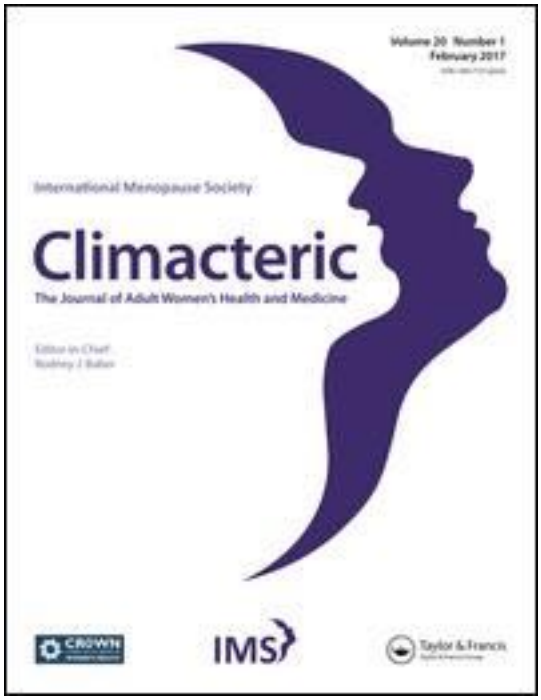

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OPINION

Menopausal hormone therapy for primary prevention: why the USPSTF is wrong

R. D. Langer[a], J. A. Simon[b], A. Pines[c], R. A. Lobo[d], H. N. Hodis[e], J. H. Pickar[f], D. F. Archer[g], P. M. Sarrel[h] and W. H. Utian[i]

[a]Principal Scientist, Jackson Hole Center for Preventive Medicine, Jackson, WY, Associate Dean for Clinical and Translational Research and Professor of Family Medicine, University of Nevada Reno School of Medicine, Reno, NV, USA; [b]Clinical Professor, Department of Obstetrics and Gynecology, George Washington University, Washington, DC, USA; [c]Clinical Professor of Internal Medicine, Sackler Faculty of Medicine, Tel-Aviv University, Israel; [d]Professor of Obstetrics and Gynecology, Columbia University Medical Center, New York, NY, USA; [e]Harry J. Bauer and Dorothy Bauer Rawlins Professor of Cardiology, Professor of Medicine and Preventive Medicine and Director, Atherosclerosis Research Unit, Division of Cardiovascular Medicine, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA; [f]Adjunct Associate Professor of Obstetrics and Gynecology, Columbia University Medical Center, New York, NY, USA; [g]Professor of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA, USA; [h]Emeritus Professor of Obstetrics, Gynecology, Reproductive Sciences, and Psychiatry, Yale University School of Medicine, New Haven, CT, USA; [i]Professor Emeritus, Reproductive Biology, Case Western Reserve University, Cleveland, OH, USA

ABSTRACT

The US Preventive Services Task Force (USPSTF) Draft Recommendation statement on Menopausal Hormone Therapy: Primary Prevention for Chronic Diseases, released in May 2017, perpetuates a major disconnect between the primary population affected, women within roughly 10 years of menopause, and the data cited. Furthermore, major elements of the evidence relied upon have been misinterpreted or misstated, particularly in regard to coronary heart disease and breast cancer, for which there is no statistically significant evidence of harm. As currently drafted, the recommendations reiterate the USPSTF statements of 2012, 2005 and 2002, and will perpetuate egregious harm to the public health. In an attempt to avoid that outcome and to facilitate a return to rational discourse regarding menopausal hormone therapy, an ad hoc group of experts in menopausal health submitted this comprehensive response to the USPSTF.

The US Preventive Services Task Force (USPSTF) Draft Recommendation statement perpetuates a major disconnect between the primary population affected and the data cited. Furthermore, major elements of the evidence relied upon have been misinterpreted. As currently drafted, the recommendations will be harmful to the public health.

We are an ad hoc group of clinical scientists well published in the area of menopausal hormone therapy (MHT). We find the USPSTF Draft Recommendation distressing in its selective interpretation of the available data, its frank and severe error in generalizing data from women a decade or more past menopause to the typical clinical population of women considering MHT near the time of menopause, and its failure to address the public health implications of this guidance, making the consistent error of using relative risks rather than absolute risks. Considering the relative importance of coronary heart disease, fragility fractures, colorectal cancer and diabetes to the public health – alongside potential harms – the balance is clearly toward benefit from MHT when initiated within 10 years of menopause in women with appropriate indications, with continuation thereafter for an indeterminate period for the prevention of chronic diseases. We share this view with the major professional societies dedicated to caring for menopausal women, including the International Menopause Society (IMS)[1] and the North American Menopause Society (NAMS)[2]. The 2017 hormone therapy position statement of NAMS has been endorsed by over 30 national and international medical organizations.

