J Clin Endocrin Metab. First published ahead of print July 14, 2010 as doi:10.1210/jc.2009-2509

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM
JULY 2010 • VOLUME 95 • SUPPLEMENT 1 • NUMBER 07

Postmenopausal Hormone Therapy

An Endocrine Society Scientific Statement

THE ENDOCRINE SOCIETY®

Postmenopausal Hormone Therapy
An Endocrine Society Scientific Statement

The Endocrine Society Scientific Statements are designed to educate basic scientists, clinical scientists, and clinicians concerning the scientific basis of disease and its application to the practice of medicine with regard to both prevention and management. Scientific Statements provide an overview of basic and clinical content on topics of emerging importance. Content is evidence-based to the extent possible but also identifies areas of basic or clinical knowledge that require additional research. Topics are selected on the basis of their emerging scientific impact on disease and broad clinical relevance to the general population. Scientific Statements are developed by a multidisciplinary Task Force of experts with representation from the various core committees within The Endocrine Society.

Scientific Statement No. 2 should be cited as follows: Santen RJ et al. 2010, Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement. The Journal of Clinical Endocrinology & Metabolism 95, Supplement 1: S1-S66

Permission requests should be directed to:
Publications Coordinator
Phone: 301.941.0238
Fax: 301.951.2617
Email: permissions@endo-society.org

Inquires or requests for further information should be directed to Society Services:
Telephone: 301.941.0210 or 888.363.6762
Email: societyservices@endo-society.org

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM
JULY 2010 • VOLUME 95 • SUPPLEMENT 1 • NUMBER 07

Postmenopausal Hormone Therapy

An Endocrine Society Scientific Statement

Richard J. Santen, D. Craig Allred, Stacy P. Ardoin, David F. Archer, Norman Boyd, Glenn D. Braunstein, Henry G. Burger, Graham A. Colditz, Susan R. Davis, Marco Gambacciani, Barbara A. Gower, Victor W. Henderson, Wael N. Jarjour, Richard H. Karas, Michael Kleerekoper, Roger A. Lobo, JoAnn E. Manson, Jo Marsden, Kathryn A. Martin, Lisa Martin, JoAnn V. Pinkerton, David R. Rubinow, Helena Teede, Diane M. Thiboutot, and Wulf H. Utian

THE ENDOCRINE SOCIETY®

Guide to Use of Scientific Statement

This Statement is designed as a comprehensive, rigorously documented, objective, scientific analysis of existing data evaluating the benefits and risks of hormone therapy for menopausal women. Individual readers may choose to delve into this document to a greater or lesser degree. The bullet points below provide guidance into the various layers of depth of each component of the Statement, the rationale for reading specific sections, and the location in the document of each section.

- **Executive summary:** describes the background and most important conclusions, ranked according to level of evidence and listed as benefits and risks. Pages S1–S5
- **Conclusions and grading of evidence:** provides a topic oriented, comprehensive listing of conclusions and grading of evidence, which follows the order of presentation in the text. Readers interested in a particular topic can find all of the conclusions regarding that topic in this section. Table 14 defines the grading categories and their definitions. Readers interested in a particular topic can find all of the conclusions regarding that topic in this section. Pages S46–S51
- **Text of the Scientific Statement:** discusses each topic in depth, citing existing evidence from a variety of sources and providing a comprehensive listing of references. Pages S7–S44
- **Future Directions:** points out key areas that require new studies or additional action in the future. Pages S44–S46
- **Tables:** provide highly detailed data in areas which are particularly controversial, important or require specific comparison among studies. Data presented here allow experts in the field to draw conclusions based from a detailed examination of published data. Pages S10, S14, S18–S20, S22–S28, S38, S39, S42, S44

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

Richard J. Santen, D. Craig Allred, Stacy P. Ardoin, David F. Archer, Norman Boyd, Glenn D. Braunstein, Henry G. Burger, Graham A. Colditz, Susan R. Davis, Marco Gambacciani, Barbara A. Gower, Victor W. Henderson, Wael N. Jarjour, Richard H. Karas, Michael Kleerekoper, Roger A. Lobo, JoAnn E. Manson, Jo Marsden, Kathryn A. Martin, Lisa Martin, JoAnn V. Pinkerton, David R. Rubinow, Helena Teede, Diane M. Thiboutot, and Wulf H. Utian

Division of Endocrinology and Metabolism (R.J.S.), Department of Obstetrics and Gynecology (J.V.P.), University of Virginia, Charlottesville, Virginia 22908; Tufts University School of Medicine (R.H.K.), Molecular Cardiology Research Institute, Tufts Medical Center, Boston, Massachusetts 02111; Jean Hailes Research Centre (H.T.), School of Public Health, Melbourne, Australia 3168; Prince Henry's Institute of Medical Research (H.G.B.), Monash Medical Centre, Melbourne, Australia 3168; Department of Medicine/Women's Health Program (S.R.D.), Monash University, Melbourne, Australia 3181; Departments of Health Research and Policy (Epidemiology) and of Neurology and Neurological Sciences (V.W.H.), Stanford University, Stanford, California 94305; Departments of Pathology and Immunology (D.C.A.) and Surgery (G.A.C.), Washington University School of Medicine, St. Louis, Missouri 63110; Department of Nutrition Sciences (B.A.G.), University of Alabama at Birmingham, Birmingham, Alabama 35294; St. Joseph Hospital (M.K.), Internal Medicine, Reichert Health Center, Ypsilanti, Michigan 48197; Division of Immunology and Rheumatology, Ohio State University School of Medicine (W.N.J., S.P.A.), Columbus, Ohio 43219; University of Pisa (M.G.), Department of Obstetrics and Gynecology, Pisa I-56100, Italy; University of Toronto (N.B., L.M.), Department of Nutritional Sciences, Department of Medicine, Toronto, Ontario, Canada M5G 2C1; Cedars-Sinai Medical Center (G.D.B.), Department of Medicine, Los Angeles, California 90048; Columbia University Medical Center (R.A.L.), Department of Obstetrics and Gynecology, New York, New York 10037; Eastern Virginia Medical School (D.F.A.), Clinical Research Center, Norfolk, Virginia 23507; North American Menopause Society (W.H.U.), Mayfield Heights, Ohio 44124; Massachusetts General Hospital (K.A.M.), UptoDate, Waltham, Massachusetts 02453; University of North Carolina at Chapel Hill (D.R.R.), Chapel Hill, North Carolina 27516; Section of Dermatology (D.M.T.), Hershey Medical Center, Pennsylvania State University School of Medicine, Hershey, Pennsylvania 17033; King's Breast Care (J.M.), King's College Hospital, London SE5 9RS, United Kingdom; and Harvard Medical School (J.E.M.), Brigham and Women's Hospital, Boston, Massachusetts 02215

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

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-2509 Received November 24, 2009. Accepted April 21, 2010.

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)**

Abbreviations: AMD, Age-related macular degeneration; BMD, bone mineral density; BMI, body mass index; CEE, conjugated equine estrogen; CHD, coronary heart disease; CI, 95% confidence interval; CVD, cardiovascular disease; DCIS, ductal carcinoma *in situ*; DHEA, dehydroepiandrosterone; DXA, dual-energy x-ray absorptiometry; EC, endometrial cancer; ER, estrogen receptor; FVL, factor V Leiden; GQOL, global QOL; HRQOL, health-related QOL; HSDD, hypoactive sexual desire disorder; HT, hormone therapy; IBC, invasive breast cancer; LNG-IUS, levonorgestrel-releasing intrauterine system; MHT, menopausal HT; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate; OAB, overactive bladder; OR, odds ratio; PMD, percentage mammographic density; QOL, quality of life; RA, rheumatoid arthritis; RCT, randomized clinical trial; RR, relative risk; RUTI, recurrent urinary tract infection; SERM, selective ER modulator; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; SUI, stress urinary incontinence; T2D, type 2 diabetes; VTE, venothromboembolism.

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 nonbone 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-

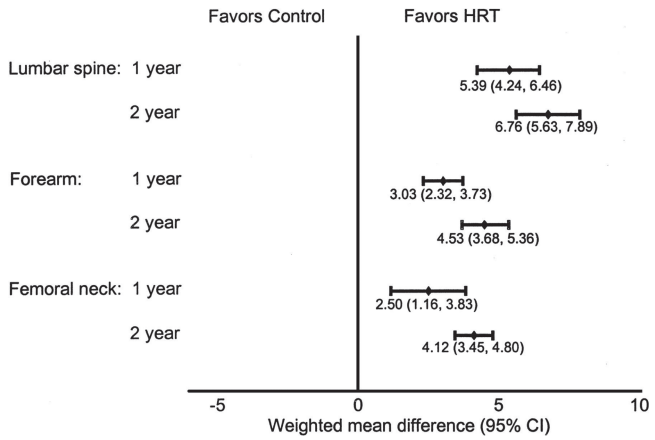


FIG. 1. Improvement in BMD with E+P therapy: a meta-analysis of 57 studies. The *bars and numbers* on the *right* indicate aspects that are improved by MHT. Illustrated on the bar is the mean of the RR (*middle portion of the bar*) with the CI limits indicated by the numbers at the *end of the bar*. 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

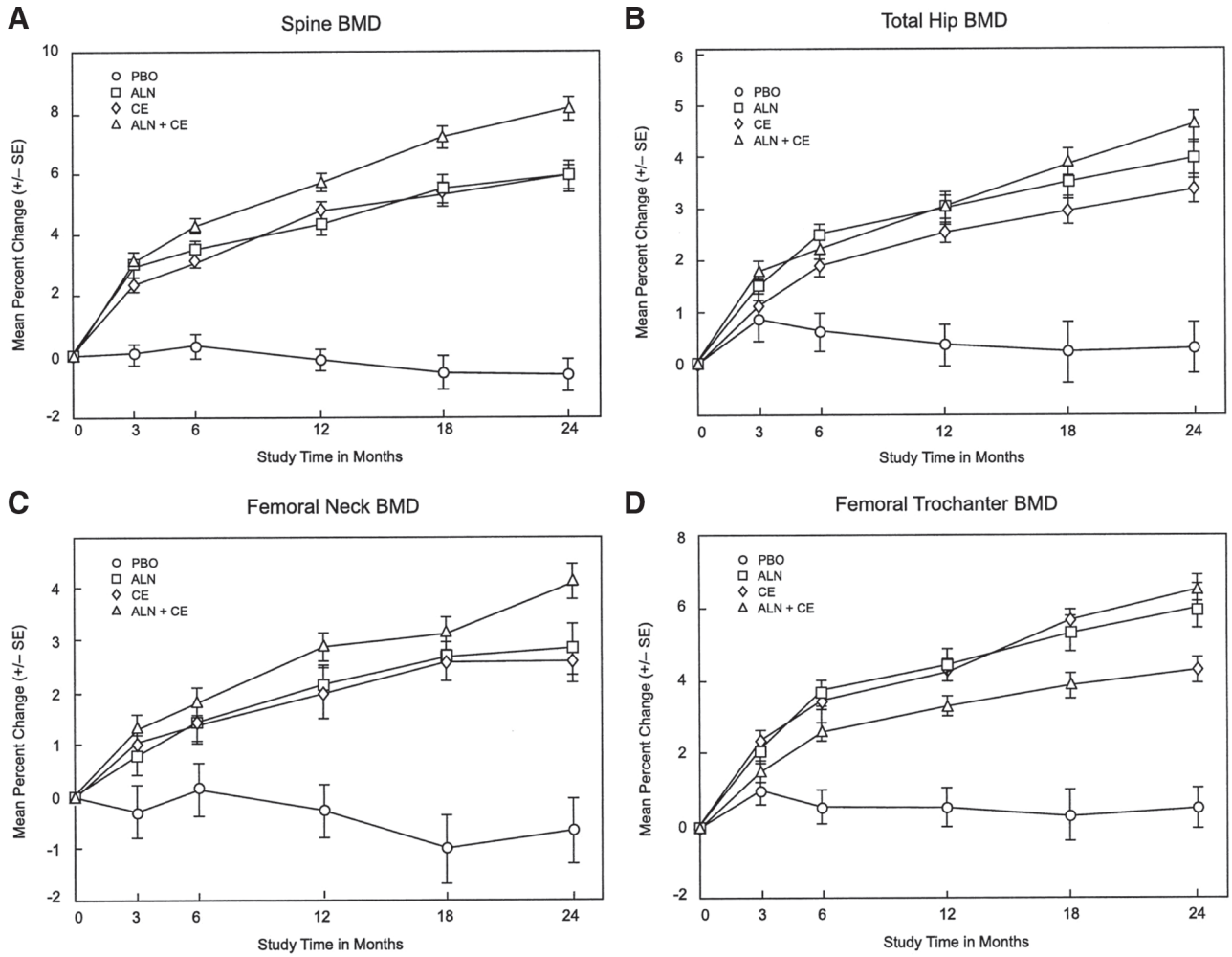


FIG. 2. Increase in BMD in postmenopausal women treated with alendronate or estrogen, alone or in combination. PLO, Placebo; ALN, alendronate; CE, conjugated estrogen. [Reproduced with permission from H. G. Bone *et al. J Clin Endocrinol Metab* 85:720–726, 2000 (75). © The Endocrine Society.]

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-

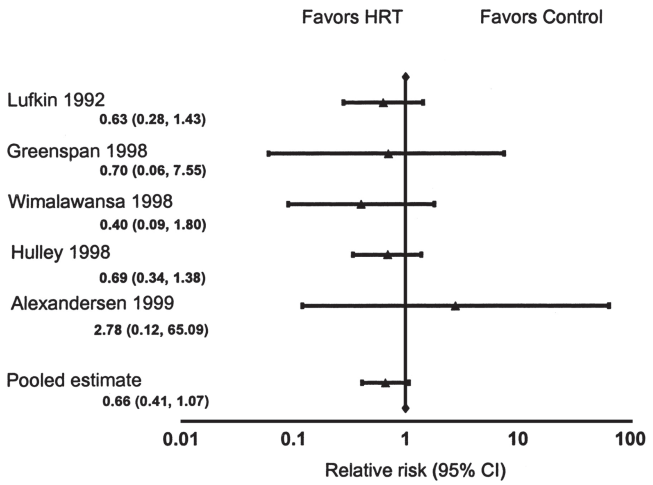


FIG. 3. RR of vertebral fracture after treatment with MHT. The *left side of the vertical bar* indicates that the therapy favors MHT. The *right side* represents data favoring controls. The *horizontal bars* represent the mean (middle portion of bar), and the ends of each bar represent the CIs. The studies 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 chondroprotective 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. McTiernan *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	<2 yr	>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 explain 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

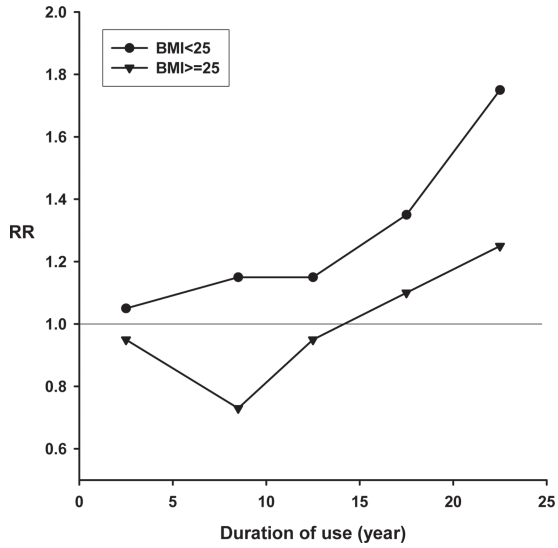


FIG. 4. RR of breast cancer as observed in the NHS as a function of BMI. One line represents women with a BMI of less than 25 kg/m^2 and the other, 25 kg/m^2 or greater. Each point on the line represents the mean RR of breast cancer for women taking E alone as MHT for 2 yr to more than 20 yr. Figure 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	<2 yr	>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 androgens; 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 RR 1.26 (0.96–2.24), E+P+T	No	164
Methyltestosterone (O)	Median, 2.83 yr	RR 1.08 (0.86–1.36), E+T RR 1.69 (1.03–2.79), E+P+T	No	171
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 hyperplasias, 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 overexpression 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 periuretheral 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 postmenopausal 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)	0.59 (0.24–1.19)			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 increased 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 Δ4-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 nonvertebral 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.

