



MORE Study: 4-Year Results

Delmas PD, Ensrud KE, Adachi JD, et al, for the Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: Four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002;87:3609-17.

Raloxifene, a selective estrogen-receptor modulator, decreases the risk of new vertebral fractures in postmenopausal women with osteoporosis, and the decreases in risk remain essentially the same from years 1 through 4, according to 4-year results from the Multiple Outcomes of Raloxifene Evaluation (MORE) study. For this randomized, placebo-controlled, double-blind study, 7,705 postmenopausal women (mean age 66) with osteoporosis, defined as a bone mineral density *T* score of -2.5 or lower and/or the presence of vertebral fracture, were assigned to either raloxifene (60 or 120 mg/day) or placebo.

The primary efficacy endpoint was incidence of new vertebral fractures, as assessed from radiographs taken at baseline and years 2, 3 and 4. The 4-year cumulative relative risk (RR) for new vertebral fracture was statistically significant for both dose groups compared with placebo: 0.64 (95% CI, 0.53-0.76) for 60 mg/day raloxifene and 0.57 (95% CI, 0.48-0.69) for 120 mg/day; the between-group difference was not statistically significant. The RR for the 60-mg/day dose during year 4 alone (0.61; 95% CI, 0.43-0.88) was statistically similar to the RR for years 0 to 3 (0.65; 95% CI, 0.53-0.79).

Comment. This report from the MORE clinical trial found that raloxifene use between 3 and 4 years showed very

similar fracture protection as during the first 3 years. During the 4 years, raloxifene reduced radiologic vertebral deformity risk about 40% overall compared with placebo; cumulative RR reductions after 4 years were similar among women with (34%) and without (49%) baseline vertebral deformity. In contrast to raloxifene's positive and sustained effect on spine fracture risk, nonvertebral fracture risk was not reduced, even after 4 years (7% reduction in risk; not statistically significant).

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Ethnic Differences in BMD, Bone Turnover Rates

Finkelstein JS, Lee ML, Sowers M, et al. Ethnic variation in bone density in premenopausal and early perimenopausal women: Effects of anthropometric and lifestyle factors. *J Clin Endocrinol Metab* 2002;87:3057-67.

African-American women have significantly higher bone mineral density (BMD) levels in both the lumbar spine and femoral neck than Caucasian, Chinese and Japanese women with essentially the same BMD levels, according to data from the Study of Women's Health Across the Nation (SWAN), a longitudinal cohort study. In this study, lumbar spine and femoral neck BMDs were assessed by dual-energy x-ray absorptiometry in 2,131 premenopausal and early postmenopausal women (mean age, 46.2 years). The study cohort consisted of 591 African-American (28%), 1,051 Caucasian (49%), 232 Chinese (11%) and 257 Japanese (12%) women living in the United States.

Unadjusted spine and hip BMDs were 7 to 12% and 14 to 24% higher, respectively, in African-American women than in the other three ethnic groups, a sig-

nificant difference. After adjustment for covariates, the BMDs remained significantly higher in African-Americans; the BMDs were statistically similar for the other three groups.

Among women of comparable weights, adjusted rates show Caucasian women have significantly lower spinal BMD than the other three groups, which were statistically similar. African-American women have significantly higher weight-adjusted hip BMD than the other three groups, which were statistically similar.

Finkelstein JS, Sowers M, Greendale GA, et al. Ethnic variation in bone turnover in pre- and early perimenopausal women: Effects of anthropometric and lifestyle factors. *J Clin Endocrinol Metab* 2002;87:3051-6.

Significant differences in bone turnover exist among different ethnic groups of premenopausal and early postmenopausal women, which may account for some of the BMD variations seen among ethnic populations, according to data from SWAN. Biochemical markers of bone turnover—serum osteocalcin (OC) and urinary N-telopeptide of type I collagen (NTX)—were measured in 2,313 U.S. women of African ($n = 651$), Caucasian ($n = 1,140$), Chinese ($n = 247$) or Japanese ($n = 275$) descent. Serum OC levels were significantly higher (11 to 24%) in Caucasian women than in the other groups. African-American women had significantly higher OC levels than Chinese women. Levels were similar in Chinese and Japanese women, and in African-American and Japanese women.

Adjustment for covariates did not alter the ethnic patterns of serum OC levels. The urinary NTX levels were significantly higher in both Caucasian and African-American women than in Chinese women. Nonsignificantly higher levels were seen in Caucasian women compared with Japanese women, and in Japanese women compared with Chinese women. Significant variations were also noted among Caucasian women living in

different regions of the United States.

