THE CONVERSATION

# Could aspirin reverse increased cancer risk in overweight people?

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Aspirin dissolves extra cancer risk in inherited condition and could have same effect for others. Soluble by Shutterstock

The health benefits of aspirin have been appearing in scientific literature for several decades, including a protective effect in those at increased risk of cancer. In a new finding published in the Journal of Clinical Oncology, we found that a regular dose of aspirin significantly reduced the long-term risk of cancer in overweight people with Lynch syndrome, a relatively common inherited condition that results in about half of gene carriers developing cancer at a young age.

Lynch syndrome is a condition that affects a set of genes responsible for detecting and repairing errors in the DNA copying process, much like a faulty spellchecker in a computer. This increases the risk of developing a range of cancers but especially in the colon and the womb, often beginning when people are in their 40s or sooner.

Being overweight increases the risk of breast, colon and prostate cancer; the American Society of Clinical Oncology has recently said that obesity is becoming a leading preventable cause of cancer. Our study reveals that being overweight is an even more serious problem in Lynch syndrome than in the general population, but that overweight

people with Lynch syndrome who had been treated with aspirin for an average of two years were no more likely to get cancer in the next five years than those who were of normal weight. In other words, whatever obesity is doing to increase cancer risk, aspirin reverses that effect in Lynch syndrome.

In public health terms, it is tempting to extrapolate into the general population. However, there has been criticism of the media response questioning whether findings from a specific group prone to cancer are relevant to the general population. To address this, its necessary to consider the primary design of the CAPP studies.

## The long game

Twenty-five years ago we had the idea to explore prevention strategies in people with an inherited predisposition to bowel cancer. These rare individuals have inherited one faulty copy of a tumour suppressor gene which means all their cells must rely on the remaining copy. If that is lost or copied incorrectly, the cell immediately loses the ability to prevent a tumour developing. Crucially, this mechanism is comparable to how “common” cancers develop, the only difference being that most of us need to lose both copies of a tumour suppressor gene inside a single cell to initiate cancer progression, whereas people with these syndromes start with a faulty copy of a gene in each cell. One copying error in any one of many millions of rapidly dividing stem cells could trigger a malignant transformation.

About 16% of all bowel cancers have a breakdown in the same mismatch repair system so risk factors and prevention strategies that work on Lynch syndrome are probably relevant to at least this segment of sporadic cancers.

Our first study, CAPP1, focused on young people with Familial Adenomatous Polyposis (FAP) who have a faulty copy of a gene that leads them to develop thousands of polyps in their colon in their teens. Our second much larger study, CAPP2, recruited 1,009 people with Lynch syndrome in 16 countries.

Lynch syndrome has no symptoms but significantly increases cancer risk. Wince by Shutterstock

In both our first and second studies we simultaneously examined the preventive effects of aspirin and resistant starch. The latter, sometimes called fermentable fibre, is fermented by gut bacteria to form fatty acids which are anti-cancer. Despite the promise, a daily supplement for up to four years was not effective. In parallel, in both CAPP1 and CAPP2 we also tested a relatively large dose of aspirin, 600mg, compared to an identical looking dose of placebos. There have now been more than 100 papers which show that aspirin diminishes all solid tumours.

In both our studies there was a marginal short-term effect. However, in the Lynch syndrome trial design we planned a longer-term follow up. When the first recruits reached their ten-

year anniversary we broke code to look at the whole group, giving a mean follow up of five years. We found that those who had received the aspirin had a major reduction in bowel and other cancers of around 50%.

This was the first time under formal randomised controlled conditions with cancer as the primary endpoint that it had been shown that aspirin could significantly reduce cancer burden. In most cases, the participants had discontinued their aspirin before the cancer emerged, suggesting an effect on precancerous cells.

## The weight issue

Our new study involved a review of the other key variables collected at the original recruitment to see if we could identify relevant sub-groups. Having collected the height and weight of participants at the start of the study, we analysed body mass index and found it was very important to cancer risk.

In the Lynch syndrome study group the overall risk of cancer was more than double in those who were overweight or obese compared to those of normal weight. On reflection, this is perhaps understandable in that the genetic risk factor is having a multiplicative effect with the environmental risk factor. But what did surprise us was the finding that the aspirin cancelled out the extra risk and put those with Lynch syndrome on a similar risk footing as those who were of normal weight.

It provides a further insight into the mechanism behind aspirin's action as others have argued that the pro-inflammatory effects of obesity are important in the increased cancer risk. This ongoing argument will be addressed by our new study, CaPP3, which will compare the effects of different aspirin doses.

The argument that people with hereditary bowel cancer should be advised to take aspirin is slowly gaining ground. The somewhat exaggerated anxiety about side effects has slowed the adoption. This reinforces the argument for all people with Lynch syndrome to join us in finding the optimal dose to minimise side effects and maximise benefits. We are now a year into CaPP3 in the UK and people with Lynch syndrome on the study will receive a blind dose over two years and then we will see over the next five years if a dose of 100mg is as good as 300mg or 600mg in preventing cancer.

## The general population

Earlier this year, Jack Cuzick and colleagues showed in study that there was a net benefit of aspirin for everyone aged over 50 when you balanced protection against cancer, heart disease and strokes against the extra risks of bleeding and ulcers in some people on aspirin. We have shown that people with extra cancer risk due to genetic predisposition also have a stronger case for taking aspirin. This latest information, taken with the rest of the evidence available, suggests that people over 50 who are overweight and have a family history of bowel cancer should give careful consideration to having a low dose aspirin as part of their routine.

Undue weight has often been given to the adverse effects of aspirin while ignoring the greater risks associated with, for example, routine colonoscopy.

However, whether aspirin should be used must be a personal choice because its impossible to avoid a small risk. Checking for stomach infection with *Helicobacter pylori*, which significantly increases ulcer risks in those taking aspirin, and treating raised blood pressure, which probably increases the risk of haemorrhagic stroke in aspirin users, are two sensible

precautions that doctors can do to reduce aspirin risks. In a non-frail population with controlled blood pressure and cleared of stomach infection, the chance of a major side effect is around one in 10,000. This is a small risk compared to the cumulative evidence of protection against cancer, heart disease and stroke.

Cancer
Obesity
Aspirin