Acknowledgments

The authors thank the following individuals who provided peer review for each section of this scientific statement: Roberta Brinton (University of Southern California), Anne Gompel (Hotel Dieu de Paris), Francine Grodstein and Sue Hankinson (Brigham

and Women's Hospital), Karla Kerlikowske (University of California at San Francisco), Wendy Kort (University of Colorado), Charles L. Loprinzi and Victor Montori (Mayo Clinic), Vivian Pinn (National Institutes of Health), William Rosner (St. Luke's/Roosevelt Hospital Center), Isaac Schiff (Massachusetts General Hospital), Evan Simpson (Prince Henry's Institute of Medical Research), Nelson Watts (University of Cincinnati), and Phyllis Wise (University of Washington). R.J.S. particularly acknowledges the contributions of Henry Burger who critically evaluated multiple components of this manuscript and provided valuable insights and judgments.

Address all correspondence and requests for reprints to: Richard J. Santen, Division of Endocrinology, P.O. Box 801416, University of Virginia Health System, Charlottesville, Virginia 22908. E-mail: RJS5Y@VIRGINIA.EDU.

Disclosure Summary: Richard J. Santen served on an advisory board for Wyeth Laboratories (now Pfizer); David F. Archer consulted for Agile Therapeutics, Bayer Healthcare, Merck, Novo Nordisk, Warner Chilcott, and Wyeth Laboratories (Pfizer), received research support from Bayer Healthcare, Duramed, Organon (now Merck and Co.), Warner Chilcott, and Wyeth Laboratories (Pfizer), and received honoraria from Bayer Healthcare, Merck, and Wyeth Laboratories (Pfizer); Glenn D. Braunstein received research support from BioSante and consulted for Acrux Australia; Henry G. Burger served on an advisory board for Wyeth Laboratories (Pfizer) and received honoraria from Bayer Schering, Schering Plough (Merck and Co.), and Novo Nordisk; Susan R. Davis received research support from Bayer Schering/BioSante, consulted for Acrux Australia, received honoraria from Organon Australia (now MSD), and gave expert testimony for Procter Gamble (now Warner Chilcott); Michael Kleerekoper served on an advisory board for Wyeth Laboratories (Pfizer); JoAnn V. Pinkerton consulted for Wyeth Laboratories (Pfizer), Eli Lilly, Novo Nordisk, and Amgen, DSMB for Boehringer Ingelheim, and worked on multicenter trials for Wyeth and Pfizer; D. Craig Allred, Stacy P. Ardoin, Norman Boyd, Graham A. Colditz, Marco Gambacciani, Barbara A. Gower, Victor W. Henderson, Wael N. Jarjour, Richard H. Karas, Roger A. Lobo, JoAnn E. Manson, Jo Marsden, Kathryn A. Martin, Lisa Martin, David R. Rubinow, Helena Teede, Diane M. Thiboutot, and Wulf H. Utian had nothing to disclose.

References

1. **Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM** 2008 A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab 93:666–673
2. **Mendelsohn ME, Karas RH** 2005 Molecular and cellular basis of cardiovascular gender differences. Science 308:1583–1587
3. **Mendelsohn ME, Karas RH** 1999 The protective effects of estrogen on the cardiovascular system. N Engl J Med 340:1801–1811
4. **Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, Ernster VL, Cummings SR** 1992 Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 117:1016–1037
5. **Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML** 2007 Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA [Erratum (2008) 299:1426] 297:1465–1477
6. **Grodstein F, Clarkson TB, Manson JE** 2003 Understanding the divergent data on postmenopausal hormone therapy. N Engl J Med 348:645–650
7. **Karas R, Clarkson TB** 2003 Considerations in interpreting the cardiovascular effects of hormone replacement therapy observed in the WHI: timing is everything. Menopausal Med 10:8–12
8. **Clarkson TB** 2007 Estrogen effects on arteries vary with stage of reproductive life and extent of subclinical atherosclerosis progression. Menopause 14:373–384
9. **Prentice RL, Langer R, Stefanick ML, Howard BV, Pettinger M, Anderson G, Barad D, Curb JD, Kotchen J, Kuller L, Limacher M, Wactawski-Wende J** 2005 Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. Am J Epidemiol 162:404–414
10. **Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, Shoupe D, Berek JS, Hankinson S, Manson JE** 2009 Ovarian conservation at the time of hysterectomy and long-term health outcomes in the Nurses' Health Study. Obstet Gynecol 113:1027–1037
11. **Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, Kuller LH, Cochrane BB, Hunt JR, Ludlam SE, Pettinger MB, Gass M, Margolis KL, Nathan L, Ockene JK, Prentice RL, Robbins J, Stefanick ML** 2007 Estrogen therapy and coronary-artery calcification. N Engl J Med 356:2591–2602
12. **Toh S, Hernández-Díaz S, Logan R, Rossouw JE, Hernán MA** 2010 Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. Ann Intern Med 152:211–217
13. **Collins P, Mosca L, Geiger MJ, Grady D, Kornitzer M, Amewou-Atisso MG, Effron MB, Dowsett SA, Barrett-Connor E, Wenger NK** 2009 Effects of the selective estrogen receptor modulator raloxifene on coronary outcomes in the Raloxifene Use for The Heart trial: results of subgroup analyses by age and other factors. Circulation 119:922–930
14. **Rachoñ D, Teede H** 2008 Postmenopausal hormone therapy and the risk of venous thromboembolism. Climacteric 11:273–279
15. **Curb JD, Prentice RL, Bray PF, Langer RD, Van Horn L, Barnabei VM, Bloch MJ, Cyr MG, Gass M, Lepine L, Rodabough RJ, Sidney S, Uwaifo GI, Rosendaal FR** 2006 Venous thrombosis and conjugated equine estrogen in women without a uterus. Arch Intern Med 166:772–780
16. **Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR** 2004 Estrogen plus progestin and risk of venous thrombosis. JAMA 292:1573–1580
17. **Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M** 1997 Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. Arterioscler Thromb Vasc Biol 17:3071–3078
18. **Teede HJ, McGrath BP, Smolich JJ, Malan E, Kotsopoulos D, Liang YL, Peverill RE** 2000 Postmenopausal hormone replacement therapy increases coagulation activity and fibrinolysis. Arterioscler Thromb Vasc Biol 20:1404–1409
19. **Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY** 2007 Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation 115:840–845
20. **Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY** 2008 Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 336:1227–1231
21. **Herrington DM, Vittinghoff E, Howard TD, Major DA, Owen J,**

Reboussin DM, Bowden D, Bittner V, Simon JA, Grady D, Hulley SB 2002 Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease. Arterioscler Thromb Vasc Biol 22:1012–1017

22. **Straczek C, Oger E, Yon de Jonage-Canonico MB, Plu-Bureau G, Conard J, Meyer G, Alhenc-Gelas M, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY** 2005 Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. Circulation 112:3495–3500
23. **Mosca L, Collins P, Herrington DM, Mendelsohn ME, Pasternak RC, Robertson RM, Schenck-Gustafsson K, Smith Jr SC, Taubert KA, Wenger NK** 2001 Hormone replacement therapy and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 104:499–503
24. **Lethbridge-Cejku M, Vickerie J** 2009 Summary health statistics for US adults: National Health Interview Survey, 2003. Vital Health Stat Series 10:225
25. **Feigin VL, Lawes CM, Bennett DA, Anderson CS** 2003 Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2:43–53
26. **Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA** 2009 Age at natural menopause and risk of ischemic stroke: the Framingham Heart Study. Stroke 40:1044–1049
27. **Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y** 2009 Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation [Erratum (2009) 119:e182] 119:480–486
28. **Seshadri S, Wolf PA** 2007 Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. Lancet Neurol 6:1106–1114
29. **Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE** 2005 A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 352:1293–1304
30. **O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson Jr SK** 1999 Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 340:14–22
31. **Dubal DB, Wise PM** 2001 Neuroprotective effects of estradiol in middle-aged female rats. Endocrinology 142:43–48
32. **Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, Kotchen T, Curb JD, Black H, Rossouw JE, Aragaki A, Safford M, Stein E, Laowattana S, Mysiw WJ** 2003 Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA 289:2673–2684
33. **Hendrix SL, Wassertheil-Smoller S, Johnson KC, Howard BV, Kooperberg C, Rossouw JE, Trevisan M, Aragaki A, Baird AE, Bray PF, Buring JE, Criqui MH, Herrington D, Lynch JK, Rapp SR, Torner J** 2006 Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. Circulation 113:2425–2434
34. **Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SA, Brzyski R, Chlebowski RT, Gass M, LaCroix A, Manson JE, Prentice RL, Rossouw J, Stefanick ML** 2008 Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 299:1036–1045
35. **Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J, Barrett-Connor E, Hulley SB** 2001 Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-Progestin Replacement Study (HERS). Circulation 103:638–642
36. **Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI** 2001 A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 345:1243–1249
37. **Bath PM, Gray LJ** 2005 Association between hormone replacement therapy and subsequent stroke: a meta-analysis. BMJ 330:342
38. **Suzuki S, Brown CM, Dela Cruz CD, Yang E, Bridwell DA, Wise PM** 2007 Timing of estrogen therapy after ovariectomy dictates the efficacy of its neuroprotective and antiinflammatory actions. Proc Natl Acad Sci USA 104:6013–6018
39. **Grodstein F, Manson JE, Stampfer MJ, Rexrode K** 2008 Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. Arch Intern Med 168: 861–866
40. **Kalish GM, Barrett-Connor E, Laughlin GA, Gulanski BI** 2003 Postmenopausal Estrogen/Progestin Intervention Trial. Association of endogenous sex hormones and insulin resistance among postmenopausal women: results from the Postmenopausal Estrogen/Progestin Intervention Trial. J Clin Endocrinol Metab 88:1646–1652
41. **Oh JY, Barrett-Connor E, Wedick NM, Wingard DL, Rancho BS** 2002 Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. Diabetes Care 25:55–60
42. **Ding EL, Song Y, Manson JE, Rifai N, Buring JE, Liu S** 2007 Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. Diabetologia 50:2076–2084
43. **Phillips GB** 2006 Endogenous sex hormones and type 2 diabetes risk. JAMA 296:168–169; author reply 169–70
44. **Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, Bassford T, Burke G, Torrens J, Howard BV** 2004 Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia 47:1175–1187
45. **Bonds DE, Lasser N, Qi L, Brzyski R, Caan B, Heiss G, Limacher MC, Liu JH, Mason E, Oberman A, O'Sullivan MJ, Phillips LS, Prineas RJ, Tinker L** 2006 The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. Diabetologia 49:459–468
46. **Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, Cauley JA, Barrett-Connor E** 2003 Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/Progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 138:1–9
47. **Manson JE, Rimm EB, Colditz GA, Willett WC, Nathan DM, Arky RA, Rosner B, Hennekens CH, Speizer FE, Stampfer MJ** 1992 A prospective study of postmenopausal estrogen therapy and subsequent incidence of non-insulin-dependent diabetes mellitus. Ann Epidemiol 2:665–673
48. **Sites CK, L'Hommedieu GD, Toth MJ, Brochu M, Cooper BC, Fairhurst PA** 2005 The effect of hormone replacement therapy on body composition, body fat distribution, and insulin sensitivity in menopausal women: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 90:2701–2707
49. **Munoz J, Derstine A, Gower BA** 2002 Fat distribution and insulin sensitivity in postmenopausal women: influence of hormone replacement. Obes Res 10:424–431
50. **Godsland IF** 2005 Oestrogens and insulin secretion. Diabetologia 48:2213–2220
51. **Norman RJ, Flight IH, Rees MC** 2000 Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution. Cochrane Database Syst Rev CD001018
52. **Aloia JF, Vaswani A, Russo L, Sheehan M, Flaster E** 1995 The influence of menopause and hormonal replacement therapy on body cell mass and body fat mass. Am J Obstet Gynecol 172:896–900
53. **Ronkainen PH, Kovanen V, Alén M, Pöllänen E, Palonen EM, Ankarberg-Lindgren C, Hämäläinen E, Turpeinen U, Kujala UM, Puolakka J, Kaprio J, Sipilä S** 2009 Postmenopausal hormone replace-

