Can daily aspirin help to reduce the incidence and mortality due to cancer?

Rothwell PM, Price JF, Fowkes FGR, Zanchetti A, Roncaglioni MC, Tognoni G, Lee R, Belch JFF, Wilson M, Mehta Z, Meade TW. (Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford; Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK; Istituto Auxologico Italiano, University of Milan; Istituto di Ricerche Farmacologiche ‘Mario Negri’, Milan, Italy; Institute of Cardiovascular Research, Vascular and Inflammatory Diseases Research Unit, University Division of Medicine and Therapeutics, Ninewells Hospital and Medical School, Dundee; London School of Hygiene and Tropical Medicine, University of London, London, UK.) Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: Analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;379:1602–12.

Rothwell PM, Wilson M, Price JF, Belch JFF, Meade TW, Mehta Z. (Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford; Centre for Population Health Sciences, University of Edinburgh, Edinburgh; The Institute of Cardiovascular Research, Vascular and Inflammatory Diseases Research Unit, University Division of Medicine and Therapeutics, Ninewells Hospital and Medical School, Dundee; London School of Hygiene and Tropical Medicine, University of London, London, UK.) Effect of daily aspirin on risk of cancer metastasis: A study of incident cancers during randomised controlled trials. Lancet 2012;379:1591–601.

SUMMARY

There is some evidence from randomized trials that short-term (2–3 years) aspirin use can lower cancer mortality. To confirm this hypothesis, in the first article the investigators collated data on 77,549 subjects from 51 randomized controlled trials (40,269 assigned to the aspirin arm and 37,280 to the control arm). There were 12 primary prevention trials where aspirin was used before a vascular event, and 39 secondary prevention trials. Studies of short-term treatment and those using aspirin for treatment or prevention of colorectal polyps were excluded. Previously published information regarding all the vascular and non-vascular deaths including cancer deaths was extracted. Where available, individual patient data of all cancer deaths was obtained from these trials. Individual patient data for all cancers during follow-up to include age, sex, smoking status, major vascular events, extracranial bleeds and cause of death were obtained for all participants of the primary prevention trials. All outcomes were analysed on the basis of intention-to-treat (ITT).

When compared with controls, aspirin use reduced risk of all non-vascular deaths (1021 v. 1173 deaths; OR 0.88, 95% CI 0.78–0.96, p=0.003) and non-vascular deaths in primary prevention trials (OR 0.88, 95% CI 0.78–0.98, p=0.02), and resulted in fewer deaths due to cancer (OR 0.85, 95% CI 0.76–0.96, p=0.008). Aspirin also tended to reduce the incidence of female reproductive cancers and death due to colorectal cancer and lymphoma, though the numbers were limited. Stratified analysis of time from randomization to death due to cancer showed a significant reduction in early deaths, i.e. within 3 years (OR 0.69, 95% CI 0.51–0.92, p=0.01). The magnitude of benefit was higher after 5 years of follow-up (OR 0.63, 95% CI 0.49–0.82, p=0.0005).

In the six primary prevention trials from which individual cancer data were available, daily low-dose aspirin reduced cancer incidence (hazard ratio [HR] 0.88, 95% CI 0.80–0.98, p=0.017) with maximum benefit after 5 years of follow-up from randomization (HR 0.81, 95% CI 0.70–0.93, p=0.003). This benefit was independent of age, sex and smoking status. With increasing duration of follow-up (<3, 3–5 and >5 years) on aspirin treatment, there was an increase in the effect on reduction of risk of cancer, but this was not seen in the effect on major vascular events or extracranial bleeds. When all three major outcomes of cancer, major vascular events and fatal extracranial bleeds were pooled, aspirin reduced their combined risk (HR 0.88, 95% CI 0.84–0.92, p=0.0002). A low-dose, slow-release formulation of aspirin designed to inhibit platelets but to have little systemic bioavailability was as effective as higher doses.

