

Colorectal cancer prevention

Colorectal cancer is a major cause of mortality in the UK and Ireland and the second most frequent cause of cancer-related mortality. The lifetime risk is 1 in 20.

Several studies have evaluated the effect of aspirin and to a lesser extent NSAID use on the risk of colorectal cancer. Most of these studies have been observational in nature and were performed in a variety of settings, primarily in the United States, and have used colorectal cancer occurrence and mortality as outcomes. Most have reported that aspirin is associated with a reduced risk of developing colorectal cancer but, until recently, they have generated little evidence on the most effective dose and duration of therapy.

The Nurses' Health Study determined rates of colorectal cancer among women who reported regular aspirin use and compared the rates in this group with the rates among women who said they did not use aspirin (1). Regular aspirin use was defined as two or more tablets per week; the doses were not specified. This study found that a protective effect was seen only after several years use. There was a slight reduction in risk among women who took aspirin for 10 to 19 years, but it was not statistically significant (relative risk, 0.70; C95%I = 0.41-1.20). However, there was a statistically significant reduction after 20 years of consistent use of aspirin (relative risk, 0.56; CI95%= 0.36-0.90; P for trend = 0.008). The greatest risk reduction occurred among women who took 4 - 6 tablets per week; higher doses (i.e. by numbers of tablets) had a similar apparent benefit. It was concluded that regular aspirin use, at doses similar to those recommended for the prevention of cardiovascular disease, substantially reduces the risk of colorectal cancer. However, this benefit may not be evident until after at least a decade of regular aspirin consumption.

An analysis of data from the Physicians' Health Study concluded that low-dose aspirin (325mg on alternate days) over a period of about five years was not

associated with a lower risk of colorectal cancer (2). The relative risk of developing colorectal cancer during aspirin use compared with placebo was 1.15 (CI95% = 0.80-1.65). For in situ cancers and polyps, the relative risk was 0.86 (CI95% = 0.68-1.10). There was no significant trend for decreasing relative risk by year of follow-up for invasive cancers (P = 0.09) or non-invasive tumours (P = 0.96). It was concluded that regular aspirin use, at a dose adequate for preventing myocardial infarction, was not associated with a substantial reduction in the incidence of colorectal cancer during five years of randomized treatment and follow-up. A small decrease in polyps in the aspirin group could not be reliably distinguished from a chance association.

The most recent studies have provided valuable information about the importance of dose and duration of use. An analysis of the US Cancer Prevention Study II Nutrition Cohort involving a total of 146,113 men and women showed that long-term daily use of aspirin (at least 5 years) at doses of at least 325 mg/day was associated with a significantly lower risk of colorectal cancer (relative risk 0.68, CI95% 0.52 - 0.90) (3). This is confirmed by a pooled analysis of two trials involving a total of 7,588 participants randomized to aspirin (300 - 1200 mg/day) or controls, and providing at least 20 years' reliable follow up (4). Use of aspirin significantly reduced the incidence of colorectal cancer (hazard ratio 0.74, CI95% 0.56 - 0.97) overall, with a greater effect among those who had taken aspirin for at least 5 years (hazard ratio 0.63, CI95% 0.47 - 0.85). This reduced risk was only apparent after a delay of 10 years and peaked after 10 - 14 years among those who adhered to their prescribed treatment (hazard ratio 0.37, CI95% 0.20 - 0.70).

Two recent interventional studies published in the New England Journal of Medicine provide stronger evidence that low-dose aspirin has a chemoprotective effect against the development of new adenomas in patients with a history of colorectal adenomas.

As colorectal adenomas may be precursors of colorectal cancers, prevention of adenomas may also prevent cancers.

In the first study (5), a randomised, double-blind trial, found that daily ingestion of enteric coated aspirin (325mg) reduced the incidence of colorectal polyps among patients with previous colorectal cancer. Final follow-up was at three years after entry into the study. Of 258 patients in the placebo group who underwent colonoscopy, polyps were found in 70 (27%), whereas 43 of 259 patients in the aspirin group were found to have polyps (17%). The adjusted relative risk of recurrent adenomas in the aspirin group was 0.65 (CI95% = 0.46-0.91). The time to detection of a new polyp was longer in the aspirin group than in the placebo group.