ment therapy modifies skeletal muscle composition and function: a study with monozygotic twin pairs. J Appl Physiol 107:25–33
54. **Samaras K, Kelly PJ, Spector TD, Chiano MN, Campbell LV** 1998 Tobacco smoking and oestrogen replacement are associated with lower total and central fat in monozygotic twins. Int J Obes Relat Metab Disord 22:149–156
55. **Kristensen K, Pedersen SB, Vestergaard P, Mosekilde L, Richelsen B** 1999 Hormone replacement therapy affects body composition and leptin differently in obese and non-obese postmenopausal women. J Endocrinol 163:55–62
56. **Sørensen MB, Rosenfalck AM, Højgaard L, Ottesen B** 2001 Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. Obes Res 9:622–626
57. **Gambacciani M, Ciaponi M, Cappagli B, De Simone L, Orlandi R, Genazzani AR** 2001 Prospective evaluation of body weight and body fat distribution in early postmenopausal women with and without hormonal replacement therapy. Maturitas 39:125–132
58. **Jensen LB, Vestergaard P, Hermann AP, Gram J, Eiken P, Abrahamsen B, Brot C, Kolthoff N, Sørensen OH, Beck-Nielsen H, Nielsen SP, Charles P, Mosekilde L** 2003 Hormone replacement therapy dissociates fat mass and bone mass, and tends to reduce weight gain in early postmenopausal women: a randomized controlled 5-year clinical trial of the Danish Osteoporosis Prevention Study. J Bone Miner Res 18:333–342
59. **Mattiasson I, Rendell M, Törnquist C, Jeppsson S, Hulthén UL** 2002 Effects of estrogen replacement therapy on abdominal fat compartments as related to glucose and lipid metabolism in early postmenopausal women. Horm Metab Res 34:583–588
60. **Gower BA, Muñoz J, Desmond R, Hilario-Hailey T, Jiao X** 2006 Changes in intra-abdominal fat in early postmenopausal women: effects of hormone use. Obesity 14:1046–1055
61. **Hänggi W, Lippuner K, Jaeger P, Birkhäuser MH, Horber FF** 1998 Differential impact of conventional oral or transdermal hormone replacement therapy or tibolone on body composition in postmenopausal women. Clin Endocrinol (Oxf) 48:691–699
62. **Haarbo J, Marslew U, Gotfredsen A, Christiansen C** 1991 Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. Metabolism 40:1323–1326
63. **Chen Z, Bassford T, Green SB, Cauley JA, Jackson RD, LaCroix AZ, Leboff M, Stefanick ML, Margolis KL** 2005 Postmenopausal hormone therapy and body composition—a substudy of the estrogen plus progestin trial of the Women's Health Initiative. Am J Clin Nutr 82:651–656
64. **Espeland MA, Stefanick ML, Kritz-Silverstein D, Fineberg SE, Waclawiw MA, James MK, Greendale GA** 1997 Effect of postmenopausal hormone therapy on body weight and waist and hip girths. Postmenopausal Estrogen-Progestin Interventions Study Investigators. J Clin Endocrinol Metab 82:1549–1556
65. **Sumino H, Ichikawa S, Yoshida A, Murakami M, Kanda T, Mizunuma H, Sakamaki T, Kurabayashi M** 2003 Effects of hormone replacement therapy on weight, abdominal fat distribution, and lipid levels in Japanese postmenopausal women. Int J Obes Relat Metab Disord 27:1044–1051
66. **Sites CK, Brochu M, Tchernof A, Poehlman ET** 2001 Relationship between hormone replacement therapy use with body fat distribution and insulin sensitivity in obese postmenopausal women. Metabolism 50:835–840
67. **Jacobsen DE, Samson MM, Kezic S, Verhaar HJ** 2007 Postmenopausal HRT and tibolone in relation to muscle strength and body composition. Maturitas 58:7–18
68. **O'Sullivan AJ, Crampton LJ, Freund J, Ho KK** 1998 The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in postmenopausal women. J Clin Invest 102:1035–1040
69. **Mogul HR,** Weight gain in menopause: the role of estrogen replacement and other factors. In: Wynn PS FM, ed. Program of the 80th Annual Meeting of The Endocrine Society, New Orleans, LA, 1998, p 362 (Abstract P2-539)
70. **Yüksel H, Odabasi AR, Demircan S, Köseoðlu K, Kizilkaya K, Onur E** 2007 Effects of postmenopausal hormone replacement therapy on body fat composition. Gynecol Endocrinol 23:99–104
71. **Reifenstein E, Albright F** 1947 The metabolic effects of steroid hormones in osteoporosis. J Clin Invest 26:24–56
72. **Aitken JM, Lindsay R, Hart DM** 1976 Long-term oestrogens for the prevention of post-menopausal osteoporosis. Postgrad Med J 52(Suppl 6):18–26
73. **Christiansen C, Christensen MS, Transbøl I** 1981 Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. Lancet 1:459–461
74. **Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, Robinson V, Henry D, O'Connell D, Cranney A** 2002 Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 23:529–539
75. **Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, Emkey R, Meunier PJ, Miller SS, Mulloy AL, Recker RR, Weiss SR, Heyden N, Musliner T, Suryawanshi S, Yates AJ, Lombardi A** 2000 Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab 85:720–726
76. **Trémollieres FA, Pouilles JM, Ribot C** 2001 Withdrawal of hormone replacement therapy is associated with significant vertebral bone loss in postmenopausal women. Osteoporos Int 12:385–390
77. **Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, Ettinger B, Lo JC, Johnston JM, Cauley JA, Danielson ME, Neer RM** 2008 Bone mineral density changes during the menopause transition in a multiethnic cohort of women. J Clin Endocrinol Metab 93:861–868
78. **Greenspan SL, Emkey RD, Bone HG, Weiss SR, Bell NH, Downs RW, McKeever C, Miller SS, Davidson M, Bolognese MA, Mulloy AL, Heyden N, Wu M, Kaur A, Lombardi A** 2002 Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 137:875–883
79. **Torgerson DJ, Bell-Syer SE** 2001 Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. BMC Musculoskelet Disord 2:7
80. **Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M** 2003 Ultra low-dose micronized 17β-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. JAMA 290:1042–1048
81. **Yates J, Barrett-Connor E, Barlas S, Chen YT, Miller PD, Siris ES** 2004 Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. Obstet Gynecol 103:440–446
82. **Cauley JA, Black DM, Barrett-Connor E, Harris F, Shields K, Applegate W, Cummings SR** 2001 Effects of hormone replacement therapy on clinical fractures and height loss: the Heart and Estrogen/Progestin Replacement Study (HERS). Am J Med 110:442–450
83. **Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, Pettinger M, Stefanick ML, Wactawski-Wende J, Watts NB** 2003 Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 290:1729–1738
84. **Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts NB, Robbins JA, Lewis CE, Beresford SA, Ko MG, Naughton MJ, Satterfield S, Bassford T** 2006 Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. J Bone Miner Res 21:817–828
85. **Tankó LB, Søndergaard BC, Oestergaard S, Karsdal MA, Christiansen C** 2008 An update review of cellular mechanisms

conferring the indirect and direct effects of estrogen on articular cartilage. Climacteric 11:4–16
86. **Bay-Jensen AC, Tabassi NC, Sondergaard LV, Andersen TL, Dagnaes-Hansen F, Garnero P, Kassem M, Delaisse JM** 2009 The response to estrogen deprivation on cartilage collage degradation markers; CTX-II is unique compared to other markers of collagen turnover. Arthritis Res Ther 11:R9
87. **Sniekers YH, Weinans H, Bierma-Zeinstra SM, van Leeuwen JP, van Osch GJ** 2008 Animal models for osteoarthritis: the effect of ovariectomy and estrogen treatment—a systematic approach. Osteoarthritis Cartilage 16:533–541
88. **Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, Levy D** 1995 The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 38:1500–1505
89. **Hanna FS, Wluka AE, Bell RJ, Davis SR, Cicuttini FM** 2004 Osteoarthritis and the postmenopausal woman: epidemiological, magnetic resonance imaging, and radiological findings. Semin Arthritis Rheum 34:631–636
90. **de Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, Bierma-Zeinstra SM** 2009 Limited evidence for a protective effect of unopposed oestrogen therapy for osteoarthritis of the hip: a systematic review. Rheumatology 48:104–112
91. **Baron YM, Brincat MP, Galea R, Calleja N** 2005 Intervertebral disc height in treated and untreated overweight post-menopausal women. Hum Reprod 20:3566–3570
92. **Gambacciani M, Pepe A, Cappagli B, Palmieri E, Genazzani AR** 2007 The relative contributions of menopause and aging to postmenopausal reduction in intervertebral disk height. Climacteric 10:298–305
93. **Cirillo DJ, Wallace RB, Wu L, Yood RA** 2006 Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. Arthritis Rheum 54:3194–3204
94. **Muscat Baron Y, Brincat MP, Galea R, Calleja N** 2007 Low intervertebral disc height in postmenopausal women with osteoporotic vertebral fractures compared to hormone-treated and untreated postmenopausal women and premenopausal women without fractures. Climacteric 10:314–319
95. **Freedman M, San Martin J, O'Gorman J, Eckert S, Lippman ME, Lo SC, Walls EL, Zeng J** 2001 Digitized mammography: a clinical trial of postmenopausal women randomly assigned to receive raloxifene, estrogen, or placebo. J Natl Cancer Inst 93:51–56
96. **Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G** 2003 Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst 95:30–37
97. **McTiernan A, Martin CF, Peck JD, Aragaki AK, Chlebowski RT, Pisano ED, Wang CY, Brunner RL, Johnson KC, Manson JE, Lewis CE, Kotchen JM, Hulka BS** 2005 Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. J Natl Cancer Inst 97:1366–1376
98. **Hofling M, Lundström E, Azavedo E, Svane G, Hirschberg AL, von Schoultz B** 2007 Testosterone addition during menopausal hormone therapy: effects on mammographic breast density. Climacteric 10:155–163
99. **Eilertsen AL, Karssemeijer N, Skaane P, Qvigstad E, Sandset PM** 2008 Differential impact of conventional and low-dose oral hormone therapy, tibolone and raloxifene on mammographic breast density, assessed by an automated quantitative method. BJOG 115: 773–779
100. **Lundström E, Wilczek B, von Palffy Z, Söderqvist G, von Schoultz B** 1999 Mammographic breast density during hormone replacement therapy: differences according to treatment. Am J Obstet Gynecol 181:348–352
101. **Vachon CM, Sellers TA, Vierkant RA, Wu FF, Brandt KR** 2002 Case-control study of increased mammographic breast density response to hormone replacement therapy. Cancer Epidemiol Biomarkers Prev 11:1382–1388
102. **Cuzick J, Warwick J, Pinney E, Warren RM, Duffy SW** 2004 Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst 96:621–628
103. **Brisson J, Brisson B, Coté G, Maunsell E, Bérubé S, Robert J** 2000 Tamoxifen and mammographic breast densities. Cancer Epidemiol Biomarkers Prev 9:911–915
104. **Cuzick J,** Change in breast density as a biomarker of breast cancer risk reduction. Warwick J, Pinney L, et al, eds. Breast Cancer Research and Treatment [abstract San antonio http://www.abstracts2view.com/sabcs/view.php?nu=SABCS08L_507]. 2009
105. 1997 Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet [Erratum (1997) 350:1484] 350:1047–1059
106. **Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R** 2000 Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA [Erratum (2000) 284:2597] 283:485–491
107. **Greiser CM, Greiser EM, Dören M** 2005 Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. Hum Reprod Update 11:561–573
108. **Prentice RL, Chlebowski RT, Stefanick ML, Manson JE, Langer RD, Pettinger M, Hendrix SL, Hubbell FA, Kooperberg C, Kuller LH, Lane DS, McTiernan A, O'Sullivan MJ, Rossouw JE, Anderson GL** 2008 Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. Am J Epidemiol 167:1407–1415
109. **Chen WY, Manson JE, Hankinson SE, Rosner B, Holmes MD, Willett WC, Colditz GA** 2006 Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med 166:1027–1032
110. **Lyytinen H, Pukkala E, Ylikorkala O** 2006 Breast cancer risk in postmenopausal women using estrogen-only therapy. Obstet Gynecol 108:1354–1360
111. **Kerlikowske K, Miglioretti DL, Ballard-Barbash R, Weaver DL, Buist DS, Barlow WE, Cutter G, Geller BM, Yankaskas B, Taplin SH, Carney PA** 2003 Prognostic characteristics of breast cancer among postmenopausal hormone users in a screened population. J Clin Oncol 21:4314–4321
112. **Beral V, Million Women Study Collaborators** 2003 Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet [Erratum (2003) 362:1160] 362:419–427
113. **Fournier A, Fabre A, Mesrine S, Boutron-Ruault MC, Berrino F, Clavel-Chapelon F** 2008 Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. J Clin Oncol 26:1260–1268
114. **Lee S, Kolonel L, Wilkens L, Wan P, Henderson B, Pike M** 2006 Postmenopausal hormone therapy and breast cancer risk: the Multiethnic Cohort. Int J Cancer 118:1285–1291
115. **Brinton LA, Richesson D, Leitzmann MF, Gierach GL, Schatzkin A, Mouw T, Hollenbeck AR, Lacey Jr JV** 2008 Menopausal hormone therapy and breast cancer risk in the NIH-AARP Diet and Health Study Cohort. Cancer Epidemiol Biomarkers Prev 17:3150–3160
116. **Espié M, Daures JP, Chevallier T, Mares P, Micheletti MC, De Reilhac P** 2007 Breast cancer incidence and hormone replacement therapy: results from the MISSION study, prospective phase. Gynecol Endocrinol 23:391–397
117. **Calle EE, Feigelson HS, Hildebrand JS, Teras LR, Thun MJ, Rodriguez C** 2009 Postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype. Cancer [Erratum (2009) 115:1587] 115:936–945
118. **Fournier A, Berrino F, Clavel-Chapelon F** 2008 Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat [Erratum (2008) 107:307–308] 107:103–111
119. **Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED, Lane DS, Hubbell FA, Assaf AR, Sarto**

GE, Schenken RS, Yasmeen S, Lessin L, Chlebowski RT 2006 Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 295:1647–1657

