

Efficacy and Safety of Raloxifene 60 Milligrams/Day in Postmenopausal Asian Women

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In healthy Caucasian postmenopausal women, raloxifene increases bone mineral density (BMD), decreases biochemical markers of bone turnover, and lowers low-density lipoprotein (LDL) cholesterol, without effects on high-density lipoprotein (HDL) cholesterol and triglycerides. This randomized, double-blind study examines the effects of raloxifene 60 mg/d (n = 483) or placebo (n = 485) in healthy postmenopausal Asian women (mean age 57 yr) from Australia, Hong Kong, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, Taiwan, and Thailand. Serum osteocalcin, serum N-telopeptide, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were assessed at baseline and 6 months. Lumbar spine BMD was measured at baseline and 1 yr in 309 women from 4 countries. Clinical adverse events were recorded at each interim visit.

At 6 months, raloxifene 60 mg/d significantly decreased osteocalcin, N-telopeptide, total cholesterol, and LDL cholesterol by medians of 15.9%, 14.6%, 5.3%, and 7.7%, respectively, from placebo. Changes in HDL cholesterol and triglycerides were similar between raloxifene and placebo. Raloxifene 60 mg/d increased mean lumbar spine BMD (1.9%) from placebo at 1 yr ($P = 0.0003$). The incidences of hot flashes (placebo 3.5%, raloxifene 5.6%, $P = 0.12$), and leg cramps (placebo 2.7%, raloxifene 4.3%, $P = 0.16$) were not different between groups. No case of venous thromboembolism was reported. The effects of raloxifene 60 mg/d on bone turnover, BMD, and serum lipids in healthy postmenopausal Asian women were similar to that previously reported in Caucasian women. (*J Clin Endocrinol Metab* 88: 3130–3136, 2003)

DISEASES OF THE elderly are becoming more common in Asian countries, as improvements in health care and nutrition enable a greater proportion of the population to live to old age. Postmenopausal women have an increased risk of cardiovascular disease and osteoporosis. Cardiovascular disease is the leading cause of death in women in developed countries (1), and approximately 36% of all deaths for females of Asian/Pacific Islander background in the United States were due to heart disease and stroke (2). The worldwide incidence of osteoporotic fractures is estimated to increase 6-fold in the next 50 yr, with the majority of fractures occurring in Asia, Latin America, and Africa (3). Along with lifestyle changes, several therapeutic interventions can decrease the risk of developing cardiovascular disease and osteoporosis, and the associated morbidity and mortality.

Abbreviations: BCE, Bone collagen equivalents; BMD, bone mineral density; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MORE, Multiple Outcomes of Raloxifene Evaluation.

Selective estrogen receptor modulators are designed to have differential effects on estrogen receptors in various tissues (4). Raloxifene, a nonsteroidal benzothioephene selective estrogen receptor modulator, exerts favorable effects on serum lipid concentrations and bone mineral density (BMD), without stimulating breast and uterine tissues. In randomized, double-blind clinical trials, raloxifene 60 mg/d significantly increased lumbar spine BMD at 2 and 3 yr and decreased levels of the bone formation marker, serum osteocalcin, as early as 6 months (5, 6). In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial involving 7705 postmenopausal women with osteoporosis, raloxifene 60 mg/d significantly decreased bone turnover markers, increased BMD, and decreased the risk of new vertebral fractures at 3 and 4 yr (7, 8). In addition, clinical trials examined the effects of raloxifene in extraskeletal tissues as secondary efficacy endpoints. Raloxifene 60 mg/d significantly decreased total cholesterol and low-density lipoprotein (LDL) cholesterol, without any changes in levels of high-density

lipoprotein (HDL) cholesterol or triglycerides, compared with placebo (5, 9). At 4 yr, raloxifene had no effects on the risk of cardiovascular events in the overall MORE cohort but significantly reduced the risk in those women with a high baseline cardiovascular risk (10). Raloxifene significantly decreased invasive breast cancer risk in the total MORE population at 4 yr (11). The occurrence of hot flashes, leg cramps, and venous thromboembolic events were significantly increased with raloxifene (5, 11–13).

To date, clinical trials for antiresorptive agents for postmenopausal osteoporosis prevention and treatment have enrolled primarily Caucasian women, and the effects of these agents not been extensively studied in other ethnic populations. The objective of this present study is to examine the effects of raloxifene 60 mg/d on bone turnover, serum lipid metabolism, and lumbar spine BMD in healthy postmenopausal Asian women.

