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NEWS BRIEFS from the Aspirin Foundation

Aspirin cuts cancer risk - new evidence

New studies suggest that taking aspirin or other NSAIDs may reduce the risk of common cancers such as breast cancer and colorectal cancer. These findings strengthen the evidence that aspirin has a protective effect against some cancers and opens the way for the development of new targeted strategies for cancer control.

Which cancers?

The new studies show that taking aspirin or NSAIDs is associated with a reduced risk of cancers of the breast, lung (in smokers), *oesophagus, and the *colon and rectum, compared with people who don't take these medicines regularly. While this information falls short of absolutely proving a cause and effect relationship, the reductions in risk are substantial and offer a strong foundation on which to base definitive trials.

*See background document under Position Papers

Breast cancer

Regular use of aspirin reduced the risk of breast cancer by 21% in postmenopausal women, say investigators in the United States. Their findings were announced in a report of the 94th annual meeting of the American Association for Cancer Research in Toronto¹.

The evidence comes from a new analysis of the Women's Health Initiative (WHI), an ongoing study of the causes of death and illness in women aged 50 - 79 years². Of 80,741 women who had no history of cancer at the beginning of the study, 1392

subsequently developed breast cancer. The use of aspirin and other NSAIDs was compared in women with or without breast cancer.

The study found that regular use of an NSAID (defined as at least two tablets per week) was associated with a 21% reduction in the risk of developing breast cancer. Longer use of NSAIDs was associated with greater protection - after 10 years, the risk was 28% lower. Aspirin itself was associated with a 21% reduction in risk.

Closer analysis revealed no other factors (such as obesity, HRT use or family history) that might explain the findings; in particular, use of paracetamol or of aspirin at doses of less than 100 mg/day had no protective effect.

Lung cancer

Investigators in New York have reported a case-control study³ of the incidence of lung cancer among people taking NSAIDs, including aspirin (*Cancer 2003;97:1732-6*). Their hospital-based study identified 1038 patients and 1002 controls. Among those using NSAIDs at least three times a week for at least one year the relative risk of lung cancer was significantly reduced by nearly one-third (odds ratio 0.68), regardless of the histological type of tumour. However, the protective effect was largely confined to people who had been or were still smokers, with odds ratios of 1.28 for never-smokers (not statistically significant) and 0.60 for ever-smokers. The effects of aspirin and NSAIDs among smokers were similar.

The investigators believe that inhibition of COX-2 is the most likely mechanism of action: tobacco tar is known to increase COX-2 activity in animal models and COX-2 activity is increased in smokers compared with non-smokers.

Colorectal cancer

Two double-blind trials⁴ from the United States have shown that aspirin reduces the risk of developing colorectal adenomas in people at increased risk, and may therefore protect against colorectal cancer (*N Engl J Med* 2003;348:883-90 & 891-9).

The larger study randomised 1121 patients with a recent history of adenomas to placebo or treatment with aspirin 81 or 325 mg/day. After 32 - 33 months' follow-up, the lower dose of aspirin was associated with a lower incidence of new adenomas (38% vs. 47% with placebo and 45% with 325 mg/day). The unadjusted relative risks for any adenoma (RR 0.81) or large adenomas (RR 0.59) were significantly lower with aspirin 81 mg/day but not at a dose of 325 mg/day.

The second study involved 635 patients who had undergone surgery for colorectal cancer and were therefore at higher risk. After an average of 13 months' treatment, aspirin 325 mg/day was associated with significantly fewer new adenomas (mean per patient 0.30 vs. 0.49 with placebo). The adjusted RR of any recurrent adenoma was 0.65 and the time to detection of a first adenoma was increased (hazard ratio 0.64) compared with placebo.

Adenoma, which is a predictor of colorectal cancer, is an accepted substitute for the cancer itself. Colorectal cancer, despite being the third commonest cancer in the UK, is relatively infrequent and would require an unfeasibly prolonged and large trial to measure it directly. These well-designed trials strongly suggest that aspirin reduces the risk of colorectal cancer in people who are at increased risk; further studies are needed to determine its cost effectiveness in this context.

Oesophageal cancer

A meta-analysis⁵ of nine case-control and cohort⁶ studies involving a total of 1813

patients with oesophageal cancer has concluded that use of aspirin is associated with a 43% reduction in risk (*Gastroenterology* 2003;124:47-56). The analysis found evidence that regular use was more protective than intermittent use (odds ratio, OR, of cancer 0.82 and 0.54 respectively). This 'dose-response relationship' suggests that the link may be causal.

The meta-analysis included studies involving NSAIDs but closer analysis showed that only aspirin exerted a statistically significant effect. The reduction in risk associated with aspirin was apparent for both adenocarcinoma and squamous cell carcinoma of the oesophagus.

These findings are supported by a pooled analysis of three case-control studies in Italy involving a total of 965 patients with cancer of the mouth, pharynx, larynx or oesophagus (*Br J Cancer* 2003;88:672-4). Use of aspirin for five or more years substantially reduced the risk of cancer overall (OR 0.33) and of each type individually.

How might aspirin reduce cancer risk?

Aspirin is often termed a 'simple analgesic' but new research shows that it is anything but - in fact, we are now learning how much we don't know about the mechanisms of action of aspirin and other NSAIDs.

The key to the mystery of how aspirin and other NSAIDs might reduce the risk of cancer appears to be the enzyme cyclooxygenase, or COX. Aspirin reduces pain, fever and inflammation by inhibiting COX. A team of US pharmacists has concluded that tumours over-express COX-2 and an NSAID can prevent or reduce cancer risk by inhibiting this enzyme (*Pharmacotherapy* 2003;23:9-28)⁷.

