Statins may reduce cancer risk through mechanisms separate to cholesterol

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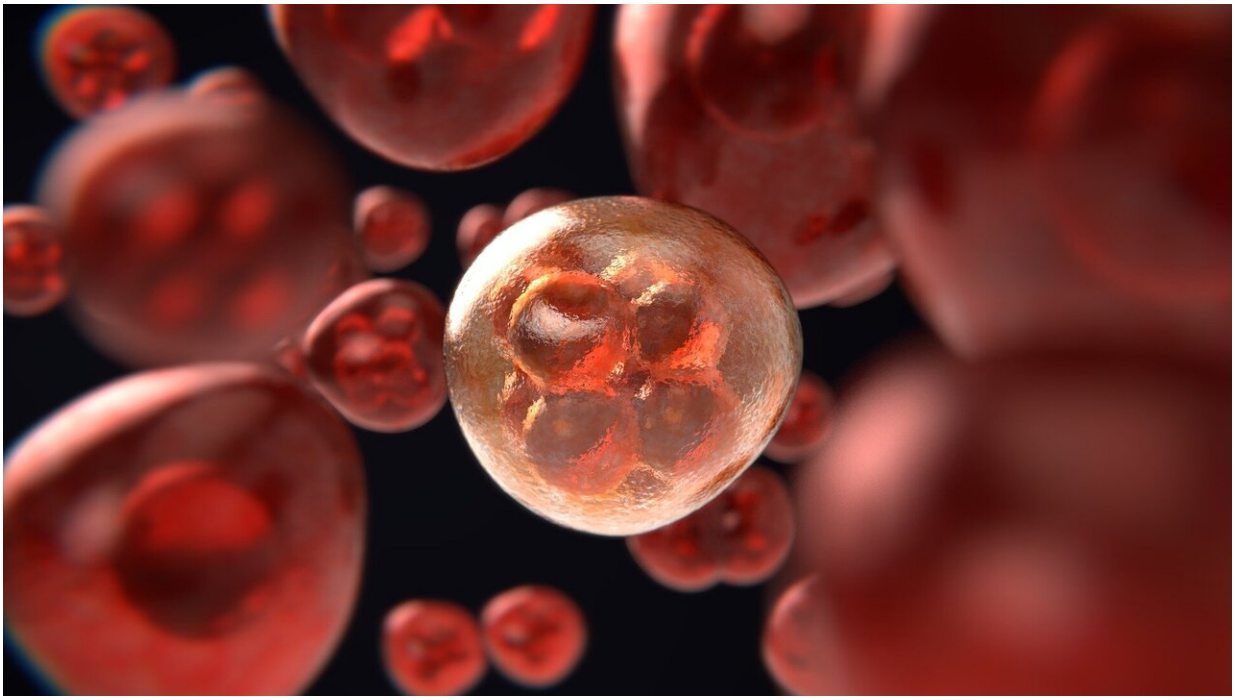

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Cholesterol-lowering drugs called statins may reduce cancer risk in humans through a pathway unrelated to cholesterol, says a study published today in *eLife*.

Statins reduce levels of LDL-cholesterol, the so-called 'bad' cholesterol, by inhibiting an enzyme called HMG-CoA-reductase (HMGCR).

Clinical trials have previously demonstrated convincing evidence that statins reduce the risk of heart attacks and other cardiovascular diseases. But evidence for the potential effect of statins to reduce the risk of cancer is less clear.

"Previous laboratory studies have suggested that lipids including cholesterol play a role in the development of cancer, and that statins inhibit cancer development," explains lead author Paul Carter, Cardiology Academic Clinical Fellow at the Department of Health and Primary Care, University of Cambridge, UK. "However, no trials have been designed to assess the role of statins for cancer prevention in clinical practice. We decided to assess the potential effect of statin therapy on cancer risk using evidence from human genetics."

To do this, Carter and the team studied genetic variants that mimic the effect of statins using a technique known as Mendelian randomization in UK Biobank, a large study of UK residents that tracks the diagnosis and treatment of many serious illnesses. Mendelian randomization assesses associations between genetically predicted levels of a risk factor and a disease outcome, in order to predict the extent to which that risk factor causes the outcome. For example, it can compare the risk of cancer in patients who inherit a genetic predisposition to high or low levels of cholesterol, in order to predict whether lowering cholesterol levels will reduce the risk of cancer. This study is the first Mendelian randomization analysis of lipid subtypes for a range of cancers across the human body.

The team obtained associations of lipid-related genetic variants with the risk of overall cancer and 22 cancer types for 367,703 individuals in UK Biobank. In total, 75,037 of these individuals had a cancer event.

Their analysis revealed that variants in the HMGCR gene region, which represent proxies for statin treatment, were associated with overall

cancer risk, suggesting that statins could lower overall cancer risk. Interestingly, variants in gene regions that represent other cholesterol-lowering treatments that work differently to statins were not associated with cancer risk, and genetically predicted LDL-cholesterol was not associated with overall cancer risk.

"Taken together, these results suggest that inhibiting HMGCR with statins may help reduce cancer risk though non-lipid lowering mechanisms, and that this role may apply across cancer sites," Carter says. "This effect may operate through other properties of statins, including dampening down inflammation or reducing other chemicals produced by the same cellular machinery which synthesizes cholesterol."

Despite the large sample size of more than 360,000 participants and the broad set of outcomes analyzed in this study, the team adds that there are a number of limitations to this work. For example, for many cancer types, there were not enough outcome events needed in the analysis to rule out the possibility of moderate causal effects.

"While there is evidence to support our assumption that genetic variants in relevant gene regions can be used as proxies for pharmacological interventions, our findings should be considered with caution until they are confirmed in clinical trials. However, our work highlights that the effectiveness of statins must be urgently evaluated by large clinical trials for potential use in cancer prevention," says senior author Stephen Burgess, Group Leader at the Medical Research Council Biostatistics Unit, part of the University of Cambridge. "While statins do have some adverse effects, our findings further weight the balance in favour of these drugs reducing the risk of major disease."

More information: Paul Carter et al, Predicting the effect of statins on cancer risk using genetic variants from a Mendelian randomization study in the UK Biobank, *eLife* (2020). DOI: 10.7554/eLife.57191

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