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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 Peter F. Schnatz, DO, Chair-Elect, 2008-2009 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Association of age at menopause and stroke risk

Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke. The Framingham Heart Study. *Stroke* 2009 Feb 20 [Epub ahead of print] **Level of evidence: II-2.**

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BACKGROUND AND PURPOSE: Women have increased lifetime stroke risk and more disabling strokes compared with men. Insights into the association between menopause and stroke could lead to new prevention strategies for women. The objective of this study was to examine the association of age at natural menopause with ischemic stroke risk in the Framingham Heart Study. **METHODS:** Participants included women who survived stroke-free until age 60, experienced natural menopause, did not use estrogen before menopause, and who had complete data (n=1430). Participants were followed until first ischemic stroke, death, or end of follow-up (2006). Age at natural menopause was self-reported. Cox proportional hazards models were used to examine the association between age at natural menopause (<42, 42 to 54, ≥55) and ischemic stroke risk adjusted for age, systolic blood pressure, atrial fibrillation, diabetes, current smoking, cardiovascular disease and estrogen use. **RESULTS:** There were 234

ischemic strokes identified. Average age at menopause was 49 years (SD=4). Women with menopause at ages 42 to 54 (hazard ratio=0.50; 95% CI: 0.29 to 0.89) and at ages ≥55 (hazard ratio=0.31; 95% CI: 0.13 to 0.76) had lower stroke risk compared with those with menopause <42 years adjusted for covariates. Women with menopause before age 42 had twice the stroke risk compared to all other women (hazard ratio=2.03; 95% CI: 1.16 to 3.56). **CONCLUSIONS:** In this prospective study, age at natural menopause before age 42 was associated with increased ischemic stroke risk. Future stroke studies with measures of endogenous hormones are needed to inform the underlying mechanisms so that novel prevention strategies for midlife women can be considered.

Comment. This analysis of stroke outcomes in women enrolled in the Framingham Heart Study (FHS) establishes that women who experienced natural menopause at a very early age (<42 y) were substantially more likely to have an ischemic stroke than women who were older at the time of menopause. The explanation for this increase in risk is not readily provided by changes in estrogen levels. The substudy measuring bone mineral density (BMD) in 654 of the 1,430 women supports a more complex mechanism. Women in both the lowest and highest quintile of BMD were at

greatest risk for ischemic stroke. As BMD is a surrogate marker of cumulative estrogen exposure, the increased risk for women with the highest BMD challenges the theory that the lowering of estrogen around the time of menopause is a major cause of atherosclerotic events. In addition, the Women's Health Initiative (WHI) findings that ischemic stroke risk was increased in older women who received hormone therapy has demonstrated that simple replacement of estrogen with or without progestin does not prevent major cardiovascular events in older women.^{1,2}

Among the FHS women in this report, the average age of ischemic stroke was 80 years. This finding does not suggest a significant relationship with age at menopause and early onset of stroke. The choice to analyze by categories of age at menopause rather than considering age as a continuous variable leaves unanswered the question of whether a threshold of menopause age increases stroke risk. The contribution of some stroke risk factors was considered in the risk models, but may still have confounded the results. In addition, other inflammatory and hemostatic risk markers were not available for this analysis. Finally, these results may not be generalizable to other populations as the FHS is comprised of middle-class, Caucasian volunteers from a single location.

Although early natural menopause is uncommon, occurring in only 56 of 1,430 (3.9%) participants in this study, risk for ischemic stroke at older age is increased twofold over women who were older at the time of menopause. Further study of these high-risk women will provide important clues to the etiology for both premature menopause and subsequent atherosclerotic outcomes.

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2. Anderson GL, Limacher M, Assaf AR, et al, for the Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-1712.