120. **Collins JA, Blake JM, Crosignani PG** 2005 Breast cancer risk with postmenopausal hormonal treatment. Hum Reprod Update [Erratum (2006) 12:331] 11:545–560
121. **Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F** 2009 Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? J Clin Oncol 27:5138–5143
122. **Daling JR, Malone KE, Doody DR, Voigt LF, Bernstein L, Coates RJ, Marchbanks PA, Norman SA, Weiss LK, Ursin G, Berlin JA, Burkman RT, Deapen D, Folger SG, McDonald JA, Simon MS, Strom BL, Wingo PA, Spirtas R** 2002 Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. Cancer 95:2455–2464
123. **Li CI, Daling JR, Malone KE, Bernstein L, Marchbanks PA, Liff JM, Strom BL, Simon MS, Press MF, McDonald JA, Ursin G, Burkman RT, Deapen D, Spirtas R** 2006 Relationship between established breast cancer risk factors and risk of seven different histologic types of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 15:946–954
124. **Reeves GK, Beral V, Green J, Gathani T, Bull D, Million Women SC** 2006 Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 7:910–918
125. **Song RX, Zhang Z, Mor G, Santen RJ** 2005 Down-regulation of Bcl-2 enhances estrogen apoptotic action in long-term estradiol-depleted ER(+) breast cancer cells. Apoptosis 10:667–678
126. **Song RX, Santen RJ** 2003 Apoptotic action of estrogen. Apoptosis 8:55–60
127. **Song RX, Mor G, Naftolin F, McPherson RA, Song J, Zhang Z, Yue W, Wang J, Santen RJ** 2001 Effect of long-term estrogen deprivation on apoptotic responses of breast cancer cells to 17β-estradiol. J Natl Cancer Inst 93:1714–1723
128. **Lewis JS, Meeke K, Osipo C, Ross EA, Kidawi N, Li T, Bell E, Chandel NS, Jordan VC** 2005 Intrinsic mechanism of estradiol-induced apoptosis in breast cancer cells resistant to estrogen deprivation. J Natl Cancer Inst 97:1746–1759
129. **Preston-Martin S, Pike MC, Ross RK, Henderson BE** 1993 Epidemiologic evidence for the increased cell proliferation model of carcinogenesis. Environ Health Perspect 101(Suppl 5):137–138
130. **Yager JD, Davidson NE** 2006 Estrogen carcinogenesis in breast cancer. N Engl J Med 354:270–282
131. **Bush TL, Whiteman M, Flaws JA** 2001 Hormone replacement therapy and breast cancer: a qualitative review. Obstet Gynecol 98:498–508
132. **Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodabough RJ, Gilligan MA, Cyr MG, Thomson CA, Khandekar J, Petrovitch H, McTiernan A** 2003 Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 289:3243–3253
133. **Anderson GL, Chlebowski RT, Rossouw JE, Rodabough RJ, McTiernan A, Margolis KL, Aggerwal A, David Curb J, Hendrix SL, Allan Hubbell F, Khandekar J, Lane DS, Lasser N, Lopez AM, Potter J, Ritenbaugh C** 2006 Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. Maturitas 55:103–115
134. **Prentice RL, Chlebowski RT, Stefanick ML, Manson JE, Pettinger M, Hendrix SL, Hubbell FA, Kooperberg C, Kuller LH, Lane DS, McTiernan A, Jo O'Sullivan M, Rossouw JE, Anderson GL** 2008 Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. Am J Epidemiol 167:1207–1216
135. **Ries LAG** 2003 SEER cancer statistics review, 1975–2000. Bethesda, MD: National Cancer Institute
136. **Lyytinen H, Pukkala E, Ylikorkala O** 2009 Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstet Gynecol 113:65–73
137. **Henderson BE, Feigelson HS** 2000 Hormonal carcinogenesis. Carcinogenesis 21:427–433
138. **Santen RJ** 2003 Risk of breast cancer with progestins: critical assessment of current data. Steroids 68:953–964
139. **Catherino WH, Jeng MH, Jordan VC** 1993 Norgestrel and gestodene stimulate breast cancer cell growth through an oestrogen receptor mediated mechanism. Br J Cancer 67:945–952
140. **Dauvois S, Simard J, Dumont M, Haagensen DE, Labrie F** 1990 Opposite effects of estrogen and the progestin R5020 on cell proliferation and GCDFP-15 expression in ZR-75-1 human breast cancer cells. Mol Cell Endocrinol 73:171–178
141. **Moore MR, Hathaway LD, Bircher JA** 1991 Progestin stimulation of thymidine kinase in the human breast cancer cell line T47D. Biochim Biophys Acta 1096:170–174
142. **Murphy LC, Dotzlaw H, Alkhalaf M, Coutts A, Miller T, Wong MS, Gong Y, Murphy LJ** 1992 Mechanisms of growth inhibition by antiestrogens and progestins in human breast and endometrial cancer cells. J Steroid Biochem Mol Biol 43:117–121
143. **Musgrove EA, Swarbrick A, Lee CS, Cornish AL, Sutherland RL** 1998 Mechanisms of cyclin-dependent kinase inactivation by progestins. Mol Cell Biol 18:1812–1825
144. **Poulin R, Baker D, Poirier D, Labrie F** 1991 Multiple actions of synthetic 'progestins' on the growth of ZR-75-1 human breast cancer cells: an in vitro model for the simultaneous assay of androgen, progestin, estrogen, and glucocorticoid agonistic and antagonistic activities of steroids. Breast Cancer Res Treat 17:197–210
145. **Sutherland RL, Lee CS, Feldman RS, Musgrove EA** 1992 Regulation of breast cancer cell cycle progression by growth factors, steroids and steroid antagonists. J Steroid Biochem Mol Biol 41:315–321
146. **Malet C, Spritzer P, Guillaumin D, Kuttenn F** 2000 Progesterone effect on cell growth, ultrastructural aspect and estradiol receptors of normal human breast epithelial (HBE) cells in culture. J Steroid Biochem Mol Biol 73:171–181
147. **Colletta AA, Wakefield LM, Howell FV, Danielpour D, Baum M, Sporn MB** 1991 The growth inhibition of human breast cancer cells by a novel synthetic progestin involves the induction of transforming growth factor β. J Clin Invest 87:277–283
148. **Kalkhoven E, Kwakkenbos-Isbrücker L, Mummery CL, de Laat SW, van den Eijnden-van Raaij AJ, van der Saag PT, van der Burg B** 1995 The role of TGF-β production in growth inhibition of breast-tumor cells by progestins. Int J Cancer 61:80–86
149. **Wiebe JP, Muzia D, Hu J, Szwajcer D, Hill SA, Seachrist JL** 2000 The 4-pregnene and 5α-pregnane progesterone metabolites formed in nontumorous and tumorous breast tissue have opposite effects on breast cell proliferation and adhesion. Cancer Res 60:936–943
150. **Graham JD, Mote PA, Salagame U, van Dijk JH, Balleine RL, Huschtscha LI, Reddel RR, Clarke CL** 2009 DNA replication licensing and progenitor numbers are increased by progesterone in normal human breast. Endocrinology 150:3318–3326
151. **Kariagina A, Aupperlee MD, Haslam SZ** 2007 Progesterone receptor isoforms and proliferation in the rat mammary gland during development. Endocrinology 148:2723–2736
152. **Dressing GE, Hagan CR, Knutson TP, Daniel AR, Lange CA** 2009 Progesterone receptors act as sensors for mitogenic protein kinases in breast cancer models. Endocr Relat Cancer 16:351–361
153. **Dressing GE, Lange CA** 2009 Integrated actions of progesterone receptor and cell cycle machinery regulate breast cancer cell proliferation. Steroids 74:573–576
154. **Lange CA** 2004 Making sense of cross-talk between steroid hormone receptors and intracellular signaling pathways: who will have the last word? Mol Endocrinol 18:269–278
155. **Anderson TJ, Battersby S, King RJ, McPherson K, Going JJ** 1989 Oral contraceptive use influences resting breast proliferation. Hum Pathol 20:1139–1144
156. **Potten CS, Watson RJ, Williams GT, Tickle S, Roberts SA, Harris**

M, Howell A 1988 The effect of age and menstrual cycle upon proliferative activity of the normal human breast. Br J Cancer 58: 163–170
157. **Hofseth LJ, Raafat AM, Osuch JR, Pathak DR, Slomski CA, Haslam SZ** 1999 Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is associated with increased epithelial proliferation in the normal postmenopausal breast. J Clin Endocrinol Metab 84:4559–4565
158. **Greendale GA, Reboussin BA, Sie A, Singh HR, Olson LK, Gatewood O, Bassett LW, Wasilauskas C, Bush T, Barrett-Connor E** 1999 Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. Ann Intern Med 130:262–269
159. **Persson I, Thurfjell E, Holmberg L** 1997 Effect of estrogen and estrogen-progestin replacement regimens on mammographic breast parenchymal density. J Clin Oncol 15:3201–3207
160. **Ross RK, Paganini-Hill A, Wan PC, Pike MC** 2000 Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 92:328–332
161. **Horwitz KB, Dye WW, Harrell JC, Kabos P, Sartorius CA** 2008 Rare steroid receptor-negative basal-like tumorigenic cells in luminal subtype human breast cancer xenografts. Proc Natl Acad Sci USA 105:5774–5779
162. **Horwitz KB, Sartorius CA** 2008 Progestins in hormone replacement therapies reactivate cancer stem cells in women with preexisting breast cancers: a hypothesis. J Clin Endocrinol Metab 93: 3295–3298
163. **Hofling M, Hirschberg AL, Skoog L, Tani E, Hägerström T, von Schoultz B** 2007 Testosterone inhibits estrogen/progestogen-induced breast cell proliferation in postmenopausal women. Menopause 14:183–190
164. **Ewertz M** 1988 Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. Int J Cancer 42:832–838
165. **Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA** 2006 Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. Arch Intern Med 166:1483–1489
166. **Brinton LA, Hoover R, Fraumeni Jr JF** 1986 Menopausal oestrogens and breast cancer risk: an expanded case-control study. Br J Cancer 54:825–832
167. **Ness RB, Albano JD, McTiernan A, Cauley JA** 2009 Influence of estrogen plus testosterone supplementation on breast cancer. Arch Intern Med 169:41–46
168. **van Staa TP, Sprafka JM** 2009 Study of adverse outcomes in women using testosterone therapy. Maturitas 62:76–80
169. **Dimitrakakis C, Jones RA, Liu A, Bondy CA** 2004 Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause 11:531–535
170. **Davis SR, Wolfe R, Farrugia H, Ferdinand A, Bell RJ** 2009 The incidence of invasive breast cancer among women prescribed testosterone for low libido. J Sex Med 6:1850–1856
171. **Jick SS, Hagberg KW, Kaye JA, Jick H** 2009 Postmenopausal estrogen-containing hormone therapy and the risk of breast cancer. Obstet Gynecol 113:74–80
172. **Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J** 2002 Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288:321–333
173. **Haas JS, Kaplan CP, Gerstenberger EP, Kerlikowske K** 2004 Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. Ann Intern Med 140:184–188
174. **Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton LJ** 2006 Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. J Clin Oncol 24:e49–e50
175. **Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, Edwards BK, Berry DA** 2007 The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 356: 1670–1674
176. **Glass AG, Lacey Jr JV, Carreon JD, Hoover RN** 2007 Breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. J Natl Cancer Inst 99:1152–1161
177. **Kerlikowske K, Miglioretti DL, Buist DS, Walker R, Carney PA** 2007 National Cancer Institute-sponsored Breast Cancer Surveillance Consortium. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. J Natl Cancer Inst [Erratum (2007) 99:1493] 99:1335–1339
178. **Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, Manson JE, Gass M, Aragaki AK, Ockene JK, Lane DS, Sarto GE, Rajkovic A, Schenken R, Hendrix SL, Ravdin PM, Rohan TE, Yasmeen S, Anderson G** 2009 Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 360:573–587
179. **Robbins AS, Clarke CA** 2007 Regional changes in hormone therapy use and breast cancer incidence in California from 2001 to 2004. J Clin Oncol 25:3437–3439
180. **Canfell K, Banks E, Clements M, Kang YJ, Moa A, Armstrong B, Beral V** 2009 Sustained lower rates of HRT prescribing and breast cancer incidence in Australia since 2003. Breast Cancer Res Treat 117:671–673
181. **Johnston M** 2006 Breast cancer drop linked to fall in use of HRT. New Zealand Herald, December 20, 2006; Public Healthcare section
182. **Katalinic A, Rawal R** 2008 Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. Breast Cancer Res Treat 107:427–430
183. **Allemand H, Seradour B, Weill A, Ricordeau P** 2008 [Decline in breast cancer incidence in 2005 and 2006 in France: a paradoxical trend (French).] Bulletin du Cancer 95:11–15
184. **Zahl PH, Maehlen J, Welch HG** 2008 The natural history of invasive breast cancers detected by screening mammography. Arch Intern Med 168:2311–2316
185. **Vaidya JS** Re: Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. J Natl Cancer Inst 100:598–599; author reply 599
186. **Soerjomataram I, Coebergh JW, Louwman MW, Visser O, van Leeuwen FE** 2007 Does the decrease in hormone replacement therapy also affect breast cancer risk in The Netherlands? J Clin Oncol 25:5038–5039; author reply 5039–5040
187. **Gompel A, Rozenberg S, Barlow DH, EMAS board members** 2008 The EMAS 2008 update on clinical recommendations on postmenopausal hormone replacement therapy. Maturitas 61:227–232
188. **Martin RM, Wheeler BW, Metcalfe C, Gunnell D** 28 March 2010 What was the immediate impact on population health of the recent fall in hormone replacement therapy prescribing in England? Ecological study. J Public Health (Oxf) doi:10.1093/pubmed/fdq021
189. **Colditz GA** 2007 Decline in breast cancer incidence due to removal of promoter: combination estrogen plus progestin. Breast Cancer Res [Erratum (2007) 9:401] 9:108
190. **Kumle M** 2008 Declining breast cancer incidence and decreased HRT use. Lancet 372:608–610
191. **Parkin DM** 2009 Is the recent fall in incidence of post-menopausal breast cancer in UK related to changes in use of hormone replacement therapy? Eur J Cancer 45:1649–1653
192. **Miki Y, Suzuki T, Tazawa C, Yamaguchi Y, Kitada K, Honma S, Moriya T, Hirakawa H, Evans DB, Hayashi S, Ohuchi N, Sasano H** 2007 Aromatase localization in human breast cancer tissues: possible interactions between intratumoral stromal and parenchymal cells. Cancer Res 67:3945–3954
193. **Blankenstein MA, Maitimu-Smeele I, Donker GH, Daroszewski J, Milewicz A, Thijssen JH** 1992 On the significance of in situ pro-

