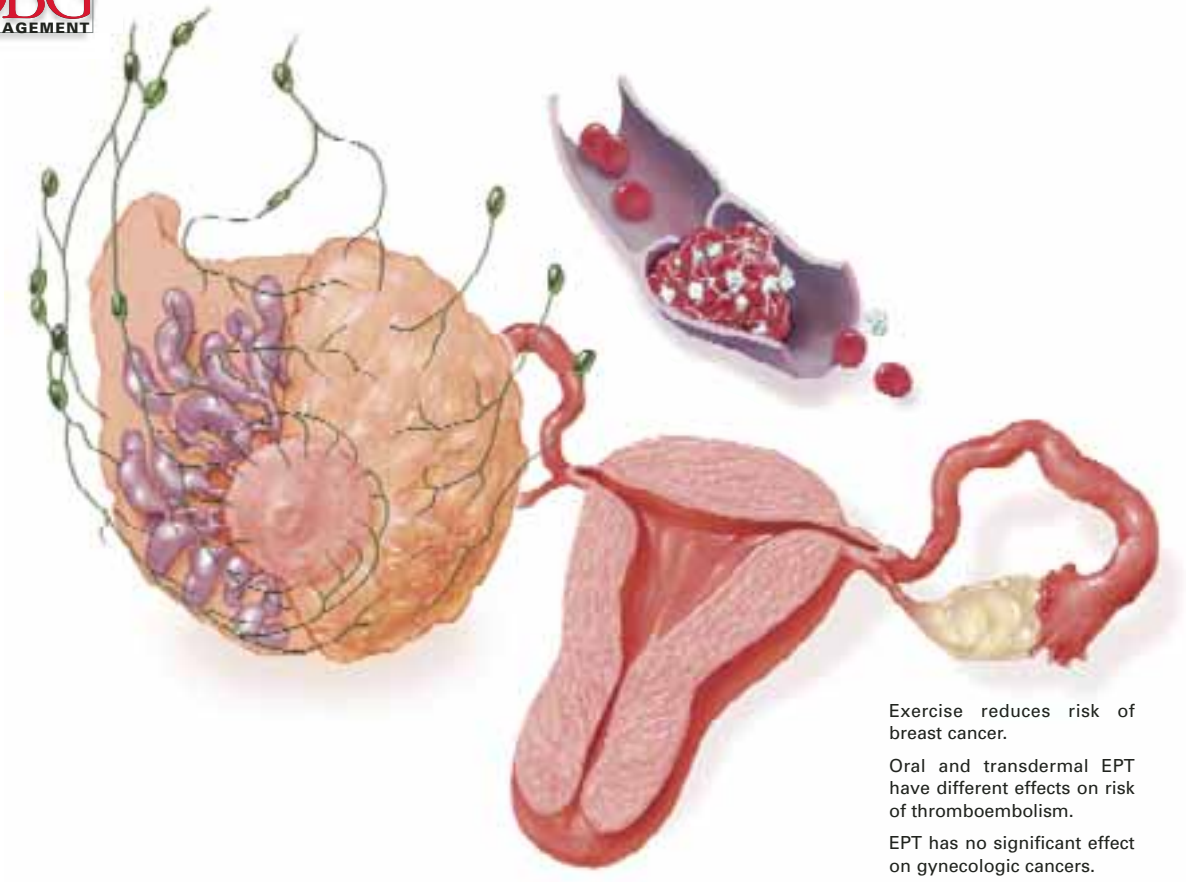

Exercise reduces risk of breast cancer.

Oral and transdermal EPT have different effects on risk of thromboembolism.

EPT has no significant effect on gynecologic cancers.

Update on menopause

An expert's insight on pivotal studies

BY WULF H. UTIAN, MD, PHD

Confusion about what to do—on the part of both physicians and patients—may be the greatest consequence of recent studies.

The past 2 years have witnessed a flurry of scientific publications on menopause and related therapies, particularly use of the sex steroid hormones. In turn, attitudes about menopause and hormone therapy have changed. Perhaps the greatest consequence of all the attention is the confusion about what to do, on the part of both provider and patient.

