Aspirin to prevent and treat cancer: The evidence continues to build

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A collection of three papers (two published in *The Lancet* and one in *The Lancet Oncology*) add to the growing evidence base suggesting that daily aspirin can be used to help prevent and possibly treat cancer. All three papers are by Professor Peter M Rothwell, University of Oxford and John Radcliffe Hospital, Oxford, and colleagues.

Previous studies by Rothwell and colleagues have established that daily aspirin reduces the long-term risk of death due to cancer (Lancet 2007, 2010, 2011). However the short-term effects are less certain, especially in women, as is how the risk/benefit of aspirin changes over time. In the first paper (*The Lancet*), the authors studied individual patient data from 51 randomised trials of daily aspirin versus no aspirin to prevent vascular events such as heart attacks.

They found that aspirin reduced the risk of a cancer death by 15% compared with controls. This improved to a 37% reduced risk of a cancer death for those on aspirin from 5 years and onwards. The reduction in cancer deaths on aspirin resulted in a 12% reduction in non-vascular deaths overall during the trials. In these trials of primary prevention, the reduction in non-vascular deaths accounted for almost all (91%) of the deaths prevented. Daily low-dose aspirin reduced cancer incidence by around a quarter from 3 years and onwards, with similar reductions in men (23%) and women (25%).

Although the reduced risk of major vascular events in these trials was initially offset by an increased risk of major bleeding, both these effects

diminished over time, leaving only the reduced risk of cancer from 3 years and onwards (an absolute reduction of 3 cases per 1000 patients per year, 12 per 1000 control versus 9 per 1000 in aspirin groups). The authors also found that case-fatality from major extracranial bleeds was also two thirds lower on aspirin than on control.

The authors say: "Alongside the previously reported reduction by aspirin of the long-term risk of cancer death, the short-term reductions in cancer incidence and mortality and the decrease in risk of major extracranial bleeds with extended use, and their low case-fatality, add to the case for daily aspirin in prevention of cancer."

They add: "In view of the very low rates of vascular events in recent and ongoing trials of aspirin in primary prevention, prevention of cancer could become the main justification for aspirin use in this setting."

A second Article in *The Lancet* reports the effect of aspirin on cancer metastasis (or how cancer grows/spreads). In this study, the authors collected new data on metastases of cancers that were diagnosed during all five large randomised trials of daily aspirin (75mg or more daily) versus control for the prevention of vascular events in the UK.

They found that, with a mean follow-up of 6.5 years, allocation to aspirin reduced risk of cancer with distant metastasis by 36%, risk of adencarcioma (common solid cancers including colon, lung, and prostate cancers) by 46%, and of other solid cancers (eg bladder, kidney) by 18%. These reductions were due mainly to a reduction by almost half in the proportion of adenocarcinomas that had metastatic disease.

The researchers also found that aspirin reduced the risk of adenocarcinoma with metastasis at initial diagnosis by almost a third (31%), and risk of metastasis on subsequent follow-up in patients without metastasis initially (by 55%), particularly in patients with

colorectal cancer(by 74%), and in patients who remained on trial treatment up to or after diagnosis (by 69%).

Aspirin reduced death due to cancer in patients who developed adenocarcinoma (especially those without metastasis at diagnosis, by around half). Aspirin reduced the overall risk of fatal adenocarcinoma in the trial populations (by 35%) but not the risk of other fatal cancers (eg blood cancers). The effects of aspirin were independent of age, and sex, and were also seen with a low-dose, slow-release formulation of aspirin designed to inhibit platelets but to have little systemic bioavailability.

"These findings provide the first proof in man that aspirin prevents distant cancer metastasis. Previous animal studies had shown that platelets play a part in metastasis of cancer via the bloodstream to distant tissues and that such metastasis might be prevented by aspirin," say the authors. "That aspirin prevents metastasis at least partly accounts for the reduced cancer mortality recently reported in trials of aspirin versus control in prevention of vascular events and suggests that aspirin will also be effective in treatment of some cancers. The lack of dependence of this effect of aspirin on its systemic bioavailability suggests that it is platelet-mediated. Other antiplatelet drugs might therefore have a similar effect on risk of metastasis and combining different drugs might increase benefit."

The third study, published in *The Lancet Oncology,* also looked at aspirin's effect on metastases, this time using a systematic review of observational versus randomised trials. The authors did this comparison because while randomised trials of aspirin could clearly establish the risk of colorectal cancer, several other solid cancers, and of metastasis, these trials lacked the statistical power to establish effects on less common cancers and on cancers in women. The potential advantage of observational studies, particularly case control studies, is that if they can be shown to produce reliable results they can be done very quickly,

rather than waiting 10-20 years for the results of prospective trials.

They found that observational studies showed a 38% reduced risk of colorectal cancer, matching well to the 42% reduction shown by randomised trials. Similar matches in risk were found for oesophageal, gastric, biliary, and breast cancer.

The authors conclude: "Observational studies show that regular use of aspirin reduces the long-term risk of several cancers and the risk of distant metastasis. Results of methodologically rigorous studies are consistent with those obtained from randomised controlled trials, but sensitivity is particularly dependent on appropriately detailed recording and analysis of aspirin use."

In a linked Comment, Dr Andrew T Chan and Dr Nancy R Cook, Brigham and Women's Hospital, Harvard Medical School, Boston, say: "Despite a convincing case that the vascular and anticancer benefits of aspirin outweigh the harms of major extracranial bleeding, these analyses do not account for less serious adverse effects on quality of life, such as less severe bleeding."

They conclude: "Rothwell and colleagues' impressive collection of data moves us another step closer to broadening recommendations for aspirin use. Moreover, future evidence-based guidelines for aspirin prophylaxis can no longer consider the use of aspirin for the prevention of vascular disease in isolation from cancer prevention."

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