References


Commentary: Aspirin and cancer prevention

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In research the horizon recedes as we advance.
And research is always incomplete
Mark Pattison 1813–84
English Educationist
Isaac Casaubon (1875) Chapter 10

The risk of colorectal cancer in relation to several chronic illnesses, previous operations and medication use was investigated as a part of a large population-based study on colorectal cancer incidence, aetiology and survival, The Melbourne Colorectal Cancer Study, and the results were reported in 1988.1 We had no specific hypotheses regarding any of the medication groups, which were aspirin, non-aspirin, non-steroidal anti-inflammatory agents, steroids, oral contraceptives, tranquillizers and sleeping pills, and these groups were included as a general category of exposures to be tested in this comprehensive case–control study. There were several findings of interest; however, the focus of this commentary is on the statistically significant protective effect among regular aspirin users for both colon and rectal cancer in both men and women, this being the first report of this association. The paper ‘Colorectal cancer, chronic illnesses, operations and medications. Case control results from the Melbourne Colorectal Cancer Study’ was also the first report of a similar but less consistent protective effect of non-aspirin, non-steroidal, anti-inflammatory drugs in use at that time. The aspirin finding was independent of the other risk factors found in our study up to that time and especially so for the various dietary risks. We wrote in 1988: ‘...this finding, whatever the mechanism may be, has potential significance in colorectal cancer chemoprevention and merits early confirmation. Aspirin is now widely used in the
chemoprophylaxis of cardiovascular disease and may also be useful in a similar way in the prevention of colorectal cancer, and perhaps also of other cancers.\textsuperscript{3} What were the consequences of this new finding?

Confirmation of this aspirin finding emerged from two studies in 1991, 3 years after our report, and several other systematic reviews right up to 2007, which in at least 20 epidemiologic studies showed a statistically significant protective effect in at least three-quarters of the studies, and with one exception, a null effect in the rest.\textsuperscript{5–8}

Several series were able to adjust statistically for confounders, and a dose–response effect was also evident in some but not all studies.\textsuperscript{5–7} Indirect evidence was provided by several cohorts who were likely regular aspirin users, such as patients with chronic arthritis and heart disease, and these cohorts showed protective effects for colorectal cancer.\textsuperscript{5} Two recently reported systematic reviews of randomized trials of long-term aspirin use support this large body of observational data.\textsuperscript{7,8}

From 1993 onwards, several reports found that the most important precursor lesion of colorectal cancer, namely colorectal adenoma, as well as metachronous adenomas, was in most studies associated with a significant risk reduction among regular aspirin users.\textsuperscript{5–7} Rodent models of chemically induced colon cancer also showed the significant protective effect of aspirin administration, and in a review conducted in 1997 by the International Agency for Research on Cancer, the expert panel concluded that ‘…in experimental animal models there is sufficient evidence for the prevention of colon cancer by acetylsalicylic acid’.\textsuperscript{4,5} Regarding mechanisms of action, aspirin possibly acts as a colorectal tumour chemopreventive agent using several biological mechanisms, of which anti-proliferative activity, increased apoptosis and anti-angiogenesis are the most prominent, and these mechanisms operate mainly through cyclooxygenese-2 inhibition, to some extent through cyclooxygenese-1 inhibition and also through other mechanisms that are probably independent of cyclooxygenese activity.\textsuperscript{4,5}

Collating all this evidence, the picture that emerges is a likely causal relationship between regular aspirin use and colorectal tumour protection, an evidence that largely satisfies the classic criteria of causality enunciated by Sir Austin Bradford Hill in 1965.\textsuperscript{9} There is some epidemiologic evidence which suggests, albeit so far not convincingly, that regular aspirin use may have a protective effect against tumours other than colorectal, with most of this evidence pointing to cancers of the breast and oesophagus, some evidence present for lung and ovarian cancer, whilst largely null effects were found for cancers of the pancreas, prostate, bladder, kidney and also for lymphomas and leukaeamias.\textsuperscript{6} Also of interest is a recently published research study that indicates that there may be subgroups of individuals in whom the aspirin effect as a colorectal tumour chemopreventive is modified. Thus, aspirin may be more effective in preventing metachronous colorectal adenomas in those who are overweight or obese when compared with those with normal weight.\textsuperscript{10}

