginal atrophy. Level of evidence: **A**
- Sensitive estradiol assays detect systemic absorption of low-dose vaginal estrogen, but only small increments occur. Level of evidence: **B**
- Doses of 7.5 to 25 μg of estradiol twice weekly do not stimulate the endometrium in the large majority of patients. Level of evidence: **B**

Quality of life

Overall indices

- MHT produces an improvement in HRQOL through decreased symptoms, sleep enhancement, and possibly mood enhancement. Level of evidence: **B**
- It is not possible to reach a conclusion about the impact of MHT on GQOL. Level of evidence: **D**

Hot flashes

- "Standard-dose" estrogen (CEE 0.625 mg, oral micronized 17β-estradiol 1 mg, transdermal 17β-estra-

diol 50 μg/d) markedly lowers the frequency and severity of hot flashes. Level of evidence: **A**

- Lower doses of estrogen are also effective for relief of hot flashes in many women. Level of evidence: **A**

Female sexuality

- Transdermal testosterone delivered at 300 μg of testosterone per day by patch increases the number of self-reported sexually satisfying events per month when compared with placebo in oophorectomized and postmenopausal women. Level of evidence: **A**
- These same studies demonstrated significant improvement in desire, arousal, responsiveness, orgasm, pleasure, and satisfaction. Level of evidence: **A**
- DHEA at an oral dose of 50 mg/d does not significantly improve sexual function in postmenopausal women with HSDD who are not using concurrent estrogen. Level of evidence: **A**

Depression and mood changes

- The antidepressant efficacy of estradiol occurs in perimenopausal but not postmenopausal women. Level of evidence: **B**
- Beneficial effects of estrogen or E+P on mood in postmenopausal women are minimal (in part reflecting low baseline symptomatology), and beneficial effects may be more likely in women with concurrent menopausal symptoms. Level of evidence: **C**

Other changes

Skin changes

- MHT may improve age-related skin changes in postmenopausal women, but no differences from placebo have been discerned in RCTs. Level of evidence: **C**

MHT and immunity

- The effect of MHT may be detrimental in many autoimmune diseases. Level of evidence: **C**

Gallbladder disease

- RCTs demonstrate that E alone and E+P similarly increase the risk of gallbladder disease in a duration-dependent fashion. Level of evidence: **A**
- Observational studies report lower risks with transdermal and low-dose estrogen than with oral. Level of evidence: **C**

Geriatric

Macular degeneration

- Neovascular macular lesions are reduced by E alone or E+P. Level of evidence: **C**
- MHT does not consistently affect drusen or early macular lesions. Level of evidence: **C**

Cognitive decline and dementia

- After menopause, MHT probably has no important effect on midlife cognitive function. Level of evidence: **B**
- Estrogen therapy initiated at the time of surgical menopause benefits verbal memory over the short term. Level of evidence: **B**
- MHT initiated after about age 60 yr does not improve memory. Level of evidence: **A**
- MHT initiated after about age 60 yr probably has no substantial effect on other cognitive skills. Level of evidence: **C**
- MHT initiated after about age 65 yr increases risk of dementia. Level of evidence: **B**
- Effects of MHT on dementia risk initiated and used during early postmenopause are unclear. Level of evidence: **C**
- Long-term risks of dementia may be reduced by MHT. Level of evidence: **D**

Special considerations

Premature menopause

- Women with bilateral oophorectomy are at increased risk of negative health outcomes in the cardiovascular system and in bone, cognition, mood, and sexuality. Level of evidence: **B**
- MHT can reverse some of these negative health risks. Level of evidence: **B**
- Declining ovarian reserve associated with vasomotor symptoms may identify a group of women that are at increased risk for decreased reproductive potential, lower than optimal peak bone mass, and adverse cardiovascular markers. Level of evidence: **B**

MHT in breast cancer survivors

- Whether standard MHT increases the recurrence risk in breast cancer survivors is unclear, with conflicting results in three RCTs. Level of evidence: **D**
- Tibolone increases risk of recurrence, particularly in women treated with aromatase inhibitors. Level of evidence: **A**
- Impaired QOL will outweigh survival issues for some women making a decision regarding use of MHT. Level of evidence: **C**

