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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](http://www.menopause.org/news.html)).

## Ovarian conservation versus oophorectomy in the NHS

Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the Nurses' Health Study. *Obstet Gynecol* 2009;113:1027-1037. **Level of evidence: II-2.**

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**OBJECTIVE:** To report long-term health outcomes and mortality after oophorectomy or ovarian conservation. **METHODS:** We conducted a prospective, observational study of 29,380 women participants of the Nurses' Health Study who had a hysterectomy for benign disease; 16,345 (55.6%) had hysterectomy with bilateral oophorectomy, and 13,035 (44.4%) had hysterectomy with ovarian conservation. We evaluated incident events or death due to coronary heart disease (CHD), stroke, breast cancer, ovarian cancer, lung cancer, colorectal cancer, total cancers, hip fracture, pulmonary embolus, and death from all causes. **RESULTS:** Over 24 years of follow-up, for women with hysterectomy and bilateral oophorectomy compared with ovarian conservation, the multivariable hazard ratios (HRs) were 1.12 (95% confidence interval [CI] 1.03-1.21) for total mortality, 1.17 (95% CI 1.02-1.35) for fatal plus nonfatal CHD, and 1.14 (95% CI 0.98-1.33) for stroke. Although the risks of breast (HR 0.75,

95% CI 0.68-0.84), ovarian (HR 0.04, 95% CI 0.01-0.09, number needed to treat=220), and total cancers (HR 0.90, 95% CI 0.84-0.96) decreased after oophorectomy, lung cancer incidence (HR=1.26, 95% CI 1.02-1.56, number needed to harm=190), and total cancer mortality (HR=1.17, 95% CI 1.04-1.32) increased. For those never having used estrogen therapy, bilateral oophorectomy before age 50 years was associated with an increased risk of all-cause mortality, CHD, and stroke. With an approximate 35-year life span after surgery, one additional death would be expected for every nine oophorectomies performed. **CONCLUSION:** Compared with ovarian conservation, bilateral oophorectomy at the time of hysterectomy for benign disease is associated with a decreased risk of breast and ovarian cancer but an increased risk of all-cause mortality, fatal and nonfatal coronary heart disease, and lung cancer. In no analysis or age group was oophorectomy associated with increased survival.

**Comment.** Prophylactic oophorectomy has been the default recommendation for women older than 40 to 50 years undergoing hysterectomy for benign disease for the ostensible benefit of preventing subsequent occurrence of ovarian cancer. This study confirms a previous decision analysis model by Parker et al in 2005<sup>1</sup> that found that ovarian

conservation up to age 65 was associated with increased long-term survival for women undergoing hysterectomy for benign disease. Since then, additional studies have confirmed the finding that ovarian conservation at the time of hysterectomy for benign disease has overall survival and health benefit. The caveat is that studies to date have been observational; however, a randomized controlled trial that rigorously examines this question has not been done. Moreover, the current evidence is consistent, resulting from a large, prospective, well-designed, and thoughtful study. When overall mortality and other diseases are considered in the context of elective concurrent bilateral oophorectomy, these risks seem to outweigh the benefit of prevention of subsequent ovarian cancer.

Notably, women who underwent bilateral oophorectomy before age 50 and never used estrogen therapy (ET) were at even greater risk for all-cause mortality, CHD, and stroke. Bilateral oophorectomy prior to menopause removes the major source of endogenous estrogens as well as a source of androgens (androstenedione and testosterone) that may be converted to estrone peripherally even beyond menopause. Rivera et al<sup>2</sup> showed that bilateral oophorectomy in women younger than age 45 is associated with increased cardiovascular mortality. Interestingly, they also found that women treated with estrogen after bilateral oophorectomy until age 45 or beyond did not exhibit an increase in mortality, suggesting that initiation of ET at the time of bilateral oophorectomy may counteract the detrimental effect of oophorectomy on CHD. This finding is similar to and substantiated by the findings of a secondary analysis of the Women's Health Initiative study<sup>3</sup> showing that when ET is started within the first decade after menopause, or between ages 50 and 59, the long-term risk of CHD is reduced. Thus, timing of the initiation of ET (or estrogen plus progestogen) after menopause appears to influence the effect on cardiovascular disease with earlier initiation of hormone therapy close to the time of menopause being beneficial.