Functional variant genotypes, such as that in the UGT1A6 enzyme, show a significantly reduced risk of colorectal adenoma with aspirin use when compared with the wild-type genotypes, suggesting that genetic polymorphism can significantly modify the effect of aspirin on colorectal tumour risk.\textsuperscript{11,12} Another line of recent investigation deals with the use of modified forms of aspirin in colorectal tumour prevention. Of particular interest has been the development of a nitric oxide-donating aspirin, which at least in experimental models inhibits colon cancer cell growth several hundred times more potently than does regular aspirin.\textsuperscript{13}

As the evidence mounted, to our satisfaction, that there was a likely causal relationship between regular aspirin use and colorectal tumour protection and that it may therefore be possible to prevent some colorectal cancers and possibly some other cancers also by the regular use of aspirin, several issues of concern were becoming increasingly evident, posing serious challenges to aspirin as a chemopreventive agent. During his acceptance speech for the Democratic Presidential nomination in July 1952, Adlai Stevenson said, ‘…there are no gains without pains…’. The three main challenges to regular aspirin use as a chemopreventive agent are the appropriate dosage, the duration of aspirin use to obtain a protective effect and the incidence of adverse events with prolonged aspirin use—three issues that are to some extent interrelated.

Neither the minimum nor the optimum dosage of aspirin that is effective in colorectal cancer chemoprevention has been clearly established. Most of the evidence, with one exception, suggests that low dose of 81 or 100 mg of aspirin used in cardiovascular chemoprevention is unlikely to be effective as a colorectal chemopreventive agent and that a dosage of at least 300 mg is needed to obtain a satisfactory protective effect.\textsuperscript{5,7,8,14–16} As discussed below, the issue with higher dosage of aspirin is that the rate of the most important adverse event in chronic aspirin administration, namely gastrointestinal (GI) haemorrhage, is probably a dose-related phenomenon.\textsuperscript{7,15,16}

The chemopreventive effects of aspirin are probably completely reversible; therefore, for effective chemoprevention, aspirin needs to be administered continuously for several years, with the most recent evidence suggesting at least 5 years, and more likely a decade.\textsuperscript{5,7,8,15,17} Both the high dosage and the necessity for such long duration of chemoprevention are likely to have a cumulative effect on the most important adverse event, GI haemorrhage.

Here it is assumed that the general contraindications to regular aspirin consumption, such as hypersensitivity to aspirin, bleeding disorders, peptic ulceration or asthma, have been excluded. GI haemorrhage is the most important adverse event of chronic aspirin consumption, although there is also a slightly increased risk of haemorrhagic stroke, but the latter will not be further considered. Unfortunately there has not been a carefully conducted randomized study extending over 10 years or longer of regular aspirin consumption of a daily dose of 300 mg and it is unlikely that such a study will be conducted in the future. Chronic aspirin users do have a higher rate of GI haemorrhage than do non-users, and after 2 or even 5 years of use in the dosage range of 175–325 mg of aspirin per day, this excess bleeding rate will occur in 1 of 100 persons, whilst another statistic puts it as 8 episodes of major GI bleeding for every 10,000 person-years of use.\textsuperscript{5,7,15,16} Of interest regarding GI bleeding is that the inclusion of vitamin C with aspirin in short-term studies of healthy, young volunteers showed a significant reduction in occult GI bleeding.\textsuperscript{18} This potentially important
finding with practical consequences that might lower the GI bleeding rate in chronic aspirin users has so far not been taken up as enthusiastically by aspirin producers as one would have expected. In a much broader sense, an accurate assessment of global benefit vs global risk of prolonged aspirin use in varying dosages is not at present available and remains an important task to be accomplished in the future.

Since 1988 it has been well established that the regular use of aspirin has a protective effect on both colorectal cancer and adenoma. Based on the evidence, the author believes that aspirin will have a role in colorectal tumour chemoprevention; however, much more work needs to be done before such an intervention can be put to widespread use. In particular, research needs to focus on the establishment of the appropriate target population for such an intervention, on the appropriate dosage of aspirin, on the duration of aspirin administration for effective protection, as well as on a global benefit vs risk assessment for chronic aspirin users. Other lines of research, such as the development of more active forms of aspirin, such as nitric oxide–releasing aspirin, and the minimization of GI haemorrhage, by the inclusion of vitamin C, are also likely to be important in defining the future role of aspirin as a chemopreventive agent. The author of this article is reminded of the Rabbinic Sage who said in the Talmud (Talmud Babli, Avot 2:21) ‘It is not thy duty to complete the work, but neither art thou at liberty to desist from it’.

References

10 Kim S, Baron JA, Mott LA et al. Aspirin may be more effective in preventing colorectal adenomas in patients with higher BMI (United States). Cancer Causes Control 2006;17:1299–304.