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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 and healthy aging. Each review has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Chrisandra L. Shufelt, MD, MS, NCMP, Chair-elect of the 2012-2013 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Shufelt.

Aspirin not associated with postmenopausal breast cancer

Zhang X, Smith-Warner SA, Collins LC, et al. Use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen and postmenopausal breast cancer incidence. *J Clin Oncol* 30:3468-3477. **Level of evidence: II-3.**

Summary. This study examined the association between breast cancer and analgesic use in 84,602 postmenopausal women from 1980 to 2008. The women were cancer free at the beginning of the study. Researchers used biennial questionnaires to collect data on their use of aspirin, NSAIDs, and acetaminophen, as well as on their reproductive history and other lifestyle factors. Proportional hazards models were used to estimate multivariable RRs and 95% CIs.

A total of 4,734 cases of incident invasive breast cancer were documented. Compared with no use of aspirin, multivariable RRs of regular aspirin use (≥2 tablets/wk) for more than 20 years were 0.91 for overall breast cancer (95% CI, 0.81 to 1.01; P_{trend} = 0.16), 0.90 for ER+/PR+ breast cancer (95% CI, 0.77 to 1.06; P_{trend} = 0.17), and 0.91 for ER–/PR– breast cancer (95% CI, 0.68 to 1.22; P_{trend} = 0.97).

The results showed that neither timing of usage nor dosage affected results; NSAID and acetaminophen use did not significantly affect breast cancer risk, nor did higher doses of each analgesic (≥6 tablets/wk) for more than 10 years. As well, no substantial associations were noted for breast cancer molecular subtypes. The study thus concluded that aspirin, other NSAIDs, and acetaminophen are not importantly associated with risk of postmenopausal breast cancer, either overall or by specific subtype.

Commentary. Inflammation is related to two modern scourges: cardiovascular disease (CVD) and cancer. Both conditions are more prevalent in the fattest and most sedentary societies. Because inflammation from obesity plays a role in both CVD and some cancers, such as breast cancer, it stands to reason that pharmacologically interrupting the inflammatory pathway may have antineoplastic effects. The recent discovery of an inflammatory-mediated process in adipose tissue of the breast[1] further fuels this hypothesis.

I am sure that your patients, like mine, have frequently inquired if they "should take aspirin to reduce cancer because Dr. Oz says I should!"[2]: "By taking two aspirin or ibuprofen a week, you'll reduce your chance of breast cancer between 21% and 28%. The anti-inflammatory properties in these drugs are also excellent for heart health."

However, this current large study of over 4,700 cases of incident invasive breast cancer by Zhang et al concludes that aspirin, NSAIDs, and acetaminophen are *not* importantly associated with the risk of postmenopausal breast cancer. So what is important? It is important to counsel our patients on lifestyle interventions to reduce inflammation and reduce the panoply of adverse health events they take part in by getting regular exercise, avoiding weight gain, stopping smoking, moderating alcohol, eating a heart-healthy Mediterranean diet, avoiding trans fats, and ingesting adequate amounts of vitamin D3 (a pro-sterol hormone).

Furthermore, for patients interested in pharmacologically reducing their risk for being diagnosed with an ER+ breast cancer, the clinician should discuss the two FDA-approved pharmacologic agents proven to reduce the diagnosis of ER+ breast cancer: tamoxifen and raloxifene. These are underused agents.[3] In addition, women at very high risk for breast cancer—with identified *BRCA* mutations, lobular carcinoma in situ, or strong family histories for breast/ovarian cancers—should be advised about the options of risk-reducing bilateral mastectomy (with or without reconstruction) and/or risk-reducing bilateral oophorectomy after age 40.

Finally, we as clinicians need to completely discourage the inappropriate hand-wringing related to our patients' erroneous and exaggerated concerns that estrogen use in hysterectomized women causes breast cancer.

