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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)).

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## Ovarian cancer risk higher with HT

Morch LS, Lokkegaard E, Andreasen AH, Kruger-Kjaer S, Lidegaard O. Hormone therapy and ovarian cancer. *JAMA* 2009;302:298-305. **Level of evidence: II-2.**

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**CONTEXT:** Studies have suggested an increased risk of ovarian cancer among women taking postmenopausal hormone therapy. Data are sparse on the differential effects of formulations, regimens, and routes of administration. **OBJECTIVE:** To assess risk of ovarian cancer in perimenopausal and postmenopausal women receiving different hormone therapies. **DESIGN AND SETTING:** Nationwide prospective cohort study including all Danish women aged 50 through 79 years from 1995 through 2005 through individual linkage to Danish national registers. Redeemed prescription data from the National Register of Medicinal Product Statistics provided individually updated exposure information. The National Cancer Register and Pathology Register provided ovarian cancer incidence data. Information on confounding factors and effect modifiers was from other national registers. Poisson regression analyses with 5-year age bands included hormone exposures as time-dependent covariates. **PARTICIPANTS:** A total of 909,946 women

without hormone-sensitive cancer or bilateral oophorectomy. **MAIN OUTCOME MEASURE:** Ovarian cancer. **RESULTS:** In an average of 8.0 years of follow-up (7.3 million women-years), 3068 incident ovarian cancers, of which 2681 were epithelial cancers, were detected. Compared with women who never took hormone therapy, current users of hormones had incidence rate ratios for all ovarian cancers of 1.38 (95% confidence interval [CI], 1.26-1.51) and 1.44 (95% CI, 1.30-1.58) for epithelial ovarian cancer. The risk declined with years since last use: 0 to 2 years, 1.22 (95% CI, 1.02-1.46); more than 2 to 4 years, 0.98 (95% CI, 0.75-1.28); more than 4 to 6 years, 0.72 (95% CI, 0.50-1.05), and more than 6 years, 0.63 (95% CI, 0.41-0.96). For current users the risk of ovarian cancer did not differ significantly with different hormone therapies or duration of use. The incidence rates in current and never users of hormones were 0.52 and 0.40 per 1000 years, respectively, ie, an absolute risk increase of 0.12 (95% CI, 0.01-0.17) per 1000 years. This approximates 1 extra ovarian cancer for roughly 8300 women taking hormone therapy each year. **CONCLUSION:** Regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increased risk of ovarian cancer.

**Comment #1.** This Danish cohort report adds to a long list of observational studies, many of which indicate a small increase in the risk of ovarian cancer in ever users of postmenopausal hormone therapy (HT). There has been a remarkable lack of consistency among the reports, especially in regard to dose, duration of exposure, mode of administration, treatment regimens (cyclic vs continuous), and even whether there is an increase in risk. Danish studies are noteworthy for the accuracy of information derived from their national registries; this is one strength of the current report. Nevertheless, this study cannot escape a fundamental problem common to all of the epidemiologic reports on this subject. The risk of ovarian cancer is influenced by a long list of factors, not just the most familiar ones such as the use of steroid hormone contraception and family history of ovarian cancer, but also conditions such as increasing body mass index, infertility, and tubal ligation. It is very difficult for observational studies to gather accurate information on the host of factors affecting ovarian cancer risk, and even this Danish study linked to national registries could not account for steroid contraceptive use, excess body weight, the use of NSAIDs, breastfeeding, caffeine intake, alcohol intake, smoking, and most important, family history of ovarian and breast cancer. Another possible confounder unaccounted for is detection bias (HT users see clinicians more often and have more examinations). The authors of the several meta-analyses on this subject have inappropriately assumed that controlling for risk factors was uniformly accomplished in all studies. Not a single epidemiologic study exists that has been able to control for all known risk factors.

Because ovarian cancer does not occur frequently, it has been difficult to analyze epidemiologic data according to histologic subtypes. This is important because it is possible that HT may promote the growth of specific tumors. Endometrioid ovarian cancer, for example, is very likely to be influenced by estrogen exposure. Some studies attempted subgroup analyses by specific cancers, and it is

impressive that an increase in ovarian cancer risk was influenced by the number of cases with endometrioid cancer or was observed *only* in cases with endometrioid cancer.<sup>1-3</sup> In the current Danish report, there were 2,681 epithelial cancers, of which 377 (14%) were endometrioid tumors. Because the increased risk in the Danish report was not large, it is appropriate to ask if the overall conclusion was influenced by a strong effect with endometrioid cancers. This subgroup analysis was not performed.

