Debate and Analysis

Aspirin for prevention of cancer and cardiovascular disease

INTRODUCTION

Aspirin was discovered in 1897 and marketed initially as an analgesic. Over the years it has been used for other purposes including the prevention of both arterial and venous thrombosis, and as an anti-inflammatory drug. More recently there has been interest in the use of aspirin for primary and secondary prevention of cancer.

A recent study published in the *Lancet*,[1] showing impressive benefits of low dose aspirin in reducing both cancer mortality and all-cause mortality, received a lot of press publicity. The *Daily Mail* for example, claimed 'Aspirin really can beat cancer'.[2] No doubt following this publicity many primary care doctors have been asked the question 'Doctor, should I be taking aspirin?'. In this article we discuss how this latest publication fits in with previous evidence, and the clinical implications of the findings in relation to the primary prevention of cancer.

ASPIRIN AND CARDIOVASCULAR DISEASE

Many studies have investigated the benefits of aspirin in relation to cardiovascular disease. A recent meta-analysis of aspirin and heart disease by the Antithrombotic Triallists' Collaboration (ATTC) has quantified these benefits.[3] This large study reported an analysis of individual patient data from trials of both primary prevention (95 000 subjects) and secondary prevention (17 000 subjects). In trials of primary prevention the aspirin dose varied between 75 mg and 500 mg. There was no significant reduction in cardiovascular mortality and a small reduction in cardiovascular events. We have calculated the number needed to treat (NNT) to prevent one cardiovascular event with aspirin treatment for 1 year was 1666. Benefits for secondary prevention were more impressive with both reduction in cardiovascular events (NNT = 66 with treatment by aspirin for 1 year) and deaths (NNT = 344 with treatment by aspirin for 1 year).

This study confirmed the importance of aspirin in secondary prevention of cardiovascular disease, but the benefits from primary prevention were much smaller, and need to be carefully balanced against known risks. As a result of this study, many clinicians, in consultation with their patients, stopped recommending aspirin for primary prevention of cardiovascular disease.

ASPIRIN AND CANCER PREVENTION

With the cardioprotective effects of aspirin well established, attention is turning to the role of aspirin in the prevention of cancer[4,5] and a number of studies have now reported an inverse association between the incidence and mortality of various cancers and the use of aspirin. Few randomised controlled trials (RCTs) have been designed specifically to test an association between aspirin and cancer. However, data on the effects of aspirin use is available from previous studies which have randomly allocated aspirin for other purposes (usually cardiovascular end points), and weaker evidence is also available from a range of observational studies (case–control and cohort studies). The evidence of a chemopreventive effect of aspirin is strongest for colorectal cancer.

Long-term follow-up of four high quality randomised trials testing aspirin for primary or secondary prevention of vascular events (14 033 patients) has indicated that daily aspirin taken for several years at doses of at least 75 mg reduces the risk of long-term incidence and mortality from colorectal cancer (20-year incidence of colorectal cancer: hazard ratio [HR]* = 0.76, 95% confidence interval [CI] = 0.60 to 0.96; 20-year mortality from colorectal cancer: HR* = 0.65, 95% CI = 0.48 to 0.88).[6] Most observational studies that have addressed this issue — and there are many — also report an inverse association between the use of aspirin (and other NSAIDs) and incidence of colorectal cancer or disease-related deaths.[4,6] Although providing less robust evidence than RCTs, these studies also tend to report around a 40% lower incidence of colorectal cancer in those taking aspirin.

Aspirin use has also been associated with a reduced incidence of other cancers including oesophagus, stomach, breast, lung, bladder, ovary, and prostate, although there is less consistency in the findings reported in the literature compared with the results for colorectal cancer. Evidence seems to be building for cancers affecting the gastrointestinal (GI) tract in particular. A meta-analysis of cohort and case–control studies found a reduced risk of oesophageal cancer (four studies: relative risk [RR]* = 0.51, 95% CI = 0.38 to 0.69), and stomach cancer (five studies: RR* = 0.73, 95% CI = 0.63 to 0.84).[7] Another meta-analysis which included four observational studies focusing on oesophageal cancer reported similar findings.[8] These two reviews included three of the same studies, and one further unique to each. A more recent review of 14 studies looking at aspirin and gastric cancer (one RCT and 13 observational) conducted a meta-analysis and found no overall effect of aspirin (odds ratio [OR]* = 0.80, 95% CI = 0.54 to 1.19), although when analysis was restricted to three RCT or cohort studies (that is, higher quality studies) there was a significant reduction in the incidence of gastric cancer (OR* = 0.74 (95% CI = 0.63 to 0.86).[9] Although the authors of these reviews highlight certain methodological limitations, and the need to interpret the findings with caution, they do suggest a possible association between aspirin use and a reduced incidence of non-colon GI cancers.

