

Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies



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Summary

Background Randomised trials have shown that aspirin reduces the short-term risk of recurrent colorectal adenomas in patients with a history of adenomas or cancer, but large trials have shown no effect in primary prevention of colorectal cancer during 10 years' follow-up. However, the delay from the early development of adenoma to presentation with cancer is at least 10 years. We aimed to assess the longer-term effect of aspirin on the incidence of cancers.

Methods We studied the effect of aspirin in two large randomised trials with reliable post-trial follow-up for more than 20 years: the British Doctors Aspirin Trial (N=5139, two-thirds allocated 500 mg aspirin for 5 years, a third to open control) and UK-TIA Aspirin Trial (N=2449, two-thirds allocated 300 mg or 1200 mg aspirin for 1–7 years, a third placebo control). We also did a systematic review of all relevant observational studies to establish whether associations were consistent with the results of the randomised trials and, if so, what could be concluded about the likely effects of dose and regularity of aspirin use, other non-steroidal anti-inflammatory drugs (NSAID), and the effect of patient characteristics.

Results In the randomised trials, allocation to aspirin reduced the incidence of colorectal cancer (pooled HR 0.74, 95% CI 0.56–0.97, $p=0.02$ overall; 0.63, 0.47–0.85, $p=0.002$ if allocated aspirin for 5 years or more). However, this effect was only seen after a latency of 10 years (years 0–9: 0.92, 0.56–1.49, $p=0.73$; years 10–19: 0.60, 0.42–0.87, $p=0.007$), was dependent on duration of scheduled trial treatment and compliance, and was greatest 10–14 years after randomisation in patients who had had scheduled trial treatment of 5 years or more (0.37, 0.20–0.70, $p=0.002$; 0.26, 0.12–0.56, $p=0.0002$, if compliant). No significant effect on incidence of non-colorectal cancers was recorded (1.01, 0.88–1.16, $p=0.87$). In 19 case-control studies (20 815 cases) and 11 cohort studies (1136 110 individuals), regular use of aspirin or NSAID was consistently associated with a reduced risk of colorectal cancer, especially after use for 10 years or more, with no difference between aspirin and other NSAIDs, or in relation to age, sex, race, or family history, site or aggressiveness of cancer, or any reduction in apparent effect with use for 20 years or more. However, a consistent association was only seen with use of 300 mg or more of aspirin a day, with diminished and inconsistent results for lower or less frequent doses.

Interpretation Use of 300 mg or more of aspirin a day for about 5 years is effective in primary prevention of colorectal cancer in randomised controlled trials, with a latency of about 10 years, which is consistent with findings from observational studies. Long-term follow-up is required from other randomised trials to establish the effects of lower or less frequent doses of aspirin.

Introduction

Colorectal cancer is the second most common cancer in developed countries, with a lifetime risk of 5%, and about 1 million new cases worldwide every year.¹ Most colorectal cancers develop from adenomas (the so-called adenoma-carcinoma sequence^{1,2}), and several randomised trials have shown that aspirin^{3–5} and cyclo-oxygenase-2 enzyme (COX-2) inhibitors^{6–8} reduce the recurrence of adenomas by about 40% in patients with previous adenomas or colorectal cancer. However, these trials had only 2–3 years follow-up and were therefore unable to establish any effect of aspirin or COX-2 inhibitors on colorectal cancer. The likelihood of malignant transformation of adenomas that develop despite aspirin or COX-2 inhibitors versus those that are prevented is uncertain. However, such information is important because, although up to 40% of people in developed countries have one or more colorectal adenomas by age 60 years, less than 10% of these adenomas progress to

cancer.⁹ Moreover, the secondary prevention of adenomas by short-term treatment with aspirin or COX-2 inhibitors cannot be assumed to be maintained on long-term treatment, nor can we assume that the same effect would be seen in primary prevention. Indeed, no effect of aspirin on diagnosis of colonic adenomas (2510 vs 2578, relative risk 0.97, 95% CI 0.92–1.02) was reported during an average of 10 years follow-up in the Women's Health Study randomised trial of low dose aspirin versus placebo.¹⁰

Long-term use of COX-2 inhibitors is not recommended because of adverse effects on vascular risk,^{11,12} but long-term treatment with aspirin is feasible in patients with or without vascular disease.^{13,14} Aspirin has been shown to reduce experimentally-induced colonic malignancies in animals,² and some observational studies have reported a reduced incidence of colorectal cancers in regular users of aspirin (or non-steroidal anti-inflammatory drugs [NSAID]),^{15–60} although there is substantial heterogeneity in apparent effect between studies,^{61,62} and the two most

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recent large cohort studies reported no effect.^{46,59} Experience with other observational risk associations has highlighted the need for randomised trials in proving causation,^{63,64} and two large trials of aspirin in primary prevention showed no effect on colorectal cancer during 10 years of follow-up.^{10,65} However, a latency of more than 10 years would be expected, considering that the delay between the initiation of development of an adenoma, the point at which aspirin is believed to act,⁹ and presentation of colorectal cancer is estimated to be 10–15 years.^{66,67}

We therefore studied the effects of aspirin on the subsequent incidence of colorectal cancers in two large randomised trials of aspirin versus no aspirin in which reliable post-trial follow-up data of more than 20 years were available. We also did a systematic review of relevant observational studies to assess whether, with appropriate stratification by duration and extent of exposure, findings for colorectal cancer were consistent with the randomised studies and, if so, what additional conclusions could be drawn about the likely effects of dose and regularity of aspirin, other NSAID, long-term continuous treatment, and the effect of age, sex, race, and family history, and site or aggressiveness of cancer.