BTMs to predict BMD response

Burnett-Bowie SA, Saag K, Sebban A, et al. Prediction of changes in bone mineral density in postmenopausal women treated with once-weekly bisphosphonates. *J Clin Endocrinol Metab* 2009 Jan 13 [Epub ahead of print] **Level of evidence: II-2.**

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BACKGROUND: In clinical practice, bone mineral density (BMD) determined by DXA is used to monitor response to osteoporosis therapy. However, 1 to 2 years are usually required to assess patients' BMD responses. The possibility of earlier indicators of a response or non-response to treatment, such as changes in bone turnover markers (BTMs), is of interest to physicians and patients. **METHODS:** In this post-hoc analysis of women treated with once-weekly bisphosphonates, we examined the association of tertile percent change from baseline in BTMs at 3 or 6 months, and association of several baseline clinical characteristics, with 24-month percent change from baseline in BMD, and with percentage of patients showing BMD non-response (defined as BMD loss at 2 or more of 4 sites) at 24 months. Multivariable analysis was performed to determine which factors were associated with BMD non-response. **RESULTS:** Patients in the tertile with the greatest decrease in each of the BTMs had the greatest mean increase in BMD and the lowest percentage of BMD nonresponders at 24 months. Several characteristics were independently associated with BMD non-response including smaller 3-month reductions

from baseline in CTX, bone ALP, and PINP, younger age of menopause, a family history of osteoporosis, and higher baseline trochanteric BMD. Baseline BTMs were not predictive of 24-month BMD response to therapy. The strongest associations were for changes in BTMs with treatment. **CONCLUSION:** In groups of patients, short term changes in markers of bone turnover appear to be predictors of longer term BMD response and non-response to bisphosphonate therapy.

Comment. It has been over 15 years that BTMs have been commercially available—yet few practitioners ever use these tests in management of osteoporosis. There was high hope that BTMs would be useful for individual patients in several ways including: 1) determining fracture risk and need for treatment; 2) determining what kind of drug to use; and 3) encouraging adherence and persistence with therapy.

This report adds to our general skepticism about application of BTMs to individual patients. Even using group data (with more power to find associations), the authors failed to find that baseline BTM values predicted response to bisphosphonate (BP) treatment among compliant users after 2 years. Furthermore, change between baseline and 3-6 month BTM values showed only weak associations with 2-year bone density changes.

Typically, studies of BMD in clinical trials of BP indicate a 90% response rate; in this paper, alendronate users had an 88% BMD response rate. Thus, the number of poor responders that could ideally be found by a perfect BTM test would be about 1 in 10. But, as the current article shows, BTM tests have poor specificity and sensitivity when applied to patients starting BPs. This is not new. Delmas et al,¹ using NTx, found that about one third of patients starting on BP did not decrease NTx the expected 30%—a lot of false positives.

BTMs have been useful in research, but for several reasons are not worth the trouble in practice. First, the cost: in the range of \$140 to

\$150 per test (double this when getting baseline and 3-6 month follow-up). Second, the inconvenience for patients: requiring morning 12-hour fasting blood sampling. Third, the low predictive value: in this paper, the correlation coefficient between BTM and BMD was only -0.25, meaning that only 6% of the variance in the BMD increase could be predicted from the BTM decrease. Finally, investigators who have examined feedback of BTM results on patients' drug persistence have found no difference between giving BTM results and simply contacting and supporting those patients newly starting.¹

It is no wonder that NAMS and other expert societies have not recommended to clinicians that they use BTMs to make early treatment decisions in individual patients.

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Reference:
Delmas PD, Vrijens B, Eastell R, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. *J Clin Endocrinol* 2007;92:1296-1304.

Estrogen plus testosterone and breast cancer risk

Ness RB, Albano JD, McTiernan A, Cauley JA. Influence of estrogen plus testosterone supplementation on breast cancer. *Arch Intern Med* 2009;169:41-46.

Level of evidence: II-2.

