

Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement

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Evidence clearly shows a chemopreventive effect for aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) on colorectal cancer and probably other cancer types; however, data on the risk–benefit profile for cancer prevention are insufficient and no definitive recommendations can be made. Aspirin has emerged as the most likely NSAID for use in chemoprevention because of its known cardiovascular benefit and available safety and efficacy data. Other traditional NSAIDs, particularly sulindac, and selective COX-2 inhibitors are now given to patients at high risk of colorectal cancer, although these drugs do not provide cardioprotection. More studies of aspirin and cancer prevention are needed to define the lowest effective dose, the age at which to initiate therapy, the optimum treatment duration, and the subpopulations for which the benefits of chemoprevention outweigh the risks of adverse side-effects. Although it might be possible to answer some of these questions with longer follow-up of existing clinical trials, randomised controlled trials with new study designs will be needed. Future projects should investigate the effects of aspirin treatment on multiple organ systems. Cancers of interest are colorectal, breast, prostate, lung, stomach, and oesophageal. The main side-effect of aspirin is peptic ulcers; therefore coadministration of aspirin with a proton-pump inhibitor is an attractive option and is under investigation in the AsPECT trial.

Introduction

Acetylsalicylic acid was first synthesised in 1897 by Felix Hoffmann and marketed by Bayer as Aspirin. After 100 years of use, new indications continue to be explored (figure 1).¹ At the fifth International Conference on Cancer Prevention in St Gallen, Switzerland (March 6–8, 2009), an international expert group met to assess evidence of the risks and benefits of aspirin and other NSAIDs as treatments to prevent cancer. Of the potential chemopreventive drugs for gastrointestinal cancer, aspirin was the only NSAID with sufficient efficacy and toxicity data to qualify for a risk–benefit analysis (except in very high-risk populations such as familial adenomatous polyposis). The panel planned to produce a consensus statement on the use of aspirin and other NSAIDs for cancer prevention; however, it became clear that gaps in our understanding of appropriate dose, duration, and age of use, would not support a formal risk–benefit analysis. Tables 1 and 2^{2–10} summarise current knowledge of the risks and benefits of aspirin. The focus of the meeting shifted to the identification of issues where further study is needed. The topics discussed by the panel and their conclusions are summarised in this Review.

Antitumour effect of aspirin and other NSAIDs

Much of the clinical evidence of a chemopreventive effect of aspirin is from epidemiological studies.^{2,11} Only one randomised controlled trial has specifically examined the effect of aspirin on the incidence of cancer in healthy people.¹² Three randomised trials that assessed outcomes from aspirin therapy have also reported cancer incidence, with a focus on colorectal cancer (table 3).^{12–17} Several randomised clinical trials have investigated the potential of aspirin to prevent colorectal adenomas—the presumed precursors of most colorectal cancers (table 3).^{12–17} Epidemiological evidence of a reduced risk of colorectal

adenomas with regular use of aspirin^{18–27} has been analysed in great detail.^{2,11,28} In this Review, we focus on the clinical implications of such evidence. NSAIDs delay or prevent colorectal and mammary carcinoma in animal models of tumorigenesis,^{29–34} but so far, no randomised clinical trials of aspirin or other NSAIDs have used cancer mortality as