Not all studies have found support for a chemopreventive effect of aspirin. Two large studies have shown no benefit, but both involved alternate day aspirin, rather than daily aspirin, which may explain the findings. The Women's Health Study in the US randomly assigned almost 40 000 healthy females aged 45 years or over to receive 100 mg aspirin or placebo every other day for an average of 10 years.[10] This

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"For every 1666 treated with aspirin for 1 year for primary prevention of heart disease there would be one less cardiovascular event but no reduction in cardiovascular deaths"

study was designed to examine the effect of aspirin on cardiovascular disease but found no effect of aspirin on the incidence of any cancer. Similarly, the Physician's Health Study randomly assigned 22 071 male physicians in the US to aspirin (325 mg) or placebo on alternate days and also saw no effect after 5 years[11] or 12 years.[12]

The most recent meta-analysis published on this topic by Rothwell and colleagues[1] studied deaths due to any type of cancer using follow-up data (individual patient data where possible) from RCTs of daily aspirin versus control, but originally undertaken to study cardiovascular disease prevention. This meta-analysis looked at deaths rather than incidence because cause of death was reliably recorded in cardiovascular prevention trials, whereas incidence of cancer may not have been. This analysis pooled data from eight trials (25 000 patients). Aspirin had to be used daily for a minimum of 4 years for inclusion, but some of the studies involved taking aspirin significantly longer. The main analysis was done after 5 years follow-up and showed that after 5 years of follow-up, cancer deaths were reduced by 21% (OR* 0.79, 95% CI = 0.68 to 0.92). The benefit was greatest for GI cancers (HR* = 0.46, 95% CI = 0.27 to 0.77) (data from seven trials for which individual patient data were available), but aspirin use appeared to have no impact on some cancers (for example, haematological malignancies).

Three of the trials (which were UK based) could provide follow-up data for 20 years, and a second analysis was done for this smaller data set (12 659 patients). After 20 years of follow-up, deaths were reduced by 20% (HR* 0.8, 95% CI = 0.72 to 0.88). We have translated this reduction in risk into NNT. For every 29 people taking aspirin for around 5 years, 20 years later one death would be prevented. Although benefits

were seen after 5 years follow-up for oesophageal, pancreatic, brain, and lung cancers, it took longer than this for the benefit to be seen for stomach, colorectal, and prostate cancers. The benefit was similar for all aspirin doses of 75 mg and above. Similar results were also seen for males and females, smokers and non-smokers. Age, however, was an important factor with no reduction in cancer mortality seen in those under the age of 55 years and the benefit increasing with age thereafter. For those aged 55–64 years the NNT was 22 at 20 years (that is, for every 22 people taking aspirin for at least 5 years, there would be one less cancer-related death 20 years later). In those aged 65 years and older, the NNT was 14 after 20 years. The paper also considered all-cause mortality and found an 8% reduction for the first 15 years (mainly attributable to the reduction in cancer mortality). However, at 20 years no reduction in all-cause mortality was observed and it is not clear why this is so.

In summary, despite some methodological limitations in the data available, there is consistent and growing evidence of a chemopreventive effect of daily aspirin use. There remain questions over the dose, duration, and length of time before an effect is seen for different cancers, and how effective aspirin is in the prevention of non-GI cancers. We also need to know more about which sub-groups of patients may be most likely to benefit.

