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The following news items present reviews of important, recently published scientific articles selected by members of The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving the health of women at midlife and beyond through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Note that opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS. Previously published news items may be viewed on the NAMS Web site ([www.menopause.org/news.html](http://www.menopause.org/news.html)).

## Progesterone may increase breast cancer risk less than progestin

Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Intl J Cancer* 2004(e-publ in advance). **Evidence level: II-2.**

Oral progestin, the synthetic form of progestogen, significantly increases the breast cancer risk associated with postmenopausal hormone therapy, but micronized oral progesterone does not increase the risk, according to data from the E3N study, a subset of the European Prospective Investigation into Cancer and Nutrition study. The E3N is a prospective cohort study conducted in France. Investigators enrolled 54,548 postmenopausal women (mean age, 52.8 years) who had not used estrogen-containing therapy for at least 1 year. During the study, women completed questionnaires every 2 years regarding use of postmenopausal hormone therapy.

Mean duration of follow-up was 5.8 years. More than half of the women (n = 29,420) used postmenopausal hormone therapy during the study, either estrogen therapy alone (ET) or estrogen plus progestogen (EPT). The mean duration of ET/EPT use was 2.8 years. Most women used transdermal estradiol, administered in either a gel or patch formulation. All progestogens used were oral formulations.

Overall, ET/EPT users had a significantly increased relative risk (RR) for breast cancer of 1.2 (95% CI, 1.1-1.4) compared with nonusers. Individually, EPT

users had a significantly increased RR of 1.3 (95% CI, 1.1-1.5), but ET alone did not increase the risk (RR, 1.1; 95% CI, 0.8-1.6). However, the difference between ET and EPT was not significant.

When comparing types of progestogens contained in EPT, the RR for progestins was 1.4 (95% CI, 1.2-1.7) and 0.9 (95% CI, 0.7-1.2) for micronized progesterone, a statistically significant between-group difference ( $P < 0.001$ ). Progestins significantly increased the breast cancer risk when added to either transdermal, percutaneous, or oral estrogen formulations, even for relatively short-term use. When used for less than 2 years, the RRs were 1.6 (95% CI, 1.3-2.0) for those receiving progestin plus transdermal/percutaneous estrogen and 1.2 (95% CI, 0.8-1.7) for those receiving progestin plus oral estrogen. When used for 2 to 4 years, the RRs were 1.4 (95% CI, 1.0-1.8) for progestin plus transdermal/percutaneous estrogen and 1.6 (95% CI, 1.2-3.2) for oral EPT.

**Comment.** This report from an ongoing French cohort study involved multiple statistical manipulations. The major conclusion is this: the risk of breast cancer is slightly increased with a postmenopausal hormone therapy regimen consisting largely of transdermal estradiol combined with synthetic progestins but not when combined with progesterone. Furthermore, this increased risk appears quickly, even with short-term use.

There are several points that raise concern. The hormone users have many differences compared with nonusers, especially in characteristics that influence the risk of breast cancer. The users were more likely to be younger, to have had an earlier

menarche and later menopause, to be parous, to have more benign breast disease, to be better educated, and to have used oral contraceptives and progestational agents before menopause. The authors state that statistical adjustments were made for these variables; however, the relative risks and confidence intervals before and after adjustment are identical. How is it possible for these risk factors to be more common in the user group and not to have an impact on the numbers after adjustment?

The statistical power of the study was concentrated in synthetic progestins users (268 cases vs 55 cases among micronized progesterone users). Because the reported differences are not large, a shift of a few cases (affected by the various risk factors noted above) could change the conclusions.

The rapid appearance of an increased breast cancer risk raises the following question: do the statistical results reflect a slight increase in risk or an impact on preexisting tumors? As this remains an unanswered question, it is not appropriate for the authors to say that the carcinogenic effect of estrogen plus progestin in continuous administration was proved by the Women's Health Initiative trial. The force of the authors' discussion is further diluted by repeated references to the Million Women Study, a study that has been soundly dissected and criticized for multiple flaws.

Because of these concerns, I wouldn't base my advice or prescription choices on these results.

