Aspirin for the prevention of colorectal cancer

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Taking aspirin each day decreases the risk of developing colorectal cancer but also increases the risk of gastrointestinal and cerebral haemorrhage. How can GPs balance those risks to determine who should take aspirin to prevent colorectal cancer?

An Australian study investigating factors associated with colorectal cancer was the first to suggest that aspirin may be protective.[1] Subsequently, five large randomised population studies investigating the role of aspirin in preventing cardiovascular disease were analysed. They suggested that daily doses of at least 75 mg of aspirin over five years reduced the risk of colon cancer by 24%, and mortality due to colon cancer by 35% over the long term.[2] There was not the same impact on rectal cancer, and it appeared that the reduced incidence was largely in proximal colon cancer. Benefit increased with longer treatment duration.

Although impressive, this trial was a secondary analysis and the cancer endpoints may have been less accurate. Also, mortality data in some studies were collected from a cancer registry during a follow-up phase of the study, which did not account for subsequent aspirin dosing after the trial and did not account for other potentially confounding factors such as screening for colorectal cancer. Also, other large randomised clinical trials, such as the Physicians' Health Study, did not show a decrease in the incidence of colorectal cancer with a 10-year follow up.[3] With 10 years of dosing and eight years of follow up, the Women's Health Study did not show an overall reduction of cancer risk but did show a risk reduction for colorectal cancer.[4] However, both studies used alternate-day dosing at 325 mg and 100 mg, respectively, rather than daily dosing.

Aspirin in people at high risk of colorectal cancer

A randomised clinical trial of aspirin use has been performed in people who are carriers of Lynch syndrome. Lynch syndrome is a germline mutation in DNA mismatch repair genes, which results in a high risk of developing cancers, including colorectal cancer, at a young age. The Colorectal Adenoma/Carcinoma Prevention Program (CAPP2) trial randomised 861 participants with Lynch syndrome to a daily dose of aspirin 600 mg or placebo. Participants who took aspirin for at least two years showed a 63% reduction in the relative risk of developing colorectal cancer compared with those who received placebo.[5] It was particularly effective in people who were overweight and were twice as likely to develop colorectal cancer. A follow-up trial CAPP3 is investigating whether this result could have been achieved with lower doses of aspirin over two years by comparing 100 mg, 300 mg and 600 mg daily dosing.

It is recommended that GPs prescribe aspirin to patients who are at a high risk of colorectal cancer such as those with Lynch syndrome. The optimal dose is still to be determined but European guidelines recommend 100 mg daily dose for this group.[6] In an Australian study, 78% of healthcare professionals (gastroenterologists, colorectal surgeons and geneticists) would prescribe aspirin for people with Lynch syndrome.[7] A survey of the intent of GPs

MedicineToday 2019; 20(3): 56-58

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in the UK who had been informed of the risks and benefits of aspirin showed that 91.3% would be willing to prescribe 100 mg to people with Lynch syndrome, but this declined to 62.3% for 600 mg.[8] Only 70.8% of GPs had heard of Lynch syndrome, so more education on recognising the possibility of Lynch syndrome and prescribing aspirin is required.

Safety of long-term aspirin

The concern about the safety of taking long-term aspirin is related to gastrointestinal (GI) and intracranial bleeding. A meta-analysis of 35 randomised clinical trials of aspirin with doses ranging from 75 to 325 mg daily showed a hazard ratio of 1.55 compared with placebo.[9] This means for people at average risk there will be one or two bleeds for every 1000 person years, and rarely these can be fatal. The risk is greater with higher doses of aspirin and if individuals have other contraindications to taking aspirin, such as aspirin allergy, renal failure or other risk factors for GI bleeding such as being anticoagulated, taking other NSAIDs, being male, older age, smoking and having hypertension.[9-11] The risk of GI bleeding may be partly alleviated by the concomitant use of proton pump inhibitors but this has not become routine practice.[12] An ongoing study is investigating whether eradication of *Helicobacter pylori* would also reduce the ulceration and bleeding associated with aspirin.[13]

The risk of intracranial bleeding is much lower at one to two bleeds each 10,000 patient years but the consequences are usually more severe.[14]

Aspirin in people at moderate risk of colorectal cancer

A large randomised trial would be the ideal way to determine the causal relationship between aspirin and risk of colorectal cancer and to balance the risks and benefits of taking aspirin in the long term across a population with moderate-to-low risk of colorectal cancer. Such a trial would probably require more than 10,000 participants and is not planned in the future. However, prospective observational studies could be helpful.

Two prospective cohort studies, the Health Professionals Follow-up Study and the Nurses' Health Study, have explored the benefits of aspirin on cancer prevention in the era of colorectal screening.[15] In these studies, 88,084 women and 47,881 men reported their aspirin use for as long as 32 years. Regular aspirin use was shown to reduce the risk of overall cancer, primarily GI tract cancer and especially colorectal cancer in which the risk was reduced by 19%, with similar results in men and women. The dose at which the benefit was seen started at the equivalent of daily low-dose aspirin. There was no benefit seen until aspirin had been taken for at least five years and the benefit increased with longer use (beyond 10 years). There were benefits both in the screened and unscreened populations.