Comment. These reports from the SWAN study provide the first glimpse of what will be important insights into skeletal health across the menopause transition in women of different ethnic groups. In the first of the two articles—differences in BMD among women of different ethnic groups—the marked differences in body size among ethnic groups confirm the casual observations that Caucasians and African-Americans are much larger than Asian-American women.

Genetic factors are known to be important determinants of peak bone mass, and significant differences in BMD values have previously been noted when comparing ethnic groups. The expected differences in BMD (African-American greater than Caucasian greater than Asian) were observed in this large cohort of women, but no differences existed in lumbar spine BMD among the four groups after adjustment for body weight. These data suggest that body weight is an important determinant and predictor of bone density, which supports the recommendations in the NAMS postmenopausal osteoporosis position statement that BMD testing be performed at an earlier age after menopause (i.e., younger than 65) in thin women.

These data are also consistent with an important caveat of bone density testing—that women who have BMD values below average have not necessarily lost bone mass. Smaller individuals have lower peak BMD values. Finding a *T* score between 0 and minus 2 in a small woman is the expected result and is not evidence of previous bone loss or an underlying disorder of bone metabolism.

The companion article evaluated the correlation of bone turnover indices among the four ethnic groups. As expected, values were higher in perimenopausal than in premenopausal women and correlated with FSH levels. Interestingly, calcium intake was not related to bone turnover, confirming other evidence that

the increase in bone resorption and the loss of bone mass in perimenopausal women is not the consequence of calcium deficiency, but rather the result of the skeletal response to estrogen deficiency.

As has been observed in other studies, little correlation exists between biochemical markers of bone turnover and BMD values in individual women. While markers may be predictive of future change in bone density, they are not predictive of current BMD values and cannot be used as a “prescreening” test to identify women with low bone density. Differences in markers across the four ethnic groups were observed, but these changes did not account for the observed differences in hip BMD. This suggests that the differences in hip BMD do not result from bone loss, but rather from differences in acquisition of bone mass during childhood and adolescence. The clinical utility of the marker data presented is limited, but these data provide the basis for important longitudinal observations.

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Flaxseed vs Hormone Therapy

Lemay A, Dodin S, Kadri N, et al. Flaxseed dietary supplement versus hormone replacement therapy in hypercholesterolemic menopausal women. *Obstet Gynecol* 2002;100:495-504.

According to this 10-month, randomized, crossover trial, flaxseed is as effective as oral estrogen plus progesterone therapy at improving mild menopause symptoms and lowering glucose and insulin levels. Unlike hormone therapy, however, it does not appear to improve the cholesterol profile or favorably modify markers of cardiovascular health.

A total of 25 postmenopausal women aged 45 to 65 with abnormal cholesterol levels (240-300 mg/dl total cholesterol,

>160 mg/dl low-density lipoprotein [LDL] cholesterol; ratio of high-density lipoprotein [HDL] cholesterol to total cholesterol >4.5; and triglycerides <3.5) were randomly assigned to either flaxseed therapy (adding 40 g/day of crushed flaxseed to their diet) or conjugated equine estrogen therapy (0.625 mg/day). Micronized progesterone (100 mg/day) was added for women with a uterus. Women were started on a 4-month hypocholesterolemia diet that avoided phytoestrogens before adding either the flaxseed supplementation or hormone therapy for a 2-month treatment period.

After a 2-month washout period following the treatment period, women crossed over to the other intervention for another 2 months of treatment. Similar improvements were seen for the two treatments in cholesterol, triglycerides, LDL and apolipoprotein-B100 levels. Both treatments effectively reduced menopause symptoms, based on the Kupperman index, and reduced glucose and insulin levels. Hormone therapy was significantly more effective than flaxseed in improving HDL, the ratio of total cholesterol to HDL and apolipoprotein-A1 levels. It also was significantly more effective in elevating sex-hormone-binding globulin and lowering fibrinogen and plasminogen activator-inhibitor type 1.

Comment. This small, carefully designed crossover study found flaxseed had no effect on multiple measures of cholesterol. These results contrast with those of other studies that have documented small beneficial effects. The authors suggest that this difference may arise from the 4-month pretreatment diet, although this diet did not significantly change serum cholesterol levels. Flaxseed did lower glucose and insulin levels. At this time, very little is known about this effect, but the implications are potentially important.