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## Raloxifene provides breast cancer benefits for at least 8 years

Martino S, Cauley JA, Barrett-Connor B, et al, for the CORE Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* 2004;96:1751-1761. **Evidence level: I.**

Postmenopausal women with osteoporosis who are treated with raloxifene receive the added benefit of reduced invasive breast cancer risks, a benefit that

continues for longer than 4 years of use, according to the randomized, double-blind, placebo-controlled Continuing Outcomes Relevant to Evista (CORE) trial, an extension of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. In the 4-year MORE trial, raloxifene reduced the breast cancer incidence by 72%. In the CORE trial, 5,213 women from the MORE trial (N = 6,511) who did not have breast cancer were continued for another 4 years on their regimens of raloxifene (60 mg/day) or placebo, as randomly assigned in the MORE trial. The end point was invasive breast cancer incidence.

At study end, raloxifene recipients had significantly reduced incidences of breast cancer (hazard ratio [HR], 0.41; 95% CI, 0.24-0.71) and estrogen receptor (ER)-positive breast cancer (HR, 0.35; 95% CI, 0.18-0.66) when compared with placebo recipients. During the 8 years combining both trials, the overall incidences of breast cancer and ER-positive breast cancer were significantly reduced by 66% (HR, 0.34; 95% CI, 0.18-0.66) and 76% (HR, 0.24; 95% CI, 0.15-0.40), respectively, compared with placebo recipients. Increased risks for thromboembolism were more than two-fold higher for raloxifene than placebo during CORE (HR, 2.17; 95% CI, 0.83-5.70). Significantly increased thromboembolism risks were also observed during MORE. No new adverse events were noted during CORE.

**Comment.** This paper raises many important issues worthy of comment. In women picked for an osteoporosis study, not because of any personal history of breast cancer or for being at risk for breast cancer, 8 years of raloxifene therapy significantly reduced their invasive breast cancer risk.

Much has been rumored about drug resistance with tamoxifen, another selective estrogen-receptor modulator, and concerns that tamoxifen may actually increase breast cancer risk with prolonged use. Studies showing those adverse events were in women with breast cancer receiving tamoxifen as adjuvant therapy for their malignancy. In reality, the 5-year limitation on tamoxifen therapy is based on these two factors: (1) no additional benefits are seen after 5 years, and (2) there are ongoing, but small, risks of deep vein thrombosis and endometrial carcinomas with tamoxifen.

It is reassuring that raloxifene through 8 years of use shows no diminution of its ability to reduce breast

cancer in these osteoporotic women. However, this does not mean that all women at risk for breast cancer (and not in need of bone pharmacotherapy) should be offered raloxifene. That answer will have to await results from the STAR (Study of Tamoxifen and Raloxifene) trial in which women at high risk for breast cancer are being compared head-to-head. Remember, MORE and CORE participants were not picked for being at high risk for breast cancer.

Interestingly, we had believed that women with osteoporosis were at lower risk for breast cancer. However, in the MORE/CORE placebo group, there was an incidence of 5.4 cases per 1,000 women-years, which is higher than the Surveillance, Epidemiology, and End Points (SEER) database rates of 4.4 and 4.5 cases per 1,000 women-years for women aged 65 to 74 and 75 and over, respectively.

In summary, data from the CORE trial and 8-year combined data from the MORE and CORE trials suggest that the reduced incidence of invasive breast cancer in women receiving raloxifene may continue beyond 5 years.

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**Comment.** This article describes breast cancer incidences from the combined MORE and CORE trials. The 72% reduction in the raloxifene group is both compelling and of great interest. The impact appears to be entirely on the ER-positive cancers. There was no effect on ER-negative cancers. This would suggest that it is the woman's estrogen level that causes the difference in tumors that have receptors capable of responding. The study subjects are women who are presumably at lower risk of getting breast cancer, as all of them have low bone density, which has been associated with a lower risk of breast cancer. With the addition of the MORE subjects, the rate was 1.4 cases per 1,000 women per year in the raloxifene group as opposed to 4.2 cases per 1,000 women per year in the placebo group.

This article should be read together with the Missmer article published in the December issue of the same journal. [Missmer *J Natl Cancer Inst* 2004] This article is a case-control study from the Nurses' Health Study that measured actual levels of these hormones and found a clear relationship of endogenous estrogen with breast cancer incidence.