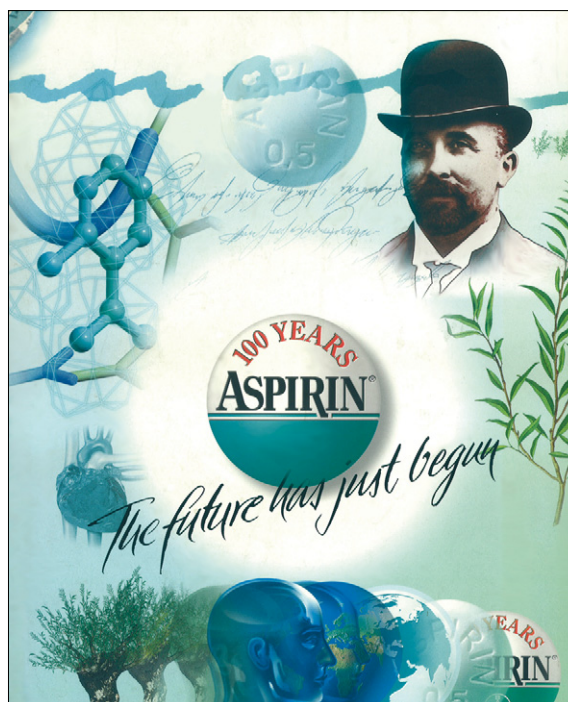


Figure 1: Aspirin was first synthesised by Felix Hoffmann in 1897. Since its initial use as an analgesic, aspirin has been proven beneficial for preventing myocardial infarction and stroke in high-risk individuals. Now the drug is being assessed for reduction of cancer risk at several sites including the colorectum, stomach, oesophagus, breast, ovary, and lung. Reproduced with permission from Bayer AG.¹

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	Number of studies	Number of participants	Relative risk ² (95% CI)	Risk (%) to age 74 (general population)*	Estimated absolute benefit† to age 74 (per 1000)
Colorectal cancer					
Case-control	11	9232	0.59 (0.54-0.64)
Male	4.64	19.0
Female	3.83	15.7
Cohort	7	5146	0.85 (0.78-0.92)
Colorectal adenoma					
Case-control	5	15 213	0.87 (0.77-0.98)
Male	30 ⁴	51.0
Female	25 ⁴	42.5
Cohort	2	1845	0.72 (0.61-0.85)
Oesophagus					
Case-control	2	643	0.41 (0.29-0.57)
Male	0.81	4.8
Female	0.33	1.9
Cohort	4	1118	0.83 (0.70-0.98)
Stomach					
Case-control	3	1557	0.67 (0.56-0.80)
Male	1.10	3.6
Female	0.41	1.4
Cohort	4	1376	0.93 (0.82-1.05)
Lung					
Case-control	2	1906	0.70 (0.56-0.88)
Male	6.69	20.1
Female	2.89	8.7
Male, current smoker	15.9 ⁵	47.7
Lifelong non-smoker	0.4 ⁵	1.2
Cohort	6	1003	0.96 (0.91-1.02)
Breast					
Case-control	6	13 822	0.80 (0.73-0.87)
Female	9.46	18.9
Cohort	12	14 738	0.94 (0.90-0.98)
Ovary					
Case-control	6	2896	0.82 (0.69-0.99)
Female	1.46	2.6
Cohort	2	449	0.98 (0.80-1.20)
Myocardial Infarction					
RCT high-risk patients ⁶	159	7602	0.74 (0.70-0.78)
RCT primary prevention ⁷	5		0.74 (NA)	14.0 (0.7% per year)	36.4
Pulmonary embolism					
RCT high-risk patients ⁶	32	350	0.75 (0.55-0.95)	2.0 (0.1% per year)	5.0
Hip or knee surgery ⁸	1	146	0.57 (0.40-0.82)

RCT=randomised clinical trial. NA=not available. *Baseline cancer rates are an average of US Surveillance, Epidemiology and End Results (SEER) white rates and rates in England⁹ or from sources cited; averages do not include important risk factors or dose effects. †Estimated potential benefit for cancer prevention (sex-specific) is based on relative risk from the case-control study.