In this regard, it is critical for the USPSTF to recognize that the Women's Health Initiative (WHI) Clinical Trial of Hormone Replacement Therapy, upon which it relies for much of the evidence cited, was not designed to evaluate mainstream use of MHT. [Note that hormone replacement therapy (HRT) is equivalent to MHT as used in this document.] It was designed to test whether the effects of MHT on the prevention of chronic diseases previously observed in women initiating treatment near the time of menopause would be found in women initiating treatment a decade or more after menopause. It was built upon considerable prior evidence from a large number of observational studies and two clinical trials consistently demonstrating benefit in the prevention of chronic diseases when MHT was initiated near menopause[3–10]. Indeed, the evidence supporting chronic dis- ease prevention with MHT initiated near menopause was already so strong when the WHI was being planned that the merits of the MHT trial in relation to its costs were questioned. The Institute of Medicine (IOM) was consulted to opine on whether the MHT trial should continue. The IOM found that it should proceed, stating: 'The effects of initiating HRT at various ages after the menopause have not been well studied. The proposed trial would offer the opportunity to study risks and benefits associated with initiating HRT at older ages'[11].

The WHI was not intended, and not statistically powered, to evaluate the common clinical use of MHT initiated near menopause[12]. To the extent that subanalyses can be con- ducted using WHI data for women within a decade of meno- pause, and to the extent that they provide statistically meaningful results – for risk or for benefit – they are germane to the question of continuing MHT for the prevention of chronic diseases. However, it is entirely inappropriate to use WHI data from the 70% of the enrolled cohort that was more than 10 years postmenopausal to opine on clinical effects in women initiating MHT near menopause. Furthermore, the analytic methods used in nearly all WHI reports stratify by age but do not adjust for age or most chronic disease risk factors. Such analyses are relevant to the population studied in the WHI HRT trial with a mean age of 63 years, and an average of 12 years postmenopause. It is inappropriate to generalize those results to a population with different characteristics, i.e. the clinical population of women initiating MHT near menopause. Unfortunately, the USPSTF has consistently made this error in its consideration of the evidence.

With regard to the timing hypothesis, it is important to acknowledge the context of the Heart and Estrogen/progestin Replacement Study (HERS), the WHI, the Women's International Study of long-Duration Oestrogen after Menopause (WISDOM), the WHI Memory Study (WHIMS) and similar trials launched in the 1990s. They were all based on the foundation of substantial and consistent evidence from more than 25 years of research at that time demonstrating benefits in the prevention of chronic disease in women start- ing MHT near menopause, and intended to test whether those benefits would be

found in women initiating MHT at older ages. Studies that have continued to follow women who started MHT near menopause, with long-term use there- after, continue to show benefits for prevention of coronary disease, fracture and dementia[13,14]. Perhaps the most import- ant contribution of HERS, WHI and WHIMS has been the consistent observation that initiating MHT a decade or more after menopause has far different effects on major organ systems than initiating MHT near menopause.

Timing clearly makes a difference. What remains to be determined in regard to 'hypotheses' are the mechanisms underlying this phenomenon. The Early versus Late Intervention with Estrogen (ELITE) trial did specifically test the effect of years since menopause on estrogen-associated protection from atheroma and demonstrated significant protection with early initiation[15]. This is documented in further detail below.

We are also concerned that the USPSTF is perpetuating the poor and unscientific clinical practice of generalizing from individual medications to a class in the use of the terms 'combined estrogen and progestin' and 'estrogen alone'.

The vast majority of the evidence relied upon by the USPSTF comes from studies that tested conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) as in the WHI HRT trial arms for women with a uterus (CEE þ MPA) and women with prior hysterectomy (CEE-alone). Good evidence from human and animal trials demonstrates differences between these specific drugs and others in their classes[9,16–18]. While we recognize that the USPSTF Draft Recommendation does need to reflect a general opinion, we believe that, when data are cited, the specific medications tested should be referenced – not the class. As discussed further below, there is also good evidence for a difference between oral and transdermal delivery in regard to thrombotic events. This difference by route of delivery is supported by metabolic data, by findings in population studies, and by outcomes in clinical trials[15,19–22].

Below we address specific points in the Draft Recommendation that we find in error. Our text conforms to the sections of the USPSTF draft document, and our comments, rejoinders and reservations refer to specific points of that document which we highlight in italics.

Section on Importance

'The excess risk that can be attributed to menopause is uncertain'

Evidence dating back to the Framingham Study publication in 1976 demonstrates that menopause itself is a primary factor in increasing the female risk of cardiovascular diseases (CVD)[23]. The inarguable decline in bone density associated with menopause, together with the female-to-male difference in fragility fracture rates at any specific age after 50 years, demonstrates the impact of menopause on fracture risk. Axiomatically, the withdrawal of MHT results in an increased risk of chronic diseases associated with natural and surgical menopause, including increased all-cause mortality, coronary heart disease (CHD) mortality, stroke mortality and bone fractures, and, importantly, hip fractures that increase mortality[24,25].

