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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 Holly L. Thacker, MD, Chair-Elect, 2007-2008 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Thacker. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Folic acid and B vitamins do not lower cardiovascular events in women

Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA* 2008;299:2027-2036. **Level of evidence: I.**

Supplemental folic acid and B vitamins do not lower the risk for important vascular events in women at high risk for such events, even though they lower homocysteine levels, found the Women's Antioxidant and Folic Acid Cardiovascular Study. The randomized, double-blind, placebo-controlled trial (RCT) conducted in Boston evaluated whether a combination of supplemental folic acid (2.5 mg/d), vitamin B₆ (50 mg/d), and vitamin B₁₂ (1 mg/d) reduces the risk of cardiovascular events in high-risk women, over 7.3 years of follow-up. The trial began in 1998 when the B vitamin component was added to the Women's Antioxidant Cardiovascular Study and 5,442 women were randomized to receive folic acid and B vitamins (n = 2,721) or matching placebo (n = 2,721).

The women were aged 40 years and older (mean age, 62.8 y) and had a history of cardiovascular disease (CVD; 64.2% of participants) or at least

three cardiac risk factors. CVD was defined as myocardial infarction (MI), stroke, coronary or peripheral revascularization, angina pectoris, or transient ischemic attack. Risk factors were hypertension, high cholesterol, diabetes, parental history of premature MI, obesity, and cigarette smoking. The primary outcome measure was a combined endpoint of cardiovascular morbidity and mortality. Secondary endpoints were the individual components of total MI, total stroke, and total coronary heart disease events (MI, coronary revascularization, and death from coronary heart disease).

During the 7.3 years, there was a similar incidence of CVD events between groups, with 406 women in the treatment group and 390 in the placebo group experiencing at least one event (226.9/10,000 person-years vs 219.2/10,000 person-years; relative risk, 1.03; 95% confidence interval, 0.90-1.19; $P = 0.65$). There were also similar risks between groups for the secondary outcomes of MI, stroke, and CVD mortality.

Comment. I am not sure how many nails it takes to close the proverbial coffin, but the null effect of B-complex vitamins and folic acid to reduce CVD clinical events despite significantly lowering homocysteine levels in

this well-done, 7-year RCT enrolling high-risk women patients should be the final one. The findings are identical to those seen in the Heart Outcomes Prevention Evaluation trial, the Norwegian Vitamin Trial, and the Vitamin Intervention for Stroke Prevention trial, among others (which enrolled mostly men), even though the therapy is successful in reducing homocysteine levels. Numerous observational, epidemiological studies have confirmed that elevated homocysteine is a predictor of cardiovascular risk. Thus logic, which so often fails in predicting the body's response to therapies, suggested B-complex and folic acid directed at reducing homocysteine would lower events significantly.

Of course, there have been numerous markers associated with CVD that upon modulation have been duds. For example, low high-density lipoprotein cholesterol (HDL-C) has been a powerful predictor of risk, but despite decades of trying to reduce CVD by raising HDL-C, we have made little progress and the National Cholesterol Education Program Adult Treatment Panel III still provides no specific HDL-C goal. There are several therapies that raise HDL-C but have not proved to be cardioprotective, such as phenytoin, oral estrogen, and torcetrapib. Very low-fat diets and probucol lower HDL-C and have positive effects on atherosclerosis. Statins, fibrates, and niacin all reduce clinical events similarly in monotherapy trials, but each has very different effects on raising HDL-C. Similarly, antioxidant vitamins have failed to impact CVD, despite the fact that oxidation is part of atherogenesis.

Maybe the answer lies in why patients with elevated homocysteine are at risk for CVD. There has never been a definite, accepted reason explaining the CVD risk seen in patients with high homocysteine. Is homocysteine the atherogenic culprit or is it simply a marker of some other pathologic process? It has been proposed that homocysteine is simply indicative of impaired renal function, a major CVD risk factor, and perhaps treatment should be directed at the kidney and not the homocysteine per se.

Others have described an important link between HDL (apoA-I) production and function; perhaps treatments need to move in that direction. We simply cannot answer these questions today.