In the case of lung cancer cells, COX is important in allowing the cells to multiply. COX-2 appears to contribute to the development of tumours by inhibiting apoptosis (programmed cell death), increasing angiogenesis (development of new blood vessels) and invasiveness,

modulating inflammation and immunosuppression, and converting precursors of carcinogens into active chemicals.

There are differences among NSAIDs: toxicity during long-term treatment is a major concern and has focused attention on selectively inhibiting COX-2, and in vitro studies suggest that NSAIDs vary in their anti-tumour activity. The authors conclude that trials now underway will further define the role of COX-2 inhibitors in preventing and treating cancer.

Laboratory evidence also suggests that NSAIDs can influence the development of cancer cells in two other ways⁸. They target a cellular pathway known as ras/mek/erk, which is commonly mutated at an early stage of lung cancer development; and they can inhibit the growth of some lung cancer cells by activating a receptor on the membrane known as PPAR (peroxisome proliferator activated receptor). It therefore seems likely that aspirin and other NSAIDs may reduce cancer risk by a three-fold action, blocking early tumour development and inhibiting tumour cell growth and proliferation.

With a strong foundation of evidence from animal models, many clinical trials are now underway to determine the effects of COX-2 inhibition against a wide range of cancers. Preliminary data also suggest that this strategy may also be a useful adjunct to radiotherapy and chemotherapy.

COX-3 - the analgesia target?

The mechanism of action of aspirin was first described in 1971 by John Vane. He showed that aspirin inhibits COX, reducing the synthesis of prostaglandins and thromboxanes which were known to be mediators of pain, fever and inflammation.

Almost 20 years later, it was found that COX exists in two forms - COX-1 and COX-2. COX-1 is a 'housekeeping' enzyme: it is always present and is important for normal physiological functions (like maintaining the mucus lining of the stomach). COX-2 occurs only in the presence of inflammation and plays an important role in the development of pain

and fever. This finding prompted the development of drugs selective for COX-2 which reduce inflammation but cause fewer side effects on the stomach.

It has long been suspected that a third version exists but COX-3 was only identified in 2002, when it was found in the brain and the heart⁹. Its role is still unclear. It was once hoped that COX-3 might explain the effects of paracetamol (despite being a familiar household medicine, its mechanism of action is still unknown) but studies have shown this is not the case. Interestingly, COX-1 and COX-3 are very similar. NSAIDs that are selective for COX-2 have little effect on COX-3, whereas older NSAIDs that inhibit both COX-1 and COX-2 also inhibit COX-3. There is some evidence that COX-2 selective NSAIDs are less effective as analgesics than non-selective NSAIDs. COX-3 may therefore offer a gateway to the development of new drugs to relieve pain.

Notes

1. Further information about the conference can be found at (www.aacr.org)
2. Further information about the Women's Health Initiative Study can be found at (www.nhlbi.nih.gov/whi/factsht.htm).
3. A case-control study is a comparison of two groups of similar people, one having the condition of interest such as a cancer (cases), the other not (controls); comparing their exposure to, for example, a drug provides an estimate of the risk of the cancer associated with the drug. Case-control studies are retrospective and are widely used to detect the risk of rare events such as cancers; they demonstrate an association but do not prove a cause and effect relationship.
4. A double-blind trial is a comparative study in which neither the investigators nor the participants are aware of who is taking a particular intervention (eg active treatment or placebo).
5. Meta-analysis is a statistical technique by which the results of different studies can be pooled and weighted according to the quality of the data. This is the most robust

form of statistical analysis and is the method of choice when the findings of several studies are inconclusive.

6. A cohort study is a study of a group of people (cohort) to examine how events (eg occurrence of cancer) vary according to the characteristics (eg use of medicines) of the group. May be prospective or retrospective; does not prove a cause and effect relationship. The Women's Health Initiative is one example.

7. This review can be accessed online at Medscape (www.medscape.com/viewarticle/448279).

8. For a more detailed review, see Schwab JM et al. *Lancet* 2003;361:981

9. Chandrasekharan NV et al. *Proc Natl Acad Sci USA* 2002;99:13926-31

Ask advice before taking daily aspirin, FDA warns consumers

The US Food and Drug Administration has advised consumers in the United States to consult a health professional before taking aspirin to reduce their risk of heart attack or stroke¹.

The protection that daily low-dose aspirin provides against heart attack and some types of stroke has received widespread publicity, prompting some people to take it without asking their doctor or pharmacist whether they need to.

'Although aspirin might seem like a quick and easy solution to any fears you might have, it's not as simple as you think', the FDA says.

Aspirin has been shown to reduce the risk of heart attack and certain types of stroke in people who are at increased risk of these conditions - for example, if they have had a heart attack before. For someone who is generally healthy, or who is taking other medication or certain dietary supplements, taking a daily aspirin could do more harm than good. Consumers are also warned that many over-the-counter analgesics do not contain aspirin and some include additional drugs which should not

be taken long-term.

The FDA points out that aspirin reduces the risk of heart attack and stroke by thinning the blood, but this same action can cause side effects such as stomach bleeding, bleeding in the brain and kidney failure. Although these problems are relatively rare, the balance between risk and benefit depends on an individual's circumstances. A health professional can assess the risks and decide whether daily aspirin will be helpful.

Over-the-counter aspirin can be taken to relieve headache, pain, swelling and fever. Advice on its use is available from a health professional and instructions for use are printed on the product packaging.

Notes for editors

1. You can access the information on the FDA's website at www.fda.gov/cder/consumerinfo/aspirinfactsheet.htm and www.fda.gov/cder/consumerinfo/dailyaspirin_brochure.htm

Further information available from:-

Further information from:

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