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## INSIDE



**Financial Disclosure:** *OB/GYN Clinical Alert*'s Editor, Leon Speroff, MD, is a consultant for Barr Laboratories and does research for Wyeth; peer reviewer Catherine LeClair, MD reports no financial relationship to this field of study

# Estrogen, Testosterone, and Breast Cancer in the Nurses' Health Study

ABSTRACT & COMMENTARY

***By Leon Speroff, MD, Editor***

***Synopsis:*** *The Nurses' Health Study reports that the postmenopausal use of testosterone increases the risk of invasive breast cancer.*

**Source:** Tamimi RM, et al. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. *Arch Intern Med*. 2006;166:1483-1489.

THE NURSES' HEALTH STUDY REPORTED THE RISK OF INVASIVE breast cancer associated with the use of combined estrogen and testosterone. At the beginning of this cohort study, only 33 women reported testosterone use, but over the next 10 years this number increased to 550. Compared to never users and after adjusting for multiple risk factors, users of estrogen plus testosterone had an increased relative risk of invasive breast cancer (1.77; CI = 1.22-2.56). This risk was greater than that reported by the Nurses' Health Study for users of estrogen alone and for users of estrogen-progestin. There was no increase in past users.

## COMMENTARY

This report from the Nurses' Health Study is complicated by the same problem in other breast cancer reports from this cohort: the hormone users (in this case, estrogen and testosterone) differ substantially from never users. This requires multiple statistical adjustments, a process that is further influenced by the number of cases involved. This analysis is limited by relatively small numbers; there were only 29 cases of breast cancer among the estrogen-testosterone users. Nevertheless, the results should raise caution in this day of increasing postmenopausal use of androgens.

If testosterone affects breast tissue, does it do so directly or is it aromatized locally into estrogen? The majority of studies indicate that testosterone inhibits proliferation of breast cancer cell lines in vitro, suggesting that aromatization is of greater

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concern. The women in the Nurses' Health Study in the testosterone group were mainly (90%) using the combination of esterified estrogen and methyltestosterone. For years, I have tried to find out if methyltestosterone is aromatized to estrogen or whether the methyl group protects it against this conversion. There is nothing in the literature, and conversations with pharmaceutical people and biochemists have not provided the answer. Other testosterone preparations such as implants and transdermal applications do carry the risk of target tissue aromatization, perhaps raising local estrogen levels to high levels in breast tissue.

The long-term consequences of androgen administration are unknown. Besides the potential effect on the breast, there is also concern regarding cardiovascular disease. We should do our best to limit duration of androgen exposure and to avoid doses that are clearly pharmacologic. Testosterone assays have no utility for the diagnosis of sexual problems, but they can be used to avoid overdosing. ■

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# OB/GYNs' Attitudes Toward Hysterectomy

ABSTRACT & COMMENTARY

***By Frank W. Ling, MD***

*Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville*

*Dr. Ling reports no financial relationship to this field of study.*

***Synopsis:*** *When presented with a case involving symptomatic leiomyomas, gynecologists' sex did not significantly affect their opinion for or against hysterectomy. Only age and practice type were independently significant in this decision making.*

**Source:** Brummitt K, et al. Gynecologists' Attitudes Toward Hysterectomy. *J Reprod Med.* 2006;51:21-25.

A SURVEY WAS MAILED TO 500 MEMBERS OF THE American College of Obstetricians and Gynecologists presenting a case of symptomatic fibroids. The respondents were asked to choose hysterectomy or a uterus-sparing procedure, 49% responded. Univariate logistic regression analysis of the demographics of those who answered showed that gender did not affect the therapeutic choice. (77.6% vs 87.1%; OR, 0.51; 95% CI, 0.26-1.01). Hysterectomy was recommended more if the physician were either in an academic setting or of a younger age. In the multivariate model, both age and academic practice remained independently significant.

## ■ COMMENTARY

My take on this study is more of a philosophical nature than practical, ie, what we as individual readers should do is get beyond the results, and look inside our own decision-making. The authors were focusing on the attitudes toward hysterectomy using a case-driven survey, trying to decipher what demographic factors influenced how the individual physicians would treat the patient. As a result, one has to wonder whether this is more of a study on attitudes toward leiomyomata rather than hysterectomy. Had the authors scripted the case differently, with an older patient, or different symptoms, etc, would the results have been the same?

