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Benefit-Risk Assessment of Raloxifene in Postmenopausal Osteoporosis

Ann Cranney[1] and *Jonathan D. Adachi*[2]

1 Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada
2 Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Contents

Abstract

Raloxifene, a nonsteroidal benzothiophene, is a second-generation selective estrogen receptor modulator (SERM) that is an antiresorptive agent. Raloxifene is a non-hormonal agent that binds to the estrogen receptor and results in estrogen agonist effects on bone and the cardiovascular system and estrogen antagonist effects on endometrial and breast tissue. Raloxifene has diverse pharmacodynamic properties due to its differential interactions with the estrogen receptor and tissue selectivity. Raloxifene was the first SERM to be approved for the prevention and treatment of postmenopausal osteoporosis. In this review, we conducted a systematic search of the literature for trials that evaluated the following outcomes: bone density, fractures, quality of life, cardiovascular outcomes, safety and adverse events. Raloxifene at the approved dosage of 60 mg/day increased lumbar spine bone density by 2.5% relative to control after 2 years of therapy. A large fracture prevention trial confirmed that treatment with raloxifene 60 mg/day for 3 years decreased the relative risk of incident vertebral fractures by 30–50% in women with prevalent fractures or osteoporosis. Extraskeletal effects of raloxifene include a reduction in total cholesterol and low density lipoprotein cholesterol levels. Assessment of the safety profile revealed that raloxifene was not associated with endometrial hyperplasia and that there was a 72% reduction in the incidence of invasive breast cancer in raloxifene-treated postmenopausal women

with osteoporosis. Adverse events associated with raloxifene included an increase in the absolute risk of venous thromboembolism and an increase in the risk of hot flashes and leg cramps. In comparison to other osteoporosis therapies, raloxifene has a lesser impact on bone mineral density, a similar effect on the occurrence of vertebral fractures, but no effect on the frequency of non-vertebral fractures. Raloxifene can be recommended for the prevention of vertebral fractures in women with osteopenia/osteoporosis who are not at high risk of non-vertebral fractures and who do not have a past history of venous thromboembolism.

The complications of postmenopausal osteoporosis are associated with a significant socioeconomic burden. Although hip fractures account for the majority of the costs of osteoporotic fractures, vertebral fractures are one of the most common fractures and women with a vertebral fracture have a 20% chance of a subsequent vertebral fracture within the following year.[1] Osteoporosis-related fractures are associated with significant morbidity and increased mortality.[2] Despite available treatments, long-term adherence with antiosteoporosis therapies is often poor.[3] A therapy that has both proven efficacy for fracture reduction and an acceptable long-term safety profile would be the preferred option for the prevention and treatment of postmenopausal osteoporosis. The results of the Women's Health Initiative (WHI) study highlight long-term safety issues and the need to demonstrate that benefits outweigh harm prior to recommending a preventive treatment for postmenopausal osteoporosis.[4] Raloxifene is a long-term treatment option for postmenopausal osteoporosis, especially for those women who have discontinued hormone replacement therapy (HRT). Raloxifene was approved in 1997 in the US and 1998 in the UK and has been prescribed to over 7 million women in 93 countries.[5]

The focus of this review was the efficacy and safety of raloxifene for the prevention and treatment of postmenopausal osteoporosis.

1. Data Selection

A comprehensive search strategy of MEDLINE, EMBASE, CINAHL, the Cochrane Library and PubMed from 1996 to April 2004 was supplemented with a review of US FDA reports[6] and reference lists from retrieved articles. Search keywords included 'postmenopausal osteoporosis', 'fractures', 'raloxifene', 'evista', 'cardiovascular disease' and 'adverse events'. Randomised trials, data from preclinical studies, case reports, postmarketing surveillance and observational studies were eligible for inclusion and relevant pharmacokinetic and pharmacodynamic articles were also included. Adverse event databases including MedWatch and the Adverse Event Reporting System (AERS) of the FDA were reviewed for reports relevant to raloxifene.[7] The literature search yielded 336 potentially relevant articles and ten additional references were retrieved from a search of the adverse event databases.