Section on Benefits of Preventive Medication

Estrogen alone [should be CEE]

‘The USPSTF found adequate evidence that the use of estrogen alone is of moderate benefit in reducing the risk for developing or dying of breast cancer ... ’

This is the only place in the USPSTF assessment with any mention of estrogen therapy reducing mortality risk. However, the reduction in breast cancer mortality is a small part of the reduction in all-cause mortality risk seen in the WHI CEE-alone cohort of women aged 50–59 years in which almost all of the mortality reduction is secondary to reduced CVD-related deaths[26,27]. Using WHI CEE-alone data for women age 50–59 years[26] and rates for hormone discontinuance between 2002 and 2011[28], it has been calculated that more than 40 000 hysterectomized women aged 50–59 years have died because women who would have used estrogen in the past failed to do so in the years following the initial WHI report in 2002[29].

The WHI findings in women starting CEE at age 50–59 years are consistent with the findings of other randomized controlled trials and cohort studies showing reduced CVD mortality in women starting various estrogen preparations at age 50 years or younger. Women who are postmenopausal before age 50 years and untreated show an increased risk for CVD-related mortality[30–32]. When treated, these women show a reduced mortality risk as compared to untreated women[33,34]. Limiting the findings of estrogen reduction of mortality risk to no more than a footnote about reduced breast cancer mortality is a disservice to the majority of post- menopausal women.

‘ ... convincing evidence that estrogen does not have a benefit on coronary heart disease’

The WHI clinical trial of CEE-alone demonstrated a roughly 40% reduction in CHD in women aged 50–59 years at randomization when clinical CHD equivalents (coronary artery bypass grafting, angioplasty) were included[35]. These were not stipulated in the initial protocol because of clinical bias against their use in women when the WHI was designed in 1992–1993. Fortunately, by the time the trial was well underway between 1998 and 2004, that bias had largely disappeared and women were receiving pre-emptive intervention for CHD. It is disingenuous to discount these CHD equivalents – no cardiologist will undertake an angioplasty and no surgeon will perform a coronary bypass in the absence of established coronary artery disease. Moreover, the substudy evaluating the development of coronary artery calcium in women 50–59 years old participating in the CEE- alone arm demonstrated significant protection with this form of MHT[36].

Section on Harms of Preventive Medication

Combined estrogen and progestin [should be CEE plus MPA]

‘ ... combined estrogen and progestin is associated with moderate harms, including an increase in the risk of invasive breast cancer’

The USPSTF appears to rely on the nominal results of the WHI CEE þ MPA arm for this opinion which have been widely published despite the fact that the study protocol called for adjusted analyses (in keeping with established standards for clinical trials). The appropriately adjusted results have been published and do not support the conclusion of increased breast cancer risk[37].

‘ ... increased risk for stroke, dementia’

The increase in stroke in the WHI CEE þ MPA arm was seen in women randomized more than a decade

after menopause. And the WHIMS CEE þ MPA arm enrolled only women aged 65 years and older. Clearly, this has no relevance to women initiating near the age of menopause, while data from other sources suggest preservation of cognitive capacity and reduced risk of dementia for women initiating early and continuing MHT[38–43].

Estrogen alone [should be CEE]

Misleading statements in the Draft Recommendation in regard to stroke and dementia are the same as for CEE þ MPA above, while CEE alone was associated with a trend for reduced breast cancer in the WHI.

Section on Clinical Considerations

Patient population under consideration

'This recommendation ... does not apply to women who are considering hormone therapy for the management of menopausal symptoms such as hot flashes ... '

The USPSTF excludes the use of MHT for symptom control from the scope of this recommendation, but fails to recognize that the pathophysiology underlying menopause symptoms, most notably vasomotor instability (hot flushes), is integral to the development of disease. Untreated vasomotor instability has been shown to impair endothelial function and is associated with increased risks for hypertension, osteoporotic fracture, CVD, depression, and cognitive impairment[44–52]. Thus, controlling hot flushes is preventing disease.

'It [the USPSTF Draft Recommendation] does not apply to women younger than age 50 years ... '

The USPSTF states the median age for menopause as 51.3 years. The bell curve for that median indicates a normal age for natural menopause to be between 47 and 55 years. Translating those figures into actual numbers of women, in the US approximately 7 million women are naturally menopausal by age 50 years. Another 7 million, by that age, are surgically postmenopause, with half of all hysterectomies/ oophorectomies done by age 45 years and 90% by age 50 years[53,54]. Considering these parallel pathways to become menopausal, two-thirds of all US women are menopausal before age 51 years[55].