Subjects and Methods

Subjects

Healthy, ambulatory postmenopausal women eligible for this study were 80 yr of age or less, with their last menstrual period at least 2 yr before study entry, and were not experiencing clinically significant postmenopausal symptoms at the beginning of the study. Postmenopausal status was verified in women who have serum estradiol levels less than 110 pmol/liter and FSH levels above 30 IU/liter. Determination of each subject's ethnic background was based upon self-report. The exclusion criteria for this study were similar to those used in other raloxifene trials, which described the criteria in detail (5–11). Briefly, the exclusion criteria included: history of breast carcinoma or estrogen-dependent neoplasia; any history of cancer in the previous 5 yr, except for skin carcinoma; bone disorders (hyperparathyroidism, Paget's disease, renal osteodystrophy, or osteomalacia); endocrine disorders requiring pharmacologic therapy, except type II diabetes and treated hypothyroidism; any personal history of deep venous thrombosis including pulmonary embolism, acute or chronic liver disease, impaired kidney function, or abnormal uterine bleeding of unknown etiology; and women who had participated in a medical, surgical, or pharmacological investigation, or any raloxifene study. Women who received therapeutic doses of any of these medications before study entry were excluded: androgen, bisphosphonates, calcitonin, systemic corticosteroids, estrogen and progestin within the past 6 months, systemic anticonvulsant or hypolipidemic medications, and therapeutic doses of fluoride or anti-convulsants. All women signed a written informed consent document before entering the study, according to the ethical principles stated in the Declaration of Helsinki. Investigators obtained local Institutional Review Board approval at each study site.

Study design

This randomized, double-blind, placebo-controlled study was conducted at 36 investigative sites in Australia, Hong Kong, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, Taiwan, and Thailand. A total of 968 healthy postmenopausal Asian women were randomly assigned to receive either raloxifene 60 mg/d ($n = 483$), or placebo ($n = 485$) in tablets identical in appearance to raloxifene. The study medication and placebo were packaged in kits numbered according to a random-number table. At randomization, kits were assigned sequentially to each woman, beginning with the lowest number available. All women received supplements of approximately 250 mg/d elemental calcium and approximately 200 IU/d vitamin D.

Subjects were treated daily for 6 months in the core phase, with clinic visits at screening, randomization (baseline) and every 2 months thereafter. Biochemical markers of bone turnover and serum lipids were measured at baseline and 6 months in all participants, and were analyzed at a central laboratory (Covance Laboratories, Inc., Indianapolis, IN; or Covance Laboratories, Inc., Geneva, Switzerland). The bone markers measured were serum osteocalcin (ELSA-OSTEO, CIS-Bio Interna-

tional, Oris Group, Gil-Sur-Yvette Cedex, France) and serum cross-linked N-telopeptide (Osteomark EIA, Ostex, Seattle, WA). Serum lipids measured included total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Upon requests from the Institutional Review Boards and/or local opinion leaders in India, Indonesia, Malaysia, and Thailand, BMD assessment was prospectively planned in the design of this clinical trial. This entailed a 6-month extension phase in the study protocol, in which BMD was measured at baseline and 12 months in all women enrolled at sites in these four countries. A total of 309 women at sites in India, Indonesia, Malaysia, and Thailand had lumbar spine BMD determined by dual x-ray absorptiometry, using Hologic-QDR (Hologic, Inc., Waltham, MA), Lunar-DPX (Lunar Corp. Radiation, Madison, WI), or Norland (Norland Medical Systems, Inc., White Plains, NY) densitometers. Each dual x-ray absorptiometry device at study site was calibrated to correct *in vivo* values and to standardize BMD measurements, according to procedures indicated by the manufacturer.

At each clinic visit, women were questioned about the occurrence and nature of adverse events. All adverse events reported at each post-baseline visit were recorded. Because fractures were not a predefined study endpoint, reports of fractures were captured as adverse events, irrespective of associated trauma, and were not confirmed with radiographs.

