Hints That Statins Reduce Colon Cancer Risk Finally Being Put to the Test

By Karyn Hede

A new clinical trial may help settle the debate over whether statins, the most widely prescribed drugs for lowering cholesterol, also help reduce colon cancer risk.

The National Cancer Institute–sponsored prospective trial is evaluating the statin rosuvastatin in patients who have had surgery for stage I and II colon cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) designed the nationwide randomized, double-blind trial, called P-5, which the U.S. Food and Drug Administration approved last March. According to principal investigator Bruce Boman, M.D., Ph.D., who is also director of cancer genetics and stem cell biology at the Helen F. Graham Cancer Center in Newark, Del., about 50 patients have already enrolled in the study, and the NSABP is registering 400 patient-accrual sites throughout the U.S.

The patients being studied have a 50% risk of colon cancer relapse. As Boman explained, “We felt that in a chemopreventive study we needed to look at a high-risk population where the benefit–risk ratio for
The trial could have substantial influence, since colorectal cancer is the thirdmost-commonly-diagnosed cancer in the U.S. as well as the third-leading cause of cancer death in both men and women. The number of individuals taking a statin to treat high cholesterol climbed from 15.8 million people in 2000 to 29.7 million people in 2005, according to the Agency for Healthcare Research and Quality.

**Previous Studies Give Mixed Results**

The debate over statins’ effect on colon cancer risk has been fueled by widely divergent conclusions drawn from several epidemiological datasets published in the mid-2000s. The strongest association was in a 2005 *New England Journal of Medicine* study that examined the medical records of 1,953 colorectal cancer patients and 2,015 matched control subjects accrued as part of the Molecular Epidemiology of Colorectal Cancer study, a population-based case-control study in northern Israel. Among the 286 long-term statin users—those taking statins for 5 or more years—the risk of developing colorectal cancer was 47% lower than in those not taking statins.

But other studies contradict the claim that statins help reduce colorectal cancer risk. A recent retrospective analysis of Women’s Health Initiative data presented at a meeting of the American Association for Cancer Research in November 2010 found no decrease in colon cancer risk in postmenopausal statin users. Among the 159,219 women, 2,000 cases of colorectal cancer emerged during the 10-year follow-up period. The contradictory results illustrate the central problem in evaluating claims of and against statins’ potential as chemopreventive therapy: Most studies use data that are not specific for evaluating statins but rather are part of large epidemiological datasets. Other studies that found no association between statin usage and colorectal cancer typically enrolled younger patients who had used statins for less time.

**Promise for Reducing Polyps**

To follow up on the *NEJM* study, Ali Siddiqui, M.D., and colleagues at Dallas Veterans Affairs Medical Center looked at the outcomes of colon cancer patients who were long-term statin users.

“We were trying to elicit whether the statins were actually working at the stage of reducing the progression of polyps to advanced polyps,” said Siddiqui, now a gastroenterologist at the Thomas Jefferson Medical School in Philadelphia.

Among the 2,626 patients who had polyps removed at colonoscopy, 35% of those who reported ongoing statin usage developed new polyps, compared to 51% of nonusers. Furthermore, patients on statins developed smaller and less advanced polyps than nonusers. Despite these encouraging results, which the journal *Gastroenterology* published in 2009, Siddiqui says not enough clinical evidence exists to consider statins a chemopreventive therapy for colorectal cancer.

“Right now, it’s difficult for me to tell patients to go on statins [for this indication],” said Siddiqui. “Our data support it, but there are studies that do not support the use of statins.”

**Molecular Biology of Statins**

Other studies are exploring the molecular biology regarding how statins may reduce colorectal cancer risk. The class of drugs that includes statins are 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMGCR) inhibitors. These compounds inhibit a key enzyme in the cholesterol-synthesis pathway, thereby reducing serum cholesterol levels. This same pathway also participates in the synthesis of molecules that act as growth factors and are involved in cell survival pathways. Those dual—and conflicting—roles may help explain the mixed results of epidemiological studies on statins’ effect on cancer cells.

A recent study on statins’ effect on colon cancer cell lines looked at whether statins boost levels of bone morphogenetic protein, which inhibits colon cancer growth. The researchers at the Academic Medical Center in Amsterdam used mouse xenograft models of several well-characterized colon cancer cell lines. Their findings, published in the journal *Gastroenterology* in 2007, suggest that some cancer cells are sensitive to statins, whereas other cancer cell types resist statins’ effects. Furthermore, although statins boosted levels of bone morphogenetic protein and inhibited growth of statin-sensitive colon cancer cells, statins actually increased cell growth in statin-resistant cell lines.

Another recent study uncovered a genetic variation in the HMGCR gene that may partially explain lack of benefit from statin use, at least in some individuals, either as a lipid-lowering agent or as chemopreventive therapy for colon cancer. Using data and blood samples from the same database reported in the 2005 *NEJM* study, a multi-institutional team of scientists studied genetic variation in 40 genes involved in cholesterol synthesis in 2,138 colon cancer case patients and 2,049 matched control subjects. Using statistical methods, the research team analyzed whether any genetic variants were associated with long-term statin use and later development of colon cancer.

The scientists found that a single genetic variant, called A/A, was associated with a lower risk of colon cancer, as well as lower low-density lipoprotein levels among all case patients and control subjects. Individuals with the alternate T/T genotype who took statins had higher low-density lipoprotein levels than those with the A/A variant and had
little of the A/A group’s reduced colon cancer risk. Further study demonstrated that the T/T genetic variant decreased the ratio of the full-length HMGCR, which binds statins, to a truncated version, which does not bind statins.

The authors of the study published in Cancer Prevention and Research in May 2010, suggest that the data may assist personalized medicine by identifying people who will benefit from statin use—if the associations are correct and prove to be causal.

“We do think this is part of the basis for understanding why there has been this tremendous variability among the different [statin and colorectal cancer risk] studies,” said Steven Lipkin, M.D., Ph.D., corresponding author of the study and an internist at Weill Cornell School of Medicine in New York.

To verify their data and to extend the reach of their work, the group is planning to collaborate with investigators coordinating the P-5 trial to conduct a correlative trial assessing HMGCR genetic variation and colon cancer risk in a blinded prospective study.

Lipkin says stratifying patients may increase the chances of finding a meaningful association in the P5 trial.

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