The truth is we really are not as smart as we think we are about most cardiovascular risk factors and so far have failed to discover others. It is speculative at best to predict what therapeutic manipulation of a given risk factor will do until it is subjected to properly designed, prospective, blinded outcome trials. It took many years before homocysteine was accepted as a risk factor and it took a decade of excellent clinical trials to prove that treating it with B-vitamin and folic acid is no longer justified. As usual, most of the previous data was from studies of men, but now we also have the answer in women. Therefore, if B-vitamin and folic acid therapy is null, screening patients with expensive homocysteine assays and following the levels over time is no longer justified. Likewise, the monies spent on vitamin therapy can be directed at better-proven therapies, including balanced diets to provide these supplements.

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Lipids predict coronary heart disease risk for women using hormone therapy

Bray PF, Larson JC, LaCroix AZ, et al, for the Women's Health Initiative Investigators. Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. *Am J Cardiol* 2008;101:1599-1605. **Level of evidence: II-2.**

In postmenopausal women without previous cardiovascular disease (CVD), lipids are a useful biomarker to identify those at increased

risk of coronary events from hormone therapy (HT), according to a nested case-control study from the Women's Health Initiative (WHI) Investigators. Moreover, the study supports the notion that in women with a favorable lipid profile, HT does not increase short-term coronary heart disease (CHD) risk. The study evaluated lipids and high-sensitivity C-reactive protein (hs-CRP) obtained at baseline and at 1-year follow-up in women from both of the WHI trials—the trial of conjugated estrogens (CE) alone and that of CE with medroxyprogesterone.

The WHI trials included postmenopausal women aged 50 to 79 years. This case-control biomarker study was nested within the two trials and included 271 patients with incident CHD (cases) and 707 patients without (controls). Women with a history of CVD were excluded. Cases were patients with myocardial infarction, CHD death, or both, in either clinical trial, that occurred in the first 4 years of follow-up. Controls were women who had no cardiovascular event throughout the course of the WHI trials. The aim of the study was to determine whether baseline lipids and hs-CRP have predictive value for HT benefit or risk of CHD events among postmenopausal women.

Several lipid measurements, but especially low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) ratio, interacted with HT to modify risk of CHD. Women with baseline LDL-C/HDL-C ratios of 2.5 or greater were at increased risk of CHD from HT (odds ratio [OR], 1.73; 95% confidence interval [CI], 1.18-2.53), but there was no increased risk from HT when the baseline LDL-C/HDL-C cholesterol ratio was less than 2.5 (OR, 0.60; 95% CI, 0.34-1.06). Measurement of hs-CRP provided no additional predictive value for risk.

Comment. I find this study exciting. It is a great use of the reexamination of the data from the WHI. Clearly, these data provide reassurance for

women with normal LDL-C/HDL-C ratios who want to initiate HT. It is helpful that the study also included a review of triglyceride levels and found them to be nonpredictive in the 4-year time frame of the study.

However, our knowledge about ongoing CVD prevention for women at low risk is not increased by this study. But for those women at a higher risk, the risk-benefit decision-making process becomes more defined—for both clinicians and patients. Clinically, this will support increased compliance to lifestyle changes and medication to lower the LDL-C/HDL-C ratio to normal prior to the initiation of HT. The mechanism suggested by the Umetani study¹ is illustrative, if indeed the cholesterol metabolite 27-hydroxycholesterol competes with estrogen for binding to vascular estrogen receptors in humans. This would support the argument that treatment for an elevated LDL-C/HDL-C ratio would decrease the cardiac risk associated with HT.

We should view the initiation of HT as the great opportunity it is: a chance to screen women for preexisting CVD and for risk assessment for development of disease. The prediabetic or metabolic syndrome—presenting patient can easily be identified at this office visit. Clinical history, a baseline electrocardiogram, and testing for fasting lipids and diabetes can make this visit the most important prevention examination in a 50-year-old woman's life.

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Reference:

1. Umetani M, Domoto H, Gormley AK, et al. 27-Hydroxycholesterol is an endogenous SERM that inhibits the cardiovascular effects of estrogen. *Nat Med* 2007;13:1185-1192.

Nurses' Health Study reports on reduction in mortality with smoking cessation

Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and smoking cessation in relation to mortality in women. *JAMA* 2008;299:2037-2047. **Level of evidence: II-1.**

Most of the excess risk of death from vascular diseases in women diminishes within 5 years of quitting cigarette smoking, while excess risk of death from lung diseases diminishes after 20 years of quitting, reports the prospective, observational Nurses' Health Study (NHS), which followed a cohort of 104,519 women since 1980, concluding follow-up for this study in 2004. This study aimed to assess the relationship between cigarette smoking and smoking cessation on total and cause-specific mortality in women. The main outcome measures were hazard ratios (HRs) for total mortality, and mortality from vascular and respiratory diseases, lung cancer, other cancers, and other causes.