Table 1: Estimated benefits of long-term (about 20 years) aspirin use in the general population

a primary endpoint. Studies of the mechanisms by which NSAIDs might inhibit carcinogenesis have not provided conclusive evidence of pathways or molecular targets that are clinically most relevant. The inducible cyclo-oxygenase isoenzyme, COX-2, is overexpressed in precursor lesions in breast (ductal carcinoma in situ), lung, and colorectum (adenomatous polyps).³⁵⁻⁴¹ Different NSAIDs can inhibit the activity of this enzyme to varying extents. Apart from COX-2 selective inhibitors (coxibs), most NSAIDs are non-selective and inhibit both COX-2 and the constitutively expressed isoenzyme COX-1.⁴¹ Most cancers progress through the action of multiple pathways that include COX-2, Wnt- β -catenin, MAP kinase, cytokine, and growth-factor signalling. Drugs that simultaneously block several pathways might be particularly effective as chemopreventive agents, if the clinical benefits outweigh the toxic effects. Some laboratory evidence suggests that aspirin works through several pathways.⁴² Further assessment of clinical endpoints will take place in the AspECT trial.⁴³

Most epidemiological studies report an inverse association between the use of NSAIDs and incidence of colorectal cancer or disease-related death;^{2,11,18,21,26,28,44-53} only one cohort study reported a positive association.⁵⁴ Both cohort and case-control studies indicated that incidence of colorectal cancer is about 40% lower in people who take NSAIDs regularly than in those who do not. Such a reduction in cancer incidence in the general population would be an important achievement for public health. In Western Europe and North America, risk of colorectal cancer before age 75 is about 4-5% in men and 2.5-3.5% in women.³ The dose and duration of treatment with NSAIDs are not well defined in most reports. Retrospective and prospective studies show reductions in incidence and size of adenomatous colorectal polyps with the use of NSAIDs^{13,15,17,19-21} and coxibs.^{55,56} Despite the consistency of this evidence, there are unresolved questions about the lowest effective dose and duration of NSAID treatment needed to achieve a meaningful reduction in cancer risk.

Not all data support a chemopreventive effect of aspirin. No preventive effect, for any cancer, was seen in two randomised controlled trials with 5-year and 10-year interventions. In the Women's Health Study,¹² 39 876 healthy women, aged at least 45 years, were randomly assigned to receive either aspirin (100 mg) or placebo every other day for an average of 10 years. This large, long-term study found that aspirin had no effect on the incidence of any specific cancer.¹² The Physicians' Health Study¹³ included 22 071 male physicians randomly assigned to receive aspirin (325 mg) or placebo on alternate days. No reduction in the incidence of colorectal cancer was seen in the intervention group versus the control group after 5 years of treatment.¹³ This null finding was confirmed in a subsequent analysis of the same study after a follow-up of 12 years.⁵⁷ In addition, the CAPP2 investigators⁵⁸ recently reported no protective

effect of 600 mg of enteric coated aspirin in a randomised clinical trial involving 1071 carriers of Lynch syndrome—the hereditary syndrome that predisposes individuals to a range of cancers, particularly colorectal and endometrial—despite therapy for up to 4 years (relative risk 1.0; 95% CI 0.7–1.4).

The results from the Women's Health and Physicians' Health randomised trials are difficult to reconcile with epidemiological and preclinical data, or with results from trials studying adenomatous polyps, unless the chemopreventive benefits of aspirin become apparent only after more than 10 years of treatment. Long-term follow-up of the British Doctors study, the UK Transient Ischaemic Attack study, and several observational studies suggest that a 10-year delay is plausible with respect to chemoprevention of colorectal cancer.¹⁴ Whether the duration of aspirin use or the duration of follow-up is more important to see an effect remains unclear. The 5-year duration of randomised treatment in the Physicians' Health Study, and the 10-year treatment and follow-up in the Women's Health Study are not long enough to answer this question. A further report from the CAPP2 trial is expected later this year. No trials of aspirin, either for chemoprevention or other use, have continued randomised treatment beyond 10 years.

On the basis of available evidence, the consensus panel regarded the antitumour effect of aspirin and sulindac as “very probable”, but that of other NSAIDs as “possible” because of the paucity of specific data on these drugs.

