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THE NORTH AMERICAN MENOPAUSE SOCIETY

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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. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by George A. Helmrich, MD, Chair-Elect, 2009-2010 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Helmrich. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

New guidelines for breast cancer screening

US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;151:716-726. **Level of evidence: III.**

DESCRIPTION: Update of the 2002 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for breast cancer in the general population. METHODS: The USPSTF examined the evidence on the efficacy of 5 screening modalities in reducing mortality from breast cancer: film mammography, clinical breast examination, breast self-examination, digital mammography, and magnetic resonance imaging in order to update the 2002 recommendation. To accomplish this update, the USPSTF commissioned 2 studies: 1) a targeted systematic evidence review of 6 selected questions relating to benefits and harms of screening, and 2) a decision analysis that used population modeling techniques to compare the expected health outcomes and resource requirements of starting and ending mammography screening at different ages and using annual versus biennial screening intervals. RECOMMENDATIONS: The USPSTF recommends against routine screening mammography in women aged 40 to 49 years. The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms. (Grade C recommendation) The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years. (Grade B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older. (I statement) The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination beyond screening mammography in women 40 years or older. (I statement) The USPSTF recommends against clinicians teaching women how to perform breast self-examination. (Grade D recommendation) The USPSTF concludes that the current evidence is insufficient to assess additional benefits and harms of either digital mammography or magnetic resonance imaging instead of film mammography as screening modalities for breast cancer. (I statement).

Comment: Although the recently issued guidelines from the USPSTF caused surprise

for some women and clinicians, many experts have been questioning for years the value of routine mammography for women in their 40s. Because they were released during a time of stormy debate regarding healthcare reform, the confusion and outrage that has surrounded the release of the task force guidelines were magnified. Increasing controversy even further is the fact that a number of organizations, including the American Cancer Society, the American College of Obstetricians and Gynecologists, the American College of Radiology, the American Society of Breast Surgeons, the Society for Breast Imaging, and Susan G. Komen for the Cure, continue to recommend screening for women in their 40s.

Over the short term, insurance plans are likely to continue covering screening for women in their 40s as well as annual screens for women 50 and over. Accordingly, women in their 40s in my practice currently can choose whether or not to be screened, and women age 50 to 74 can choose annual or biennial screening. Over the last month, I have noted that most of my patients in their 50s and 60s continue to prefer annual screening. Over the long term, I anticipate that insurance plans will restrict coverage, moving in the direction suggested by the USPSTF guidelines.

Here are four closing points for women and clinicians:

1. Notwithstanding the controversy, we and our patients should continue to recognize that all responsible experts and organizations agree that screening mammography reduces breast cancer mortality.
2. Biennial screening has long been the norm in a number of countries with breast cancer outcomes similar to those in the United States.
3. Guidelines for routine screening mammography do not apply to higher-risk individuals, including those with first-degree relatives with breast cancer or *BRCA* mutations. Such women should receive annual mammogram screens and, in some circumstances, breast magnetic resonance imaging.
4. Finally, a tissue diagnosis should be obtained for all women with palpable breast lumps, regardless of imaging findings.

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References:
1. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA* 2009;302:1685-1692.
2. Partridge AH, Winer EP. On mammography--more agreement than disagreement. *N Engl J Med* 2009;361: 2499-2501.

Physical activity and bone mass

Hamilton CJ, Thomas SG, Jamal SA. Associations between leisure physical activity participation and cortical bone mass and geometry at the radius and tibia in a Canadian cohort of postmenopausal women. *Bone* 2009 Nov 5. [Epub ahead of print]. **Level of evidence: II-2.**

The purpose of this study of a Canadian cohort of healthy postmenopausal women (n = 234; mean age, 62) was to determine associations between leisure physical activity participation and bone mass, and geometry at the radius and tibia using peripheral quantitative computed tomography (pQCT). Leisure physical activity participation was assessed using the Minnesota Leisure Time Physical Activity Questionnaire to generate a total activity score (mean, 105; range, 0-840). Researchers used pQCT to measure bone mass and geometry at the distal and midshaft sites of the nondominant radius and tibia.

