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Invited Review

The role of aspirin in preventing colorectal cancer

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Abstract

Background: Colorectal cancer (CRC) is one of the most common cancers in the developed world and is the second leading cause of cancer-related mortality in the UK and USA. Regular use of aspirin can reduce cancer incidence, recurrence, metastasis and cancer-related mortality.

Sources of data: Peer-reviewed journals, governmental and professional society publications.

Areas of agreement: There is a wide body of evidence from observational studies and randomized trials that aspirin reduces risk of CRC. There is a delay of several years between initiation and effect. There is interpersonal variation in aspirin metabolism but pharmacogenetic testing is not yet sufficiently sensitive or specific to justify routine use.

Areas of disagreement: There is uncertainty about the optimal dose and the duration of aspirin. There is debate around use for the general population but there is growing consensus on use in those at increased risk of developing cancer.

Growing points: Understanding is growing of the possible mechanisms by which aspirin exerts its anticancer effects. Large-scale meta-analyses are quantifying the cost–benefit ratio in the general population. International trials are underway to assess the optimal dose in high-risk individuals and the role of aspirin as an adjuvant in those who present with a malignancy.

Key words: colorectal cancer, aspirin, chemoprevention

Does aspirin reduces risk of CRC?

Acetylsalicylic acid is a non-steroidal anti-inflammatory drug (NSAID), which is used as an analgesic, antipyretic or prophylactic drug for cardiovascular diseases. It was first introduced into the market in 1899 by Bayer, registered under the name of 'Aspirin'. An estimated 10–20 billion tablets are consumed annually in the USA alone for cardiovascular diseases prophylaxis thus making it one of the most used drugs in the world.[1,2]

The first observational evidence favouring aspirin came from a Melbourne Case Control study which revealed a 42% reduction in risk of CRC in NSAID users.[3] This finding was supported by meta-analysis of 18 subsequent epidemiological studies which revealed a long term risk reduction of up to 41% in those randomised to aspirin but with significant variation between studies attributed to differing strategies of case selection.[4,5]

In the 1990s, two large-scale randomized controlled trials (RCTs) were launched involving aspirin as one of their interventions and with cancer as a primary endpoint. The US-based Women's Health Study allocated 39 876 healthy women to alternate day 100 mg aspirin or vitamin E versus controls with a 10-year follow-up. At publication in 2005 there was no evidence of a reduced cancer risk.[6] Following the subsequent publications reported below showing a delayed protective effect, the authors returned to the study population and discovered an 18% reduction in colorectal cancer (CRC) among the women who had taken the active aspirin (Fig. 1A).[7]

The second RCT had CRC as its primary endpoint; CAPP2 focused on people with Lynch syndrome, also known as hereditary non-polyposis colon cancer, which is caused by loss of function mutation in one of the mismatch repair genes. The first in the series of Cancer Prevention Programme (CAPP) trials had focused on adolescents with familial adenomatous polyposis. In CAPP1, 206 gene carriers were randomized to 600 mg aspirin or placebo and 30 g of resistant starch or placebo in a 2×2 factorial design with adenoma counts and size of the largest polyp as endpoints.[8] Aspirin reduced the size of the largest polyp in those who were in study for over a year but was not proven to have reduced the number of adenomas, though, their large number made analysis difficult.[8] Similarly, meta-analysis of adenoma prevention trials in those with a history of previous colonic neoplasia revealed a modest protective effect of regular aspirin use.[9]

The CAPP2 trial began recruiting in 1998 and extended to 43 centers in 16 countries.[10] One thousand and nine patients were randomized to either 600 mg daily aspirin or placebo and 30 g of a resistant starch, Novelose, for 2–4 years with a planned follow-up to 10 years. Analysis of adenomas and cancers at

