

Do statins decrease the risk of colorectal cancer?

Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennett HS, et al. Statins and the risk of colorectal cancer. *N Engl J Med* 2005;352:2184-92.

Background: Colorectal cancer is the second leading cause of death from malignant disease in Canada. Laboratory research suggests that statins may prevent the growth of colorectal cancer cell lines.¹

Design: This population-based case-control study was conducted in northern Israel between 1998 and 2004. Researchers interviewed 1953 patients with colorectal cancer and 2015 control patients matched for age, sex, clinic location and ethnic group to ascertain use of statins for at least 5 years, along with potential confounders such as family history of colorectal cancer, use of aspirin or other NSAIDs, hypercholesterolemia, and levels of physical activity and vegetable consumption. Self-reported statin use was validated using prescription records for 96.5% of participants.

Results: Fewer patients with colorectal cancer had used statins for at least 5 years before the diagnosis of cancer compared with control patients (6.1% v. 11.6% respectively). After adjustment for potential confounding factors, use of statins was associated with a significantly lower risk of colorectal cancer (odds ratio 0.57, 95% confidence interval 0.44-0.73). Consistent findings were observed in secondary analyses according to cancer location (colon v. rectum) and use of aspirin or other NSAIDs, and among subgroups of patients with hypercholesterolemia, ischemic heart disease and inflammatory bowel disease. On the basis of the incidence of colorectal cancer in the Israeli population, the authors estimated that 4814 people would need to

be treated with statins for 5 years to prevent 1 case of colorectal cancer.

Commentary: Emerging evidence suggests that statins favourably influence a diverse range of physiologic processes independent of their effects on cholesterol levels, such as endothelial function, bone density and oxidant stress. These are sometimes termed *pleiotropic effects*. The authors of this study used an observational approach to examine whether statin therapy might reduce the risk of colorectal cancer.

Although it is tempting to infer from the study results that statins significantly reduce the risk of colorectal cancer, such a conclusion is premature. Indeed, previous studies of this same question have produced different results.^{2,3} Observational studies are excellent tools for exploring potential associations, but they rarely prove causality because of their susceptibility to hidden bias and confounding.

In the context of this study, consider first the exposure of interest: 5 or more years of statin therapy. Patients who take statins differ in many ways from those who do not: they visit their physicians more often and may display other, more health-conscious behaviours. This is especially true of those exceptional patients who persist with statin therapy for 5 or more years. Despite a commendable effort, the investigators were able to adjust for only some of these important differences.

Consider also the study's outcome: colorectal cancer. This disease often has a long latency period, and a compelling argument can be made that 5 years of drug exposure is insufficient. An even more important limitation of this

study relates to the selection of the control patients. Not only are they systematically different from cases (again in both measurable and unmeasurable ways), but whether they were truly free of colorectal cancer is not known, since information about previous screening is not provided.

Practice implications: Although the findings of this study are intriguing, whether or not statins actually decrease the risk of colorectal cancer can only be determined by a randomized, controlled clinical trial. However, some patients (particularly those at increased risk of colorectal cancer) may wish to take statins on the basis of these results. The wisdom of this strategy remains unproven, and without another indication for statin use, a case-by-case assessment of the potential risks of therapy is warranted. Under no circumstances should statin use undermine the importance of regular screening and healthy lifestyle habits, the merits of which are established.

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