Total activity score was positively and significantly associated with total content, total area, cortical content, and cortical area at the midshaft sites of the radius and tibia, as well as bone bending and torsional strength parameters at the midshaft radius and tibia ($P < 0.05$ for all associations). No associations were observed between total activity score and trabecular bone parameters. Leisure physical activity participation was positively associated with

bending and torsional strength at weight-bearing and non-weight-bearing bone sites, as well as cortical bone mass and geometry. In postmenopausal women, leisure physical activity may have the potential to modify bone strength and influence bone fragility.

Comment. This interesting study reports bone peripheral pQCT data at the radius and tibia of active Canadian women. As it is observational, the reported associations between bone structural parameters and calculated strength indices are not necessarily reflective of the effects of exercise. These data will, however, be useful in designing appropriate randomized controlled clinical trials on the effects of activity on cortical and trabecular bone. In addition, the small changes noted and the large coefficient of variation make such measurements of no utility in individual patients.

The authors have found small but statistically significant associations between physical activity and bone strength, with the effects being on cortical bone. In interpreting the results of this trial to our patients, we should certainly encourage exercise and can suspect that this will improve cortical bone strength. The amount of exercise optimal for this effect and the effects of this improvement on fracture prevention remain the topics of future clinical trials.

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New NAMS position statement on osteoporosis management

The North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:25-54. **Level of evidence: III.**

OBJECTIVE: To update the evidence-based position statement published by The North American Menopause Society (NAMS) in 2006 regarding the management of osteoporosis in postmenopausal women. METHODS: NAMS followed the general principles established for evidence-based guidelines to create this updated document. A panel of clinicians and researchers expert in the field of metabolic bone diseases and/or women's health was enlisted to review the 2006 NAMS position statement, compile supporting statements, and reach consensus on recommendations. The panel's recommendations were reviewed and approved by the NAMS Board of Trustees. RESULTS: Osteoporosis, which is especially prevalent among older postmenopausal women, increases the risk of fractures. Hip and spine fractures are associated with particularly high morbidity and mortality in this population. Given the health implications of osteoporotic fractures, the primary goal of osteoporosis therapy is to prevent fractures, which is accomplished by slowing or stopping bone loss, maintaining bone strength, and minimizing or eliminating factors that may contribute to fractures. The evaluation of postmenopausal women for osteoporosis risk requires a medical history, physical examination, and diagnostic tests. Major risk factors for postmenopausal osteoporosis (as defined by bone mineral density) include advanced age, genetics, lifestyle factors (such as low calcium and vitamin D intake, smoking), thinness, and menopause status. The most common risk factors for osteoporotic fracture are advanced age, low bone mineral density, and previous fracture as an adult. Management focuses first on nonpharmacologic measures, such as a balanced diet, adequate calcium and vitamin D intake, adequate exercise, smoking cessation, avoidance of excessive alcohol intake, and fall prevention. If pharmacologic therapy is indicated, government-approved options are bisphosphonates, selective estrogen-receptor modulators, parathyroid hormone, estrogens, and calcitonin. CONCLUSIONS: Management strategies for postmenopausal women involve identifying those at risk for fracture, followed by instituting measures that focus on reducing modifiable risk factors through dietary and

lifestyle changes and, if indicated, pharmacologic therapy.

Comment. Postmenopausal osteoporosis is a common disorder in a growing population. Low bone mass and/or osteoporosis of the hip are estimated to be present in up to 68% of Caucasian-American women age 50 or above, and up to 18% of those women have osteoporosis. Besides being common, the consequences are dramatic. Approximately 50% of postmenopausal women who sustain a hip fracture will have long-term impaired mobility and up to 25% will require long-term care. Furthermore, and even more concerning, is a 25% increased risk of mortality within 1 year of a hip fracture. Although osteoporosis is a common condition, many women are not aware of its dangers. The fact that this condition is usually asymptomatic, combined with the fact that the first indicator of the disease is often a fracture, increase the challenges of proper risk assessment and prevention.

