

## Perspective

## Statins and the Colorectum: Hope for Chemoprevention?

Perspective on Bertagnolli et al., p. 588 and Lipkin et al., p. 597

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## Abstract

This perspective on Bertagnolli et al. (beginning on p. 588 in this issue of the journal) and Lipkin et al. (beginning on p. 597) considers the likelihood that statins have chemopreventive efficacy in the large bowel. An observational analysis within a clinical trial of celecoxib found no benefit of statin use on the risk of colorectal adenomas (and some suggestions of an adverse effect). On the other hand, variation in the 3-hydroxy-3-methylglutaryl coenzyme A reductase gene modified the association of statins with risk of colorectal cancer. The perspective discusses the implications of these data and how they fit into the context of previous investigations. *Cancer Prev Res*; 3(5); 573–5. ©2010 AACR.

Samuel Johnson reportedly quipped that an acquaintance's second marriage was "the triumph of hope over experience." Similarly, hopes for a drug that can prevent cancer as well as cardiovascular disease survive despite repeated negative experiences with  $\beta$ -carotene,  $\alpha$ -tocopherol, ascorbic acid, and folic acid. To date, only aspirin has shown preventive efficacy for both cardiovascular disease and neoplasia. Is there hope that statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, a class of drugs used to treat hypercholesterolemia] might provide similar preventive benefits?

Statins are a significant advance in cardiovascular prevention, providing a marked decrease in risk of cardiovascular events as well as in all-cause mortality (1). This risk-benefit profile contrasts with previous lipid-lowering interventions, which seemed to increase noncardiovascular mortality (2). In fact, low cholesterol levels are associated with an increased risk of colorectal cancer, particularly in males (3). This association has generally been thought to be the consequence of the cancer itself prior to its clinical manifestation, because omitting cancers diagnosed within a few years of baseline has often (although not always) resulted in a substantial attenuation of the association in cohort studies (3, 4). Cholesterol levels seem to be a sort of acute-phase reactant, decreasing with acute and chronic illnesses (5). The early thinking about the effects of statins on cancer occurred in the context of these findings, and there were lingering worries that cholesterol reduction by these drugs might increase the risk of

cancer, as was seen in some early cholesterol-lowering trials (2). Indeed, a 1996 review and interpretation of preclinical data suggesting the carcinogenicity of statins (6) seems to have motivated the first investigation of the association of these drugs with cancer risk.

An accompanying editorial questioned the interpretation of the worrisome preclinical data (7), but later that year, a randomized trial of pravastatin for the prevention of cardiovascular disease found an increased risk of breast cancer in subjects randomized to the statin (12 cases versus 1; ref. 8). An early observational study (9) provided some support for this adverse effect, but subsequent trials (10) and observational studies (11) did not confirm the findings. Interest turned to possible antineoplastic effects, motivated by preclinical antineoplastic evidence (12) and an early epidemiological study (13). As this history shows, statins have never been unambiguously promising for cancer chemoprevention.

In aggregate, the cardiovascular clinical trials do not suggest a protective effect of statins on risk of colorectal cancer (11, 14). However, in relatively recent (2007, 2008) meta-analyses of observational studies, there have been suggestions of a modestly decreased risk, largely limited to case-control studies (14, 15). The first fully powered study to assess an association of statins with colorectal cancer was a report by Poynter et al. (16) of data from the parent study for the analysis by Lipkin et al. The Poynter article shows the strongest inverse association of statins with risk of colorectal cancer reported to date. As it turns out, there is some evidence of heterogeneity between its results and those of other observational studies (14), providing soft suggestions that its findings could be an outlier.

Colorectal cancers probably take a decade to evolve from early colorectal adenomas and several decades to evolve from normal mucosa. Unless statins have a late effect on the carcinogenesis cascade, they cannot be expected to alter colorectal cancer risk in only a few years. Effects within a few years are certainly possible in

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chemoprevention: the selective estrogen receptor modulators tamoxifen and raloxifene fairly rapidly reduce the risk of breast cancer (17). Whether such rapid hormone-like effects are possible for colorectal cancer is an open question, but there is no evidence of it so far. Even aspirin, more or less proven to have a cancer-preventive effect in the colorectum, takes 10 or more years before a protective effect against colorectal cancer emerges (18). Because statins were only introduced in 1987, studies of their association with colorectal cancer could not be convincingly negative until the early 2000s at the earliest, and indeed, there are only scant data available thus far regarding statin use of 10 years or more.

Studies of statins in the setting of colorectal adenomas may be particularly valuable because it is plausible that these early neoplastic lesions might be modulated by a few years of treatment. In this issue of the journal, Bertagnolli and colleagues report data from the Adenoma Prevention with Celecoxib trial, whose main aim was to evaluate the chemopreventive effects of celecoxib on adenoma risk (19). They report no evidence of decreased risks from statins, agreeing with a previous negative analysis (20), but conflicting with another observational study that did show decreased risks (21). In analyses that are borderline statistically significant, they report increased risks.

Although embedded in a clinical trial, the statin analysis by Bertagnolli et al. is observational, not randomized. Of course, patients take statins for a reason: hyperlipidemia (typically hypercholesterolemia). So the appropriate controls for a statin-treated population would be hypercholesterolemic subjects that are untreated or treated with something else. These controls will be difficult to find, however, because statins have largely taken over as the treatment of choice for hypercholesterolemia. Careful control for indications for statin use should, in theory, allow for a non-statin control group, but this may be difficult if almost all hypercholesterolemic subjects take statins. Statin users seem to be more health conscious than are nonusers: they have higher rates of use of nonsteroidal anti-inflammatory drugs and of screening colonoscopy, complicating observational analyses (22). Careful atten-

tion to these factors will be necessary if future research attempts to assess the possible chemopreventive effects of long-term treatment.

One possible explanation for the somewhat inconsistent association of statins with risk of colorectal cancer could be genetic variation. Also reporting in this issue of the journal, Lipkin and colleagues found that the colorectal cancer-statin association varied according to genotype of the HMG-CoA reductase (*HMGR*) gene, with relative risks varying from 0.30 to 0.60 (23). It is theoretically possible that the variants might differ from population to population and so explain the varying observational findings. However, the prevalence of relevant genetic variant was similar in Israel and in a Northern European population (24), and even the highest relative risk in this study is substantially lower than what would be expected from other observational studies. It seems unlikely that variation in *HMGR* explains variation in the reported findings on statins and colorectal cancer, but it is intriguing that this pharmacogenomics study could lead to the identification of individuals among whom statins decrease risk. Of course, if the overall effect of statins is null, then there also would be a group with increased risk.

So where does that leave us with regard to statins and colorectal cancer? Is it "the end of the road," as proposed in one recent commentary (25)? The negative data that Bertagnolli et al. provide add to the accumulating evidence that, at least overall, statins probably do not prevent colorectal neoplasia, although it is conceivable that there are benefits with high cumulative doses (22, 26, 27) or in genetically defined subgroups. It may not be the end of the road for statins and the colorectum, but certainly, the route to the hoped-for destination is getting more difficult.

## Disclosure of Potential Conflicts of Interest

J.A. Baron: consultant/advisory board, Merck and Bayer.

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