There is some evidence that daily low-dose aspirin can lower the early cancer mortality for some cancers. It was hypothesized that aspirin could slow tumour growth or the development of metastasis. To study this, in the second article, the investigators studied the effect of daily aspirin use on the risk of cancer metastasis in randomized trials comparing daily aspirin versus control for prevention of cardiovascular events.

The investigators analysed five large randomized controlled trials (17,285 participants) from UK where daily aspirin (≥75 mg) was compared with controls receiving placebo. Electronic and paper records of all patients with new incident cancer were reviewed and information on all their assessments, follow-up and all death certificates were extracted and reviewed blinded to treatment allocation. Date of diagnosis of cancer, site, stage, relevant investigations, histology, treatment and details of metastases were obtained. Presence of metastasis at diagnosis or on follow-up was noted. The effect of aspirin use on metastasis was analysed with ITT principle after stratification according to histology, age, sex and smoking status. Treatment with aspirin reduced the risk of incident cancers (OR 0.88, 95% CI 0.78–0.99, p=0.04) and death due to cancer (OR 0.77, 95% CI 0.65–0.91, p=0.002). Significantly fewer patients allocated to aspirin had definite metastases at initial diagnosis and on follow-up compared to those not on aspirin. Risk of metastases, except those to the bone, was reduced irrespective of site, i.e. lung, liver, brain and multiple sites.

Aspirin reduced the risk of development of metastatic adenocarcinoma, especially colorectal cancer (OR 0.36, 95% CI 0.18–0.74 p=0.005), but not non-adenocarcinoma solid tumours. Current smokers benefited the most from aspirin treatment, especially women smokers. No benefit was demonstrated among non-smokers in this population (HR 1.12, 95% CI 0.65–1.94). Patients on aspirin diagnosed with colorectal cancer during the trial or on follow up were less likely to have advanced disease (stage III–IV). Subjects diagnosed with non-metastatic colorectal cancer during the trial had reduced risk of developing metastases on subsequent follow-up in the aspirin group compared with controls (HR 0.26, 95% CI 0.11–0.57, p=0.0008).

This suggests that aspirin use prevents metastasis and could explain the early reduction of cancer in the preventive trials. This finding raises the possibility of using aspirin in the treatment of some cancers by providing proof of principle.

COMMENT

Cancer is a leading cause of premature deaths among adults globally (Globocan). Given the current cost of treatment of cancer and other non-communicable diseases and the colossal economic burden it causes on individuals, families and governments, chemoprevention if proved beneficial would be the ideal solution. Much effort has been put in to developing a cancer prevention pill. The hope arises when a safe, widely used, universally available and very affordable drug such as aspirin is shown to have several health benefits with short- and long-term use. The temptation to take aspirin as an effective cancer prevention
pill is strong. Its extensive use in randomized controlled trials for primary and secondary prevention of cardiovascular disease offers a unique opportunity to evaluate aspirin’s role in reducing cancer mortality. Patients who are on aspirin for various reasons have been known to have reduced risk of developing cancers in general and gastrointestinal cancers in particular.4,4 There is some evidence that low-dose aspirin also reduces the development of metastasis and early mortality.7,8 In view of this background, it is important to have good evidence for recommending aspirin on a short-term basis to prevent cancer, metastasis and deaths.

The two studies by Professor Rothwell and colleagues have bridged the knowledge gap in this area. One of the studies shows that short-term use of aspirin reduces cancer incidence and cancer mortality. The other study shows that aspirin use can prevent the development of metastasis from cancer. The authors provide good-quality evidence to support the view that an aspirin a day might keep several cancers away. Aspirin is widely used for secondary prevention of cardiovascular disease.9 The role of aspirin in primary prevention of cardiovascular disease is still uncertain, given the possibility of serious adverse events such as intra- and extracranial bleeding.10,11