Statistical analyses

All data analyses were performed on an intent-to-treat basis in women who had at least one follow-up visit after randomization. For continuous data such as biochemical markers of bone turnover and BMD, the percentage change from baseline to endpoint within each group was analyzed using Student's *t* test. Due to the skewness of most of the variables, rank-transformed data were used in the analyses. The ANOVA model, with fixed effects for therapy and investigator and therapy-by-investigator, evaluated the differences between treatment groups. The interaction of therapy-by-investigator was tested at the two-sided 0.10 level of significance and, if found to be insignificant, was dropped from the model. To determine if results differed between countries, additional subgroup analyses used ANOVA, with therapy and country as fixed effects. The significance of the country-by-therapy interaction term was tested at the two-sided 0.10 level. For categorical data such as adverse events, Pearson's χ^2 test was used to test treatment group differences. Except in the tests of interaction noted above, statistical inferences were made based on a two-sided, significance level of 0.05.

Results

There were no significant differences in the baseline characteristics between the study groups (Table 1). All women who participated in this study were Asian, from the following ethnic origins: Chinese (34.9%), Indian (12.8%), Pakistani (12.4%), and Vietnamese (4.0%). The remaining 35.8% of the study population consisted of women from other ethnic backgrounds including Burmese, Japanese, Korean, Mongolian, and mixed Asian parentage. In the subset of women who had lumbar spine BMD measured at baseline, 37.5% had osteoporosis, defined as a BMD T-score less than or equal to -2.5 according to the World Health Organization criteria (14), and 42.4% had low bone mass (BMD T-score between -1.0 and -2.5). From the 968 women enrolled, 865 women (89.4%) completed the study. There were no differences among the groups in the overall discontinuation rate or in any specific reason for discontinuation.

The primary efficacy endpoint of this study was to determine the effect of raloxifene 60 mg/d on serum osteocalcin and serum cross-linked N-telopeptide at baseline and 6 months. The median values of osteocalcin were significantly decreased by 2.4 mg/ml and 5.2 mg/ml, corresponding to

TABLE 1. Baseline demographics for all randomly assigned subjects^a

Characteristics	Placebo (n = 485)	Raloxifene 60 mg/d (n = 483)	Total (n = 968)
Age (yr)	57.5 ± 6.7	57.3 ± 7.1	57.4 ± 6.9
Years since menopause	9.7 ± 7.2	9.5 ± 7.3	9.6 ± 7.2
Body mass index (kg/m ²)	25.1 ± 4.0	24.9 ± 4.1	25.0 ± 4.0
Triglycerides (mmol/liter)	1.16 [0.86, 1.74] ^b	1.26 [0.87, 1.82]	1.21 [0.86, 1.80]
LDL cholesterol (mmol/liter)	3.78 [3.16, 4.42]	3.70 [3.10, 4.39]	3.75 [3.14, 4.41]
HDL cholesterol (mmol/liter)	1.32 [1.09, 1.56]	1.29 [1.04, 1.53]	1.29 [1.08, 1.54]
Total cholesterol (mmol/liter)	5.74 [5.12, 6.53]	5.67 [5.03, 6.41]	5.70 [5.04, 6.47]
Serum osteocalcin (ng/ml)	21.4 [17.0, 26.6]	20.4 [16.4, 25.4]	20.9 [16.8, 26.1]
Serum N-telopeptide (nmol BCE/liter)	14.0 [11.6, 17.7]	13.9 [11.2, 17.4]	14.0 [11.4, 17.6]
Total lumbar spine BMD ^b (mg/cm ²)	911.13 ± 129.71	905.23 ± 150.68	908.24 ± 140.21

^a Data are mean ± SD, except for bone marker and serum lipid values, which are expressed as medians. The values in the brackets indicate the 25th and 75th percentiles of the population.

^b Baseline bone mineral density (BMD) measurements were obtained in a subset of 328 women at study sites in India, Indonesia, Malaysia, and Thailand. BMD values were standardized according to Hologic calibration.