Many organizations responded with considered, evidence-based, practical guidelines. The most detailed and practice-oriented of these guidelines is the North American Menopause Society's (NAMS's) September 2003 Position Statement on use of estrogen and progestogen in peri- and postmenopausal women (www.menopause.org). Even as this *Update on Menopause* is being written, the report of the terminated estrogen-only arm of the Women's Health Initiative (WHI) is in press and may further change clinical practice. NAMS will present an updated report on all these developments at the 2004 scientific meeting in Washington, DC, October 6 to 9, 2004. In the interim, the current recommendations hold, and the following publications are of clinical relevance.

WHI

Higher levels of exercise reduce breast cancer risk

McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA*. 2003;290:1331–1336.

■ **LEVEL II-2 EVIDENCE:** COHORT OR CASE-CONTROLLED TRIAL

The risk of breast cancer in postmenopausal women who exercised moderately for only a few hours a week was reduced by 18% compared with inactive women—and risk was reduced more in women who exercised moderately but for considerably more hours per week.

A total of 74,171 postmenopausal women aged 50 to 79, with no history of breast cancer, were enrolled. At a mean follow-up of 4.7 years, an increasing total current physical activity score was associated with a statistically significant reduced risk for breast cancer ($P = .03$ for trend). The women in whom the 18% (95% confidence interval [CI], 0.68-0.97) reduced risk of breast cancer was observed exercised the equivalent of 1.25 to 2.5 hours per week of brisk walking (5.1-10.0 metabolic hours). Women who exercised the equivalent of 10 or more hours of brisk walking per week had slightly greater reductions.

The greatest benefit was in women with a body mass index (BMI) below 24.1, but benefits were seen in women with BMIs ranging from 24.1 to 28.4. In evaluating the effect of previous strenuous-intensity exercise, a statistically significant decreased risk of breast cancer was seen for women who had engaged in strenuous exercise at age 35 (relative risk [RR], 0.86; 95% CI, 0.78-0.95); no significant associations were found for strenuous exercise at ages 18 or 50.

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COMMENT

Modest protection, but encourage exercise anyway

This large, prospective cohort study performed in the mid-1990s strengthens the growing body of evidence that higher levels of physical activity afford modest protection against breast cancer. Recreational physical activity appears to be associated with reduced risk for breast cancer in postmenopausal women; longer exercise durations showed only slightly greater reduction in risk.

The strengths of this study are its large numbers, prospective nature, and detailed reporting of breast cancer outcomes. Limitations include possible confounders such as prior oral contraceptive use, and use of self-administered questionnaires to estimate physical activity.

One very important question is raised by this study: Given the low increase in absolute risk of breast cancer reported by the WHI with estrogen plus progestin[1]—which barely reached statistical significance (total breast cancer RR, 1.24; 95% CI, 1.02-1.50)—and given the statement in the McTiernan study that "the reduced risk associated with increased levels of total physical activity was seen across all the categories of these variables" (including current or past use, or no previous use of hormone therapy), does the reduction of incidence with physical activity in hormone therapy users lower the level of risk to nonsignificance or to that of nonexercisers in the placebo group? The answer cannot be determined from this report, but it would be illuminating.

These findings are preliminary, and confirming studies are needed. There is little harm in encouraging women to exercise, however.

1. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289:3243–3253.

WHI

Estrogen-progestin has no significant effect on gynecologic cancers

Anderson GL, Judd HL, Kaunitz AM, et al, for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA*. 2003;290:1739–1748.

■ **LEVEL I EVIDENCE:** RANDOMIZED, CONTROLLED TRIAL

Continuous combined estrogen plus progestin therapy (EPT) does not have a statistically significant effect on either ovarian or endometrial cancer compared with placebo, according to this report.

In this randomized, double-blind, placebo-controlled trial, 16,608 women were assigned to either EPT (0.625 mg/day conjugated equine estrogens plus 2.5 mg/day medroxyprogesterone acetate) or placebo; none of the women had undergone a hysterectomy.

After an average follow-up of 5.6 years:

- There were 20 cases of invasive ovarian cancer in the EPT group (n = 8,506) and 12 cases in the placebo group (n = 8,102). Compared with placebo, the hazard ratio (HR) for invasive ovarian cancer among EPT recipients was a nonsignificant 1.58 (95% CI, 0.77-3.24 [adjusted 95% CI, 0.59-4.23]).
- For endometrial cancer, 27 and 31 cases occurred, respectively, which translated statistically to a nonsignificant hazard ratio for EPT recipients of 0.81 (95% CI, 0.48-1.36).