The decline in use of MHT has affected women of all ages and it is naïve to think that a 'D' assessment for use by older women will not have an impact on younger menopausal women. When these women fail to use MHT, in addition to an increase in mortality risk, they also experience accelerated risks for major diseases including CVD, osteoporosis, dementia, mood disorders, and sexual dysfunction[56–60]. The FDA indications for MHT for women in their forties and younger include both symptom control and disease prevention. In addition to recognizing the preponderance of benefit over risk in women with indications for MHT initiating treatment within 10 years of menopause, or before approximately 60 years old, we would urge the Task Force to make a more comprehensive statement about the benefits and risks of MHT for women beginning treatment before 50 years old, i.e. women younger than those studied in the WHI.

Treatment and intervention

‘Currently, evidence is limited to determine whether differ- ent types, doses, or modes of delivery of hormone therapy affect its benefit-to-harm profile or the prevention of chronic conditions’

There is consistent evidence from population studies, along with strong biological plausibility, for no increased risk of venous thromboembolic events with transdermal estradiol[15,19–22]. There is similar evidence from population studies and animal experiments demonstrating reduced proliferative stimulation in breast tissue with progesterone compared with MPA[61–63]. And, as cited earlier, there is strong evidence from human and animal trials demonstrating differences between types of MHT[9,16–18].

‘A black box warning indicates that estrogen, with or without progestin, should be prescribed at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman’

This statement on FDA-approved labeling cites the WHI for supporting evidence. The WHI tested only one dose, so there is no evidence supporting lowest effective dose. The WHI results for CHD, the major chronic disease risk for postmenopausal women, demonstrated decreasing event rates over time, supporting benefit with longer duration of treatment[35,64,65]. To the extent that HERS is relevant (given its older age range), it too demonstrated a trend towards reduced CHD with longer-duration MHT[66].

‘The use of menopausal hormone therapy results in some benefits but also some significant harms’

This section cries out for the use of net absolute risks to weigh the public health consequences of the diseases cited; the verbiage here is of little use. We have included illustrations demonstrating that there is strong net benefit in the final section of this document.

Section on Research Needs and Gaps

‘Evidence about whether the benefits and harms of menopausal hormone therapy vary by age, race/ethnicity, or time since menopause is limited’

Such evidence is limited only if the literature is viewed pre- dominantly through 'the glass' of the WHI, HERS, WISDOM and related studies that were designed to test effects in older women. Nonetheless, underpowered as it was to evaluate effects in women within 10 years of menopause, WHI subanalyses do support prevention of CHD by CEE alone in such women, with no harm in that age range for CEE þ MPA[35,36,64]. There is a substantial literature based on women initiating early, but much of it was published before the library was swamped by the aforementioned trials[4,5,67,68]. In the more recent literature, results from the Danish Osteoporosis Study (DOPS), a clinical trial cut short by the WHI publications, continue to support benefit in the prevention of chronic disease events when MHT is initiated

relatively early in menopause[33]. The beneficial changes in chronic disease risk factors demonstrated in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, which restricted enrollment to women <10 years since menopause, are also supportive[9].

The ELITE trial provides clear support for a difference in atheroma development according to years since menopause when MHT is initiated. In the ELITE trial, healthy postmenopausal women without CVD were stratified according to time since menopause (<6 years, early postmenopause, or >10 years, late postmenopause) when randomized to MHT versus placebo. After a median of 5 years, the effect of estradiol with or without progesterone on subclinical atherosclerosis progression differed between the early (median time since meno- pause, 3.5 years) and late postmenopause (median time since menopause, 14.3 years) strata (p1⁄40.007 for the interaction). The rate of atherosclerosis progression was significantly lower in the MHT-treated group relative to placebo in the women in the early postmenopause group (p1⁄40.008), whereas the rate of atherosclerosis progression did not differ between MHT and placebo in the late postmenopause group (p 1⁄4 0.29)[15].

Section on Scope of Review

'Of these trials, the WHI trial was the largest and was the only trial designed and sufficiently powered to evaluate the effectiveness of hormone therapy for primary prevention of the multiple conditions that are the focus of this recommendation statement'

The WHI was adequately powered to address these questions in a population with an average age of 63 years that was an average of 12 years postmenopause. Relying on this population for guidance on a treatment that is clinically relevant to a population that is on average 12 years younger, with clear differences in organ system status, risk factors, and clinical needs, is unscientific and entirely inappropriate. Furthermore, while standard practice in reporting clinical trials is to publish results adjusted for major confounders, and although the WHI Protocol stated that Cox analyses would be performed with suitably defined time-dependent covariates, all of the primary reports published by the WHI focused on nominal, unadjusted results[69]. When adjustment was applied, it was nearly always simply for multiple looks at the data, not for covariates that could influence disease outcomes. None of the primary disease outcomes in the WHI remained significant when multivariate adjusted analyses were reported.