2. Pharmacodynamics

2.1 Mechanism of Action

Raloxifene is a selective estrogen receptor modulator (SERM) that acts as a competitive inhibitor of 17-β estradiol at the estrogen receptor. The term SERM is used to describe compounds that interact with the estrogen receptor, but have tissue-specific activities that differ from estrogen. Raloxifene acts as an estrogen antagonist on the endometrium and breast, but has estrogen agonist effects on both bone and the lipid profile.[8] In the body, there are multiple estrogen receptors (ERs), both nuclear and membrane-bound, with two isoforms of the nuclear receptors, α and β. These α and β receptors are found in different proportions in many body tissues. Estrogen α receptors are usually activators, while estrogen β receptors can inhibit estrogen α receptors. Both types of receptors contain two transcription-activating factors and differences in the function of these two factors, combined with coactivator and corepressor proteins and the differential activation of distinct regions of the estrogen receptor, may explain the mixed estrogen-agonist antagonist actions of raloxifene.[9,10] Binding of the raloxifene

ligand to the estrogen receptor results in a conformational change of the receptor and prevents key coregulator proteins from interacting and activating the estrogen receptor.[9] Raloxifene also activates the gene that codes for transforming growth factor β3 (TGF-β3), which then increases the rates of programmed death of osteoclasts and differentiation of osteoblasts and regulates bone remodelling.[10] In addition, raloxifene reduces the production of interleukins that stimulate osteoclast recruitment, differentiation and activity, such as interleukin-6, resulting in reduced bone resorption.[11]

Raloxifene has been shown to reduce levels of both bone formation (serum osteocalcin) and bone resorption markers (urinary C-telopeptide and N-telopeptide).[12-14]

3. Pharmacokinetics

Raloxifene is absorbed rapidly after oral administration and approximately 60% of the oral dose is absorbed from the gastrointestinal tract.[15,16] Raloxifene undergoes extensive first pass glucuronidation in the liver. Peak plasma concentrations occur 6 hours after oral administration. The median bioavailability of raloxifene is only 2% in postmenopausal women and plasma elimination half-life is 27.7 hours.[16] Raloxifene is highly bound to plasma proteins (>95%) *in vitro*.[17] The pharmacokinetics of raloxifene may be altered in patients with hepatic dysfunction, but not in those with renal impairment. Raloxifene is primarily excreted in the faeces and <0.2% is excreted unchanged in the urine.[17]

3.1 Drug Interactions:

Raloxifene does not alter the binding of other highly protein-bound drugs *in vitro*, although it does have the potential to affect protein binding of drugs such as diazepam and lidocaine; therefore, raloxifene should be used with caution in patients taking these medications.[12] Coadministration of warfarin with raloxifene produces significant reductions in the clearance and volume of distribution of warfarin, and also reduces the maximum prothrombin response to warfarin and the prothrombin area under the concentration-time curve.[18] For this reason, close monitoring of anticoagulation is recommended in patients taking warfarin who commence or discontinue raloxifene treatment. Cholestyramine causes a 60% reduction in the absorption and enterohepatic cycling of raloxifene and, therefore, coadministration with raloxifene is not recommended.[5]

In a case report, Siraj et al.[19] documented a potential interaction between raloxifene and levothyroxine in a 79-year-old woman with primary hypothyroidism and pernicious anaemia. This woman experienced increasing levothyroxine requirements 2–3 months after she started taking raloxifene 60 mg/day. The woman's hypothyroidism improved when she took both medications separately and reoccurred when the two medications were administered together. The mechanism of malabsorption of levothyroxine was not certain.