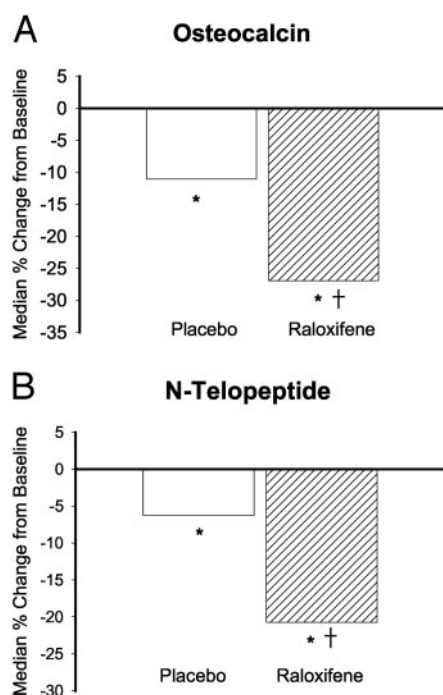


FIG. 1. At 6 months, raloxifene 60 mg/d significantly decreased the serum concentrations of the biochemical markers, osteocalcin (A) and N-telopeptide (B) from baseline (*, $P < 0.05$) and compared with placebo (†, $P < 0.05$).

median percentage changes of 11.1% and 27.0% below baseline, in the placebo and raloxifene groups, respectively. The difference in the median percent change between the groups was statistically significant ($P < 0.001$, Fig. 1A). N-telopeptide values were significantly decreased below baseline by 0.80 nmol bone collagen equivalents (BCE)/liter and 2.95 nmol BCE/liter in the placebo and raloxifene groups, respectively. The median percentage decreases in N-telopeptide were 6.3% and 20.9% in the placebo and raloxifene groups, respectively. The difference in the median percent change between the groups was statistically significant ($P < 0.001$, Fig. 1B). The bone turnover response with raloxifene compared with placebo was consistent between countries, as the treatment-by-country interaction was not significant.

Also, the investigator-by-therapy interaction was not significant.

As a secondary efficacy endpoint, serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were determined at baseline and 6 months. Raloxifene 60 mg/d decreased total cholesterol by a median of 4.64% below baseline ($P < 0.05$) and the 5.34% difference between the raloxifene and placebo groups was significant ($P < 0.05$, Fig. 2A). The median decrease in LDL cholesterol was 7.69% below baseline in the raloxifene group but was unchanged in the placebo group, and the difference between groups was statistically significant ($P < 0.05$, Fig. 2B). HDL cholesterol was significantly increased by 1.51% and 2.67% above baseline in the placebo and raloxifene groups, respectively (Fig. 2C), but the difference between groups was not statistically significant. The triglyceride level was significantly decreased by a median of 1.56% from baseline with raloxifene ($P < 0.05$). The difference in the median percent change between groups was not statistically significant. The serum lipid response with raloxifene compared with placebo was consistent between countries, as the treatment-by-country interaction was not significant. The investigator-by-therapy interaction was also not significant.

A subgroup of 309 women enrolled at sites in India, Indonesia, Malaysia, and Thailand had paired lumbar spine BMD measurements at baseline and 12 months. BMD decreased by 0.3% in the placebo group and increased by 1.5% in the raloxifene 60 mg/d group at 12 months, resulting in a differential increase of 1.9% between groups ($P = 0.0003$, Fig. 3).

The total numbers of women who reported adverse events were not statistically significantly different between groups. Sixteen women in the placebo group (3.3%) and 13 (2.7%) in the raloxifene group discontinued due to adverse events. The incidence of adverse events, which were previously reported in other raloxifene clinical trials, are shown for this Asian population (Table 2). One woman in the raloxifene group reported a rib fracture. The occurrences of vasodilatation (hot flashes) and leg cramps were not significantly different between the placebo and raloxifene groups in the present study (Table 2). The incidence of individual reported adverse events was not significantly different between groups, with the exception of dyspepsia, which was reported by 4 (0.8%)

FIG. 2. At 6 months, raloxifene 60 mg/d significantly changed the concentrations of total cholesterol (A), HDL cholesterol (B), LDL cholesterol (C), and triglycerides (D) from baseline (*, $P < 0.05$). The decreases in total and LDL cholesterol in the raloxifene group were also greater than in the placebo group (†, $P < 0.05$). The levels of HDL cholesterol at 6 months were significantly increased above baseline in both the placebo and raloxifene groups (*, $P < 0.05$).