Methods

Randomised trials

Two randomised trials of aspirin versus no aspirin began in the UK around 1980: the British Doctors Aspirin Trial⁶⁸ and the UK Transient Ischaemic Attack Aspirin Trial (UK-TIA trial).⁶⁹ The methods and results of these trials have been published previously.^{68,69} Sustained long-term post-trial follow-up was available for all cancers via the UK National Cancer Registry. Our follow-up study was approved by our institutional research ethics committee.

In the British Doctors Aspirin Trial, 5139 male doctors resident in the UK and born on or after 1900 were recruited in 1978 (N=4377) or 1979 (N=762). Eligibility required no contraindication to the use of aspirin, no regular aspirin use, and no history of peptic ulcer disease, stroke, or myocardial infarction. Randomisation (in a 2:1 ratio) was to daily aspirin (500 mg ordinary, soluble, or effervescent aspirin, as desired, or, if subsequently requested, 300 mg enteric coated aspirin) unless some contraindication developed, versus no aspirin unless some specific indication developed. Placebo tablets were not used. Treatment was to continue for 5–6 years (until 1984). All participants were asked to complete a brief questionnaire every 6 months about their health and their use of aspirin or other antiplatelet agents. At the end of the trial a further questionnaire was sent and was completed by 99% of all surviving participants. Participants were also flagged with the National Cancer Registry and the Office of the Registrar General, and all records of cancers and deaths were thereby obtained until 2001, 23 years after the study began (or until emigration from the UK).

The UK-TIA trial recruited 2449 patients from 33 centres in the UK and Ireland between 1979 and 1985 (median 1982).

Eligibility required a recent (usually within 3 months) transient ischaemic attack or minor ischaemic stroke, age older than 40 years, no history of major disabling stroke, and no aspirin intolerance, alcoholism, chronic renal failure, or peptic ulceration. Patients who already took aspirin regularly or who had severe non-vascular disease were excluded. Randomisation was to 1200 mg aspirin a day (two 300 mg aspirin tablets twice a day) versus 300 mg a day (two 150 mg aspirin tablets in the morning and two placebo tablets in the evening) versus placebo (two placebo tablets twice a day). Patients were followed up by a physician every 4 months until their death or the scheduled end of the trial in 1986. At each follow-up visit, data for adverse effects and compliance with the trial medication were recorded. Each patient was registered with the Office of the Registrar General and all death certificates were obtained until the end of 2005, again 23 years after the median entry date. We also obtained data for all incident cancers diagnosed during and after the trial from relevant cancer registries, which now cover the whole of the UK and Ireland. Data for cancer registration in England and Wales (2297 patients) and Scotland (62 patients) were available from the start of the trials. The Cancer Registry of Northern Ireland (79 patients) has been fully operational since May, 1994, and the Irish National Cancer Registry since January, 1994 (11 patients). Additional ethics approval was sought and granted for linkage with the cancer registries.

For long-term follow-up of both cohorts, all outcomes were coded according to the 9th or 10th revision of the International Classification of Diseases by medically qualified staff who were masked to treatment allocation: ICD9 (colon: 153, 1530–1539; rectum: 154, 1540–1541; carcinoma-in situ: colon—2303, rectum—2304) and ICD10 (colon: C180–C188; colorectal junction: C19X; rectum: C20X; carcinoma-in situ: colon—D010, colorectal junction—D011, rectum—D012).

All analyses were by intention-to-treat unless otherwise specified. The primary outcome was colorectal cancer. Other cancers were secondary outcomes. The two aspirin treatment arms in the UK-TIA trial were combined to increase statistical power and to give a 2:1 aspirin versus no-aspirin randomisation ratio in both trials. The effect of aspirin on the occurrence of colorectal cancers during the total period of follow-up was assessed in 10-year bands from the start of treatment in each trial individually and in the pooled sample, and as Kaplan-Meier cumulative incidence graphs.

The scheduled duration of trial treatment in the UK-TIA trial varied from 1 year to more than 7 years depending on date of randomisation, whereas the British Doctors Aspirin Trial randomised on just two specific dates and the scheduled treatment duration was exactly 5 or 6 years. To study the effects of comparable lengths of treatment in the two trials, we also analysed the subgroup of UK-TIA trial patients randomised before October, 1981, and who therefore also had a scheduled treatment duration of

5 years or more. The assumption that any effect of aspirin on colorectal cancer would be proportional to the duration of treatment was also tested in the whole UK-TIA trial population by comparing the effect of treatment in this subgroup with that in patients with a scheduled treatment duration of less than 5 years as a treatment duration–aspirin allocation interaction term in a Cox model. This analysis was also done with treatment duration as a continuous variable.

We assessed the effect of compliance with trial treatment by excluding patients who stated that they did not comply with treatment at more than half of their follow up assessments. For this analysis we excluded cancers occurring during the trial period to avoid any bias due to reverse causation (since the development of cancer could affect compliance). In the British Doctors Study, in which the control group did not take placebo pills, we also excluded from our analyses of outcomes non-compliant patients who were randomised to no aspirin but who had taken aspirin regularly for more than half of the 5–6 year trial treatment period.

To establish the latency of any effect of aspirin on colorectal cancer, we assessed the risk of cancer during 5 year periods of follow-up after the scheduled trial treatment period. Hazard ratios (HR) and 95% CI for diagnosis of colorectal cancer were calculated separately for each period in pooled data stratified by trial using Cox regression.