MHT and total mortality

- MHT was associated with a 40% reduction in mortality in women in trials in which participants had a mean age less than 60 yr or were within 10 yr of menopause onset. Level of evidence: **B**

Alternative forms of MHT

Tibolone as MHT

- Tibolone (a hormonal alternative widely available worldwide but not in the United States) alleviates postmenopausal vasomotor symptoms and improves urogenital atrophy. Level of evidence: **A**
- In osteoporotic women over the age of 60 yr, tibolone significantly reduces the incidence of vertebral and nonvertebral fractures. Level of evidence: **A**
- Tibolone reduces the risk of breast cancer in postmenopausal women. Level of evidence: **B**
- Tibolone is associated with a reduction of colon cancer. Level of evidence: **B**
- Tibolone has been associated with an increased risk of stroke in older women, but not in younger women. Level of evidence: **A**
- Tibolone does not increase the risk of VTE disease or CHD events. Level of evidence: **B**
- Tibolone does not induce endometrial hyperplasia or carcinoma in postmenopausal women. Level of evidence: **A**
- Tibolone improves sexual well-being in postmenopausal women presenting with low libido, with greater improvements in desire, arousal, satisfaction, and receptiveness than those seen with transdermal estrogen-progestogen therapy. Level of evidence: **B**
- Tibolone increases the risk of breast cancer recurrence. Level of evidence: **A**

Raloxifene as MHT

- Raloxifene improves BMD and reduces vertebral but not hip fractures. Level of evidence: **A**
- The incidence of VTE is significantly higher than with placebo. Level of evidence: **A**
- No increase in CHD or stroke occurs (although stroke mortality was increased in those on raloxifene with stroke). Level of evidence: **A**
- Raloxifene reduces the incidence of endometrial carcinoma. Level of evidence: **B**
- Raloxifene decreases the risk of development of breast cancer. Level of evidence: **A**

The majority of available data from RCTs represent results from the various WHI trial publications. Because the average age of women in these studies was 63 yr, the RRs and benefits reported are not applicable to women starting MHT shortly after the onset of menopause or between ages 50 and 55 yr (the usual age for starting MHT). To provide information regarding this subgroup, existing observational and incidence data were used to calculate risks and benefits for women ages 50 to 59 yr or less than 10 yr after onset of menopause. To summarize the large amount of data, the findings from several studies are illustrated in a standard way as shown in Fig. 5, A and B. This figure depicts the number of women per 1000 taking either E alone or E+P for 5 yr who would be expected to experience a specific risk or benefit. The data used and calculations made are detailed in Supplemental Data (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). It should be noted that the data are predominantly taken from women in the United States, and statistics will vary according to country and ethnic group. Estimates represent standard oral doses of E alone and E+P, and rates may differ with lower doses, different estrogens or progestogens, and use of the transdermal route.

From its inception, this Scientific Statement was designed to evaluate the evidence regarding the risks and benefits of MHT and not to provide recommendations. The goal was to construct an overall assessment of existing data with emphasis on the level of evidence supporting the conclusions. Although individual recommendations could have been a major component of this document, we concluded that this would be beyond the scope of a Scientific Statement and blur the distinction between the Guidelines written by The Endocrine Society and Scientific Statements. Nonetheless, the data suggest that for menopausal women ages 50 to 59 yr or younger than age 60 yr, the benefits of MHT outweigh the risks in many instances and particularly for relief of symptoms due to estrogen deficiency. Judgments about treatment require assessment of the needs in an individual patient and her potential for risks. Assessment methods to determine individual risks for breast cancer, CHD, fracture, stroke, diabetes, and venothromboembolic episodes are available. A global recommendation would be to individualize therapy, taking into account symptoms and risk factors, as a means to determine who might be treated with MHT. Current guidelines suggest use of MHT with the lowest effective dose and for the shortest duration possible.

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