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Nulliparity does not modify endometrial cancer risk

Schonfeld SJ, Hartge P, Pfeiffer, RM, et al. An aggregated analysis of hormonal factors and endometrial cancer risk by parity. *Cancer* 2012 Dec 20. doi: 10.1002/cncr.27909. [Epub ahead of print] **Level of evidence: III.**

Summary. It is clear that nulliparity is associated with an increased risk of endometrial cancer. It is less clear whether nulliparity modifies the association between other established hormone-related risk factors. Although the proportion of nulliparous women has increased since the mid-1970s, studies to date have been too small to test the hypothesis that endometrial cancer risk factors are more common in nulliparous women than parous women.

Schonfeld et al conducted a large, pooled analysis of data aggregated on 26,936 postmenopausal, Caucasian, nulliparous women (360 endometrial cancers) and 146,583 postmenopausal, Caucasian, parous women (1,378 endometrial cancers) from four US prospective studies (1979-2006). HRs and 95% CIs were estimated in stratified analyses. Endometrial cancer was higher among nulliparous women, as expected (nulliparous vs parous: HR, 1.42; 95% CI, 1.26-1.60). Stratified associations between endometrial cancer and hormone-related risk factors did not differ between nulliparous versus parous women: For both groups, oral contraceptives and earlier menopause were associated with reduced risk. The highest HRs were for obesity; a BMI of 30 kg/m^2 (vs <25 kg/m^2) increased the risk of

endometrial cancer threefold among nulliparous women (HR, 3.04; 95% CI, 2.34-3.94) and parous women (HR, 2.88; 95% CI, 2.52-3.29).

The authors concluded that nulliparity does not modify risks of endometrial cancer associated with established hormone-related risk factors.

Commentary. The important finding of this study was that nulliparous patients had a statistically significant 41% increased HR of developing endometrial cancer regardless of other factors such as BMI, menopausal HT use, or oral contraceptive use. The mechanism by which parity may decrease risk is not fully understood but several hypotheses exist. One thought is that elevated progesterone levels during pregnancy may inhibit estrogen-driven endometrial cellular proliferation. In turn, this likely promotes the differentiation and apoptosis of endometrial cells.[1] Another thought is that vaginal delivery itself or perhaps postpartum involution of the uterus has an effect on the endometrial lining of the uterus, which may already contain hyperplastic or malignant cells.[2] A final possibility is that some nulliparous patients are infertile because of chronic anovulatory disorders, and the longer periods of unopposed estrogen they experience may contribute to higher endometrial cancer rates.[3]

The strength of Schonfeld et al is that it combines 4 large prospective trials that included a huge number of patients and cancers. A limitation is that although the women were part of prospective trials, ascertainment of malignancy relied on retrospective self-report, retrieval of medical and pathology reports, linkage with state cancer registries and the National Death Index to identify the cancers. Histologic type was only available for 50% of the cancers and the authors commented that "most were endometrioid adenocarcinomas." This is important because the traditional teaching that nulliparity is a greater risk factor for endometrial cancer is tied to this cell type, which accounts for 80% to 85% of uterine cancers.

The conclusion is also of great clinical importance currently because the incidence of nulliparity among US women in their 40s has doubled in the last 30 years from 10% in the mid-1970s to 18% in 2008.[4]

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Aspirin & VTE

Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, Gibbs H, Hague W, Xavier D, Diaz R, Kirby A, Simes J; ASPIRE Investigators. Low-dose aspirin for preventing recurrent venous thrombo-embolism. *N Engl J Med* 2012;367:1979-1987. **Level of evidence: I.**

Summary. Is aspirin effective in preventing a recurrence of venous thromboembolism (VTE) in patients with a first episode of unprovoked VTE? A total of 822 patients who had completed initial anticoagulant therapy after a first episode of unprovoked VTE received aspirin (100 mg/d) or placebo for up to 4 years, with a primary outcome of recurrence of VTE.

During follow-up, VTE recurred in 73 of 411 placebo patients and in 57 of 411 aspirin patients (HR with aspirin, 0.74; 95% CI, 0.52 to 1.05; $P = 0.09$). Aspirin reduced the rate of two secondary composite outcomes: by 34%, it reduced VTE, myocardial infarction (MI), stroke, or cardiovascular death; and by 33%,

aspirin reduced the rate of VTE, MI, stroke, major bleeding, or death from any cause.

