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This e-newsletter presents 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 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. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS. Disclosures are available on request. Oversight for this newsletter issue was by Robert A. Wild, MD, PhD, MPH, Chair-Elect, 2006-2007 NAMS Professional Education Committee. Past issues of this e-newsletter may be viewed on the NAMS Web site ([www.menopause.org/news.html](http://www.menopause.org/news.html)).

## Breast cancer risk elevated after 5 years of some types of estrogen-only therapy

Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol* 2006;108:1354-1360. **Level of evidence: II-2.**

Use of oral or transdermal estradiol for less than 5 years does not increase the risk for breast cancer, but risk does occur after 5 years of use and increases with longer duration and dosage, according to this study from Finland of a cohort representing the nation's entire postmenopausal population. The study evaluated risk for breast cancer with estrogen-only therapy and whether it varies by dose, constituent, and route of administration.

All women over age 50 (N= 283,680) who had used an estrogen-only regimen (oral or transdermal estradiol [n = 84,729], oral estriol [n = 7,941], or vaginal estrogens [n = 18,314]) for 6 months or more from 1994 to 2001 were identified. Women using conjugated estrogens were excluded. All women using a particular regimen were identified from the Finnish National Reimbursement Register, which contains data on postmenopausal hormone therapy

purchases since 1994. They were followed for breast cancer until the end of 2002 or death. A total of 2,171 cancer cases were identified from the Finnish Cancer Registry, which receives notification of cancers from physicians, hospitals, and laboratories and for which coverage is almost 100%.

After 5 years of use, estradiol was associated with an increased risk of breast cancer. Oral estriol and vaginal estrogen were not associated with any increase in risk. The incidence ratio for breast cancer with systemic estradiol use of less than 5 years was 0.93 (95% confidence interval [CI], 0.80-1.04), and for 5 years or more, 1.44 (95% CI, 1.29-1.59) with similar risk for the oral and transdermal formulations. The standardized incidence ratio related to estimated estradiol use of 5 to 10 years was 1.34 (95% CI, 1.16-1.54); for 10 to 20 years, 1.57 (95% CI, 1.31-1.86); and for more than 20 years, 1.75 (95% CI, 1.16-2.55).

Risk was significantly elevated when the mean dose of oral estradiol was higher than 1.9 mg/day and was used for 5 years or more. The trend for dose, however, was not statistically significant ( $P$  for trend = 0.27). For the transdermal route, risk was not associated with dosage. The authors note that the risk associated with estradiol use of 5 to 10 years results in two to three additional cases

of breast cancer per 1,000 women in 10 years of follow-up.

**Comment.** Several recent publications have confirmed previous observational data that up to 5 years of postmenopausal use of estrogen alone does not increase, and may even decrease, invasive breast cancer risk. The Lyytinen study captures observational data from all Finnish women older than age 50 who filled a prescription for estradiol (tablets, patches, gels) based on a national registry (110,984 women and 648,022 women-years). This population provides particularly important data on use of short-term versus long-term estradiol without a progestogen. For short-term use (<5 years), the results are reassuring, with a standardized incidence ratio of 0.93 (95% CI, 0.80-1.04) in the subgroup who never took estrogen prior to entry into the study (ie, estrogen-naïve). This study is concordant with the randomized controlled trial Women's Health Initiative (WHI) estrogen-alone data (hazard ratio [HR], 0.77; 95% CI, 0.59-1.01)<sup>1</sup> and the observational Nurses' Health Study (NHS) (HR, 0.96; 95% CI, 0.75-1.22)<sup>2</sup> for similar estrogen-naïve patients.

It is interesting to note that Lyytinen, the WHI update on breast cancer,<sup>3</sup> and the NHS all reported trends toward reduced risks of breast cancer in women receiving estrogen alone for less than 5 years. The results were statistically significant in WHI for subgroups with no prior menopausal hormone use (HR, 0.65; 95% CI, 0.46-0.65), localized disease (HR, 0.69; 95% CI, 0.51-0.95), and drug compliance (HR, 0.67; 95% CI, 0.47-0.97). This short-term reduction in risk with oral estrogen in particular may reflect an effect of estrogen in reducing hyperinsulinemia, a risk factor for breast cancer, as it has been estimated that 50% of the participants in the WHI estrogen-only arm would have the metabolic syndrome.<sup>4,5</sup> This paradoxical reduction in risk may also reflect a proapoptotic effect of estrogen on a reservoir of preexisting tumors exposed to low concentrations of estrogen since menopause, particularly given the significant reduction in the number who never used hormones in the WHI (Santen, unpublished data).