More importantly, the study shows that there are real differences out there. Not much of a surprise, though, right? We all know that each of us is most

strongly influenced by the residency program in which we are trained; and that there is always a little voice in the back of our head that is telling us to recommend surgery (or not) depending on the case. That voice often sounds a lot like our departmental chair, the head of gynecology, or one of our mentors on the gynecologic service.

It's nice to know that gender is not an independent factor in decision-making, although there is certainly the perception among some that female gynecologists will be more user-friendly or empathetic than their male counterparts. Indeed, how you were trained and by whom remain critical in each decision you make everyday, whether it be related to hysterectomy or any other clinical decision. It should be noted that this study shows that age is a factor. One could interpret this as saying that the more experienced you are, the less patient you are about uterus-sparing procedures. Another interpretation could give your years in the trenches more credit by saying that you have learned that uterus-sparing procedures are more likely to fail and that the patient will, in the long run, be more satisfied with surgery right away. By the same token, why were those in academics less likely to recommend hysterectomy? Were they smarter and, therefore, knew more about the options than their community-based colleagues? Were they less motivated to do the procedure because they were on a salary rather than on a productivity-based compensation plan? You can't draw broad-stroke conclusions about individuals who are lumped together in a survey like this one, but you can look at your own decision-making process.

The survey presented a 36-year-old multiparous patient who had undergone a tubal ligation but who now had menorrhagia and central pelvic pain. She bled heavily from the 14-week-size uterus despite 3 months of progestin therapy. So what would you do in your practice? I am less interested in the final decision of what you would do (hysterectomy, myomectomy, hormones, expectant management, or uterine artery embolization) than I am in how you get there. How important is reimbursement? I hope not much. How important are the patients' attitudes? I hope a lot. Do you catch where I'm coming from? This study shows that gender is not a factor. I'm glad for that. Hopefully that is the case with you as an individual. What are the important driving factors in what you recommend for the next woman who comes in with symptomatic fibroids? I would be interested to know what the little voice in the back of your mind is telling you. ■

# New Light on the Link Between Chronic Stress and Ovarian Cancer Tumorigenesis

ABSTRACT & COMMENTARY

***By Robert L. Coleman, MD***

*Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston*

*Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.*

***Synopsis:*** *Blocking ADRB-mediated angiogenesis could have therapeutic implications for the management of ovarian cancer.*

**Source:** Thaker PH, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med*. 2006;12:939-944.

WHILE STRESS HAS WELL DOCUMENTED EFFECTS ON immune, neurochemical and endocrinological function, its role in cancer progression is less well understood. It is appreciated, in preclinical studies, that stress can affect the growth of some tumors through modulation of the immune response to tumor cells. However, regulation in solid tumors, like ovarian cancer, is less certain. The hypothesis that the stress mediators could directly affect tumor growth through angiogenic mechanisms was explored.

## Methods

Mice bearing ovarian cancer arising in the organ of origin (also known as orthotopic cancer model) were randomly assigned to social isolation through a novel physical restraining device or no isolation. This was done so as to not induce acute stress as a confounding variable. They were then randomly assigned to treatment intervention, which consisted of both $\beta_1$ and $\beta_2$ blockade. Efficacy was measured by number and extent of metastatic disease as well as tumor weight. Tumor biopsies were evaluated for the effects of angiogenesis, such as mean vessel counts and new vessel formation. The impact of stress blockade on these features was also studied.

## Results

Chronic stress, as induced through physical restraint,

dramatically increased tissue catecholamine levels and accelerated the growth of tumors in this orthotopic model. Tumor burden and patterns of invasive disease was substantially greater and more adverse as well. Details from specific experiments on both cell lines and harvested tumor nodules isolated this effect to activation of the β-adrenergic pathway. Selective stimulation and blocking of $\beta_1$ and $\beta_2$ further isolated the genesis of this observation to the β-receptor, which was also found to be present in ovarian cancer cells. Inhibition of this pathway with propranolol (a non-specific β-blocker) administration led to inhibition of the stress-induced tumor growth. When tumors from stressed and treated animals were evaluated, it was clearly documented that tumor growth accompanied substantial activation of tumor angiogenesis (measured by tumor VEGF level, expression of bFGF, MMP2 and MMP9 and mean vessel density). These effects too were affected positively by β-stimulation and negatively by $\beta_2$ blockade. Regulation of $\beta_1$ activity had no effect on tumor growth or inhibition.