Since the publication of the NAMS 2006 position statement on osteoporosis, there have been significant contributions to the literature. These contributions include new data about existing and emerging therapies, the introduction of the WHO online fracture risk assessment tool (FRAX), and new recommendations by other organizations, including the National Osteoporosis Foundation, the Society of Obstetricians and Gynaecologists of Canada, and the World Health Organization. An editorial board of five physicians with clinical and research expertise in women's health and metabolic bone disease assisted with the update.

The NAMS 2010 position statement is an excellent, evidenced-based review of the pertinent information about postmenopausal osteoporosis. This is a valuable resource that will help guide practitioners in women's health, internal medicine, family medicine, and geriatrics, or any caregiver who is providing counsel and treatment to postmenopausal women.

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Hormones, adiposity, insulin resistance, and diabetes

Kalyani RR, Franco M, Dobs AS, et al. The association of endogenous sex hormones, adiposity, and insulin resistance with incident diabetes in postmenopausal women. *J Clin Endocrinol Metab* 2009;94:4127-4135. **Level of evidence: II-1.**

Endogenous bioavailable testosterone and estradiol (E_2) have been positively associated with incident type 2 diabetes (T2DM) in postmenopausal women, while sex hormone-binding globulin (SHBG) has been negatively associated. The objective of this study was to examine the association of endogenous sex hormones with T2DM in postmenopausal women and possible explanatory factors.

The Multi-Ethnic Study of Atherosclerosis (MESA) was a prospective study of 1,612 postmenopausal women ages 45 to 84, followed from 2000 to 2006, who were not taking hormone therapy, did not have prevalent cardiovascular disease or T2DM, and had complete ascertainment of sex hormones. T2DM was defined based on fasting glucose or treatment for diabetes. During follow-up, there were 116 incident cases of T2DM. Across higher quartiles of bioavailable testosterone and E_2 and lower quartiles of SHBG, researchers found significantly greater hazards of developing T2DM (all P for trend ≤ 0.001). Bioavailable testosterone was no longer associated with T2DM after adjustment for body mass index (BMI) and insulin resistance. The associations of E_2 and SHBG with T2DM persisted in fully adjusted models (both P for trend < 0.02), but were partially explained by BMI and insulin resistance. Dehydroepian-

drosterone had no relationship with T2DM.

Researchers concluded that adiposity and insulin resistance explained most of the association of bioavailable testosterone but only partially explained the associations of E_2 and SHBG with T2DM.

Comment. This cross-sectional study of various endogenous sex hormone levels and the incidence of T2DM and impaired glucose tolerance (IGT) in a postmenopausal population ages 45 to 84 was complicated by the fact that in postmenopausal women obesity has a marked effect on the level of sex steroids, raising estrogen levels. Some obese women have elevated testosterone as part of a syndrome disorder such as polycystic ovary syndrome, which affects a significant part of the population (5%-10%). This may be an underlying cause of the obesity.

In postmenopausal women, estrogens are largely the product of conversion of adrenal androgens in the liver and periphery, particularly in fat. In this study, the level of testosterone was correlated with increasing weight. It was no longer related to IGT once weight (as BMI) was accounted for. However, the same was not true for estrogens, and in this study higher E_2 levels were associated with an increased relative hazard of developing T2DM of 1.92. The estrogen levels in this group were twice those of the reference group (0.084-1.42 nmol/L) as compared to the control group (0.0-0.43 nmol/L).

This finding is very difficult to understand as it has already been fairly well documented that estrogen deficiency is associated with metabolic syndrome and IGT.[1-2] Men who have an aromatase deficiency had either T2DM or at least IGT.[2] Replacement of estradiol in this condition leads to an improvement in carbohydrate tolerance and fasting glucose and insulin.[3] The levels of estrogen involved are extremely low in normal postmenopausal women. The loss of estrogens around menopause has also been associated with IGT.[1] This further complicates understanding the present findings that the higher the endogenous estrogens are, the higher the like-lihood of the woman developing IGT or T2DM.

