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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).

Marked decline in breast cancer risk after stopping EPT

Chlebowski RT, Kuller LH, Prentice RL, et al, for the WHI Investigators. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med* 2009;360:573-587. **Level of evidence: I.**

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BACKGROUND: Following the release of the 2002 report of the Women's Health Initiative (WHI) trial of estrogen plus progestin, the use of menopausal hormone therapy in the United States decreased substantially. Subsequently, the incidence of breast cancer also dropped, suggesting a cause-and-effect relation between hormone treatment and breast cancer. However, the cause of this decrease remains controversial. **METHODS:** We analyzed the results of the WHI randomized clinical trial—in which one study group received 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate daily and another group received placebo—and examined temporal trends in breast-cancer diagnoses in the WHI observational-study cohort. Risk factors for breast cancer, frequency of mammography, and time-specific incidence of breast cancer were assessed in relation to combined hormone use. **RESULTS:** In the clinical trial, there were fewer breast-cancer diagnoses in the group receiving estrogen plus progestin than in the placebo group

in the initial 2 years of the study, but the number of diagnoses increased over the course of the 5.6-year intervention period. The elevated risk decreased rapidly after both groups stopped taking the study pills, despite a similar frequency of mammography. In the observational study, the incidence of breast cancer was initially about two times as high in the group receiving menopausal hormones as in the placebo group, but this difference in incidence decreased rapidly in about 2 years, coinciding with year-to-year reductions in combined hormone use. During this period, differences in the frequency of mammography between the two groups were unchanged. **CONCLUSIONS:** The increased risk of breast cancer associated with the use of estrogen plus progestin declined markedly soon after discontinuation of combined hormone therapy and was unrelated to changes in frequency of mammography.

Comment #1. This report from the WHI is not the first about the change in breast cancer prevalence that occurred after the initial WHI publications in 2002, but it is of value because it documents that the change cannot be attributed solely to a decrease in the use of mammography.

Puzzling questions remain: Why was not a similar change in prevalence observed in some

countries that experienced the same decline in estrogen and progestin therapy (EPT) use after 2002, and why did the decline in breast cancer prevalence actually begin before 2002? In my view, the failure to find a decrease in some populations is probably secondary to method problems, and the decrease that began before 2002 correlates with a decline in the use of mammography. The decrease after 2002 has been observed in women in whom screening mammography was unchanged, and there are sufficient numbers of consistent reports to conclude that breast cancer prevalence decreased since 2002, reflecting mainly a decrease in estrogen receptor-positive tumors, and mirroring the decrease in use of EPT. In the most recent update of the Surveillance, Epidemiology and End Results data, a significant 3% decrease in the rate of breast cancer occurred in the period from 2001 to 2005.¹

The discussion in this WHI report is balanced and ends with a reasonable conclusion. The same cannot be said about the articles that appeared in US newspapers based on the WHI press release that followed the oral presentation of the data at the San Antonio Breast Cancer Symposium on December 13, 2008. The articles announced that hormone use for 5 years doubles the risk of breast cancer, and highlighted the “dangers” of this treatment. The senior author, Ronald Chlebowski, was quoted as saying about whether or not to start EPT treatment: “It does change the balance.” There was no attempt to translate the numbers into actual cases, the attributable risk, and the implication was firm: EPT causes breast cancer.

But these data do not prove causality. There is nothing new in this report that would change clinical practice. An appropriate interpretation to convey to patients is that EPT may not increase or decrease the incidence of breast cancer; rather, the rapid changes in incidence may be due to changes in the prevalence of diagnosis.

The unanswered question remains: Does EPT cause an increase in breast cancer or do the epidemiologic data reflect an impact of EPT on

preexisting tumors? The most striking feature of these recent reports is the short latent period between discontinuation of EPT and a reduction in prevalence. This is consistent with the uniform findings in all studies of an increase in breast cancer risk only in current users, with a rapid reduction after cessation of treatment. These effects of EPT are in keeping with the multiple reports of better outcomes in EPT users diagnosed with breast cancer because of better-differentiated tumors, explained as an impact on preexisting tumors. The rapidity of hormonal effects documented in epidemiologic data only makes sense, it seems to me, by linking EPT to preexisting tumors. If EPT is affecting preexisting tumors, one would expect small and undetectable tumors to stop changing (at least temporarily) when women discontinue EPT (and thus be below the detection limit). If this is the case, it raises a very important question of great concern.