PHARMACOLOGY OF ASPIRIN

There are a number of mechanisms through which aspirin may reduce cardiovascular disease and cancer. The effect of aspirin on the two cyclo-oxygenase (COX) enzymes, COX-1 and COX-2 are best known. These enzymes modulate the production of a number of prostaglandins which have activity in a number of cellular systems. Aspirin has a much higher affinity for COX-1, which is preferentially blocked at lower doses, but higher doses block both enzymes. In platelets, COX-1 increases thromboxane, which promotes platelet aggregation and COX-2 promotes prostacyclin which inhibits platelet aggregation. Consequently, there is an antithrombotic effect at low doses which is reduced at higher doses. Clinically this is demonstrated by the dose dependent effect of aspirin on the prevention of vascular thrombotic disease in trials in humans.[13] COX-2 in gastric mucosa produces prostaglandin E2 which protects the mucosa from ulceration. Inhibition by aspirin explains the increased risk of gastric ulceration.

Both in vivo and in vitro studies in animals have shown that aspirin protects against chemically-induced tumours, mediated through the COX-2 enzyme.[5] COX-2 is over-expressed in pre-malignant lesions of breast, lung, and colorectal cancers in humans.[4] The importance of this mechanism has been demonstrated in colorectal cancer in humans where aspirin reduces those cancers that over-express COX-2 but not those with weak or absent expression.[14] There are other mechanisms by which aspirin may prevent cancer. Aspirin has been shown in vitro to reduce the micro satellite instability (due to a mutation in a mismatch repair gene) in hereditary non-polyposis colon cancer.[15] In vitro studies have also shown that aspirin stimulates apoptosis and inhibits angiogenesis.[16] These effects are partly mediated through inhibition of COX-2 but the effects can be shown in cells that do not express COX-2, mediated by other pathways.[5]

SIDE EFFECTS OF ASPIRIN

Many studies have reported the increased risk of GI ulcers and increased risk of bleeding from the gut as well as intracranial bleeds. The meta-analysis by the ATTC quantified the harms of aspirin

***** Papers quoted in this article have variously referred to relative risks, hazards ratios, and odds ratios as a method for comparing the event rate in one group versus another (in this case aspirin use versus non-aspirin). For the purposes of this article, where event rates are generally small, these can be considered as comparable measures.

"For every 3333 people treated with aspirin for a year there would be one extra significant bleed"

using the larger primary prevention studies; most trials recruited subjects from 45 or 50 years up to 73–94 years, thus giving risks over a wide age range.[3] Aspirin increased the risk of major extra cranial bleed from 219 in the control group to 335 in the aspirin group over a total of 660 000 person years of follow-up (0.07% per year to 0.1% per year. RR* 1.54; 95% CI = 1.30 to 1.82) Most of these bleeds were GI and were defined as a bleed causing death or needing a blood transfusion. Unexpectedly there were fewer fatal bleeds in the aspirin group compared with the controls (9 versus 20). Therefore, we have calculated that for every 3333 people treated with aspirin for a year there would be one extra significant bleed. Aspirin also increases intracranial bleeding and in these studies there was an excess of 27 haemorrhagic strokes in 666 000 patient years of follow-up. Twenty-two of these 27 excess haemorrhagic strokes were fatal.

For patients taking aspirin over several years it is important to consider the cumulative risk of side effects over the time of aspirin administration. A meta-analysis of studies of aspirin showed that the risk was higher for any GI haemorrhage in patients taking up to 162.5 mg per day: the rate of bleeding over 28 months increased from 1.45% in the placebo group to 2.30% in the aspirin group, an annual increased rate of 0.36% (NNT= 278).[17] The results of the British doctors' study using 500 mg aspirin suggested the increased risk of haemorrhage was similar in the first year (1.1%) compared with the subsequent 5 years (a further 1.1% in total).[18] The risk of serious side effects from aspirin also increased with age. For example non-fatal GI or extra-cranial bleeding increased from 0.3% over 5 years in 50–59-year-old females to 0.9% in 65–74-year-old females and from 0.5% over 5 years in 50–59-year-old males to 1.2% in 65–74-year-old males.[3]