Observational studies

We did a systematic review of published observational studies of the association between use of aspirin or NSAID and risk of colorectal cancer. Studies were identified by two observers from PubMed, National Library of Medicine (last accessed on Dec 31, 2006) with the search terms: (“neoplasms” [MeSH Terms] OR cancer [Text Word]) AND (aspirin OR salicyl* OR “anti-inflammatory agents, non-steroidal” [MeSH Terms] OR “anti-inflammatory agents, non-steroidal” [Pharmacological Action] OR NSAID [Text Word]). We restricted the search to studies in people but had no language restriction. We searched the reference lists of all papers identified and any previous systematic reviews. We included cohort or case-control studies if they reported data for use of aspirin or NSAID and the risk of colorectal cancer. We excluded studies done in populations with specific pre-existing diseases (eg, rheumatoid diseases, polyposis coli).

Data were extracted by two independent reviewers (EF and PMR) for: study type (case-control or cohort), population (community or hospital-based, age, sex, race, time-period recruited, exclusions), control group and matching (case-control studies), length of follow-up (cohort studies), definition of regular use, main findings (including any stratification by dose, frequency and duration of use, age, sex, race, and family history of colorectal cancer), and effect of adjustment for age, sex, or other potential confounders in cohort studies.

We analysed data for both use of aspirin or NSAID combined and separately, where reported. Where several overlapping papers had been published on a single study, we used the most recent (and usually largest) analysis. Methods of determination of exposure (eg, interview, prescription data, etc) differed and definitions of regular use varied considerably between studies. We therefore based our initial analyses on the broadest definition of any use of aspirin, NSAID, or both, and then compared studies with similar definitions of regular use. For duration of previous use of aspirin or NSAID in case-control studies and in cohort studies, we aimed to use less than 10 years versus 10 years or more, if reported. We also extracted data for the most regular or longest duration reported in each study, which we termed maximum reported use (eg, 300 mg aspirin or more per day for 10 years or more).

For case-control studies, we calculated odds ratios (OR) for use of aspirin or NSAID in cases versus controls and pooled estimates by random-effects meta-analysis if overall heterogeneity between studies was $p < 0.1$, or by fixed-effects meta-analysis according to the Mantel-Haenszel method if $p \geq 0.1$. Heterogeneity was calculated by the χ^2 method.

In cohort studies, data were usually reported only as events per person-years of follow-up or as adjusted hazard ratios, or both, and so formal meta-analysis was not possible (or appropriate in view of the inevitable differences between users and non-users in crucial confounders such as age and sex). However, qualitative assessments could be made. All analyses were done in SPSS version 15.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study, and had responsibility for the decision to submit for publication.

Results

Randomised trials

5139 individuals (mean [SD] age 61.6 [7.0] years; 31% smokers) were randomised in the British Doctors Aspirin Trial and 2449 (mean [SD] age 60.3 [9.0] years; 73% male, 53% smokers) in the UK-TIA trial. All recruits to the British Doctors Aspirin Trial were treated for 5–6 years (mean 5.7, SD 0.89) and 99% of survivors completed a final questionnaire at the end of scheduled follow up in 1984.⁶⁸ Patients in the UK-TIA trial were treated for 1–7 years and all were accounted for at the end of the scheduled follow-up in 1986.⁶⁹ Subsequent national registration of cancers and deaths extended follow-up to a median of 23 years in both trials. Mean survival from randomisation was 18.0 (SD 6.5) years in the British Doctors Aspirin Trial and 14.4 (7.9) years in the UK-TIA trial.

Ascertainment of cancers was reliable. For example, of ten colorectal cancers identified during clinic follow-up in

	All patients				All patients allocated to aspirin for at least 5 years (ie, all British Doctors Aspirin Trial and first 937 patients in UK-TIA Aspirin Trial)			
	Placebo (N=2527)	Aspirin (N=5061)	HR (95% CI)	p	Placebo (N=2025)	Aspirin (N=4051)	HR (95% CI)	p
Colorectal cancer	87 (3.4%)	129 (2.5%)	0.74 (0.56–0.97)	0.02	77 (3.8%)	100 (2.5%)	0.63 (0.47–0.85)	0.002
All other solid cancers*	380 (15.0%)	800 (15.8%)	1.06 (0.94–1.20)	0.36	311 (15.4%)	642 (15.8%)	1.01 (0.88–1.16)	0.87
Oesophagus	15 (0.6%)	27 (0.5%)	0.90 (0.48–1.69)	0.75	13 (0.6%)	20 (0.5%)	0.76 (0.38–1.53)	0.44
Gastric	22 (0.9%)	44 (0.9%)	1.00 (0.60–1.66)	0.99	15 (0.7%)	31 (0.8%)	1.01 (0.54–1.86)	0.99
Pancreas	19 (0.8%)	39 (0.8%)	1.02 (0.59–1.76)	0.95	16 (0.8%)	35 (0.9%)	1.07 (0.59–1.94)	0.82
Bladder/urethra	43 (1.7%)	90 (1.8%)	1.04 (0.72–1.50)	0.84	40 (2.0%)	77 (1.9%)	0.94 (0.64–1.38)	0.76
Renal	10 (0.4%)	21 (0.4%)	1.06 (0.50–2.25)	0.88	7 (0.3%)	16 (0.4%)	1.11 (0.46–2.70)	0.82
Lung	81 (3.2%)	156 (3.1%)	0.97 (0.74–1.27)	0.82	57 (2.8%)	112 (2.8%)	0.96 (0.70–1.32)	0.79
Prostate	115 (5.0%)	232 (5.0%)	0.99 (0.79–1.24)	0.93	112 (5.8%)	201 (5.2%)	0.87 (0.69–1.10)	0.25
Breast†	10 (4.2%)	19 (4.5%)	1.09 (0.51–2.35)	0.82	5 (6.0%)	7 (4.2%)	0.90 (0.26–3.07)	0.86
Melanoma	7 (0.3%)	26 (0.5%)	1.85 (0.80–4.27)	0.15	7 (0.3%)	23 (0.6%)	1.62 (0.70–3.77)	0.26
Haematological cancers	64 (2.5%)	112 (2.2%)	0.87 (0.64–1.18)	0.37	50 (2.5%)	97 (2.4%)	0.95 (0.67–1.33)	0.75

