Hormones and Healthy Bones
Joint Project of
National Osteoporosis Foundation and Association of Reproductive Health Professionals

Literature Review (January 2009)
Breast Cancer Treatment

1. Albrand G, Terret C. Early breast cancer in the elderly: assessment and management considerations. *Drugs Aging.* 2008;25:35-45.
   Abstract: Breast cancer is a common tumour in the elderly and management of early disease in particular is a major challenge for oncologists and geriatricians alike. The process should begin with the Comprehensive Geriatric Assessment (CGA), which should be undertaken before any decisions about treatment are made. The important role of co-morbidities and their effect on life expectancy also need to be taken into account when making treatment decisions.The primary treatments for early breast cancer are surgery, adjuvant radiotherapy and adjuvant systemic therapy. Unfortunately, lack of a specific literature relating to early breast cancer in the elderly means formulating an evidence-based approach to treatment in this context is difficult. We have developed a new approach based on the CGA and comprehensive oncological assessment. This approach facilitates the development of an individualized oncogeriatric care plan and follow-up based on several considerations: the average patient's life expectancy at a given age; the patient's co-morbidities, level of dependence, and the impact of these considerations on diagnostic and therapeutic options as well as life expectancy; and the potential benefit-risk balance of treatment.In the elderly patient with breast cancer, the standard primary therapy is surgical resection (mastectomy or breast-conserving therapy). While node dissection is a major component of staging and local control of breast cancer, no data are available to guide decision-making in women aged >70 years. Primary endocrine therapy (tamoxifen) should be offered to elderly women with estrogen receptor (ER)-positive breast cancer only if they are unfit for or refuse surgery. Trials are needed to evaluate the clinical effectiveness of aromatase inhibitors as primary therapy for infirm older patients with ER-positive tumours. Breast irradiation should be recommended to older women with a life expectancy >5 years, particularly those with large tumours, positive lymph nodes or negative hormone receptors. Adjuvant hormone therapy remains a reasonable therapeutic option in elderly women with positive hormone receptor tumours. Aromatase inhibitors have demonstrated a better toxicity profile and effectiveness as adjuvant therapy than tamoxifen in young postmenopausal women but have not been specifically studied in the elderly population. The efficacy of adjuvant chemotherapy for breast cancer has been established by meta-analysis and numerous randomized trials but, again, women aged > or = 70 years have rarely been included in such trials. At present, it is difficult to provide a validated recommendation for use of adjuvant chemotherapy in elderly patients with breast cancer.There are no follow-up recommendations specifically for elderly patients after treatment of early breast cancer. However, American Society of Clinical Oncology breast cancer surveillance guidelines suggest physician office visits every 3-6 months for 3 years, followed by visits every 6-12 months for 2 years, then annually. Women taking aromatase inhibitors should also undergo bone mineral density measurement every 2 years.The new approach to assessment and management of early breast cancer in the elderly outlined in this article should be considered an intermediate step because additional evidence to support clinical practice is still needed. Bearing this in mind, physicians should encourage enrollment of elderly breast cancer patients in clinical trials.

2. Barrett-Connor E, Cauley JA, Kulkarni PM, Sashegyi A, Cox DA, Geiger MJ. Risk-benefit profile for raloxifene: 4-year data From the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. *J Bone Miner Res.* 2004;19:1270-5.
Abstract: Posthoc analysis of the MORE osteoporosis treatment trial assessed risk-benefit profile of raloxifene in 7705 postmenopausal women. A major disease outcomes global index resulted in annual rates of 1.39% and 1.83% in the raloxifene and placebo groups, respectively (HR, 0.75; 95% CI, 0.62-0.92), compatible with a favorable risk-benefit profile for raloxifene for treating postmenopausal osteoporosis. INTRODUCTION: The Women's Health Initiative (WHI) trial reported overall risks that exceeded benefits from use of estrogen-progestin in healthy postmenopausal women. The objective of this posthoc analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial was to assess the safety profile of raloxifene, a selective estrogen receptor modulator indicated for the prevention and treatment of osteoporosis, using the global index method from the WHI trial. MATERIALS AND METHODS: A total of 7705 postmenopausal women (mean age, 67 years) were enrolled in the MORE osteoporosis treatment trial and randomly assigned to receive placebo or one of two doses of raloxifene (60 or 120 mg/day) for 4 years. A global index of clinical outcomes, defined as described for the WHI trial (the earliest occurrence of coronary heart disease, stroke, pulmonary embolism, invasive breast cancer, endometrial cancer, colorectal cancer, hip fracture, or death because of other causes) was applied to the MORE trial data. Physicians blinded to treatment assignment adjudicated events. Intention-to-treat survival analysis of time-to-first-event was performed using a proportional hazards model. RESULTS AND CONCLUSIONS: The annualized rate of global index events was 1.83% in the placebo group and 1.39% in the combined raloxifene dose groups (hazard ratio [HR], 0.75; 95% CI, 0.62-0.92). Analyzing individual dose groups separately yielded the same results (HR for 60 mg/day, 0.75; 95% CI, 0.60-0.96: HR for 120 mg/day, 0.75; 95% CI, 0.59-0.95). Subgroup analyses showed no significant interactions between age or hysterectomy status and the effect of raloxifene on the global index (interaction $p > 0.1$), whereas the global index risk reduction seemed to be greater in obese women compared with nonobese women (interaction $p = 0.03$). The significant 25% reduction in global index is compatible with a favorable risk-benefit safety profile when raloxifene is used for osteoporosis treatment in postmenopausal women. These results require confirmation in ongoing clinical trials.

3. Bell R, Lewis J. Assessing the risk of bone fracture among postmenopausal women who are receiving adjuvant hormonal therapy for breast cancer. *Curr Med Res Opin.* 2007;23:1045-51.
Abstract: OBJECTIVE: To understand better the true impact of widespread adoption of adjuvant aromatase inhibitor (AI) therapy on postmenopausal breast cancer patients' risk of bone fracture. METHODS: Data from three different studies were used to estimate the relative risk of bone fracture for each of the following groups of women (i.e., versus a control group of healthy postmenopausal women): (a) healthy postmenopausal women receiving tamoxifen; (b) postmenopausal women who had received treatment for early breast cancer; (c) postmenopausal breast cancer patients on adjuvant tamoxifen therapy; (d) postmenopausal breast cancer patients on adjuvant anastrozole therapy. The results of these analyses were then used to estimate the likely incidence of clinical fracture among such populations in 'real-life' clinical practice. RESULTS: Breast cancer survivors were calculated to be at increased risk of clinical bone fracture (i.e., RR 1.15 vs. control group over 5 years). Breast cancer patients initiated on adjuvant anastrozole were also calculated to be at increased risk of bone fracture (RR = 1.36 vs. control group over 5 years), while

the calculated risk of fracture among tamoxifen-treated breast cancer patients was similar to that observed in the control population (RR = 0.91). CONCLUSION: Breast cancer patients are at increased risk of clinical bone fracture (compared with the general postmenopausal population) and adjuvant anastrozole therapy slightly adds to this risk. Importantly, however, the absolute risk of bone fracture appears to remain low in each of the evaluated patient populations, suggesting that fear of fracture should not prevent the initiation of adjuvant aromatase inhibitor therapy.

4. Boyack M, Lookinland S, Chasson S. Efficacy of raloxifene for treatment of menopause: a systematic review. *J Am Acad Nurse Pract.* 2002;14:150-65.
Abstract: PURPOSE: To critically appraise recent randomized controlled trials (RCT) of raloxifene and its effects on the long-term consequences of menopause. DATA SOURCES: All RCTs of greater than six months duration in post-menopausal women found in MEDLINE through July 2000. CONCLUSIONS: Raloxifene lowered lipids, but estrogen had a more beneficial effect on HDL and fibrinolytic markers. Raloxifene had a more beneficial effect on triglycerides, inflammatory and thrombogenic markers. Compared to placebo, raloxifene reduced vertebral fractures but had a similar although lesser effect on bone mineral density and markers of bone turnover than estrogen. Estrogen receptor positive breast cancer was reduced by 90% with no increase in the incidence of endometrial cancer with raloxifene. The most serious side effect of raloxifene was an increased incidence of deep vein thromboses and pulmonary emboli. IMPLICATIONS: Raloxifene has been shown to be beneficial using cardiovascular and osteoporosis end-points in studies of short duration. More RCTs of longer duration with comparisons to other traditional treatments are needed before raloxifene becomes the treatment of choice.

5. Brufsky A. Management of cancer-treatment-induced bone loss in postmenopausal women undergoing adjuvant breast cancer therapy: a Z-FAST update. *Semin Oncol.* 2006;33:S13-7.
Abstract: The prevention of cancer-treatment-induced bone loss (CTIBL) in long-term adjuvant breast cancer therapy is a high priority. Postmenopausal women with cancer, already at increased risk of bone loss because of age-related estrogen deficiency, face accelerated bone loss with the use of estrogen-depleting therapies such as third-generation aromatase inhibitors (AIs). Although effective in reducing cancer recurrence rates in the adjuvant setting, AIs are associated with bone loss and an increased risk of fractures. Bisphosphonates, which act by inhibiting osteoclastic bone resorption, have been shown to increase bone mineral density (BMD) and reduce fracture risk in postmenopausal women with established osteoporosis. Furthermore, the potent bisphosphonate zoledronic acid has been shown to be efficacious in reducing bone loss in premenopausal women receiving combination adjuvant hormone therapy (goserelin, a gonadotropin-releasing hormone agonist, plus either an AI or tamoxifen). The use of zoledronic acid to prevent CTIBL in postmenopausal women receiving adjuvant AI therapy with letrozole is currently being investigated in the Zometa/Femara Adjuvant Synergy Trial (Z-FAST). Postmenopausal women with stage I-IIIa estrogen-receptor-positive and/or progesterone-receptor-positive breast cancer starting letrozole are randomized to receive either upfront zoledronic acid or delayed zoledronic acid. At 6 months, assessable women in the upfront group showed a mean increase of 1.55% in lumbar spine (L1 - L4) BMD, compared with a mean decrease of 1.78% in women in the delayed group, resulting in a difference of 3.33% between groups; moreover, women in the former group showed a mean increase of 1.02% in total hip BMD, compared with a mean decrease of 1.40% in those in the latter group, resulting

in a significant difference of 2.42% between groups (P <.001). Thus, the Z-FAST BMD results show that upfront zoledronic acid prevents CTIBL in postmenopausal women receiving adjuvant letrozole therapy for early breast cancer. Combining the anticancer efficacy of letrozole with the bone-protective effect of zoledronic acid may be a successful treatment in this setting.

6. Brufsky AM. Managing bone loss in women with early-stage breast cancer receiving aromatase inhibitors. *Clin Breast Cancer.* 2007;8 Suppl 1:S22-34.
Abstract: Third-generation aromatase inhibitors (AIs; anastrozole, letrozole, exemestane) have replaced tamoxifen as the adjuvant treatment of choice for postmenopausal women with hormone receptor-positive early-stage breast cancer. Because bone loss is a predictable adverse event of AI therapy, early recognition, prevention, and/or treatment of AI-induced bone loss is needed. One to 5 years of AI therapy causes a bone mineral density (BMD) loss of up to 7.2% in postmenopausal women; however, current clinical guidelines do not recommend initiating bisphosphonate therapy for the treatment of BMD loss until fragility fractures or frank osteoporosis occur. Results of recent trials evaluating the use of intravenous (I.V.) zoledronic acid as prevention and treatment of AI-induced bone loss in women with early-stage breast cancer receiving letrozole suggest a potential benefit to the concurrent use of zoledronic acid and letrozole. To our knowledge, clinical trials assessing oral or other I.V. bisphosphonates for these indications have not been published. Recently, concerns of bisphosphonate-induced renal safety and osteonecrosis of the jaw have emerged. Studies evaluating bisphosphonates in women with breast cancer have reported lower rates of renal dysfunction than those reported in patients with metastatic cancer receiving bisphosphonates, and no cases of jaw osteonecrosis. The use of bisphosphonates in this population requires further study to more clearly define the most appropriate timing and length of therapy as well as the long-term efficacy and safety of these drugs. Until these data become available, balancing the safety concerns with the potential benefits of I.V. bisphosphonates to minimize or prevent AI-induced bone loss in women with early-stage breast cancer is required.