ASPIRIN AND PRIMARY PREVENTION OF CANCER: CLINICAL IMPLICATIONS

The renewed interest in the potential of aspirin as a preventive drug following Rothwell's recent publication[1] must be tempered by the observations made about its limitations.[19] Rothwell's initial meta-analysis included eight trials but only three provided data for long-term follow-up and one of these did not provide individual patient data. Cancer was not the main outcome of these trials and the effect on all-cause mortality was present at 15 years but not significant after 20 years. (It is important to reduce overall mortality, not just deaths from cancer.) There are several large trials underway investigating the use of aspirin for prevention that have specifically defined cancer as an outcome measure. However, these may not provide definitive answers either; one trial is confined to people over 70 years[20] and another confined to males.[21]

A decision to alter clinical practice and recommend aspirin on a population basis must be seen in context. In favour of change are coherent pathophysiological mechanisms by which aspirin would be expected to have an effect on the incidence of cardiovascular disease and cancer. This is supported by epidemiological studies which confirm the benefits (and risks) of aspirin. Against change is the lack of randomised trials specifically looking at aspirin and its effect on cancer and the uncertainty about the exact magnitude of the benefit and the optimum age, dose, and duration for administering aspirin. Although we have discussed aspirin in relation to its action on the cardiovascular system, cancer, and GI tract separately, it is important to bear in mind that when taking aspirin, people expose themselves to all the risks and all the benefits simultaneously. It is difficult to directly compare the benefits of reductions in cancer and heart disease versus an increase in significant morbidity from bleeding and individual patients will have views on how they perceive the different outcomes.

Box 1. Risks and benefits of aspirin

Risks and benefits of taking 75 mg aspirin for 5 years for 1000 healthy people aged 55–64 years (based on Rothwell[1] and ATTC[2])

In the first 5 years:
- 1.5 additional significant extra-cranial bleeds
- 0.5 additional intra-cranial bleeds
- 3 fewer cardiovascular events (cardiac plus strokes)
- No change in overall cardiovascular deaths

At 20 years, with the initial 5 years of taking aspirin:
- 45 fewer deaths from cancer
- No reduction in deaths from any cause

Aspirin is already a widely prescribed drug. In our own practice, where we have stopped prescribing for primary prevention of cardiovascular disease, the prescription rate for aspirin was still 1% for people aged 45–54 years, 3% for 55–64 years, and 17% for those 65 years and above. These figures do not include patients buying aspirin over the counter for either primary or secondary prevention. In a community survey in South Wales, use was much higher: 28% of males and 19% of females over 50 years were taking aspirin regularly for primary prevention.[22] Another clinical consideration is the widespread use of proton pump inhibitor drugs which reduce the risk of aspirin causing ulceration and possibly GI bleeding.[23] Currently in our practice 14% of patients aged 55 years or over receive a proton pump inhibitor or H_2 antagonist.

CONCLUSION

Despite the increasing body of evidence, it may be premature to actively encourage the whole population to take aspirin; there is still uncertainty about the magnitude of benefit. A colleague observed that this was comparable to the situation with prostate specific antigen (PSA) screening for prostate cancer but with one main difference: the evidence for aspirin is getting stronger while the evidence for PSA testing is weakening. So, how should a GP respond to the question 'Doctor, should I be taking aspirin?' There is no strong evidence that patients under the age of 55 years will benefit. These patients can afford to wait for the publication of further studies. The benefit from aspirin takes 5–10 years to accrue so there is little point in subjecting a person with short life expectancy to the initial harms of aspirin when they are unlikely to enjoy the benefits. In between these ages, assessment should be on an individual basis. The risk of taking aspirin increases with age, previous peptic ulcer, and treatment with steroids, anticoagulants and other NSAIDs and these additional risks should be assessed.[23]

Patients enquiring about aspirin should be counselled about the risks and benefits. We have given some guidance for clinicians based on the main trials discussed previously (Box 1). The main points to cover are that risks and benefits are roughly equivalent during the first 5 years on

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aspirin. However, over the next 15 years there is a benefit in reduction in cancer deaths but no proven overall reduction in mortality. Those who wish to proceed should be told to take 75 mg aspirin every day for 5 years. Any side effects should be reported immediately. After 5 years the person should be re-assessed because future evidence may suggest a longer duration of aspirin administration is beneficial.

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