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BACKGROUND: Concern that the use of exogenous testosterone may increase breast cancer risk coexists with rising use of this medication in the United States. We sought to examine the relationship between the use of estrogen plus testosterone (E + T) therapy (esterified estradiol plus methyltestosterone) and the occurrence of breast cancer. **METHODS:** A total of 31,842 postmenopausal

participants in the Women's Health Initiative Observational Study were followed for a mean of 4.6 years. At the 3-year visit, E + T users were compared with non-hormone therapy users for time to incident invasive breast cancer. Cox proportional hazards estimates were adjusted for known predictors of breast cancer including prior hormone use and screening mammography. RESULTS: Thirty five women using E + T at visit 3 developed invasive breast cancer. Use of E + T had a nonsignificant impact on invasive breast cancer risk (adjusted hazard ratio, 1.42; 95% confidence interval, 0.95-2.11). The most commonly used E + T preparation, Estratest, was associated with a significant elevation in invasive breast cancer (adjusted hazard ratio, 1.78; 95% confidence interval, 1.05-3.01). However, rates of breast cancer were lower in longer-term E + T users than in shorter-term E + T users. CONCLUSION: Although our results have less strength than an initial report linking E + T to breast cancer, we found a modest, albeit nonsignificant, elevation in breast cancer risk associated with E + T use.

Comment. This study found a nonsignificant trend toward an increased breast cancer risk. Analysis limited to women using Estratest, however, revealed a significant increase in risk and most of the women in the study used Estratest. A prior report of a cohort of women in the Nurses' Health Study by Tamimi¹ also suggested an increased risk with estrogen plus testosterone when compared to estrogen alone (2.48; 95% CI, 1.53-4.04). The majority (but not all) of reported data suggests that androgen levels, when measured in postmenopausal women, correlate positively with breast cancer risk and persist when adjusted for estrogen levels.²

Based on these studies, are we to tell our patients that androgens contribute to the risk of breast cancer? The answer at the present time is "no" according to this reviewer. The number of women taking estrogen plus an androgen in the two studies cited was small (1,705 in the Ness study and 550 in the Tamimi study), and a total of only 64 breast cancer cases occurred in these

patients. As these were both observational studies, the balance in risks between users and nonusers is important for assessing the validity of the results. In Ness et al, the user group was more educated, more physically active, drank more alcohol, had lower body mass index, earlier ages at menarche and menopause, a lower rate of pregnancy and higher rate of breast feeding, and a higher past history of smoking than the nonuser group. The users also had a significantly higher prevalence of benign breast disease. Another problem with the Ness study is that users for a short period of time had a higher risk of breast cancer than longer-term users. Based on the duration of use statistics, the absolute risk from estrogen plus an androgen would be very small, if this risk exists. All of these factors lead to the conclusion that a randomized control trial is necessary to determine the risk of breast cancer from use of estrogen plus an androgen.

If breast cancer risk is increased with estrogen plus testosterone, what is the hypothesis that might explain this phenomenon? Androgens can be aromatized in breast tissue to estrogens and might cause increased breast tissue estrogen levels. While plausible, it is of interest that Estratest, which was the most commonly used estrogen plus androgen combination, contained methyltestosterone, a compound shown to be an aromatase inhibitor.³ On the other hand, Intrinsa, the testosterone patch in development, contains an aromatizable androgen, testosterone. Accordingly, studies in the future need to examine the roles of aromatizable and nonaromatizable androgens separately.

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Editor's Note: On March 13, 2009, Solvay Pharmaceuticals announced its decision to discontinue supplying Estratest and Estratest H.S. (esterified estrogens and methyltestosterone) tablets in the United States effective April 1, 2009.