4. Therapeutic Use

4.1 Efficacy of Raloxifene for Fracture Prevention

We reviewed randomised controlled trials of raloxifene that included bone mineral density (BMD) or fractures as an outcome.[12,13,20-25] Of eight trials, only two evaluated fractures as an endpoint[13,22] and only the MORE (Multiple Outcomes of Raloxifene Evaluation) trial was adequately powered to assess differences in the frequency of vertebral fractures between treatments.[13] A smaller 1-year trial by Lufkin et al.[22] (n = 143), which included 133 patients who had follow-up x-rays, was not designed to detect a reduction in fractures. The mean age of the women in this trial was 68.4 years, the mean BMD T score was −2.4 and all participants had at least one prevalent vertebral fracture. Women were randomised to raloxifene 60 mg/day, raloxifene 120 mg/day or control. For vertebral fractures the relative risk (RR) was 1.16 (95% CI 0.77, 1.76; p = 0.48) and for non-vertebral fractures the RR was 0.52 (95% CI 0.12, 2.18; p = 0.37); both were non-significant. The Lufkin et al.[22] trial defined a vertebral fracture by either a ≥15% or a ≥30% decrease in vertebral height, and with the 15% reduction as the cutoff, raloxifene did not reduce incident vertebral fractures. However, when a more conservative limit of 30% was used, a dose-related reduction in vertebral fractures was observed.[22,26]

Table I. Clinical outcomes – absolute benefit-risk (derived from results of the MORE [Multiple Outcomes of Raloxifene Evaluation] trial)[13,27]

Outcome	Absolute risk			Number needed
	controls (%)	raloxifene (%)	difference (%)	to treat
Radiographic vertebral fractures (60 mg/d)	10	6.5	+3.5	29
Radiographic vertebral fractures (60 and 120 mg/d) 3y	10	5.9	+4.1	25
Clinical vertebral fractures in women with osteopenia	1.25	0.30	+0.95	100
Breast cancer	1.1	0.3	+0.8	132
Venous thromboembolism	0.30	0.95	−0.65	154[a]

a Number needed to harm.

In the MORE study, women with osteoporosis with a T score below −2.5 (group I) or with a low BMD and one or more prevalent vertebral fractures (group II) were randomised to either raloxifene (60 or 120 mg/day) or control.[13] This study enrolled 7705 women and 6828 women had follow-up x-rays. All women received supplemental calcium (500 mg/day) and vitamin D_3 (400–600 IU/day). Primary endpoints included incident vertebral fractures and BMD of the lumbar spine and femoral neck. Radiographic vertebral fractures were defined as a decrease in anterior, mid or posterior vertebral height of ≥20% and ≥4mm. The mean age of women was 66.5 years and the mean lumbar spine T score was −2.6. There was a statistically significant overall reduction in the risk of new radiographic vertebral fractures of 30% (RR 0.7; 95% CI 0.50, 0.80) after 3 years of treatment with raloxifene 60 mg/day. In women treated with raloxifene 60 mg/day, the risk of new vertebral fractures was decreased by 30% in those with osteoporosis and prevalent fractures and by 50% in those with osteoporosis but no prevalent vertebral fracture. There was a significant 60% RR reduction in clinical vertebral fractures (incident vertebral fracture on x-ray associated with acute back pain) after 3 years of treatment with raloxifene (RR 0.4; 95% CI 0.3, 0.7).

The number that would need to be treated with raloxifene 60 mg/day to prevent one radiographic vertebral fracture was 46 for women without osteoporosis and no prevalent fractures and the number that would need to be treated in women with prevalent vertebral fractures was 16.[13] From the MORE trial, the number that would need to be treated to prevent one clinical vertebral fracture with raloxifene was 100 for women with osteopenia and 91 for women with osteoporosis[27] (table I).