duction of oestrogens in human breast cancer tissue. J Steroid Biochem Mol Biol 41:891–896
194. **Pasqualini JR, Chetrite G, Blacker C, Feinstein MC, Delalonde L, Talbi M, Maloche C** 1996 Concentrations of estrone, estradiol, and estrone sulfate and evaluation of sulfatase and aromatase activities in pre- and postmenopausal breast cancer patients. J Clin Endocrinol Metab 81:1460–1464
195. **Dunbier AK, Anderson H, Ghazoui Z, Folkerd EJ, A'hern R, Crowder RJ, Hoog J, Smith IE, Osin P, Nerurkar A, Parker JS, Perou CM, Ellis MK, Dowsett M** 2010 Relationship between plasma estradiol levels and estrogen-responsive gene expression in estrogen receptor-positive breast cancer in post-menopausal women. J Clin Oncol 28:1161–1167
196. **Yue W, Wang JP, Hamilton CJ, Demers LM, Santen RJ** 1998 In situ aromatization enhances breast tumor estradiol levels and cellular proliferation. Cancer Res 58:927–932
197. **Larionov AA, Berstein LM, Miller WR** 2002 Local uptake and synthesis of oestrone in normal and malignant postmenopausal breast tissues. J Steroid Biochem Mol Biol 81:57–64
198. **Reed MJ, Beranek PA, Ghilchik MW, James VH** 1986 Estrogen production and metabolism in normal postmenopausal women and postmenopausal women with breast or endometrial cancer. Eur J Cancer Clin Oncol 22:1395–1400
199. **Haynes BP, Straume AH, Geisler J, A'Hern R, Helle H, Smith IE, Lønning PE, Dowsett M** 2010 Intratumoral estrogen disposition in breast cancer. Clin Cancer Res 16:1790–1801
200. **Dunbier AK, Anderson H, Ghazoui Z, Folkerd EJ, A'hern R, Crowder RJ, Hoog J, Smith IE, Osin P, Nerurkar A, Parker JS, Perou CM, Ellis MJ, Dowsett M** 2010 Relationship between plasma estradiol levels and estrogen-responsive gene expression in estrogen receptor-positive breast cancer in postmenopausal women. J Clin Oncol 28:1161–1167
201. **Grodin JM, Siiteri PK, MacDonald PC** 1973 Source of estrogen production in postmenopausal women. J Clin Endocrinol Metab 36:207–214
202. **Allred DC, Wu Y, Mao S, Nagtegaal ID, Lee S, Perou CM, Mohsin SK, O'Connell P, Tsimelzon A, Medina D** 2008 Ductal carcinoma in situ and the emergence of diversity during breast cancer evolution. Clin Cancer Res 14:370–378
203. **Betsill Jr WL, Rosen PP, Lieberman PH, Robbins GF** 1978 Intraductal carcinoma. Long-term follow-up after treatment by biopsy alone. JAMA 239:1863–1867
204. **Page DL, Dupont WD, Rogers LW, Landenberger M** 1982 Intraductal carcinoma of the breast: follow-up after biopsy only. Cancer 49:751–758
205. **Rosen PP, Braun Jr DW, Kinne DE** 1980 The clinical significance of pre-invasive breast carcinoma. Cancer 46(4 Suppl):919–925
206. **Wellings SR, Jensen HM, Marcum RG** 1975 An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. J Natl Cancer Inst 55:231–273
207. **Welch HG, Black WC** 1997 Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? Ann Intern Med 127:1023–1028
208. **Alpers CE, Wellings SR** 1985 The prevalence of carcinoma in situ in normal and cancer-associated breasts. Hum Pathol 16:796–807
209. **Bartow SA, Pathak DR, Black WC, Key CR, Teaf SR** 1987 Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. Cancer 60:2751–2760
210. **Bhathal PS, Brown RW, Lesueur GC, Russell IS** 1985 Frequency of benign and malignant breast lesions in 207 consecutive autopsies in Australian women. Br J Cancer 51:271–278
211. **Kramer WM, Rush Jr BF** 1973 Mammary duct proliferation in the elderly. A histopathologic study. Cancer 31:130–137
212. **Nielsen M, Jensen J, Andersen J** 1984 Precancerous and cancerous breast lesions during lifetime and at autopsy. A study of 83 women. Cancer 54:612–615
213. **Nielsen M, Thomsen JL, Primdahl S, Dyreborg U, Andersen JA** 1987 Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. Br J Cancer 56:814–819
214. **Ryan JA, Coady CJ** 1962 Intraductal epithelial proliferation in the human breast: a comparative study. Can J Surg 5:12–19
215. **Willett WC, Rockhill B, Hankinson SE, Hunter D, Colditz GA** 2009 Non-genetic factors in the causation of breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. Diseases of the breast. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 223–276
216. **Kaplan RM, Porzsolt F** 2008 The natural history of breast cancer. Arch Intern Med 168:2302–2303
217. **Jørgensen KJ, Gøtzsche PC** 2009 Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. BMJ 339:b2587
218. **Dietel M, Lewis MA, Shapiro S** 2005 Hormone replacement therapy: pathobiological aspects of hormone-sensitive cancers in women relevant to epidemiological studies on HRT: a mini-review. Hum Reprod 20:2052–2060
219. **Deligdisch L, Holinka CF** 1987 Endometrial carcinoma: two diseases? Cancer Detect Prev 10:237–246
220. **Lax SF** 2004 Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. Virchows Archiv 444:213–223
221. **Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D** 1995 Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 85:304–313
222. **Shields TS, Weiss NS, Voigt LF, Beresford SA** 1999 The additional risk of endometrial cancer associated with unopposed estrogen use in women with other risk factors. Epidemiology 10:733–738
223. **Shapiro S, Kelly JP, Rosenberg L, Kaufman DW, Helmrich SP, Rosenshein NB, Lewis Jr JL, Knapp RC, Stolley PD, Schottenfeld D** 1985 Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. N Engl J Med 313:969–972
224. **Effects of hormone replacement therapy on endometrial histology in postmenopausal women** 1996 The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 275:370–375
225. **Collins J, Donner A, Allen LH, Adams O** 1980 Oestrogen use and survival in endometrial cancer. Lancet 2:961–964
226. **Schwartzbaum JA, Hulka BS, Fowler Jr WC, Kaufman DG, Hoberman D** 1987 The influence of exogenous estrogen use on survival after diagnosis of endometrial cancer. Am J Epidemiol 126:851–860
227. **Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, Liu J, McNeeley SG, Lopez AM** 2003 Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 290:1739–1748
228. **Beral V, Bull D, Reeves G, Million Women Study Collaborators** 2005 Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet 365:1543–1551
229. **Doherty JA, Cushing-Haugen KL, Saltzman BS, Voigt LF, Hill DA, Beresford SA, Chen C, Weiss NS** 2007 Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer. Am J Obstet Gynecol 197:139–137
230. **Eden JA, Hacker NF, Fortune M** 2007 Three cases of endometrial cancer associated with "bioidentical" hormone replacement therapy. Med J Aust 187:244–245
231. **Creasman WT, Henderson D, Hinshaw W, Clarke-Pearson DL** 1986 Estrogen replacement therapy in the patient treated for endometrial cancer. Obstet Gynecol 67:326–330
232. **Chapman JA, DiSaia PJ, Osann K, Roth PD, Gillotte DL, Berman ML** 1996 Estrogen replacement in surgical stage I and II endometrial cancer survivors. Am J Obstet Gynecol 175:1195–1200
233. **Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS, Gynecologic Oncology Group** 2006 Randomized double-blind trial of

estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. J Clin Oncol 24:587–592

234. **Lacey Jr JV, Mink PJ, Lubin JH, Sherman ME, Troisi R, Hartge P, Schatzkin A, Schairer C** 2002 Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA [Erratum (2002) 288: 2544] 288:334–341
235. **Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS** 2007 Menopausal hormone therapy and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev 16:2548–2556
236. **Mørch LS, Løkkegaard E, Andreasen AH, Krüger-Kjaer S, Lidegaard O** 2009 Hormone therapy and ovarian cancer. JAMA 302:298–305
237. **Greiser CM, Greiser EM, Dören M** 2007 Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis. Hum Reprod Update 13:453–463
238. **Zhou B, Sun Q, Cong R, Gu H, Tang N, Yang L, Wang B** 2008 Hormone replacement therapy and ovarian cancer risk: a meta-analysis. Gynecol Oncol [Erratum (2008) 110:455] 108:641–651
239. **Guidozzi F, Daponte A** 1999 Estrogen replacement therapy for ovarian carcinoma survivors: a randomized controlled trial. Cancer 86:1013–1018
240. **Johnson JR, Lacey Jr JV, Lazovich D, Geller MA, Schairer C, Schatzkin A, Flood A** 2009 Menopausal hormone therapy and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 18:196–203
241. **Grodstein F, Newcomb PA, Stampfer MJ** 1999 Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 106:574–582
242. **Nanda K, Bastian LA, Hasselblad V, Simel DL** 1999 Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. Obstet Gynecol 93:880–888
243. **Newcomb PA, Storer BE** 1995 Postmenopausal hormone use and risk of large-bowel cancer. J Natl Cancer Inst [Erratum (1995) 87:1416] 87:1067–1071
244. **Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, Knopp R, Lowery M, Satterfield S, Schrott H, Vittinghoff E, Hunninghake D** 2002 Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). JAMA 288:58–66
245. **Ritenbaugh C, Stanford JL, Wu L, Shikany JM, Schoen RE, Stefanick ML, Taylor V, Garland C, Frank G, Lane D, Mason E, McNeeley SG, Ascensao J, Chlebowski RT** 2008 Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. Cancer Epidemiol Biomarkers Prev 17:2609–2618
246. **Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao J, Rodabough RJ, Rosenberg CA, Taylor VM, Harris R, Chen C, Adams-Campbell LL, White E** 2004 Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 350:991–1004
247. **Tong JL, Ran ZH, Shen J, Fan GQ, Xiao SD** 2008 Association between fecal bile acids and colorectal cancer: a meta-analysis of observational studies. Yonsei Med J 49:792–803
248. **Tanaka Y, Kato K, Mibu R, Uchida S, Asanoma K, Hashimoto K, Nozaki M, Wake N** 2008 Medroxyprogesterone acetate inhibits proliferation of colon cancer cell lines by modulating cell cycle-related protein expression. Menopause 15:442–453
249. **Castiglione F, Taddei A, Degl'Innocenti DR, Buccoliero AM, Bechi P, Garbini F, Chiara FG, Moncini D, Cavallina G, Marascio L, Freschi G, Gian LT** 2008 Expression of estrogen receptor β in colon cancer progression. Diagn Mol Pathol 17:231–236
250. **Di Leo A, Barone M, Maiorano E, Tanzi S, Piscitelli D, Marangi S, Lofano K, Ierardi E, Principi M, Francavilla A** 2008 ER-β expression in large bowel adenomas: implications in colon carcinogenesis. Dig Liver Dis 40:260–266
251. **Chlebowski RT, Schwartz AG, Wakelee H, Anderson GL, Stefanick ML, Manson JE, Rodabough RJ, Chien JW, Wactawski-Wende J, Gass M, Kotchen JM, Johnson KC, O'Sullivan MJ, Ockene JK, Chen C, Hubbell FA** 2009 Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet 374: 1243–1251
252. **Slatore CG, Chien JW, Au DH, Satia JA, White E** 2010 Lung cancer and hormone replacement therapy: association in the Vitamins and Lifestyle Study. J Clin Oncol 28:1540–1546
253. **Chlebowski RT, Anderson GL, Manson JE, Schwartz AG, Wakelee H, Gass M** 2010 Estrogen alone and lung cancer in premenopausal women. Gynecol Oncol 116(Suppl 1), Abstract LBA
254. **Olsson H, Bladström A, Ingvar C** 2003 Are smoking-associated cancers prevented or postponed in women using hormone replacement therapy? Obstet Gynecol 102:565–570
255. **Schabath MB, Wu X, Vassilopoulou-Sellin R, Vaporciyan AA, Spitz MR** 2004 Hormone replacement therapy and lung cancer risk: a case-control analysis. Clin Cancer Res 10:113–123
256. **Schwartz AG, Wenzlaff AS, Prysak GM, Murphy V, Cote ML, Brooks SC, Skafar DF, Lonardo F** 2007 Reproductive factors, hormone use, estrogen receptor expression and risk of non small-cell lung cancer in women. J Clin Oncol 25:5785–5792
257. **Rodriguez C, Spencer Feigelson H, Deka A, Patel AV, Jacobs EJ, Thun MJ, Calle EE** 2008 Postmenopausal hormone therapy and lung cancer risk in the cancer prevention study II nutrition cohort. Cancer Epidemiol Biomarkers Prev 17:655–660
258. **Andersson KE, Chapple CR, Cardozo L, Cruz F, Hashim H, Michel MC, Tannenbaum C, Wein AJ** 2009 Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. Curr Opin Urol 19:380–394
259. **Yamaguchi O, Nishizawa O, Takeda M, Yokoyama O, Homma Y, Kakizaki H, Obara K, Gotoh M, Igawa Y, Seki N, Yoshida M** 2009 Clinical guidelines for overactive bladder. Int J Urol 16:126–142
260. **Cardozo L, Lose G, McClish D, Versi E** 2004 A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. Acta Obstet Gynecol Scand 83:892–897
261. **Moehrer B, Hextall A, Jackson S** 2003 Oestrogens for urinary incontinence in women. Cochrane Database Syst Rev 2:CD001405
262. **Cardozo L, Lose G, McClish D, Versi E, de Koning GH** 2001 A systematic review of estrogens for recurrent urinary tract infections: third report of the hormones and urogenital therapy (HUT) committee. Int Urogynecol J Pelvic Floor Dysfunct 12:15–20
263. **Fantl JA, Cardozo L, McClish DK** 1994 Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol 83:12–18
264. **Al-Badr A, Ross S, Soroka D, Drutz HP** 2003 What is the available evidence for hormone replacement therapy in women with stress urinary incontinence? J Obstet Gynaecol Can 25:567–574
265. **Perrotta C, Aznar M, Mejia R, Albert X, Ng CW** 2008 Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. Cochrane Database Syst Rev 2:CD005131
266. **Eriksen B** 1999 A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol 180:1072–1079
267. **Raz R, Stamm WE** 1993 A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med 329:753–756
268. **Weisberg E, Ayton R, Darling G, Farrell E, Murkies A, O'Neill S, Kirkegard Y, Fraser IS** 2005 Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet. Climacteric 8:83–92
269. **Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH** 2001 Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. Fertil Steril 75:1065–1079
270. **Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L** 1998 Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hor-