The observational evidence is growing, indicating that we need to rethink the current practice of prophylactic bilateral oophorectomy at the time of hysterectomy for benign disease. Ovarian conservation should be the default recommendation unless bilateral oophorectomy has clear benefit, such as when hysterectomy is being done for definitive treatment of endometriosis, or if there is increased risk for ovarian or breast cancer such as family history or presence of genetic markers *BRCA1* and *BRCA2*. Clearly, a woman's individual risks must be considered, and when there is an indication for oophorectomy, this concurrent procedure is appropriate. Additionally, if bilateral oophorectomy is performed prior to age 50, in the absence of contraindications, initiation and continuation of ET at least until age 45 should be considered to counteract the unfavorable effects of oophorectomy on overall health.

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## Does depression affect menopausal symptoms?

Reed SD, Ludman EJ, Newton KM, et al. Depressive symptoms and menopausal burden in the midlife. *Maturitas* 2009;62:306-310. **Level of evidence: II-3.**

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**OBJECTIVE:** The goal of this study was to assess whether menopausal symptoms were more common and/or more severe among

women with depressive symptoms. **METHODS:** A cross-sectional survey of 1358 women, ages 45-70, at two large integrated health plans (Seattle; Boston) was performed. Information on demographics, medical and reproductive history, medication use, menopausal experience and depressive symptoms (PHQ-8) were collected. Women taking HT were excluded. Logistic regression models adjusted for age and body mass index tested the associations between menopausal symptoms (hot flashes, night sweats, vaginal dryness and dyspareunia) and presence of moderate/severe depressive symptoms. **RESULTS:** 770 women were included; 98 (12.7%) had moderate/severe depressive symptoms and 672 (87.3%) had no/mild depressive symptoms. Women with moderate/severe depressive symptoms were almost twice as likely to report recent vasomotor symptoms (hot flashes and or night sweats) vs. women with no/mild depressive symptoms (adjusted odds ratio (aOR) 1.67, 95%CI 1.04-2.68), and to report them as severe (aOR 1.63, 95%CI 0.95-2.83). A higher symptom burden was observed despite the fact that 20% of women with moderate/severe depressive symptoms (vs. 4.6% no/mild depressive symptoms) were using an SSRI or SNRI, medications known to improve vasomotor symptoms. The percentage of women with menopausal symptoms, and the percentage with severe vasomotor symptoms were linearly associated with the depressive symptom score. **CONCLUSIONS:** Depressive symptoms “amplified” the menopausal experience, or alternatively, severe vasomotor symptoms worsened depressive symptoms.

**Comment.** The findings of this large-scale survey are not unexpected but are relevant—namely that depression seems to “amplify” both the experience and intensity of vasomotor symptoms associated with menopause. The study was well done and controlled for confounding variables such as age and body mass index, but still found that women with moderate/severe depression were almost twice as likely to report

recent hot flashes, night sweats, or both than women with no or mild depressive symptoms.

The authors acknowledge the correlational nature of their findings and note that severe vasomotor symptoms might worsen depressive symptoms. Certainly, if the sleep interruptions associated with night sweats interfere with refreshing sleep, depressive symptoms will be exacerbated—feelings of fatigue, irritability, and lack of energy. Sleep disruption is already a hallmark of depression. Nevertheless, the authors make the reasonable argument that depression may be associated with greater severity of bodily symptoms and/or may result in poorer self-care regimens such as diet or exercise, which will exacerbate vasomotor symptoms.

Notwithstanding the likely bidirectional nature of the findings, the authors suggest that their study has clinical implications—namely that identification and treatment of depression in midlife women may ameliorate the experience or severity of menopausal complaints. Although the severely depressed sample of women in this research were already on SSRIs or SNRIs, the authors pose three possible explanations: “(1) their antidepressant therapy was suboptimal, (2) they might have benefited from HT, or (3) even in the face of optimal management of depressive and vasomotor symptoms, these women’s symptoms would remain refractory to therapy.”