A recent *post hoc* analysis of women with osteopenia and osteoporosis without vertebral fractures found that for women with osteopenia, raloxifene decreased the risk of incident vertebral fractures (RR 0.53; 95% CI 0.32, 0.88) and the risk of clinical vertebral fractures, although the number of clinical vertebral fractures was very small.[27] Analysis of 4-year data confirmed the continued efficacy of raloxifene for the reduction of vertebral fractures (RR 0.60; 95% CI 0.52, 0.69).[28] After 1 year of therapy with raloxifene 60 mg/day there was a significant reduction in clinical vertebral fractures with an RR of 0.32 (95% CI 0.13, 0.80), which corresponded to a risk reduction of 68%.[29]

For non-vertebral fractures, after 3 years of therapy with raloxifene the RR was 0.9 (95% CI 0.8, 1.1), consistent with a non-significant reduction in non-vertebral fractures.[13] A similar RR was noted in the results of a 4-year extension trial.[28] A *post hoc* analysis of the MORE data showed that in women with severe prevalent vertebral fractures (n = 614), raloxifene decreased the risk of new non-vertebral fractures by 47%, with an RR of 0.53 (95% CI 0.29, 0.99; p = 0.046).[30]

The reduction in vertebral fractures seen with raloxifene is similar to that reported with potent nitrogen containing bisphosphonates, although the reduction in fractures appears to be only partially explained by changes in BMD.[31] The relationship between vertebral fracture reduction and BMD was examined in a logistic regression analysis and the authors found that only 4% of the observed reduction in fracture risk could be accounted for by an increase in bone density.[31]

An analysis of biochemical markers of bone formation in a subgroup of women from the MORE trial revealed that patients with the greatest changes in osteocalcin and bone-specific alkaline phosphatase appeared to have the largest reduction in vertebral fracture risk.[14] Bone biopsy studies in patients treated with raloxifene have not shown any evidence of qualitative abnormalities, such as marrow fibrosis or mineralisation defects. Raloxifene has been demonstrated to decrease the activation frequency and bone formation in a fashion similar to that seen with HRT.[32]

Riggs and Hartmann[11] have suggested that reduction of vertebral fractures by raloxifene results from the normalisation of bone turnover, prevention of further micro-architectural disruption and prevention perforation of trabecular plates by osteoclasts.

4.2 Effects on Bone Mineral Density

BMD was evaluated as a surrogate outcome in multiple trials of raloxifene.[12,13,20,21,25] In a dose-finding trial by Delmas et al.,[24] the dosages of raloxifene included 30, 60 or 150 mg/day; the greatest increases in lumbar spine BMD were seen with the 150 mg/day dosage and the greatest increases in total hip BMD were seen with the 60 mg/day dosage. In the prevention trial, 2 years of treatment with raloxifene 60 mg/day resulted in increases in BMD of 2.4%, 2.4% and 2.0% for lumbar spine, total hip and total body BMD, respectively, compared with placebo.

In a meta-analysis of results of four prevention and treatment trials (n = 6053), 2 years of treatment with raloxifene was associated with an increase in lumbar spine BMD of 2.51% (95% CI 2.21, 2.82; $p < 0.01$), with increases of 1.33% in total body BMD and 2.11% in hip BMD.[33] The effect of raloxifene on the BMD of the lumbar spine, femoral neck and total hip was similar in both the prevention and treatment trials.

There is also evidence that raloxifene prevents the bone loss that is associated with use of gonadotropin-releasing hormone (GnRH), as shown in one randomised trial in premenopausal women treated for uterine leiomyomas with leuprolide acetate, a GnRH agonist.[34]

4.3 Effects on Health-Related Quality of Life

Vertebral fractures have been shown to be associated with chronic back pain and impaired health-related quality of life (QOL).[35] In the MORE trial, the effect of prevalent and incident vertebral fractures on QOL was evaluated using the disease-specific Osteoporosis Quality of Life Assessment Questionnaire (OPAQ) in a subset of 1395 women.[36] Women with prevalent vertebral fractures at baseline had significantly lower OPAQ scores for physical function, emotional status, clinical symptoms and overall health-related QOL than women without prevalent fractures. There was no documented improvement in QOL in women with osteoporosis who were treated with raloxifene when compared with controls.