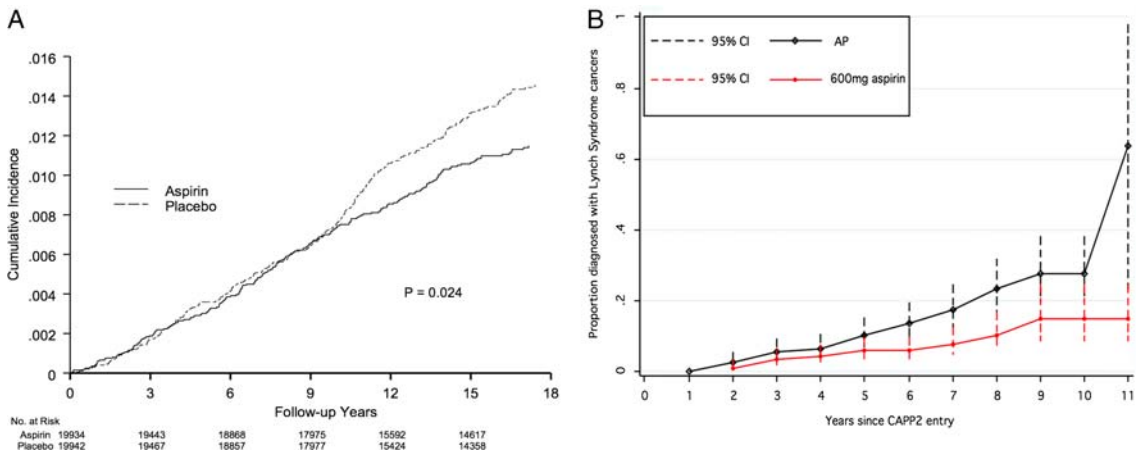

Fig. 1 RCT of aspirin versus placebo in (**A**) Women's Health Study and (**B**) CAPP2. Graphs depict incidence of CRCs in aspirin versus placebo group during the long-term follow-up of the two RCTs which included cancer as an endpoint. Figures reproduced with permission from Cook *et al.*[7] and Burn *et al.*[10]

the end of the intervention stage revealed no significant reduction in adenomas and a non-significant excess of major bleeding events (7 versus 5) offset by a reduction in probable occlusive events.[11] A subsequent report analyzed cancers across the cohort when the first recruits reached the planned 10-year follow-up mark giving a mean follow-up of 55.7 months for the group as a whole. Patients randomized to aspirin had risk reduction of up to 60% compared to placebo with a beneficial effect being seen for all cancer related to the genetic predisposition such as endometrial and upper gastrointestinal cancers (Fig. 1B).[10] The last of the CAPP2 recruits began treatment in 2006. The final analysis covering 10 years follow-up for the whole study population is now in preparation.

The 2011 CAPP2 report coincided with the culmination of major studies by Rothwell and colleagues.[12] Extended follow-up of over 25 000 people who had participated in the early cardiovascular trials showed a significant risk reduction in CRC and other cancers commencing around 5 years after the initial recruitment compared to the placebo groups.[12] Therefore, there is a strong evidence for aspirin in reducing CRC risk in both general and high-risk populations.

There is further evidence from observational studies and follow-up randomized trials that show reduced risk for distant metastasis in people with CRC by up to 70% and reduced risk for distant metastatic CRC by up to 50% who take aspirin regularly.[13] Allocation to aspirin treatment is also associated with reduced risk of death by 50% in people with adenocarcinoma without metastasis at initial diagnosis.[14] Several RCTs are now underway to validate the use of aspirin as an adjuvant, the largest of which is ADD-ASPIRIN coordinated by the UK Medical Research Council (www.addaspirintrial.org), which will compare daily 100 and 300 mg doses to placebo in a range of common cancers such as breast, colorectum, esophagus and prostate, among 10 000 people across centers in the UK and India.

What dose and duration of aspirin should be prescribed?

The CAPP2 trial showed the protective effect of 600 mg daily aspirin was apparent 5 years after randomization.[10] In contrast, the Women's Health Study showed 18% reduction in gastrointestinal cancers with the effect commencing 10 years post randomization in people who were randomized to 100 mg alternate day aspirin.[7] The dose-related adverse events in aspirin users are well documented so there is a clinical imperative to determine whether the difference in these studies is the result of the different doses employed or whether people with a hereditary predisposition are more responsive to the effects of aspirin. Support for the latter view comes from the recent observational study from the Colon Cancer Family Register. This very large-scale NIH funded observational study contains over 1800 people known to have Lynch syndrome.[15] Based on their self-reported use of NSAIDs, a recent report revealed a major protective effect: 75% risk reduction in those on aspirin, with an almost identical effect among those taking ibuprofen.[15]

In the review of trial participants by Rothwell and colleagues, there was evidence of a particular benefit in protection against cancers in the ascending colon, an area of particular risk in those with an inherited predisposition. While other factors may be at play in those who self-report aspirin use, there is a plausible argument that the high-risk people are more responsive to low dose aspirin and may see equivalent reduction in cancer with the lower safer doses of aspirin. The CaPP3 trial, which began recruiting in 2014, is a randomized trial in patients predisposed to Lynch syndrome where they will be randomized to either 100, 300 or 600 mg/day enteric coated aspirin for 2 years and compare CRC incidence and bleeding rates during the 5–10-year follow-up period (www.capp3.org).

Since aspirin is an anti-platelet agent, bleeding risk is its most important side effect. There is a relative increase in risk of hemorrhagic strokes by 32–36% and extracranial (mostly gastrointestinal) bleeds by 30–70% from baseline with low or standard dose aspirin treatment.[16] It is possible that the ~1 in 10 000 extra risk of intracerebral bleeding is in part related to unrecognized hypertension; aspirin does not cause such hemorrhage. Rather, it exacerbates the clinical impact of a burst vessel.

