Trial Watch

STATINS LOSE PREVENTION GROUND

Epidemiological and clinical trial data have indicated that the cholesterol-lowering agents statins might protect against the development of several different types of cancer, including colorectal cancer. However, results from a planned secondary analysis of the Adenoma Prevention with Celecoxib (APC) trial have not upheld these findings. Moreover, a different study indicates that genetic variation affects the efficacy of statins in the prevention of cancer.

The APC trial, which investigated the efficacy of the cyclooxygenase 2 inhibitor celecoxib in reducing the incidence of new adenomas analysed 2,035 patients with adenoma who were at a high risk of developing colorectal cancer. The previously published primary end point analyses indicated that over a 3-year surveillance period the incidence of new adenomas was reduced by 33% in patients taking 200 mg of celecoxib, and by 45% in those taking 400 mg, twice daily. In the secondary analysis, data collected to 5 years after enrolment in the study (including, a full medical history, medication use and colonoscopy data) were used to examine the effect of any statins taken by the study patients on the incidence of newly detected adenomas. Of the patients enrolled in the study, 36% used statins and adenoma detection rates were no different between users of statins and non-users in the placebo arm of the trial. Patients receiving a placebo who took a statin for >3 years had a significantly increased risk of adenoma development. At this year's annual American Association of Cancer Research meeting, the lead author, Monica Bertagnolli, concluded "given our results, we do not think that it is reasonable to further study statins for chemoprevention of colorectal cancer, as the chance that they have this activity is very small".

Statins inhibit 3-hydroxy-3-methylglutyral CoA reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis, and genetic variations in *HMGCR* are known to affect the efficacy of statins. Steven Lipkin and colleagues assessed the genotype of 40 genes known to regulate cholesterol synthesis and metabolism in a population-based case–control study of 2,138 patients with colorectal cancer who were taking statins and 2,049 population-based controls. They identified a single nucleotide polymorphism (SNP) in *HMGCR* (rs12654264), and the A/A phenotype was associated with a greater reduction of risk of developing colorectal cancer with statin use, compared with statin users who had the T/T genotype. In colorectal cancer cell lines with the A/A genotype treated with a statin, the reduction in cholesterol levels was greater than in cells of the T/T genotype. Further analyses indicate that the rs12654264 SNP affects the splicing of *HMGCR*. Cells with the A allele express a full-length mRNA and not a splice variant in which exon 13 (which encodes part of the statin-binding domain) is spliced out. The authors argue that these data indicate that the use of statins to reduce the incidence of cancer might be of a greater benefit to patients with a responsive genotype.

ORIGINAL RESEARCH PAPER Bertagnolli, M. M. *et al.* Statin use and colorectal adenoma risk: results from the adenoma prevention with celecoxib trial. *Cancer Prev. Res.* **3**, 588–596 (2010) | Lipkin, S. M. *et al.* Genetic variation in 3-hydroxy-3-methylglutaryl CoA reductase modifies the chemopreventive activity of statins for colorectal cancer. *Cancer Prev. Res.* **3**, 597–603 (2010)