*Excluding colorectal cancers and non-melanoma skin cancers. †UK-TIA Aspirin Trial only.

Table 1: Pooled analyses of data from the British Doctors Aspirin Trial and the UK-TIA Aspirin Trial on the effect of randomisation to a period of treatment with aspirin on the incidence of common cancers during a median of 23 years of follow-up

	Mean length of treatment/adjusted for compliance	0–9 years	10–19 years	All (including 20 years or more)
UK-TIA Aspirin Trial				
Allocated placebo (n=817)	4.0/3.1 years	8	15	23
Allocated treatment (n=1632): observed (expected) cancers	3.9/3.0 years	18 (16)	15 (30)	37 (46)
p		0.78	0.05	0.41
Hazard ratio (95% CI)		1.14 (0.49–2.61)	0.51 (0.25–1.00)	0.82(0.49–1.38)
British Doctors Aspirin Trial				
Allocated control (n=1710)	5.6/5.5 years	17	38	64
Allocated treatment (n=3429): observed (expected) cancers	5.7/4.0 years	28 (34)	50 (72)	92 (128)
p		0.52	0.05	0.04
Hazard ratio (95% CI)		0.82 (0.45–1.49)	0.64(0.42–0.97)	0.70(0.51–0.97)
Pooled				
Allocated control (n=2527)	5.1/4.7 years	25	53	87
Allocated treatment (n=5061): observed (expected) cancers	5.1/3.7 years	46 (50)	65 (106)	129 (174)
p		0.73	0.007	0.02
Hazard ratio (95% CI)		0.92 (0.56–1.49)	0.60(0.42–0.87)	0.74(0.56–0.97)

Table 2: Incidence of colorectal cancer in all patients in the UK-TIA Aspirin Trial and the British Doctors Aspirin Trial stratified into 10-year follow-up periods

the UK-TIA trial, all were subsequently identified by cancer registries or death certificates. Similarly, of the 50 colorectal cancers ascertained after the end of UK-TIA trial, 48 were identified via cancer registries and only two by death certificates alone.

Intention-to-treat analysis from date of randomisation showed a significant reduction in the incidence of colorectal cancer during follow-up (table 1). When follow-up was separated into 10-year periods, no reduction in incidence of colorectal cancer was seen in either trial during the first

10 years after randomisation, but there was a significant reduction in incidence during the second 10 years in both trials (table 2).

For risk of non-colorectal cancer, intention-to-treat analysis from date of randomisation showed no effect of allocation to aspirin either in the pooled analysis (table 1) or in each trial separately (British Doctors Aspirin Trial: 617 of 3429 vs 297 of 1710, HR 1.02, 95% CI 0.89–1.18, p=0.73; UK-TIA trial: 284 of 1632 vs 141 of 817, 1.04, 0.85–1.28, p=0.69), or when the pooled analysis was restricted to patients with scheduled trial treatment for 5 years or more (ie, when UK-TIA patients with shorter durations of treatment were excluded). Nor was any reduction in incidence seen for any individual non-colorectal cancer (all p≥0.25).

In the UK-TIA trial, there was a treatment duration–aspirin allocation interaction with an increase in effect of aspirin on risk of colorectal cancer with increasing duration of scheduled trial treatment (dichotomised at 5 years, p=0.004; continuous, p=0.009). To match the British Doctors Aspirin Trial comparison, we analysed the subgroup of UK-TIA trial patients (n=937) with scheduled treatment duration of 5 years or more. In both trials, allocation to aspirin for 5 years or more resulted in a significant reduction in incidence of colorectal cancer during long-term follow-up (figure 1): British Doctors Aspirin Trial HR 0.70, 95% CI 0.51–0.97, p=0.03; UK-TIA trial 0.29, 0.12–0.69, p=0.006; pooled sample (adjusted for study) 0.63, 0.47–0.85, p=0.002. The numbers of cancers in the two aspirin groups in the UK-TIA trial (300 mg daily vs 1200 mg daily) were too few to allow reliable comparison.

Compliance with randomised treatment was moderate during the British Doctors Aspirin Trial. During the first year after randomisation, 661 (19%) of the 3429 doctors

allocated to take aspirin stopped doing so, and a further 5% stopped during each of the next 5 years. In the group allocated to avoid aspirin, 2% began to use it (regularly or irregularly) every year, often because vascular disease had developed. Data for aspirin use after completion of the trials are not available. Compliance in the UK-TIA trial was better, but about 12% of patients stopped trial medication before the 4-month follow-up (although some restarted later), and 12% of patients randomised to placebo started taking non-trial aspirin at some stage during the trial. Figure 1 also shows, for both trials separately and pooled, the incidence of colorectal cancer from the end of the trial after exclusion of patients who were non-compliant at more than 50% of follow-up assessments during the trials. Cancers identified during the trial period are excluded to avoid potential bias (ie, if the development of cancer had affected compliance with treatment). The effect of aspirin on colorectal cancer was greater after exclusion of non-compliers in the British Doctors Aspirin Trial.