### Conclusions

Behavioral stress as induced through restraint causes tumor growth in mice bearing orthotopic ovarian cancers. The mechanism of this observation appears to be through the β-adrenergic pathway where angiogenesis is induced. Blockade of this pathway could have therapeutic application in the management of ovarian cancer.

### COMMENTARY

While this kind of paper is a bit of a departure from our usual focus, the scope of these finding are broad and have an important impact on discovery of new and novel mechanisms for ovarian cancer growth and metastases. The establishment of a reliable hybrid human-murine model of ovarian cancer allowed these investigators to carefully and convincingly dissect the specific mechanism for observed cancer growth, induced by behavioral stress. Among these manipulations were treatment and gene-silencing techniques geared specifically to the human cancer. Another was the documentation of the lack of angiogenic effects in cells that lacked the β-adrenergic receptor. The link between stress, β-adrenergic stimulation, angiogenesis, and tumor growth has heretofore not been previously outlined and the observation that β-blockade can prevent this inducement has substantial implications for new cancer therapy.

Another interesting correlate utilized in this study was non-invasive imaging during therapy experiments. It has become increasingly recognized that antivascular targeting, particularly those affecting the VEGF pathway, cause changes in the tumor microenvironment. Newly established vessels are poorly arranged and sparsely coated with supportive mesenchymal cells called pericytes. This causes the vasculature to be leaky and morphologically irregular. Tissue effects are characterized by edema and increased plasma to extracellular space fluid transfer, which, in the present case, was accelerated by stress. Dynamic contrast enhanced MRI or DCE-MRI was used to document this effect in control and stressed animals. Currently, the technology along with CT-PET imaging is undergoing validation as a reliable method of assessing target modulation in human cancer trials. Despite their promise, functional imaging is imperfect and new selective contrast agents are being evaluated. For instance, an important unanswered question of anti-VEGF targeting is whether tumor associated angiogenesis leads to a reduction in new vessels or just reduced perfusion. The situation is analogous to rubbing one's eyes and encumbering the filling of established microvessels ("pink eye").

While the authors' observations point to a pathway of tumorigenesis, it is important to note that not all stress is necessarily bad. We count on immediate catecholamine release and action for many survival mechanisms. Nor do these results provide insight into how pain or surgical stress can positively or negatively affect tumor growth. Nonetheless, the report points to an important pathway that appears to have a pharmacological solution and may be implicated in future studies of ovarian cancer treatment. ■

# Managing Poor Response to Hormone Therapy

SPECIAL REPORT

***By Leon Speroff, MD, Editor***

HORMONE THERAPY IS HIGHLY EFFECTIVE FOR relieving symptoms associated with menopause and for preventing postmenopausal osteoporosis. Some women, however, respond unsatisfactorily to standard doses of hormone therapy. When hormone therapy is administered to control menopausal symptoms, response is assessed by the patient's report of symptom relief, but the subjective nature of this response makes it difficult to measure the efficacy of the treatment. Assessing true efficacy requires an objective measurement, such as bone mineral density. Evidence indicates that from 5% to 15% of post

menopausal women on hormone therapy continue to lose bone and experience fractures.[1-3]

## Is Bone Poor Response Real?

Analysis of data from randomized trials evaluating raloxifene and alendronate for osteoporosis treatment revealed that many women whose bone density decreased after the first year of active treatment subsequently gained bone density in the second year of therapy.[4] Extreme results with any laboratory measurement are often due to random error, and subsequent results return to the normal range—a phenomenon known as regression to the mean. Thus, it was argued that bone treatments should not be discontinued when measurements after one year indicate loss of bone density. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, true bone loss was rarely documented in women who had repeated bone density measurements.[5]

Extrapolation of these conclusions to the clinical practice setting must consider the differences between clinical trial participants and real-world patients. Adherence to treatment is far better among clinical trial participants than among nonstudy patients. In addition, clinical trial participants represent a very homogeneous group of individuals because of highly selective inclusion and exclusion criteria. There is good reason to suspect that poor response reflects the considerable variation from individual to individual in metabolism and clearance of administered estrogen, and that there exists a considerable group of women who metabolize and clear estrogen at a greater rate, thus requiring a higher dose.