The two studies summarized above included all the randomized trials of daily aspirin versus controls. The advantage of this approach is the availability of a large sample size amplified by multiple years of exposure to aspirin. Random allocation of aspirin and blinded collation and analysis of cancer data minimizes bias, improving the quality of evidence generated. The inclusion of all non-vascular deaths for analysis where cancer data are not available reduces the risk of inclusion bias. Analysis of individual patient data of cancer also increases the accuracy of the estimate of effect of aspirin. The authors found that aspirin intake reduces incidence of cancer and cancer death during long-term use. It is unlikely that the lower mortality in aspirin users is the result of detecting more early-stage gastrointestinal cancers triggered by work-up for gastrointestinal bleeding or anaemia while on aspirin. The arguments against this include the absence of early increase in incidence of cancers after enrolment, lower all-cancer incidence and mortality, as well as finding a similar benefit with aspirin use compared to warfarin use. Another interesting aspect is the analysis of overall risk-versus-benefit profile in low-dose primary prevention trials. After stratifying by time period of follow-up, the study showed that reduction in all-cause mortality after 3 years was mainly due to the effect on reduction of fatal cancers. This was also due to the fact that effect of aspirin on major vascular events and extracranial bleeds reduced after that time period. Unlike these outcomes, effect on reduction of cancer increased with increasing duration of exposure to aspirin and follow-up.

The major drawback of these studies is that these trials were not planned to study cancer-related outcomes. Hence, the data regarding the stage, site and extent of metastases, and cause of death in cases where mortality occurred shortly after randomization were not accurately recorded. Although low doses at 75 mg/day appear to have prevented cancer in these trials, there are insufficient data for head-on comparison of various doses in any single trial. The two studies do not provide information on minor bleeding or on quality-of-life. There are several ongoing trials as well as follow-up of some older trials that will clarify the position further in the coming years. In the meantime, Rothwell and colleagues have pushed the case for broadening the indications for use of aspirin in primary prevention. Future trials and evidence-based guidelines on primary prevention using aspirin should consider using composite end-points that combine cardiovascular disease and cancer.

Implications for healthcare in India

Cardiovascular disease, cancer and other non-communicable diseases prematurely kill several millions of Indians every year.2 General preventive measures including having a good balanced diet, facilities for regular physical activities, avoidance of several oncogenic infections and protection from exposure to tobacco in early life are not available to most Indians. At the same time, urbanization with the diet including more calories and atherogenic lipids will trigger the need to use preventive pills for non-communicable diseases in coming years.12 There are several ongoing polypill studies in India that will provide some evidence for the use of aspirin with other agents such as beta-blockers, ACE inhibitors and statins.13 However, these trials are also being done with cardiovascular disease mortality as the primary end-point and cancer mortality would be insignificant in these studies given the sample size.

The studies included in the Rothwell papers were conducted among Caucasian populations with a traditionally higher incidence of cancers such as colorectal cancer and adenocarcinoma of the oesophagus. It is difficult to extrapolate their results to the Indian setting. There are no population-based data on the benefits and harms of low-dose aspirin use in Indians. Furthermore, the overall lower incidence of all cancers is one-third the western figures,2 and that of colorectal cancer is about one-sixth of the western figures.14 This would greatly influence the extrapolation of any western findings to Indians. The number needed-to-treat would triple as cancer is three times less common in India. This will limit the likelihood of a randomized trial being done in India since the sample size requirements would be three times higher due to the lower incidence of cancer in India. Widespread prevalence of Helicobacter pylori infection among Indian adults would predispose them to a higher risk of gastrointestinal bleeding. Lack of competent endoscopy and gastroenterology facilities to deal with gastrointestinal bleeding could result in even higher mortality. All these factors would lower the number needed-to-harm. Therefore, the use of low-dose aspirin to prevent cancer in India cannot be recommended.

Nonetheless, because of the huge burden of cardiovascular mortality in India, the ongoing polypill studies will guide the use of aspirin in primary prevention of cardiovascular disease. Aspirin for cancer prevention will remain a secondary end-point in India.

REFERENCES

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