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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).

Testosterone improves sexual function in women not taking estrogen

Davis SR, Moreau M, Kroll R, et al, for the APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med* 2008; 359:2005-2017. **Level of evidence: I.**

Therapy with a testosterone patch placed on the abdomen and delivering 300 µg daily provides some benefit to postmenopausal women with hypoactive sexual desire disorder (HSDD) who are not using estrogen therapy (ET) or estrogen plus progestin therapy (EPT), according to this randomized, double-blind, placebo-controlled study. The Phase III Research Study of Female Sexual Dysfunction of Women on Testosterone without Estrogen was initiated to determine the efficacy and safety of the testosterone patch in postmenopausal women not receiving estrogen who are suffering from HSDD and included women from 65 centers in the United States, Canada, Australia, the United Kingdom, and Sweden. The trial was conducted for 52 weeks and included 814 healthy postmenopausal women (aged 20-70 y) who were randomly assigned to receive a patch delivering either 150 µg or 300 µg testosterone per day or placebo. Participants were seen at baseline and at weeks 6, 12, 24, 36, and 52.

Efficacy was measured through women's responses on a weekly sexual activity log for 24 weeks and their scores on a Profile of Female Sexual Function and a Personal Distress Scale that were completed at baseline and at weeks 12 and 24. Adverse events were assessed at each visit through week 52. Some women continued treatment for a second year to provide additional safety data. The primary endpoint was a change through week 24 in frequency of satisfying sexual episodes over 4 weeks.

Baseline scores for frequency of satisfying sexual events, sexual desire, and distress were similar among groups. By week 24, the increase in 4-week frequency of satisfying events was significantly greater in the group with the 300 µg/day patch, with an increase of 2.1 episodes versus 0.7 episodes for placebo; $P < 0.001$. There was an increase in satisfying episodes of 1.2 in 4 weeks for the group receiving 150 µg testosterone. Both groups receiving testosterone had significantly increased scores for sexual desire and decreased scores for distress by week 24. The overall incidence of adverse events among groups was similar, with incidence of androgenic events highest in the 300-µg group, mainly increased hair growth. Breast cancer occurred in three women in the testosterone groups by week 52.

and in an additional woman receiving hormone in the extension phase.

Comment. Prior clinical trials (typically lasting 3-6 mo) with exogenous testosterone have been well conducted. The majority of trials show modest overall improvement in desire, sexual responsiveness, and frequency of orgasm as well as the number of satisfying sexual episodes (an endpoint required by the Food and Drug Administration [FDA] as evidence of efficacy). The short duration of these trials has worried those concerned about potential for serious adverse effects. Studies have been restricted to postmenopausal women taking ET or EPT.

Here, Davis et al assess testosterone therapy in postmenopausal women presumably estrogen deficient for up to 2 years. Efficacy was shown in women who had natural menopause but not in those with surgically induced menopause (probably because of a lack of statistical power). It is reasonable to ask whether the absolute increase of satisfying sexual episodes of 2.1 per month (1.4 more events per month than in the placebo group) was of value. The article does not indicate whether the women were asked if this was meaningful for them. Baseline data suggest it probably was. The mean number of such episodes almost doubled for the high-dose group (84% vs. 28% for placebo).

All groups had reaction at the application site (49.5%-52.8%, which is high) and various androgenic events (acne, alopecia, and voice deepening in less than 8% of each group). A little more than half in each group completed 52 weeks. Reasons for dropping out are well illustrated. Increased unwanted hair growth was significantly more common with 300 µg of testosterone per day (19.9% vs. 10.5% in the placebo group). Of greater concern are the four cases of breast cancer in the groups receiving testosterone, including one case detected 3 months after the extension period ended, versus zero in the placebo group. This could simply be due to chance, yet it is potentially worrisome and cannot be ignored. Findings suggest the need for caution until we understand more about testosterone's

possible link with breast cancer and until we are better able to predict which patients are more likely to have negative effects.

Transdermal testosterone is available in Europe for use in surgically postmenopausal women who have persistent symptoms of HSDD despite adequate nonconjugated ET. However, the FDA in the United States is concerned about potential adverse effects over the long term. Breast cancer risk and potential detrimental lipoprotein physiology with unknown cardiovascular disease risk, as well as androgenic side effects (well documented here), have been the major challenges. The reported lipid profiling in this study is reassuring yet not definitive. Small, dense lipoprotein particle concentrations are a better predictor of events but were not measured. The pharmaceutical industry sponsored and analyzed this multisite study.

Because of a lack of FDA-approved testosterone patches in the United States for women, compounding pharmacy preparations for transdermal testosterone are often prescribed. If this route is chosen, full disclosure of off-label use and documentation of the known and unknown risks is strongly recommended. With the breast cancer concern and the need for studies with large numbers of women enrolled to answer this concern, it is likely that the FDA will continue to be very conservative regarding this issue.