Several large studies (Women's Health Initiative, Heart and Estrogen/Progestin Replacement Study), have reported a reduced incidence of new onset of T2DM of about 35% in the women given Premarin and medroxyprogesterone.[4,5]

Several of the authors of this paper have previously described the glucose tolerance status in this same cohort of subjects.[6] They reported increasing impaired fasting glucose with higher dehydroepiandrosterone levels and greater incidence of T2DM with higher estradiol levels and lower SHBG. This was an earlier time point in the same population-based study. It is possible that the higher estradiol and the increased incidence of T2DM are related to some other factor affecting both parameters. No causal relationship has yet been established.

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References:
1. Carr MC. The emergence of metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;88:2404-2411.
2. Lin L, Ercan O, Raza J, et al. Variable pheno-types associated with aromatase (CYP19) insufficiency in humans. *J Clin Endocrinol Metab* 2007;92:982-990.
3. Bilezikian JP, Morishima A, Bell J, Grumbach MM. Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. *N Engl J Med* 1998;339: 599-603.
4. Crespo CJ, Smit E, Snelling A, Sempos CT, Anderson RE, NHANES III. Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 2002; 25:1675-1680.
5. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy:

the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2003;138:1-9.
6. Golden SH, Dobs AS, Vaidya E, et al. Endogenous sex hormones and glucose tolerance status in post-menopausal women. *J Clin Endocrinol Metab* 2007; 92:1289-1295.

Endometrial cancer in post-menopausal women using EPT

Jaakkola S, Lyytinen H, Pukkala E, Ylikorkala O. Endometrial cancer in postmenopausal women using estradiol-progestin therapy. *Obstet Gynecol* 2009;114:1197-1204. **Level of evidence: II.**

OBJECTIVE: To estimate the risk of endometrial cancer in all Finnish postmenopausal women using various forms of estradiol-progestin therapy. METHODS: All Finnish women (aged more than 50 years) who had used estradiol-progestin therapy in 1994-2006 for at least 6 months (n=224,015) were identified from the national medical Reimbursement Registry and linked to the Finnish Cancer Registry. A total of 1,364 type I and 38 type II endometrial cancers were recorded by the end of 2006. The incidence of endometrial cancer in estradiol-progestin therapy users was compared with that in the general population in this cohort study. RESULTS: The use of a continuous estradiol-progestin therapy regimen for 3 years or more was associated with a 76% reduction of the risk for type 1 cancer (95% confidence interval [CI] 6-60%). In contrast, the use of a sequential estradiol-progestin therapy regimen for at least 5 years was accompanied with a 69% elevation (95% CI 43-96%) if the progestin was added monthly, and with a significantly higher, 276% risk elevation (95% CI 190-379%) if progestin was added at 3-month intervals. Sequential regimens containing norethisterone acetate, medroxyprogesterone acetate or dydrogesterone administered orally showed no significant differences in the endometrial safety. Oral and transdermal norethisterone acetate were associated with similar risk elevations. Women using a monthly sequential estradiol-progestin regimen tended to be diagnosed with endometrial cancer in an earlier stage than the background population. CONCLUSION: Use of a continuous rather than a sequential estradiol-progestin regimen decreases the risk of endometrial cancer, whereas the route of administration or type of progestin does not differ in terms of endometrial cancer risk.

Comment. Risk factors for type I (estrogen-associated) endometrial cancer include nulliparity, obesity, endogenous hyper-estrogenism, hereditary nonpolyposis colon cancer syndrome, prior history of breast cancer, use of tamoxifen, and unopposed or in-adequately opposed exogenous estrogen use. They are preceded by endometrial hyperplasia. Progestins have been shown to be protective of this type of cancer, although differences exist in their progestational activity and ability to bind to progesterone receptors. Type II endometrial cancers, including serous papillary, clear cell, or squamous carcinomas, appear to be age related and originate from polyps or nonhyperplastic endometrial lesions.