Lyytinen indicates that long-term estrogen alone may increase the relative risk (RR) of breast cancer (RR, 1.44; 95% CI, 1.29-1.59 for >5 years' use). Notably, increased risk was observed with oral, transdermal, and gel preparations. The NHS, in contrast, reported that this risk began to increase only after more than 15 years of predominantly oral therapy with the rate of ER+/PR+ tumors statistically significantly increased after 15 years current use (RR, 1.48; 95% CI, 1.05-2.07). If confirmed in additional studies, these data suggest that the mechanisms of estrogen effect, when used short term (antihyperinsulinemic, proapoptotic), may differ from those occurring with long-term use (initiation, promotion).

As with other observational data, this study serves to point out potential confounding factors in interpretation, such as the presence or absence of ovaries after hysterectomy, the lumping together of estrogen-naïve and preexposed women, the lack of distinction between lean and obese women, the identification of women with the metabolic syndrome/insulin resistance, and the use of a control group composed of estrogen users and nonusers. Taking these issues into account, current data suggest no increase and perhaps a decrease in breast cancer risk with estrogen alone for less than 5 years in estrogen-naïve women and an increased risk if taken long term, particularly for more than 5 years in women of normal body mass index—longer in women with obesity.

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## Effects of vitamin E or B on cognitive function (two studies)

Kang JH, Cook N, Manson J, Buring JE, Grodstein F. A randomized trial of vitamin E supplementation and cognitive function in women. *Arch Intern Med* 2006;166:2462-2468. **Level of evidence: I.**

A substudy of the Women's Health Study finds there is no improvement or decline in cognitive function or decline in older women after a mean of 9.6 years of vitamin E supplementation. The double-blind, placebo-controlled trial randomized 39,876 healthy US women to receive vitamin E (600 IU of alpha-tocopherol acetate on alternate days) or placebo between 1992 and 1995. The substudy followed 6,377 of these women (ages 65 or older) for 4 years beginning in 1998, a mean of 5.6 years after randomization, for changes in cognitive function.

General cognition, verbal memory, and category fluency were assessed using five tests conducted by telephone interview at the initiation of the study and at 2-year intervals. The tests were adapted from the Mini-Mental State Examination and the East Boston Memory Test. The primary outcome measure was a global composite score on all five tests; a secondary outcome measure was a composite score of verbal memory.

At the first assessment, scores on the five tests did not differ for the two treatment groups (5.6

years after randomization: mean difference,  $-0.01$ ; 95% confidence interval [CI],  $-0.04$ - $0.03$ ).

In addition, there were no differences in the global scores between the vitamin E and placebo groups at the two follow-up assessments (after 9.6 years of treatment: mean difference,  $0.00$ ; 95% CI,  $-0.04$ - $0.04$ ). For the secondary endpoint of verbal memory, there were no differences in scores between groups at any of the assessments (at final assessment: mean difference,  $0.01$ ; 95% CI,  $-0.03$ - $0.05$ ). There were no differences in mean change in cognitive performance for any of the assessments between the treatment groups.

There was a suggestion of a positive effect in women who previously had low dietary intake of vitamin E ( $<6.1$  mg/d). For these women, the vitamin E recipients had less decline in cognitive function compared with the placebo group. The difference in mean change in global score over time between the two groups was  $0.05$  (95% CI,  $0.01$ - $0.09$ ). For women with previously high dietary intake of vitamin E, the groups had similar adverse cognitive change. Among women who exercised less than once a week, the vitamin E group had a more favorable cognitive change than the placebo group; the mean change in global score over time was  $0.06$  (95% CI,  $0.03$ - $0.10$ ). Among women who exercised at least once a week, there was no difference in change in cognitive function over time between the two groups.

While the study did not demonstrate overall cognitive benefit or reduced cognitive decline, the authors speculate that initiation of treatment at an earlier age or for longer duration, using higher dosages of vitamin E or mixed tocopherols, could possibly show a positive effect.

Balk EM, Raman G, Tatsioni A, Chung M, Lau J, Rosenberg IH. Vitamin B<sub>6</sub>, B<sub>12</sub>, and folic acid supplementation and cognitive function: a systematic review of randomized trials. *Arch Intern Med* 2007;167:21-30. **Level of evidence: III.**

Inadequate evidence exists at this time for a beneficial effect of supplementation with vitamins B<sub>6</sub>, B<sub>12</sub>, or folic acid on cognitive

function in either normal elderly adults or those with impaired cognitive function, found this systematic review of studies that examined the effect of these vitamins on cognition. The current study used a literature search of MEDLINE to identify English language, randomized controlled trials in which specific type of vitamin, dose, and route of administration were reported. All were trials of adult participants with outcomes related to cognitive impairment or function. A total of 14 trials was reviewed. The trials were considered to be of variable and mostly low quality, with small numbers of participants and a large degree of heterogeneity in dose, route of administration, and duration of treatment.