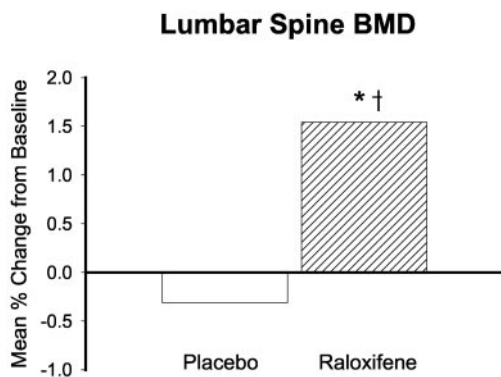
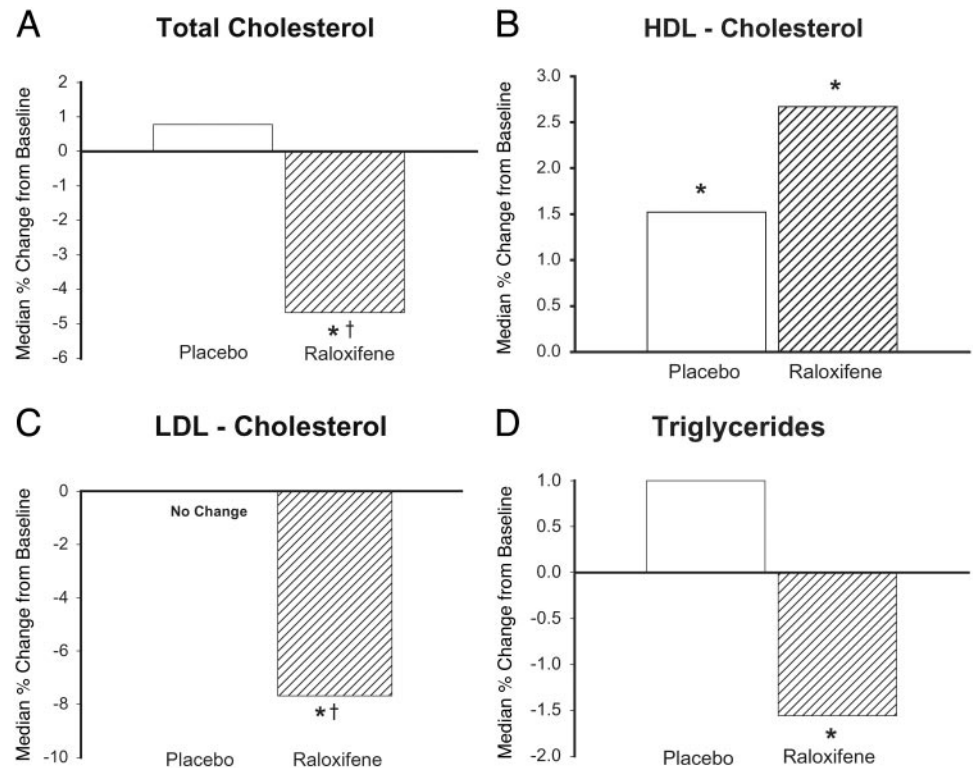


FIG. 3. Raloxifene 60 mg/d significantly increased lumbar spine bone mineral density (BMD) compared with baseline (*, $P < 0.05$) and placebo (†, $P < 0.05$) at 1 yr. Baseline and endpoint lumbar spine BMD measurements were obtained in subgroup of 309 women from India, Indonesia, Malaysia, and Thailand.

and 14 (2.9%) women in the placebo and raloxifene groups, respectively ($P = 0.017$). No case of venous thromboembolic event was reported in this trial.

Discussion

In the first large-scale clinical trial to study the effects of raloxifene in postmenopausal Asian women, raloxifene 60 mg/d was found to have similar effects on biochemical markers of bone turnover, serum lipid concentrations, and lumbar spine BMD to that reported in previous trials involving primarily Caucasian women. In the present study, raloxifene 60 mg/d decreased serum N-telopeptide and osteocalcin levels by medians of 14.6% and 15.9%, respectively, whereas LDL cholesterol, total cholesterol, and triglyceride

concentrations were decreased by medians of 7.7%, 5.3%, and 2.6%, respectively, compared with placebo at 6 months. At 1 yr, raloxifene 60 mg/d increased lumbar spine BMD by 1.9% compared with placebo in postmenopausal Asian women.