Risk–benefit ratio of aspirin and other NSAIDs

The side-effects of NSAIDs are well documented and are, for the most part, attributed to inhibition of COX activity. The risk of bleeding associated with use of aspirin results from inhibition of COX-1 activity in platelets, which prevents aggregation. Aspirin-induced bleeding predominantly involves the gastrointestinal and genitourinary tracts, but can cause intracranial haemorrhage in rare cases. High doses of aspirin and other non-selective COX-2 inhibitors block the production of prostaglandin E2 in gastric epithelium and increase the risk of gastric ulceration and bleeding. Similarly, high doses of coxibs and non-selective NSAIDs inhibit prostacyclin production by COX-2 in vascular endothelium, increasing the risk of thrombotic cardiovascular events in some people. The risk of serious gastrointestinal bleeds over 10 years increases from about 1% in untreated individuals to about 2–3% in those who take regular aspirin.¹⁰ This risk increases with age⁵⁹ and dose.^{60,61} The incidence of gastric or duodenal ulcers as a result of NSAID use increased linearly from about 10% in those younger than 45 years to 25% in those older than 75 years.⁵⁹ By comparison, the incidence of bleeding events increased from about 1% to 6% for people in the same age-groups who took a placebo. Cranial haemorrhage is much rarer and accurate risk estimates are not available, in part because

	Number of studies	Number of participants	Relative risk ² (95% CI)	Risk (%) to age 74 (general population)*	Estimated excess absolute risk to age 74 (per 1000)
Serious gastrointestinal bleed³					
Case-control	6	6146	2.2 (2.1–2.4)	2.0 (0.1% per year)	24
Cohort	11	5994	3.1 (2.8–3.3)		
Gastric/duodenal ulcer					
RCTs ¹⁰	24	1294	1.68 (1.51–1.88) No relation with dose	12.1 (1.42% over 28 months)	82.3
Occlusive stroke					
RCT high-risk patients ⁶	158	3192	0.70 (0.65–0.76)		
RCT primary prevention ⁷	4	597	1.03 (0.87–1.21)	6.0 (0.3% per year)	1.8
Haemorrhagic stroke					
RCT high-risk patients ⁶	158	579	1.22 (1.03–1.44)		
RCT primary prevention ⁷	4	85	1.36 (0.88–2.1)	0.8 (0.04% per year)	2.9

RCT=randomised clinical trial. *Baseline cancer rates are an average of US Surveillance, Epidemiology and End Results (SEER) white rates and rates in England³ or from sources cited; averages do not include important risk factors or dose effects.

Table 2: Estimated risks of long-term (about 20 years) aspirin use in the general population

it is difficult to distinguish cranial haemorrhage from occlusive cerebrovascular events, which are reduced by aspirin. Standard contraindications for the use of aspirin include previous history of gastrointestinal ulcers, bleeding disorders, and allergic reactions to the drug. Apart from these few indications, however, identification of the individuals most prone to adverse effects is not currently possible.

A specific benefit of aspirin over other NSAIDs is a lowered risk of occlusive cardiovascular events.⁶ Use of aspirin is widespread for the secondary prevention of myocardial infarction and ischaemic stroke in patients with pre-existing cardiovascular disease and for primary prevention in high-risk groups. Current indications for the prophylactic use of aspirin are based on cardiovascular risk and side-effects, but do not take into account other potential benefits. Prophylaxis is clearly indicated for individuals with a high risk of cardiovascular events but not for individuals with an average risk, for whom the benefit of aspirin treatment would be at least partially offset by the adverse effect of bleeding. Age further complicates the balance between risks and benefits. Risks of serious bleeding and gastrointestinal ulceration increase substantially after 60 years of age. Age-specific changes in the risk–benefit ratio of prophylactic treatment with aspirin to prevent premalignant lesions or cancer remain unclear.

Because of uncertainties about the minimum dose and duration of aspirin treatment needed to decrease cancer incidence, and the mixed beneficial and adverse effects on the cardiovascular and other organ systems, the panel concluded that further clinical studies were needed to assess the risk–benefit profile of NSAIDs.