Section on Benefits and Harms of Preventive Medication

Breast cancer

'During the intervention phase of the WHI trial (median duration 5.6 years) women assigned to combined estrogen and progestin had a significantly increased risk of breast cancer compared with women assigned to placebo (HR 1.24 [95% CI 1.01 to 1.53]'

This is a nominal result; it is not adjusted for covariates or even multiple looks at the data over time, both of which were to be applied per protocol[12]. A properly adjusted result was published and was not statistically significant (hazard ratio 1.20; 95% confidence interval (CI) 0.94–1.53)[37]. Furthermore, the stark contrast with the reduced risk in the CEE-alone arm implies that the progestin, in this case MPA, accounts for some of the difference. It is also essential to recognize that, as referenced in the WHI Protocol, breast cancer cell doubling times would require at least 9, and perhaps as many as 14, years of post-exposure follow-up to detect the initiation of breast cancer by a drug[12]. The purported increase in the WHI CEEþMPA arm began in the third year. Thus, there could not have been breast cancer initiation.

A far more likely explanation is that MPA promoted growth of existing cancer lesions[70]. There is evidence from large population studies that other progestational agents, e.g. progesterone itself, do not promote proliferation or growth of existing lesions to the extent noted for MPA[61,62].

In addition, the use of hazard ratios in the WHI CEE þ MPA breast cancer analyses masks another critical fact. The increased hazard was not due to an increased rate in women randomized to CEEþMPA. Rather, it was due to an unexplained decreased rate in women randomized to placebo in the CEE þ MPA arm who were prior users of MHT. This striking fact is illustrated in Figure 1, drawn from Anderson and col- leagues[37]. Of the four trend lines illustrated in Figure 1, the only one with a different slope is that representing the sub- group of women with prior MHT exposure who were randomized to placebo. The trends for the other placebo subgroup and for both subgroups randomized to CEE þ MPA are all virtually identical. Also, there is a striking comparison to be made with rates in the larger, overlapping WHI Diet Modification trial (DM trial) recruited at a similar time. That trial tested a change from the typical US diet to a low-fat eating pattern to prevent breast cancer. The annualized rate of breast cancer in the intervention women in the DM trial was 0.42, while that rate was actually less, 0.40, in women randomized to CEEþMPA with no prior MHT[37,71]. In contrast, the rate in the outlier group illustrated in Figure 1, women randomized to placebo with prior MHT exposure, was 0.25. Meanwhile, the rate for DM 'placebo' women randomized to usual diet was 0.45, further illustrating the huge discordance in the women with prior MHT use randomized to the placebo subgroup. Yet the DM trial was reported as ‘suggesting reduced risk associated with a low-fat dietary pattern’, while the CEE þ MPA indicating breast cancer harm[69,71,72].

Thromboembolic events

This section cites only studies of oral medications. The pro- coagulation ‘first-pass’ hepatic metabolic effect on coagula- tion factors is well known[20]. In contrast, a large number of studies demonstrate no increased hazard for thromboembolic events with non-oral estrogen delivery[15,19,21,22].

Stroke

This section is relevant to women of the ages represented in the studies cited. It is not relevant to the typical candidate for MHT. As documented above, there was no stroke risk in WHI women aged 50–59 years when randomized to MHT.