The results of the present study are comparable with those reported in other trials involving primarily Caucasian populations (5, 6, 15) or Taiwanese women (16). All of these osteoporosis prevention studies enrolled healthy early postmenopausal women with similar mean age and body mass index at baseline (Table 3). Women in the present study reported a greater number of years since menopause compared with the European cohort, despite the similarity in mean age at baseline (Table 3). Although it is believed that Asian women experience menopause at an earlier age, two epidemiological studies, each involving over 2000 women, have found the mean age of menopause to be around 51 yr in Caucasians (17) and Asians (18). Although the calcium supplementation used in this study (250 mg/d) was less than that used in other raloxifene studies, the osteocalcin and N-telopeptide levels were significantly decreased from baseline in the placebo group. These calcium supplements may have effects on bone turnover, due to the low dietary calcium intake of less than 500 mg/d in Asians (19).

In all raloxifene studies, osteocalcin and N-telopeptide levels were consistently decreased by median changes of 11–30% below baseline (Table 3), despite the biological fluctuations in bone remodeling and assay imprecision that may cause differences in the magnitude of change (20). The median 9.8% reduction in serum N-telopeptide observed at 6 months was half of the median 21.2% decrease in urinary N-telopeptide observed at 12 months in the multinational

TABLE 2. Adverse events that were also reported in other trials with raloxifene

Adverse event	Placebo (n = 485)	Raloxifene 60 mg/d (n = 483)	P value
Vasodilatation ^a	17 (3.5%)	27 (5.6%)	0.12
Dizziness	14 (2.9%)	8 (1.7%)	0.20
Sweating	3 (0.6%)	3 (0.6%)	1.00
Peripheral edema	2 (0.4%)	2 (0.4%)	1.00
Leg cramps	13 (2.7%)	21 (4.3%)	0.16
Venous thromboembolism	0 (0%)	0 (0%)	1.00
Serious treatment-emergent adverse events	12 (2.5%)	13 (2.7%)	0.83

^a Reported as hot flashes or hot flushes.

TABLE 3. Comparison of raloxifene trials in healthy postmenopausal women of different ethnic backgrounds: baseline characteristics and baseline to endpoint changes^a

Baseline characteristics	Asia Pacific ^b (n = 483)	Taiwan ^c (n = 92)	European ^d (n = 152)	Multinational ^e (n = 286)	Euralox ^f (n = 495)
Ethnic background	100% Asian	100% Asian	99% Caucasian	99% Caucasian	98.6% Caucasian
Age (yr)	57.3	57.0	55	54.9	56.1
Years since menopause	9.5	Not available	5	Not available	7.1
Body mass index	24.9	Not available	25.9	26.5	25.9
Baseline to endpoint changes					
Triglycerides	−1.6%	+3.2%	+3.2% ^g	+1.8% ^h	−3.6%
LDL cholesterol	−7.7%	−14.0%	−10.1% ^g	−7.6% ^h	−3.8%
HDL cholesterol	+2.7%	+6.5%	−3.7% ^g	−2.0% ^h	+4.2%
Total cholesterol	−4.6%	−4.9%	−6.4% ^g	−5.9% ^h	−7.2%
Serum osteocalcin	−27.0%	−17.5%	−15.0% ^g	−30.3% ^h	Not done
Serum N-telopeptide	−20.9%	Not done	Not done	−11.4% ⁱ	Not done
Lumbar spine BMD	+1.5%	+1.4%	+1.6% ^g	+1.3% ^h	Not done

^a Presented data were from (n) women in the raloxifene 60 mg/d group in each study. Bone marker and serum lipid data were reported from the 6-month time point, except as indicated. BMD data were reported from the 12-month time point, except as indicated. Baseline values were presented as means. Changes from baseline to endpoint were presented as median percentages, except for BMD, which was presented as mean percentages.

^b The present trial, conducted in 10 Asian countries, had a placebo arm.

^c This trial, conducted in Taiwan, had a hormone replacement therapy comparator arm (16).

^d This trial, conducted in eight Western European countries, had four arms (placebo, raloxifene 30, 60, and 150 mg/d) (5).

^e This trial, conducted in the U.S., Canada, and eight Western European countries, had four arms (placebo, raloxifene 30, 60, and 150 mg/d) (6).

^f This trial, conducted in Israel, South Africa and 17 European countries, had a hormone replacement therapy comparator arm (15).

^g Data were from the 24-month endpoint.

^h Data were from the 36-month endpoint, except as indicated.