To establish the latency of the effect of aspirin on colorectal cancer, we studied 5-year periods of follow-up after the trials. Table 3 shows HR and 95% CI for incidence of colorectal cancer for each period in pooled data stratified by trial using Cox regression. There was no significant effect during 5–9 years after randomisation, but a substantial reduction in risk was seen 10–14 years after randomisation. This effect was increased after restriction to patients with 5 years or more of scheduled trial treatment and after exclusion of patients who were non-compliant at more than 50% of follow-up assessments during the trials (figure 2). No significant effect on colorectal cancer was seen more than 15 years after randomisation (table 2). There was also no reduction in risk of colorectal cancer in an alternative analysis of the period more than 10 years after the end of trial treatment for each patient (pooled HR 0.79, 95% CI 0.52–1.21, $p=0.33$).

Observational studies

Our electronic search yielded 7728 hits. We identified 249 potentially relevant articles from the abstracts and a further 21 articles after reviewing reference lists. Thus, 270 publications were reviewed in detail. Two publications were in Chinese and the rest in English. Of the 46 reports included here,^{15–60} 43 were identified independently by both reviewers.

For the case-control studies, we identified 31 publications describing 19 independent case-control studies of the association between aspirin or NSAID and colorectal cancer (webtable 1), which included data for more than 20000 cancer cases.^{15–45} All studies matched cases and controls for age and sex. For some studies, data were extracted from several different reports and so the number of studies quoted and numbers of references given do not always agree. One study reported a cohort study and a nested case-control study, both of which were included.^{44,45}

Although the definitions of use of aspirin or NSAID and the percentage of the control group defined as users

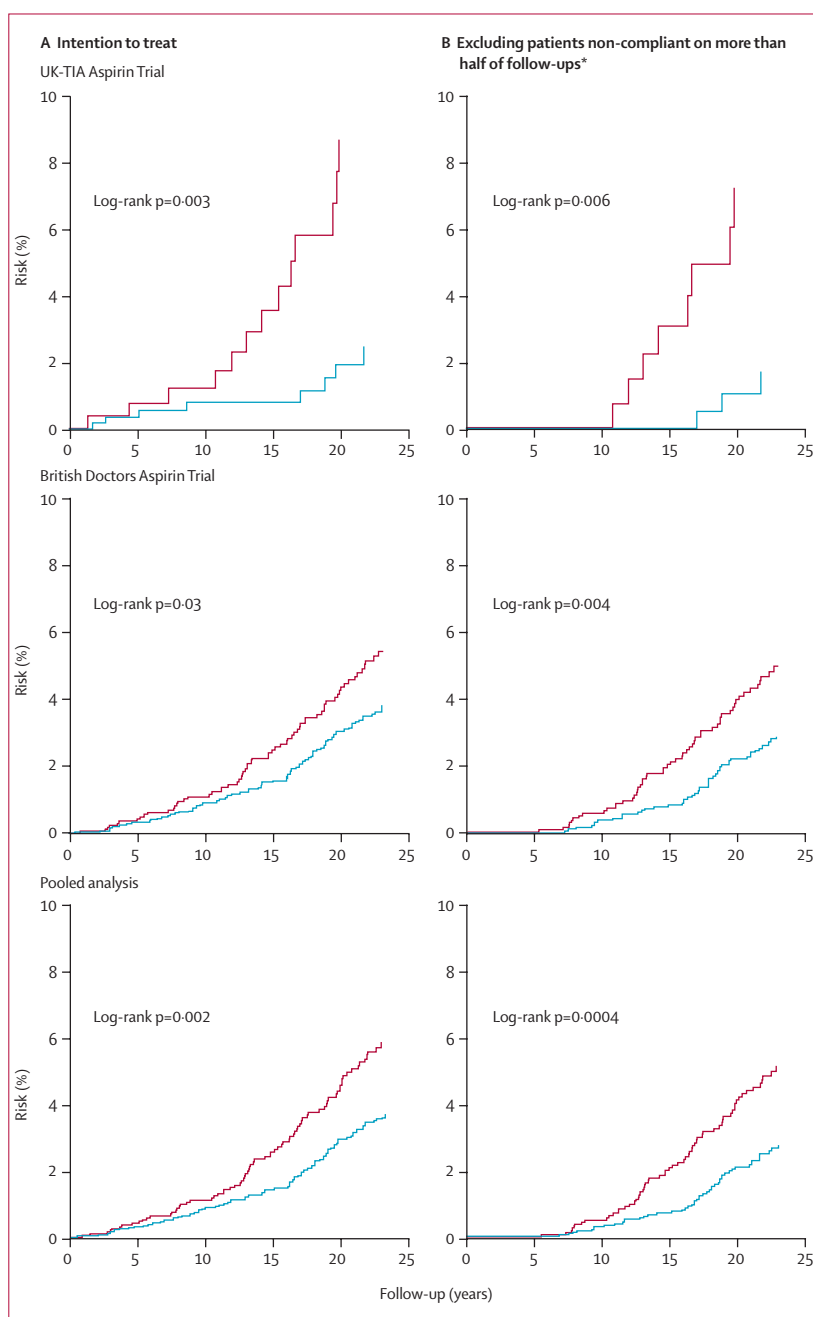


Figure 1: Risk of colorectal cancer in patients allocated aspirin (blue line) versus no aspirin (red line) during long-term follow-up of the UK-TIA Aspirin Trial and the British Doctors Aspirin Trial