In the Hypertension Optimal Treatment trial, which examined different approaches to the management of high blood pressure, the 18 790 participants were also randomized to 75 mg/day aspirin or placebo.[17] There was no difference in the risk of hemorrhagic stroke or fatal complications but a clear excess of gastric bleeds in the aspirin group.[17]

There is a sharp increase in gastrointestinal bleeding risk beyond the age of 70 years. Data from the Nurses' Health Study show that the risk of gastrointestinal bleeding increases with increase in dose and duration of aspirin use.[16,18] Hence, it is imperative to carry out a study that will measure risk–benefit profile of prescribing low dose or high dose aspirin treatment in individuals at risk of CRC. There is clear evidence that *Helicobacter pylori* infection exacerbates the risk of gastric bleeds in aspirin users.[19] All people considering long-term aspirin prophylaxis should be investigated for occult infection. Therapy is not always effective so a second test after treatment is valuable.[20]

Cuzick and colleagues have examined the overall risk–benefit ratio for aspirin. Figure 2 summarizes the overall benefit. The cardiovascular benefits are offset by adverse events in a whole population approach involving treatment of 55–65 year olds. When the protective effect against cancer is factored in, however, the benefits are clear with an overall 4% reduction in mortality.[16]

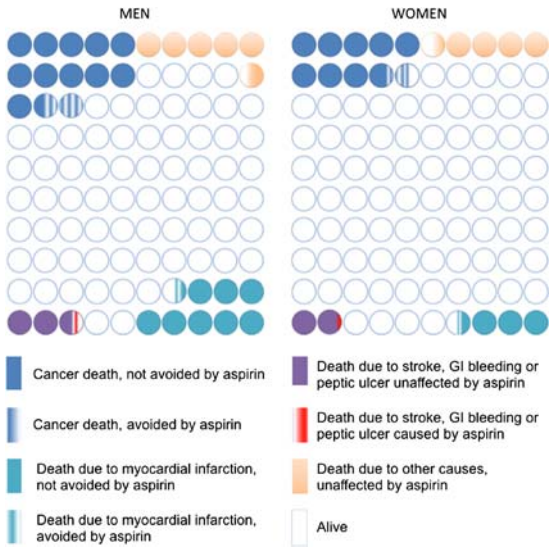

Fig. 2 Summary estimates of the risk–benefit ratio of long-term aspirin use starting at the age of 55 years, on death over the next 20 years in 100 average risk-men and women. Figure reproduced with permission from Cuzick *et al.*[16]

What is the biological mechanism behind aspirin's chemopreventive effect?

Several biological pathways have been proposed as the source of aspirin's chemopreventive effect. The primary target of aspirin is cyclooxygenase-1 (COX1) enzyme where it inhibits its enzymatic activity by blocking the access to the catalytic site, which in turn provides anti-platelet effect.[21] Experimental evidence suggests that cancer patients exhibit increased platelet activation, which in turn aids in tumor metastasis by protecting cells from immune surveillance and by helping in attaching tumor cells to the endothelial lining.[22] Thus reduced risk of metastasis observed in trials[13] could be, at least in part, a direct effect of inhibition of the COX1 isoform in platelets.

The second isoform of cyclooxygenase, COX2, is induced in response to pro-inflammatory and cell division stimuli in monocytes and epithelial cells. Its activity has been shown to be modified by aspirin in a dose-dependent manner[23,24] to produce lipoxins that are involved in resolution of inflammatory reactions rather than prostaglandin E2 that can cause resistance to apoptosis, cell migration and angiogenesis.[25,26] Thus, modification of the COX2 enzyme by aspirin leads to an anti-inflammatory response. It has been suggested that the reduced risk associated with aspirin is mediated through its impact on the common overexpression of COX2 in CRC tumors.[27]

In addition to the COX-dependent pathway, there is a growing evidence of the chemopreventive effects of aspirin through COX-independent pathways. To date, the only COX-independent target known to interact with aspirin is IκB kinase (IKK). *In vivo* and *in vitro* studies have shown that aspirin and salicylic acid, a primary metabolite of aspirin, inhibits IKK, which prevents activation of NF-κB thereby inhibiting proliferation and reducing inflammatory and

angiogenic responses.[28] However, another study showed activation and nuclear translocation of NF-κB in CRC cell lines that was induced by aspirin, which was followed by apoptosis.[29] The study also showed that this effect was specific to the cells of colonic origin only, thus suggesting a tissue-specific effect of aspirin on NF-κB signaling.[29,30]

Other chemopreventive mechanisms mentioned in the literature include nuclear caspase-dependent cleavage of Sp1, Sp3 and Sp4 specificity protein transcription factors induced by aspirin,[31] decrease in the ATPase and selective inhibition of DNA cleavage activity of topoisomerase IIα enzyme by salicylic acid,[32] inhibition of 6-phosphofructo-1-kinase activity by aspirin and salicylic acid,[33] and activation of polyamine catabolism by increasing expression and activity of spermidine N-acetyltransferase in colonic mucosa by aspirin.[34]