mones and Urogenital Therapy Committee. Obstet Gynecol 92: 722–727
271. **Kovalevsky G** 2005 Female sexual dysfunction and use of hormone therapy in postmenopausal women. Semin Reprod Med 23:180–187
272. **Suckling J, Lethaby A, Kennedy R** 2006 Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 4:CD001500
273. **Long CY, Liu CM, Hsu SC, Wu CH, Wang CL, Tsai EM** 2006 A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. Menopause 13: 737–743
274. **Santen RJ, Pinkerton JV, Conaway M, Ropka M, Wisniewski L, Demers L, Klein KO** 2002 Treatment of urogenital atrophy with low-dose estradiol: preliminary results. Menopause 9:179–187
275. **Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W** 2008 Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. Obstet Gynecol 112:1053–1060
276. **Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M** 2008 Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. Obstet Gynecol 111:67–76
277. **Rioux JE, Devlin C, Gelfand MM, Steinberg WM, Hepburn DS** 2000 17β-Estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause 7:156–161
278. **Schmidt G, Andersson SB, Nordle O, Johansson CJ, Gunnarsson PO** 1994 Release of 17-β-oestradiol from a vaginal ring in postmenopausal women: pharmacokinetic evaluation. Gynecol Obstet Invest 38:253–260
279. **Fraser IS, Ayton R, Farrell E, Weisberg E, Darling G, Murkies A** 1995 A multicentre Australian trial of low dose estradiol therapy for symptoms of vaginal atrophy using a vaginal ring as delivery system. Maturitas 22(Suppl):S41
280. **Labrie F, Cusan L, Gomez JL, Côté I, Bérubé R, Bélanger P, Martel C, Labrie C** 2009 Effect of one-week treatment with vaginal estrogen preparations on serum estrogen levels in postmenopausal women. Menopause 16:30–36
281. **Cicinelli E, Di Naro E, De Ziegler D, Matteo M, Morgese S, Galantino P, Brioschi PA, Schonauer A** 2003 Placement of the vaginal 17β-estradiol tablets in the inner or outer one third of the vagina affects the preferential delivery of 17β-estradiol toward the uterus or periurethral areas, thereby modifying efficacy and endometrial safety. Am J Obstet Gynecol 189:55–58
282. **Weiderpass E, Baron JA, Adami HO, Magnusson C, Lindgren A, Bergström R, Correia N, Persson I** 1999 Low-potency oestrogen and risk of endometrial cancer: a case-control study. Lancet 353: 1824–1828
283. **Alder E** 1998 The Blatt-Kupperman menopausal index: a critique. Maturitas 29:19–24
284. **Alder EM** 2002 How to assess quality of life: problems and methodology. In: Schneider HP, ed. Hormone replacement therapy and quality of life. New York: Parthenon Publishing; 11–21
285. **Utian WH, Janata JW, Kingsberg SA, Schluchter M, Hamilton JC** 2002 The Utian Quality of Life (UQOL) Scale: development and validation of an instrument to quantify quality of life through and beyond menopause. Menopause 9:402–410
286. **Utian WH** 2007 Quality of life (QOL) in menopause. Maturitas 57:100–102
287. **Brunner RL, Gass M, Aragaki A, Hays J, Granek I, Woods N, Mason E, Brzyski R, Ockene J, Assaf A, LaCroix A, Matthews K, Wallace R** 2005 Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative Randomized Clinical Trial. Arch Intern Med 165:1976–1986
288. **Hays J, Ockene JK, Brunner RL, Kotchen JM, Manson JE, Patterson RE, Aragaki AK, Shumaker SA, Brzyski RG, LaCroix AZ, Granek IA, Valanis BG** 2003 Effects of estrogen plus progestin on health-related quality of life. N Engl J Med 348:1839–1854
289. **Barnabei VM, Cochrane BB, Aragaki AK, Nygaard I, Williams RS, McGovern PG, Young RL, Wells EC, O'Sullivan MJ, Chen B, Schenken R, Johnson SR** 2005 Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol 105:1063–1073
290. **Freeman EW, Sammel MD, Lin H, Nelson DB** 2006 Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 63: 375–382
291. **Nielsen TF, Ravn P, Pitkin J, Christiansen C** 2006 Pulsed estrogen therapy improves postmenopausal quality of life: a 2-year placebo-controlled study. Maturitas 53:184–190
292. **Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, Meredith SK, Martin J, Meade TW** 2008 Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ 337:a1190
293. **Zethraeus N, Johannesson M, Henriksson P, Strand RT** 1997 The impact of hormone replacement therapy on quality of life and willingness to pay. Br J Obstet Gynaecol 104:1191–1195
294. 2005 NIH State-of-the-Science Conference Statement on management of menopause-related symptoms. NIH Consens State Sci Statements 22:1–38
295. **Maclennan AH, Broadbent JL, Lester S, Moore V** 2004 Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev 4:CD002978
296. **Nelson HD** 2004 Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. JAMA 291:1610–1620
297. **Bachmann GA, Schaefers M, Uddin A, Utian WH** 2007 Lowest effective transdermal 17β-estradiol dose for relief of hot flushes in postmenopausal women: a randomized controlled trial. Obstet Gynecol 110:771–779
298. **Loprinzi CL, Sloan J, Stearns V, Slack R, Iyengar M, Diekmann B, Kimmick G, Lovato J, Gordon P, Pandya K, Guttuso Jr T, Barton D, Novotny P** 2009 Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. J Clin Oncol 27: 2831–2837
299. **Huang A, Yaffe K, Vittinghoff E, Kuppermann M, Addis I, Hanes V, Quan J, Grady D** 2008 The effect of ultralow-dose transdermal estradiol on sexual function in postmenopausal women. Am J Obstet Gynecol 198:265–267
300. **Nijland EA, Nathorst-Böös J, Palacios S, van de Weijer PW, Davis S, Stathopoulos VM, Birkhaeuser MH, von Mauw E, Mulder RJ, Schultz WC** 2009 Improved bleeding profile and tolerability of tibolone versus transdermal E2/NETA treatment in postmenopausal women with female sexual dysfunction. Climacteric 12: 114–121
301. **Lobo RA, Rosen RC, Yang HM, Block B, Van Der Hoop RG** 2003 Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. Fertil Steril 79:1341–1352
302. **Warnock JK, Swanson SG, Borel RW, Zipfel LM, Brennan JJ, ESTRATEST Clinical Study Group** 2005 Combined esterified estrogens and methyltestosterone versus esterified estrogens alone in the treatment of loss of sexual interest in surgically menopausal women. Menopause 12:374–384
303. **Buster JE, Kingsberg SA, Aguirre O, Brown C, Breaux JG, Buch A, Rodenberg CA, Wekselman K, Casson P** 2005 Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. Obstet Gynecol 105:944–952
304. **Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, Moufarege A, Rodenberg C, Buch A, Purdie DW** 2006 Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal wom-

en: a randomized, placebo-controlled trial. Menopause [Erratum (2006) 13:850] 13:387–396
305. **Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, Bachman G, Aguirre OA, Lucas JD, Rodenberg C, Buch A, Watts NB** 2005 Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch Intern Med 165:1582–1589
306. **Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S, Koch H, Moufarege A, Studd J** 2008 Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 359:2005–2017
307. **Panjari M, Bell RJ, Jane F, Adams J, Morrow C, Davis SR** 2009 The safety of 52 weeks of oral DHEA therapy for postmenopausal women. Maturitas 63:240–245
308. **Werner AA, Johns GA, Hoctor EF, Ault CC, Kohler LW, Weis MW** 1934 Involutional melancholia: probably etiology and treatment. JAMA 103:13–16
309. **Wittson CL** 1940 Involutional melancholia. Psychiatric Quarterly 14:167–184
310. **Zweifel JE, O'Brien WH** 1997 A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology [Erratum (1997) 22:655] 22:189–212
311. **Almeida OP, Lautenschlager NT, Vasikaran S, Leedman P, Gelavis A, Flicker L** 2006 A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: effect on mood, cognition and quality of life. Neurobiol Aging 27:141–149
312. **Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA** 2002 Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. JAMA 287:591–597
313. **Schmidt PJ, Nieman L, Danaceau MA, Tobin MB, Roca CA, Murphy JH, Rubinow DR** 2000 Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol 183: 414–420
314. **Soares CN, Almeida OP, Joffe H, Cohen LS** 2001 Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 58:529–534
315. **Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M** 2004 Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. Biol Psychiatry 55: 406–412
316. **Rudolph I, Palombo-Kinne E, Kirsch B, Mellinger U, Breitbarth H, Gräser T** 2004 Influence of a continuous combined HRT (2 mg estradiol valerate and 2 mg dienogest) on postmenopausal depression. Climacteric 7:301–311
317. **Olson MB, Bairey Merz CN, Shaw LJ, Mankad S, Reis SE, Pohost GM, Smith KM, McGorray SP, Cornell CE, Kelsey SF** 2004 Hormone replacement, race, and psychological health in women: a report from the NHLBI-Sponsored WISE Study. J Womens Health (Larchmt) 13:325–332
318. **Steffen AM, Thompson LW, Gallagher-Thompson D, Koin D** 1999 Physical and psychosocial correlates of hormone replacement therapy with chronically stressed postmenopausal women. J Aging Health 11:3–26
319. **Stephens C, Ross N** 2002 The relationship between hormone replacement therapy use and psychological symptoms: no effects found in a New Zealand sample. Health Care Women Int 23:408–414
320. **Bukulmez O, Al A, Gurdal H, Yarali H, Ulug B, Gurgan T** 2001 Short-term effects of three continuous hormone replacement therapy regimens on platelet tritiated imipramine binding and mood scores: a prospective randomized trial. Fertil Steril 75:737–743
321. **Onalan G, Onalan R, Selam B, Akar M, Gunenc Z, Topcuoglu A** 2005 Mood scores in relation to hormone replacement therapies during menopause: a prospective randomized trial. Tohoku J Experimental Medicine 207:223–231
322. **Cagnacci A, Neri I, Tarabusi M, Volpe A, Facchinetti F** 1999 Effect of long-term local or systemic hormone replacement therapy on post-menopausal mood disturbances. Influences of socio-economic and personality factors. Maturitas 31:111–116
323. **Cohen LS, Soares CN, Poitras JR, Prouty J, Alexander AB, Shifren JL** 2003 Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. Am J Psychiatry 160:1519–1522
324. **Soares CN, Arsenio H, Joffe H, Bankier B, Cassano P, Petrillo LF, Cohen LS** 2006 Escitalopram versus ethinyl estradiol and norethindrone acetate for symptomatic peri- and postmenopausal women: impact on depression, vasomotor symptoms, sleep, and quality of life. Menopause 13:780–786
325. **Rasgon NL, Altshuler LL, Fairbanks LA, Dunkin JJ, Davtyan C, Elman S, Rapkin AJ** 2002 Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. J Clin Psychiatry 63(Suppl 7):45–48
326. **Albertazzi P, Natale V, Barbolini C, Teglio L, Di Micco R** 2000 The effect of tibolone versus continuous combined norethisterone acetate and oestradiol on memory, libido and mood of postmenopausal women: a pilot study. Maturitas 36:223–229
327. **Ross LA, Alder EM, Cawood EH, Brown J, Gebbie AE** 1999 Psychological effects of hormone replacement therapy: a comparison of tibolone and a sequential estrogen therapy. J Psychosom Obstet Gynaecol 20:88–96
328. **Elfituri A, Sherif F, Elmahaishi M, Chrystyn H** 2005 Two hormone replacement therapy (HRT) regimens for Middle-Eastern postmenopausal women. Maturitas 52:52–59
329. **Pearce J, Hawton K, Blake F, Barlow D, Rees M, Fagg J, Keenan J** 1997 Psychological effects of continuation versus discontinuation of hormone replacement therapy by estrogen implants: a placebo-controlled study. J Psychosom Res 42:177–186
330. 2004 Hormone therapy–skin. Obstet Gynecol 104:92S–96S
331. **Toutain CE, Brouchet L, Raymond-Letron I, Vicendo P, Bergès H, Favre J, Fouque MJ, Krust A, Schmitt AM, Chambon P, Gourdy P, Arnal JF, Lenfant F** 2009 Prevention of skin flap necrosis by estradiol involves reperfusion of a protected vascular network. Circulation Res 104:245–254
332. **Castelo-Branco C, Duran M, González-Merlo J** 1992 Skin collagen changes related to age and hormone replacement therapy. Maturitas 15:113–119
333. **Sauerbronn AV, Fonseca AM, Bagnoli VR, Saldiva PH, Pinotti JA** 2000 The effects of systemic hormonal replacement therapy on the skin of postmenopausal women. Int J Gynaecol Obstet 68:35–41
334. **Maheux R, Naud F, Rioux M, Grenier R, Lemay A, Guy J, Langevin M** 1994 A randomized, double-blind, placebo-controlled study on the effect of conjugated estrogens on skin thickness. Am J Obstet Gynecol 170:642–649
335. **Phillips TJ, Symons J, Menon S, HT Study Group** 2008 Does hormone therapy improve age-related skin changes in postmenopausal women? A randomized, double-blind, double-dummy, placebo-controlled multicenter study assessing the effects of norethindrone acetate and ethinyl estradiol in the improvement of mild to moderate age-related skin changes in postmenopausal women. J Am Acad Dermatol 59:397–404.e3
336. **Rittié L, Kang S, Voorhees JJ, Fisher GJ** 2008 Induction of collagen by estradiol: difference between sun-protected and photodamaged human skin in vivo. Arch Dermatol 144:1129–1140
337. **Straub RH** 2007 The complex role of estrogens in inflammation. Endocr Rev 28:521–574
338. **Bebo Jr BF, Fyfe-Johnson A, Adlard K, Beam AG, Vandenbark AA, Offner H** 2001 Low-dose estrogen therapy ameliorates experimental autoimmune encephalomyelitis in two different inbred mouse strains. J Immunol 166:2080–2089
339. **Brunelli R, Frasca D, Perrone G, Pioli C, Fattorossi A, Zichella L, Doria G** 1996 Hormone replacement therapy affects various im-