For the UK-TIA trial analysis is restricted to patients with 5 years or more of scheduled trial treatment. *For analysis excluding non-compliant patients, cancers that presented during the trial are excluded.

varied greatly between studies (webtable 1), most indicated a reduced use of aspirin or NSAID (any use, irregular or regular) in cases (pooled OR 0.80, 95% CI 0.73–0.87, $p<0.0001$). However, there was substantial heterogeneity between studies ($p<0.0001$), with stronger associations in smaller studies (figure 3), and a strong inverse relation (weighted regression: $r^2=0.60$, $p=0.0002$)

See Online for webtable 1

	All patients	All compliant* patients	All patients with scheduled trial treatment of ≥ 5 years	All compliant* patients with scheduled trial treatment of ≥ 5 years
5–9 years†	1.08 (0.55–2.14) p=0.83	0.83 (0.38–1.80) p=0.63	0.93 (0.42–2.09) p=0.86	0.67 (0.25–1.78) p=0.67
10–14 years	0.51 (0.29–0.90) p=0.02	0.43 (0.23–0.79) p=0.007	0.37 (0.20–0.70) p=0.002	0.26 (0.12–0.56) p=0.0002
15–19 years	0.70 (0.43–1.14) p=0.15	0.67 (0.39–1.14) p=0.14	0.69 (0.42–1.15) p=0.16	0.66 (0.37–1.16) p=0.15
≥ 20 years	0.90 (0.42–1.95) p=0.79	0.85 (0.36–2.03) p=0.72	0.73 (0.33–1.63) p=0.45	0.65 (0.26–1.63) p=0.35

*Defined as those who were taking allocated trial treatment on at least 50% of follow-up assessments during the trials. †Excluding patients diagnosed with colorectal cancer during the trials. Numbers of colorectal cancers in each time period were: 42 (5–9 years); 49 (10–14 years); 68 (15–19 years); 18 (≥ 20 years).

Table 3: Hazard ratios (95% CI) for incidence of colorectal cancer in a pooled analysis (stratified by trial) of data from the British Doctors Aspirin Trial and the UK-TIA Aspirin Trial of long-term follow-up after the scheduled trial treatment period, stratified into 5-year periods after randomisation

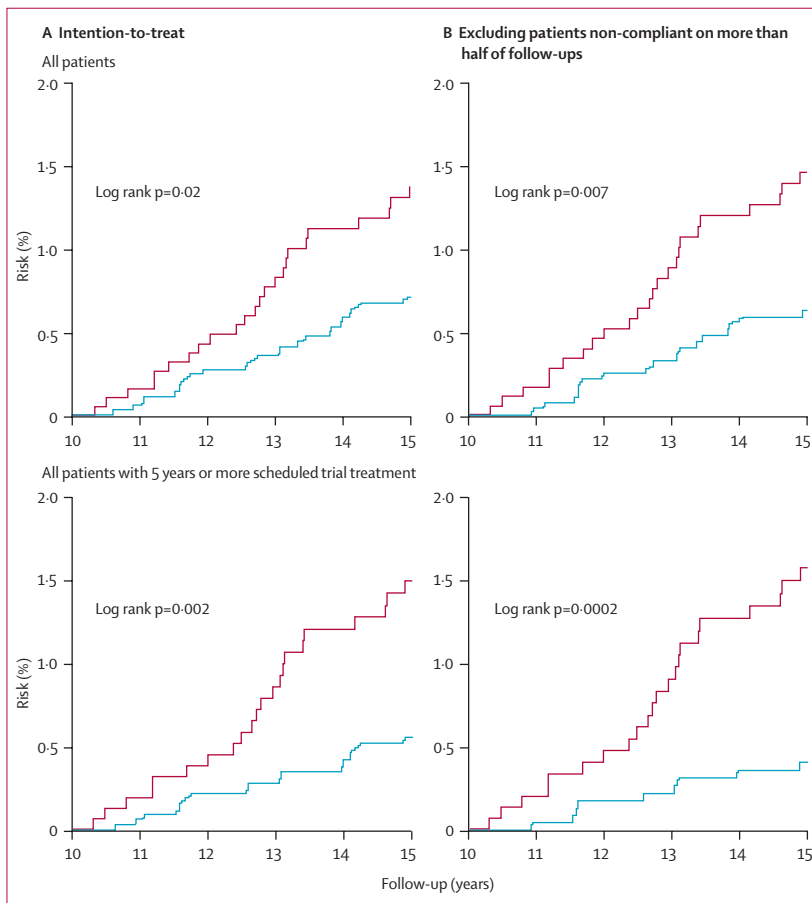


Figure 2: Risk of colorectal cancer 10–14 years after randomisation in patients allocated aspirin (blue line) versus no aspirin (red line) in a pooled analysis of data from the British Doctors Aspirin Trial and the UK-TIA Aspirin Trial

See Online for webtable 2 between the average of the proportion of cases and the proportion of controls defined as users and the relative use of aspirin or NSAIDs in cases versus controls. This inverse relation remained when analysis was confined to the 13 studies from the USA and Canada (weighted regression: $r^2=0.71$, $p=0.0003$)^{16–18,28,30,32–35,38,40,43,44} to reduce effects of genuine differences in background use and doses of aspirin or NSAID.