Effect of multivitamins on cancer and CVD

Neuhouser ML, Wassertheil-Smoller S, Thomson C, et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Arch Intern Med* 2009;169:294-304. **Level of evidence: II-2.**

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BACKGROUND: Millions of postmenopausal women use multivitamins, often believing that supplements prevent chronic diseases such as cancer and cardiovascular disease (CVD). Therefore, we decided to examine associations between multivitamin use and risk of cancer, CVD, and mortality in postmenopausal women. **METHODS:** The study included 161 808 participants from the Women's Health Initiative clinical trials (N=68 132 in 3 overlapping trials of hormone therapy, dietary modification, and calcium and vitamin D supplements) or an observational study (N=93 676). Detailed data were collected on multivitamin use at baseline and follow-up time points. Study enrollment occurred between 1993 and 1998; the women were followed up for a median of 8.0 years in the clinical trials and 7.9 years in the observational study. Disease end points were collected through 2005. We documented cancers of the breast (invasive), colon/rectum, endometrium, kidney, bladder, stomach, ovary, and lung; CVD (myocardial infarction, stroke, and venous thromboembolism); and total

mortality. **RESULTS:** A total of 41.5% of the participants used multivitamins. After a median of 8.0 years of follow-up in the clinical trial cohort and 7.9 years in the observational study cohort, 9619 cases of breast, colorectal, endometrial, renal, bladder, stomach, lung, or ovarian cancer; 8751 CVD events; and 9865 deaths were reported. Multivariate-adjusted analyses revealed no association of multivitamin use with risk of cancer (hazard ratio [HR], 0.98, and 95% confidence interval [CI], 0.91-1.05 for breast cancer; HR, 0.99, and 95% CI, 0.88-1.11 for colorectal cancer; HR, 1.05, and 95% CI, 0.90-1.21 for endometrial cancer; HR, 1.0, and 95% CI, 0.88-1.13 for lung cancer; and HR, 1.07, and 95% CI, 0.88-1.29 for ovarian cancer); CVD (HR, 0.96, and 95% CI, 0.89-1.03 for myocardial infarction; HR, 0.99, and 95% CI, 0.91-1.07 for stroke; and HR, 1.05, and 95% CI, 0.85-1.29 for venous thromboembolism); or mortality (HR, 1.02, and 95% CI, 0.97-1.07). **CONCLUSION:** After a median follow-up of 8.0 and 7.9 years in the clinical trial and observational study cohorts, respectively, the Women's Health Initiative study provided convincing evidence that multivitamin use has little or no influence on the risk of common cancers, CVD, or total mortality in postmenopausal women.

Comment. Two principal difficulties in many recent studies of nutrient effects are: 1) failure to include a low-intake control group and 2) failure to use (and validate) a nutrient dose sufficient to produce the desired effect. Both faults are exhibited in the paper by Neuhouser et al. Most nutrients exhibit a threshold (or plateau) characteristic, as manifested, for example, during iron supplementation (ie, iron raises hemoglobin in patients with iron deficiency, but only up to normal levels, above which further iron intake has no further effect on blood hemoglobin.) As many papers reported from WHI have clearly shown, the enrolled cohort of women exhibited substantial healthy volunteer bias as reflected, for example, in calcium intakes nearly twice what had been found in NHANES-III, and hip

fracture rates approximately half what had been predicted from Medicare data. What the Neuhouser paper documented is that individuals in WHI, who were already getting enough of many key nutrients, exhibited no further benefit from getting more. It doesn't show that those nutrients have no benefit.

The second issue is the dosage question. Typical multivitamins contain, for example, 400 IU of vitamin D. This is usually enough to raise serum 25(OH)D by about 4 ng/ml. In several studies, this dose-evoked change in vitamin D status has been shown to be inadequate to produce appreciable benefit. All studies showing a benefit of vitamin D (including several

randomized trials) used doses of 800 to 2,000 IU/d. WHI was designed nearly 20 years ago, and it would not be appropriate to criticize its designers for not knowing information that had not yet been developed. But neither is it appropriate to publish papers that presume adequacy of design and proceed to reach sweeping conclusions of "no benefit," such as did Neuhouser et al.

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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.

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| 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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