Study shows why statins protect some against cancer

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(PhysOrg.com) -- Weill Cornell researchers report almost half of Caucasians taking statins are probably not protected against cancer as well as other people because of a particular inherited gene variant.

Statins -- popular drugs that lower cholesterol -- help protect some people against colorectal cancer, but not other people. Now researchers at NewYork-Presbyterian Hospital/Weill Cornell Medical Center report why.

Almost half -- 44 percent -- of Caucasians taking statins are probably not protected against cancer as well as other people because of a particular inherited gene variant, the researchers report in the May issue of *Cancer Prevention Research*.

The finding might help personalize the use of statins by using a test to determine if patients have the "right" gene to benefit from current statin drugs and by providing insight into how to create a new class of statins for those who have the "wrong" gene profile.

"Given that approximately 25 million individuals worldwide currently use statins, we anticipate this discovery may prompt development of more precise, personalized and cost-effective cancer risk reduction strategies," says the study's co-lead author, Dr. Steven M. Lipkin, associate professor of medicine and of genetic medicine at Weill Cornell Medical College and a geneticist and internist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

The research team genotyped 40 genes known to be important for synthesis and metabolism of cholesterol in people who participated in a population case-control study of colorectal cancer in northern Israel. Included were 1,780 people with colon cancer and 1,863 without colon cancer; many of the participants, who were predominantly Caucasian, had used statins for a long time. In the initial study, statin use was associated with a 50 percent relative risk of developing colorectal cancer in this population.

The researchers identified one gene (within the so-called HMGCR gene, which produces a critical enzyme involved in formation of cholesterol) that was associated with statin protection against colorectal cancer. A follow-up pharmacogenetic analysis showed that people with a particular variant the researchers dubbed "A," compared with those who had a "T" variant, had much stronger protection. Because a person gets a variant from each parent, the stronger colorectal cancer protection came from individuals with the A/A genotype, compared with the T/T genotype. Those with an A/T genotype had intermediate protection.

Lipkin estimates that in this Caucasian population, 56 percent had at least one A variant in that genomic position.

Using laboratory colorectal cancer cells, the researchers then discovered that the protein produced by the T gene variant does not bind to the statin like the A variant does, because of the production of a protein that is slightly altered.

"Carriers of the A allele express more of the full-length protein that binds statins, and are therefore more sensitive to statins and are more likely to experience the colorectal cancer risk reduction associated with long-term use. That is especially true if a person has two A alleles," says Lipkin. "Carriers of the T allele are less sensitive to statins because they are missing part of the protein that binds to statins. A protective effect

against colorectal cancer development is largely absent from people who have two T alleles."

"We anticipate that genotyping for these alleles in patients may help identify those who are most likely to benefit from statins, and spare others who will not respond from any side effects of the drugs," Lipkin says.

He said that most of the many statin drugs on the market work by binding on to the HMGCR protein. Most of the participants in this study used simvastatin (trade names Zocor, Simlup, Simcard, Simvacor and others) and pravastatin (marketed as Pravachol or Selektine).

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