	Duration of treatment (years)	Follow-up (years)	Number of participants	Number of cases	Relative risk* (95% CI)	Comment
Invasive colorectal cancer†						
Women's Health Study ¹²						
100 mg qod	10	10	19 934	133	0.97 (0.77–1.24)	Women aged ≥45 years
Placebo	10	10	19 942	136
Physicians' Health Study ¹³						
325 mg qod	5	12	11 037	173	1.03 (0.83–1.28)	Male physicians aged 40–84 years
Placebo	5	12	11 034	168
British Doctors Aspirin Trial ¹⁴						
500 mg	5–6	23	3429	92	0.70 (0.51–0.97)	Physicians aged ≤80 years, highest chemopreventive effect after 10–19 years of follow-up
No treatment	5–6	23	1710	64
UK Transient Ischaemic Attack Aspirin Trial ¹⁴						
300 mg or 1200 mg	1–7	23	1632	37	0.82 (0.49–1.38)	Age >40 years, history of transient ischaemic attack, highest chemopreventive effect after 10–19 years of follow-up
Placebo	1–7	23	817	23
Colorectal adenomas‡						
Baron et al 2003 ¹⁵						
85 mg	3	3	377	140	0.81 (0.69–0.96)	Recent history of colorectal adenomas
325 mg	3	3	366	160	0.96 (0.81–1.13)	..
Placebo	3	3	355	171
Sandler et al 2003 ¹⁶						
325 mg	1	2.5	259	43	0.65 (0.46–0.91)	History of colorectal cancer
Placebo	1	2.5	258	60
APACC Trial ¹⁷						
160 mg or 300 mg	4	1	126	38	0.73 (0.52–1.04)	History of colorectal adenomas
Placebo	4	1	112	46

qod=every other day. *Risk relative to placebo (reference) group. †Incidence of colorectal cancer in randomised primary prevention trials assessing aspirin. ‡Incidence of colorectal adenomas in randomised secondary prevention trials assessing aspirin.

Table 3: Incidence of colorectal cancer and adenomas in trials of aspirin for cancer prevention

Without a clear indication of the overall effects on health, evidence was deemed insufficient to make a recommendation on the use of aspirin or other NSAIDs for cancer prevention. Therefore, the panel sought to identify necessary research.

Research questions

Most of the physiological effects of aspirin and other NSAIDs are dose dependent. Low-dose aspirin (100 mg or less and possibly as low as 30–50 mg per day) reduces the risk of thrombotic cardiovascular events, with only a small increase in risk of bleeding. Low-dose aspirin selectively inhibits thromboxane synthesis in platelets that pass through the portal circulation. Only small amounts of the drug survive passage through the liver to reach the systemic circulation. High doses of aspirin and other NSAIDs reach the systemic circulation and inhibit prostaglandin E₂ production in gastric epithelium and prostacyclin synthesis in vascular endothelial cells. Because of its selective effect on platelets, low-dose aspirin prevents thrombotic cardiovascular events with minimum adverse effects in the gastric epithelium.

By contrast with low-dose aspirin for cardiovascular benefit, the optimum dose of aspirin for cancer prevention is not well defined. Baron and colleagues¹⁵ report that 81 mg might be more effective than 325 mg in preventing colorectal adenomas, whereas other data (largely observational) suggest that doses of 325 mg or more might be necessary to achieve the maximum chemopreventive effect.¹⁸ Two trials of aspirin doses of 100 mg and 325 mg every other day for prevention of colorectal cancer reported negative results;^{12,57} however, follow-up was less than 10 years. Two other randomised trials of 300 mg, 500 mg, or 1200 mg daily showed a decrease in cancer incidence compared with placebo.¹⁴ Uncertainties about the lowest effective dose for cancer prevention need to be resolved, because the incidence of peptic ulcers and bleeding increases with higher doses.^{60,61} Randomised clinical trials are needed to identify the best prophylactic dose for multiple endpoints.