Aspirin did not significantly reduce the rate of recurrence of VTE but did result in a significant reduction in the rate of major vascular events, with improved net clinical benefit, echoing earlier studies finding a therapeutic benefit of aspirin administered after anticoagulant therapy for a first episode of unprovoked VTE.

Comment. VTE, encompassing both deep vein thrombosis and pulmonary embolism, is common and occurs at an annual rate of 2 to 3 cases per 1,000 persons in the general population.[1] In patients whose VTE presents in the setting of surgery, trauma, or pregnancy (a "provoked" VTE), the risk of recurrence following at least 3 months of anticoagulant therapy is approximately 1% per year. The risk of recurrent VTE in patients with "unprovoked" or spontaneous thromboembolism is much greater, with a 10% annual recurrence rate once anticoagulant therapy is discontinued. The decreased risk of VTE recurrence associated with prolonged anticoagulant therapy, often recommended in this population, must be balanced against the increased risk of bleeding and patient inconvenience.

For nearly two decades, the potential of aspirin (ASA) to reduce initial risk of VTE has been recognized. This benefit was confirmed in 2000 in a clinical trial of patients undergoing surgery for hip fracture and elective arthroscopy.[2] That ASA therapy prevents MI and stroke in high-risk patients is also well accepted, and has recently been reviewed as specifically pertains to women.[3]

This current study, the ASPIRE (Aspirin to Prevent Recurrent Venous Thromboembolism) placebo-controlled randomized clinical trial examined whether several years of low-dose (100 mg/day) aspirin (ASA) therapy reduced recurrent VTE in patients with a history of unprovoked VTE who had already completed a course of anticoagulant therapy. The trial did not demonstrate a significant reduction in recurrent VTE with aspirin therapy, although the secondary composite outcome of major vascular events that included VTE, MI, stroke, or cardiovascular death was reduced by 34% without an increase in bleeding.

As prospectively planned, the ASPIRE trial results were then combined with an earlier trial of ASA therapy (the Warfarin and Aspirin (WARFASA) study, which had shown ASA to be effective in reducing recurrent VTE in persons with a history of unprovoked VTE.[4] When the data from the two trials were evaluated in a meta-analysis, low-dose ASA therapy was shown to significantly reduce both recurrent VTE and arterial events such as MI and stroke.

Several take-home messages stand out from these trials. First, risk of recurrence of an unprovoked VTE is much higher than a provoked VTE, and thus careful identification of patients with unprovoked VTE and consideration of prolonged anticoagulant therapy is indicated. Second, transitioning to ASA therapy following a recommended course of anticoagulant therapy may reduce recurrent VTE as well as CVD events in this potentially high-risk population. Third, these findings do not apply to prevention or management of VTE in women taking hormone therapy (HT). In these two trials of low-dose ASA therapy, the percentage of female subjects ranged from 35% to 45%; the average age was between 55 and 62 years. Women were carefully questioned to ensure that *none* of those enrolled and considered to have an unprovoked VTE had used HT within the last 2 months.

A prospective, randomized trial to formally evaluate the effects of HT, ASA, and statin therapy on VTE incidence in healthy, recently postmenopausal women would be of practical importance to inform management decisions. Results of trials to date have been contradictory. In the Heart and Estrogen-Progestin Replacement Study (HERS), women taking

either ASA or statin therapy at baseline had a 50% lower risk of VTE than women not reporting use of these drugs.[5] The women in the HERS trial all had confirmed coronary heart disease at baseline, and the use of ASA and statin therapy was initiated by their personal clinicians for secondary prevention of CVD. Results from the Women's Health Initiative trials of both unopposed estrogen and combined HT did not support the use of aspirin or statin therapy to prevent VTE among healthy women receiving HT.[6]

In summary, as measures to reduce healthcare costs continue to be emphasized, the ASPIRE and WARFASA trials in patients with unprovoked VTE reinforce the effectiveness of low-cost, readily available, and extensively characterized ASA therapy (following an initial course of anticoagulation) for reducing both venous and arterial thromboses in these high-risk patients.