The higher quartile of endogenous estrogen levels was associated with a 3.3 relative risk of breast cancer. This was also only true for ER-positive breast cancers with no relationship to ER-negative cancers. Neither progesterone nor androgen levels reached statistical significance.

Taking both articles together, they add to the cumulative literature that estrogen levels play a major role in breast cancer. Whether this is a permissive role or causative one is not clear. Raloxifene, which blocks estrogen at the receptor level, may be as good as or better than tamoxifen in preventing breast cancer. The STAR trial is currently comparing Evista against tamoxifen in breast cancer prevention.

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## **DHEA lowers abdominal fat, improves insulin action in older postmenopausal women**

Villareal DT, Holloszy JO. Effect of DHEA on abdominal fat and insulin action in elderly women and men. *JAMA* 2004;292:2243-2248. **Evidence level: I.**

Dehydroepiandrosterone (DHEA) therapy reduces both abdominal obesity and insulin resistance in elderly women, according to this randomized, double-blind, placebo-controlled trial. A total of 56 men and women aged 65 years and older (mean age, 71 years) were randomized to receive DHEA therapy (50 mg/day) for 6 months. DHEA is an androgen available without a prescription. Magnetic resonance imaging was used to quantify abdominal fat, and an oral glucose tolerance test was used to measure insulin sensitivity.

At study end, female DHEA recipients had significant decreases in both abdominal visceral fat area and abdominal subcutaneous fat area compared with placebo recipients: a 13 cm<sup>2</sup> drop compared with a 3 cm<sup>2</sup> gain for both abdominal fat measurements. Total abdominal fat changes also were significant as DHEA recipients dropped 27 cm<sup>2</sup> while placebo recipients gained 11 cm<sup>2</sup>. Glucose tolerance testing showed a significant improvement

in the insulin sensitivity index among DHEA recipients of 1.4 versus a loss of 0.7 among placebo recipients ( $P = 0.005$ ).

**Comment.** The benefits of DHEA supplementation in reversing or slowing the catabolism of aging have been advocated, but the supporting data are mixed. Advocates have claimed that DHEA has possible positive effects on immunomodulation, bone metabolism and density, memory, quality of life, muscle strength, and even risk for cardiovascular disease. One intriguing hypothesis is that effects on insulin resistance may be a mediating factor resulting in positive effects on body mass index and obesity. Villareal adds intriguing data to this debate with this well-conducted, randomized, controlled trial.

Drawbacks of these findings include the necessary use of surrogate end points regarding the medical benefit of DHEA supplementation in elderly women. It remains uncertain if a modest decrease in abdominal subcutaneous fat has any clinical significance. Additionally, an improvement in glucose tolerance testing in nondiabetic women, while certainly an encouraging finding, does not yet translate to any positive health outcome. Given recent unexpected consequences of postmenopausal hormone therapy use and that little is known about the long-term use of DHEA supplementation, it would be premature to advocate its widespread use based solely on these findings.

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## Metabolic syndrome, high inflammation factors linked to cognitive impairment

Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA* 2004;292:2237-2242. **Evidence level: II-2.**

The metabolic syndrome contributes to cognitive impairment in older men and women, although it appears to primarily affect those with high levels of inflammation, according to this 5-year prospective,

observational study. A total of 2,632 elderly men and women (mean age, 74 years) were enrolled. The primary end point was the association at 3 and 5 years of the metabolic syndrome (as defined in National Cholesterol Education Program guidelines) and high inflammation (defined as serum levels of interleukin 6 and C-reactive protein above the median) with any decline in cognition (defined as drops in the Modified Mini-Mental State Examination Scores of at least 5 points).

At study end, those with the metabolic syndrome had a 20% greater relative risk (RR) for cognitive impairment than those without the syndrome (RR, 1.20; 95% CI, 1.02-1.41). Levels of inflammation factors also played a role in increasing the cognitive impairment risk. When compared with participants without the metabolic syndrome, participants with the syndrome and high inflammation factors had an increased risk of cognitive impairment (RR, 1.66; 95% CI, 1.19-2.32); those with low inflammation factors did not have an increased risk (RR, 1.08; 95% CI, 0.89-1.30).