How many of these preexisting tumors will cease growing? How many will be cured by defense mechanisms? How many will emerge later at a greater stage and grade of disease with worse outcomes? Only time will tell, but it is possible that a delay in diagnosis may turn out to be another harmful effect of the publicity associated with the WHI.

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References:

1. Surveillance Epidemiology and End Results. Trends in Breast Cancer Rates. Available at: <http://seer.cancer.gov/statfacts/html/breast.html>. Accessed February 5, 2009.

Comment #2. The WHI recently updated results on breast cancer risk after discontinuation of the combination EPT arm. Overall results were published for the post-intervention phase in 2008.¹ With mean follow-up of 2.4 years for this phase, a nonsignificant increased risk of breast cancer was still observed (HR, 1.27; 95% CI, 0.91-1.78), with a

possible downward trend in cancer risk with follow-up. In contrast, most other large epidemiologic studies have generally not shown an increased risk of breast cancer with past use of hormone therapy (HT), although not all of these studies reported separate results for past users of estrogen alone compared to EPT.^{2,3}

This newest report is a more detailed analysis on breast cancer outcomes and also drew data from the observational cohort of the WHI. HRs for 6-month time intervals were calculated for both the intervention and nonintervention phase of the clinical trial. In an intention-to-treat analysis, there was no difference in the slopes of the HRs over time comparing the intervention and post-intervention phases ($P = 0.28$). However, after adjusting for adherence by censoring nonadherent subjects, there was a statistically significant difference in the slopes with HRs increasing over time for women using EPT, but declining after discontinuation ($P = 0.005$). Although breast cancer cases appeared to decline more in the intervention arm compared to placebo, mammography rates were similar in both arms. During the postintervention phase, both breast biopsies and mammograms with abnormalities were more common in the EPT arm compared to placebo. Similar results for breast cancer incidence rates were seen using the observational data, although mammography rates were higher among women who used HT compared to those who did not.

After the WHI results were released in 2002, there was a large decline in HT use in the United States.⁴ Several investigators then reported a decline in US breast cancer rates correlating with reporting of the WHI trial results.⁵ Given the temporal association, it was speculated that this decrease in breast cancer incidence may have been due to the widespread discontinuation of HT, although other investigators noted that there was also a concomitant decline in mammography utilization, which may also have explained the changes.⁶ However, mammography rates were similar in the intervention arms of the WHI trial and were stable over time for women in the observational study, so it would seem unlikely

that changes in mammography utilization alone can explain the recent decline in US breast cancer rates. Others have also commented that the rapid rate of decline in breast cancer rates with discontinuation may not be biologically plausible, because breast cancers normally take several years to develop and the increased incidence of breast cancer with HT is only seen with longer-term use. It is possible, however, that removal of EPT could rapidly influence hormone-sensitive tumor growth in much the same ways that tamoxifen and aromatase inhibitors can cause tumor regression in women with metastatic breast cancer after only a few months of treatment.

Since the postintervention phase of the WHI arm has only 2.4 years of follow-up, the results are still too preliminary to know the true time course for changes in breast cancer risk. In addition, changes in time trends were only statistically significant after adjustment for adherence. Adjustment for adherence is not routinely done for randomized trials, since this may violate the original randomization scheme and is contrary to the routine intention-to-treat analyses. Finally, it should be noted that these results would apply only to women taking EPT. The WHI did not observe an increased risk of breast cancer in the unopposed estrogen arm after mean follow-up of 6.8 years.⁷

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References:

1. Heiss G, Wallace R, Anderson GL, et al, for the WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036-1045.
2. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047-1059. [Erratum in: *Lancet* 1997;350:1484]
3. Beral V, for the Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the

- Million Women Study. *Lancet* 2003;362:419-427.
4. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA* 2004;291:47-53.
 5. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007;356:1670-1674.
 6. Ponti A, Rosso S, Zanetti R, Ricceri F, Tomatis M, Segnan N. Re: Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 2007;99:1817-1818; author reply 1819.
 7. Anderson GL, Limacher M, Assaf AR, et al, for the Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-1712.

Two WHIMS papers show HT does not increase cerebrovascular disease but shrinks brain volume

Coker LH, Hogan PE, Bryan NR, et al. Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. *Neurology* 2009;72:125-134.