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Extending the Screening Power of the Pap Smear?

Kinde I et al. Evaluation of DNA from the Papanicolaou test to detect ovarian and endometrial cancers. *Sci Transl Med* 2013 Jan 9; 5:167ra4.

Summary. Widespread deployment of Papanicolaou (Pap) smears, arguably the most successful cancer-screening program ever implemented, has resulted in a dramatic drop in cervical cancer incidence and mortality. Samples obtained during cervical cancer screening are often also assessed for human papillomavirus DNA. To determine whether genetic material included in such samples might enable effective screening for endometrial and ovarian malignancies, investigators used whole-exome sequencing to search Pap smear specimens for mutations known to be associated with gynecologic cancers. With massively parallel DNA-sequencing technology, they identified at least one of these mutations in Pap specimens from 100% of 24 women with endometrial cancer and 41% of 22 women with ovarian cancer.

Based on these observations, the investigators developed a sequence-based approach to screen Pap specimens from the general population for a panel of mutations in 12 genes. When they analyzed specimens from 12 women with endometrial cancer, 2 with ovarian cancer, and 14 with no cancer, mutations were detected in all 14 women with gynecologic cancers and in none of the cancer-free women.

Comment. The recent recognition that human cancers result from mutations in a limited set of genes suggests the possibility of developing new diagnostic tests for cancer. Vaginal ultrasound and cytologic analysis of cervical cells have both failed for endometrial cancer screening.[1] Vaginal ultrasound plus CA 125 assessment

shows promise in screening for ovarian cancer in high-risk mutation carriers,[2] but has not proved effective for broader screening.[3] Although the present findings are probably years away from clinical implementation, they suggest that the power of the Pap smear may extend beyond cervical cancer screening.

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Menopause Editor's picks from January 2013

NAMS spotlights selections from the most recent issue of the Society's official journal, *Menopause*, chosen by its Editor-in-Chief, Dr. Isaac Schiff.

Progression rates of carotid intima-media thickness and adventitial diameter during the menopausal transition. Samar R. El Khoudary, PhD, MPH, Rachel P. Wildman, PhD, MPH, Karen Matthews, PhD, Rebecca C. Thurston, PhD, Joyce T. Bromberger, PhD, and Kim Sutton-Tyrrell, DrPH.
Independent of age at baseline and race, progression rates of intma-media thickness and adventitial diameter were significantly greater in late perimenopausal women compared with premenopausal women. This suggests that the perimenopausal stage could be the point at which the most dramatic vascular changes occur and therefore should be the target for risk reduction strategies in postmenopausal women.

♦

Understanding discontinuation of oral adjuvant endocrine therapy by women with hormone receptor-positive invasive breast cancer nearly 4 years from diagnosis Robin J. Bell, MB, BS, PhD, MPH, FAFPHM, Pamela Fradkin, MBBS, Max Schwarz, MB, BS, FRACP, FACP, FAChPM, and Susan R. Davis, MB, BS, PhD, FRACP.
In this study of use of oral adjuvant endocrine therapy in a large cohort of women with their first episode of hormone receptor positive invasive breast cancer, nearly four years from diagnosis, approximately one in five women were not on treatment. Although discontinuation due to side effects remains an important issue, nearly half the women not on treatment at this time had never commenced oral adjuvant endocrine therapy.

♦

Midlife women: symptoms associated with menopausal transition and early postmenopause and quality of life. Catherine A. Greenblum, PhD, FNP-BC, ARNP, Meredeth A. Rowe, PhD, RN, FAAN, Donna Felber Neff, PhD, RN, and Jesse S. Greenblum, MD, MS, FACOG.
In this study the symptoms found to most significantly affect quality of life were sleep disturbance, fatigue, and anxiety suggesting appropriate management of these symptoms may be beneficial to women undergoing the transition to postmenopause.

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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