7. Burshell AL, Song J, Dowsett SA, et al. Relationship between bone mass, invasive breast cancer incidence and raloxifene therapy in postmenopausal women with low bone mass or osteoporosis. *Curr Med Res Opin.* 2008;24:807-13.
Abstract: OBJECTIVE: To evaluate the relationship between bone mass and risk of breast cancer and to determine the effect of raloxifene therapy on breast cancer incidence in women categorized by bone mass into low bone mass and osteoporosis subgroups. DESIGN: In this post hoc analysis, data were analyzed from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, enrolling postmenopausal women with low bone mass (N = 7705), and the Continuing Outcomes Relevant to Evista (CORE) trial, a follow-up to MORE enrolling 4011 MORE participants. Total follow-up was for up to 8 years. Women with a total hip bone mineral density (BMD) T-score < -1 to > -2.5 or T-score < or = -2.5 (referent, NHANES III database) were classified as having low bone mass or osteoporosis, respectively. Women with a pre-existing vertebral fracture were considered as having osteoporosis irrespective of BMD T-score. Analyses were performed for invasive breast cancers and invasive estrogen-receptor (ER) positive breast cancers. RESULTS: Women with low bone mass (N = 3829) had a twofold higher incidence of invasive ER-positive breast cancer than those with osteoporosis (N = 3836) (HR 2.13, 95% CI 1.12-4.03). The incidence of all invasive breast cancers did not differ significantly between the bone mass groups. The incidences of invasive and invasive ER-positive breast cancers were

65-78% lower in women assigned raloxifene versus placebo in both the low bone mass and osteoporosis groups ($p < 0.05$). CONCLUSIONS: In this post hoc analysis of postmenopausal women participating in MORE and CORE, bone mass was a predictor of invasive ER-positive breast cancer. Raloxifene treatment reduced the risk of invasive and invasive ER-positive breast cancers in women with low bone mass and those with osteoporosis. Since participants were older postmenopausal women with low bone mass, whether these findings can be generalized to other postmenopausal women is unclear.

8. Camacho PM, Dayal AS, Diaz JL, et al. Prevalence of secondary causes of bone loss among breast cancer patients with osteopenia and osteoporosis. *J Clin Oncol.* 2008;26:5380-5.
Abstract: PURPOSE: To determine the prevalence of secondary causes of bone loss among patients with breast cancer with osteopenia and osteoporosis. PATIENTS AND METHODS: All women referred to a bone health clinic over a 6-year period for bone evaluation were included in this retrospective study and stratified based on presence or absence of a breast cancer history. The prevalence of secondary causes of bone loss in the two groups was compared. RESULTS: Of the 238 women identified, 64 women had breast cancer. The non-breast cancer group (n = 174) was significantly older (P = .015), had a lower mean weight (P = .019), lower 25 hydroxy-vitamin D level (P = .019), and greater degree of bone loss in both the spine and hip (P < .001 and 0.004, respectively). The presence of at least one secondary cause of bone loss, excluding cancer-related therapies, was seen in 78% of the breast cancer patient group and in 77% of the non-breast cancer group (P = not significant). Newly diagnosed metabolic bone disorders were seen in 58% of the breast cancer population. The most common was vitamin D deficiency, seen in 38% of patients in the breast cancer group and 51% of patients in the non-breast cancer group. Idiopathic hypercalciuria was diagnosed in 15.6%, primary hyperparathyroidism in 1.6%, and normocalcemic hyperparathyroidism in 3.1% of the breast cancer population. CONCLUSION: A high prevalence of secondary causes of bone loss among patients with breast cancer supports a comprehensive evaluation in these patients, particularly those considering therapy with an aromatase inhibitor.

9. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat.* 2001;65:125-34.
Abstract: Raloxifene, a selective estrogen receptor modulator approved for the prevention and treatment of postmenopausal osteoporosis, has shown a significant reduction in breast cancer incidence after 3 years in this placebo-controlled, randomized clinical trial in postmenopausal women with osteoporosis. This article includes results from an additional annual mammogram at 4 years and represents 3,004 additional patient-years of follow-up in this trial. Breast cancers were ascertained through annual screening mammograms and adjudicated by an independent oncology review board. A total of 7,705 women were enrolled in the 4-year trial; 2,576 received placebo, 2,557 raloxifene 60 mg/day, and 2,572 raloxifene 120 mg/day. Women were a mean of 66.5-years old at trial entry, 19 years postmenopause, and osteoporotic (low bone mineral density and/or prevalent vertebral fractures). As of 1 November 1999, 61 invasive breast cancers had been reported and were confirmed by the adjudication board, resulting in a 72% risk reduction with raloxifene (relative risk (RR) 0.28, 95% confidence interval (CI) 0.17, 0.46). These data indicate that 93 osteoporotic women would need to be treated with raloxifene for 4 years to prevent one case of invasive breast cancer. Raloxifene reduced the risk of estrogen receptor-positive

invasive breast cancer by 84% (RR 0.16, 95% CI 0.09, 0.30). Raloxifene was generally safe and well-tolerated, however, thromboembolic disease occurred more frequently with raloxifene compared with placebo (p=0.003). We conclude that raloxifene continues to reduce the risk of breast cancer in women with osteoporosis after 4 years of treatment, through prevention of new cancers or suppression of subclinical tumors, or both. Additional randomized clinical trials continue to evaluate this effect in postmenopausal women with osteoporosis, at risk for cardiovascular disease, and at high risk for breast cancer.

10. Cirpan T, Akercan F, Itil IM, Gundem G, Bilgen I, Yucebilgin MS. Does raloxifene therapy affect mammographic breast cancer screening in postmenopausal patients? *Eur J Gynaecol Oncol.* 2006;27:177-8.
Abstract: OBJECTIVE: The aim of the study was to determine mammographic breast density changes during raloxifene therapy in postmenopausal patients MATERIALS AND METHODS: Fifty-five cases who were using raloxifen therapy were included in this retrospective analysis. Raloxifene was given for osteopenia and osteoporosis according to low bone mineral density measured by dual-energy X-ray absorptiometry (DEXA). None of the patients were using hormone replacement therapy 12 months before the initiation of raloxifene treatment or during the study. Mammographic breast density was determined by mammography before the initiation of raloxifene treatment (baseline) and after 12 to 16 months of therapy. The Breast Imaging Reporting and Data System (BI-RADS) breast density score was used for the evaluation of mammographic density. RESULTS: There was no change in mammographic breast density when the baseline and the first mammography taken after the initiation of therapy were compared (p = 0.32). There was no significant correlation between the duration of raloxifene treatment and mammographic density measured after raloxifene treatment (r = -0.158, p = 0.25). Only in one patient did the BI-RADS classification of 2 change to 3 after 12 months of therapy. CONCLUSIONS: In conclusion, raloxifene therapy for 12 to 16 months does not increase mammographic breast density in postmenopausal women with low bone mass.

11. Clemett D, Spencer CM. Raloxifene: a review of its use in postmenopausal osteoporosis. *Drugs.* 2000;60:379-411.
Abstract: Raloxifene is a selective estrogen receptor modulator that partially mimics the effects of estrogens in bone and the cardiovascular system, while functioning as an antiestrogen in endometrial and breast tissue. In randomised placebo-controlled studies involving postmenopausal women or patients with osteoporosis, raloxifene 60 to 150 mg/day was effective in increasing bone mineral density (BMD) over 12- to 36-month periods. At the 60 mg/day recommended dosage, increases of 1.6 to 3.4%, 0.9 to 2.3% and 1.0 to 1.6% were reported in lumbar spine, femoral neck and total hip, respectively, versus < or =0.5% with placebo. Raloxifene 60 or 120 mg/day decreased the risk of vertebral fractures over a 36-month period in postmenopausal patients with osteoporosis. Significant reductions in radiographic fracture risk versus placebo (30 and 50%) occurred regardless of whether patients had existing fractures at baseline. Although raloxifene did not affect the overall incidence of nonvertebral fractures, a reduction in the incidence of ankle fracture was reported in comparison with placebo. In postmenopausal women, raloxifene 60 mg/day significantly reduced serum levels of total and low density lipoprotein cholesterol from baseline, compared with placebo. High density lipoprotein cholesterol and triglyceride levels were unaffected. Raloxifene 60 or 120 mg/day reduced the risk of invasive breast cancer by 76% during a median of 40 months' follow-up in postmenopausal patients with

osteoporosis and no history of breast cancer. A relative risk reduction of 90% was reported for estrogen-receptor positive invasive breast cancers; estrogen-receptor negative cancer risk was unaffected by raloxifene. Raloxifene was generally well tolerated in clinical trials at dosages up to 150 mg/day. Adverse events thought to be related to raloxifene treatment were hot flushes and leg cramps. Venous thromboembolism was the only serious adverse event thought to be related to raloxifene treatment and a relative risk of 3.1 compared with placebo treatment was reported in patients with osteoporosis. Vaginal bleeding occurred in < or =6.4% of raloxifene-treated women but was reported by 50 to 88% of those receiving estrogens or hormone replacement therapy (HRT). Raloxifene treatment was not associated with stimulatory effects on the endometrium. CONCLUSIONS: Raloxifene significantly increases BMD in postmenopausal women and reduces vertebral fracture risk in patients with osteoporosis. In clinical trials, raloxifene was generally well tolerated compared with placebo and HRT, although its propensity to cause hot flushes precludes use in women with vasomotor symptoms. In particular, the lack of stimulatory effects on the endometrium and the reduction in invasive breast cancer incidence indicate raloxifene as an attractive alternative to HRT for the management of postmenopausal osteonorosis.

12. Coleman RE. Current and future status of adjuvant therapy for breast cancer. *Cancer.* 2003;97:880-6.
Abstract: Adjuvant systemic treatments have greatly improved the prognosis of women with early breast cancer. Combination chemotherapy and, for patients with oestrogen receptor-positive (ER+) tumours, endocrine treatment has been found to reduce the frequency of relapse and improve survival. New adjuvant strategies include the introduction of taxanes into adjuvant chemotherapy schedules, the use of aromatase inhibitors in place of, or in addition to, tamoxifen, and the use of adjuvant bisphosphonates. Combination chemotherapy has been found to reduce the annual odds of recurrence and death in pre- and postmenopausal women. The benefits, however, are on average less in older patients. Anthracycline-based regimens are more effective than traditional regimens of cyclophosphamide, methotrexate, and fluorouracil (CMF). The benefits of adjuvant cytotoxic and endocrine treatments are additive. There is considerable debate as to the role of taxanes in adjuvant therapy. Improved outcome has been observed in one large trial, especially in those patients with ER-negative tumours. High-dose chemotherapy has not fulfilled its early promise. Ovarian suppression and/or tamoxifen remain the treatments of choice. The annual odds of relapse and death have been reduced by approximately one-third and one-quarter, respectively. Several very large studies are in progress to assess the potential of aromatase inhibitors in the adjuvant setting. Direct comparisons with tamoxifen, as well as switching after several years from tamoxifen to an aromatase inhibitor, are strategies under evaluation. Early results from one of these trials evaluating anastrozole (the Arimidex, Tamoxifen, Alone or in Combination [ATAC] trial) has reported a reduced relapse rate after a median follow-up of 3 years in favour of anastrozole. However, this was at the expense of accelerated bone loss, and strategies to minimise this side effect of aromatase inhibitors are under investigation. Although many studies have indicated that bisphosphonates prevent the development of metastatic bone disease in animals, the clinical role of prophylactic bisphosphonates in early breast cancer is not clearly defined. Three studies with oral clodronate have been published, two of them indicating a protective effect on the development of bone metastases and improved survival, and one suggesting a disadvantage to the use of adjuvant clodronate. Further large adjuvant trials with clodronate and zoledronic acid are in progress. Adjuvant bisphosphonates also have been found to reduce bone loss associated with cancer

treatments and preserve skeletal health. It may be possible to replace the current oral regimens for prevention of bone loss with a single annual infusion of the highly potent bisphosphonate zoledronic acid.