mune cell subsets and natural cytotoxicity. Gynecol Obstet Invest 41:128–131
340. **Liu HB, Loo KK, Palaszynski K, Ashouri J, Lubahn DB, Voskuhl RR** 2003 Estrogen receptor α mediates estrogen's immune protection in autoimmune disease. J Immunol 171:6936–6940
341. **Porter VR, Greendale GA, Schocken M, Zhu X, Effros RB** 2001 Immune effects of hormone replacement therapy in post-menopausal women. Exp Gerontol 36:311–326
342. **Costenbader KH, Feskanich D, Stampfer MJ, Karlson EW** 2007 Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. Arthritis Rheum 56:1251–1262
343. **Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS** 2002 Hormonal and reproductive risk factors for development of systemic lupus erythematosus: results of a population-based, case-control study. Arthritis Rheum 46:1830–1839
344. **Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, Merrill JT, Sammaritano L, Lockshin M, Alarcón GS, Manzi S, Belmont HM, Askanase AD, Sigler L, Dooley MA, Von Feldt J, McCune WJ, Friedman A, Wachs J, Cronin M, Hearth-Holmes M, Tan M, Licciardi F** 2005 The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 142:953–962
345. **Walitt B, Pettinger M, Weinstein A, Katz J, Torner J, Wasko MC, Howard BV** 2008 Effects of postmenopausal hormone therapy on rheumatoid arthritis: the Women's Health Initiative randomized controlled trials. Arthritis Rheum 59:302–310
346. **Doran MF, Crowson CS, O'Fallon WM, Gabriel SE** 2004 The effect of oral contraceptives and estrogen replacement therapy on the risk of rheumatoid arthritis: a population based study. J Rheumatol 31:207–213
347. **Hall GM, Daniels M, Huskisson EC, Spector TD** 1994 A randomised controlled trial of the effect of hormone replacement therapy on disease activity in postmenopausal rheumatoid arthritis. Ann Rheum Dis 53:112–116
348. **Hernandez-Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, Chang RW, Hennekens CH, Speizer FE** 1990 Exogenous sex hormones and the risk of rheumatoid arthritis. Arthritis Rheum 33:947–953
349. **van den Brink HR, van Everdingen AA, van Wijk MJ, Jacobs JW, Bijlsma JW** 1993 Adjuvant oestrogen therapy does not improve disease activity in postmenopausal patients with rheumatoid arthritis. Ann Rheum Dis 52:862–865
350. **Beebe JL** 1997 Reproductive history, oral contraceptive use, and estrogen replacement therapy and the risk of developing scleroderma. Lacey LV, Mayes MD, Gillespie BW, et al, editors. Arthritis Rheumatol 41 supplemetn 9:419
351. **Fraenkel L, Zhang Y, Chaisson CE, Evans SR, Wilson PW, Felson DT** 1998 The association of estrogen replacement therapy and the Raynaud phenomenon in postmenopausal women. Ann Intern Med 129:208–211
352. **Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B** 1995 Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. Am J Respir Crit Care Med 152:1183–1188
353. **Holmqvist P, Wallberg M, Hammar M, Landtblom AM, Brynhildsen J** 2006 Symptoms of multiple sclerosis in women in relation to sex steroid exposure. Maturitas 54:149–153
354. **Smith R, Studd JW** 1992 A pilot study of the effect upon multiple sclerosis of the menopause, hormone replacement therapy and the menstrual cycle. J R Soc Med 85:612–613
355. **Asherson RA, Harris EN, Hughes GR, Farquharson RG** 1988 Complications of oral contraceptives and antiphospholipid antibodies: reply to the letter by Bruneau *et al*. Arthritis Rheum 31: 575–576
356. **Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD** 2002 A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. Rheumatology 41:924–929
357. **Nagler RM, Pollack S** 2000 Sjogren's syndrome induced by estrogen therapy. Semin Arthritis Rheum 30:209–214
358. **Parke AL** 2000 Sjogren's syndrome: a women's health problem. J Rheumatol Suppl 61:4–5
359. **Simon JA, Hunninghake DB, Agarwal SK, Lin F, Cauley JA, Ireland CC, Pickar JH** 2001 Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease. The Heart and Estrogen/Progestin Replacement Study. Ann Intern Med 135:493–501
360. **Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, Larson JC** 2005 Effect of estrogen therapy on gallbladder disease. JAMA 293:330–339
361. **Liu B, Beral V, Balkwill A, Green J, Sweetland S, Reeves G** 2008 Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. BMJ 337:a386
362. **Grodstein F, Colditz GA, Stampfer MJ** 1994 Postmenopausal hormone use and cholecystectomy in a large prospective study. Obstet Gynecol 83:5–11
363. **Gallus S, Negri E, Chatenoud L, Bosetti C, Franceschi S, La Vecchia C** 2002 Post-menopausal hormonal therapy and gallbladder cancer risk. Int J Cancer 99:762–763
364. **Feskanich D, Cho E, Schaumberg DA, Colditz GA, Hankinson SE** 2008 Menopausal and reproductive factors and risk of age-related macular degeneration. Arch Ophthalmol 126:519–524
365. **Haan MN, Klein R, Klein BE, Deng Y, Blythe LK, Seddon JM, Musch DC, Kuller LH, Hyman LG, Wallace RB** 2006 Hormone therapy and age-related macular degeneration: the Women's Health Initiative Sight Exam Study. Arch Ophthalmol 124:988–992
366. **Seitzman RL, Mangione C, Ensrud KE, Cauley JA, Stone KL, Cummings SR, Hochberg MC, Hillier TA, Yu F, Coleman AL** 2008 Postmenopausal hormone therapy and age-related maculopathy in older women. Ophthalmic Epidemiol 15:308–316
367. **Klein BE, Klein R, Lee KE** 2000 Reproductive exposures, incident age-related cataracts, and age-related maculopathy in women: the Beaver Dam Eye Study. Am J Ophthalmol 130:322–326
368. **Freeman EE, Muñoz B, Bressler SB, West SK** 2005 Hormone replacement therapy, reproductive factors, and age-related macular degeneration: the Salisbury Eye Evaluation Project. Ophthalmic Epidemiol 12:37–45
369. **Snow KK, Cote J, Yang W, Davis NJ, Seddon JM** 2002 Association between reproductive and hormonal factors and age-related maculopathy in postmenopausal women. Am J Ophthalmol 134:842–848
370. 1992 Risk factors for neovascular age-related macular degeneration. The Eye Disease Case-Control Study Group. Arch Ophthalmol 110:1701–1708
371. **Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC** 2004 Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256:240–246
372. **Brinton RD** 2009 Estrogen-induced plasticity from cells to circuits: predictions for cognitive function. Trends Pharmacol Sci 30:212–222
373. **Henderson VW, Guthrie JR, Dudley EC, Burger HG, Dennerstein L** 2003 Estrogen exposures and memory at midlife: a population-based study of women. Neurology 60:1369–1371
374. **Kok HS, Kuh D, Cooper R, van der Schouw YT, Grobbee DE, Wadsworth ME, Richards M** 2006 Cognitive function across the life course and the menopausal transition in a British birth cohort. Menopause 13:19–27
375. **Fuh JL, Wang SJ, Lee SJ, Lu SR, Juang KD** 2006 A longitudinal study of cognition change during early menopausal transition in a rural community. Maturitas 53:447–453

376. **Herlitz A, Thilers P, Habib R** 2007 Endogenous estrogen is not associated with cognitive performance before, during, or after menopause. Menopause 14:425–431
377. **Luetters C, Huang MH, Seeman T, Buckwalter G, Meyer PM, Avis NE, Sternfeld B, Johnston JM, Greendale GA** 2007 Menopause transition stage and endogenous estradiol and follicle-stimulating hormone levels are not related to cognitive performance: cross-sectional results from the Study of Women's Health Across the Nation (SWAN). J Womens Health (Larchmt) 16:331–344
378. **Henderson VW, Sherwin BB** 2007 Surgical versus natural menopause: cognitive issues. Menopause 14:572–579
379. **Maki PM, Gast MJ, Vieweg AJ, Burriss SW, Yaffe K** 2007 Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. Neurology 69:1322–1330
380. **Carlson MC, Zandi PP, Plassman BL, Tschanz JT, Welsh-Bohmer KA, Steffens DC, Bastian LA, Mehta KM, Breitner JC** 2001 Hormone replacement therapy and reduced cognitive decline in older women: the Cache County Study. Neurology 57:2210–2216
381. **Kang JH, Weuve J, Grodstein F** 2004 Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. Neurology 63:101–107
382. **Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, Hsia J, Margolis KL, Hogan PE, Wallace R, Dailey M, Freeman R, Hays J** 2004 Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291:2959–2968
383. **Resnick SM, Maki PM, Rapp SR, Espeland MA, Brunner R, Coker LH, Granek IA, Hogan P, Ockene JK, Shumaker SA** 2006 Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J Clin Endocrinol Metab 91:1802–1810
384. **Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E** 2002 Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/Progestin Replacement Study. Am J Med 113:543–548
385. **Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI** 2005 Estrogen therapy and risk of cognitive decline: results from the Women's Estrogen for Stroke Trial (WEST). Am J Obstet Gynecol 192:387–393
386. **Yaffe K, Vittinghoff E, Ensrud KE, Johnson KC, Diem S, Hanes V, Grady D** 2006 Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. Arch Neurol 63:945–950
387. **Kritz-Silverstein D, Barrett-Connor E** 2002 Hysterectomy, oophorectomy, and cognitive function in older women. J Am Geriatr Soc 50:55–61
388. **Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, Melton 3rd LJ** 2007 Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 69:1074–1083
389. **Sherwin BB** 1988 Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. Psychoneuroendocrinology 13:345–357
390. **Phillips SM, Sherwin BB** 1992 Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 17:485–495
391. **Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A** 1999 Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology 52:78–84
392. **Edland SD, Rocca WA, Petersen RC, Cha RH, Kokmen E** 2002 Dementia and Alzheimer disease incidence rates do not vary by sex in Rochester, Minn. Arch Neurol 59:1589–1593
393. **Asthana S, Baker LD, Craft S, Stanczyk FZ, Veith RC, Raskind MA, Plymate SR** 2001 High-dose estradiol improves cognition for women with AD: results of a randomized study. Neurology 57:605–612
394. **Henderson VW, Paganini-Hill A, Miller BL, Elble RJ, Reyes PF, Shoupe D, McCleary CA, Klein RA, Hake AM, Farlow MR** 2000 Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. Neurology 54:295–301
395. **Wang PN, Liao SQ, Liu RS, Liu CY, Chao HT, Lu SR, Yu HY, Wang SJ, Liu HC** 2000 Effects of estrogen on cognition, mood, and cerebral blood flow in AD: a controlled study. Neurology 54:2061–2066
396. **Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, Doody R, Koss E, Pfeiffer E, Jin S, Gamst A, Grundman M, Thomas R, Thal LJ** 2000 Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA [Erratum (2000) 284:2597] 283:1007–1015
397. **Rigaud AS, André G, Vellas B, Touchon J, Pere JJ, French Study Group** 2003 No additional benefit of HRT on response to rivastigmine in menopausal women with AD. Neurology 60:148–149
398. **Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones 3rd BN, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-Smoller S, Wactawski-Wende J** 2003 Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289:2651–2662
399. **Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH** 2004 Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291:2947–2958
400. **Paganini-Hill A, Henderson VW** 1996 Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med 156:2213–2217
401. **Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, Andrews H, Mayeux R** 1996 Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 348:429–432
402. **Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A, Bacal C, Lingle DD, Metter E** 1997 A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology [Erratum (1998) 51:654] 48:1517–1521
403. **Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, Steffens DC, Breitner JC** 2002 Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA 288:2123–2129
404. **Yaffe K, Sawaya G, Lieberburg I, Grady D** 1998 Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA 279:688–695
405. **Hogervorst E, Williams J, Budge M, Riedel W, Jolles J** 2000 The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience 101:485–512
406. **Henderson VW** 2006 Estrogen-containing hormone therapy and Alzheimer's disease risk: understanding discrepant inferences from observational and experimental research. Neuroscience 138:1031–1039
407. **Brett KM, Chong Y** 2001 Hormone replacement therapy: knowledge and use in the United States. Hyattsville, MD: National Center for Health Statistics
408. **Yaffe K, Krueger K, Sarkar S, Grady D, Barrett-Connor E, Cox DA, Nickelsen T** 2001 Cognitive function in postmenopausal women treated with raloxifene. N Engl J Med 344:1207–1213
409. **Yaffe K, Krueger K, Cummings SR, Blackwell T, Henderson VW, Sarkar S, Ensrud K, Grady D** 2005 Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. Am J Psychiatry 162:683–690
410. **Shuster LT, Gostout BS, Grossardt BR, Rocca WA** 2008 Prophy-

lactic oophorectomy in premenopausal women and long-term health. Menopause Int 14:111–116

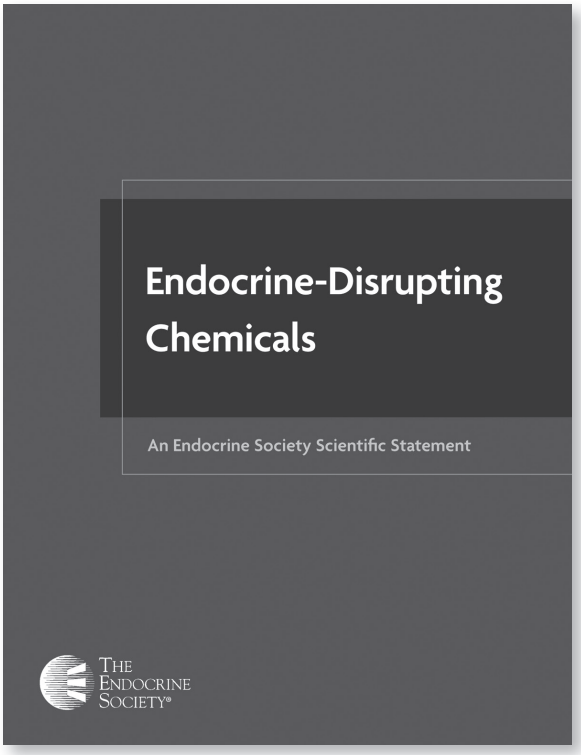
411. **Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S** 2004 Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 291:1701–1712
412. **Utian WH, Archer DF, Bachmann GA, Gallagher C, Grodstein F, Heiman JR, Henderson VW, Hodis HN, Karas RH, Lobo RA, Manson JE, Reid RL, Schmidt PJ, Stuenkel CA** 2008 Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. Menopause 15:584–602
413. **Parker WH, Manson JE** 2009 Oophorectomy and cardiovascular mortality: is there a link? Menopause 16:1–2
414. **Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton 3rd LJ** 2006 Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol 7:821–828
415. **Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS** 2007 Ovarian conservation at the time of hysterectomy for benign disease. Clin Obstet Gynecol 50:354–361
416. **Shoupe D, Parker WH, Broder MS, Liu Z, Farquhar C, Berek JS** 2007 Elective oophorectomy for benign gynecological disorders. Menopause 14:580–585
417. **Kannel WB, Wilson PW** 1995 Risk factors that attenuate the female coronary disease advantage. Arch Intern Med 155:57–61
418. **Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT** 2006 Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause 13:265–279
419. **Hsia J, Barad D, Margolis K, Rodabough R, McGovern PG, Limacher MC, Oberman A, Smoller S** 2003 Usefulness of prior hysterectomy as an independent predictor of Framingham risk score (The Women's Health Initiative). Am J Cardiol 92:264–269
420. **Mack WJ, Slater CC, Xiang M, Shoupe D, Lobo RA, Hodis HN** 2004 Elevated subclinical atherosclerosis associated with oophorectomy is related to time since menopause rather than type of menopause. Fertil Steril 82:391–397
421. **Løkkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT** 2006 The association between early menopause and risk of ischaemic heart disease: influence of hormone therapy. Maturitas 53:226–233
422. **Rivera CM, Grossardt BR, Rhodes DJ, Brown Jr RD, Roger VL, Melton 3rd LJ, Rocca WA** 2009 Increased cardiovascular mortality after early bilateral oophorectomy. Menopause 16:15–23
423. **Vearncombe KJ, Pachana NA** 2009 Is cognitive functioning detrimentally affected after early, induced menopause? Menopause 16:188–198
424. **Rocca WA, Grossardt BR, Geda YE, Gostout BS, Bower JH, Maraganore DM, de Andrade M, Melton 3rd LJ** 2008 Long-term risk of depressive and anxiety symptoms after early bilateral oophorectomy. Menopause 15:1050–1059
425. **Sherwin BB, Henry JF** 2008 Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. Front Neuroendocrinol 29:88–113
426. **Henderson VW** 2009 Estrogens, episodic memory, and Alzheimer's disease: a critical update. Semin Reprod Med 27:283–293
427. **Pinkerton JV, Henderson VW** 2005 Estrogen and cognition, with a focus on Alzheimer's disease. Semin Reprod Med 23:172–179
428. **Crandall CJ, Zheng Y, Crawford SL, Thurston RC, Gold EB, Johnston JM, Greendale GA** 2009 Presence of vasomotor symptoms is associated with lower bone mineral density: a longitudinal analysis. Menopause 16:239–246
429. **Sowers MR, Jannausch M, McConnell D, Little R, Greendale GA, Finkelstein JS, Neer RM, Johnston J, Ettinger B** 2006 Hormone predictors of bone mineral density changes during the menopausal transition. J Clin Endocrinol Metab 91:1261–1267
430. **Guthrie JR, Lehert P, Dennerstein L, Burger HG, Ebeling PR, Wark JD** 2004 The relative effect of endogenous estradiol and androgens on menopausal bone loss: a longitudinal study. Osteoporos Int 15:881–886
431. **Riggs BL, Melton 3rd LJ** 1986 Involutional osteoporosis. N Engl J Med 314:1676–1686
432. **Hui SL, Wiske PS, Norton JA, Johnston Jr CC** 1982 A prospective study of change in bone mass with age in postmenopausal women. J Chronic Dis 35:715–725
433. **Gallagher JC** 2007 Effect of early menopause on bone mineral density and fractures. Menopause 14:567–571
434. **MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, Mojica W, Timmer M, Alexander A, McNamara M, Desai SB, Zhou A, Chen S, Carter J, Tringale C, Valentine D, Johnsen B, Grossman J** 2008 Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med 148:197–213
435. **Melton 3rd LJ, Khosla S, Malkasian GD, Achenbach SJ, Oberg AL, Riggs BL** 2003 Fracture risk after bilateral oophorectomy in elderly women. J Bone Miner Res 18:900–905
436. **Gulekli B, Davies MC, Jacobs HS** 1994 Effect of treatment on established osteoporosis in young women with amenorrhoea. Clin Endocrinol (Oxf) 41:275–281
437. **Farquhar C, Marjoribanks J, Lethaby A, Suckling JA, Lamberts Q** 2009 Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2:CD004143
438. **Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH** 2002 Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA 287:2668–2676
439. **Lindsay R** 2004 Hormones and bone health in postmenopausal women. Endocrine 24:223–230
440. **Shifren JL, Avis NE** 2007 Surgical menopause: effects on psychological well-being and sexuality. Menopause 14:586–591
441. **Bromberger JT, Matthews KA, Schott LL, Brockwell S, Avis NE, Kravitz HM, Everson-Rose SA, Gold EB, Sowers M, Randolph Jr JF** 2007 Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). J Affect Disord 103:267–272
442. **Nathorst-Böös J, von Schoultz B** 1992 Psychological reactions and sexual life after hysterectomy with and without oophorectomy. Gynecol Obstet Invest 34:97–101
443. **Davison SL, Bell R, Donath S, Montalto JG, Davis SR** 2005 Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 90:3847–3853
444. **Rhodes JC, Kjerulff KH, Langenberg PW, Guzinski GM** 1999 Hysterectomy and sexual functioning. JAMA 282:1934–1941
445. **Nathorst-Böös J, Wiklund I, Mattsson LA, Sandin K, von Schoultz B** 1993 Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. Acta Obstet Gynecol Scand 72:656–660
446. **Dennerstein L, Koochaki P, Barton I, Graziottin A** 2006 Hypoactive sexual desire disorder in menopausal women: a survey of Western European women. J Sex Med 3:212–222
447. **Judd HL, Lucas WE, Yen SS** 1974 Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. Am J Obstet Gynecol 118:793–798
448. **Singh M, Sumien N, Kyser C, Simpkins JW** 2008 Estrogens and progesterone as neuroprotectants: what animal models teach us. Front Biosci 13:1083–1089
449. **Marsden J, Whitehead M, A'Hern R, Baum M, Sacks N** 2000 Are

