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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause and healthy aging. Each review has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Kathryn Macaulay, MD, NCMP, Chair-elect of the 2014 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Macaulay.

Update on Endocrine Society guidelines for androgen therapy in women

Although we have more data on implications of androgen levels, there is still a large knowledge gap

Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(10): 3489-3510. **Level of evidence: III.**

Summary. The Endocrine Society Task Force continues to recommend against making a diagnosis of androgen deficiency syndrome in healthy women because a well-defined syndrome and data are lacking. The Task Force recommends against the general use of testosterone for the indications of infertility, sexual dysfunction (other than hypoactive sexual desire disorder), cognitive health, cardiovascular health, bone health, or general well-being. Because of limited data on effectiveness and safety, they recommend against routine use of dehydroepiandrosterone. They find that evidence supports short-term efficacy and safety of high physiologic doses of testosterone treatment of postmenopausal women with sexual dysfunction because of hypoactive sexual desire disorder. Any woman receiving testosterone therapy should be monitored for signs of androgen excess.

Comment. For those of us who prescribe or recommend androgen therapy or who just address regular inquiries from midlife women about their waning libido, these guidelines by Wierman and colleagues provide us with a review of the state of the evidence—or perhaps one should say the absence of conclusive evidence to clarify the implications of varying androgen levels in women across their lifespans or indications for supplementation of the same.

It is enlightening to reread the 2006 predecessor to this document.[1] At that time, there were no generally available, reliable measures of testosterone for women, and although there were some studies looking at many correlates of various androgen levels and/or supplementation, the cohorts were often small and the results contradictory. The 2006 guideline concluded that there were no indications for androgen treatment of women.

Circa 2014, the assays for testosterone are improved. There are more data on the physiologic and pathologic implications of androgen levels in women, but these are still limited and often inconsistent. The current guideline supports the use of testosterone to treat "properly diagnosed" hypoactive sexual desire disorder in women who request therapy and even gives us some parameters to monitor this intervention. They sidestep the fact that there is no approved androgen product for

women but do tell us not to use those formulated for men.

Although I commend this guideline to my colleagues, the knowledge gap remains large. I guess I can continue to prescribe testosterone with some ambivalence—still wondering whether the women who report therapeutic success are experiencing a placebo effect, not knowing how long testosterone is safe, and hoping for more good science about the issues midlife women face.

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1. Wierman ME, Basson R, Davis SR, et al. Androgen therapy in women: an Endocrine Society Clinical Practice guideline. *J Clin Endocrinol Metab*. 2006;91(10): 3697-3710.

Comparison of three methods for fracture risk prediction

None are supported by data for use in younger postmenopausal women

Crandall CJ, Larson JC, Watts NB, et al. Comparison of fracture risk prediction by the US Preventive Services Task Force strategy and two alternative strategies in women 50-64 years old in the Women's Health Initiative. *J Clin Endocrinol Metab*. October 16, 2014 [Epub ahead of print]. **Level of evidence: II-3.**

Summary. Crandall and colleagues examined the sensitivity, specificity, and area under the receiver operating characteristic curve of the Fracture Risk Assessment Tool (FRAX; recommended by the US Preventive Services Task Force [USPSTF]), the Osteoporosis Self-Assessment Tool (OST), and the Simple Calculated Osteoporosis Risk Estimate (SCORE) for discrimination of incident major osteoporotic fracture (MOF) over 10 years of follow-up in postmenopausal women aged 50 to 64 years. Sensitivity of the strategies ranged from 25.8% to 39.8%, specificity ranged from 60.7% to 65.8%, and area under the curve values ranged from 0.52 to 0.56. Researchers determined that their findings did not support use of the USPSTF strategy, OST, or SCORE to identify younger postmenopausal women at higher risk of fracture.

Comment. Osteoporosis and low bone mass affect approximately 17 to 23 million postmenopausal women,[1] with half of all postmenopausal women experiencing an osteoporosis-related fracture during their lifetime.[2] The conundrum lies in the fact that although there is consensus regarding screening in patients aged 65 years and older, this is not the case for women aged 50 to 64 years—yet most fractures occur in these women, raising the obvious question of how we identify them. The USPSTF recommends screening women aged younger than 65 years whose 10-year predicted risk of a major osteoporotic fracture is at least 9.3% using FRAX without bone mineral density (BMD) testing. The logic behind this screening recommendation is to identify women with a risk of fracturing equal to the likelihood in a 65-year-old white female with no other risk factors.[3,4] The American College of Obstetricians and Gynecologists recommends that bone density should be screened with dual-energy x-ray absorptiometry (DXA) in postmenopausal women aged younger than 65 years if they have a history of fragility fracture, body weight less than 127 pounds, a medical cause of bone loss (eg, medication[s] or disease[s]), a parental history of a hip fracture or are current smokers or alcoholics or have rheumatoid arthritis.[5]

It should be noted that FRAX was created as a tool to predict fracture, not osteoporosis[4] or the need to perform DXA testing. This fact is important to keep in mind as we consider the long-term implications of these results. The use of FRAX without BMD as a predictor of osteoporosis has not yet been validated, although it has been widely used for this purpose. Therefore, to compare FRAX to OST and SCORE is helpful to advance our

knowledge about FRAX as a predictor of osteoporosis.