14 studies stratified analyses by the extent of use of aspirin or NSAID (webtable 1). The association of the maximum use reported (most regular or longest duration) was consistent in these 14 studies (OR 0.64, 95% CI 0.59–0.70, $p<0.0001$, heterogeneity $p=0.87$) and in all 19 studies (OR 0.59, 0.52–0.67, $p<0.0001$, heterogeneity $p=0.02$, figure 3), and was no longer related to the average of the proportion of cases and the proportion of controls defined as users ($r^2=0.10$, $p=0.18$). Eight studies looked specifically at irregular or occasional use of aspirin or NSAID and found no association with colorectal cancer (OR 1.01, 0.93–1.09, $p=0.87$, heterogeneity $p=0.05$).

Nine studies^{16,17,20,25,28,32,34,35,37} stratified analyses by duration of regular use of aspirin or NSAID—shorter duration: either less than 5 years or less than 10 years (OR 0.79, 95% CI 0.74–0.84, $p<0.0001$, heterogeneity $p=0.11$); or longer duration: either 5 years or more or 10 years or more (0.69, 0.63–0.76, $p<0.0001$, heterogeneity $p=0.21$). Five studies^{16,17,28,35,37} reported data for regular use for 10 years or more (pooled OR 0.60, 0.52–0.69, $p<0.0001$, heterogeneity $p=0.50$). Only 3.6% (range 3.3%–13.4%) of controls in these studies reported regular use for 10 years or more.

For the cohort studies, we identified 17 reports on 11 independent cohort studies of the association between aspirin or NSAID and colorectal cancer (webtable 2), which included 1136110 individuals with 5999 colorectal cancers during follow-up. Eight studies focused on aspirin alone.^{44–60} Data were usually reported as events per person-years of follow-up or as adjusted HR, and so meta-analysis was not possible. However, several observations could be made. First, results from all but two studies suggested a reduction in colon cancer with the maximum reported exposure (webtable 2). The two studies that noted no effect had only limited data for aspirin exposure, with no data for duration of use.^{51–54} Second, in most studies adjustment for age, sex, and other potential confounders did not weaken associations. Third, in all six studies in which analyses were stratified by duration of previous use of aspirin or NSAID, use for 10 years or more was associated with a larger reduction in subsequent risk of colorectal cancer than use for less