Clearly, this study raises as many questions as it answers, although it points to the importance of conducting well-controlled prospective longitudinal research on *depressed women compared to nondepressed women* as they undergo the menopause transition.

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## Ovarian cancer screening: no basis for optimism

Partridge E, Kreimer AR, Greenlee RT, et al, for the PLCO Project Team. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol* 2009;113:775-782. **Level of evidence: II.**

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**OBJECTIVE:** To test whether annual screening with transvaginal ultrasonography and CA 125 reduces ovarian cancer mortality. **METHODS:** Data from the first four annual screens, denoted T0-T3, are reported. A CA 125 value at or above 35 units/mL or an abnormality on transvaginal ultrasonography was considered a positive screen. Diagnostic follow-up of positive screens was performed at the discretion of participants' physicians. Diagnostic procedures and cancers were tracked and verified through medical records. **RESULTS:** Among 34,261 screening arm women without prior oophorectomy, compliance with screening ranged from 83.1% (T0) to 77.6% (T3). Screen positivity rates declined slightly with transvaginal ultrasonography, from 4.6 at T0 to 2.9-3.4 at T1-T3; CA 125 positivity rates (range 1.4-1.8%) showed no time trend. Eighty-nine invasive ovarian or peritoneal cancers were diagnosed; 60 were screen detected. The positive predictive value (PPV) and cancer yield per 10,000 women screened on the combination of tests were similar across screening rounds (range 1.0-1.3% for PPV and 4.7-6.2 for yield); however, the biopsy (surgery) rate among screen positives decreased from 34% at T0 to 15-20% at T1-T3. The overall ratio of surgeries to screen-detected cancers was 19.5:1. Seventy-two percent of screen-detected cases were late stage (III/IV). **CONCLUSION:** Through four screening rounds, the ratio of surgeries to screen-detected cancers was high, and most cases were late stage. However, the effect of screening on mortality is as yet unknown.

**Comment:** Cancer screening is successful to the extent that it can identify malignant (or premalignant) lesions at a point in their natural history at which treatment leading to cure can be administered. After the first four rounds of

screening for ovarian cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, it appears that the screening modalities used—transvaginal ultrasonography and measurement of serum CA 125 levels—are not able to achieve an early-stage diagnosis in any appreciable proportion of women with ovarian cancer. Even among the 60 screen-detected cases in this study, 72% were diagnosed at stages III to IV. Adding in the 29 women with ovarian cancer who had been screened but whose tumor was diagnosed independent of screening (“interval” cases), the fraction of stage III to IV disease among cancer cases in screened women would approach 80%—the same percentage as in women with ovarian cancer who had refused screening altogether. Only about 1 in 100 study participants who screened as positive actually had ovarian cancer; about 1 in 20 who underwent surgery for possible ovarian cancer actually had this disease. Failure to achieve a large improvement in stage-at-diagnosis argues that this approach to screening is unlikely to be valuable enough to justify its dollar and physical costs.

The authors of this report correctly conclude that “a determination on whether screening with these two modalities will reduce ovarian cancer mortality must await the final results of the PLCO trial.” For example, it may be that some stage III to IV cancers in screened women have been diagnosed relatively earlier than had screening not been done, allowing for treatment by means of surgery and chemotherapy to produce a higher likelihood of cure. Nonetheless, until the mortality results of PLCO become available, clinical practice should heed the recommendation of the US Preventive Services Task Force that “ovarian screening with CA 125 and transvaginal ultrasound is not recommended.”