No appreciable differences were found in the distributions of tumor histology, stage, or grade for either cancer site. However, significantly more women using EPT required endometrial biopsies (33% versus 6%; $P < .001$).

- For cervical cancers, 8 and 5 cases were reported, respectively, with a nonsignificant HR of 1.44 (95% CI, 0.47-4.42).

COMMENT

Bias against hormone therapy?

The authors concluded that EPT may increase the risk of ovarian cancer but has no significant effect on the risk of endometrial cancer. They commented, however, that, since the EPT arm of the trial was prematurely stopped, the precision of the results is limited and examination of longer-term exposure is precluded.

This paper once again raises the question of whether the writers of the WHI trial have a bias against hormone therapy. In this report, the EPT arm of the WHI trial had an observed annual incidence of 34 ovarian cancer cases per 100,000 person-years—somewhat less than the anticipated population-based rate of 45 per 100,000 person-years. In the authors' words, the ovarian cancer rate in the EPT group "was elevated (HR 1.58; 95% CI 0.77-3.24 [adjusted 95% CI, 0.59-4.23]) but not statistically significant." The Kaplan-Meier estimates of cumulative hazards also did not reach statistical significance. Yet in the conclusion of the abstract, the authors state that continuous combined EPT "may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo."

Regarding the conclusion on endometrial cancer risk, the observed incidence for EPT users was 62 per 100,000 person-years, which is also lower than the anticipated population-based rate of 83 per 100,000 person-years. The authors state that this was a "small, nonsignificant reduction" in endometrial cancer risk (HR 0.81; 95% CI, 0.48-1.36). Yet, in the conclusion, while claiming that the nonsignificant difference in ovarian cancer suggests an increased risk, the authors do not state that the nonsignificant reduction in endometrial cancer suggests a decreased risk.

What do the authors expect us to believe, their data or their conclusions?

My interpretation of the data in this article is that ovarian and uterine cancers need not be of major concern when determining a woman's

risk-benefit ratio for hormone therapy.

A retraction. Of interest, when this issue was raised in subsequent *JAMA* correspondence, the WHI authors agreed—representing perhaps the first time that a WHI report publicly retracted a potentially biased conclusion.[1,2]

Fewer biopsies will be needed with lower dosage. It is not surprising that women taking hormonal therapy containing estrogen had more bleeding and, therefore, more endometrial biopsies than women taking placebo, because a known effect of estrogen is proliferation of the endometrial lining. With the lower-dose hormonal preparations currently available (which result in lower systemic estrogen levels and less endometrial stimulation), uterine bleeding episodes in menopausal hormone therapy users should diminish, along with the number of endometrial biopsies.

1. Utian WH. Hormone therapy and risk of gynecologic cancers [letter]. *JAMA*. 2004;291:42.
2. Anderson GL, Judd HL, Kaunitz AM, et al. Hormone therapy and risk of gynecologic cancers—Reply. *JAMA*. 2004;291:43.

MILLION WOMEN STUDY

Breast cancer risks increased by estrogen plus progestogen

Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362:419–427.

■ **LEVEL II-2 EVIDENCE:** COHORT OR CASE-CONTROLLED

Current use but not past use of postmenopausal hormone therapy is associated with an increased risk of incident and fatal breast cancer, especially for estrogen-progestogen therapy (EPT), according to this large observational study from Britain. Risks increased among current users as total duration of use increased.

A total of 1,084,110 women aged 50 to 64 were enrolled between May 1996 and March 2001 and followed to the study finish (end of 2002). Mean follow-up was 2.6 years for breast cancer incidence and 4.1 years for mortality. Nearly half of the women had used postmenopausal hormone therapy, either estrogen therapy alone (ET) or EPT. Primary endpoints were diagnosis of breast cancer and death from breast cancer.

Current ET or EPT use (compared with nonuse) was associated with a statistically significant increased risk of both breast cancer incidence (RR, 1.66; 95% CI, 1.58-1.75) and breast cancer mortality (RR, 1.22; 95% CI, 1.00-1.48). Past use did not increase the risk of incident (RR, 1.01; 95% CI, 0.94-1.09) or fatal disease (RR, 1.05; 95% CI, 0.82-1.34), and the risk decreased with time since last use.