Unfortunately, the USPSTF recommendations performed poorly in identifying young postmenopausal women with osteoporosis, with a sensitivity of 34%.[6] A recent study evaluating the predictive ability of the USPSTF screening strategy found that it only identified 24% of the women screened who had osteoporosis, and analysis of the area under the curve was only modestly better than by chance alone.[7] Similar results identified body mass index (BMI) as a reasonable predictor of osteoporosis. The results of the recent study[7]suggested that a BMI less than 28 kg/m^2 was a better predictor of osteoporosis than the USPSTF recommendation, OST, the Osteoporosis Risk Assessment Instrument, or SCORE. A BMI less than 28 kg/m^2 identified postmenopausal women aged younger than 65 years who have osteoporosis with the highest sensitivity (95%) and the lowest negative likelihood ratio in this age group. These findings should not be interpreted to mean that we should use BMI alone. Current recommendations and tools available are not ideal, and a great deal of work remains.[8] This leaves medical professionals with a dilemma: how do we identify patients at risk for fracture in the female population aged 50 to 64 years?

It may be prudent as we seek better screening modalities to focus on prediction of which younger-aged women will eventually fracture, not those with T-score–defined osteoporosis. The USPSTF recommendation is as yet unproven, and the current study did not support FRAX without BMD, OST, or SCORE as useful tools in identifying women in this population who are at higher risk for fracture. Of note, the sensitivity of the USPSTF strategy in predicting fracture over 10 years was 4.7% in women aged 50 to 54 years and 37.3% in those women aged 60 to 64 years. In other words, those fracture prediction models based on clinical risk factors of fracture, such as age, tend to miss the younger (for example 50 to 54 year old women) who will eventually fracture in 10 years. While facing this challenge, at present, more research is needed to develop the best prediction tool for osteoporosis in the young postmenopausal group, balancing the desire to find at-risk women while avoiding overtesting, over-spending, and overtreating. As we continue to refine our ability to screen most appropriately, we hope to limit osteoporotic fractures in our postmenopausal patients.

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6. Crandall CJ, Larson JC, Gourlay ML, et al. Osteoporosis screening in postmenopausal women 50 to 64 years old: comparison of US Preventive Services Task Force strategy and two traditional strategies in the

Women's Health Initiative. *J Bone Miner Res*. 2014; 29(7):1661-1666.
7. Jiang X, Good L, Schnatz PF. USPSTF osteoporosis screening strategy: Confirming its predictive ability may prove challenging. *Menopause*. 2014;21:1330.
8. Jiang X, Good L, Schnatz PF. Osteoporosis screening in women aged 50-64 years: BMI alone compared to current screening modalities? *Menopause*. 2014;21:1327.

Cancer incidence after dietary intervention in WHI Dietary Modification Trial

Women didn't stick to low-fat diet after intervention, little effect on cancer long term

Thomson CA, Horn LV, Caan BJ, et al. Cancer incidence and mortality during the intervention and postintervention periods of the Women's Health Initiative Dietary Modification Trial. *Cancer Epidemiol Biomarkers Prev*. September 25, 2014. [Epub ahead of print] **Level of evidence: I.**

Summary. This randomized, controlled, low-fat intervention for prevention of breast and colorectal cancers was conducted in 48,835 postmenopausal US women aged 50 to 79 years. Total invasive cancer, breast cancer, colorectal cancer, and cancer-specific and overall mortality were among the outcomes. There was a reduced risk for estrogen-receptor positive/progesterone-receptor negative breast tumors during follow-up. In women with higher baseline fat intake and greater reduction in fat intake, point estimates of breast cancer risk were hazard ration (HR), 0.76 (95% confidence interval [CI], 0.62-0.92) during the intervention versus HR, 1.11 (95% CI, 0.84-1.4) during postintervention follow-up. During the postintervention period or the combined intervention and follow-up periods, there were no intervention effects on invasive breast or colorectal cancer, other cancers, or cancer-specific or overall mortality. In intervention women, dietary fat intake increased postintervention.

Comments. Many researchers have linked dietary habits, particularly fat intake, to risk of cancer. Here, Thomson and colleagues present the first long-term randomized, controlled trial on the subject to date; the current study is a continuation of the Women's Health Initiative Dietary Modification trial. The authors hypothesized that reducing fat intake to less than 20% of total energy intake would positively affect the incidence of invasive breast cancer and colorectal cancer in these women. Although the initial reports suggest modest reductions in risk of certain cancers associated with this dietary change, the long-term follow-up data indicate that the risk reduction previously appreciated had not been sustained. Importantly, adjustments for change in body weight and body mass index did not affect hazard ratios, implicating dietary intake rather than body fat makeup as the true mediating process investigated in this study.

