This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist’s practice. Recognized experts in the field provide their opinions and practical advice. Wen Shen, MD, MPH, the Editor of Menopause e-Consult, encourages your suggestions for future topics. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Shen.

**Question:**
How should we treat menopausal symptoms in a woman with a family history of heart disease?

**Commentary by:**
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Any woman with a family history of heart disease or premature atherosclerosis needs to be evaluated and treated in the context of this potential for increased risk. Family history of heart disease remains a significant risk factor for the development of atherosclerosis. It is one of the five Adult Treatment Panel III risk factors. A 2012 *JAMA* report reviewing traditional and novel cardiovascular risk factors for assessment in the MESA study concluded that family history, along with coronary artery calcium, ankle-brachial index, and high-sensitivity C-reactive protein, were associated with coronary heart disease (CHD). The hazard ratio for family history was 2.18 (95% confidence interval, 1.38-3.42).

Family history is also prominent in the risk evaluation algorithm presented in the 2011 American Heart Association (AHA) guidelines on the prevention of heart disease in women. Even when excluding traditional risk factors for CHD, first-degree relatives of patients with subclinical atherosclerosis have been shown to have a higher burden of subclinical atherosclerosis.

**KEEPS, HERS & cardiovascular disease**
Publication of the Women’s Health Initiative (WHI) data raised concerns about a link between cardiovascular disease and the use of hormone therapy (HT). Although these data have been much debated, recent presentation of the Kronos Early Estrogen Prevention Study (KEEPS) results suggests that low-dose estrogen used early for a short time is not associated with worsening of cardiovascular risk markers. If anything, trends toward subclinical atherosclerosis in this study favored the active treatment groups.

We should remember, however, earlier data from the Heart and Estrogen/progestin Replacement Study (HERS) in postmenopausal women with established coronary disease. Although there was no benefit from oral conjugated equine estrogen plus medroxyprogesterone acetate, there was a trend showing more CHD events in the HT group than in the placebo group in the initial year. Follow-up data published in 2002 suggest that much of this risk was ameliorated in women treated with statin therapy.

**HT recommendations from NAMS**
When treating menopausal symptoms, NAMS states the following in relation to CHD:
“Combined data incorporating both the ET [estrogen alone therapy] and EPT [estrogen plus progestin therapy] trials of the WHI show a statistical trend of an HT effect relative to placebo on CHD by time since menopause, indicating that the women who initiate HT more than 10 years beyond menopause are at increased risk for CHD, and those women who initiate HT within 10 years of menopause tend to have a lower risk of CHD. However, statistical modeling of the combined WHI data, including data from the WHI observational studies, did not find that CHD risks varied by the timing of HT initiation.”

Paroxetine for vasomotor symptoms
The current NAMS statement was published before the recent FDA approval of the first nonhormonal product to treat vasomotor symptoms—paroxetine, the selective serotonin reuptake inhibitor (SSRI). Concern about psychiatric medications and cardiovascular risk does exist. A recent review suggests that antidepressants, including SSRIs, may cause weight gain in some patients, but they have minimal adverse effects on lipids and lipoproteins. The effects of this class of medications on CHD risk are often difficult to separate from the risk of depression itself.

Evaluation of risk factors
Treatment using currently available therapy must minimize any CHD risk, and this begins with an appropriate evaluation. A complete physical exam should be obtained, including weight, height, body mass index, blood pressure evaluation, and gestational history. Lab evaluation should include a fasting lipid profile, blood sugar, and glycosylated hemoglobin. Stress testing is not useful for routine CHD risk assessment; however, in the patient with symptoms that suggest ischemia (which can present differently in women than in men), it can be used to rule out obstructive coronary disease. Patients who have been sedentary, are considering exercise as part of a risk reduction program, or have other cardiovascular risk factors can undergo stress testing before starting an exercise program.

Carotid ultrasound and coronary computed tomography can sometimes yield additional risk stratification. A low-risk carotid intima-media thickness is associated with a 1% 10-year ischemic heart disease risk versus 10% with a high-risk carotid intima-media thickness and a relatively greater risk predicted for women than men. In women, coronary calcium scores lag about a decade behind equivalent scores in men. These tests, however, have not been prospectively evaluated as risk-stratification tools before initiating HT for menopausal symptoms.

The above data can be used with various available risk calculators. The AHA 2011 statement recommends lifetime risk evaluation. Although Framingham risk scoring is the standard in the United States, use of the Reynolds risk score resulted in risk reclassification in 40% of women with intermediate Framingham risk scores.