13. Coleman RE, Body JJ, Gralow JR, Lipton A. Bone loss in patients with breast cancer receiving aromatase inhibitors and associated treatment strategies. *Cancer Treat Rev.* 2008;34 Suppl 1:S31-42.
Abstract: Hormone-receptor-positive breast cancer in postmenopausal women is treated increasingly with aromatase inhibitors because of increased efficacy and reduced incidence of endometrial cancer compared with tamoxifen. However, aromatase inhibitor therapy increases bone turnover as a result of nearly complete oestrogen depletion, leading to increases in bone loss and fragility fractures that erode patients' functional independence and quality of life. Management of patients with aromatase inhibitor-associated bone loss (AIBL) is currently evolving and intervention strategies are under investigation. Although no treatments are specifically approved for AIBL, bisphosphonates are currently the intervention of choice for patients with low bone mineral density or evidence of rapid bone turnover, along with adequate calcium and vitamin D supplementation and a healthy lifestyle. In this setting, the majority of information available regarding bisphosphonate efficacy is from studies of intravenous zoledronic acid (4 mg) every 6 months. Data from four large international studies (three of identical design in postmenopausal women and one in premenopausal women) indicate that zoledronic acid is effective in the management of AIBL. Treatment algorithms based on risk factors and bone mineral density are under development, and the results of ongoing studies should help define optimal bone health management for patients undergoing aromatase inhibitor treatment for early breast cancer.

14. Confavreux CB, Fontana A, Guastalla JP, Munoz F, Brun J, Delmas PD. Estrogen-dependent increase in bone turnover and bone loss in postmenopausal women with breast cancer treated with anastrozole. Prevention with bisphosphonates. *Bone.* 2007;41:346-52.
Abstract: Aromatase inhibitors have demonstrated their superiority to tamoxifen as adjuvant therapy for early breast cancer in postmenopausal women, but are associated with an increased risk of fractures. The aim of our study was to analyze bone loss, bone turnover and their determinants in postmenopausal women treated with anastrozole. We investigated bone loss and bone turnover markers (BTM) in a prospective open cohort study of 118 postmenopausal women treated with anastrozole for an early hormone-dependent breast cancer. Women without osteoporosis were not treated and compared with an age-matched control group of 114 healthy women. Osteoporotic patients (T-score<or=-2.5 S.D.) received weekly risedronate. Bone mineral density (BMD), and the BTM serum osteocalcin and serum C-terminal cross linking telopeptide of type I collagen (CTX) and 17beta-estradiol were measured at baseline and 1 year later. In the surveillance group, anastrozole induced after 1 year of treatment a marked bone loss at the spine (mean+/-S.E.M., [95% confidence interval]) -3.3+/-0.4% [-4.1 to -2.5]), and hip (2.8+/-0.4% [-3.6 to -2]) that was significantly greater than in controls ($p<0.0001$). Anastrozole induced an increase in bone remodelling: osteocalcin (+36.6%, $p<0.0001$) and CTX (+34%, $p<0.0001$). In univariate models, a recent menopause, a low body mass index, a complete chemotherapy (>or=6 courses) and a marked antiestrogenic response--defined by a level of 17beta-estradiol<or=2 pg/ml at 1 year or a decrease >50% between baseline and 1 year--were associated with greater bone loss. In multivariate model, women in the highest quartile of bone loss at the spine (>5.6% at 1 year) and hip (>4.9%) had a marked antiestrogenic response with OR of 10.4 [95% C.I. 1.9-57.2] ($p=0.007$) and 5.7 [1.3-25] ($p=0.024$) respectively. Among

patients in the surveillance group, those with a normal T-score at both sites (n=46) had also a significant bone loss at spine -3.3+/-0.5% [-4.3 to -2.3], p<0.0001 and at the hip -2.9+/-0.6% [-4.1 to -1.7] p<0.0001. In osteoporotic women treated simultaneously with anastrozole and risedronate, bone loss was prevented at hip, and increased at the spine (+4.1+/-0.9% [2.3 to 5.9], p=0.008), and BTM decreased (-24%, -39% for CTX, p=0.003 and 0.001 vs. changes in the untreated group). Anastrozole increases bone turnover and induces an accelerated bone loss that is significantly related to the suppression of 17beta-estradiol production induced by aromatase inhibitor. The bisphosphonate risedronate prevents anastrozole induced bone loss.

15. Cosman F. Selective estrogen-receptor modulators. *Clin Geriatr Med.* 2003;19:371-9.
Abstract: Tamoxifen is useful for adjuvant treatment of breast cancer and in some women for the prevention of breast cancer. The risk-benefit ratio in regard to the skeleton and perhaps other organ systems may very well be different for postmenopausal versus premenopausal women. In postmenopausal women, tamoxifen (20 mg/d) increased BMD in the spine and perhaps the hip; however, the effect on fracture risk is unclear. Therefore, for postmenopausal women with osteoporosis, consideration should be given to the addition of an agent that is shown to have efficacy against fractures (such as bisphosphonates), even while these women are on tamoxifen. For women at only modest or moderate risk, with bone density above the osteoporosis range (T score above -2.5) and no major fracture history, tamoxifen is probably adequate for 5 years of use. Potentially serious adverse effects include venous thromboembolism, uterine cancer, benign uterine disease, and cataracts. Raloxifene (60 mg/d) protects against vertebral fractures over 4 years in women with osteoporosis, produces small increases in bone mass of the spine, hip, and total body, and reduces bone turnover in postmenopausal women with or without osteoporosis. No significant effect has yet been demonstrated on nonvertebral fractures after 4 years of treatment. Raloxifene has the additional benefit of substantially reducing the risk of ER-positive invasive breast cancer and does not increase the risk of uterine disease. Raloxifene increases the risk of venous thromboembolic disease to the same degree as tamoxifen and estrogen. Therefore, SERMS and estrogens are generally contraindicated in women with a previous history of venous thromboembolism or those who are at significantly increased risk. Raloxifene is probably most useful in women who have osteoporosis (T score = -2.5) or who are at risk (T score less than -1.5 with clinical risk factors) in the middle menopausal period (age 55-65) or in the early menopausal period in women who have no significant hot flashes. At this stage in life, vertebral fractures are common, but hip fractures are not. Therefore, women who take raloxifene can expect a reduction in the likelihood of having a vertebral fracture, and possibly breast cancer. The lack of definitive efficacy against hip fracture is not a major deterrent to use of this agent in this age group because hip fracture risk is very low. Raloxifene might not be the treatment of choice for elderly women who are at particularly high risk of hip fracture.

16. Cranney A, Adachi JD. Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. *Drug Saf.* 2005;28:721-30.
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.

17. Eisen A, Trudeau M, Shelley W, Messersmith H, Pritchard KI. Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: a systematic review. *Cancer Treat Rev.* 2008;34:157-74.
Abstract: BACKGROUND: A systematic review was undertaken to review the evidence for the use of third-generation aromatase inhibitors (anastrozole, letrozole and exemestane) as adjuvant therapy for post-menopausal women with early-stage, hormone receptor-positive breast cancer and to develop and support recommendations for their use, with regard to three areas: aromatase inhibitors compared to tamoxifen, aromatase inhibitors in sequence with tamoxifen for a total of five years, and aromatase inhibitors given after five years of tamoxifen therapy. METHODS: MEDLINE, EMBASE, American Society of Clinical Oncology and San Antonio Breast Cancer Symposium proceedings, and the Cochrane Library were searched to May 2007 for reports of randomized controlled trials that met the inclusion criteria. RESULTS: Nine randomized controlled trials and one meta-analysis of three of these trials were identified that reported efficacy data. Eight of these trials reported significantly improved disease-free survival in the arms that involved aromatase inhibitors. The meta-analysis reported significantly improved overall survival among all patients, as did one individual trial. One trial of five years letrozole or placebo after five years tamoxifen found improved overall survival among node-positive patients. CONCLUSIONS: Aromatase inhibitors provide an alternative to tamoxifen as adjuvant therapy for post-menopausal, hormone-receptor-positive breast cancer patients. The options include anastrozole and letrozole for five years, as well as anastrozole and exemestane following two to three years of tamoxifen, for a total five years of hormonal therapy. Five years of letrozole should be considered following five years of tamoxifen. Patients receiving aromatase inhibitors should be monitored for changes in bone mineral density and for cardiovascular disease risk factors and outcomes.

18. Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol.* 2008;26:4875-82.

Abstract: PURPOSE: Adjuvant aromatase inhibitor therapy is well established in postmenopausal women with hormone receptor-positive breast cancer, but such therapy is complicated by accelerated bone loss and increased fracture risk. We investigated the ability of denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor-kappaB ligand, to protect against aromatase inhibitor-induced bone loss. PATIENTS AND METHODS: Eligible women with hormone receptor-positive nonmetastatic breast cancer treated with adjuvant aromatase inhibitor therapy were stratified by duration of aromatase inhibitor therapy (< or = 6 v > 6 months), received supplemental calcium and vitamin D, and were randomly assigned to receive placebo (n = 125) or subcutaneous denosumab 60 mg (n = 127) every 6 months. At enrollment, all patients were required to have evidence of low bone mass, excluding osteoporosis. The primary end point was percentage change from baseline at month 12 in lumbar spine bone mineral density (BMD). RESULTS: At 12 and 24 months, lumbar spine BMD increased by 5.5% and 7.6%, respectively, in the denosumab group versus placebo (P < .0001 at both time points). Increases were observed as early as 1 month and were not influenced by duration of aromatase inhibitor therapy. Increases in BMD were also observed at the total hip, total body, femoral neck, and the predominantly cortical one-third radius. Bone turnover markers decreased with denosumab treatment. Overall incidence of treatment-emergent adverse events (AEs) was similar between treatment groups. CONCLUSION: In women with nonmetastatic breast cancer and low bone mass who were receiving adjuvant aromatase inhibitor therapy, twice-yearly administration of denosumab led to significant increases in BMD over 24 months at trabecular and cortical bone, with overall AE rates similar to those of placebo.

19. Ensrud K, Genazzani AR, Geiger MJ, et al. Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol.* 2006;97:520-7.
Abstract: The impact of selective estrogen receptor modulators on cardiovascular disease outcomes in postmenopausal women remains unclear. This analysis assessed the effect of raloxifene on the incidence of cardiovascular adverse events in postmenopausal women followed for < or =8 years as participants in a 4-year osteoporosis treatment trial and a subsequent 4-year follow-up trial. The Continuing Outcomes Relevant to Evista (CORE) trial, designed to determine the effect of raloxifene on the incidence of invasive breast cancer, was a 4-year follow-up study to the 4-year Multiple Outcomes of Raloxifene Evaluation (MORE) osteoporosis treatment trial. Of the 7,705 participants originally enrolled in MORE, 4,011 were enrolled in CORE and thus participated in both trials (MORE-CORE participants). The incidence of serious cardiovascular (i.e., coronary and cerebrovascular) adverse events during 8 years, confirmed by external adjudication in the 2 trials, was compared between treatment groups using Cox proportional hazards models. The 8-year incidence of serious cardiovascular adverse events did not differ significantly between the raloxifene (5.5%) and placebo (4.7%) groups (hazard ratio [HR] 1.16, 95% confidence interval [CI] 0.86 to 1.56). Similar results were obtained when coronary (HR 1.22, 95% CI 0.82 to 1.83) or cerebrovascular (HR 1.19, 95% CI 0.78 to 1.84) events were analyzed separately, and when cardiovascular events were analyzed in the 459 MORE-CORE participants who were at increased risk of cardiovascular events by previously established criteria (HR 1.03, 95% CI 0.58 to 1.82). In conclusion, we found no evidence of a beneficial or harmful effect of raloxifene on the incidence of cardiovascular events overall, or coronary or cerebrovascular events, in postmenopausal osteoporotic women at relatively low risk of cardiovascular events.