Participants reported whether they smoked or had ever smoked, how much they smoked, and ages at beginning and quitting smoking. Deaths were reported by families or were identified by searching the National Death Index. Deaths were grouped in broad categories of vascular disease, respiratory diseases, lung cancer, all smoking-related cancers (from the 2004 Surgeon General's report), other cancers, and other causes.

A total of 12,483 deaths occurred in the study cohort: 4,485 (35.9%) among never smokers, 3,602 (28.9%) among current smokers, and 4,396 (35.2%) among past smokers. Compared with never smokers, current smokers had an increased risk of dying from any cause (HR, 2.81; 95% confidence interval [CI], 2.68-29.5), and risk increased significantly with number of cigarettes smoked. Roughly 64% of deaths in current smokers and 28% of deaths in past smokers were attributable to cigarette smoking. In current smokers, 69% of vascular deaths, 90% of respiratory deaths, 95% of lung cancer deaths, and 86% of smoking-related cancer deaths were

attributable to cigarette smoking. The HR for smoking-related cancers was 7.25 (95% CI, 6.43-8.18).

A 13% reduction in risk of all-cause mortality occurred in the first 5 years after quitting, decreasing to the level of a never smoker 20 years after quitting. Risk for vascular diseases diminished rapidly in the first 5 years after quitting; risk for death from lung diseases decreased to that of one who never smoked after 20 years. For lung cancer, a 21% reduction in risk occurred within the first 5 years, but excess risk did not disappear for 30 years.

Comment. With over 20,000 women followed for over 20 years, the NHS stands as a benchmark in health research. Overall, this powerful study gives insight into many healthcare topics including smoking-related health issues. Kenfield and colleagues used this prospective study to further define smoking-related mortality and the effects of smoking cessation in women. The investigators confirmed our knowledge that current and former smokers have higher rates of mortality than never smokers. In particular, besides the usual suspects of known smoking-related cancers (an amazingly high risk for lung cancer, 8-14 times higher risk for smokers), heart disease, and lung disease, the study demonstrated that colon cancer mortality was increased in current and former smokers. We can now add colon cancer to the list of smoking-related cancers. Thus, the risk of colon cancer is another reason to quit smoking.

Some smokers would say, "What is the harm? I don't smoke that much." The findings suggest that even light smokers (a few cigarettes per day) have increased risk of death, particularly due to heart disease, compared to nonsmokers. For heart disease, the risk did not rise with amount smoked as dramatically as it did for diseases such as chronic obstructive pulmonary disease (COPD). The increase in risk of death from respiratory disease correlated with an increase in the number of cigarettes smoked per

day. Women should conclude that any amount of smoking is bad.

Smoking cessation does make a difference. The researchers found that smoking cessation decreased the risk of mortality from each disease studied. With 20 to 30 years of smoking cessation, smokers who have quit can decrease their risk of death due to COPD and lung cancer to near that of a never smoker. In the past, the standard dogma was that a previous smoker's risk never returned to that of a never smoker. This research gives even more credence to the fact that smoking cessation is one of the most important interventions for living a healthy life.

Clearly, as a nation, smoking-related disease research and smoking cessation programs should be the top priority of our public health policy. I believe that better programs must be developed to increase the awareness of the health hazards of smoking. We also must focus education efforts on school-age children because the initiation of smoking can occur at a very early age—about a quarter of high school students report currently smoking. If we do not strive to make a difference, we will be witnesses to a worsening epidemic of smoking-related illnesses.

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Anovulation and hormonal cycle highly variable, anovulatory cycle not predictive of hot flashes

Skurnick JH, Weiss G, Goldsmith LT, Santoro N, Crawford S. Longitudinal changes in hypothalamic and ovarian function in perimenopausal women with anovulatory cycles: Relationship with vasomotor symptoms. *Fertil Steril* 2008 [Epub ahead of print].

Level of evidence: II-1.

In anovulatory perimenopausal women, instead of a predictable hormonal progression through different cycle types to menopause, the loss of ovarian function and pituitary and hypothalamic

feedback is a highly variable process in which cycle patterns can differ from year to year and ovulation can recur. In addition, a woman's anovulatory cycle is not predictive of the occurrence of vasomotor symptoms.