Three trials of vitamin B<sub>6</sub> and six trials of vitamin B<sub>12</sub> found no effect on cognitive function. One small study did find an improvement with folate supplementation in patients with low baseline folate. Six trials of supplementation with combinations of the vitamins found no effect on cognitive function. Given the sparsity of studies that qualified for inclusion, the low numbers of participants, and heterogeneity of data and outcomes, inadequate evidence currently exists for a beneficial effect of B vitamin supplementation on cognitive function, the study concluded.

**Comment.** Age-associated cognitive decline is characterized by a subtle progressive loss of cognitive function beginning in the fourth and fifth decades of life and represents the cumulative effects of multiple factors. The challenge of intervention trials in healthy populations is that the outcome is not a defined event, such as a hip fracture. The outcome is the slowing of the natural trajectory of cognitive decline, on the order of 1%-2% per decade. To detect a 50% effect, one would have to be able to measure a change of 1% over 10 years. Thus, even the Kang et al study with 6,000 participants followed for almost 10 years was underpowered.

It is also important to appreciate that these clinical trials involve populations without evidence of a deficiency of the vitamins used in the intervention at superphysiological doses. In

observational studies, the referent population is deficient, with exposures measured in decades. In the few clinical trials in which the population was deficient, effects on cognitive function were observed.<sup>1,2</sup> This is due in part to that fact that the deficient subjects were experiencing a decline in function at a much greater rate.

What can we conclude from these studies? The benefits of supplementation on healthy nondeficient individuals in order to slow cognitive decline is uncertain. However, the risks of supplementation are much less so. Several trials have demonstrated an increase in cardiovascular mortality with vitamin E in excess of 400 units per day—no benefit.<sup>3</sup> With B vitamins designed to lower homocysteine and cardiovascular endpoints, at least one trial has demonstrated a possible increase in cardiovascular events—again no benefit.<sup>4</sup> Trials of beta-carotene and vitamin A to reduce cancers demonstrated increased risk of these cancers and mortality.<sup>4</sup> In summary, although there is insufficient evidence that supplementing with vitamins in excess of the physiological requirements in otherwise healthy individuals is beneficial, there is growing evidence that this supplementation is harmful. More may not be better.

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## Gabapentin with an antidepressant no more effective in treating hot flashes than gabapentin alone

Loprinzi CL, Kugler JW, Barton DL, et al. Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. *J Clin Oncol* 2007;25:308-312. **Level of evidence: I.**

Gabapentin alleviates hot flashes in women who have a poor response to treatment of them with antidepressants, and continuing an antidepressant along with gabapentin does not have an additive effect. This prospective, randomized trial conducted at the Mayo Clinic and other medical centers (referred from a cancer treatment randomization office) assessed whether the combined agents would more effectively alleviate hot flashes versus gabapentin alone. In the 5-week trial, 118 women who were using an antidepressant to treat hot flashes (median age, 53.5 years) without satisfactory diminishment of symptoms were randomized to receive either both the gabapentin and antidepressant or be weaned from the antidepressant and receive gabapentin alone. Women kept a diary of frequency and severity of hot flashes and other symptoms over the course of the 5-week study.

Approximately three quarters of the participants had a personal history of breast cancer; the remainder were reluctant to use hormone therapy due to concerns about breast cancer. Approximately two thirds were using tamoxifen or an aromatase inhibitor, and most of the women were using venlafaxine or paroxetine at study entry.

During the first week, the women were observed in order to establish baseline levels of vasomotor symptoms. All participants then began gabapentin, initially 300 mg at bedtime for 3 days, then twice daily for 3 days, then three times daily for 22 days. Those randomized to continue antidepressant therapy continued at their current dose and schedule; those randomized to discontinue decreased their dose by half for

1 week and then discontinued. A total of 91 women provided complete data at week 5.

Regardless of whether the antidepressant was continued, participants reported an approximately 50% reduction ( $P < 0.05$ ) in the frequency of hot flashes (54%; 95% confidence interval [CI], 34%-70% for combined treatment vs 49%; 95% CI, 26%-58% for gabapentin alone), as well as of hot flash scores (56%; 95% CI, 26%-71% for combined treatment vs 60%; 95% CI, 33%-73% for gabapentin alone). By week 2, a trend toward more negative mood changes and nervousness was noted in those who discontinued antidepressants. Overall, self-reported quality of life parameters were similar throughout the study in the two groups of participants.