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HT regimen and route modify effect on MI risk

Lokkegaard E, Andreassen AH, Jacobsen RK, Nielsen LH, Agger C, Lidegaard O. Hormone therapy and risk of myocardial infarction: a national register study. *Eur Heart J* 2008;29:2660-2668. **Level of evidence: II-2.**

Type of hormone therapy (HT) regimen and route of administration could modify the influence of HT on risk for myocardial infarction (MI), but overall there is no association between HT and MI risk, a Danish study states. The Danish Sex Hormone Register Study assessed risk for MI associated with HT by using national registry information on all healthy Danish women aged 51 to 69 years from 1995 through 2001, which included 698,098 women. Information extracted from registries included ages, diagnoses from all hospitalizations, causes of death, prescriptions reimbursed, and level of education. Detailed information on prescription hormone products, daily doses, and administration form was available. The study assessed the influence of duration of HT use, type of regimen, route of administration, progestogen type, and estrogen dose on risk for MI.

Compared with never use, the overall relative risk (RR) for MI with current use of HT was 1.03 (95% confidence interval [CI], 0.95-1.11). Risk for MI with current HT use was increased among women aged 51 to 54 years (RR, 1.24; 95% CI, 1.02-1.51), but risk with current HT use decreased with increasing age. In women aged 60 to 69 years, RR for MI with current HT use was 0.92 (95% CI, 0.80-1.06). Overall, the RR for MI with past use of HT was 0.81 (95% CI, 0.71-0.93). Compared with never users, risk according to duration of use was 1.06 for short-term (<1 y), 1.03 for middle-term (1-4 y), and 0.99 for long-term (>4 y) use.

The highest risk for MI was found with continuous-combined estrogen-progestogen therapy (EPT) (RR, 1.35; 95% CI, 1.18-1.53), with no excess risk found with the cyclic-combined EPT or tibolone. There was decreased risk for MI with dermal unopposed estrogen (RR, 0.62; 95% CI, 0.42-0.93)—significantly lower than that for oral unopposed estrogen ($P = 0.04$). For EPT, there was no difference in risk between oral and dermal treatment. Vaginal estrogen was associated with a significantly decreased risk of MI (RR, 0.56; 95% CI, 0.44-0.71). There was no increased risk of MI with increasing estrogen

dose, and there was no indication of an effect on risk for different progestogen types.

Comment. This study reminds us of what we do and do not know about the effect of estrogens on cardiovascular risk. First, it is important to realize that this study was a review of a database and not a prospective trial. The investigators were working with a very comprehensive database and did an excellent job identifying potential issues with the data set. When compared with the Women's Health Initiative (WHI) data, there is agreement, suggesting that we can trust this information. For the unopposed estrogen group, the hazard ratio (HR) was 0.94 compared to 0.95 for WHI. For the EPT regimens, the overall HR was 1.35 compared to 1.24 for WHI.

WHI and the Heart and Estrogen/progestin Replacement Study (HERS) give us information about one particular type of HT and one particular method of delivery (oral). It is important to understand that this may not translate to all other regimens or delivery systems. It was very interesting that the investigators found a lower risk of MI associated with dermal applications, especially for unopposed estrogen. In addition, they found no increased risk for women with preexisting cardiovascular risk factors such as diabetes, hyperlipidemia, or hypertension. This was in contrast to earlier work by the same group.

Finally, and what may be most interesting in this analysis, the investigators were able to adjust for women who had undergone bilateral oophorectomy at a young age (and therefore at perhaps increased risk for MI) who may have benefited more from HT. Excluding these women, the investigators point out, should not necessarily decrease risk estimates because of the protective effect. Based on this evaluation, the data do not support a timing hypothesis for perimenopausal HT reducing cardiovascular risk.

The more we learn about HT and cardiovascular risk, the more complex the issue

becomes. Studies like Lokkegaard et al only support the need for more randomized controlled trials with different HT preparations, regimens, and delivery systems. In addition, HT should continue to be used short term when indicated for symptomatic relief.

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In *BRCA1* mutation carriers, no increased risk for breast cancer with HT use

Eisen A, Lubinski J, Gronwald J, et al, and the Hereditary Breast Cancer Clinical Study Group. Hormone therapy and the risk of breast cancer in *BRCA1* mutation carriers. *J Natl Cancer Inst* 2008;100:1361-1367. **Level of evidence: II-2.**

Using hormone therapy (HT) is not associated with an increased risk for breast cancer in postmenopausal women with a *BRCA1* mutation, this study suggests. In fact, researchers found a decreased risk with HT use among this small cohort with the mutation. Participants were drawn from the larger cohort of the Hereditary Breast Cancer Clinical Study, a prospective study to evaluate nongenetic modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers. Cases were diagnosed with invasive breast cancer after reaching menopause. Controls had experienced menopause and did not have breast cancer. Cases and controls were matched for year of birth, age at menopause, and type of menopause; 236 matched sets with the *BRCA1* mutation were generated. A questionnaire administered to each woman garnered information on medical and reproductive history and past and current HT use (average age, 58.2 y; range, 32-85 y). The study analyzed whether HT use after surgical or natural menopause is associated with subsequent risk for breast cancer in women with *BRCA1* mutation.