The risks associated with ET and with EPT differed significantly. Current ET users had a 30% increased risk for breast cancer (95% CI, 1.21-1.40) while current EPT users had a 100% increased risk (95% CI, 1.88-2.12). However, vaginal or other local EPT formulations did not increase the risk (RR 0.67, 95% CI, 0.30-1.49). No significant differences in risk were found between specific types or doses of EPT or between continuous combined and continuous cyclic regimens.

COMMENT

Limitations of observational studies

This extremely large observational study found levels of breast cancer risk associated with ET and EPT similar to those reported by the WHI and as predicted in 1997 by the Collaborative Group on Hormonal Factors in Breast Cancer study.[1] The Million Women Study implicates an expanded number of ET and EPT products and routes of administration.

Acting as devil's advocate, I will point out that this is an observational study with large potential for error. The major weakness is that it is a snapshot of hormone therapy use taken at the time of the women's entry into the study, which was at the time of their 3-year mammogram. No further information was gleaned from the women regarding subsequent changes in hormone therapy use, such as whether they terminated use or changed the dose or route.

Also, the patient-provided data at entry showed a 96% agreement with the actual prescription written by the physician. The 4% variance, although it seems small, is of some concern given the narrow difference in relative risks and the large number of study participants. This is a weakness of any observational study; even if the prescription is filled, evidence that it was actually taken is inadequate.

Finally, the authors report that current use of hormone therapy at baseline increased the risk of breast cancer, although the relative risk was not as large as for disease incidence. They were not able to come up with reliable estimates of mortality attributable to breast cancer.

In conclusion, the Million Women Study can be accepted only as an observational study providing confirmation of a small increase in the absolute risk for breast cancer in women on hormone therapy.

"Million Women" can be accepted only as an observational confirmation of a small increase in absolute risk of breast cancer.

Further implications. The suggestion that these results apply to products beyond those tested in the WHI is in agreement with the NAMS Advisory Panel's 2003 statement on Postmenopausal Hormone Therapy, which supports the view that although it is not possible to make general conclusions about all members of the estrogen and progestogen families, an improved benefit-risk profile of other EPT agents cannot be assumed.

1. 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.

CONTINUED

Transdermal estrogen/progestogen had no effect on risk of venous thromboembolism in postmenopausal women.

ESTHER STUDY

Oral and transdermal EPT have different effects on risk of thromboembolism

Scarabin PY, Oger E, Plu-Bureau G, for the EStrogen and THromboEmbolism Risk (ESTHER) Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428–432.

■ **LEVEL II-2 EVIDENCE:** COHORT OR CASE-CONTROLLED STUDY

Oral estrogen plus progestogen therapy (EPT) significantly increases the risk of venous thromboembolism (VTE), but transdermal EPT has no effect on the VTE risk, according to this hospital-based, case-control study of postmenopausal women in France.

Investigators enrolled 155 women aged 45 to 70 years who had been diagnosed with VTE, defined as either pulmonary embolism or deep vein thrombosis, and 381 matched controls. In women with VTE, 21% were using oral EPT and 19% were using transdermal EPT. In controls, 7% and 24% were using oral or transdermal EPT, respectively. An adjusted analysis showed that, compared with nonuse, current use of oral EPT significantly increased the VTE risk (adjusted odds ratio, [OR] 3.5; 95% CI, 1.8-6.8); transdermal EPT did not increase the VTE risk (OR, 0.9; 95% CI, 0.5-1.6). A between-group comparison showed that current oral EPT users had a significantly increased VTE risk (OR, 4.0; 95% CI, 1.9-8.3) over transdermal EPT users.

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By Sebastian Faro, MD, PhD
Professor and Chairman
Department of Obstetrics and Gynecology
University of Texas, Houston

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COMMENT

More studies needed but unlikely

A prime consideration for nonoral EPT for postmenopausal women is avoidance of the first-pass hepatic effect of oral medications, thereby reducing potential for the adverse effects associated with oral therapies. This study demonstrates a difference between oral and transdermal therapy, but the number of patients is small and, while promising, it is probably not a final answer to the problem.