Level of evidence: I.

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OBJECTIVE: The Women's Health Initiative Memory Study (WHIMS) hormone therapy (HT) trials reported that conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA) increases risk for all-cause dementia and global cognitive decline. WHIMS MRI measured subclinical cerebrovascular disease as a possible mechanism to explain cognitive decline reported in WHIMS. **METHODS:** We contacted 2,345 women at 14 WHIMS sites; scans were completed on 1,424 (61%) and 1,403 were accepted for analysis. The primary outcome measure was total ischemic lesion volume on brain MRI. Mean duration of on-trial HT or placebo was 4 (CEE+MPA) or 5.6 years (CEE-Alone) and scans were conducted an average of 3 (CEE+MPA) or 1.4 years (CEE-Alone) post-trial termination. Cross-sectional analysis of MRI lesions was conducted; general linear models were fitted to assess treatment group differences using analysis of covariance. A (two-tailed) critical value of $\alpha = 0.05$ was used. **RESULTS:** In women evenly matched

within trials at baseline, increased lesion volumes were significantly related to age, smoking, history of cardiovascular disease, hypertension, lower post-trial global cognition scores, and increased incident cases of on- or post-trial mild cognitive impairment or probable dementia. Mean ischemic lesion volumes were slightly larger for the CEE+MPA group vs placebo, except for the basal ganglia, but the differences were not significant. Women assigned to CEE-Alone had similar mean ischemic lesion volumes compared to placebo. **CONCLUSIONS:** Conjugated equine estrogen-based hormone therapy was not associated with a significant increase in ischemic brain lesion volume relative to placebo. This finding was consistent within each trial and in pooled analyses across trials.

Resnick SM, Espeland MA, Jaramillo SA, et al. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. *Neurology* 2009; 72:135-142. **Level of evidence: I.**

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OBJECTIVES: To determine whether menopausal hormone therapy (HT) affects regional brain volumes, including hippocampal and frontal regions. **METHODS:** Brain MRI scans were obtained in a subset of 1,403 women aged 71-89 years who participated in the Women's Health Initiative Memory Study (WHIMS). WHIMS was an ancillary study to the Women's Health Initiative, which consisted of two randomized, placebo-controlled trials: 0.625 mg conjugated equine estrogens (CEE) with or without 2.5 mg medroxyprogesterone acetate (MPA) in one daily tablet. Scans were performed, on average, 3.0 years post-trial for the CEE + MPA trial and 1.4 years post-trial for the CEE-Alone trial; average on-trial follow-up intervals were 4.0 years for CEE + MPA and 5.6 years for CEE-Alone. Total brain, ventricular, hippocampal, and frontal lobe volumes, adjusted for age, clinic site, estimated intracranial volume, and dementia risk factors, were the main outcome variables. **RESULTS:** Compared with placebo, covariate-adjusted mean frontal lobe volume was 2.37

cm³ lower among women assigned to HT ($p = 0.004$), mean hippocampal volume was slightly (0.10 cm^3) lower ($p = 0.05$), and differences in total brain volume approached significance ($p = 0.07$). Results were similar for CEE + MPA and CEE-Alone. HT-associated reductions in hippocampal volumes were greatest in women with the lowest baseline Modified Mini-Mental State Examination scores (scores <90). CONCLUSIONS: Conjugated equine estrogens with or without MPA are associated with greater brain atrophy among women aged 65 years and older; however, the adverse effects are most evident in women experiencing cognitive deficits before initiating hormone therapy.

Comment #1. The mechanism by which hormone therapy (HT) increased dementia risk and cognitive decline in older women in WHIMS was believed by many to be due to vascular disease. HT increased the risk of stroke in the WHI, and subclinical vascular disease is a risk factor for dementia. Two new reports from the WHIMS-MRI study dispel that notion, and instead link the WHIMS findings to loss of brain volume, especially in the frontal cortex. Particularly interesting were results from subanalyses that showed that brain volume varied with the magnitude of ischemic lesion volume and with pretreatment cognitive status; women with little evidence of cerebrovascular disease and normal cognitive function did not show the brain volume loss. Both of these subanalyses are consistent with Brinton's "healthy cell bias of estrogen,"¹ which suggests that estrogen exerts protective effects on healthy cells but negative effects on unhealthy cells.