**Comment:** Because vasomotor symptoms are common in late perimenopausal and early postmenopausal women, and many symptomatic women are concerned about the risks of hormone therapy, much interest has focused on nonhormonal treatment of hot flashes. Identifying nonhormonal treatments for menopausal hot flashes that are more effective than placebo has proved challenging. Acupuncture, yoga, Chinese herbs, dong quai, evening primrose oil, ginseng, kava, red clover extract, black cohosh, and soy/phytoestrogens have not consistently been found more effective than placebo. Likewise, the antidepressants citalopram and sertraline have not been found effective, and results for fluoxetine and venlafaxine have been inconsistent. Although paroxetine has been found to have a modest benefit in symptomatic breast cancer survivors, most studies of symptomatic women without this history have not demonstrated efficacy.<sup>1</sup>

The need for three times daily administration is a disadvantage of treating menopause-related symptoms with gabapentin. The more frequent negative mood changes and nervousness in those randomized to discontinue antidepressants likely reflect the positive impact that antidepressants were having on those who discontinued these medications. Overall, these findings indicate that

off-label use of gabapentin may be useful in breast cancer survivors taking antiestrogens whose vasomotor symptoms do not respond to antidepressants. The authors suggest that, in this setting, delaying discontinuation of the antidepressant might be useful so that any ensuing undesirable mood changes not be inappropriately attributed to gabapentin.

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## Later menopause associated with reduced risk for pancreatic cancer

Prizment AE, Anderson KE, Hong CP, Folsom AR. Pancreatic cancer incidence in relation to female reproductive factors: Iowa Women's Health Study. *JOP* 2007;8:16-27. **Level of evidence: II-2.**

Variables related to an early age at menopause influence the risk for pancreatic cancer, and variables associated with a later age at menopause reduce the risk, according to the Iowa Women's Health Study, a prospective, population-based study designed to examine risk factors for breast and other cancers. The cohort of 37,459 peri- and postmenopausal women (aged 55-69 at baseline) provided information at baseline in 1986 and were followed until 2003. The baseline questionnaire asked about body size, lifestyle and sociodemographic factors, diet, and medical and reproductive history. This portion of the study evaluated the association between the incidence of pancreatic cancer and reproductive characteristics. The hypothesis for an association was based upon the facts that pancreatic cancer is more common in men than in women, steroid hormone receptors occur in the pancreas, and antiestrogenic agents inhibit the growth of pancreatic cancer in human models.

A multivariate-adjusted model was used to study associations between pancreatic cancer and age at first birth, number of births, ages at menarche and menopause, and use of hormone therapy (HT). Also studied were natural as opposed to medically induced menopause and women with intact ovaries compared to others who had oophorectomy. Cases of pancreatic cancer were identified through the Iowa State Health Registry, and only cases of exocrine pancreatic cancer were included. Over the course of 18 years, 228 cases of pancreatic cancers occurred (mean age at diagnosis, 73 years).

No associations were found between pancreatic cancer and age at menarche, number of live births, age at first birth, use of HT, or use of oral contraceptives. Incidence of pancreatic cancer was reduced in women who experienced menopause at an older age. The hazard ratio (HR) for pancreatic cancer for women experiencing menopause between the ages of 45 to 49 was 0.61 (95% confidence interval [CI], 0.40-0.94) compared to women who reached menopause before age 45. For those who experienced menopause between ages 50 to 54, the HR was 0.75 (95% CI, 0.51-1.09); and for women who experienced menopause after age 55, the HR was 0.35 (95% CI, 0.18-0.68; *P* for trend = 0.005).

Risk was decreased in women who ovulated for a longer period of their life and who did not have total oophorectomy. For women with intact ovaries compared to those with oophorectomy, the HR was 0.70 (95% CI, 0.50-0.99). Hence, only reproductive variables related to menopause (age at menopause, length of ovulation, oophorectomy, and hysterectomy without total oophorectomy) are associated with pancreatic cancer.

**Comment.** This study draws attention to the fact that extended endogenous sex steroid exposure in postmenopausal women may have important effects on disease states outside of those that normally make the news, namely cardiovascular

disease, osteoporosis, and breast cancer. From the clinician's standpoint, this may further reinforce the importance of not arbitrarily removing normal-appearing ovaries at the time of hysterectomy in the pre- or perimenopausal woman if, in fact, a later age of menopause and longer periods of ovulation are related to a lower incidence of pancreatic cancer, which has a poor 5-year survival rate.

Whether estrogen or other sex steroids have anticarcinogenic effects in humans remains to be determined. However, estrogen has been shown

to inhibit the growth of preneoplastic lesions in the laboratory setting.

The fact that pancreatic cancer is related to modifiable risk factors such as smoking, diet, and diabetes further stresses our role as primary care providers in encouraging all of our patients to pursue a healthy lifestyle.

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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.
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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