The Danish study does not provide any new information to help clinicians and patients in thinking about the risk of ovarian cancer and HT. Overall, there is an indication that ever users of HT, no matter what formulation, progestogen, or treatment regimen, have a small increase in the risk of epithelial ovarian cancers. The data are consistent with a promotional effect on existing malignancies, because the risk diminishes after discontinuation of treatment. The risk is small, perhaps because it is limited to specific and hormonally sensitive tumors, such as endometrioid cancers.

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**Comment #2.** The health advantages and disadvantages of postmenopausal HT use are important to understand because many women are currently taking or have taken HT. It is well established that different types of

postmenopausal HT increase risk of breast cancer, but results from past studies for ovarian cancer are less clear. Morch et al, in one of the largest prospective studies to date with over 900,000 women, had the ability to examine the role of how different types of HT, varying doses, and routes of administration influenced ovarian cancer risk. Overall, they reported that postmenopausal HT use of any kind increased risk.

The most important contribution of this article was the ability to examine estrogen-only therapy versus estrogen plus progestogen therapy because most prior studies have only been able to consider estrogen-only therapy. Since both forms of HT were shown to increase risk of ovarian cancer in this study, women with a family history of ovarian cancer or who are at an increased risk of this disease should consider alternatives to taking HT. Another key finding was that women who had stopped taking HT were still at a slight increased risk of ovarian cancer. Thus, it is important that women who are using HT now or in the past see their healthcare provider if they experience abdominal symptoms or bleeding lasting more than several days.

Ultimately, this study confirms prior work that postmenopausal HT can increase the risk of female reproductive cancer and as such these medications should be used judiciously and only for short durations.

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## Causal relationship of CRP and CVD

Elliott P, Chambers JC, Zhang W, et al. Genetic Loci associated with C-reactive protein levels and risk of coronary heart disease. *JAMA* 2009;302:37-48. **Level of evidence: II-2.**

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**CONTEXT:** Plasma levels of C-reactive protein (CRP) are independently associated with risk of coronary heart disease, but whether CRP is causally associated with coronary heart disease or merely a marker of underlying atherosclerosis is uncertain. **OBJECTIVE:** To investigate association of genetic loci with CRP levels and risk of coronary heart disease. **DESIGN, SETTING, AND PARTICIPANTS:** We first carried out a genome-wide association (n = 17,967) and replication study (n = 13,615) to identify genetic loci associated with plasma CRP concentrations. Data collection took place between 1989 and 2008 and genotyping between 2003 and 2008. We carried out a mendelian randomization study of the most closely associated single-nucleotide polymorphism (SNP) in the CRP locus and published data on other CRP variants involving a total of 28,112 cases and 100,823 controls, to investigate the association of CRP variants with coronary heart disease. We compared our finding with that predicted from meta-analysis of observational studies of CRP levels and risk of coronary heart disease. For the other loci associated with CRP levels, we selected the most closely associated SNP for testing against coronary heart disease among 14,365 cases and 32,069 controls. **MAIN OUTCOME MEASURE:** Risk of coronary heart disease. **RESULTS:** Polymorphisms in 5 genetic loci were strongly associated with CRP levels (% difference per minor allele): SNP rs6700896 in LEPR (-14.8%; 95% confidence interval [CI], -17.6% to -12.0%; P = 6.2 x 10<sup>-22</sup>), rs4537545 in IL6R (-11.5%; 95% CI, -14.4% to -8.5%; P = 1.3 x 10<sup>-12</sup>), rs7553007 in the CRP locus (-20.7%; 95% CI, -23.4% to -17.9%; P = 1.3 x 10<sup>-38</sup>), rs1183910 in HNF1A (-13.8%; 95% CI, -16.6% to -10.9%; P = 1.9 x 10<sup>-18</sup>), and rs4420638 in APOE-CII (-21.8%; 95% CI, -25.3% to -18.1%; P = 8.1 x 10<sup>-26</sup>). Association of SNP rs7553007 in the CRP locus with coronary heart disease gave an odds ratio (OR) of 0.98 (95% CI, 0.94 to 1.01) per 20% lower CRP level. Our mendelian randomization study of variants in the CRP locus showed no association with

