Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients

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CRD summary
This review found no evidence that statins could reduce the risk of colorectal cancer. Restriction of inclusion criteria by study size for randomised trials, possible publication bias and lack of validity assessment were limitations. However, the authors' cautious conclusions appear reliable based on the evidence presented.

Authors' objectives
To evaluate the effect of statins on colorectal cancer risk.

Searching
MEDLINE and Web of Science were searched from inception to December 2006. Search terms were reported. Reference lists and abstracts from related conferences were also scanned.

Study selection
Randomised controlled trials (RCTs) or observational studies (case-control or cohort) evaluating statin exposure and the risk of colorectal cancer were eligible for inclusion in the review. Eligible RCTs were those comparing a statin with placebo or no treatment, studying at least 2,000 participants and with a minimum duration of three years. The primary outcome of interest was the incidence of colorectal cancer.

The majority of included RCTs evaluated simvastatin, pravastatin and lovastatin compared with placebo, although one compared a statin to usual care. The average follow-up ranged from 4.8 to 10.4 years. The observational studies were mostly case-control studies that evaluated statin exposure (actual drug details not reported), apart from one cohort study evaluating all cholesterol-lowering drugs. They adjusted for possible confounding factors, which varied between studies but all adjusted for age and gender.

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

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

Data extraction
Risk ratios and 95% confidence intervals (CI) were calculated for each RCT on an intention-to-treat basis. For observational studies, the risk ratios from the analyses with the most adjustment for confounding factors were extracted. Some studies reported different effect sizes (odds ratios, rate ratios) but these were included in the review as risk ratios as the risk of colorectal cancer was low.

Two reviewers independently extracted the data, with disagreements resolved by consensus and referring to the original paper.

Methods of synthesis
Separate meta-analyses were performed by study design. Both fixed-effect (Mantel-Haenszel) and random-effects (DerSimonian and Laird) models were used. Statistical heterogeneity was assessed using Cochran's Q test (p<0.10 was considered significant) and the I² statistic. Differences in pooled results between the RCTs and observational studies were assessed using a statistical test of interaction. Subgroup analyses were performed for placebo-controlled RCTs and those of lipophilic and lipophobic statins only. Subgroup analyses of the observational studies evaluated studies published in full (not abstracts), cohort studies, and case-control studies. Publication bias was assessed using Egger's test and the Begg and Mazumdar test.
Results of the review

RCTs: Six RCTs (n=55,113 patients providing a total of 325,000 person-years of follow-up) were included. The overall colorectal cancer incidence was 1.08% in the statin group and 1.14% in the control group. There was no evidence of an association between statin use and colorectal cancer (risk ratio 0.95, 95% Confidence Interval (CI): 0.81 to 1.11). Results from the random-effects model were similar. There was little evidence of heterogeneity ($I^2=9\%$). There was also no evidence of publication bias. Subgroup analyses found similar results for placebo-controlled trials, lipophilic statins and lipophobic statins.

Observational studies: Nine case-control studies (n=approximately 979,681 patients) and three cohort studies (n=498,613 patients) were included. The overall colorectal cancer incidence was approximately 0.03%. Statin use was associated with a modest but statistically significant reduction in colorectal cancer risk (risk ratio 0.92, 95% CI: 0.90 to 0.95). Results from the random-effects model were similar and there was little evidence of heterogeneity ($I^2=16\%$) or publication bias. A similar significant reduction was seen for the subgroup of case-control studies only and studies published in full-text only (eight studies), but not for the cohort studies.

All studies combined: Tests of interaction showed no evidence of a difference between the results of the RCTs and observational studies ($p=0.69$ for fixed-effect models and $p=0.72$ for random-effects models). The pooled analysis of all studies showed a statistically significant reduction in colorectal cancer risk (risk ratio 0.92, 95% CI: 0.89 to 0.96) with little heterogeneity ($I^2=7\%$) and no evidence of publication bias.

Authors’ conclusions
These results did not support the theory that statins strongly reduce colorectal cancer risk when taken at low doses for managing high cholesterol. However, a modest risk reduction associated with higher doses of statins cannot be ruled out.

CRD commentary
This review specified inclusion criteria for study design, interventions and outcomes, but only including RCTs with at least 2,000 participants seemed restrictive. The search covered only two databases, so publication bias might be a problem, which the authors themselves acknowledged. However, no evidence of publication bias was found from statistical tests. There were no restrictions on language. Data were extracted by two reviewers independently but it was not reported if studies were selected in the same way. The authors stated that they did not assess study validity because quality scoring is thought to be controversial, but they did perform subgroup analyses by study design. However, some assessment of study validity would have been beneficial, as studies using the same design can vary considerably in quality. Statistical heterogeneity was assessed. Meta-analyses used both fixed-effect and random-effects models. The authors’ cautious conclusion that there was no evidence relating statin use to colorectal cancer risk seems appropriate.

Implications of the review for practice and research
Practice: The authors stated that until additional evidence is established relating to statin use and the risk of colorectal cancer, physicians need to ensure that statin use is restricted to the approved indications.

Research: The authors did not state any implications for research.

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