QOL was also assessed in a 1-year trial comparing raloxifene and estrogen in healthy postmenopausal women. In this trial, QOL was assessed using the validated Women's Health Questionnaire (WHQ), which is designed to measure physical and emotional well being.[37] Mean total QOL domains were not affected by treatment with raloxifene, but anxiety/fear scores improved with raloxifene, while estrogen had no effect. Neither raloxifene nor estrogen had effects on the memory, depressed mood, sleep problems or attractiveness domains of the WHQ. Another study that included QOL as a secondary endpoint found that raloxifene was associated with a trend towards an improvement in a number of domains, although there was no significant difference when compared with controls.[38] Modugno et al.[39] evaluated the effect of raloxifene on sexual function in a subset of participants in the MORE trial and found that changes in sexual function did not differ between the raloxifene and placebo groups. Two trials included an evaluation of the effect of raloxifene on cognitive function and both trials did not show a negative impact on this parameter, despite an increase in the incidence of hot flashes.[40,41]

4.4 Effects on Other Organ Systems

Extraskeletal effects of raloxifene compared with placebo include a significant reduction in surrogate markers of cardiovascular risk. Raloxifene 60 mg/day resulted in decreased levels of serum low-densi-

ty lipoprotein cholesterol, lipoprotein B, total cholesterol, homocysteine, tumour necrosis factor-α and serum fibrinogen.[25] In contrast with HRT, raloxifene was not associated with significant changes in high density lipoprotein cholesterol, triglyceride, tissue plasminogen activator or C reactive protein levels. To date, there has been no evidence of increased risks of cardiovascular outcomes with raloxifene in comparison with results seen with HRT in the WHI.[42,43] In the subset of women at increased risk of cardiovascular disease, there was a significantly decreased risk of cardiovascular events in those treated with raloxifene versus control (RR 0.60; 95% CI 0.38, 0.95).[42] The impact of raloxifene on cardiovascular endpoints will be further clarified after the completion of the RUTH (Raloxifene for Use in The Heart) trial, that has enrolled women who have either pre-existing heart disease or are at increased risk of major coronary events.[44] Cardiovascular endpoints include coronary death, nonfatal myocardial infarction and coronary revascularisation procedures. RUTH also includes the incidence of breast cancer as a co-primary endpoint.

The uterine safety of raloxifene has been evaluated in both preclinical and clinical trials and, unlike HRT or tamoxifen, raloxifene does not stimulate the uterus. Raloxifene has not been associated with an increased rate of vaginal bleeding, endometrial hyperplasia or endometrial carcinoma when compared with placebo.[24,45,46] Compared with continuous combined HRT, raloxifene did not cause vaginal bleeding and was not associated with increased endometrial thickness or uterine volume at 12 months.[47] A case report by Maia et al.[48] has described the development of an endometrial polyp in a woman taking raloxifene. The incidence of urinary incontinence was significantly greater among women who were treated with unopposed estrogen than in women treated with raloxifene.[49]

Raloxifene has been shown to reduce the risk of invasive breast cancer by 72% compared with placebo after 4 years of treatment in the MORE trial.[50-52] However, no reduction was seen in the occurrence of estrogen receptor negative breast cancer. Breast cancer was not a primary endpoint in the MORE trial and the baseline risk of breast cancer for women in each arm of the study was not available. Raloxifene is not currently indicated for breast cancer prevention. Additional information on the effects of raloxifene on the occurrence of breast cancer has recently become available from CORE (Continuing Outcomes Relevant to Evista), a 4-year, follow-up trial of subjects enrolled in the MORE trial. Raloxifene continued to reduce the risk of invasive breast cancer and estrogen receptor positive invasive breast cancer with reductions in risk of 59% and 66%, respectively.[53] An ongoing randomised trial, STAR (Study of Tamoxifen And Raloxifene), is designed to evaluate the efficacy of raloxifene 60 mg/day versus tamoxifen 20 mg/day in women at high risk of breast cancer, and will provide additional information on the role of raloxifene for the chemoprevention of invasive breast cancer.[54]