The prevalence of poor response is supported by the two-year Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial.[6] This trial demonstrated that lower doses of estrogen are effective for preventing bone loss, but there is a dose-response relationship between bone density and estrogen dose. The percentage of women who experienced more than 2% bone loss at the hip increased from 8.7% with a dose of 0.625 mg conjugated estrogens to 13.8% with a dose of 0.3 mg. Considering the current emphasis on lower-dose estrogen therapy, it is appropriate to be concerned whether each individual woman is experiencing an adequate response.

## Management of Poor Response

Patients who are losing bone density despite hormone therapy require evaluation. Other causes of bone loss must be ruled out. Patients being treated for hypothyroidism should have TSH measurements at least annually to assess whether the current dose of thyroid supplementation is appropriate. Calcium and vitamin D intake must be adequate in order for any antiresorptive agent to be fully effective in protecting against bone loss. I recommend the measurement 25-hydroxy vitamin D aiming to maintain a level greater than 30 ng/mL.

### Summary of Clinical Approach

- Check compliance and dose by measuring blood estrogen levels; adjust dose by titering with estradiol measurements
- Rule out other causes of bone loss:
  - *Drugs:* Heparin, anticonvulsants, high intake of alcohol
  - *Chronic Disease:* Renal and hepatic
  - *Endocrine Diseases:* Excess glucocorticoids.
    Hyperthyroidism
    Estrogen deficiency
    Hyperparathyroidism
  - *Nutritional:* Calcium, phosphate, vitamin D deficiencies, eating disorders
- Follow with markers of bone turnover or bone density measurements

Rapid estrogen metabolism and clearance leading to low circulating estrogen levels are probably far more prevalent as a cause of poor response to standard estrogen therapy than is recognized. One practical approach is to titer the dose of estrogen utilizing the blood concentration of estradiol. This approach is supported by a study in Finland in which 11% of women were losing spinal bone and 26% were losing bone at the hip despite hormonal treatment.[7] Evaluation of these women revealed the uniform characteristic of a low blood estradiol levels.

## Adjusting the Estrogen Dose

Measuring estradiol levels in postmenopausal women is complicated by the fact that standard laboratory estrogen assays are designed for higher blood levels than those encountered after menopause. Clinicians must establish the sensitivity of the assay performed in their laboratories and learn what range of results can be reliably measured in postmenopausal women. With a sensitive assay, estrogen therapy can be titered, aiming at levels between 50 and 100 pg/mL.

An acidic vaginal pH (less than 4.5) correlates well with adequate systemic estrogen levels, and this simple method has been advocated as a means to assess the efficacy of estrogen therapy.[8,9] The validity of this

approach, however, has not been established in a carefully designed clinical trial.

## Conclusion

As clinicians and the pharmaceutical industry promote lower doses of estrogen, a greater rate of poor response as measured by bone density can be expected. Women who are losing bone despite treatment deserve evaluation, but once other causes of bone loss are ruled out and adequate calcium and vitamin D intake is established, consideration should be given to identifying women who might benefit from a simple adjustment of the estrogen dose. ■

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# The Peritoneum—To Close or Not to Close During a Cesarean Section?

ABSTRACT & COMMENTARY


***By John C. Hobbins, MD***

*Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver*

*Dr. Hobbins reports no financial relationship to this field of study.*



***Synopsis:*** *The practice of non-closure of the peritoneum should be performed at cesarean.*



**Source:** Komoto Y, et al. Prospective study of non-closure or closure of the peritoneum at cesarean delivery in 124 women: Impact of prior peritoneal closure at primary cesarean on the interval time between first cesarean section and the next pregnancy and significant adhesion at second cesarean. *J Obstet Gynaecol Res*. 2006;32:396-402.


THERE CONTINUES TO BE CONTROVERSY REGARDING the merits and risks of one- or two-layer closure of the uterus during cesarean section. Also, although opinions abound concerning whether or not to close the peritoneum during a cesarean section, until now there has been sparse evidence in the literature to back either side.[1,2] A recent report from Japan suggests that you "non closers" are on the right track.

