Statins and cancer: a systematic review and meta-analysis
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CRD summary
This review concluded that statins did not have short-term effects on cancer in adult patients, but the strength of the evidence was weak and further research is needed. Given the uncertainties surrounding the techniques used to pool data and assess heterogeneity, coupled with several methodological and reporting limitations, the authors' conclusions should be interpreted with caution.

Authors' objectives
To examine the evidence on the association between statin therapy and cancer.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to October 2007 for publications in any language. Search terms were reported. In addition, the authors' personal libraries, and references of relevant reviews and other publications, were manually searched.

Study selection
Studies of patients aged 18 years or older, that compared statin treatment with an inactive control (placebo or no statins), and reported cancer incidence, were eligible for inclusion. Eligible studies were required to have a follow-up of one year. Studies on cerivastatin or describing statin treatment in cancer or transplant patients were excluded.

The main endpoint for included trials was the effect of statins on cardiovascular endpoints, while the main endpoint for observational studies was the effect of statins on cancer.

Included studies were published between 1993 and 2007. The majority of included participants were reported to be middle-aged, but ages ranged from 18 to at least 100 years. Treatments included atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin. Observational studies used register data, self-report data, or data from clinical records.

One reviewer screened papers for relevance, referring to other reviewers where necessary.

Assessment of study quality
One reviewer assessed the quality of the studies according to the following criteria: sample size; randomisation; allocation methods; blinding; compliance; drop-outs; follow-up duration and losses to follow-up; missing data; effect measure; potential confounders; and applicability to the target population (middle-aged northern Europeans). Studies were also assessed on overall strength of evidence for each outcome.

Data extraction
One reviewer extracted data on cancer type and statin type to calculate median risk ratios (RRs) with their ranges, and mean risk ratios with their 95% confidence intervals (CIs). Odds ratios were assumed to approximate risk ratios. Median rate differences per 100,000 person years were also calculated. Where studies had multiple treatment arms with different doses of a statin, cancer incidences were pooled.

Methods of synthesis
Median risk ratios with their ranges were pooled by cancer type. Mean risk ratios with their 95% confidence intervals were pooled using the inverse of the variance and were also reported in the review. Studies with weak levels of evidence were excluded from the synthesis.

Heterogeneity was investigated based on study populations, predictors, outcomes, follow-up times, risks among the controls, effect measures, effect sizes, and continuity of effect sizes.
Results of the review

Forty-two studies were included in the review: 17 randomised controlled trials (n=67,393 participants); 10 cohort studies (925,295 participants); and 15 case-control studies (641,326 participants). Sample sizes ranged from 249 to 483,733 participants. The median follow-up was four years (ranging between two and 12 years). Study quality was reported to be moderate to good, but with some studies of moderate quality.

Cancer incidence: Statins had no significant effect on the overall incidence of cancer (median RR 0.96, range 0.72 to 1.2; 20 studies). The median rate difference per 100,000 person-years ranged from -50 to 69. The authors reported that statins showed some protection from certain cancers, but it was unclear whether these were statistically significant.

Different statins: The median risk ratio on different cancer outcomes ranged from 0.34 to 0.91 for atorvastatin, from 0.34 to 1.2 for fluvastatin, from 0.52 to 1.7 for lovastatin, from 0.58 to 1.7 for pravastatin, and from 0.67 to 1.6 for simvastatin. The median rate per 100,000 person-years varied from -76 to 384 for lovastatin, from -68 to 148 for pravastatin, and from -103 to 69 for simvastatin.

Effect estimates were reported to be dependent on study design.

Authors' conclusions

The evidence suggested that statins did not have short-term effects on the risk of cancer, but the strength of the evidence was mostly weak. The evidence on the potential benefits or harms of statins was inconclusive. Further research is needed.

CRD commentary

The review question was clear and was supported by broad inclusion criteria. The literature search was appropriate and was not restricted by language, minimising the potential for language bias. The review also included a search for 'grey' literature, which reduced the possibility that relevant papers may have been missed. The authors reported the process for study selection, data extraction, and validity assessment, but as only one reviewer was involved, so the potential for reviewer error and bias cannot be ruled out. The authors stated that the quality of the included RCTs was assessed, but only levels of evidence were reported, and it was unclear how quality was assessed for the other study designs.

There were a number of large studies, but details on patient and study characteristics, in particular, details on statin dosage, were lacking. Heterogeneity was reported to have been assessed, but little data were presented. The authors did acknowledge the differences in certain study characteristics (e.g. outcome definition), which suggested that there may have been heterogeneity among studies, so it is unclear whether the pooling of the results was appropriate. Furthermore, the authors did not report the methods used to combine the results, so it was unclear whether the methods used were appropriate. Given the uncertainties surrounding the techniques used to pool data and assess heterogeneity, coupled with several methodological and reporting limitations, the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that high quality cohort studies are needed to assess the long-term effects of different statins on cancer. Further research is also required to evaluate the association between statin use and increased risk of cancer in the elderly, and statin use in patients whose low density lipoprotein cholesterol levels are low.

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