A systematic review and meta-analysis of bone metabolism in prostate adenocarcinoma

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CRD summary
The review concluded that patients with prostate cancer who received androgen deprivation therapy were at increased risk of osteoporosis and fractures compared to patients who did not undergo therapy and compared to healthy controls. Potential for review bias, uncertainties surrounding study quality and limited meta-analysis mean the authors' conclusions should be treated with caution.

Authors' objectives
To assess the incidence of bone loss and osteoporosis in patients with prostate cancer who were treated versus those who were not treated with hormone therapy.

Searching
MEDLINE (from 1966), EMBASE (from 1990) and CANCERLIT (from 1966) were searched to 2009 for relevant articles in any language; search terms were reported. Abstracts from the proceedings of annual meetings of the American Society of Clinical Oncology were searched between 1998 and 2008. Reference lists from retrieved articles and relevant reviews were manually searched.

Study selection
Studies that assessed the use of hormone therapy in patients with prostate cancer were eligible for inclusion if they reported fracture outcome, incidence of osteoporosis or bone mineral density data.

The included studies assessed patients with prostate cancer only or compared patients with prostate cancer to patients with prostate cancer and receiving hormone therapy (androgen deprivation therapy) or to healthy controls. The mean age of patients ranged between 66 and 79 years and was similar across all study groups. The mean time of hormone therapy varied from 2.9 to 120 months. Bone mineral density was assessed using a dual energy X-ray absorptiometry in all except two studies to determine the incidence of osteopenia (low bone mineral density). Fewer than half the studies used biomarkers of bone turnover.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
Two reviewers independently extracted incidences of osteoporosis, osteopenia and fractures to calculate risk ratios (RRs) and 95% confidence intervals (CIs). Data extraction were checked by a third reviewer and discrepancies were resolved through consensus. Primary authors were contacted for further data, where necessary.

Methods of synthesis
A fixed-effect model was used to pool adjusted risk ratios and 95% CIs. Statistical heterogeneity was assessed using the \( X^2 \) and \( I^2 \). Statistical heterogeneity was explored using stratified analyses for various study characteristics: incidence of fractures as the primary outcome (yes versus no); type of outcome measure (self-reported versus ambulatorial); bone metastases in the sample (yes versus no); mean follow-up (≥5 years versus <5 years); type of fracture (lumbar spine versus inferior member).

Bivariate correlations (Spearman's rho coefficient) were used to assess the relationship between hormone therapy time and bone mineral density (results not reported here).

Publication bias was assessed using funnel plots and the Begg test.
Results of the review
Thirty-two studies (n=116,911, range 12 to 50,613) were included in the review: 70,684 patients had prostate cancer, 45,161 had prostate cancer and were being treated with hormone therapy, and 1,066 were healthy controls. A table of patient characteristics indicated that 51,605 patients with prostate cancer without hormone therapy and 26,082 patients with prostate cancer and treated with hormone therapy were included in the review.

Patients who received hormone therapy had lower total bone mineral density than patients who did not receive hormone therapy; levels were similar compared with healthy controls.

Risk of osteoporosis increased in patients with prostate cancer who were treated with hormone therapy compared to patients not treated with hormone therapy (adjusted RR 1.30, 95% CI 1.22 to 1.40, I^2=36%; five studies). Compared to healthy controls, patients with prostate cancer without hormone therapy had a reduced risk of developing osteoporosis (adjusted RR 0.39, 95% CI 0.16 to 0.96, I^2=0%; two studies). Patients who received hormone therapy had an increased risk (RR 2.26, 95% CI 1.00 to 5.09).

Incidence of fracture was significantly increased in patients who received hormone therapy compared to patients who did not (adjusted RR 1.17, 95% CI 1.14 to 1.20, I^2=96%; five studies). Stratified analyses showed consistently increased risk of fracture in patients who received hormone therapy for all study characteristics assessed.

There was no evidence of publication bias.

Authors' conclusions
Patients with prostate cancer who underwent androgen deprivation therapy had lower levels of bone mineral density and higher rates of osteoporosis and fractures compared to patients with prostate cancer who did not undergo androgen deprivation therapy and compared to healthy controls.

CRD commentary
The review question and inclusion criteria were clearly stated. A satisfactory search of the literature was undertaken without language restrictions, which reduced potential for language bias. There was no evidence of publication bias for osteoporosis or fracture; both assessments included fewer than 10 studies and this made the reliability of the findings unclear. Study quality was not formally assessed and study designs were not reported. Data extraction was undertaken in duplicate; it was unclear whether applied to study selection, so reviewer error and bias could not be ruled out. Few patient and study characteristics were reported (such as other treatments received by patients and details of treatment regimens).

There was some evidence of statistical heterogeneity and so use of a fixed-effect model was not appropriate. Adjusted risk ratios were reported for most outcomes, but it was unclear what they were adjusted for. The authors stated that the lack of adjustment for the presence of metastasis, calcium ingestion and genetic predisposition should be considered as a limitation of the review. Given that 32 studies were included in the review, only a small number of studies were included in the meta-analyses.

Potential for review bias and uncertainties surrounding the included studies and limited number of studies included in the meta-analysis mean the authors' conclusions should be treated with caution.

Implications of the review for practice and research
The authors did not state any implications for research and practice.

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None stated.

Bibliographic details
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.