20. Garreau JR, Delamelena T, Walts D, Karamlou K, Johnson N. Side effects of aromatase inhibitors versus tamoxifen: the patients' perspective. *Am J Surg.* 2006;192:496-8.
Abstract: BACKGROUND: Hormonal therapy is a mainstay in the management of estrogen receptor-positive (ER+) breast cancer. Tamoxifen (TAM) has been the drug widely used until the recent emergence of the aromatase inhibitors (AIs). Although AIs appear to be better tolerated than tamoxifen, they do have a different safety profile and these side effects have not been well characterized in community practice. We surveyed patients with ER+ breast cancers who received adjuvant hormonal therapy to determine how these medications impacted their quality of life and whether side effects or cost influenced decisions to continue therapy. METHODS: A mailed questionnaire and community cancer registry were used. RESULTS: Four hundred fifty-two of 902 surveys were returned for a 50% response rate. Eighty-two percent of respondents were placed on (adjuvant hormonal therapy) some form of estrogen-blocking therapy. Fifty-four percent of these were placed on tamoxifen and 46% on an AI. The most troublesome symptoms for tamoxifen and AI users, respectively, included hot flashes (35%/30%), weight gain (14%/15%), insomnia (17%/17%), and joint aches (12%/23%, P = .002). Thirty-nine percent of TAM users and 46% of AI users were taking medications to control their symptoms. Fifty percent of TAM users and 39% of AI users took vitamin E to help control hot flashes. Forty-two percent of TAM users versus 32% of AI users took Advil (Wyeth, Richmond, VA) for muscle/joint aches; 47.5% of AI users switched medication to improve symptoms as compared with only 37% of tamoxifen users (P = .015). The average cost of medications to control side effects for both tamoxifen and AI users was $67.36 per month. CONCLUSIONS: In our survey, both tamoxifen and AI users reported significant and different side effects. AI users suffered more frequently from musculoskeletal complaints, and more AI users switched therapy. Both AI and tamoxifen users used adjunctive medications for symptom control. In both groups, a large number used vitamin E to help hot flashes despite weak evidence to support its effectiveness in this setting. Cost of therapy and symptom control was not a major barrier to care.

21. Gluck O, Maricic M. Skeletal and nonskeletal effects of raloxifene. *Curr Osteoporos Rep.* 2003;1:123-8.
Abstract: Raloxifene, a selective estrogen receptor modulator, is approved for the prevention and treatment of postmenopausal osteoporosis. Prevention studies with raloxifene have demonstrated preservation of bone density and suppression of bone turnover markers in young postmenopausal women. The Multiple Outcomes of Raloxifene Evaluation study was the pivotal treatment trial for raloxifene. It demonstrated significant reduction in the risk for vertebral fractures after 1 and 3 years. Significant reduction of nonvertebral fractures with raloxifene has not yet been demonstrated. In addition to the effects of raloxifene on bone, potentially beneficial effects on the cardiovascular system, breast, and uterus have been described. Most of these nonskeletal effects have been reported as secondary endpoints from large osteoporosis trials with raloxifene. Prospective, randomized, double-blind studies of raloxifene with breast cancer prevention and cardiovascular protection as primary endpoints are now underway.

22. Gold DT, Silverman SL. Do estrogen or selective estrogen receptor modulators improve quality of life for women with postmenopausal osteoporosis? *Curr Osteoporos Rep.* 2007;5:3-7.
Abstract: Osteoporotic fractures result in significant deficits in health-related quality of life (HRQOL). The accumulation of deficits resulting from osteoporosis and fractures is now

recognized as a major cause of reduced HRQOL in women after the menopause and in later life. Some of these same postmenopausal women may also have deficits in HRQOL related to vasomotor symptoms during the menopausal transition. Although estrogen therapy has not been shown to improve overall HRQOL in late postmenopausal women in randomized, controlled trials, it may improve menopausal symptoms. In contrast, selective estrogen receptor modulators (SERMs) such as raloxifene may increase vasomotor symptoms. Although estrogen is not indicated for the primary prevention of osteoporosis, estrogen therapy may be considered for the postmenopausal woman at risk of osteoporotic fracture who is symptomatic and who is not at high risk of breast cancer or cardiovascular events. Raloxifene decreases risk of invasive breast cancer and may be considered in women at high risk of breast cancer. Decision making about osteoporosis treatment should also consider the impact of the treatment on HRQOL.

23. Grady D, Cauley JA, Geiger MJ, et al. Reduced incidence of invasive breast cancer with raloxifene among women at increased coronary risk. *J Natl Cancer Inst.* 2008;100:854-61.
Abstract: BACKGROUND: In the Raloxifene Use for The Heart trial, 10 101 postmenopausal women with coronary heart disease (CHD) or multiple CHD risk factors were randomly assigned to 60 mg/d raloxifene or to placebo and followed for a median of 5.6 years. Raloxifene, a selective estrogen receptor modulator, was found to reduce the risk of invasive breast cancer and vertebral fractures but not the risk of cardiovascular events. Here, we provide further details about breast cancer incidence by tumor characteristics, duration of treatment, and subgroup. METHODS: Reported breast cancer was adjudicated by an independent committee based on medical records and pathology reports. The primary analyses used Cox proportional hazards models with time to first breast cancer as the outcome. Subgroup effects were analyzed using similar models with terms for treatment by subgroup. All statistical tests were two-sided. RESULTS: As previously reported, raloxifene reduced the incidence of invasive breast cancer by 44% (hazard ratio [HR] = 0.56; 95% confidence interval [CI] = 0.38 to 0.83; absolute risk reduction = 1.2 invasive breast cancers per 1000 women treated for 1 year). The lower incidence of invasive breast cancer reflected a 55% lower incidence of invasive estrogen receptor (ER)-positive tumors (HR = 0.45; 95% CI = 0.28 to 0.72). However, raloxifene treatment did not reduce the incidence of noninvasive breast cancer or of invasive ER-negative breast cancer. The reduced incidence of invasive breast cancer was similar across subgroups, including those defined by age, body mass index, family history of breast cancer, prior use of postmenopausal hormones, and 5-year estimated risk of invasive breast cancer. CONCLUSION: Raloxifene reduces risk of invasive ER-positive breast cancer regardless of a woman's baseline breast cancer risk but does not reduce risk of noninvasive or ER-negative breast cancers. These results confirm those of the Multiple Outcomes of Raloxifene Evaluation, a previous randomized trial among women with osteoporosis.

24. Hadji P. Aromatase inhibitor-associated bone loss in breast cancer patients is distinct from postmenopausal osteoporosis. *Crit Rev Oncol Hematol.* 2009;69:73-82.
Abstract: Women with breast cancer are increasingly being diagnosed and treated earlier in the disease process, resulting in significantly improved clinical outcomes. Aromatase inhibitor (AI) therapy has shown superior efficacy compared with tamoxifen in postmenopausal women and is quickly becoming the therapy of choice in this setting. However, adjuvant AI therapy depletes residual estrogen and is associated with rapid bone loss and increased fracture risk distinctly different from those observed in postmenopausal osteoporosis. Aromatase inhibitor-associated bone loss (AIBL) occurs at a rate at least 2-

fold higher than bone loss seen in healthy, age-matched postmenopausal women, resulting in a significantly higher fracture incidence regardless of the AI administered. Thus, antiresorptive treatments designed to address postmenopausal osteoporosis may not be sufficient in this unique population. Furthermore, current guidelines for the management of bone health in women with breast cancer may not correctly identify patients who may benefit from therapy. Consequently, breast cancer patients receiving adjuvant AI therapy will require specialized management strategies to identify and treat patients at high risk for fracture. Recently, nitrogen-containing bisphosphonates have emerged as the treatment of choice for the prevention of AIBL and the reduction of fracture risk in this setting.

25. Hadji P, Body JJ, Aapro MS, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. *Ann Oncol.* 2008;19:1407-16.
Abstract: BACKGROUND: Recent studies indicate that women with breast cancer are at increased risk of fracture compared with their age-matched peers. Current treatment guidelines are inadequate for averting fractures in osteopenic women, especially those receiving aromatase inhibitor (AI) therapy. Therefore, we sought to identify clinically relevant risk factors for fracture that can be used to assess overall fracture risk and to provide practical guidance for preventing and treating bone loss in women with breast cancer receiving AI therapy. METHODS: Systematic review of pertinent information from published literature and meeting abstracts through December 2007 was carried out to identify factors contributing to fracture risk in women with breast cancer. An evidence-based medicine approach was used to select risk factors that can be used to determine when to initiate bisphosphonate treatment of aromatase inhibitor-associated bone loss (AIBL). RESULTS: Fracture risk factors were chosen from large, well-designed, controlled, population-based trials in postmenopausal women. Evidence from multiple prospective clinical trials in women with breast cancer was used to validate AI therapy as a fracture risk factor. Overall, eight fracture risk factors were validated in women with breast cancer: AI therapy, T-score <-1.5, age >65 years, low body mass index (BMI <20 kg/m(2)), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use >6 months, and smoking. Treatment recommendations were derived from randomized clinical trials. CONCLUSIONS: The authors recommend the following for preventing and treating AIBL in women with breast cancer. All patients initiating AI therapy should receive calcium and vitamin D supplements. Any patient initiating or receiving AI therapy with a T-score >/=-2.0 and no additional risk factors should be monitored every 1-2 years for change in risk status and bone mineral density (BMD). Any patient initiating or receiving AI therapy with a T-score <-2.0 should receive bisphosphonate therapy. Any patient initiating or receiving AI therapy with any two of the following risk factors-T-score <-1.5, age >65 years, low BMI (<20 kg/m(2)), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use >6 months, and smoking-should receive bisphosphonate therapy. BMD should be monitored every 2 years, and treatment should continue for at least 2 years and possibly for as long as AI therapy is continued. To date, the overwhelming majority of clinical evidence supports zoledronic acid 4 mg every 6 months to prevent bone loss in women at high risk. Although there is a trend towards fewer fractures with zoledronic acid, studies completed to date have not been designed to capture significant differences in fracture rate, and longer follow-up is needed.

26. Hansdottir H. Raloxifene for older women: a review of the literature. *Clin Interv Aging.* 2008;3:45-50.

Abstract: Raloxifene is a non-steroidal selective estrogen-receptor modulator (SERM) which is used for prevention and treatment of postmenopausal osteoporosis. Raloxifene decreases the incidence of vertebral fractures by 30%-50% in postmenopausal women with osteoporosis but has not been shown to decrease the incidence of hip fractures or other non-vertebral fractures. At the present time, estrogen-replacement therapy and bisphosphonate treatment are the only medical treatments that are proven to prevent hip fractures with the exception of vitamin D and calcium replacement, which has been shown to prevent hip fractures in elderly individuals and nursing home residents. Raloxifene has been shown to have additive effects on bone turnover and bone mineral density (BMD) when used along with alendronate and teriparatide. Raloxifene could have a role in renal failure as it has been shown to increase BMD of the vertebra over 1 year of therapy. Raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer. The increased incidence of venous thromboembolism is the main concern of raloxifene therapy and previous history of venous thromboembolism is a contraindication for use of raloxifene. Raloxifene has a role in treatment of vertebral osteoporosis in older women. The decision to use raloxifene should be based on evaluation of fracture risk and on potential other benefits than fracture reduction along with consideration of side effects.

27. Johnell O, Cauley JA, Kulkarni PM, Wong M, Stock JL. Raloxifene reduces risk of vertebral fractures [corrected] in postmenopausal women regardless of prior hormone therapy. *J Fam Pract.* 2004;53:789-96.
Abstract: OBJECTIVE: We examined whether past use of hormone therapy influences the effects of raloxifene on the risk of new vertebral fracture, cardiovascular events, or breast cancer. STUDY DESIGN: The Multiple Outcomes of Raloxifene Evaluation (MORE) trial examined vertebral fracture incidence as the primary endpoint, breast cancer incidence as a secondary endpoint. Cardiovascular events were collected as secondary safety endpoints. POPULATION: The MORE trial enrolled 7705 postmenopausal women. Of the 7682 women who reported their previous HT use status, 29% used HT before screening. OUTCOMES MEASURED: Separate logistic regression models analyzed the relationships between prior HT use and the risk of vertebral fracture, cardiovascular events, or breast cancer. Interaction terms with P<.10 were considered to be statistically significant. Confidence intervals for relative risks (RR) were calculated using the Mantel-Haenszel method. RESULTS: Raloxifene 60 mg/d, the clinically approved dose for osteoporosis prevention and treatment, reduced the risk of vertebral fractures by 54% (RR=0.46) and 29% (RR=0.71) in women with and without prior HT use, respectively (interaction P=.05). A lower incidence of invasive breast cancer in women with prior HT use (RR=0.23) and in women without prior HT use [RR=0.31; interaction P=.60] was observed in women receiving raloxifene (pooled doses). Irrespective of prior HT use, women treated with raloxifene (pooled doses) had no change in incidence of cardiovascular events (interaction P=.56). CONCLUSIONS: The risk of vertebral fractures was lower in women treated with raloxifene, regardless of prior HT use, but there was a suggestion that the effect was greater in women who had used HT. Women randomized to receive raloxifene exhibited a decreased incidence of invasive breast cancer, compared with women receiving placebo. No change occurred in the incidence of cardiovascular events, regardless of prior HT use.