Vasomotor symptom treatment
Once the above evaluation is complete, risks should be addressed before instituting therapies. Lifestyle modification should be encouraged in all patients. Referral to an internist, lipidologist, or cardiovascular prevention specialist can be considered. Elevated triglycerides need to be addressed with diet and pharmacologic therapy as needed before estrogen use. Patients requiring statin therapy should be started on these medications before estrogen use as well. Blood pressure needs to be controlled and monitored throughout therapy, along with lipid and glucose monitoring. Although data from HERS and WHI suggest a beneficial effect of estrogen on glycemic status, women with diabetes require appropriate risk reduction before starting therapy.

Ultimately, any woman with a family history of heart disease requiring HT for menopausal symptoms can be safely and effectively treated after a thorough and complete cardiovascular risk assessment, with intervention as needed. Consultation with appropriate primary care
providers and specialists often can be helpful in assuring that the patient is treated and symptoms are alleviated.

**Disclosure:** Dr. Underberg reports: Consultant/Advisory Board: Aegerion, LipoScience, Merck, Novartis, Roche, Sanofi; Speakers Bureau: Abbott, Amarin, AstraZeneca, Daiichi Sankyo, GlaskoSmithKline, Liposcience, Merck; Grants/Research Support: Kowa Research Institute.

**References**


**Case:**

A 55-year-old woman who reached menopause 3 years ago and does not take HT has read in a magazine that screening mammography can overdiagnose breast cancer. She has no family history of breast cancer and is otherwise healthy. She wants to know whether she should continue having screening mammography.

**Management issues by:**

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Any intervention in medicine has risks and benefits. This is true for an intervention used to treat an existing condition as well as an intervention aimed at preventing a condition. Because current US guidelines recommend biennial screening mammography for all women between the ages of 50 and 74 years, we need to be very sure that the harm of this practice does not outweigh the benefits.

**On screening mammography**

Intuitively, screening is very attractive: identifying a disease state before clinical presentation may allow earlier treatment and an improved prognosis. In the case of breast cancer, the only way screening can reduce mortality is to reduce the incidence of large tumors. Despite being successful at increasing the incidence of small tumors, the capacity of
screening mammography to reduce the incidence of large tumors has been modest.\(^1\)

Evidence from randomized trials—the gold standard for assessing the efficacy of an intervention—shows that screening results in a 20% reduction in breast cancer-specific mortality.\(^2\) However, what this relative improvement means in absolute terms has changed since these trials were completed more than 25 years ago. Adjuvant treatments for early (operable) breast cancer are now highly effective,\(^3\) and women are treated with them whether they were diagnosed by screening or not. So the “window of opportunity” for screening to affect breast cancer mortality in the current treatment environment is closing.

**Risk of overdiagnosis**

If the potential benefit of screening is small because of treatment, isn’t it still worth screening if we can afford to do so? Perhaps so, if there are no risks. But there are risks, one of which is overdiagnosis—the identification of a cancer which is growing so slowly that it would not become apparent in the woman’s lifetime if she had not been screened. At a histologic level, the overdiagnosed woman has invasive cancer, but we cannot yet tell which cancers are overdiagnosed on the basis of their histology. The problem is that women who are in the overdiagnosed category will be treated in the same way—with surgery and/or adjuvant radiotherapy, chemotherapy, or endocrine and immune therapies—as women whose cancers would go on to cause them harm if left untreated. Apart from the effect on the woman of believing she has a potentially fatal condition, these adjuvant treatments are not harmless. Radiotherapy increases the risk of dying from cardiovascular disease. There are also cardiac risks from chemotherapy. These risks may be considered reasonable for women who have a potentially fatal disease, but for women who are overdiagnosed, this treatment is harmful.

How big is the problem of overdiagnosis? Breast cancer is a genetically heterogeneous disease, and mammographic screening programs vary, so it is not surprising that estimates of the magnitude of overdiagnosis also vary considerably between screened populations. The gold-standard method of estimating overdiagnosis is randomized trials; however, in many trials, the control group was offered screening after trial completion. The 2012 UK inquiry into the benefits and harms of mammographic screening estimated 11% overdiagnosis in the women invited for screening in the long term,\(^2\) based on the trials in which the control group was not offered screening. Other estimates are based on comparisons between or within countries or from modeling, allowing for potential confounders such as trends in body mass index, parity, and use of HT. Bleyer and Welch estimate that 31% of all US breast cancers are overdiagnosed.\(^1\)

**Conclusion**

Women do not know about overdiagnosis, and they have a poor understanding of risk.\(^4\) We need to change that. We also need to change the way we think about cancer, including breast cancer—that it is not a condition that leads predictably to death.

The woman described in the scenario is likely to be at an average lifetime risk of breast cancer. Such women need to be provided with balanced information about benefits and harms described in absolute terms, as in the patient information leaflet developed by the Nordic Cochrane Centre,\(^5\) so that they can make a truly informed choice about screening mammography.

**Disclosure:** Dr. Bell reports none.

**References**


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