The reduced incidence of VTE in postmenopausal women on transdermal EPT does justify further randomized controlled clinical trials; however, given the low prevalence of VTE, conducting such a study would be nearly impossible. It would be interesting if data from the Million Women Study were analyzed for effects of different routes of ET/EPT administration on VTE.

3 RANDOMIZED, CONTROLLED TRIALS

Isoflavones are no better than placebo for hot flashes

Soy 40%, placebo 40%

Penotti M, Fabio E, Modena AB, Rinaldi M, Omodei U, Vigano P. Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertil Steril.* 2003;79:1112–1117.

■ **LEVEL I EVIDENCE:** RANDOMIZED CONTROLLED TRIAL

Soy-derived isoflavones are no more effective than placebo in reducing hot flashes, according to this 6-month, randomized, double-blind, placebo-controlled trial. In all, 62 postmenopausal women aged 45 to 60 years who had at least 7 hot flashes per day were randomized to either soy-derived isoflavones (72 mg/day) or placebo. Primary endpoints were the daily number of hot flashes, endometrial thickness, and arterial pulsatility index. At study end, both the isoflavone and

placebo groups had a 40% reduction in the number of hot flashes. Soy had no effect on either endometrial thickness or the arterial pulsatility index of either the uterine or cerebral arteries.

Effects in women with breast cancer

Nikander E, Kikkinen A, Metsa-Heikkila M, et al. A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstet Gynecol*. 2003;101:1213–1220.

■ **LEVEL I EVIDENCE:** RANDOMIZED CONTROLLED TRIAL

Phytoestrogen tablets do not effectively relieve menopause-related symptoms, including hot flashes, in postmenopausal women with breast cancer, according to this randomized, placebo-controlled, double-blind, crossover trial from Finland. Investigators enrolled 62 postmenopausal women (mean age, 54) who had been treated for breast cancer but were not currently taking tamoxifen. Subjects received phytoestrogen tablets (114 mg/day) or placebo for 3 months, and switched to the other treatment after a 2-month washout.

Menopause-related symptoms, including hot flashes, were recorded on the Kupperman index. At study end, the overall Kupperman index score was reduced by 15.5% in the phytoestrogen group (mean drop, 4.2) and by 14.7% in the placebo group (mean, 4.0); the between-group difference was not statistically significant.

When evaluated separately from the rest of the Kupperman index, the hot flash component was reduced more in the placebo group (14.3%) than in the study group (10%), although the difference was not statistically significant.

The quality of life parameters measured—capacity to work and mood changes—were not affected by phytoestrogen therapy.

Phytoestrogen treatment was well tolerated and caused no significant changes in liver enzymes, creatinine, body mass index, or blood pressure. In a subset analysis, investigators evaluated results based on high and low levels of endogenous equol; results did not differ between the groups.

Red clover vs placebo

Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) study. *JAMA*. 2003;290:207–214.

■ **LEVEL I EVIDENCE:** RANDOMIZED CONTROLLED TRIAL

Isoflavones derived from red clover were no more effective than placebo in reducing the incidence of hot flashes, in this randomized, double-blind, placebo-controlled trial. A total of 252 women were assigned either to placebo or active treatment with 1 of 2 red clover isoflavone products: Promensil (82 mg/day isoflavones) or Rimostil (57 mg/day isoflavones). Follow-up was 12 weeks. The primary outcome was frequency of hot flashes. Secondary outcomes were quality of life and side effects. After 12 weeks, the mean reduction in hot flash incidence was 41% for Promensil, 34% for Rimostil, and 36% for placebo, a significant reduction from baseline for all 3 groups ($P < .001$). Results in the isoflavone groups, however, were statistically no different from placebo, even though Promensil recipients had significantly more rapid reductions in hot flashes than Rimostil or placebo recipients. Quality of life improvements and side effects were similar in the 3 groups.

COMMENT

The clinical implications

These 3 negative trials of isoflavones (2 extracted from soy, 1 from red clover) confirm previous reports of their essential inefficacy. The clinical implications:

- Women with mild hot flashes might consider either no pharmacotherapy or low-dose selective serotonin-reuptake inhibitors.
- Women with moderate to severe hot flashes that disrupt quality of life may continue to benefit from short-term, low-dose hormone therapy. ■

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