Invasive Breast Cancer Participants with No Prior Hormone Use

Invasive Breast Cancer Participants with Any Prior Hormone Use

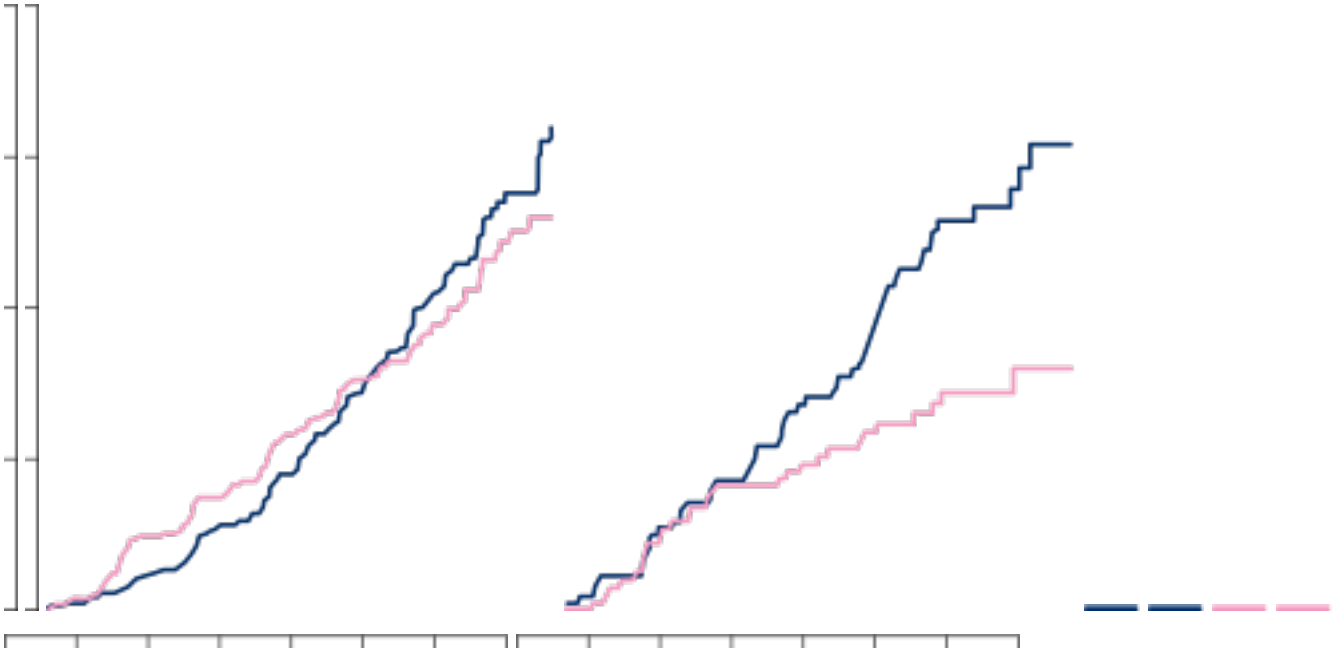

Figure 1. Invasive breast cancer over time in the Women's Health Initiative trial with CEE þ MPA (shown as EþP above), stratified by prior use of menopausal hormone therapy, showing major divergence only for women with prior use randomized to placebo. Adapted with permission from Anderson et al.[37].

Cognitive impairment

As noted in the Draft Recommendation, observational studies of women starting MHT near the age of menopause have suggested that it may prevent dementia. The WHI Memory Study enrolled women aged 65 and older. It demonstrates another aspect of organ system differences with age and is not relevant to women who are the mainstream candidates for MHT. Moreover, the ELITE trial also provides Class 1 evidence that MHT relative to placebo has no effect on cognition, including verbal episodic memory, executive functions and global cognition, whether initiated in women within 6 years of menopause or after 10 years of menopause[73].

Fractures

Osteoporosis and fractures carry a huge burden on those who are afflicted in general and have financial implications in regard to health-care systems in particular. All over the world, MHT has an approved indication of prevention of osteoporosis, and in some countries also an additional indication of treatment of osteoporosis. High-quality data from clinical trials have demonstrated an increase in bone mineral density during MHT compared to placebo or no treatment[9]. Some major studies, such as the WHI, showed a substantial decrease in the risk for fractures, including fractures of the hip[74–76]. Notably, in contrast to clinical trials of drugs specifically developed for osteoporosis treatment, with the trials conducted in osteopenic or osteoporotic women, the WHI demonstrated fracture prevention in women unselected for poor bone density. Compared with placebo, there were 47 and 53 fewer fractures per

10000 women-years in the WHI CEEþMPA and CEE-only arms, respectively. The correspond- ing numbers for hip fracture were 5 and 7 fewer per 10 000 women-years, compared with the placebo arms[74,75]. Furthermore, a significant increase in the incidence of hip fractures that coincided with the dramatic decrease in the use of MHT post-WHI has been demonstrated[25]. Unlike bisphosphonates, which have been associated with excessive bone mineralization, estrogen facilitates normal bone architecture[77]. There is no question that estrogen is an effective and metabolically appropriate preventive strategy for osteoporotic fractures, and that osteoporosis is a chronic disease with tremendous impact in postmenopausal women.

Diabetes

Reducing the incidence of newly diagnosed diabetes mellitus and improving glucose handling in healthy or diabetic patients have become major, global health-care challenges. Evidence from clinical studies showed that postmenopausal hormone therapy has favorable effects in this respect. Actually, all key studies on hormone therapy, such as PEPI, HERS and WHI, pointed at a significant reduction in the incidence of type 2 diabetes mellitus on the order of 15–20%. The latter two studied women who were well into their menopausal years. The Kronos Early Estrogen Prevention Study (KEEPS), which enrolled healthy, recently postmenopausal women, found an improvement in HOMA values in

those who were treated with an estradiol patch[78]. In another study using short-term transdermal estradiol, women within 6 years of menopause, as opposed to those more than 10 years from menopause, had a reduction in the glucose disposal rate (using a clamp), suggesting improved insulin action only in younger women[79]. The data on the effects of MHT in the prevention of diabetes mellitus or in diabetic women were recently summarized in a comprehensive review by Mauvais-Jarvis and colleagues[80]. They concluded that MHT may be of benefit in reducing the burden of diabetes mellitus.