**Comment.** This study confirms that specific clinical indicators can be associated with decreased mentation in an aging population. In their report, Yaffe and colleagues indicate that over a 5-year observation period, there is a decrease of tested cognition in selected men and women aged 70 to 79 years who have the metabolic syndrome and increased inflammatory markers when compared with similarly aged, nonaffected controls. Having the metabolic syndrome alone did not result in a difference.

Although Caucasian women in this study were most likely to exhibit the metabolic syndrome, there is no indication of whether there is an effect of sex on the cognition outcomes. The lack of information on the hormonal history of the subjects is noteworthy. Because estrogen therapy has repeatedly been shown to be cardioprotective and neuroprotective, and an anti-inflammatory immunomodulator, it would be of great interest to know the history of hormone therapy in the subjects.

By the time they were tested, those with high inflammatory markers were considerably more ill than the others in the group. For example, the high inflammatory-marker group already had experienced more clinically diagnosed strokes and myocardial infarctions at enrollment. This may have been

related to the concurrent metabolic syndrome and/or to their higher rate of smoking and alcohol abuse.

In any case, it seems clear that before the study began, the subjects in the metabolic syndrome and high inflammatory-marker group had undergone sufficient complications to make it extremely difficult to separate the underlying pathophysiology from its outcomes as causing the differences in cognition over time. For example, since minimal cognitive dysfunction is associated with Alzheimer's disease, not vascular dementia, it would have been useful to know whether these results were related to the emergence of dementia in this aging population.

These questions do not nullify the study; rather, they point out the vital need for long-term studies that begin with younger individuals and are accompanied by diagnostic studies that separate degenerative brain disease from cerebrovascular disease. Such studies should be more easily interpreted and could lead to the development and application of preventive measures before the occurrence of the cardiac and cerebral vascular complications that must have had an impact on the present study's results.

Yaffe and colleagues are to be congratulated on focusing our attention on outcomes of the metabolic syndrome and elevated inflammatory markers and the importance of early and continuing prevention of their complications.

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## HT use, dose size declined sharply after initial WHI report published

Buist DSM, Newton KM, Miglioretti DL, et al. Hormone therapy prescribing patterns in the United States. *Obstet Gynecol* 2004;104:1042-1050. **Evidence level: II-2.**

The number of women using postmenopausal hormone therapy (HT), either estrogen therapy alone (ET) or estrogen plus progestogen (EPT), declined significantly after findings from the Women's Health Initiative (WHI) were released, according to

this observational study of prescription data on women enrolled in health maintenance organizations (HMOs). Data for 169,586 women aged 40 to 80 in five HMOs in the United States were reviewed to determine the rates of HT initiation and discontinuation before and after the first WHI report, published in June 2002. Rates of HT use between Sept 1, 1999, and June 31, 2002, were used as a baseline. These were compared with HT use rates during December 2002 (follow-up). All oral and transdermal ET/EPT products were included.

Five months after the first WHI report, the percentage of women using EPT declined 46%, from 14.6% (baseline) to 7.9% (follow-up). ET use declined 28%, from 12.6% to 9.1%. The size of estrogen doses also declined. At baseline, more than 80% of HT users received a 0.625 mg or higher daily dose of conjugated equine estrogens, or its equivalent. At follow-up, those receiving 0.625 mg/day dropped by 43.7% and those receiving a higher dose dropped 18.9%. In contrast, the prevalence rate for those using smaller doses increased 5.8%, although the actual number of users was small (2,981 at follow-up vs more than 20,000 for the larger doses).

Discontinuation rates increased initially, going from 2.5% at baseline to 13.8% in October 2002. They then stabilized or declined, although the rates remained significantly higher. These rates translated to relative risks of discontinuation of 5.52 (95% CI, 5.30-5.75) for EPT and 2.59 (95% CI, 2.43-2.76) for ET in October 2002, and 4.74 (95% CI, 4.51-4.98) and 2.37 (95% CI, 2.21-2.54), respectively, in December 2002. Rates of HT therapy initiation showed significant declines at follow-up, with relative risks dropping by 54% for EPT (95% CI, 0.40-0.52) and 24% for ET (95% CI, 0.68-0.85).

