Statin use and the risk of prostate cancer: a metaanalysis of 6 randomized clinical trials and 13 observational studies

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CRD summary
The authors concluded that whilst there was no evidence of an association between statin use and total prostate cancer, it appeared there was a protective association between statin use and advanced prostate cancer. The authors' conclusions reflected the evidence presented but, given inadequate study details, inappropriate synthesis methods and lack of validity assessment, their reliability is unclear.

Authors' objectives
To evaluate the relationship between statin use and risk of prostate cancer.

Searching
The databases MEDLINE (1966 to Nov 2007) and the Science Citation Index on the Web of Science (1970 through Nov 2007) were searched without language restrictions. Search terms were reported. Reference lists of relevant articles, and abstracts from the American Society of Clinical Oncology and of the American Association for Cancer Research were searched for additional studies. The authors stated that there was no search for unpublished or original data.

Study selection
Eligible for inclusion in the review were randomised controlled trials (RCTs) or observational studies (case control or cohort studies) that evaluated exposure to statins and risk of prostate cancer. RCTs were considered eligible for inclusion if: they evaluated a statin therapy compared with placebo or no treatment; there was no other intervention difference between the experimental and the control group; the study duration was at least three years; at least 1,000 male participants were enrolled; and prostate cancer incidence or mortality was reported. Studies of all design were excluded if there was insufficient data for calculating a relative risk and a confidence interval.

Of the RCTs included in the review, all were placebo controlled and usedLovastatin, pravastatin, fluvastatin or simvastatin.

Two reviewers independently selected the studies for inclusion in the review. It was not stated how disagreements were resolved.

Assessment of study quality
The authors stated that they did not assess study validity.

Data extraction
Data was extracted in order to calculate relative risks (RRs) and 95% confidence intervals (CIs).

Two reviewers independently performed the data extraction and any disagreements were resolved through consensus.

Methods of synthesis
Studies were grouped according to study design, RCTs versus observational studies. For each group, relative risks were combined in a meta-analysis using a random-effects (DerSimonian and Laird) model. Heterogeneity was assessed using the Q statistic and the I² test. Publication bias was assessed using the Begg's test and the Egger's test. Subgroup analyses were performed according to study design (case control versus cohort studies), and whether statins were lipophilic or lipophobic. Sensitivity analysis was performed by excluding one study at a time from the meta-analyses.

Results of the review
Nineteen studies were included in the review: six RCTs (n=40 patients, 178 men) and 13 observational studies (six
cohort studies and seven case control studies, n=840,000 men).

Meta-analysis of the six RCTs showed that there was no statistically significant association between statin use and prostate cancer (RR 1.06, 95% CI 0.93 to 1.20). There was no evidence of statistically significant heterogeneity or of publication bias.

Meta-analysis of 13 observational studies also showed no statistically significant association between statin use and prostate cancer (RR 0.89, 95% CI 0.65 to 1.24). However, there was evidence of statistically significant heterogeneity ($I^2=98\%$) and of publication bias (Begg's test p=0.03, Egger's test p=0.08). Further results of subgroup analyses were reported in the review.

There was no statistically significant association between long term use of statin (greater or equal to five years of use) and risk of total prostate cancer (RR 0.93, 95% CI 0.77 to 1.13; six observational studies). However, there was evidence of statistically significant heterogeneity ($I^2=75\%$).

There was a statistically significant protective association between statin use and advanced prostate cancer (RR 0.77, 95% CI 0.64 to 0.93; five observational studies), with no evidence of statistically significant heterogeneity or publication bias.

**Authors' conclusions**
There was no evidence of an association between statin use and total prostate cancer, but there seemed to be a protective association between statin use and the risk of advanced prostate cancer.

**CRD commentary**
This review addressed a clear research question and was supported by adequate inclusion criteria. The search strategy was adequate with no language restrictions, but there was no search for unpublished material, which means that relevant studies might have been missed. There was no assessment of validity, so the reliability of the evidence could not be assessed. Inadequate details of primary studies were provided, with no information on statin dosage or population characteristics. The pooling of observational studies would seem inappropriate given the statistically significant heterogeneity observed. The authors' conclusions reflected the evidence presented but, given inadequate study details, inappropriate synthesis methods and lack of validity assessment, their reliability is unclear.

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

**Research:** The authors stated that further epidemiological research is needed to assess the risk of advanced prostate cancer among statin users controlling for prostate specific antigen testing.

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