coronary heart disease: OR, 1.00; 95% CI, 0.97 to 1.02; per 20% lower CRP level, compared with OR, 0.94; 95% CI, 0.94 to 0.95; predicted from meta-analysis of the observational studies of CRP levels and coronary heart disease (z score, -3.45;  $P < .001$ ). SNPs rs6700896 in LEPR (OR, 1.06; 95% CI, 1.02 to 1.09; per minor allele), rs4537545 in IL6R (OR, 0.94; 95% CI, 0.91 to 0.97), and rs4420638 in the APOE-CI-CII cluster (OR, 1.16; 95% CI, 1.12 to 1.21) were all associated with risk of coronary heart disease. **CONCLUSION:** The lack of concordance between the effect on coronary heart disease risk of CRP genotypes and CRP levels argues against a causal association of CRP with coronary heart disease.

**Comment.** The central role played by activation of the inflammatory system in the pathogenesis of atherosclerosis is now widely accepted. This has driven investigators to try to identify circulating biomarkers of inflammatory activation that could be used to screen subjects to identify those at increased risk for cardiovascular disease (CVD), much in the same way that is routinely done for circulating lipids. C-reactive protein (CRP) has clearly emerged as the leading candidate for such a biomarker. There is extensive and generally concordant epidemiological data supporting the conclusion that elevated levels of CRP, detected using a high-sensitivity CRP assay, are associated with increased CVD risk, and that elevated levels of CRP predict increased CVD risk independent of other traditional CVD risk factors.<sup>1</sup>

The recently published JUPITER study brought screening for CRP levels one step closer to clinical practice. In that study, Ridker et al demonstrated that treatment with the HMG-CoA reductase inhibitor (statin) rosuvastatin decreased a composite CVD endpoint by 44% in apparently healthy men and women with LDL cholesterol levels below 130 mg/dl, but whose baseline CRP levels were elevated above 2 mg/L.<sup>2</sup> In terms of the clinical application of CRP testing, JUPITER represents an important landmark study because it demonstrates that an intervention in subjects identified by having increased CRP levels, who

would not otherwise be candidates for treatment based on their lipid levels, provides benefit in terms of reducing their risk of CVD events.

A major unanswered question in this field is whether CRP is a “marker” of atherosclerotic burden, or does it play a pathophysiologic role in driving atherosclerosis? This report by Elliott et al used highly sophisticated genetic analyses coupled with clinical outcomes analyses and demonstrated that genetic variants that are associated with circulating levels of CRP are not also associated with CVD risk. They interpret their findings as arguing against a causal role for CRP in atherosclerosis.

This is an exceptionally well-done study that makes an important contribution to this field. However, several limitations of this approach are worthy of mention. First, the approach that was used in this analysis examines whether the *genetic* determinants of circulating CRP levels are associated with CVD risk. This does not include an assessment of what could be called “acquired” CRP levels (ie, those determined by nongenetic effects such as lifestyle, metabolic factors, etc). An analogy may help clarify this: Blood pressure is clearly an independent predictor of CVD risk, and blood pressure is also determined in part by genetics, and in part by environmental factors. So, while an individual’s genetically determined blood pressure may impact only modestly on their CVD risk, blood pressure that is increased by such factors as poor diet, obesity, and sedentary lifestyle may contribute importantly to CVD risk. The same may be true for CRP. Second, the effect size of the genetic determination of CRP levels is relatively small. Each of the genotypes identified is associated with about an 11% to 22% increase in CRP. These are quite small differences when compared to levels of CRP observed clinically, which may differ between individuals by as much as tenfold.

Finally, there are preclinical data that do support a possible causative role of CRP in atherosclerosis, including, for example, the

ability of CRP to activate vascular endothelial cells in cell culture models.