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## Homocysteine levels associated with hip fracture

LeBoff MS, Narweker R, LaCroix A, et al. Homocysteine levels and risk of hip fracture in postmenopausal women. *J Clin Endocrinol Metab* 2009;94:1207-1213. **Level of evidence: II-2.**

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**BACKGROUND:** Recent studies suggest that high homocysteine levels are associated with an increased risk of fractures. Homocysteine levels are known to be influenced by vitamin B and folate supply or status, and poor renal function can result in higher levels independent of nutritional adequacy. **OBJECTIVE:** The aim of the study was to determine the associations between fasting homocysteine levels and incident hip fractures, and the effects of other factors on hip fracture risk. **DESIGN:** We conducted a case-control study in the Women's Health Initiative Observational Study, a study of postmenopausal women (n = 93,676) recruited in the United States. We selected 400 incident cases of hip fracture and 400 controls matched on age, ethnicity, and blood draw date among women not on osteoporosis therapies. Outcome measures included physician-adjudicated, incident hip fractures. Baseline lifestyle and nutritional questionnaires were performed. **RESULTS:** The risk of hip fracture increased 1.38-fold [95% confidence interval (CI), 1.14, 1.66] for each SD increase in serum homocysteine level after adjustment for fracture risk factors. This association was not affected by adjustment for dietary folate, B6, or B12 intake, but it diminished after adjustment for cystatin-C level (odds ratio, 1.08; 95% CI, 0.66-1.79), a measure of renal function not affected by muscle mass. Among women in the highest quartile of homocysteine and cystatin-C compared to those without elevations in either biomarker, the risk of hip fracture was substantially elevated (odds ratio, 2.8; 95% CI, 1.61-4.87). **CONCLUSIONS:** This study indicates that high homocysteine levels are associated with an increased risk of hip fracture, which could be accounted for by poor renal function.

**Comment.** High levels of homocysteine (Hcy) are known for increasing risk for atherosclerosis, fibrinoembolic disease, and cognitive impairment. The first correlation of Hcy to bone health was an observation that patients who suffered from homocystinuria also had early onset osteoporosis. Two observational studies in 2004 found a twofold increase in hip fractures<sup>1</sup> and an increase in nonvertebral fractures<sup>2</sup> in women with high Hcy levels. Interestingly, these correlations were at the same Hcy level observed for the risk for cardiovascular disease (CVD) and dementia. No causal relationship was drawn from these studies.

In 2005, a Japanese study<sup>3</sup> found that supplementing stroke victims who had increased Hcy levels for 2 years with folic acid and vitamin B12 resulted in lower hip fracture rates and Hcy levels when compared to placebo. The Hordaland Homocysteine Study<sup>4</sup> found similar results to LeBoff, but included more poor health variables. Last year, however, several studies pointed to poor renal function as the casual factor of high Hcy levels. Poor renal function theoretically leads to poor excretion of Hcy, leading to poor matrix development. Finally, one study<sup>5</sup> found that women with high bone marker levels have higher Hcy levels, lower BMDs, poorer physical performance, and higher bone turnover. Their conclusion was that high Hcy is a marker for frailty.

The question remains: "Is Hcy the cause of fractures or a marker of risk? It may inhibit collagen cross linking, which affects the way calcium and other minerals bind to it, leading to osteoporosis. The link is minimal in in vivo studies. The marker theory states that high Hcy is a reflection of poor nutrition. High Hcy perhaps is a marker for estrogen depletion. Because testosterone maintains bone matrix better, women are more susceptible to osteoporosis, especially when Hcy is high (increases after menopause). This current study reveals that renal function may be the most important piece of the puzzle. Should we use

Hcy as a fracture marker solely, as we once thought for CVD?

The story for Hcy is still evolving. Presently, we know that women with elevated Hcy levels are also at higher risk for overall poorer health and greater morbidity and mortality.

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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.

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In addition, this year’s meeting marks the last meeting for Dr. Wulf Utian as Executive Director before his retirement at year’s end. As a friend and colleague of Dr. Utian’s, you will no doubt want to offer your good wishes in person. A special session, “20 Years of Progress in Menopausal Medicine: The Utian Years,” has been planned, followed by an evening reception on Wednesday, September 30.

For more information, visit [www.menopause.org/meetings/2009HCP.aspx](http://www.menopause.org/meetings/2009HCP.aspx).

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