ⁱ Serum N-telopeptide was measured at 12 months.

raloxifene study (6) and reflects the differences between the serum and urinary N-telopeptide assays (21). The increases in lumbar spine BMD ranged from 1.3–1.6% from baseline in early postmenopausal Caucasian and Asian women treated with raloxifene 60 mg/d for 1–3 yr (Table 3). The efficacy of raloxifene on bone turnover, serum lipids, and BMD in Asian women is generally comparable to that observed in Caucasian women.

The median changes in total and LDL cholesterol levels from baseline to 6 months in the raloxifene 60 mg/d group (Table 3) were similar to the 2- and 3-yr changes observed in other raloxifene studies involving primarily Caucasian women (5, 6), suggesting that effects on serum lipids may be achieved after 6 months. Raloxifene 60 mg/d decreased serum triglycerides by a median of 4% from placebo at 6 months in early postmenopausal Caucasian women (9), compared with the median 1.6% decrease in the present study. The larger percentage decrease may be partly explained by lower baseline triglyceride levels, which were 1.10 mmol/liter in the previous study (9), and 1.21 mmol/liter in the present study. Other baseline characteristics, such as mean age, years past menopause, and body mass index were sim-

ilar in the present Asian population and the previous trial (9). Changes in serum lipids observed in Asian women at 6 months are comparable to those observed in longer-term raloxifene studies involving Caucasian women.

In contrast, the safety profile of raloxifene in the Asian women studied in this trial differed from that reported in other studies of Caucasian women. The overall incidence of vasodilatation reported in the present study was less than 5% and was not significantly different between placebo and raloxifene. The reported incidence of hot flashes was approximately 25% with raloxifene 60 mg/d in other trials, which lasted up to 30 months (6, 12, 13). However, the only significant difference (7%) in the cumulative incidence of hot flashes between placebo and raloxifene was reported within the first 6 months (12), suggesting that most reports of hot flashes would have been captured in the 6-month time frame of the present study. Although the occurrence of menopausal symptoms such as hot flashes was lower in postmenopausal Asian women compared with Caucasians, there is great variability in the incidence and severity of reported symptoms between Asian countries (18, 22). The only adverse event that was statistically significant between groups in this trial was

dyspepsia, which was reported by 4 and 14 women in the placebo and raloxifene groups, respectively. The clinical significance of this result is unclear, as various symptoms were described and all reported cases of dyspepsia were minor and did not result in discontinuation. While no cases of venous thromboembolic events were reported in the present study, there was inadequate statistical power to determine the incidence of venous thromboembolic events, which are uncommon. The incidence of idiopathic venous thromboembolic events was 6/100,000 person-yr in Asian women, compared with 23/100,000 person-yr in Caucasian women (23). Thus, venous thromboembolic events may not have been observed in this study of 968 women, the majority of which were in the study for 6 months. It is not known if any venous thromboembolic event could have occurred if all women were in the study for 1 yr. In summary, raloxifene has a favorable safety profile in this population of postmenopausal Asian women.

The present study has some limitations. While raloxifene had changes in bone markers and serum lipids at 6 months, studies of longer duration are necessary to directly compare these changes to those observed in Caucasian women after 2 or 3 yr. Also, 1-yr changes in lumbar spine BMD may not reflect the full extent of raloxifene efficacy, as other studies have shown that BMD at other sites continues to increase after 1 yr (5). Even though comparisons of results between countries showed remarkable homogeneity, there may be subtle differences in raloxifene efficacy among Asian women from different ethnic backgrounds and geographic regions that were not apparent in the present analyses, which combined the results from several countries. As fractures were not a predefined study endpoint, scheduled spinal radiographs were not taken in this study. Fractures were captured as adverse events, irrespective of associated trauma, and were not confirmed with radiographs. Changes in BMD and bone turnover markers are independent predictors of subsequent fracture risk, and a combination of these endpoints may be more predictive than either endpoint alone (24). In addition, this study did not examine other factors that contribute to bone strength and fracture risk, such as microarchitecture and degree of mineralization (24). The patient's age, extraskeletal risk factors for fracture, type of fracture, ethnicity, geography, and cost-effectiveness of treatment are additional considerations for making clinical decisions on therapeutic intervention for osteoporosis (25).

In conclusion, this study demonstrates that the efficacy of raloxifene on bone turnover, serum lipid concentrations, and BMD in Asian women is similar to that previously reported in Caucasian populations, whereas the tolerability profile may be different in Asian women.

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