Urinary incontinence

Urinary incontinence should be considered in the broader context of the genitourinary syndrome of menopause (GSM), of which vaginal atrophy is a major component, and may affect women for over one-third of their life[81]. It is a chronic medical condition[82]. Upwards of 50% of postmenopausal women experience symptoms of GSM, which several years ago was estimated to be 32 million women in the US[83,84]. Associated symptoms may affect not only the daily activities and quality of life but also relationships and sexual activities of postmenopausal women[82]. Vulvovaginal atrophy responds exceedingly well to estrogen, with or without progestogen, and regardless of whether the estrogen is administered by the oral, transdermal or vaginal route. Studies in postmenopausal women with vaginal atrophy have demonstrated that estrogen can improve vaginal cytology, reduce vaginal pH, increase vaginal fluid secretions and mucosal thickness, and provide symptomatic relief[84]. For women with significant symptoms related to GSM, estrogen therapy remains the therapeutic standard[81]. In clinical practice, the treatment is generally continued after resolution of symptoms to prevent recurrence. The USPSTF blanket recommendation against the use of estrogen and estrogen/progestin for the prevention of chronic conditions does not appear to have considered the chronicity and impact of GSM in aging women.

Colorectal cancer

Colorectal cancer is the third most common cancer in women, excluding skin cancer, and is also the third leading cause of cancer deaths, contributing to a significant public health concern. Both oral contraceptive use and hormonal therapy have been shown to decrease the risk of colon cancer in women. A meta-analysis of observational data showed a significant 20% reduction with hormone use, both estrogen and estrogen/progestogen[85]. In the WHI reports, there was a significant reduction in colon cancer with combined therapy, and a reduced rate with estrogen alone that was not statistically significant[86]. In the WHI, combined therapy during the intervention phase resulted in a reduced hazard ratio of 0.62 (95% CI 0.47–0.95) that translated to six fewer cases per 10000 person-years[27]. The age-stratified data suggest that the lack of significant reduction with estrogen alone was due to an aberrant increase in the number of cases of colon can- cer in the 70–79-year-old group[87]. Thus the bowel may also be sensitive to the timing of MHT. There is biological plausibility for the protective effect of estrogen in that induction of estrogen receptor b by estrogen can induce apoptosis in polypoid lesions[88].

Section on Subgroups

'Age did appear to influence the effects of estrogen-alone therapy on the risk of myocardial infarction, all-cause mortality, and colorectal cancer'

This is a critical point that is not taken into account by the main thrust of the USPSTF Draft Recommendation.

'In the WHI trial, younger women (ages 50 to 59 years) who took estrogen-alone had lower risk of myocardial infarction, though not total coronary heart disease events[27]'

The publication that specifically focused on this question was by Hsia and colleagues[35]. That report demonstrated a lower risk of all CHD events in women aged 50–59 years at randomization. That point is further supported by the WHI Coronary Artery Calcium (CAC) study publication demonstrating reduced CAC in women aged 50–59 years randomized to CEE- alone[36].

Section on Timing of Preventive Medication

'To date, no good-quality randomized trials have prospectively evaluated the timing of hormone therapy initiation relative to the onset of menopause on associated benefits and harms'

In a recent Cochrane analysis, women who started hormone therapy within 10 years of menopause had 30% lower mor- tality (relative risk 0.70; 95% CI 0.52–0.95), 48% lower coronary heart disease (relative risk 0.52; 95% CI 0.29–0.96) and no effect on risk of stroke relative to placebo[89]. Moreover, as documented above, the ELITE trial was specifically designed to test the effects of timing of initiation. It demonstrated benefit in reduced atheroma in women initiating MHT<6 years from menopause. In addition, the DOPS trial, which randomized women aged 45–58 years to MHT, demonstrated both reductions in major chronic disease events, and greater reductions in younger women, even within that recently menopausal age span[33].

Section on Estimate of Magnitude of Net Benefit

The term ‘magnitude’ implies a quantitative assessment, yet the language of this section is limited to vague qualitative terms. The chronic diseases discussed in this recommendation have tremendous public health implications, and their relative incidence covers several orders of magnitude. We would strongly encourage the USPSTF to provide absolute risk estimates for each, with attention to age at initiation and future risk. Providing a cumulative estimate of long-term benefit–risk across major disease entities for women initiating MHT within 10 years of menopause – the mainstream group to which these recommendations will be applied – would be of great help to women and their health-care providers.

Conclusion and public health considerations

We conclude with a perspective on the significant negative public health impact of the Draft Recommendation if not modified to address the specific concerns detailed above.