More controls than cases had used HT (29% vs. 20%); the average duration was 3.7 years for controls and 4.0 years for cases. Compared with

never use, women who had used HT had a lower risk of breast cancer (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.35-0.96; $P = 0.03$). There was no modification of the OR for duration of use, and the association was similar for current and past users. Results were also similar for women who had undergone surgical as opposed to natural menopause. For women who used estrogen only, there was an inverse association with breast cancer risk (OR, 0.51; 95% CI, 0.27-0.98; $P = 0.04$). Results were similar with combined estrogen and progestogen (OR, 0.66; 95% CI, 0.34-1.27; $P = 0.21$). Surprisingly, HT use was reported for 12% of patients with estrogen-receptor positive (ER+) tumors but only 23% of women with estrogen-receptor negative (ER-) tumors. ER status was available in 44% of cases.

Comment. There is a growing body of evidence suggesting that the premature loss of ovarian function caused by bilateral oophorectomy performed before natural menopause is associated with several negative outcomes including an increased risk of premature death, cardiovascular disease, cognitive impairment or dementia, parkinsonism, osteoporosis and bone fractures, decline in psychological well-being, and decline in sexual function. HT use may prevent some but not all of these negative outcomes. After receiving a positive genetic test result, 68% of women in the United States and 54% of women in Canada with a *BRCA1* or *BRCA2* mutation undergo oophorectomy.¹ The surgery has been associated with risk reductions of 50% or more for breast cancer and of 80% for ovarian or peritoneal cancer. Some women might be reluctant to undergo premenopausal oophorectomy because of the adverse effects of surgical menopause and are concerned that if HT were taken to alleviate symptoms, then their risk of breast cancer might rise.

The majority of *BRCA1*-associated breast cancers in the current study (68%) were ER-. If the adverse effect of HT were limited to ER+ cancers, then we would not expect to see an acute effect of similar magnitude in mutation

carriers. It may be also that HT use protects against the early stages of cancer development, which results in a decline in the incidence of breast cancer later in life. Published studies show that in the noncarrier population, the increased breast cancer risk associated with HT appears to be stronger for ER+ cancers than ER-.² If HT were a risk factor for ER+ breast cancer in *BRCA1* mutation carriers as well, one would expect that a greater proportion of women with ER+ breast cancers had used HT than women with ER- breast cancers. This was not seen, and these findings suggest that the use of menopausal HT is not associated with an increase in the risk of breast cancer among women with a *BRCA1* mutation, but the numbers of cases known to be ER+ are too small to draw a definite conclusion.

It may be also that HT use protects against the early stages of cancer development, which results in a decline in the incidence of breast cancer later in life. If HT promotes the growth of existing ER+ breast cancers but protects against the early stages of development of new breast cancers (ER+ and ER-), then we would expect HT to protect against breast cancer in *BRCA1* mutation carriers (who are mostly ER-).

Editorial writers have argued that the results presented by Eisen et al regarding HT use in postmenopausal *BRCA1* mutation carriers provide some evidence for safety but are insufficient to reliably inform routine clinical practice.³ Decision making regarding menopausal HT in women at increased risk of breast cancer is complex. The current HT package insert identifies climacteric symptoms as the main indication of HT use at the lowest dose and shortest duration consistent with therapeutic goals. We do not know how many postmenopausal women with *BRCA1* mutations have limiting symptoms of hot flashes, vaginal/vulvar problems, and/or sexual dysfunction that cannot be addressed using nonhormonal approaches, nor do we know how to define the term “limiting” as a threshold for HT use.

Eisen et al say that it is not possible to recommend an optimal duration of HT, but some

experts (eg, the National Comprehensive Cancer Network) have suggested that “short-term hormone replacement therapy” be prescribed until the time of natural menopause (ie, age 50-54).⁴ After that age, consideration should be given to the use of tamoxifen for breast cancer risk reduction. In mathematical models, prophylactic oophorectomy lengthens life expectancy in women with *BRCA1/2* mutations, irrespective of whether HT is used after oophorectomy. Women with *BRCA1/2* mutations who undergo prophylactic oophorectomy after completion of childbearing should decide about short-term HT based largely on quality-of-life issues rather than life expectancy, and consider discontinuing treatment at the time of expected natural menopause, approximately age 51.