In contrast to the careful methods used to measure lipids, clotting and glycemic control, the methods used to measure symptoms were not well detailed. The

Kupperman index, though widely used, has not been validated, and it captures a variety of midlife complaints, many of which have no documented response to hormone therapy. Hot flashes and night sweats are components of the Index that would most likely be responsive to HRT, but no information is given about the prevalence of these symptoms. In women of this age, it is likely that menopause symptoms are resolving spontaneously (as evidenced by the decrease in the Index during the pretreatment period).

It should also be noted that studies of menopause therapies are subject to a strong placebo effect. Without a placebo control, more careful measurement of symptoms or information about the Kupperman index in the time between the two treatments, it is uncertain whether the changes in symptoms were related to the passage of time or to treatment with flaxseed. The conclusion that flaxseed is similar to HRT in reducing menopause symptoms does not seem warranted with these methods.

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Hormone Use Does Not Increase Endometrial Carcinoma

Mount SL, Wegner EK, Eltabbakh GH, et al. Significant increase of benign endometrial cells on Papanicolaou smears in women using hormone replacement therapy. *Obstet Gynecol* 2002;100:445-50.

Hormone therapy (estrogen plus a progestogen) is associated with a significant increase in benign endometrial cells on Papanicolaou smears in postmenopausal women, but women taking hormone therapy have less abnormal histology than women not taking hormone therapy, according to this observational cohort study. Investigators reviewed re-

sults from 52,552 Pap smears taken from postmenopausal women (31% used hormone therapy) and found a 1.1% prevalence of benign endometrial cells. Of those, 245 were from hormone users and 324 from nonusers, a statistically increased relative risk (1.56; 95% CI, 1.32-1.84). However, hormone users had significantly fewer abnormal endometrial histology findings (2.6%) than nonusers (7.4%). Endometrial carcinoma was also lower in hormone users (1.5% vs 3.7%), but the difference was not statistically significant.

Comment. When cervical cytology in a postmenopausal woman indicates the presence of benign endometrial cells, clinicians may question whether additional evaluation is needed. This study points out that such cells are more likely to be present in Pap smears in women taking hormone therapy than in nonusers. In addition, when such cells are present, the likelihood of endometrial cancer is lower (1.5%) in hormone users than in nonusers (3.7%). However, even a 1 to 2% likelihood of cancer warrants performing an endometrial biopsy. Bottom line: If benign endometrial cells are noted on cervical cytology in a postmenopausal woman, endometrial biopsy is appropriate regardless of whether the woman is taking hormone therapy.

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Osteoarthritis Rates Increased With Postmenopausal Hormone Therapy

von Muhlen D, Morton D, von Muhlen CA, Barrett-Connor E. Postmenopausal estrogen and increased risk of clinical osteoarthritis at the hip, hand, and knee in older women. *J Womens Health Gen Based Med* 2002;11:511-18.

Use of postmenopausal hormone therapy (either estrogen alone or combined with a progestogen) significantly increases the overall incidence of clinical osteoarthritis (OA), as well as OA of the hand and hip, but not OA of the knee, according to data from the Rancho Bernardo Study, a longitudinal, observational study of 1,001 community-dwelling women aged 43 to 97.

Hormone use for at least 1 year was verified in 63.4% of women (average duration, 14.6 years). The overall prevalence of OA was 34.5% among hormone users and 30.9% among nonusers ($P < 0.02$). At individual sites, the rates of OA in hormone users compared with non-hormone users were as follows: hand (15.8% vs 13.5%; $P < 0.02$), knee (22.9% vs 21.5%; $P < 0.23$) and hip (4.1% vs 1.1%; $P < 0.002$). Also, significantly more hormone users had OA at multiple sites: 7.7% vs 4.7% ($P < 0.02$). Women with OA had longer duration of hormone use than women without OA (median years, 16 vs 11; $P < 0.01$). The increased rates remained statistically significant after adjustment for potentially confounding variables.

Comment. This study showed that hormone therapy (either estrogen alone or combined with a progestogen) increased osteoarthritis of the hand, hip and multiple-site arthritis among community-dwelling women aged 43 to 97. Although results reached statistical significance, the clinical relevance of this study may be diminished by the absolute risk of hormone therapy causing osteoarthritis to be low, and the dwindling numbers of patients using this therapy.

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