What do these findings mean for the clinician? First, the new findings shed important new light on why women should not initiate conjugated estrogens (CE) plus MPA or CE alone after age 65. Although HT will not increase the risk for subclinical cerebrovascular disease, it will shrink brain volumes in the frontal lobe. Note that both new studies measured the impact of long duration HT in elderly women who had discontinued treatment. Therefore, these negative effects on brain volume are evident even after dis-

continuation of therapy. Second, the relevance of these new findings for younger postmenopausal women or older long-term users of HT are not known. Most current users of HT are either perimenopausal or young postmenopausal women who recently initiated HT for vasomotor symptoms or are older postmenopausal women who are long-term users of HT.

A number of studies have investigated brain volume in samples that more closely represent the typical HT user. Those studies are smaller in scale than the WHIMS-MRI study, but they generally suggest that HT helps to maintain brain volume, or at minimum does not lead to brain volume loss. On the other hand, there is evidence that CE plus MPA decreases performance on a memory task that is dependent on the hippocampus, even when used by healthy younger postmenopausal women. Further investigations are needed. Third, the new findings reinforce the need for additional studies on how the health status of women and their age in relation to menopause might alter the impact of HT on cognition and brain function.

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Reference:
1. Brinton RD. The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. *Trends in Neurosciences* 2008;31:529-537.

Comment #2. Of the 16,608 women involved in the WHI, 4,532 women ages 65 to 79 and free of probable dementia were also recruited to WHIMS. Although the early termination of the WHI shortened the planned observation in WHIMS, 108 women developed dementia.

The later WHIMS-MRI study was initiated to obtain brain imaging information that might explain the mechanism of cognitive decline in HT recipients. The investigators carefully measured abnormalities in the white matter of

the brain that are attributed to vascular injury, fully expecting to find an increased burden of ischemic lesions in the women who had been assigned to HT. As would be expected, ischemic lesion volume was associated with increased age and stroke risk factors such as smoking and cardiovascular disease. Ischemic lesion volume was also associated with new diagnoses of cognitive impairment and dementia, thus supporting the role of vascular disease in the development of cognitive decline. However, to the investigators' surprise, there were no significant differences in the burden of ischemic lesions among the HT groups to suggest that HT played a significant causative role.

The investigators also made careful measurements of brain volume as brain shrinkage over time has been associated with cognitive decline. Although the overall measurements of brain volume were not significantly different among HT groups, there were some differences seen when measuring specific regions of the brain. For example, the volume of the frontal lobes was significantly smaller in women assigned to HT. The frontal lobes are the seat of our executive thinking and planning, and as such are important determinants of our cognitive function. Also, the hippocampus, part of the "memory bank," was modestly smaller in women assigned to HT, but this was most prominent for those women who had the lowest cognitive screening scores at baseline. This observation suggests that the women with lower cognitive scores at baseline already had the beginnings of dementia when they entered the study.

Although the WHIMS-MRI data do not explain the mechanism of increased cognitive decline with HT, they enforce the importance of vascular risk factors in the development of white matter injury as evident on MRI and the presence of cognitive impairment. Because women who chose to participate in the WHIMS-MRI study were younger and fewer years postmenopause, with higher baseline cognitive scores, the findings could have been more prominent if the older women had participated. Since baseline imaging was not obtained, the time course of

progression of hippocampal volume loss could not be calculated, thus it is not possible to determine whether HT accelerated this process or not. As the youngest women in the WHI (50-65 y) were not included in the WHIMS study, it is also unknown if these results can be translated to those women.

Postmenopausal HT increases the risk of stroke and is not recommended for the prevention of vascular events or in women who have experienced a stroke. Ischemic lesions can be identified on MRI scans in the absence of a history of stroke. Ischemic lesions are associated with increasing age and the presence of risk factors for vascular disease. As these lesions are linked to the development of cognitive decline and dementia, it is important for women to know their vascular risk factor profile, be treated properly, and have regular follow-up to ensure their long-term control. It is not known whether HT in the early postmenopausal period in young women will have beneficial or detrimental effects and remains under study.