28. Jordan VC. Beyond raloxifene for the prevention of osteoporosis and breast cancer. *Br J Pharmacol.* 2007;150:3-4.
Abstract: Selective oestrogen receptor modulators (SERMs) can build bone in the postmenopausal woman and lower circulating cholesterol. These oestrogen-like properties

contrast with the anti-oestrogenic properties observed in the breast where SERMs inhibit the oestrogen-mediated development and growth of ER positive breast cancers. The two clinically useful SERMs, tamoxifen and its chemical cousin raloxifene, are currently used successfully either for the treatment and prevention of breast cancer (tamoxifen) or the treatment and prevention of osteoporosis (raloxifene). However, raloxifene has the beneficial side-effect of breast cancer prevention. These multifunction medicines provide proof of concept that novel molecules can be selectively targeted to diseases mediated by the endocrine system.

29. Jordan VC. SERMs: meeting the promise of multifunctional medicines. *J Natl Cancer Inst.* 2007;99:350-6.
Abstract: The successful development and clinical evaluation of the selective estrogen receptor modulators in the Study of Tamoxifen and Raloxifene trial provides an occasion to reflect on the milestone that has been achieved and the potential for further progress in the chemoprevention of breast cancer. The evolution of tamoxifen from a successful treatment for breast cancer to the first chemopreventive for any cancer took two decades. Clinicians gained an enormous amount of experience with the use of tamoxifen as a treatment, and, as a result, there were few surprises in terms of efficacy or the side effect profile when the medicine was used to prevent breast cancer in high-risk women. In contrast, raloxifene emerged via the novel path of the evidence-based hypothesis that a drug targeted at one disease, osteoporosis, could also prevent breast cancer. Changes in health care strategies to implement chemoprevention take time, but the evidence now suggests that chemoprevention has become a reality in clinical practice.

30. Jordan VC. Tamoxifen: catalyst for the change to targeted therapy. *Eur J Cancer.* 2008;44:30-8.
Abstract: In the early 1970s, a failed post-coital contraceptive, ICI 46,474, was reinvented as tamoxifen, the first targeted therapy for breast cancer. A cluster of papers published in the European Journal of Cancer described the idea of targeting tamoxifen to patients with oestrogen receptor positive tumours, and proposed the strategic value of using long-term tamoxifen therapy in an adjuvant setting with a consideration of the antitumour properties of the hydroxylated metabolites of tamoxifen. At the time, these laboratory results were slow to be embraced by the clinical community. Today, it is estimated that hundreds of thousands of breast cancer patients are alive today because of targeted long-term adjuvant tamoxifen therapy. Additionally, the first laboratory studies for the use of tamoxifen as a chemopreventive were published. Eventually, the worth of tamoxifen was tested as a chemopreventive and the drug is now known to have an excellent risk benefit ratio in high risk pre-menopausal women. Overall, the rigorous investigation of the pharmacology of tamoxifen facilitated tamoxifen's ubiquitous use for the targeted treatment of breast cancer, chemoprevention and pioneered the exploration of selective oestrogen receptor modulators (SERMs). This new concept subsequently heralded the development of raloxifene, a failed breast cancer drug, for the prevention of osteoporosis and breast cancer without the troublesome side-effect of endometrial cancer noted in post-menopausal women who take tamoxifen. Currently, the pharmaceutical industry is exploiting the SERM concept for all members of the nuclear receptor superfamily so that medicines can now be developed for diseases once thought impossible.

31. Kellen JA. Raloxifene. *Curr Drug Targets.* 2001;2:423-5.
Abstract: Efforts to interfere with the initiation and promotion of breast and other cancers by endocrine manipulation are not new. It is of obvious benefit to cancer patients to administer substances that combine minimal general toxicity with maximal oestrogen inhibition. Raloxifene is a relatively recent addition to a group of compounds loosely designated as antioestrogens, which implies their ability to antagonize oestrogen effects via competitive binding to the various receptors. This is a reductionist simplification, since their effect varies and ranges from interaction with lipid transduction cascades, covalent binding to proteins and DNA, regulation of growth factors, erbB2, mdr1 and probably p53 expression, complexing with E-cadherin/catenin to active induction of apoptosis and many other effects on the genome. Also, the action of most antioestrogens is not solely antagonistic and different compounds do exert some agonistic effects in various tissues. Apart from some "pure" antioestrogens, the benzothiophene derivative Raloxifene has been found to combine a high degree of selective oestrogen suppression with several other desirable characteristics, such as reduction of bone demineralisation and antiatherogenic effects without endometrial stimulation. It is well tolerated, has been successfully tested as a chemopreventive agent for breast cancer in certain groups of the population and does not prevent ovulation in women with normal menstrual cycles. Certainly, Raloxifene is only another forerunner of upcoming "designer" oestrogen modulators, but it represents a welcome addition to the therapeutic choices available for the control of some menopausal problems as well as for the prevention and treatment of breast cancer, as outlined in the following brief review.

32. Lester JE, Dodwell D, Purohit OP, et al. Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. *Clin Cancer Res.* 2008;14:6336-42.
Abstract: PURPOSE: The aromatase inhibitor anastrozole is a highly effective well-tolerated treatment for postmenopausal endocrine-responsive breast cancer. However, its use is associated with accelerated bone loss and an increase in fracture risk. The ARIBON trial is a double-blind, randomized, placebo-controlled study designed to evaluate the impact of bisphosphonate treatment on bone mineral density (BMD) in women taking anastrozole. EXPERIMENTAL DESIGN: BMD was assessed in 131 postmenopausal, surgically treated women with early breast cancer at two U.K. centers. Of these, 50 patients had osteopenia (T score -1.0 to -2.5) at either the hip or lumbar spine. All patients were treated with anastrozole 1 mg once a day and calcium and vitamin D supplementation. In addition, osteopenic patients were randomized to receive either treatment with ibandronate 150 mg orally every month or placebo. RESULTS: After 2 years, osteopenic patients treated with ibandronate gained +2.98% (range -8.9, +19.9) and +0.60% (range -9.0, +6.9) at the lumbar spine and hip, respectively. Patients treated with placebo, however, lost -3.22% (range -16.0, +4.3) at the lumbar spine and -3.90% (range -12.3, +7.2) at the hip. The differences between the two treatment arms were statistically significant at both sites ($P < 0.01$). At 12 months, urinary n-telopeptide, serum c-telopeptide, and serum bone-specific alkaline phosphatase levels declined in patients receiving ibandronate (30.9%, 26.3%, and 22.8%, respectively) and increased in those taking placebo (40.3%, 34.9%, and 37.0%, respectively). CONCLUSIONS: Monthly oral ibandronate improves bone density and normalizes bone turnover in patients treated with anastrozole.

33. Limburg CE. Screening, prevention, detection, and treatment of cancer therapy-induced bone loss in patients with breast cancer. *Oncol Nurs Forum.* 2007;34:55-63.

Abstract: PURPOSE/OBJECTIVES: To identify protocols to screen, detect, prevent, and treat cancer therapy-induced bone loss resulting in osteoporosis in patients with breast cancer. DATA SOURCES: Published books and articles. DATA SYNTHESIS: Normal bone remodeling is affected by hormonal stimulation. Breast cancer therapies target hormones that promote cancer cell growth. Chemotherapy regimens and hormone ablation may cause ovarian failure, resulting in decreased hormone levels. A decrease in hormones, in estrogen- and progesterone-positive and -negative patients, introduces an environment for decreased bone remodeling, which may result in thinning bone and osteoporosis. The acceleration of bone loss leading to osteoporosis can result in higher fracture rates among breast cancer survivors. CONCLUSIONS: With proper use of screening tools, patient education, and advice about lifestyle changes, all prior to cancer treatment, healthcare professionals may decrease or prevent bone loss in patients with breast cancer. Doing so minimizes healthcare costs and decreases morbidity and mortality rates in breast cancer survivors. IMPLICATIONS FOR NURSING: As more individuals diagnosed with breast cancer are surviving for extended periods of time, oncology nurses are providing long-term follow-up care. Part of the care should include proper screening and patient education for healthier recovery and prevention of further healthcare complications as a result of cancer treatment.

34. Lippman ME, Cummings SR, Disch DP, et al. Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. *Clin Cancer Res.* 2006;12:5242-7.
Abstract: PURPOSE: To assess the effect of raloxifene, indicated for osteoporosis treatment and prevention, on invasive breast cancer in subgroups of postmenopausal women defined by risk factors for breast cancer. EXPERIMENTAL DESIGN: Data from the 4-year Multiple Outcomes of Raloxifene Evaluation (MORE) trial (N=7,705) and a follow-up study, the 4-year Continuing Outcomes Relevant to Evista (CORE) trial (N=4,011), were analyzed. Prespecified subgroups were defined by age (>or=65 versus<65 years), age at menopause (>or=49 versus<49 years), body mass index (>or=25 versus<25 kg/m2), family history of breast cancer (yes/no), serum estradiol level (5-10 versus<5, >10 versus<5 pmol/L), prior estrogen therapy (yes/no), and bone mass at MORE baseline, and 5-year predicted risk, assessed using the modified Gail model (>or=1.67 versus<1.67%), at CORE baseline. Time-to-first invasive breast cancer was analyzed using Cox proportional hazards models. RESULTS: In the placebo group, older age, higher estradiol level, and a family history of breast cancer were associated with an increased breast cancer risk (P<0.05). Raloxifene therapy was associated with a reduced breast cancer risk in both women at lower and those at higher breast cancer risk. Hazard ratio point estimates were 0.11 to 0.67, corresponding to a 33% to 89% reduction in breast cancer risk with raloxifene versus placebo. The therapy by family history interaction was significant (P=0.04). CONCLUSIONS: Raloxifene therapy was associated with a reduced risk of invasive breast cancer in postmenopausal women irrespective of the presence/absence of risk factors; its effect was greater in women with a family history of breast cancer.

35. Mackey JR, Joy AA. Skeletal health in postmenopausal survivors of early breast cancer. *Int J Cancer.* 2005;114:1010-5.
Abstract: Estrogen plays an important role in the skeletal health of all women. Many therapies used in the treatment of breast cancer reduce estrogen levels and have the potential to affect bone negatively by increasing the risk of osteoporosis and associated bone fractures. The long-term effects of systemic endocrine therapy on bone, therefore, are

an important consideration in the adjuvant setting. Tamoxifen has been shown to have a moderate protective effect on postmenopausal bone due to its partial estrogen agonist activity; however, its long-term use is potentially associated with negative side effects, such as an increased risk of thromboembolic disease and endometrial cancer. Newer agents, the third-generation aromatase inhibitors (AIs), anastrozole, letrozole and exemestane, for example, do not possess estrogen agonist effects and have improved breast cancer outcomes when compared to the standard 5 years of tamoxifen. However, patients treated with adjuvant AIs have been shown to have an increased incidence of osteoporosis and osteoporotic fractures. In order to select the optimal adjuvant therapy for each patient, it is important to assess the overall risk:benefit ratio for each endocrine strategy. All postmenopausal women should follow published guidelines to assess the risk of osteoporosis and, where appropriate, they should receive bone mineral density monitoring. Postmenopausal women with breast cancer who are at increased risk of osteoporotic fracture should be identified and managed with appropriate nonpharmacologic and pharmacologic measures.

36. Maricic M, Gluck O. Review of raloxifene and its clinical applications in osteoporosis. *Expert Opin Pharmacother.* 2002;3:767-75.
Abstract: Raloxifene, a selective oestrogen receptor modulator, is currently utilised for both the prevention and treatment of postmenopausal osteoporosis. Prevention studies with raloxifene have demonstrated preservation of bone density, suppression of markers of bone turnover and maintenance of normal bone histology for up to 4 years in young postmenopausal women. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial, the pivotal treatment trial of raloxifene, demonstrated significant reductions in the risk of vertebral fractures after 1 and 3 years, which is comparable to other currently available agents. Significant reductions in non-vertebral fractures with raloxifene have not been demonstrated yet. In addition to the effects of raloxifene on bone, a number of beneficial non-skeletal effects have been reported on the breast, uterus and cardiovascular system. These latter findings are mainly derived from secondary end points and analyses of the large osteoporosis studies with raloxifene. Two large, prospective, randomised, double-blind studies examining the effects of raloxifene on breast cancer prevention and cardiovascular protection are now underway. Recent information on the effects of raloxifene in postmenopausal osteoporosis, breast cancer prevention and cardiovascular disease in high-risk women and those with uterine disorders is reviewed in this article.

37. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst.* 2004;96:1751-61.
Abstract: BACKGROUND: The randomized, double-blind Multiple Outcomes of Raloxifene Evaluation (MORE) trial found that 4 years of raloxifene therapy decreased the incidence of invasive breast cancer among postmenopausal women with osteoporosis by 72% compared with placebo. We conducted the Continuing Outcomes Relevant to Evista (CORE) trial to examine the effect of 4 additional years of raloxifene therapy on the incidence of invasive breast cancer in women in MORE who agreed to continue in CORE. METHODS: Women who had been randomly assigned to receive raloxifene (either 60 or 120 mg/day) in MORE were assigned to receive raloxifene (60 mg/day) in CORE (n = 3510), and women who had been assigned to receive placebo in MORE continued on placebo in CORE (n = 1703). Breast cancer incidence was analyzed by a log-rank test, and a Cox proportional hazards model was used to compute hazard ratios (HRs) and 95%

confidence intervals (CIs). All statistical tests were two-sided. RESULTS: During the CORE trial, the 4-year incidences of invasive breast cancer and estrogen receptor (ER)-positive invasive breast cancer were reduced by 59% (HR = 0.41; 95% CI = 0.24 to 0.71) and 66% (HR = 0.34; 95% CI = 0.18 to 0.66), respectively, in the raloxifene group compared with the placebo group. There was no difference between the two groups in incidence of ER-negative invasive breast cancer during CORE (P = .86). Over the 8 years of both trials, the incidences of invasive breast cancer and ER-positive invasive breast cancer were reduced by 66% (HR = 0.34; 95% CI = 0.22 to 0.50) and 76% (HR = 0.24; 95% CI = 0.15 to 0.40), respectively, in the raloxifene group compared with the placebo group. During the CORE trial, the relative risk of thromboembolism in the raloxifene group compared with that in the placebo group was 2.17 (95% CI = 0.83 to 5.70). This increased risk, also observed in the MORE trial, persisted over the 8 years of both trials. CONCLUSIONS: The reduction in invasive breast cancer incidence continues beyond 4 years of raloxifene treatment in postmenopausal women with osteoporosis. No new safety concerns related to raloxifene therapy were identified during CORE.

38. Martino S, Disch D, Dowsett SA, Keech CA, Mershon JL. Safety assessment of raloxifene over eight years in a clinical trial setting. *Curr Med Res Opin.* 2005;21:1441-52. Abstract: OBJECTIVE: Osteoporosis is a chronic disorder that warrants long-term therapy. If benefits are to outweigh risks, the long-term safety profiles of these therapies must be favorable. The aim of this study was to assess the safety of raloxifene over 8 years in 4011 postmenopausal women with osteoporosis in a clinical trial setting through adverse event reporting. METHODS: Data analyzed comprised all reported adverse events collected at each visit of both the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, and the subsequent Continuing Outcomes Relevant to Evista (CORE) trial. MORE was an international, 4-year double-blind, randomized, placebo-controlled study, designed to assess the effect of raloxifene on bone mineral density and vertebral fracture incidence in 7705 (placebo, 2576; raloxifene, 5129) postmenopausal women with osteoporosis. Breast cancer was a secondary endpoint. Based on the breast cancer findings of MORE, the CORE trial, a 4-year double-blind, placebo-controlled trial of a subset of MORE participants, was subsequently conducted. CORE enrolled 4011 (placebo, 1286; raloxifene, 2725) participants and was designed to examine raloxifene's effect on breast cancer incidence. Safety analyses were performed using the intention-to-treat principle, and comparison between therapies was analyzed using a two-sided Fisher's exact test. RESULTS: Over the 8 years of follow-up of 4011 women, there was no difference in all-cause mortality or hospitalization incidence between raloxifene and placebo groups ($p > 0.1$). Excluding breast cancer and non-melanoma skin cancer, cancer incidence was 4.6% and 6.3% in the raloxifene and placebo group, respectively ($p = 0.027$). Raloxifene was associated with a 1.7-fold increase in venous thromboembolism incidence (95% confidence interval 0.93-3.14), with an absolute risk difference of 0.9 per 1000 woman-years. There was no difference in the incidence of myocardial infarction, stroke, uterine cancer, endometrial hyperplasia, ovarian cancer or postmenopausal bleeding between the raloxifene and placebo treatment groups ($p > 0.5$). Uterine polyps, hot flushes and muscle cramps were more common in those receiving raloxifene versus placebo ($p = 0.028$, $p < 0.001$, and $p = 0.008$, respectively). CONCLUSION: These 8-year data support the known clinical safety profile of raloxifene, established in the MORE trial.

39. Mincey BA, Duh MS, Thomas SK, et al. Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors. *Clin Breast Cancer.* 2006;7:127-32.
Abstract: BACKGROUND: Aromatase inhibitors (AIs) are a novel hormonal therapy for patients with breast cancer. However, AIs can cause bone loss by blocking estrogen production. This study aims to assess the association between AIs and treatment-related bone loss in a large managed-care population of women with breast cancer. PATIENTS AND METHODS: With use of medical and pharmacy claims, data from > 5 million beneficiaries between January 1, 1998, and January 31, 2005, we identified 12,368 patients with > or = 2 breast cancer claims in a 6-month period who also had no bone metastases and no previous osteoporosis or fracture claims. Patients who had received antiestrogen (eg, tamoxifen) therapy were also excluded. One thousand three hundred fifty-four patients receiving an AI (anastrozole, exemestane, or letrozole) were compared with 11,014 controls who did not receive an AI with respect to their risk of bone loss. The observation start date for the AI and control groups was defined as the service date of the first AI claim and breast cancer claim, respectively. The endpoints include (1) bone loss, consisting of osteoporosis or osteopenia, and (2) clinical fractures. RESULTS: The univariate analysis found that the prevalence of bone loss was 8.7% in the AI group versus 7.1% in the control group, resulting in a significant relative risk of 1.3 (95% confidence interval [CI], 1.1-1.6; P = 0.01). The prevalence of bone fracture was also significantly increased in the AI group compared with the controls (13.5% vs. 10.3%) with a relative risk of 1.4 (95% CI, 1.2-1.6, P = 0.001). Multivariate Cox proportional hazards regressions showed that after adjusting for age and comorbidities, the risk of bone loss remained significantly higher in the AI group than in the non-AI group, with a 27% (95% CI, 4%-55%; P = 0.02) and 21% (95% CI, 3%-43%; P = 0.02) increase in the risk of bone loss and fractures, respectively. CONCLUSION: This retrospective longitudinal analysis of a large cohort of patients with breast cancer corroborates previous findings from smaller clinical trials and demonstrates that AI therapies carry an increased risk of bone loss. Monitoring and treatment management strategies to reduce bone loss risk are warranted in women receiving an AI for breast cancer.

40. Morris GJ, Mitchell EP. Bisphosphonate therapy for women with breast cancer and at high risk for osteoporosis. *J Natl Med Assoc.* 2007;99:35-45.
Abstract: Bisphosphonates are effective inhibitors of osteoclast activity and bone resorption, and are standard treatments for osteoporosis, hypercalcemia of malignancy, and metabolic bone disease. Bisphosphonates have also been established to effectively reduce skeletal-related events due to malignancy metastatic to bone. Bisphosphonates are now being incorporated into breast cancer treatment regimens in order to combat osteoporosis caused by ovarian suppression, chemotherapy treatment, aromatase inhibitors and the postmenopausal state itself. A large body of evidence suggests that African-American women are at higher risk for osteoporosis-related morbidity than their Caucasian counterparts. In this review, we highlight recommendations toward screening for osteoporosis in high-risk populations. We summarize the mechanisms of action of bisphosphonates in the treatment of osteoporosis and then summarize national recommendations toward incorporating the use of bisphosphonates as support for the bone health of breast cancer patients, as well as patients at high risk for osteoporosis.

41. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. *Cochrane Database Syst Rev.* 2005:CD003474.

Abstract: BACKGROUND: Bone is the most common site of metastatic disease associated with breast cancer affecting more than half of women during the course of their disease. Bone metastases are a significant cause of morbidity due to pain, pathological fractures, hypercalcaemia and spinal cord compression, and contribute to mortality. Bisphosphonates, which inhibit osteoclast-mediated bone resorption, are standard care for tumour-associated hypercalcaemia, and have been shown to reduce bone pain, improve quality of life, and to delay skeletal events and reduce their number in patients with multiple myeloma. Several randomized controlled trials have evaluated the role of bisphosphonates in breast cancer. OBJECTIVES: To assess the effect of bisphosphonates on skeletal events, bone pain, quality of life and survival in women with early and advanced breast cancer. SEARCH STRATEGY: Randomized controlled trials were identified using the specialized register maintained by the Cochrane Breast Cancer Group (the search was applied to the databases Medline, Central/CCTR, Embase, CancerLit, and included handsearches from a number of other relevant sources). See: Cochrane Collaboration Collaborative Review Group in Breast Cancer search strategy. SELECTION CRITERIA: Randomized controlled trials evaluating skeletal events in women with metastatic breast cancer and early breast cancer comparing: 1. treatment with a bisphosphonate with the same treatment without a bisphosphonate 2. treatment with one bisphosphonate with treatment with a different bisphosphonate. DATA COLLECTION AND ANALYSIS: Studies were selected by two independent reviewers. Studies fulfilling the eligibility criteria were evaluated for quality, particularly concealment of allocation to randomized groups. Data were extracted from the published papers or abstracts independently by the two primary reviewers for each of the specified endpoints (skeletal events, bone pain, quality of life and survival). Data on skeletal events and survival were presented as numbers of events, risk ratios and ratios of event rates. Meta-analyses were based on the fixed-effects model (Mantel-Haenszel). Subjective qualitative ratings were used to summarize the quality of life and pain data. MAIN RESULTS: Twenty one randomized studies were included. All studies in advanced breast cancer included women with clinically evident bone metastases (osteolytic and/or mixed osteolytic/osteoblastic) by plain xray and/or radionucleotide bone scans. In nine studies that included 2189 women with advanced breast cancer and existing bone metastases, bisphosphonates reduced the risk of developing a skeletal event by 17% (RR 0.83; 95% confidence interval (CI) 0.78-0.89; P < 0.00001). This effect was more modest, but still highly significant if episodes of hypercalcaemia were excluded (10 studies, 2656 women, RR 0.85; 95% CI 0.79-0.91 P = 0.0001). Overall, intravenous bisphosphonates reduce the risk of developing a skeletal event by 17 % (95% CI 0.78-0.89) compared with oral bisphosphonates, which reduce the risk of developing a skeletal event by 16 % (95% CI 0.76-0.93). Of the currently available bisphosphonates, 4 mg IV zolendronate reduces the risk of developing a skeletal event by 41% (RR 0.59, 95% CI 0.42-0.82), compared with 33 % by 90 mg IV pamdronate (RR 0.77, 95% CI 0.69-0.87), 18 % by 6 mg IV ibandronate (RR 0.82, 95% CI 0.67-1.00), 14 % by 50mg oral ibandronate (RR 0.86, 95% CI 0.73-1.02) and 16 % by 1600 mg oral clodronate (RR 0.84, 95% CI 0.72-0.98).Compared with placebo or no bisphosphonate, with bisphosphonates the skeletal event rate was lower in all of 12 studies in women with clinically evident bone metastases (median reduction of 29%, range 14-48%); statistically significant reductions were reported in 10 trials (four intravenous pamidronate, two oral clodronate, one intravenous ibandronate and two oral ibandronate, a single intravenous zolendronate study).Studies of intravenous zolendronate, pamidronate and oral clodronate in women with advanced breast cancer and clinically evident bone metastases showed significant delays in the median time to a skeletal event. Event-free survival was also reported to be longer in women receiving 6