One hundred and twenty-four patients having cesareans were randomized to either having both parietal and visceral peritoneum closed (70) or not having this done during the exit portion of the operation (54). Every other part of the procedure was identical between groups, and the uteri were closed in 2 layers. Not surprisingly, the closure (C) group had significantly longer operative times than the non closure (NC) group (46.7 minutes vs 39.7 minutes), but also the need for analgesia was greater (2.4 doses vs 2.0 doses). The most interesting findings came from the 50 patients returning for a repeat cesarean section (27 C's and 23 NC's). Adhesions were encountered in 11/27 of the C group and only 2/23 in the NC group ($P < 0.05$). The need to lyze adhesion prior to uterine incision was 6/27 in the C group vs 0/23 in the NC patients. In the C group the total operative time was longer (46.7 minutes vs 39.7 minutes) for the repeat cesarean as well as the time taken from skin incision to uterine incision (11.1 minutes vs 7.6 minutes). Last, and this is fascinating, the time in months between pregnancies was statistically significantly longer in the C group (45.7 vs 33.6).

## COMMENTARY

Here is a simple study in a relatively obscure journal which was well constructed and patiently carried out that provides evidence-based insight as to how to best perform a cesarean section. Leaving the peritoneum alone on the way out shortened the operation itself, indirectly diminished the need for pain alleviation, decreased adhesion formation, and decreased operative time for a subsequent cesarean section.

The fact that it took, on average, 12 months longer for C group patients to become pregnant again got my attention. Was it because of a relative infertility perhaps secondary to adhesions, motility, or other reasons that only our fertility brethren can explain? Was it because they needed a little more time to sort through their memories of their last birth experience? Or was this just a statistical fluke based on an underpowered study with only 50 patients returning for a repeat cesarean section?

Those of my colleagues who still close the peritoneum steadfastly claim that this will enhance healing and decrease adhesion formation. They may not wish to read this study. ■

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# Breast Cancer Risk in the WHI Estrogen-Progestin Trial Arm

ABSTRACT & COMMENTARY


***By Leon Speroff, MD***



***Synopsis:*** *The WHI reports an increase in breast cancer is concentrated in prior hormone users, but the overall adjusted risk of breast cancer is not statistically significant.*



**Source:** Anderson GL, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas.* 2006 Jun 29; [Epub ahead of print];www.sciencedirect.com.


Anderson and colleagues from the WHI performed subgroup analyses focusing on how prior hormone therapy use influenced the risk of breast cancer found in the estrogen-progestin trial arm.[1] Prior hormone users totaled 4311 participants (26%), with 42% reporting less than 2 years of use (17% used hormones 5 to 10 years previously, and 26% more than 10 years before enrolling in the WHI study). Prior users had an increased hazard ratio compared to placebo (1.96; CI = 1.17-3.27) in contrast to no increase among never users (1.02; CI = 0.77-1.36). The WHI concluded that this difference could reflect an increasing risk with cumulative exposure to hormone therapy. The subgroup analysis suggested that no increase in breast cancer was seen in never users, perhaps because of insufficient duration of exposure.

## COMMENTARY

Many of the factors associated with a reduced risk of breast cancer were slightly but significantly more prevalent in the group of prior hormone users, such as younger age, more education, lower body mass, and more physically active. On the other hand, some factors associated with an increased risk of breast cancer were more common in prior users (smoking, alcohol use, vasomotor symptoms, and lower bone density). The overall risk of breast cancer in the treated estrogen-progestin group was the same as previously reported by the WHI (1.24; CI = 1.02-1.50).[1] However, after adjusting for the multiple factors recognized to influence the risk of breast cancer, the hazard ratio was 1.20, and no longer statistically significant, CI = 0.94-1.53). Remarkably, the authors comment that the adjustment "did not substantially alter this risk estimate." Is it not substantial if the risk goes from significant to nonsignificant? Is it appropriate for the WHI in its conclusion to say "the significant increase in breast cancer risk found in the trial overall . . . ?"

A year-by-year analysis of prior users and never users is provided in a Figure. Every single line in this figure, with one exception, crosses 1.0, is not statistically significant, and the confidence intervals are very wide. The only statistically significant line is for prior users at year 5 of the study, and this confidence interval is the widest of all, 1.18-10.73. When the adjusted overall risk is no longer statistically significant, how confident can we be in the results of subgroup analyses with smaller numbers?

This report from the WHI is promoting the idea that increasing duration of exposure is necessary for an increasing risk. Yet, they provide this result: "Duration of prior hormone therapy use, and specifically duration of prior combined hormone use, did not significantly modify the risk of breast cancer."