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Denosumab important agent to treat postmenopausal osteoporosis

Miller PD, Bolognese MA, Lewiecki EM, et al, for the Amg Bone Loss Study Group. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008;43:222-229. **Level of evidence: I.**

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INTRODUCTION: Denosumab is a fully human monoclonal antibody that inhibits receptor activator of nuclear factor-kappa B

ligand (RANKL), an essential mediator of osteoclast formation, function, and survival that has been shown to decrease bone turnover and increase bone mineral density (BMD) in treated patients. We assessed the long-term efficacy and safety of denosumab, and the effects of discontinuing and restarting denosumab treatment in postmenopausal women with low bone mass. **METHODS:** Postmenopausal women with a lumbar spine T-score of -1.8 to -4.0 or proximal femur T-score of -1.8 to -3.5 were randomized to denosumab every 3 months (Q3M; 6, 14, or 30 mg) or every 6 months (Q6M; 14, 60, 100, or 210 mg); placebo; or open-label oral alendronate weekly. After 24 months, patients receiving denosumab either continued treatment at 60 mg Q6M for an additional 24 months, discontinued therapy, or discontinued treatment for 12 months then re-initiated denosumab (60 mg Q6M) for 12 months. The placebo cohort was maintained. Alendronate-treated patients discontinued alendronate and were followed. Changes in BMD and bone turnover markers (BTM) as well as safety outcomes were evaluated. **RESULTS:** Overall, 262/412 (64%) patients completed 48 months of study. Continuous, long-term denosumab treatment increased BMD at the lumbar spine (9.4% to 11.8%) and total hip (4.0% to 6.1%). BTM were consistently suppressed over 48 months. Discontinuation of denosumab was associated with a BMD decrease of 6.6% at the lumbar spine and 5.3% at the total hip within the first 12 months of treatment discontinuation. Retreatment with denosumab increased lumbar spine BMD by 9.0% from original baseline values. Levels of BTM increased upon discontinuation and decreased with retreatment. Adverse event rates were similar among treatment groups. **CONCLUSIONS:** In postmenopausal women with low BMD, long-term denosumab treatment led to gains in BMD and reduction of BTM throughout the course of the study. The effects on bone turnover were fully reversible with discontinuation and restored with subsequent retreatment.

Comment. Denosumab will represent a new and important approach to treatment of osteoporosis

in postmenopausal women obtain the approval of the Food and Drug Administration. In a 3-year study,¹ more than 7,800 women with osteoporosis were randomized to receive 60 mg subcutaneous denosumab every 3 months or placebo. In this large and pivotal study, denosumab significantly reduced the risk of vertebral fractures (68% reduction) and hip fractures (40% reduction). The safety profile was observed to be similar to that of placebo.

In the 4-year extension study by Miller et al, treatment with denosumab was associated with robust increases in BMD at the spine and hip. Discontinuation resulted in rapid loss of these BMD gains. Retreatment resulted in rapid regain of BMD, as observed with initial treatment. Treatment with alendronate also resulted in BMD gains at the spine and hip. Discontinuation of this bisphosphonate resulted in modest BMD decreases at the spine over 2 years, and more substantial declines in hip BMD.

As the authors point out, the clinical implications of the decrease in BMD associated with discontinuation of denosumab are unknown. What seems clear, however, is that the impact of denosumab administration on bone metabolism appears fully reversible. In contrast, bisphosphonate administration results in prolonged retention in bone. Only further research and surveillance will clarify any clinical pros and cons of rapid reversibility of denosumab. However, the availability of denosumab offers an important and unique new option for the treatment of osteoporosis in the form of a convenient subcutaneous injection administered every 6 months.

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Reference:
Cummings S, McClung M, Christiansen C, et al. A phase III study of the effects of denosumab on vertebral, non-vertebral, and hip fracture in women with osteoporosis: results from the FREEDOM trial. Presented at the Amer-

ican Society for Bone and Mineral Research Annual Meeting,, Montreal, QC, Canada, September 16, 2008.

Is alcohol consumption associated with atrial fibrillation in women?

Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in women. *JAMA* 2008;300:2489-2496. **Level of evidence: II-2.**

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CONTEXT: Previous studies suggest that consuming moderate to high amounts of alcohol on a regular basis might increase the risk of developing atrial fibrillation in men but not in women. However, these studies were not powered to investigate the association of alcohol consumption and atrial fibrillation among women. **OBJECTIVE:** To prospectively assess the association between regular alcohol consumption and incident atrial fibrillation among women. **DESIGN, SETTING, AND PARTICIPANTS:** Participants were 34 715 initially healthy women participating in the Women's Health Study, a completed randomized controlled trial conducted in the United States. Participants were older than 45 years and free of atrial fibrillation at baseline and underwent prospective follow-up from 1993 to October 31, 2006. Alcohol consumption was assessed via questionnaires at baseline and at 48 months of follow-up and was grouped into 4 categories (0, > 0 and < 1, > or = 1 and < 2, and > or = 2 drinks per day). Atrial fibrillation was self-reported on the yearly questionnaires and subsequently confirmed by electrocardiogram and medical record review. **MAIN OUTCOME MEASURE:** Time to first episode of atrial fibrillation. **RESULTS:** Over a median follow-up of 12.4 years, 653 cases of incident atrial fibrillation were confirmed. Age-adjusted incidences among women consuming 0 (n = 15,370), more than 0 and less than 1 (n = 15,758), 1 or more and less than 2 (n = 2228), and 2 or more (n = 1359) drinks per day were 1.59, 1.55, 1.27, and 2.25 events/1000 person-years of follow-up. Thus, compared with nondrinking women, women consuming 2 or

more drinks per day had an absolute risk increase of 0.66 events/1000 person-years. The corresponding multivariate-adjusted hazard ratios (HRs) for incident atrial fibrillation were 1, 1.05 (95% CI, 0.88-1.25), 0.84 (95% CI, 0.58-1.22), and 1.60 (95% CI, 1.13-2.25), respectively. The increased hazard in the small group of women consuming 2 or more drinks per day persisted when alcohol intake was updated at 48 months (HR, 1.49; 95% CI, 1.05-2.11) or when women were censored at their first cardiovascular event (HR, 1.68; 95% CI, 1.18-2.39). **CONCLUSIONS:** Among healthy middle-aged women, consumption of up to 2 alcoholic beverages per day was not associated with an increased risk of incident atrial fibrillation. Heavier consumption of 2 or more drinks per day, however, was associated with a small but statistically significant increased risk of atrial fibrillation.

Comment. This is the largest study yet of whether chronic alcohol use is associated with an increased or decreased incidence of atrial fibrillation (AF) in middle-aged women. It is well known that alcohol abuse is associated with cardiomyopathy and congestive heart failure, both of which are associated with AF. Yet many people develop AF without a known cause, resulting in a dilemma as to what the etiology of their disorder might be.

In a study of the Framingham cohort, having more than three drinks per day was associated with an increased incidence of AF in the whole population, but was not statistically significant in the women. However, the numbers were too low to be sure about the outcome. The present study tries to correct that by examining 34,715 female health professionals. These women are unlikely to use a lot of alcohol, as it might interfere with their employment or daily functioning. The large majority (89.7%) had fewer than one drink per day or none. Only 3.9% drank more than two drinks per day.

There were only 653 new AF events, with only 2.9% of AF events in those who had more than two drinks per day. The only significant risk

was in the women over age 60 who had more than two drinks per day. Nonsmokers in this group also had significantly increased risk of AF. There were not enough women who had three or more drinks per day to analyze the findings independently. Of note, one to two drinks per day reduced the incidence of AF. Among those who drank more than two drinks per day, only those with a body mass index of less than 30 kg/m² were at increased risk. (Perhaps more than two drinks per day resulted in a reduction in weight?) Normal cholesterol and more than two drinks a day was also statistically significant for an increased risk of AF.

Overall, the findings of this study are not very impressive. I believe the only way to really prove whether alcohol is associated with increased or

decreased incidence of AF would be to repeat this study in a similar number of women who are likely to have more than three drinks per day. On the other hand, it would appear from this article and previous research that one to two drinks per day reduce the incidence of hypertension, coronary artery disease, stroke, and AF below the risk for the nondrinking population, for both men and middle-aged women.

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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.

Call for Abstracts by April 30, 2009

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 20th Annual Meeting (September 30-October 3, 2009) in San Diego, CA.

- Submit your abstracts through the NAMS Web site: www.menopause.org/meetings/abstracts1call.aspx
- Information submitted for consideration must not be identical to that presented at any meeting prior to the NAMS meeting, and the study must have been published as of April 30, 2009
- The abstract submission deadline is April 30, 2009
- Top abstracts will be accepted for oral presentation and up to four poster prizes will be awarded (top prize: \$1,000)
- All accepted abstracts will be published in the NAMS journal, *Menopause*, after the meeting

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