If the conclusions reached by Elliott et al are correct—that CRP does not play a causal role in atherosclerosis—what are the clinical implications of this? The main implication would be support for the idea that use of interventions to lower CRP is unlikely to reduce CVD risk. Currently, however, this remains only a theoretical issue as there are no known interventions that specifically lower CRP. The second issue of major clinical relevance is if these findings negate the findings in JUPITER noted above, that treating patients who have elevated CRP levels with statins may reduce CVD risk. The answer to this is no. Whether or not CRP plays a causative role in atherosclerosis or is just a marker of disease, JUPITER supports that screening of CRP in otherwise healthy subjects without elevated levels of LDL identifies a group of patients with sufficient CVD risk in whom statin therapy can significantly lower that risk. The current findings of Elliott et al do not alter that clinical scenario.

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## Diabetes protection with HT

Pentti K, Tuppurainen MT, Honkanen R, et al. Hormone therapy protects from diabetes: the Kuopio osteoporosis risk factor and prevention study. *Eur J Endocrinol* 2009;160:979-983. **Level of evidence: II-3.**

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**OBJECTIVES:** The purpose of this population-based prospective cohort study was to examine the effect of hormone therapy (HT) on incidence of diabetes mellitus (DM). **DESIGN AND METHODS:** Eight thousand four hundred and eighty-three DM-free postmenopausal women aged 52-62 from the population-based Kuopio osteoporosis risk factor and prevention study were followed for 5 years from 1994-1999. Information about the use of HT and health events was obtained from three repeated questionnaires in 1989, 1994, and 1999. DM morbidity before and during the follow-up was obtained from the Registry of Specially Refunded Drugs of the Finnish Social Insurance Institution. Kaplan-Meier survival curves and Cox's proportional-hazards models were used to estimate the risk of incident DM in relation to the use of HT. **RESULTS:** During the follow-up, 40.8% DM-free postmenopausal women had never used HT, 27.3% women were HT past users and 31.9% women had used HT presently during the follow-up. During the follow-up, 162 incident DM cases were recorded. Compared with never users of HT, the adjusted hazard ratio of DM was 0.81 (95% confidence interval (CI) 0.57-1.16) for only past users, 0.53 (95% CI 0.24-1.15) in part-time (during the follow-up <2.5 years) users and 0.31 (95% CI 0.16-0.60) in continuous (during the follow-up 2.5-5.0 years) users of HT. **CONCLUSIONS:** HT use decreases the incidence of DM in postmenopausal women.

**Comment.** A number of previous studies have reported a reduction in the development of diabetes in women using hormone therapy (HT). In the Heart and Estrogen/progestin Replacement Study,<sup>1</sup> a 35% risk reduction was reported in women on 0.625 mg/day of conjugated estrogen and 2.5 mg/day of medroxyprogesterone acetate compared to placebo. The Nurses' Health Study similarly reported a 20% lower incidence of diabetes in women actively using HT versus placebo.<sup>2</sup> Other studies have been less promising about this benefit, but most of these studies suffered from suboptimal sample size.

While the findings of this particular study are not unexpected, the degree of risk reduction presented by Pentti et al is quite remarkable. The authors note a diabetes incidence of 5.6/1,000 person-years in HT-naive women; 4.45/1,000 person-years in past users; 2.34/1,000 person-years in those using HT for less than 2.5 years; and 1.29/1,000 person-years in those using HT for 2.5 to 5.0 years. This amounts to a 62% risk reduction. The authors postulate that the length of HT use may account for this profound risk reduction, and may distinguish this study from previous studies.

Many hypotheses exist as to why HT may offer protection against diabetes. Most suggest that it is the estrogenic component of HT that provides the potential protection. A number of studies have shown that varying (or removing) the progestational agent seems to have little impact on fasting glucose and insulin results. Estrogen may exert favorable effects on the deposition of abdominal fat, attenuate the gluconeogenic response, and directly exert effects on insulin secretion and sensitivity.<sup>3</sup> The relative contribution of these effects in vivo on the development of diabetes requires further investigation.

Pentti et al present an impressive sample size of over 8,400 subjects. However, as noted by the authors, the baseline characteristics of the subjects using HT favor a healthier physical profile. While covariant analysis was performed to minimize these baseline differences, it does raise the question of an underlying source of bias. Previous studies have questioned whether women using HT may be better off socioeconomically, more educated, more proactive regarding their health care, and lead healthier lifestyles.<sup>4</sup> Could these less tangible differences account for both the lower body mass index reported in this group, and their reduced risk of developing diabetes? It is something to contemplate.

The story of HT and its effects on insulin and glucose is still evolving, and the details are yet to be elucidated. While associations are evident,

definitive physiologic and mechanistic studies are needed to provide further insight into the nature of this relationship.