5. Tolerability and Safety of Raloxifene

The main adverse effect seen with raloxifene is an increased risk of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, and this risk is highest in the initial 2 years of treatment. The RR for deep vein thrombosis with raloxifene versus control after 3 years was 3.1 (95% CI 1.5, 6.2) and the RR for pulmonary embolism was 4.5 (95% CI 1.1, 19.5).[13] The risk of VTE with raloxifene is similar to that described with HRT and is highest in the initial 4 months, although the risk persists.[53,55] In the follow-up CORE trial the RR for thromboembolism in the raloxifene group was 2.17 (95% CI 0.83, 5.70) compared with placebo.[53] The estimated number needed to harm with raloxifene is 154, so that for every 154 women treated with raloxifene for 3 years, one case of VTE will be diagnosed (table I). VTE events were increased in the breast cancer prevention trials with raloxifene.[52] Azevedo et al.[56] demonstrated in a small group of postmenopausal women that raloxifene therapy was associated with reductions of plasma antithrombin activity. Retinal vein thrombosis has been reported rarely in both clinical trials and postmarketing surveillance studies.[57]

Other concerns are that women who have developed marked triglyceridaemia (>5.6 mmol/L) in response to estrogen treatment may develop elevated triglyceride levels with raloxifene; in addition, a potential adverse effect of raloxifene was highlighted in a case report of a 49-year-old postmenopausal woman who developed hepatitis, jaundice, morbili-

form rash and eosinophilia, 30 days after starting raloxifene treatment.[58]

There was an increased risk of discontinuation due to adverse events associated with raloxifene when compared with placebo in a meta-analysis of three randomised trials.[31] Raloxifene was associated with adverse effects such as leg cramps and hot flashes.[49] The pooled risk for leg cramps with raloxifene was increased, but not significantly (RR 1.64; 95% CI 0.84, 3.20; p = 0.15). There was a significant increase in hot flashes with raloxifene compared with placebo, with a RR of 1.46 (95% CI 1.23, 1.74; p < 0.01) based on pooled results from four trials; 12.5% of postmenopausal women experiencing hot flashes with raloxifene compared with 7.7% of those receiving placebo.[33] The incidence of hot flashes decreased over time. Other potential adverse events include an influenza-like syndrome and peripheral oedema.[28] Unlike tamoxifen, raloxifene was not associated with an increased risk of cataracts (RR 0.9; 95% CI 0.8, 1.1), vaginal bleeding, or endometrial cancer (RR 0.9, 95% CI 0.3, 2.7).[59] In clinical trials, raloxifene was not associated with an increase in breast pain, although one case report documented a postmenopausal woman who developed breast pain associated with increased breast density after starting raloxifene.[60]

Analysis of the MORE trial results revealed an increase in treatment-emergent diabetes in the raloxifene arm; however, the clinical significance of this finding is uncertain and subsequent studies have shown that raloxifene does not affect glycaemic control in women with or without diabetes.[43,61]

6. Efficacy and Safety of Raloxifene Compared with Other Osteoporosis Therapies

Bisphosphonates are antiresorptive therapies that have similar treatment indications to raloxifene in many countries. These agents can have a greater effect on BMD (4–8% increase in the lumbar spine) than raloxifene (2.6%).[62] This difference has been also noted in head-to-head comparison trials of raloxifene and alendronate (increase in total hip BMD of 2.3% with alendronate vs 0.8% with raloxifene).[20,63,64] Johnell et al.[20] conducted a 1-year randomised trial in 331 postmenopausal women with osteoporosis (T score <−2.0) and found that increases in the surrogate outcome of lumbar spine BMD were greater with raloxifene and alendronate combined (5.3%) than with alendronate (4.3%) or raloxifene alone (2.1%). Bisphosphonates (alendronate, risedronate) and anabolic agents such as teriparatide (parathyroid hormone 1-34) have proven efficacy for the reduction of vertebral fractures and for the reduction of non-vertebral fractures (table II).[62,65] Raloxifene has similar efficacy in the reduction of vertebral fractures when compared with other osteoporosis therapies, although there are no published comparative trials. However, raloxifene has not been shown to reduce the risk of hip or overall non-vertebral fractures, except in a *post hoc* analysis of individuals with severe prevalent vertebral fractures.[30]