A 3-year interval between colonoscopies has been proven to be effective in Lynch syndrome in reducing cancers but the high frequency of 'interval cancers' prompted most clinical teams to use a 1–2 yearly interval.[35] It seems likely that many Lynch syndrome cancers emerge directly from dysplastic mismatch repair-deficient crypts rather than having a long 'adenoma' stage.[36] In CAPP2, the reduction in cancer incidence in those taking aspirin did not become apparent until around 5 years after commencement. This suggests that the aspirin is having its primary effect at a premalignant stage. The effect of aspirin in the Women's Health Study emerged after a decade and a similar delay is apparent across all studies.

In plants, salicylates are induced in response to infection in order to drive apoptosis, or programmed cell death, a form of 'scorched earth' defense.[37] It is plausible that aspirin is having a similar impact on the aberrant crypt stem cells that have lost the second allele of the mismatch repair gene mutated in the germline. Such depletion would explain the long delay between introduction of aspirin and the fall in cancer rates.[38] Furthermore, the dramatic fall in natural dietary salicylates with modern farming methods offers a further explanation of the emergence of CRC as a disease of the developed world.

The recent demonstration that the PD-1 blocker, pembrolizumab, can destroy mismatch repair-deficient cancers by 'unleashing' a massive T cell response,[39] taken together with the evidence of a beneficial impact of aspirin on premalignant lesions offers the intriguing possibility of a future cancer prevention strategy involving routine aspirin prophylaxis, supplemented by short episodes of immune 'disinhibition' in those with a genetic predisposition.

Should aspirin be prescribed as a prophylactic and/or adjuvant therapy?

As the case for routine use of prophylactic aspirin grows, so does the need to better understand the adverse events and whether it might be possible to 'personalize' the dose and perhaps avoid use in those most likely to suffer an adverse effect.

Several single-nucleotide polymorphisms (SNPs) have been identified in genes involved in aspirin metabolism or aspirin's mode of action that modulates its chemopreventive efficacy. For example, SNPs rs1105879 and rs2070959 in the *UGT1A6* gene, which is involved in aspirin metabolism, have been shown to have gene–environment interaction whereby, carriers of the SNP variant allele using aspirin had 34% risk reduction in adenoma formation compared to individuals with wild-type genotype.[40] A recent genome wide association study-based meta-analysis of 10 case-control and cohort studies as part of the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) identified SNP rs2965667 near *MGST1* gene which showed a significant gene–environment interaction whereby, 34% risk reduction for CRC was observed among aspirin and/or NSAID users with wild-type genotype but 89% increase in risk in individuals with the variant allele.[41] SNPs in other genes such as *ODC1, IL16* and *COX2* have been identified to modulate aspirin's efficacy.

Despite evidence for genetic variants being one of the sources of aspirin's variable efficacy, the relative effect on the risk of CRC or CRA has been modest and hence requires further studies to identify key genetic markers, which can be used in clinics to make an informed decision about the risk–benefit ratio for an individual.

A recent analysis of the CAPP2 trial data showed that there was 2.5-fold increase in risk of

developing CRC in overweight or obese patients who were genetically predisposed to Lynch syndrome.[42] In the subgroup analysis, the authors observed that the obesity-related excess risk of CRC was confined only to the placebo, whereas the risk was nullified in the aspirin group.[42] Hence, the authors suggested prescribing aspirin to overweight and obese patients at high risk of developing CRC. Results from the current CaPP3 dose inferiority trial would provide answer as to which dose of aspirin is likely to provide maximum chemopreventive effect with minimum risk of side effects.

Based on their extensive review of the evidence of risk and benefit of using aspirin in the general population, Cuzick *et al.* concluded that prophylactic use of 75–325 mg/day aspirin for a minimum of 5 years in the age range 55–65 would have a favorable risk–benefit ratio.[16]

Conclusion

There is overwhelming evidence that aspirin prevents cancer and probably also reduces the risk of recurrence when used as an adjuvant. There are still many questions around optimal dose and duration and the precise mechanism of action but such questions apply to many routine medical interventions. The net benefit in those at increased risk of CRC is now sufficient to justify formal recommendation of aspirin prophylaxis, supported by gastric acid suppression if needed and with care to exclude *H. pylori* infection and hypertension to minimize the risk of adverse effects. The recent decision by the UK Government to support efforts to facilitate repurposing of generic therapies will facilitate an early recognition of aspirin as the agent of choice in CRC prevention.

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Conflict of interest statement

John Burn has acted as a consultant for Bayer Pharma who manufacture aspirin.

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