How does all this fit with the idea that the data reflect the effect of hormone therapy on pre-existing tumors.

Interestingly, the prior users who ended up in the placebo group had a lower incidence of breast cancer per year compared to the women without prior exposure. After adjustment for the various risk factors, this reduction was not statistically significant (0.66; CI = 0.41-1.05). The WHI recognized that this was a "puzzle." It seems to me that this is tantalizing, a result consistent with early detection of pre-existing tumors. The WHI concludes that the results are consistent with the hypothesis that the risk of breast cancer increases with longer exposure; however, the data do not answer the question: are we seeing effects on pre-existing tumors.

Most importantly, the overall result of an increased risk of breast cancer in the estrogen-progestin arm was no longer statistically significant after adjusting for risk factors. This is good news! The WHI results are not consistent with a large effect, and the findings are finding it hard to escape the influence of differences in risk factors and personal characteristics. ■

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## CME Questions

7. **The following statements regarding estrogen-progestin therapy and the risk of breast cancer in the WHI are true *except*:**
   a. Prior hormone users differ from never users in many ways.
   b. The WHI analyses suggest that increasing risk follows longer exposure.
   c. The overall risk of breast cancer in the estrogen-progestin arm is a significant 1.20.
   d. Subgroup analyses are limited by small numbers.

8. **Which of the following factors is independently associated with the recommendation for or against hysterectomy?**
   a. Gender
   b. Age
   c. Race
   d. Geographic region
   e. Type of residency

9. **The following statements are true regarding testosterone treatment of postmenopausal women *except*:**
   a. Women with libido problems have low testosterone levels.
   b. Pharmacologic amounts of testosterone do stimulate libido.
   c. Breast tissue can aromatize testosterone to estradiol.
   d. It is not known whether methyltestosterone is aromatized.

**Answers:** 7 (c); 8 (b); 9 (a)



## CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
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# Raloxifene's Role for Estrogen- and Age-Related Problems

What is the role of raloxifene for the treatment of osteoporosis and breast cancer prevention? Raloxifene is a selective estrogen-receptor modulator similar to tamoxifen. There has been considerable interest in the drug in the role of treatment for osteoporosis and, perhaps, breast cancer prevention, especially in light of the Women's Health Initiative findings on conjugated estrogen/progesterone. A new study does little to clarify the issue, however, suggesting, like previous studies, that raloxifene has benefits, but also significant risks associated with its use.

As part of the Raloxifene Use for The Heart (RUTH) trial, more than 10,000 postmenopausal women with CHD or multiple risk factors for CHD were randomized to raloxifene 60 mg daily or placebo and followed for a median of 5.6 years. The 2 primary outcomes were coronary events and the rate of breast cancer. Raloxifene had no effect on the risk of primary coronary events (533 vs 553 events; HR, 0.95; 95% CI, 0.84 -1.07) but was associated with a reduced risk of invasive breast cancer (40 vs 70 events; HR, 0.56; 95% CI, 0.38-0.83). However, the all-cause death rate was the same in both groups, and raloxifene use was associated with an increased rate of fatal stroke (59 vs 39 events; HR, 1.49; 95% CI, 1.00-2.24) and venous thromboembolism (103 vs 71 events; HR 1.44: 95% CI, 1.06-1.95). The drug was associated with a reduced risk of clinical vertebral fractures (64 vs. 97 events: HR, 0.65; 95% CI, 0.47-0.89) (*N Engl J Med*. 2006;355:125-137). In an accompanying editorial, Marcia L. Stefanik, PhD, from the Stanford University Medical School reviews risk benefit profiles of raloxifene for women.

Reviewing data from the RUTH trial, as well as other studies, the author suggests that a key issue in contemplating raloxifene use is balancing the benefits of reduction in the risk of breast cancer and vertebral fractures with the increase risk of venous thromboembolism and fatal stroke. She suggests that raloxifene should be contemplated in women with an increased risk of breast cancer, but asks" What level of breast cancer risk would justify the use of raloxifene for prevention of breast cancer for a given person . . ." and suggest that the answer to that question is currently unknown. She also states that, "For now, there's no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns." (*N Engl J Med*. 2006;355:190-192).