Anovulatory women in the Daily Hormone Study (n = 159), a substudy of the Study of Women's Health Across the Nation, were studied at three visits for their cycle patterns and vasomotor symptoms over 2 years. Mean ages at visit one was 49 ± 2.6 years; at visit two, 50 ± 2.6 years; and at visit three, 51 ± 2.6 years. The objective was to determine whether the progression to menopause follows a predictable hormonal course through the three anovulatory cycle types and whether this correlates with vasomotor symptoms. The three cycle types are: type 1, estrogen rise with luteinizing hormone (LH) surge/anovulation; type 2, estrogen rise without LH surge/anovulation; and type 3, absence of the estrogen rise and LH surge/anovulation. Daily urinary follicle-stimulating hormone, LH, estrogen, and P metabolites were measured through one cycle or 50 days. A daily diary of vasomotor symptoms was kept by the women through the cycle as well, and this same protocol was employed at each yearly visit.

The progression to menopause is not an unremitting, progressive course through the three cycle types, the study found. A woman in any of the three anovulatory patterns can revert to any other pattern or back to ovulation. In addition, anovulation does not predict menopause within 2 years. Vasomotor symptoms did not clearly correlate with anovulatory cycle type. The strongest predictor of vasomotor symptoms was having had symptoms at a prior visit.

Comment. Vasomotor symptoms are the most common complaint in perimenopausal women. Their etiology has been attributed to decreasing estrogen levels; hence the popularity of hormone therapy (HT).

However, we are learning more about the role

of estrogen in menopause-related symptoms. While hypoestrogenism results in vaginal atrophy and is reversed with vaginal HT, Skurnick et al show that vasomotor symptoms in perimenopause are not necessarily associated with estrogen levels. Women with elevated levels of estrogen (type 2 cycles) also reported vasomotor symptoms. This is very important, because many of these women will probably seek medical treatment for their symptoms. Should they use HT, or other therapies such as SSRIs? Would patients with type 2 cycles be at increased risk for complications such as breast cancer and thromboembolic events?

Skurnick et al also point out the fluctuations of ovulatory and nonovulatory cycles during perimenopause. Hence, patients should be counseled on the need for continued contraception throughout perimenopause, as long as needed.

Many more questions still need to be investigated regarding the hypothalamic and central nervous system involvement in menopause.

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Editor's picks: Highlights from the July-August 2008 issue of *Menopause*

NAMS is pleased to spotlight the most recent issue of the Society's official journal, *Menopause*—selected by its Editor-in-Chief, Dr. Isaac Schiff. The complete contents and more about the journal can be found on the NAMS Web site (www.menopause.org).

Moriyama CK, Oneda B, Bernardo FR, et al. A randomized, placebo-controlled trial of the effects of physical exercises and estrogen therapy on health-related quality of life in postmenopausal women. *Menopause* 2008;15:613-618.

This 6-month double-blind, randomized, placebo-controlled trial shows that physical exercise can reduce menopausal symptoms and enhance health-related quality of life among women who had a hysterectomy, independent of taking or not taking hormone therapy.

◆
Perry CD, Alekel DL, Ritland LM, et al. Centrally located body fat is related to inflammatory markers in healthy postmenopausal women. *Menopause* 2008;15:619-627.

The purpose of this multicenter study was to identify whether centrally located fat and/or overall adiposity were related to C-reactive protein, fibrinogen, tumor necrosis factor α , interleukin-6, and interleukin-1 β in healthy postmenopausal women.

◆
Mahady GB, Low Dog T, Barrett ML, et al. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause* 2008;15:628-638.

The article presents the US Pharmacopeia Dietary Supplements Information Expert Committee safety review of black cohosh. The committee proposed a cautionary label statement for US Pharmacopeia black cohosh dietary supplement monographs.

◆
The North American Menopause Society. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause* 2008;15:584-602.

The North American Menopause Society has made significant additions and modifications to its 2007 position statement. An addendum to explain and teach the concepts of risk is included.

◆
Vogel VG, Guest Editor. Managing the risk of breast cancer in postmenopausal women. *Menopause* 2008;15(Pt 2 of 2):777-816.

Written by eight specialists in women's health and cancer, these articles aim to support clinicians who care for adult women, some of whom might be at increased risk for breast cancer and need advice about interventions, where appropriate, to decrease the likelihood that they will develop an invasive breast cancer in their lifetimes.

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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