Bone health in postmenopausal women with early breast cancer: how protective is tamoxifen?

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CRD summary
The authors concluded that tamoxifen had some benefit on bone mineral density, but not fracture incidence, in postmenopausal women with early breast cancer. While aspects of this systematic review were well-conducted, methodological limitations and poor evidence suggest that the conclusions are unlikely to be reliable.

Authors’ objectives
To assess the effectiveness of tamoxifen on bone health in postmenopausal women with early stage breast cancer.

Searching
PubMed was searched for English language publications. Search terms were reported. Reference lists of relevant publications were also checked for additional studies.

Study selection
Studies of tamoxifen treatment in postmenopausal women, aged 45 years or older, with early stage breast cancer were included in the review. Outcomes of interest were bone mineral density and bone fracture. Studies published as full text papers with non-tamoxifen controls were eligible for inclusion.

Where reported, the included studies evaluated women ranging in age from 41 to 84 years. Breast cancer disease was most commonly described as stage I to II or axillary-node negative, but it appeared that many studies also included women with advanced cancer. Tamoxifen therapy dosages ranged from 20 to 40 mg/day, and the duration of treatment ranged from one to greater than five years. Bone mineral density was measured in the spine, hip, arm and total body; where reported, the most common methods to assess bone mineral density were photon absorptiometry and dual energy x-ray absorptiometry. Control comparisons included baseline measures, matched controls, placebo, no adjuvant therapy, or healthy controls.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of the studies was assessed using a published checklist which evaluated 27 criteria within five categories: reporting, external validity, internal validity-bias, internal validity-confounding, and statistical power. The maximum quality score that could be achieved was 32.

The authors did not state how many reviewers were involved in the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a narrative synthesis, with studies grouped by outcome measure, and for tamoxifen given alone or alongside chemotherapy or hormone replacement therapy.

Results of the review
Twenty-seven studies were included in the review (the overall number of participants was not clear). Twenty-three trials evaluated tamoxifen alone; eight were randomised controlled trials (RCTs); 15 were cohort studies; one was a cross-sectional study. The study designs for the remaining four studies were not reported. Where reported, the average quality
score of the included trials was 13 (range 7 to 23).

**Tamoxifen alone:** Changes in spinal bone mineral density were evaluated in 16 studies; the majority demonstrated a protective effect of tamoxifen treatment. Changes in hip bone mineral density were inconsistent (10 studies). No significant increase in arm bone mineral density was observed in any study (seven studies). Two studies reported increased rates of fracture in patients treated with tamoxifen.

**Tamoxifen plus chemotherapy** (three studies): Tamoxifen after chemotherapy was found to partially prevent or reverse bone loss in the hip (one study). Combined therapy had no significant effect on bone mineral density in two studies.

**Tamoxifen and hormonal replacement therapy (HRT):** Two studies reported that spinal bone mineral density was decreased in participants who had received HRT, whilst those who did not have a HRT history had unchanged or increased spinal bone mineral density (statistical results not reported).

**Authors’ conclusions**
Despite the apparent positive impact of tamoxifen on bone mineral density, there was some evidence to suggest an increased risk of fracture incidence.

**CRD commentary**
This review addressed a clear question and was supported by appropriate inclusion criteria. However, some of the studies included participants who may not have met the inclusion criteria (some women may have had advanced breast cancer). Only one database was searched to identify relevant articles and the search was restricted to English language publications, thus introducing the potential for language and publication biases; some relevant studies may have been missed. Validity was assessed and the authors noted that the better quality studies demonstrated a lower increase in bone mineral density with tamoxifen treatment. Details of the number of reviewers involved in the systematic review process were not described, thus introducing the potential for reviewer error and bias. Comprehensive details of 23 of the 27 included studies were reported, but statistical results were not presented for any of the studies. Most of the studies appeared to be of relatively low quality with small sample sizes. Also, many studies compared treatment with baseline, which may have not adequately assessed effectiveness. While aspects of this systematic review were well-conducted, methodological limitations and poor evidence suggest that the conclusions are unlikely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that recommendations for practice were not clear due to the discrepancy between bone mineral density change and fracture incidence. They also stated that tamoxifen should not replace osteoporosis prevention therapy for breast cancer patients at high risk of osteoporosis.

**Research:** The authors stated that more research is necessary to clarify the discrepancy between bone mineral density change and fracture incidence.

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