### *The Truth About Multivitamins*

More than half of the adult population in the United States takes multivitamins on a regular basis, yet little is known about the benefits or lack of benefits of vitamins. The National Institutes of Health has published a "State-of-the-Science Conference Statement" on multivitamin/mineral

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supplements and chronic disease prevention as an early release article on the *Annals of Internal Medicine* web site on August 1. The statement deals with the current patterns of vitamin use, nutrient intake of vitamin users and nonusers, the efficacy of single vitamins and minerals, the efficacy of multivitamins, the safety of multivitamins, and where future research is needed. Regarding single vitamins and minerals, the results have been disappointing.

Beta-carotene was found to cause an increase in lung cancer incidence and deaths in smokers and male asbestos workers and no benefit in preventing other types of cancers. Other cancer preventative studies have shown no benefit from beta-carotene and, some have even suggested, increase rate of stroke and CVD in women smokers. Vitamin A has not been the subject of individual trials but, when paired with beta-carotene or zinc, there is no impact on the incidence of cancer.

Four trials have looked at vitamin E, and the results have been mixed. The largest was the Women's Health Study, which suggested a decrease rate of cardiovascular deaths with vitamin E but no decrease in the incidence of CVD events. Vitamin $B_6$ was looked at, and 2 small studies showed no benefit regarding cognitive decline in elderly men and women. Folic acid with or without vitamin $B_{12}$ has been shown to decrease the rate of neural tube defects in women of childbearing age, but was not shown to prevent cognitive decline in older adults. Selenium was found to decrease the rate of liver cancer in Chinese patients who were at risk, and there may be some benefit in reducing the rate of lung, prostate, and colorectal cancer. Calcium has been shown to increase bone mineral density in post menopausal women, and calcium coupled with vitamin D has been shown to decrease the risk for hip and non-vertebral fractures. Calcium and vitamin D may increase risk of kidney stones, and has not been shown to reduce the risk of colorectal cancer.

The use of multivitamins and mineral supplementation (MVM) has been studied in 5 randomized, controlled trials. Although the study methodology was quite variable, there is a suggestion that MVM may decrease risk of cancer. No studies have shown any benefit as far as cardiovascular disease, and the benefit for cataract prevention is mixed. Progression of macular degeneration may be slowed by certain multivitamins, and may represent the single most important benefit from multivitamins. The conference statement also stated that the FDA should be given more oversight over the vitamin industry, and that more rigorous randomized controlled studies should be done of individual vitamins, minerals, and MVM, including safety of these products, as well as the interactions with nutrients and medications (www.annals.org 1 August 2006, to be published in print 5 September 2006).

## Statins and Hepatitis C

Statins may be effective therapy for hepatitis C infections, and may even be used in combination with interferon to inhibit replication of the hepatitis C virus, according to new study. Japanese researchers recently evaluated the effect of various statins with or without interferon on hepatitis C replication. The synthetic statin fluvastatin was the strongest inhibitor of HCV replication, while atorvastatin and simvastatin were less effective. Lovastatin's effect was relatively weak, while pravastatin displayed no anti-HCV activity. The authors suggest that statins, especially fluvastatin, could be "potentially useful as new anti-HCV reagents" in combination with interferon (*Hepatology*. 2006;44:117-125).

## Preventing Hot Flashes

Gabapentin may be as effective as estrogen in preventing hot flashes in postmenopausal women, based upon a recent study. In a randomized, double-blind, placebo-controlled trial on 60 postmenopausal women randomized to conjugated estrogen 0.625 mg daily, gabapentin titrated to 2400 mg daily, or placebo for 12 weeks. The primary outcome, the hot flash composite score, was no different between estrogen or gabapentin (72% improvement vs 71%), with placebo reducing symptoms by 54%. No differences were seen in severity of hot flashes or depression symptoms, although side effects were slightly higher in the gabapentin group (*Obstet Gynecol*. 2006;108:41-48). The authors acknowledge that this is a small study with a significant placebo effect. However, in light of the Women's Health Initiative findings, non-estrogen alternatives for heart flashes are welcome.

## FDA News

The FDA is opening the door to allow Duramed's Plan B emergency contraceptive to be available over-the-counter to women 18 and older. Previously the FDA had tabled the OTC application indefinitely, but new FDA leadership is more receptive. The drug is currently available only by prescription. ■