Data suggest that aspirin should be taken for several years for substantial protection against cancer; however, whether it should be taken continuously or if stopping treatment after 10 years might have a continued benefit is

unclear. Two randomised studies reported a decrease in the incidence of colon cancer that lasted for more than 10 years after stopping of aspirin treatment.¹⁴ This effect was not seen in other (observational) studies.⁶² How long the carry-over effect will continue in trials of high-dose aspirin and whether low-dose aspirin will have a benefit in post 10-year follow-up are unknown. In view of the long follow-up time needed to answer both questions, priority should be given to continuing the follow-up of current trials of aspirin dose.

Observational evidence of a chemopreventive effect of aspirin and other NSAIDs has been reported for oesophageal, gastric, lung, breast, prostate, and colorectal cancer. Most of these cancers develop after age 60 years, but the best age to start NSAIDs for cancer prevention is unknown. Given the apparent delay in the chemopreventive effect of NSAIDs (about 10 years), optimum treatment might start at age 40–50 years. Most individuals who develop premalignant lesions do so in their 50s and 60s, several years before the appearance of cancer, so this age range might be the best time for cancer prevention. Additionally, because the risk of serious side-effects of aspirin increases steeply after age 60 years, long-term treatment before this age might be needed to avoid adverse effects.

Treatment of many people to prevent a few cancers is not an efficient approach to chemoprevention. In this context, even rare side-effects can adversely affect the overall risk–benefit profile. A better approach is to focus preventive interventions for individuals with a substantial risk of cancer. Although age, lifestyle, environment, and particularly a history of high-risk adenomas contribute to an individual's risk of cancer, genetic factors are likely to be important determinants. Additional molecular and genetic studies are needed to better identify individuals who are at risk of cancers that respond to aspirin treatment, and to identify those most likely to experience serious toxic effects. Advances in risk prediction will improve the overall risk–benefit profile of interventions.

A large body of evidence supports an antitumour effect of aspirin and other NSAIDs on colorectal cancer. Additionally, aspirin might also protect against oesophageal, gastric, lung, breast, and prostate tumours.^{2,52} Evidence in these organ systems is sparse and will need to be further assessed in large controlled trials. Trial design is a challenge because many studies of aspirin stop when cardiovascular efficacy is proven but before the duration of treatment is sufficient to assess cancer prevention.

A key factor in trial design is the duration of treatment and follow-up needed to find significant differences in the incidence of cancer between treatment groups. Long trial times and the large number of participants needed to achieve adequate power means that chemoprevention trials are expensive and laborious. Therefore, we should maximise insights from trials that already exist. In view of the delayed protective effect of

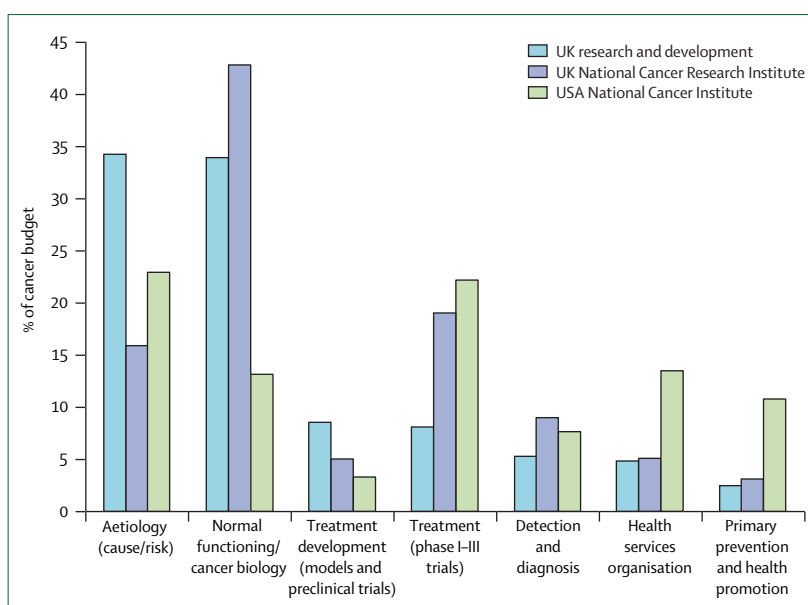


Figure 2: Categories of cancer spending (%) in the UK and USA
Adapted from a thesis by Jankowski J, Oxford University, 2007.⁶⁵