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## Bisphosphonate use and BMD monitoring

Bell KJ, Hayen A, Macaskill P, et al. Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. *BMJ* 2009; 338:b2266. **Level of evidence: I.**

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**OBJECTIVE:** To assess the value of monitoring response to bisphosphonate treatment by means of measuring bone mineral density. **DESIGN:** Secondary analysis of trial data using mixed models. **Data source** The Fracture Intervention Trial, a randomised controlled trial that compared the effects of

alendronate and placebo in 6,459 postmenopausal women with low bone mineral density recruited between May 1992 and May 1993. Bone density measurements of hip and spine were obtained at baseline and at one, two, and three years after randomisation. **MAIN OUTCOME MEASURES:** Between-person (treatment related) variation and within-person (measurement related) variation in hip and spine bone mineral density. **RESULTS:** The mean effect of three years' treatment with alendronate was to increase hip bone mineral density by  $0.030 \text{ g/cm}^2$ . There was some between-person variation in the effects of alendronate, but this was small in size compared with within-person variation. Alendronate treatment is estimated to result in increases in hip bone density  $\geq 0.019 \text{ g/cm}^2$  in 97.5% of patients. **CONCLUSIONS:** Monitoring bone mineral density in postmenopausal women in the first three years after starting treatment with a potent bisphosphonate is unnecessary and may be misleading. Routine monitoring should be avoided in this early period after bisphosphonate treatment is commenced.

**Comment.** What would you think of a recommendation to stop checking thyroid-stimulating hormone before refilling thyroid supplements? How about stopping blood pressure checks on your patients on a stable blood pressure regimen? Using the Fracture Intervention Trial participants to reflect the general population for chronic medication compliance can be misleading. With compliance rates for long-term osteoporosis medications documented as low as 50%, how will we know that our patients are taking their prescribed medications? When the patient with slow gut transit has poor oral absorption of the medication, or takes it with coffee and does not absorb it, how will we be able to pick up on this? The vast majority of osteoporosis patients are being treated in a primary care practice, not in a subspecialty osteoporosis center where extensive laboratory tests are being done with each evaluation. Therefore, the repeat DXA scan

showing a decrease in patients on appropriate treatment is an important clue to uncover significant vitamin D deficiency, celiac disease, multiple myeloma, and other conditions. Concerns have been raised about chemical differences in generic versus brand-name alendronate that may affect its efficacy. With the vast majority of our patients being switched to generic alendronate, we need proof that the generic medication is bioequivalent.

The authors correctly stated that there are a large number of bone density scanners in the United States, thus making it critical that patients be followed up on the same machine for consistency. Starting a new baseline on different scanners does not help in the care of patients once treated, and is a cost burden to the system. It is also important that patients be referred to sites where a densitometrist certified by the International Society for Clinical Densitometry is reading scans according to current guidelines.

The conclusions of this article are based on several assumptions that do not fit with what I have seen in my clinical practice. Anecdotally, it has not been my experience that 97.5% of patients get significant increases in hip bone density within 3 years of alendronate treatment. Also, many patients have different treatment effects on the hip and spine bone density. Finally, I do not agree that "most problems with adherence to osteoporosis treatments occur within 3 months of starting treatment." I believe many patients intermittently stop treatment when they hear a news story about possible side effects such as osteonecrosis of the jaw, or atrial fibrillation. I do agree with the authors that monitoring bone density can be misleading if the immediate reaction to a decrease is to stop or change a treatment regimen. In these patients, it is most important to look into a secondary cause for their treatment failure, most of which involves a simple history. However, if we choose to forego this monitoring, we are missing a great

opportunity to diagnose the common diseases that can affect bone density, as well as rectifying common barriers to compliance.

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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.

#### **NAMS 20TH ANNUAL SCIENTIFIC MEETING**

“A New Experience: Bringing Technology to Menopausal Health”  
San Diego, California  
September 30-October 3, 2009

There are many compelling reasons to consider attending this year’s meeting. The CME scientific program is outstanding, with all sessions focusing on exciting technological advances to enhance health. The cornerstones of the NAMS Annual Meeting—cutting-edge science, world-class experts, and networking—will take place against the backdrop of the spectacular Manchester Grand Hyatt.

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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