Bisphosphonates do not have the safety concern of the increased risk of venous thromboembolic disease observed with raloxifene. However, they are associated with an increased risk of upper gastrointestinal adverse effects, such as esophageal erosions and ulcerative esophagitis, whereas raloxifene is not.[67,68] These adverse gastrointestinal events have been documented in both clinical trials[69-71] and postmarketing surveillance studies and tend to occur more commonly in patients with a prior history of upper gastrointestinal tract disease.[68,72,73]

Table II. Efficacy of osteoporosis therapies

Fracture	Raloxifene[13] [RR (95% CI)]	Alendronate[66] [RR (95% CI)]	Etidronate[62] [RR (95% CI)]	Risedronate[62] [RR (95% CI)]	Teriparatide[65] [RR (95% CI)]	HRT[4] [RR (95% CI)]
Vertebral fractures	0.6 (0.52, 0.69)	0.52 (0.43, 0.65)	0.63 (0.44, 0.92)	0.64 (0.54, 0.77)	0.35 (0.22, 0.55)	0.66 (0.44, 0.98)
Non-vertebral fractures	0.9 (0.8, 1.1)	0.51 (0.38, 0.69)	No effect	0.73 (0.61, 0.87)	0.47 (0.25, 0.88)	0.66 (0.45, 0.98)

HRT = hormone replacement therapy; **RR** = relative risk.

7. Pharmacoeconomic Considerations

The National Institute for Clinical Excellence (NICE) conducted an economic analysis and modelled the effect of raloxifene on vertebral fractures, including potential benefits on breast cancer. The cost effectiveness of raloxifene (vs no treatment except adequate calcium and vitamin D) was dependent on whether the impact on breast cancer (RR 0.38) was included. When the breast cancer benefit was included the cost per quality-adjusted life-year gained was ≤£27 998 for women with a fragility fracture and osteoporosis.[26] When the breast cancer benefit was not included, the cost per quality-adjusted life-year for all risk and age groups was >£75 000, except for those women aged 70 and 80 years with a doubled risk of osteoporosis fracture (T score 3.2) or other risk factors.[26]

8. Place of Raloxifene in the Management of Postmenopausal Osteoporosis

Raloxifene represents an antiresorptive therapy that can be recommended for the prevention and treatment of osteoporosis in postmenopausal women. There is strong evidence that raloxifene increases bone density and reduces vertebral fractures, although the effect on bone density is less than that seen with other antiresorptive agents such as alendronate and risedronate. There is no currently proven overall efficacy of raloxifene on nonvertebral fractures apart from efficacy data from a *post hoc* analysis of women with severe prevalent fractures.[30] For this reason, raloxifene may be best suited for the prevention of osteoporotic fractures in women with osteoporosis or osteopenia who are not at high risk of non-vertebral or hip fractures. Raloxifene should not be prescribed to women with a significant past history of VTE.[11,74]

A technology report by NICE recommended that raloxifene be used as a treatment option for women who are intolerant to bisphosphonates or as an alternative to HRT.[26] Future trials evaluating the impact on breast cancer, cardiovascular and cerebrovascular outcomes will further clarify the benefit-risk profile of raloxifene. At this time, raloxifene seems to be most appropriate for women who are at increased risk for vertebral fractures, especially those who are intolerant to nitrogen containing bisphosphonates. Raloxifene may also represent a therapeutic option for women discontinuing HRT who are not troubled by menopausal symptoms and have osteopenia/osteoporosis.

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Correspondence and offprints: Dr *Ann Cranney*, C402, Clinical Epidemiology Program, Ottawa Hospital Civic Campus, Ontario, 1053 Carling Avenue, Ottawa, K1Y 4E9, Canada.