Although the authors report that the statistics do not support their overall hypothesis, one must remember that the intervention itself did result in an appreciable decrease in certain cancer rates, particularly in the estrogen-receptor positive/progesterone-receptor negative breast cancer tumor subtype. However, as has been observed in many studies of lifestyle modifications, temporary changes do not necessarily provide significant long-term benefits; similarly, in this study, HRs describing cancer risk returned to (or nearly to) preintervention figures after return to normal dietary habits. Interestingly, the risk of colorectal cancer increased in participants during the intervention phase and decreased during the postintervention phase. As a clinician, I see these results as supporting counseling of patients regarding lifelong lifestyle modifications as opposed to temporary changes. Additionally, the ability to quantify the risk reduction that one might enjoy on committing to such lifestyle changes is quite important, because these data could be presented to patients, guiding conversations and possibly serving as motivation for women who wish to actively affect their risk of developing cancer. The present study included only women whose baseline fat intake was greater than 32% of overall energy intake, most of whom were overweight or obese, and the most drastic reductions in risk were observed in women who

reported the highest baseline fat intake. Future studies to further characterize the effects of a low-fat diet on women with differing baseline fat intake could help clinicians to target their counseling efforts. Furthermore, the investigators have focused only on overall fat intake, rather than the type of fat being consumed. Because previous studies have implicated animal fat in cancer development, it would be of interest to determine whether the types of fat consumed in this population are associated with cancer incidence in these patients. This may also be of significant consequence to clinicians counseling women on dietary habits and cancer risk. Patients may be more likely to achieve consumption of different, healthier types of fat rather than to decrease their intake drastically, in particular because it appears that women were not able to restrict their fat intake to the extent the investigators desired.

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Is there such a thing as too much milk?

In a Swedish observational study, high milk consumption was associated with excess risks for fractures and death

Michaelsson K, Wolk A, Langenskiold S, et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ.* 2014;349:g6015.

Summary. Dairy products are promoted to lower fracture risk. However, milk contains D-galactose, which induces oxidative stress and chronic inflammation in animal models and, thus, might have deleterious long-term health effects. In this observational study of 61,000 women and 45,000 men who completed food-frequency questionnaires, Swedish investigators assessed whether high milk consumption is associated with excess risk for fractures and death.

During a mean follow-up of 20 years, women who drank ≥3 glasses of milk daily (compared with those who drank <1 glass) had higher risks for all-cause death (adjusted hazard ratio, 1.9), cardiovascular-related death (HR, 1.9), cancer-related death (HR, 1.4), any fracture (HR, 1.2), and hip fracture (HR, 1.6); significant dose-response relations were observed. During a mean follow-up of 11 years, men who drank ≥3 glasses of milk daily had higher risks for all-cause death (HR, 1.1) and cardiovascular-related death (HR, 1.2). Milk consumption was associated positively with elevated urinary and serum levels of biomarkers for oxidative stress and inflammation in both sexes. However, consumption of cheese and fermented milk products (eg, yogurt) was not associated with these effects.

Comment. These authors theorize that D-galactose accounts for the excess risks for death and fracture associated with high milk consumption. This theory is supported by the observation that consuming cheese and fermented milk products—which do not contain D-galactose—was not associated with such negative health effects. Thus, although the authors cannot rule out the possibility of residual confounding and reverse causation, perhaps milk is not a magic bullet.

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Menopause Editor's picks from November 2014

NAMS spotlights selections from the most recent issue of the Society's official journal, *Menopause*, chosen by its editor in chief, Isaac Schiff, MD.

Incidence of hypercalciuria and hypercalcemia during vitamin D and calcium supplementation in older women.
John Christopher Gallagher, MD, Lynette M. Smith, MSc, and Vinod Yalamanchili, MD.

♦

Use of pragmatic community-based interventions to enhance recruitment and adherence in a randomized trial of Tai Chi for women with osteopenia: insights from a qualitative substudy.
Mary Fischer, PhD, WHNP-BC, NCMP, Nancy Fugate-Woods, PhD, RN, FAAN, and Peter M. Wayne, PhD.

♦

Knowledge and personal use of menopausal hormone therapy among Chinese obstetrician-gynecologists: results of a survey.
Yanjie Wang, MD, Xin Yang, MD, Xiaodong Li, MD, Xiaojing He, MD, and Yang Zhao, MD.

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The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I	Properly randomized, controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

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What's your biggest concern with androgen therapy? Post on our Member Forum to discuss November's *First to Know* papers: www.menopause.org/member-login?ReturnUrl=%2fforum