aspirin on colorectal cancer, and similar findings for tamoxifen on breast cancer,^{63,64} chemopreventive treatments might be most effective for premalignant lesions that progress over decades, so that lengthy follow-up is needed to see the full benefit of treatment. The proven benefits of aspirin for cardiovascular disease (although small for individuals at average risk) give it an advantage over other NSAIDs for further study of cancer chemoprotection. However, other NSAIDs such as sulindac also warrant investigation.

Trials of cancer prevention could be improved by better identification of individuals at high risk for tumours; a higher event rate would allow differences to be seen more clearly. Another challenge for this type of trial is the choice of a suitable endpoint. In clinical settings, the follow-up of precancerous lesions until cancer develops is unethical, so new approaches are needed. Assessment of colon cancer as an endpoint is nearly impossible in trials in which patients in both the control and intervention groups have endoscopic surveillance and removal of high-risk polyps. A study design with the identification of colorectal adenomas as an intermediate endpoint allows for smaller, shorter trials. If colorectal adenomas are the primary endpoint, however, only adenomas with a high risk for progression to cancer should be included as endpoints. More work is needed to reliably identify high-risk adenomas. By comparison with colorectal cancer, the identification of good surrogate markers for other cancers is at an even earlier stage, but mammographic density might be such an endpoint for breast cancer.

Another challenge in cancer prevention is the development of an infrastructure where high-risk individuals are identified and are given counselling and

Search strategy and selection criteria

This is not a comprehensive review of the literature, which is available in other reports.^{7,11,29} This paper is a focused discussion of the key outstanding issues. All relevant studies were identified by checking recent comprehensive reviews and in consultation with the panellists.

support to adopt prevention measures that are effective. Inadequate funding currently limits progress in cancer prevention (figure 2).⁶⁵ About 10% of cancer funding in the USA, and less than 5% in the UK, is spent on prevention. Within this small proportion, chemoprevention receives only 25%.

Conclusion

Only treatment with aspirin combines the benefit of protection against cardiovascular disease with the potential to reduce the risk of some types of cancer. Aspirin might eventually be useful for the primary prevention of some cancers in patients who already qualify for prophylactic antiplatelet therapy on the basis of cardiovascular criteria. Aspirin or other NSAIDs might also prove effective for secondary chemoprevention of gastrointestinal cancers in patients with no antecedent risk of gastrointestinal bleeding. Upper gastrointestinal bleeding, a common side-effect of aspirin therapy, is effectively prevented with a proton-pump inhibitor, so coadministration of aspirin and proton-pump inhibitors is an attractive option in this setting, and is currently being studied in the AsPECT study of esomeprazole and aspirin in patients with Barrett's oesophagus.^{43,66} Coxibs and other NSAIDs are unlikely to be useful for cancer prevention beyond their current use in young patients with familial adenomatous polyposis. Large-scale studies are needed to assess whether long-term aspirin treatment can prevent gastrointestinal and other cancers. Future studies should address outstanding questions about dose, the best age to begin treatment, and duration of therapy. Randomised clinical trials will be essential to establish the efficacy and safety of a clearly-defined treatment regimen.

Contributors

All authors participated in the panel discussion and supplied material for the manuscript. The manuscript was drafted by JC and FO and all authors contributed to the revision and final approval.

Conflicts of interest

FM is co-founder of Cancer Prevention Pharmaceuticals. JJ is a consultant to AstraZeneca. PHB receives funding for basic science from Lilly Pharmaceuticals. JAB is a consultant for Bayer.

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