This study confirms that continuous combined estradiol-progestin therapy (EPT) is associated with a marked protective effect with a 76% decrease endometrial cancer risk. However, these findings raise concern about the significant increased risk of type I endometrial cancer with sequential regimens of 69% risk after 5 years of use, with greater risk (276%) found with long-cycle progestin therapy (every 3 months) and longer durations (156% at 10 years). No differences in risk of endometrial cancer were found between oral or transdermal or types of progestin. Absolute risk of endometrial cancer with regimens given sequentially for 10 years would be an extra 8 cases per 1,000, with 3 to 4 fewer cases per 1,000 if given continuously.

Progestins vary in ability to bind to progesterone receptors and control endometrial bleeding; when given continuously with estrogen, all progestins protected against endometrial cancer. The use of sequential EPT in this cohort study was associated with a significant increased risk of endometrial

cancer. Practitioners need to balance potential increased risks of breast cancer or cardiovascular disease with combined EPT use with the increased risk of endometrial cancer if sequential EPT is used.

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Editor's picks from January-February *Menopause*

NAMS spotlights the most recent issue of the Society's official journal, *Menopause*, selected by its Editor-in-Chief, Dr. Isaac Schiff.

Huang WF, Tsai YW, Wen YW, Hsiao FY, Kuo KN, Tsai CR. Osteoporosis treatment and atrial fibrillation: alendronate versus raloxifene. *Menopause* 2010;17:57-63.

No differences were found between alendronate and raloxifene on the risk of atrial fibrillation and flutter in women with osteoporosis.

♦

Vallance JK, Murray TC, Johnson ST, Elavsky S. Quality of life and psychosocial health in postmenopausal women achieving public health guidelines for physical activity. *Menopause* 2010;17:64-71.

The present study found that 43% of postmenopausal women were achieving public health physical activity guidelines.

♦

Lindh-Astrand L, Bixo M, Linden Hirschberg A, Sundstrom-Poromaa I, Hammar M. A randomized controlled study of taper-down or abrupt discontinuation of hormone therapy in women treated for vasomotor symptoms. *Menopause* 2010;17:72-80.

This study failed to show any difference in number or severity of hot flashes, quality of life, or resumption of hormone therapy (HT) regardless of type of discontinuation.

♦

Bolge SC, Balkrishnan R, Kannan H, Seal B, Drake CL. Burden associated with chronic sleep maintenance insomnia characterized by nighttime awakenings among women with menopausal symptoms. *Menopause* 2010;17:80-87.

Chronic insomnia characterized by nighttime awakenings is associated with greater health-care utilization, greater lost work productivity, and poorer health-related quality of life among women with menopausal symptoms.

♦

Burleson MH, Todd M, Trevathan WR. Daily vasomotor symptoms, sleep problems, and mood: using daily data to evaluate the domino hypothesis in middle-aged women. *Menopause* 2010;17:87-96.

In a sample of 55 middle-aged women who made daily self-reports for 36 weeks, occurrence of vasomotor symptoms or sleep problems on a given day predicted higher negative mood and lower positive mood ratings on the following day.

♦

Ghezzi F, Cromi A, Siesto G, et al. Use of laparoscopy in older women undergoing gynecologic procedures: is it time to overcome initial concerns? *Menopause* 2010; 17:96-103.

Outcomes analysis of a single-institution cohort of older women who were candidates to undergo a major gynecologic abdominal procedure demonstrates short-term advantages of laparoscopy compared with traditional open surgery in terms of reduction in hospital stay and fewer postoperative complications.

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.

2010 Call for Abstracts

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 21st Annual Meeting (October 6-9, 2010) in Chicago, IL.

- Submit your abstracts through the NAMS Web site: www.menopause.org
- Information submitted for consideration must not be identical to that presented at any meeting prior to the NAMS meeting, and the study must have been published as of April 30, 2010
- The abstract submission deadline is April 30, 2010
- Top abstracts will be accepted for oral presentation and up to four poster prizes will be awarded (top prize: $1,000)
- All accepted abstracts will be published in the NAMS journal, *Menopause,* after the meeting

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