randomized trials of hormone replacement therapy in symptomatic women with breast cancer feasible? Fertil Steril 73:292–299
450. **Chlebowski RT, Kim JA, Col NF** 2003 Estrogen deficiency symptom management in breast cancer survivors in the changing context of menopausal hormone therapy. Semin Oncol 30:776–788
451. **Holmberg L, Iversen OE, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J, Jassem J, Dobaczewska D, Fjosne HE, Peralta O, Arriagada R, Holmqvist M, Maenpaa J** 2008 Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst [Erratum (2008) 100: 685] 100:475–482
452. **DiSaia PJ, Brewster WR, Ziogas A, Anton-Culver H** 2000 Breast cancer survival and hormone replacement therapy: a cohort analysis. Am J Clin Oncol 23:541–545
453. **Xydakis AM, Sakkas EG, Mastorakos G** 2006 Hormone replacement therapy in breast cancer survivors. Ann NY Acad Sci 1092: 349–360
454. **Col NF, Kim JA, Chlebowski RT** 2005 Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. Breast Cancer Res 7:R535–R540
455. **Batur P, Blixen CE, Moore HC, Thacker HL, Xu M** 2006 Menopausal hormone therapy (HT) in patients with breast cancer. Maturitas 53:123–132
456. **von Schoultz E, Rutqvist LE** 2005 Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. J Natl Cancer Inst 97:533–535
457. **Holmberg L, Anderson H** 2004 HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer–is it safe?), a randomised comparison: trial stopped. Lancet 363:453–455
458. **Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A** 2007 Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 99:272–282
459. **Veronesi U, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, Viale G, Costa A, Sacchini V, Travaglini R, D'Aiuto G, Oliviero P, Lovison F, Gucciardo G, del Turco MR, Muraca MG, Pizzichetta MA, Conforti S, Decensi A** 2007 Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst 99:727–737
460. **Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Sellin R, Yip CH, Egberts J, Mol-Arts M, Mulder R, van Os S, Beckmann MW** 2009 Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol 10: 135–146
461. **Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Seilin R, Yip CH, Egberts J, Mol-Arts M, Mulder R, van Os S, Beckmann MW, on behalf of the LIBERATE Study Group** 2009 Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol [Erratum (2009) 10: 209] 10:135–146
462. **Trinh XB, Tjalma WA, Makar AP, Buytaert G, Weyler J, van Dam PA** 2008 Use of the levonorgestrel-releasing intrauterine system in breast cancer patients. Fertil Steril 90:17–22
463. **Lyytinen HK, Dyba T, Ylikorkala O, Pukkala EI** 2010 A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as well. Int J Cancer 126:483–489
464. **Kendall A, Dowsett M, Folkerd E, Smith I** 2006 Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. Ann Oncol 17:584–587
465. **Osborne CR, Duncan A, Sedlacek S, Paul D, Holmes F, Vukelja S, Kasper M, Wilks S, Schneider A, McGee R, Meyer WG, O'Shaughnessy JA** 2009 The addition of hormone therapy to tamoxifen does not prevent hot flashes in women at high risk for developing breast cancer. Breast Cancer Res Treat 116:521–527
466. **Sestak I, Kealy R, Edwards R, Forbes J, Cuzick J** 2006 Influence of hormone replacement therapy on tamoxifen-induced vasomotor symptoms. J Clin Oncol 24:3991–3996
467. 2009 Early and locally advanced breast cancer: diagnosis and treatment. Full guideline developed for NICE by the National Colaborating Centre for Cancer. Cardiff, Wales: National Collaborating Centre for Cancer, Velindre NHS Trust. http://www.nice.org.uk/nicemedia/live/12132/43413/43413.pdf
468. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
469. **Pritchard KI, Khan H, Levine M, Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer** 2002 Clinical practice guidelines for the care and treatment of breast cancer: 14. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer. CMAJ 166: 1017–1022
470. **Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE** 2009 Bayesian meta-analysis of hormone therapy and mortality in younger post-menopausal women. Am J Med 122:1016–1022.e1
471. **Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E** 1998 Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. JAMA 280:605–613
472. **Salpeter SR, Walsh JM, Greyber E, Ormiston TM, Salpeter EE** 2004 Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. J Gen Intern Med 19: 791–804
473. **Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, Rosner B, Fuchs C, Hankinson SE, Hunter DJ, Hennekens CH, Speizer FE** 1997 Postmenopausal hormone therapy and mortality. N Engl J Med 336:1769–1775
474. **Kloosterboer HJ** 2001 Tibolone: a steroid with a tissue-specific mode of action. J Steroid Biochem Mol Biol 76:231–238
475. **Dören M, Rübig A, Coelingh Bennink HJ, Holzgreve W** 2001 Differential effects on the androgen status of postmenopausal women treated with tibolone and continuous combined estradiol and norethindrone acetate replacement therapy. Fertil Steril 75: 554–559
476. **Hammar M, Christau S, Nathorst-Böös J, Rud T, Garre K** 1998 A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. Br J Obstet Gynaecol 105:904–911
477. **Swanson SG, Drosman S, Helmond FA, Stathopoulos VM** 2006 Tibolone for the treatment of moderate to severe vasomotor symptoms and genital atrophy in postmenopausal women: a multicenter, randomized, double-blind, placebo-controlled study. Menopause 13:917–925
478. **Delmas PD, Davis SR, Hensen J, Adami S, van Os S, Nijland EA** 2008 Effects of tibolone and raloxifene on bone mineral density in osteopenic postmenopausal women. Osteoporos Int 19:1153–1160
479. **Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C, Bilezikian J, Kerzberg EM, Johnson S, Zanchetta J, Grobbee DE, Seifert W, Eastell R** 2008 The effects of tibolone in older postmenopausal women. N Engl J Med 359:697–708
480. **Nelson HD, Fu R, Griffin JC, Nygren P, Smith ME, Humphrey L** 2009 Systematic review: comparative effectiveness of medications to reduce risk of breast cancer. Ann Intern Med 151:703–715, W-226–235
481. **Archer DF, Hendrix S, Gallagher JC, Rymer J, Skouby S, Ferenczy A, den Hollander W, Stathopoulos V, Helmond FA** 2007 Endometrial effects of tibolone. J Clin Endocrinol Metab 92:911–918

482. **Nijland EA, Weijmar Schultz WC, Nathorst-Boös J, Helmond FA, Van Lunsen RH, Palacios S, Norman RJ, Mulder RJ, Davis SR** 2008 Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trail. J Sex Med 5:646–656
483. **Winkler UH, Altkemper R, Kwee B, Helmond FA, Coelingh Bennink HJ** 2000 Effects of tibolone and continuous combined hormone replacement therapy on parameters in the clotting cascade: a multicenter, double-blind, randomized study. Fertil Steril 74:10–19
484. **Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, Reginster JY, Pols HA, Recker RR, Harris ST, Wu W, Genant HK, Black DM, Eastell R** 2002 Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab 87:3609–3617
485. **Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, Rautaharju P, Harper KD** 2002 Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 287:847–857
486. **Barrett-Connor E, Cox DA, Song J, Mitlak B, Mosca L, Grady D** 2009 Raloxifene and risk for stroke based on the Framingham Stroke Risk Score. Am J Med 122:754–761
487. **Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, Farrerons J, Karasik A, Mellstrom D, Ng KW, Stepan JJ, Powles TJ, Morrow M, Costa A, Silfen SL, Walls EL, Schmitt H, Muchmore DB, Jordan VC, Ste-Marie LG** 2001 Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple Outcomes of Raloxifene Evaluation. Breast Cancer Res Treat [Erratum (2001) 67:191] 65:125–134
488. **Lippman ME, Cummings SR, Disch DP, Mershon JL, Dowsett SA, Cauley JA, Martino S** 2006 Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. Clin Cancer Res 12:5242–5247
489. **Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon Jr ER, Wade 3rd JL, Robidoux A, Margolese RG, James J, Lippman SM, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC, Wolmark N** 2006 Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA [Erratum (2006) 296:2926] 295:2727–2741
490. **DeMichele A, Troxel AB, Berlin JA, Weber AL, Bunin GR, Turzo E, Schinnar R, Burgh D, Berlin M, Rubin SC, Rebbeck TR, Strom BL** 2008 Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population-based case-control study. J Clin Oncol 26:4151–4159
491. **Cranney A, Adachi JD** 2005 Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. Drug Safety 28:721–730
492. **Pines A, Sturdee DW, Birkhauser MH, de Villiers T, Naftolin F, Gompel A, Farmer R, Barlow D, Tan D, Maki P, Lobo R, Hodis H** 2008 HRT in the early menopause: scientific evidence and common perceptions. Climacteric 11:267–272
493. **Birkhäuser MH, Panay N, Archer DF, Barlow D, Burger H, Gambacciani M, Goldstein S, Pinkerton JA, Sturdee DW** 2008 Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. Climacteric 11:108–123
494. **Islam S, Liu Q, Chines A, Helzner E** 2009 Trend in incidence of osteoporosis-related fractures among 40- to 69-year-old women: analysis of a large insurance claims database, 2000–2005. Menopause 16:77–83
495. **Panay N, Ylikorkala O, Archer DF, Gut R, Lang E** 2007 Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief. Climacteric 10:120–131
496. **Lobo RA** 2004 Evaluation of cardiovascular event rates with hormone therapy in healthy, early postmenopausal women: results from 2 large clinical trials. Arch Intern Med 164:482–484
497. **Yim CH, Choi JT, Choi HA, Kang YS, Moon IG, Yoon HK, Han IK, Kang DH, Han KO** 2005 Association of estrogen receptor α gene microsatellite polymorphism with annual changes in bone mineral density in Korean women with hormone replacement therapy. J Bone Miner Metab 23:395–400
498. **Herrington DM, Howard TD** 2003 ER-α variants and the cardiovascular effects of hormone replacement therapy. Pharmacogenomics 4:269–277
499. **Clarkson TB** 2008 Can women be identified that will derive considerable cardiovascular benefits from postmenopausal estrogen therapy? J Clin Endocrinol Metab 93:37–39
500. **Kharode Y, Bodine PV, Miller CP, Lyttle CR, Komm BS** 2008 The pairing of a selective estrogen receptor modulator, bazedoxifene, with conjugated estrogens as a new paradigm for the treatment of menopausal symptoms and osteoporosis prevention. Endocrinology 149:6084–6091
501. **Lobo RA, Pinkerton JV, Gass ML, Dorin MH, Ronkin S, Pickar JH, Constantine G** 2009 Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril 92:1025–1038
502. **Archer DF, Lewis V, Carr BR, Olivier S, Pickar JH** 2009 Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. Fertil Steril 92:1039–1044
503. **Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G** 2009 Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 92:1045–1052
504. **Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA** 1996 Cloning of a novel receptor expressed in rat prostate and ovary. Proc Natl Acad Sci USA 93:5925–5930
505. **Hartman J, Ström A, Gustafsson JA** 2009 Estrogen receptor β in breast cancer—diagnostic and therapeutic implications. Steroids 74:635–641
506. **Brinton EA, Hodis HN, Merriam GR, Harman SM, Naftolin F** 2008 Can menopausal hormone therapy prevent coronary heart disease? Trends Endocrinol Metab 19:206–212
507. **Montori VM** 2009 GRADE: a system for assessing level of evidence.
508. **Baerug U, Winge T, Nordland G, Faber-Swensson E, Heldaas K, Norling B, Larsen S, Arce JC** 1998 Do combinations of 1 mg estradiol and low doses of NETA effectively control menopausal symptoms? Climacteric 1:219–228
509. **Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, Selzer RH, Liu Cr CR, Liu Ch CH, Azen SP** 2001 Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 135:939–953
510. **Cherry N, Gilmour K, Hannaford P, Heagerty A, Khan MA, Kitchener H, McNamee R, Elstein M, Kay C, Seif M, Buckley H** 2002 Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. Lancet 360:2001–2008
511. **Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, Hennekens C, Rosner B, Speizer FE** 1995 The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 332:1589–1593

Also Available:

Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement



Please visit:
www.endo-society.org/journals

Scientific Statements provide an overview of basic and clinical science content on topics of emerging importance. Content is evidence-based to the extent possible but also identifies areas of basic or clinical knowledge that require additional research. Topics are selected on the basis of their emerging scientific impact on disease and broad clinical relevance to the general population.

THE ENDOCRINE SOCIETY®

8401 Connecticut Avenue, Suite 900
Chevy Chase, Maryland 20815
www.endo-society.org

Advancing excellence in endocrinology and promoting its essential role as an integrative force in scientific research and medical practice.