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Nurses' Health Study: healthy lifestyle lowers mortality in middle-aged women

Van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: pro-

spective cohort study in US women. *BMJ* 2008 [Epub ahead of print]. **Level of evidence: II-2.**

Following a healthy lifestyle markedly lowers mortality in middle-aged women, finds the prospective Nurses' Health Study (NHS), which examined combinations of lifestyle factors in relation to cancer, cardiovascular, and all-cause mortality during 24 years of follow-up. The 77,782 women (aged 34-59 y at start of study) initially completed a questionnaire on known and suspected risk factors for disease and were free of cardiovascular disease and cancer. They were followed with biennial questionnaires on lifestyle and health conditions. Risk of mortality was the main outcome measure in relation to five lifestyle factors: cigarette smoking, being overweight, little moderate-to-vigorous physical activity, no light-to-moderate alcohol intake, and low-quality diet. Population-attributable risks—the proportion of deaths during follow-up that could have been avoided by healthy lifestyle adherence—were also measured.

Diet was tracked with food frequency questionnaires, and healthiness of the diet was assessed by a healthy eating score. Disease history, cigarette smoking, frequency of physical activity, and body mass index (BMI) were assessed on the biennial questionnaires. Deaths were reported by next of kin, postal authorities, or through searching for nonresponders in the National Death Index. Cause of death was determined through medical records.

There were 8,882 deaths with 1,790 from cardiovascular disease and 4,527 from cancer. Smoking, higher BMI, less physical activity, and lower healthy diet score were all associated with increased cardiovascular, cancer, and all-cause mortality. Light alcohol consumption was associated with lower cardiovascular risk. Each lifestyle factor independently and significantly predicted mortality, and mortality increased with increasing numbers of risk factors. The risk for combining the five risk factors compared with none was 8.17 (4.96-13.47, 95% confidence interval) for cardiovascular mortality, 3.26 (2.45-4.34) for cancer mortality, and 4.31 (3.51-5.31)

for all-cause mortality. The population-attributable risk all-cause mortality for these five factors combined was 51% for younger women and 63% for older women.

Comment. For more than 30 years, the NHS has provided a wealth of data gleaned from the well-designed observational study. Certainly the contributions from this large cohort have generated an impressive historical database identifying a multitude of health-promoting and disease-provoking behaviors in the female registered nurses participating in the study. Although the study may be criticized by some for its nonrandomized methodology, the sample size (77,782 participants in this reported study), the fact that more than 90% of the nurse participants have responded to questionnaires sent biannually, and the findings that this cohort reflects the lifestyle behaviors of the general population all serve to support the reliability of the data.

The latest findings recently published are not “new” concepts, and will not create an “aha” moment for clinicians, or even the general public. The conclusion validates current knowledge: “following a healthy lifestyle markedly lowers mortality in middle-aged women.” As clinicians, we repeatedly share these lifestyle pearls with our patients, applauding those who so steadfastly follow patient guidelines that result in improved health outcomes, and feeling frustrated with the population who desire the “magic pill” rather than alter their behavior.

Here is one more strong study with results to share with patients: stop smoking, lose weight, increase activity, and consume a healthy diet. Even altering one lifestyle factor is associated with lower mortality, but altering combined behaviors has an even greater impact on life-lengthening benefits. So, beyond this information, what is the plea of clinicians when presented with these data? Identify the components that consistently motivated those clients who chose to alter their lifestyle and achieve healthy outcomes. The frustrating part

of my practice over the years has been to admit that knowledge does not always change behavior. Even in this health-conscious and knowledgeable nursing cohort, known health-promoting behaviors were not implemented among the large group. I would like to see further investigation into identifying intrinsic and extrinsic motivational factors that led the nurses to develop appropriate healthful behaviors. Perhaps, then, more women can achieve good health as

more clinicians are equipped with the scholarly tools to motivate their patients.

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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.

Become a NAMS Menopause Practitioner in 2009

The North American Menopause Society (NAMS) invites all licensed healthcare professionals to become credentialed as a Menopause Practitioner by sitting for the NAMS competency examination in 2009.

What are the benefits of holding this credential? Here is just a partial list:

- Validation of a level of expertise which only the preeminent menopause organization can offer
- Possibility of more patient referrals, job promotion, and higher salaries
- Enhanced credibility and the personal satisfaction of providing your patients with the best possible care

The next exam will be administered on May 16, 2009, in 12 U.S. cities and Toronto, ON, Canada. The registration deadline for this exam is March 7 (late registration deadline of April 11 requires an additional \$75 processing fee).

The competency exam will also be offered just prior to the start of the 20th Annual Meeting in San Diego, CA (September 30-October 3, 2009).

Complete information, including an applications, may be found in the *2009 Candidate Handbook* available on the NAMS Web site (www.menopause.org/compexam.aspx).

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