mg of ibandronate compared with controls.Compared with placebo or no bisphosphonate, with bisphosphonates significant improvements in bone pain were reported in seven studies (90 mg iv pamidronate, 4 mg iv zolendronate, 6 mg iv ibandronate, 1600 mg oral clodronate and 50 mg oral ibandronate). Eight studies tested the effect of bisphosphonates compared with placebo on patient-rated quality of life using a referenced scale. Improvements in global quality of life were reported in only the three studies of iv and oral ibandronate.Treatment with bisphosphonates does not appear to affect survival in women with advanced breast cancer.Intravenous zolendronate (4 mg) appeared to be as effective as pamidronate (90mg) when directly compared in a single randomized double-blind study, based on the risk of developing a skeletal related event, the median time to first skeletal event and skeletal morbidity rate (events per year). Updated re-evaluation of the primary data in the overall population, by multiple event analysis using the method of Anderson-Gill, showed a reduction in the risk of developing any skeletal complication (including hypercalcamia) of 20 % (zolendronate 4 mg compared with pamidronate 90 mg, RR = 0.80, 95% CI 0.66 - 0.97, p = 0.025), suggesting a possible advantage of zolendronate 4 mg compared with pamidronate 90 mg.In the three studies of bisphosphonates in 320 women with advanced breast cancer without clinically evident bone metastases, there was no significant reduction in the incidence of skeletal events (RR 0.99; 95% CI 0.67-1.47; P = 0.97). In the three studies of oral clodronate that included 1653 women with early breast cancer, there was no statistically significant evidence of reduction in the risk of developing skeletal metastases (RR 0.82; 95% CI 0.66-1.01; P = 0.07), or of visceral metastases (RR 0.95; 95% CI 0.80-1.12, p = 0.53). However there was evidence of improved survival (RR 0.82; 95% CI 0.69-0.97, p = 0.02). However there was statistically significant heterogeneity among these studies and a random effects meta-analysis emphasizes the uncertainty of this finding (RR 0.75; 95% CI 0.45 - 1.25; p = 0.19). Toxicity or adverse events were described in 18 of the 21 studies. In general, few serious adverse events were reported. Toxicity associated with bisphosphonates is generally mild and infrequent. Renal toxicity is the main issue with intravenous zolendronate and is dose (8 mg) and infusion time related (< 15 minutes). With daily oral calcium (500 mg) and vitamin D (300-400IU) no significant renal impairment or hypocalcamia was observed with a 15 minute infusion of 4 mg IV zolendronate compared with 90 mg pamidronate. Monitoring of renal function with every cycle of zolendronate was undertaken in all studies and is recommended in practice. No significant renal toxicity was observed with intravenous pamidronate or ibandronate. Mild gastrointestinal toxicity is the main toxicity with oral clodronate and oral ibandronate. AUTHORS' CONCLUSIONS: In women with advanced breast cancer and clinically evident bone metastases, the use of bisphosphonates (oral or intravenous) in addition to hormone therapy or chemotherapy, when compared with placebo or no bisphosphonates, reduces the risk of developing a skeletal event and the skeletal event rate, as well as increasing the time to skeletal event. Some bisphosphonates may also reduce bone pain in women with advanced breast cancer and clinically evident bone metastases and may improve global quality of life. The optimal timing of initiation of bisphosphonate therapy and duration of treatment is uncertain. In women with early breast cancer the effectiveness of bisphosphonates remains an open question for research.

42. Perez EA. Safety of aromatase inhibitors in the adjuvant setting. *Breast Cancer Res Treat.* 2007;105 Suppl 1:75-89.
Abstract: The third-generation aromatase inhibitors (AIs) letrozole, anastrozole, and exemestane are replacing tamoxifen as adjuvant therapy in most postmenopausal women with early breast cancer. Although AIs have demonstrated superior efficacy and better

overall safety compared with tamoxifen in randomized controlled trials, they may not provide the cardioprotective effects of tamoxifen, and bone loss may be a concern with their long-term adjuvant use. Patients require regular bone mineral density monitoring, and prophylactic bisphosphonates are being evaluated to determine whether they may protect long-term bone health. AIs decrease the risks of thromboembolic and cerebrovascular events compared with tamoxifen, and the overall rate of cardiovascular events in patients treated with AIs is within the range seen in age-matched, non-breast-cancer populations. AIs are also associated with a lower incidence of endometrial cancer and fewer vaginal bleeding/discharge events than tamoxifen. Compared with tamoxifen, the incidence of hot flashes is lower with anastrozole and letrozole but may be higher with exemestane. Generally, adverse events with AIs are predictable and manageable, whereas tamoxifen may be associated with life-threatening events in a minority of patients. Overall, the benefits of AIs over tamoxifen are achieved without compromising overall quality of life.

43. Recker RR, Kendler D, Recknor CP, et al. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone.* 2007;40:843-51.
Abstract: The double-blind, randomized raloxifene alendronate comparison trial was the first study designed to compare two osteoporosis therapies head-to-head for fracture risk reduction. The original protocol planned to treat 3000 postmenopausal women with alendronate 10 mg/day (ALN) or raloxifene 60 mg/day (RLX) for 5 years, and to recruit women (50-80 years old) with a femoral neck bone mineral density (BMD) T-score between -2.5 and -4.0, inclusive, no prevalent vertebral fractures, and no prior bone-active agent use. The trial was stopped early, due to difficulty in finding treatment-naive women to meet enrollment goals within the planned timeline, resulting in insufficient power to show non-inferiority between therapies in the primary endpoint (number of women with >or=1 new osteoporotic vertebral or nonvertebral fracture). Except for vertebral fractures, fracture analyses were based upon 1412 of the 1423 women randomized (mean age of 66 years). After 312+/-254 days (mean+/-SD), 22 women in the ALN group and 20 in the RLX group had new vertebral or nonvertebral fractures. Four women in the ALN group and none in the RLX group had moderate/severe vertebral fractures, a pre-specified endpoint (P=0.04). Lumbar spine, femoral neck, and total hip BMD were increased from baseline at 2 years in each group (P<0.001), with greater increases in the ALN group (each P<0.05). Similar numbers of women in each group had >or=1 adverse event and discontinued due to an adverse event. The only adverse events with an incidence that differed between groups were colonoscopy, diarrhea, and nausea; each was more common with ALN treatment (each P<0.05). One woman in each group had a venous thromboembolic event. One case of breast cancer occurred in each group. In summary, as this trial was terminated early, there was insufficient power to compare the fracture risks between alendronate and raloxifene. Safety profiles were as expected from clinical trial and post-marketing reports. TRIAL REGISTRATION: ClinicalTrials.gov Identifier NCT00035971.

44. Rugo HS. Strategies for the prevention of treatment-related bone loss in women receiving adjuvant hormonal therapy. *Clin Breast Cancer.* 2007;7 Suppl 1:S21-8.
Abstract: More than 220,000 women will be diagnosed with breast cancer this year, and approximately 75% of these women will be long-term survivors of this disease. Survival has improved largely because of advances in adjuvant hormone therapy and chemotherapy, as well as early detection strategies. Because most women will receive adjuvant treatment,

and the majority will survive cancer, it is increasingly important to understand the resultant toxicities and to devise monitoring and treatment strategies to avoid adverse long-term effects. Loss of bone mineral density leading to osteoporosis and increased risk of fracture as well as other morbidities is a well known complication of estrogen suppression associated with use of aromatase inhibitors (AIs) in postmenopausal women, and ovarian suppression with GnRH agonists or chemotherapy in premenopausal women. Hormone receptor positivity is increasingly frequent with increasing patient age, so that a large number of women already at risk for osteopenia associated with menopause are at risk for further bone loss caused by adjuvant hormone therapy with AIs. This article will review data on bone mineral density loss and risk of fracture in the large, randomized phase III trials comparing tamoxifen to AIs using the upfront, switching or extended hormone therapy approach. Data from prophylactic bisphosphonate intervention trials in both post- and premenopausal women will be discussed. Ongoing trials are described.

45. Sawka AM, Ioannidis G, Papaioannou A, et al. Are oral bisphosphonates effective in improving lumbar bone mineral density in breast cancer survivors with osteopenia or osteoporosis? *J Obstet Gynaecol Can.* 2005;27:759-64.
Abstract: OBJECTIVE: Breast cancer survivors with osteoporosis or osteopenia are commonly encountered in primary care and gynaecology practices. Our objective was to determine whether treatment with oral bisphosphonates (alendronate or cyclic etidronate) was more effective than calcium with vitamin D in improving lumbar spine bone mineral density (BMD) within one year in breast cancer survivors. METHODS: Breast cancer survivors with at least one year of clinical follow-up were identified from the prospective observational Canadian Database of Osteoporosis and Osteopenia (CANDOO). Analysis of covariance was used to examine the effects of bisphosphonate therapy on change in lumbar spine BMD at one year compared with the effects of calcium with vitamin D (analysis adjusted for baseline L2-L4 BMD, current tamoxifen use, number of prevalent vertebral fractures [VFs], and time since diagnosis of breast cancer, and age). RESULTS: Eighteen patients took calcium and vitamin D, 25 took cyclic etidronate, and 27 took oral alendronate. Adjusted one-year BMD increases for alendronate and cyclic etidronate compared to calcium and vitamin D were as follows: alendronate 4.53% (95% confidence interval [CI] 1.26%, 7.81%, P = 0.008), and cyclic etidronate 1.85% (-1.55%, 5.25%, P = 0.280). BMD increases were significantly greater in patients with prevalent VF compared to those without VF (P = 0.025). In contrast, time since diagnosis of breast cancer was significantly associated with a decrease in BMD (P = 0.002). We were unable to detect any effect of current tamoxifen use, baseline lumbar spine BMD, or age on changes in BMD at one year. CONCLUSION: Treatment with alendronate was associated with significantly greater improvements in lumbar spine BMD within one year in breast cancer survivors when compared with treatment with cyclic etidronate or calcium and vitamin D.

46. Silverman SL, Delmas PD, Kulkarni PM, Stock JL, Wong M, Plouffe L Jr. Comparison of fracture, cardiovascular event, and breast cancer rates at 3 years in postmenopausal women with osteoporosis. *J Am Geriatr Soc.* 2004;52:1543-8.
Abstract: OBJECTIVES: To compare event rates for osteoporotic fractures, cardiovascular events, and breast cancer in postmenopausal women with osteoporosis. DESIGN: A prospective, observational study of the placebo group in the double-blind, randomized Multiple Outcomes of Raloxifene Evaluation trial. SETTING: One hundred eighty clinical research centers in 25 countries. PARTICIPANTS: Postmenopausal women (n=2,565, mean age=67) with osteoporosis were given calcium (500 mg/d) and vitamin D (400-600

IU/d) supplements. MEASUREMENTS: The occurrence of at least one new fracture, cardiovascular event, or breast cancer diagnosis at 3 years was identified and adjudicated. RESULTS: The occurrence of any fracture was the most common event in these women. In women without prevalent vertebral fractures (n=1,627), the event rates per 1,000 patient-years were 45.4 for any fracture, 15.2 for vertebral fracture, 4.7 for clinical vertebral fracture, 0.9 for hip fracture, 8.3 for any cardiovascular event, and 5.2 for all breast cancer. In women with prevalent vertebral fractures (n=938), the event rates per 1,000 patient-years were 117.4 for any new fracture, 77.1 for new vertebral fracture, 25.7 for clinical vertebral fracture, 5.8 for hip fracture, 15.1 for any cardiovascular event, and 2.6 for all breast cancer. The effect of prevalent fracture status on event rates was not dependent on whether women were older or younger than 65, but women aged 65 and older had a 3.6 times greater occurrence of cardiovascular events than younger women, irrespective of prevalent fracture status. CONCLUSION: These data on the relative incidence of clinically significant skeletal and extra-skeletal outcomes may be useful in choosing an agent for health maintenance for postmenopausal women with osteoporosis.

47. Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. *J Bone Miner Res.* 2005;20:1514-24.
Abstract: In the CORE breast cancer trial of 4011 women continuing from MORE, the incidence of nonvertebral fractures at 8 years was similar between placebo and raloxifene 60 mg/day. CORE had limitations for assessing fracture risk. In a subset of 386 women, 7 years of raloxifene treatment significantly increased lumbar spine and femoral neck BMD compared from the baseline of MORE. INTRODUCTION: The multicenter, double-blind Continuing Outcomes Relevant to Evista (CORE) trial assessed the effects of raloxifene on breast cancer for 4 additional years beyond the 4-year Multiple Outcomes of Raloxifene Evaluation (MORE) osteoporosis treatment trial. MATERIALS AND METHODS: In CORE, placebo-treated women from MORE continued with placebo (n = 1286), whereas those previously given raloxifene (60 or 120 mg/day) received raloxifene 60 mg/day (n = 2725). As a secondary endpoint, new nonvertebral fractures were analyzed as time-to-first event in 4011 postmenopausal women at 8 years. A substudy assessed lumbar spine and femoral neck BMD at 7 years, with the primary analysis based on 386 women (127 placebo, 259 raloxifene) who did not take other bone-active agents from the fourth year of MORE and who were > or =80% compliant with study medication in CORE. RESULTS: The risk of at least one new nonvertebral fracture was similar in the placebo (22.9%) and raloxifene (22.8%) groups (hazard ratio [HR], 1.00; Bonferroni-adjusted CI, 0.82, 1.21). The incidence of at least one new nonvertebral fracture at six major sites (clavicle, humerus, wrist, pelvis, hip, lower leg) was 17.5% in both groups. Posthoc Poisson analyses, which account for multiple events, showed no overall effect on nonvertebral fracture risk, and a decreased risk at six major nonvertebral sites in women with prevalent vertebral fractures (HR, 0.78; 95% CI, 0.63, 0.96). At 7 years after MORE randomization, the differences in mean lumbar spine and femoral neck BMD with raloxifene were 1.7% (p = 0.30) and 2.4% (p = 0.045), respectively, from placebo. Compared with MORE baseline, after 7 years, raloxifene treatment significantly increased lumbar spine (4.3% from baseline, 2.2% from placebo) and femoral neck BMD (1.9% from baseline, 3.0% from placebo). BMDs were significantly increased from MORE baseline at all time-points at both sites with raloxifene. CONCLUSION: Raloxifene therapy had no effect on nonvertebral fracture risk after 8 years, although CORE had limitations for fracture risk assessment. BMD increases were maintained after 7 years of raloxifene.

48. Stevenson M, Jones ML, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess.* 2005;9:1-160.
Abstract: OBJECTIVES: To establish the clinical effectiveness and cost-effectiveness of selective oestrogen receptor modulators, bisphosphonates and parathyroid hormone (subject to licensing) for the prevention and treatment of osteoporosis and the prevention of osteoporotic fractures in postmenopausal women. DATA SOURCES: Electronic databases. REVIEW METHODS: Studies that met the review's entry criteria were eligible for inclusion in the meta-analyses provided that they reported fracture incidence in terms of the number of patients suffering fractures. Meta-analysis was carried out using the random-effects model. A model was constructed to estimate the cost-effectiveness of osteoporosis interventions. The model calculated the number of fractures that occurred and provided the costs associated with osteoporotic fractures, and the quality-adjusted life-years (QALYs). In addition, the conditions of breast cancer and coronary heart disease (CHD) were modelled, as some interventions have been shown to affect the risk of these conditions. RESULTS: Ninety randomised controlled trials (RCTs) met the inclusion criteria. They related to the five interventions (alendronate, etidronate, risedronate, raloxifene and teriparatide) and to five comparators (calcium, calcium plus vitamin D, calcitriol, hormone replacement therapy and exercise), as well as placebo or no treatment. All five interventions have been shown to reduce the risk of vertebral fracture in women with severe osteoporosis with adequate calcium intakes. However, none of these drugs has been demonstrated, by direct comparison, to be significantly more effective than either each other or the other active interventions reviewed in this report. The intervention costs of treating all osteoporotic women, for a period of 5 years, were in the region of pound 900-1500 million for alendronate, etidronate, risedronate and raloxifene. The cost per QALY ratios fell dramatically with age. Assuming the risks of a woman with severe osteoporosis at the threshold of osteoporosis, no treatment had a cost per QALY below pound 35,000 at 50 years of age. At 60 years of age, the cost per QALY of raloxifene was pound 26,000 assuming no impact on hip fractures, and pound 31,000 assuming an adverse effect. However, these results are driven by the effect on breast cancer and the assumptions made regarding this disease state. No other intervention had a cost per QALY below pound 35,000. When analyses were conducted assuming that the fracture risk is doubled at each site, alendronate and risedronate had cost per QALY ratios below pound 30,000 at all ages. For women at the threshold of osteoporosis, without a prior fracture and aged 70 years, the cost per QALY of the three bisphosphonates ranged from pound 34,000 to pound 41,000. Raloxifene had a cost per QALY of pound 23,000, assuming no effect on hip fracture, given assumptions regarding breast cancer. At 80 years of age, the cost per QALY of alendronate and risedronate was below pound 20,000. This was true for etidronate when incorporating observational data, but the value rose to pound 69,000 when only RCT data were used. No other intervention had a cost per QALY below pound 35,000. It was assumed that doubling the risk of fracture for women without a prior fracture would give results similar to patients at the threshold of osteoporosis with a prior fracture. CONCLUSIONS: Of the five interventions, only raloxifene appeared to reduce the risk of vertebral fracture in postmenopausal women unselected for low bone mineral density (BMD). However, as the full data have not been made public, there is some uncertainty regarding this result. None of the five interventions has been shown to reduce the risk of non-vertebral fracture in women unselected for low BMD. All of the proposed interventions provided gains in QALYs compared with no treatment in women with

sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the age of the patient. The estimated costs varied widely for the interventions. These net costs were markedly different by age, with some interventions becoming cost-saving at higher age ranges in patients with a prior fracture. Areas for future research include: the evidence base for the efficacy of fracture prevention in the very elderly, reanalysis of raloxifene using a dedicated breast cancer and CHD model, and more trials considering the cost-effectiveness of teriparatide.

49. Tham YL, Sexton K, Weiss HL, Elledge RM, Friedman LC, Kramer RM. The adherence to practice guidelines in the assessment of bone health in women with chemotherapy-induced menopause. *J Support Oncol.* 2006;4:295-8, 304.
Abstract: Premenopausal women are diagnosed with 25% of all invasive breast cancers;adjuvant chemotherapy given to many of this population may induce menopause and increase the risk of osteoporosis development. Guidelines issued by the American Society of Clinical Oncology recommend regular assessment of bone health in such women. To assess appropriate attention to bone health, we performed a retrospective, cross-sectional survey of young women at high risk of osteoporosis secondary to chemotherapy-induced premature menopause. In all, 102 women with chemotherapy-induced menopause, 75% of whom were 40 years of age or younger, were asked whether they underwent screening and preventive measures for osteoporosis. Only 56% had discussed bone health with their healthcare providers; age at diagnosis, race, and use of tamoxifen were not linked to the likelihood of such discussions. Regular exercise was recommended to 73% of the women, calcium supplementation to 56%, and bone mineral density (BMD) testing to 40%. Approximately one half of the women regularly exercised and took a calcium supplement; however, over 37% of those using a supplement took less calcium than that recommended to prevent osteoporosis. Further, 32% reported having had BMD testing;women 40 years of age or younger were less likely to have had such tests (27%) than were older women (48%;P = 0.05). More emphasis must be given to educating breast cancer survivors with chemotherapy-induced menopause about bone health and its maintenance. Approved therapies to prevent osteoporosis probably are underused in this population.

50. Tosteson AN, Grove MR, Hammond CS, et al. Early discontinuation of treatment for osteoporosis. *Am J Med.* 2003;115:209-16.
Abstract: PURPOSE: To identify factors associated with early treatment discontinuation of three agents commonly prescribed for women with low bone density. METHODS: A telephone survey was conducted in 2000 to 2001 in a random sample of women aged 45 years or older who had bone density T-scores -1.0 or lower and who had initiated treatment with hormone replacement therapy, raloxifene, oral endronate. Logistic regression was used to estimate adjusted odds ratios for early treatment discontinuation. RESULTS: Among 956 women who were interviewed an average of 7 months after treatment initiation, 334 were taking hormone therapy, and 88 (26%) had discontinued; 256 were taking raloxifene, and 48 (19%) had discontinued (P = 0.03 vs. hormone therapy); and 366 were taking alendronate, and 70(19%) had discontinued (P = 0.02 vs. hormone therapy).Women with bothersome side effects (somewhat bothered: odds ratio [OR] = 4.0; 95% confidence interval [CI]: 2.5 to 6.5; very or extremely bothered: OR = 25; 95% CI: 16 to 39) or who thought that their bone density test results did not show osteoporosis (OR = 1.6; 95% CI: 1.0 to 2.5) were more likely to discontinue therapy, as compared with women reporting regular exercise (OR = 0.7; 95% CI: 0.4 to 1.0) or a willingness to take prescribed

medications (OR = 0.6; 95% CI: 0.4 to 0.9).After adjustment for side effects and patient characteristics, the odds of early treatment discontinuation did not differ significantly among treatments. CONCLUSION: Improved adherence to osteoporosis treatment requires that treatment side effects be minimized and women be educated regarding their bone density test results.

51. Waltman NL, Ott CD, Twiss JJ, Gross GJ, Lindsey AM, Moore TE. Bone mineral density and bone turnover in postmenopausal women treated for breast cancer. *Cancer Nurs.* 2008;31:182-90.
Abstract: Chemotherapy and endocrine treatments for breast cancer are believed to increase risk of osteoporosis by causing early menopause in premenopausal women and by further depleting estrogen levels in postmenopausal women. Multivariate analyses were used to evaluate the contributions of 7 predictors (age, body mass index [BMI], family history of osteoporosis, months since menopause, past use of chemotherapy, and current use of tamoxifen or aromatase inhibitors) in explaining variability in bone mineral density (BMD) at the hip and the spine and bone turnover in 249 postmenopausal women who are breast cancer survivors. This report was an analysis of baseline data from a federally funded (1 R01 NR07743-01A1) intervention study on osteoporosis prevention. Mean age of the women was 58.5 years, and average BMI was 26.7 kg/m; 98% were white. All had measurable bone loss, 167 had chemotherapy, 76 were on tamoxifen, and 21 were on aromatase inhibitors. Women with higher BMI had higher BMD at the hip ($P < .001$) and the spine ($P = .004$). Women on tamoxifen had lower measures of bone formation (Alkphase B) ($P < .001$), suggesting less bone turnover, and higher BMD at the hip ($P = .035$). There was a trend for women who had received chemotherapy to have lower BMD at the spine ($P = .06$). The implications of these findings are discussed in the article.

52. Yonehara Y, Iwamoto I, Kosha S, Rai Y, Sagara Y, Douchi T. Aromatase inhibitor-induced bone mineral loss and its prevention by bisphosphonate administration in postmenopausal breast cancer patients. *J Obstet Gynaecol Res.* 2007;33:696-9.
Abstract: AIM: To investigate aromatase inhibitor-induced bone mineral loss and its prevention by bisphosphonate administration in postmenopausal breast cancer patients. METHODS: Subjects were 17 postmenopausal breast cancer patients (mean age, 63.3 +/- 9.9 years) receiving non-steroidal aromatase inhibitor (AI; anastrozole, 1 mg daily) only and 10 such patients (mean age, 65.0 +/- 5.1 years) receiving AI + bisphosphonate (risedronate sodium, 2.5 mg daily) for 6 months. All of the subjects had undergone surgical resection and had positive estrogen receptor tumor status. Age, age at menopause, years since menopause, height, weight, and body mass index (Wt/Ht(2)) were recorded. Lumbar spine (L2-4) bone mineral density (BMD), T-, and Z-scores were assessed on dual-energy X-ray absorptiometry before and after therapy. RESULTS: In the AI-only group BMD, T-, and Z-scores significantly decreased from the baseline during the 6-month therapy period ($P < 0.05$). Mean decreases in L2-4 BMD and Z-score were 2.5% and 3.0%, respectively. In the AI + bisphosphonate group, however, BMD, T-, and Z-scores significantly increased from the baseline values ($P < 0.01$). Mean increases in L2-4 BMD and Z-score were 4.5% and 3.3%, respectively. CONCLUSION: AI carries a potential risk of bone mineral loss despite the short therapy duration. Bisphosphonate has a preventive effect on this loss.