**Comment.** The strength of this study is that the investigators used data from a large sample of women aged 40 to 80 years in HMOs in five US sites. As indicated in the abstract, there was a substantial drop in the number of ET/EPT prescriptions after discontinuation of the EPT arm of the WHI. Unfortunately, the ET arm of the WHI ended in 2004, so data from that study were not available for this study. Also, prescriptions for vaginal or compounded estrogens were not included, which I believe is an error because it would be important to note how the prescription practices changed for those formulations.

As is already known, the prevalence for ET/EPT use prior to 2002 was highest for women around age 55. The authors do not address how these women perceived the WHI data, in which the mean age of women was 63. There was a notable decrease in the doses of estrogen prescribed after WHI, which I see as directly related to the FDA guidelines established after the WHI that suggest using the lowest dose possible for the shortest duration. It was reassuring that prescribing practices and usage patterns did not change for women aged 40 to 44, as they are the population who presumably reached menopause early and would most benefit from hormone use.

In conclusion, the study presents interesting data about changes in ET/EPT use after the WHI study conclusions. However, it does not address how the situation has changed since the ET arm of the study was stopped or what other hormone formulations and preparations that women are using as substitutes to treat their symptoms.

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## US Surgeon General issues osteoporosis recommendations

US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General*. Rockville, MD: US Department of Health and Human Services; 2004. **Evidence level: Position statement.**

An estimated 10 million Americans older than age 50 have osteoporosis and another 34 million are at risk for osteoporosis, according to this first-ever report on the nation's bone health from the US Surgeon General. Women over age 50 have a 50% risk of suffering an osteoporosis-related fracture in their remaining life, and the risk increases with age. This 404-page report was prepared by the Surgeon General with the assistance of many experts in the field of skeletal health. It is based on an evaluation of relevant scientific data, which was used to provide recommendations on improving bone health and reduce the risk of osteoporosis.

Specific recommendations include consuming adequate amounts of calcium (1,200 mg/day for women older than 50) and vitamin D (400 IU/day for women aged 51-70); being physically active for at least 30 minutes a day, including weight-bearing activities to improve strength and balance; taking measures to minimize the risk of falls in the home; and limiting or avoiding alcohol use and smoking.

The report recommends bone density testing for all women over the age of 65 and for any woman who has suffered a fracture, including a minor fracture, after age 50. The report calls on healthcare professionals to evaluate the osteoporosis risks for all patients at any age, especially factors that may indicate an increased risk, such as having multiple fractures under age 50; taking medications such as oral glucocorticoids, thyroid treatments, radiation or chemotherapy, antiepileptics, gonadal hormone suppressors, and immunosuppressive agents; or having a disease that can lead to bone loss, such as hyperthyroidism, chronic lung disease, chronic hepatic or renal disease, Cushing's disease, or rheumatoid arthritis.

**Comment.** As part of the decade of the bone and joint (2002-2011), the United States has joined other nations in committing resources for research and public health programs to promote a better understanding of the musculoskeletal system. Congress commissioned this report from the Surgeon General to help bridge the gap between clinician and public awareness of bone health and bone disease and what is known, based on scientific evidence.

The report is organized around five major questions:

1. What is bone health? This provides the scientific background using lay terminology.
2. What is the status of bone health? This describes the magnitude of the problem as it exists in our society.
3. What can individuals do to improve their bone health? This includes lifestyle choices, among other options.
4. What can healthcare professionals do to promote bone health? The three chapters in this section provide an excellent, concise, and "user friendly" evidence-based review for clinicians.
5. What can health systems and population-based approaches do to promote bone health? This attempts to look at the role of key public and

private stakeholders in developing a national action plan that can benefit all Americans.

The final section of the report reviews the major messages and visions for the future. It also provides action steps for implementation aimed at individuals of all ages.

In summary, the US Surgeon General's Report highlights the scientific advances in bone health that have occurred over the last few decades. It does not offer any new guidelines for the prevention, diagnosis, or treatment of bone disease, but it does review what is already known and how it can be implemented. It also validates the importance of

bone health for healthy aging. I encourage all healthcare providers to review this impressive document at [www.surgeongeneral.gov/library](http://www.surgeongeneral.gov/library).

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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 U.S. 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, preferably from more than one center or research group.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies); uncontrolled experiments with dramatic results.
Level III	Opinions of respected authorities that are based on clinical experience; descriptive studies and case reports; reports from expert committees.

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