Aspirin has also been found to reduce the recurrence of colorectal cancer after diagnosis in several epidemiological and one large observational study, and several prospective adjunct trials are ongoing.[16]

How does aspirin reduce the risk of colorectal cancer?

The mechanisms by which aspirin works to reduce colorectal cancer are still being explored. Cancer can result from inflammatory processes that alter DNA, and aspirin works as an anti-inflammatory drug. Aspirin also inhibits the cyclooxygenase (COX) enzyme and indirectly affects COX2 through inhibition of platelet function.[17] COX enzymes are involved in the production of prostaglandins, which block programmed cell death, and their levels are high in people with colon cancer.

The genetics of the cancer also have a role in whether aspirin reduces mortality. For example, 70% of patients with colorectal cancer have a normal copy of the gene *KRAS* and 30% a mutation of *KRAS* but only those with the normal copy have a longer survival with use of aspirin.[18] More targeting of patients with colon cancer who will benefit from aspirin may be possible. A case-controlled study of patients with colorectal cancer that tested gene-by-environment interactions found that the association of aspirin with risk of colorectal cancer varies according to genetic change at two single nucleotide polymorphisms on chromosomes 12 and 15.[19]

PRACTICE POINTS

- People with Lynch syndrome who are at high risk of colorectal cancer will benefit from low-dose (100 mg) aspirin daily.
- People at moderate risk of colorectal cancer aged between 50 and 70 years who are also at risk of cardiovascular disease benefit from low-dose (100 mg) aspirin daily if they do not have an increased risk of bleeding.
- In patients treated for colorectal cancer, daily low-dose aspirin may help prevent recurrence.

US Preventive Services Taskforce and Cancer Council Australia recommendations

No agency has recommended low-dose aspirin alone to reduce the risk of colorectal cancer. However, in 2016 the US Preventive Services Taskforce (USPSTF) weighed the evidence of risk and benefit of low-dose aspirin and recommended its use when there was both a risk of cardiovascular disease and colorectal cancer.[20] Specifically, they recommended low-dose aspirin in adults aged 50 to 59 years who have a 10% or greater risk of cardiovascular disease over 10 years, have a life expectancy of at least 10 years, are not at increased risk of bleeding and are willing to take aspirin for at least 10 years. They recommended this with a moderate degree of certainty that the benefit outweighs the risk. In adults aged 60 to 69 years, the USPSTF believe there is a lesser degree of benefit over risk and if

they meet the same requirements as above they should be given the choice to take low-dose aspirin, depending on how high a value they place on the benefit compared with the risk. For people aged 70 years and above or under 50 years, the USPSTF do not believe that there is sufficient evidence to make a recommendation.

Risk of cardiovascular disease is based on older age, male sex, race/ethnicity, high lipid levels, hypertension, diabetes and smoking. To calculate the 10-year risk of cardiovascular disease, the USPSTF used a calculator derived from the American College of Cardiology/American Heart Association.[21] The recommendations outlined above are for people with an average risk of colorectal cancer. The USPSTF found that aspirin reduced the incidence of colorectal cancer after five to 10 years of use. The common aspirin doses were 75 mg or 100 mg daily. There is no evidence for altering the dose of aspirin for risk of colorectal cancer in individuals with characteristics such as obesity, but studies comparing aspirin doses are ongoing.

Similar recommendations are made in the Cancer Council Australia guidelines.[10] They also consider people at average risk of colorectal cancer aged between 50 and 70 years. They stress that the decisions should be individualised, taking into account age, sex and potential risk of cardiovascular disease and bleeding. The guidelines state that it is not known whether the risk reduction and mortality reduction of colorectal cancer with use of aspirin can be extrapolated to people who do not have a risk of cardiovascular disease.

The practice points in the Box summarise current recommendations for use of aspirin in preventing colorectal cancer. Although the question of aspirin use is engaging, GPs can make a great impact on colorectal cancer by encouraging their patients to participate in bowel cancer screening and promoting improved lifestyle behaviours around diet (increasing fibre, limiting red meat and alcohol) and exercise.

Conclusion

People with Lynch syndrome who are at high risk of colorectal cancer benefit from daily low-dose aspirin (100 mg). Daily low-dose aspirin should also be offered to people at moderate risk of colorectal cancer aged between 50 and 70 years who are also at risk of cardiovascular disease, if they do not have an increased risk of bleeding. In this population, the evidence of benefit exceeding risk is greatest for the 50- to 59-year olds. Aspirin may also prevent recurrence in patients treated for colorectal cancer. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: None.

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