Coronary heart disease

CHD is the leading cause of death in women and thus represents an essential public health concern. Strong evidence suggests that, in women initiating estrogen-alone treatment close to the onset of menopause, CHD and total mortality are decreased by approximately 30–40%, with minimal risk for adverse events[90]. The DOPS trial found a nearly 50% reduction in CHD and mortality in younger women randomized to estradiol and norethindrone acetate, in parallel with a reduction in breast cancer and mortality[33]. A study of all Finnish women who used MHT (combination or estrogen alone) from 1994 to 2009 that included 3.3 million MHT exposure-years in approximately 500000 women who were compared to age-matched non-users of MHT found that the risk of CHD death was reduced by 18% to 54% and was positively related to MHT exposure time. Risk of stroke death was also reduced, as was the risk of all cause mortality[91].

Are there any other proven therapies for primary prevention in women? Lifestyle interventions, which are often not sustainable, have been shown to reduce the 10-year coronary risk by only 12–14%[92]. While statins and aspirin have been used for prevention in men, there are no statistically significant results supporting the application of these strategies for the primary prevention of CHD, or for reduced mortality, in women[93–99]. Moreover, there are data suggesting an increase in diabetes in women with statin therapy[100,101].

Consistency of the data for reduction of chronic diseases when MHT is initiated near menopause

The almost complete consistency of data (not just focusing on one trial) provides powerful proof of concept. Note also that, whenever there is an outlier study, it is usually the CEE þ MPA arm of the WHI trial. In this regard, see Figure 2, especially the complete consistency with the reduction of all- cause mortality in both arms of the WHI HRT trial.

The absolute risks reported from the WHI, especially in women <60 years of age when randomized to MHT, are ‘rare’ according to the WHO categories of risk, <1/1000 events/year of MHT. The risk of breast cancer reported in the WHI is 0.8 additional breast cancer events per 1000 women- years of MHT[72], which, in clinical perspective, parallels the breast cancer risk reported with the use of statins by

women: 0.5–7.7 additional breast cancer events per 1000 women- years[102]. Moreover, both the WHI CEE-alone arm and DOPS show reductions in breast cancer events[33,87]. In women <60 years of age, considering both the WHI CEE + MPA and CEE-alone arms, the only statistically significant harm is deep vein thrombosis in the CEE + MPA arm.

Preventative strategies advocated by the USPSTF in place of MHT, for example statins for them primary prevention of CHD, actually carry higher risks of adverse outcomes. Statins are associated with higher relative risks of breast cancer than CEE + MPA, while CEE alone carried no risk of this highly feared outcome in the WHI. Also, statins are associated with an increased risk of diabetes, while MHT is protective.

Absolute numbers of benefits and harms

We conclude by returning to Figure 2 which illustrates the absolute benefits and harms drawn from the summary results of the WHI HRT trial. As discussed extensively above, these findings have been misreported, with harms that were non- significant in per protocol analyses described as significant. However, even with this important caveat, taking these data as a whole, benefits do clearly outweigh risks.

In closing, we reiterate that these observations have tremendous implications for public health and the burden of chronic disease, both human and economic.

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Dr Simon reports roles in advisory boards or as a consultant for: AbbVie, Inc. (North Chicago, IL), Allergan, Plc (Parsippany, NJ), AMAG Pharmaceuticals, Inc. (Waltham, MA), Ascend Therapeutics (Herndon, VA), Azure Biotech, Inc. (River Vale, NJ), Millendo Therapeutics, Inc. (Ann Arbor, MI), Radius Health, Inc. (Waltham, MA), Roivant Sciences, Inc. (New York, NY), Sanofi S.A. (Paris, France), Sebela Pharmaceuticals, Inc. (Roswell, GA), Sermonix Pharmaceuticals, Inc. (Columbus, OH), Shionogi Inc. (Florham Park, NJ), Symbiotec Pharmalab (Indore, India), TherapeuticsMD (Boca Raton, FL), Valeant Pharmaceuticals (Laval, Canada). Dr Simon has been within the past year, or is currently serving on the speakers' bureaus of: Novo Nordisk (Bagsvrerd, Denmark), Shionogi Inc. (Florham Park, NJ), and Valeant Pharmaceuticals (Laval, Canada). Dr Simon has received within the past year, or is currently receiving grant/research support from: AbbVie, Inc. (North Chicago, IL), Allergan, Plc (Parsippany, NJ), Agile Therapeutics (Princeton, NJ), Bayer Healthcare LLC (Tarrytown, NY), New England Research Institute, Inc. (Watertown, MA), ObsEva SA (Geneva,

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Dr Lobo has been a consultant and participated as a principal investi- gator in clinical trials for TherapeuticsMD (Boca Raton, FL). He has also consulted for AMAG Pharmaceutics (Waltham, MA) and Mithra (Liege, Belgium).

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