In the second study (6), patients with a history of colonic adenomas were randomly assigned to receive daily aspirin or placebo. This was a double blind 3-year trial, with 377 patients on 81mg aspirin and 372 on 325mg aspirin daily. Compared with placebo, aspirin 81mg daily was associated with a 19% reduction in the risk of recurrent adenomas (CI95% = 0.69-0.96). However, the 325mg dose was not beneficial, relative risk reduction 0.96 (CI95% = 0.81-1.13) which was not statistically significant. Why the 81mg dose but not the 325mg dose was beneficial was difficult for the authors to explain, especially in view of the report in the same journal by Sandler et al (5).

These prospective studies provide proof of the principle that aspirin can reduce the risk of colorectal polyps in a population at high risk for the development of such adenomas.

In a third randomised, double-blind, placebo-controlled trial, regular aspirin use reduced the risk of recurrent colorectal adenoma in women at low risk (7). The duration of use was not important: short- and long-term users had similar reductions in risk. The dose-response relationship was clear, and the effect at the highest level of aspirin was very strong. The risk reduction ranged from 20% at doses of 0.5 - 1.5

tablets per week to 50% at more than 14 tablets per week. Daily use of aspirin appears to have a moderately protective effect against the development of colorectal cancer. However, this may only become apparent after several years of prophylactic therapy. Furthermore, the most effective dose has yet to be established. The harms of higher doses of aspirin might outweigh the benefits of a reduced risk of colon cancer, especially if the incidence of serious aspirin-related bleeding was much greater than the incidence of colon cancer. The use of aspirin to prevent colorectal cancer should therefore be limited to persons at higher risk of adenomas (eg those with previous colon cancer or a family history). Before aspirin can be recommended for chemoprevention in the general adult population, these results suggest that a more thorough evaluation of the risks and benefits of routine aspirin use is needed at doses not previously considered (7).

The mechanism by which aspirin and other NSAIDs prevent colorectal carcinogenesis are not fully understood (8). One suggestion is that they induce apoptosis of neoplastic cells via mechanisms both dependent and independent of inhibition of the enzyme cyclo-oxygenase (COX). Another is that they induce the expression of a protein, p21, that is involved in the regulation of normal cell growth. Convincing evidence is now available that inhibition of COX-2 is an important mechanism. Analysis of tumour specimens from 130,274 men and women identified 636 new cases of colorectal cancer during a total follow up of 2,446,431 patient-years (9). Of these tumours, 67 percent were found to over-express COX-2. Regular use of aspirin significantly reduced the risk of colorectal cancer by 36 percent in participants with COX-2 over-expression (absolute incidence 37 per 100,000 among aspirin users vs. 56 per 100,000 among non-users). The incidence of tumours with weak or absent expression of COX-2 was similar among aspirin users and non-users (27 vs. 28 per 100,000 respectively).

References:

1. Giovannucci E et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995;333(10):609-614
2. Gann PH et al. Low-dose aspirin and incidence of colorectal tumours in a randomized trial. *J Natl Cancer Inst* 1993;85(15):1220-1224
3. Jacobs EJ, Thun MJ, Bain EB et al. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. *J Natl Cancer Inst* 2007;99:608-15
4. Flossman E, Rothwell PM, British Doctors Aspirin Trial and the UK TIA Aspirin trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomized and observational studies. *Lancet* 2007;369:1603-13
5. Sandler RS et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 2003;348(10):883-890
6. Baron JA et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003;348(10):891-899
7. Chan AT et al. A prospective study of aspirin use and the risk for colorectal adenoma. *Ann Intern Med* 2004;140:157-66.
8. Huls G et al. Non-steroidal anti-inflammatory drugs and molecular carcinogenesis of colorectal carcinomas. *Lancet* 2003;362:230-232
9. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med* 2007;356:2131-42

Updated July 2007