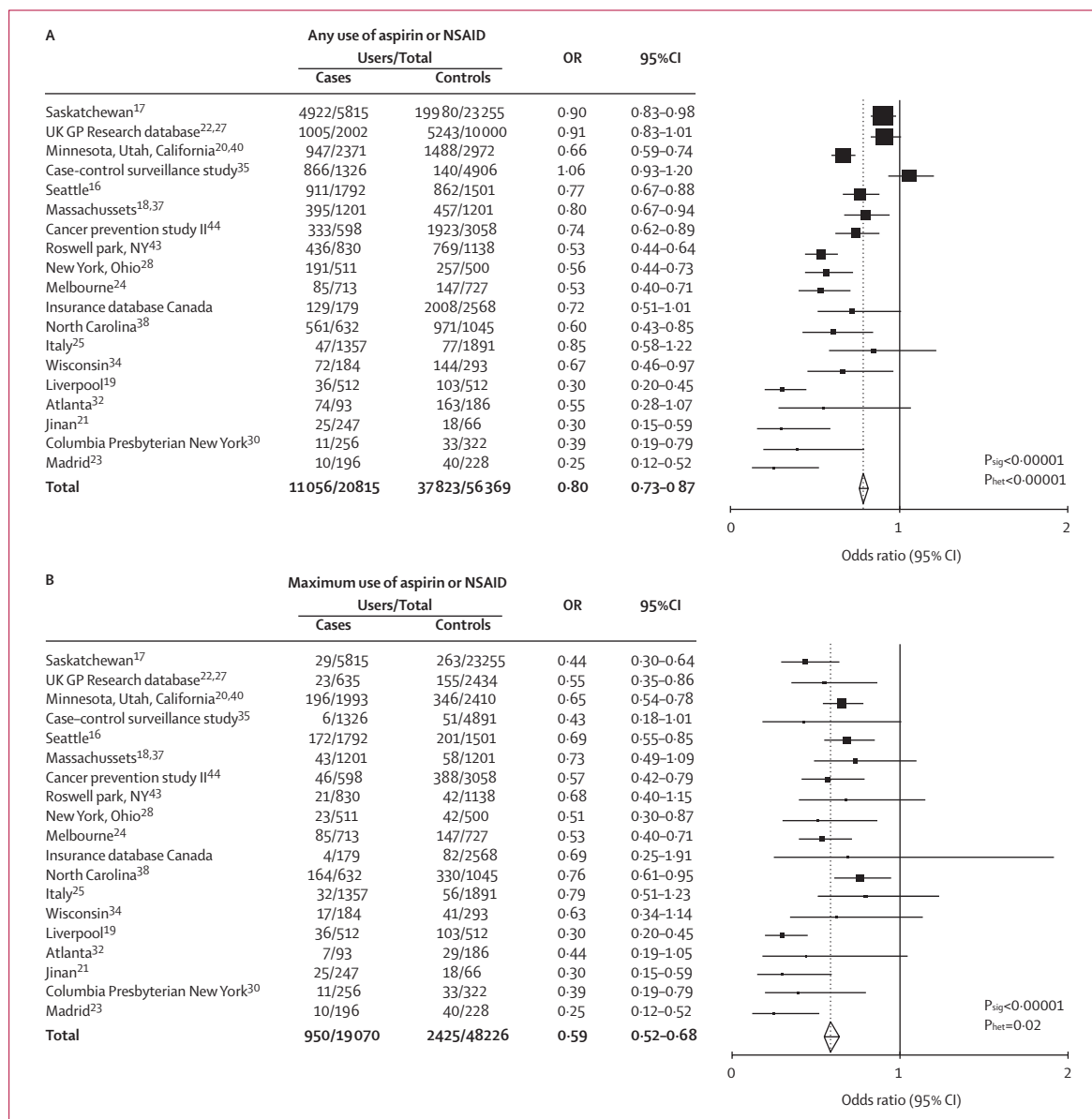


Figure 3: Relative use of aspirin or NSAID in cases of colorectal cancer versus age and sex matched controls in 19 case-control studies for (A) any use of aspirin or NSAID and (B) maximum reported use of aspirin or NSAID. Studies are ordered by the inverse of the variance of the odds ratio in (A).

than 10 years.^{46-50,57,59} In the three studies in which data for duration of use were reported in more detail, there was no clear effect until after 10 years of use (webtable 2).^{46,47,50}

For the secondary analyses, associations did not differ systematically between studies in North America (13 case-control studies;^{16,17,20,28,30,32-35,37,38,43,44} nine cohort studies^{44,46-48, 51,54,58,59,60}) and studies done elsewhere, by year of publication, or by setting (hospital-based *vs* population-based). There were no consistent differences in the above associations for colon cancer versus rectal cancer (nine case-control studies;^{17-19,21,22,25,26,35-37,40,41,43} four cohort studies^{47,49,50,58,60}), by site of colon cancer (five case-control

studies;^{19,20,28,35,37} four cohort studies^{47,50,58,60}), by aggressiveness (fatal or metastatic) of cancer (four case-control studies,^{22,28,37,38} three cohort studies^{44,47-49,57}), by sex (ten case-control studies;^{17,18,20,22,24,25,28,29,35,38,42,43} four cohort studies^{44,45,50,51,54,55,57}) between single-sex studies (men: one cohort study;⁴⁸ women: one case-control study,³⁴ two cohort studies^{47,49,58}), by race (two case-control studies^{20,38,39}), or by family history of colorectal cancer (two case-control studies;^{18,20} one cohort study⁴⁷). Also, effects did not change systematically with age.^{18,20,22,35-37}

Eight case-control studies assessed regular use of aspirin and NSAID separately,^{21,22,24,33,34,37,38,40} and found similar associations with colorectal cancer: aspirin alone

OR 0.75, 95% CI 0.63–0.88, $p=0.0004$, heterogeneity $p=0.02$; NSAID alone 0.70, 0.58–0.83, $p<0.0001$, heterogeneity $p=0.05$.

Several case-control^{28,43} and cohort studies^{44,45,47,50,57,58} reported stronger associations with increasing numbers of doses of aspirin or NSAID per week and with daily use. Several other studies reported similar dose-response effects.^{17,31,32} Three case-control studies also reported the apparent effect of daily aspirin stratified by dose:^{22,33,37} one found no association for 75 mg or 150 mg daily, but a significant 40% relative odds reduction for colorectal cancer with 300 mg daily;²² one reported no significant difference across five dose categories ranging from less than 162.5 mg a day to 650 mg or more a day,³⁷ but noted a significant association (OR 0.68, 0.53–0.88, $p=0.003$) only for 325 mg or more a day; and one reported a strong association of NSAID with both colorectal cancer and adenoma, but no significant association with aspirin in patients on mainly 75 mg a day.³³

Three cohort studies reported some dose-response data for aspirin use.^{46,47,50} Chan and colleagues⁴⁷ reported a 53% relative risk reduction in colorectal cancer in patients taking aspirin 325 mg more than 14 times a week, a smaller association for 6–14 times a week, and no overall association for less than six times a week, although a reduction was seen with two to five a week for 10 years or more. Larsson and colleagues⁵⁰ mainly studied use of aspirin 500 mg and only report a reduction in colorectal cancer with more than six tablets per week. Allison and colleagues⁴⁶ reported a trend towards a reduction in colorectal cancer with aspirin use for more than 10 years, but this was not further stratified by aspirin dose.

Discussion

The randomised studies provide good evidence that at least 300 mg aspirin a day for about 5 years is effective in the primary prevention of colorectal cancer, with a 10-year latency of effect that is consistent with the apparent effects in the observational studies and with our understanding of the adenoma-carcinoma sequence.^{1,9,66,67} The greater effect of aspirin allocation on incidence of colorectal cancer in the double-blind placebo controlled UK-TIA trial than in the open-label British Doctors Aspirin Trial would be expected on the basis of the high rates of non-compliance with trial treatment in the British Doctors Aspirin Trial. Given the evidence of a latency of the effect of aspirin of about 10 years in both trials and in the observational studies, the best estimate of the effect on colorectal cancer that would be expected from continuous long-term aspirin use is therefore the effect 10–14 years after randomisation in patients who had scheduled trial treatment for 5 years or more and who were reasonably compliant (pooled HR 0.26, 95% CI 0.12–0.56, $p=0.0002$, table 3, figure 2).

We had no data for the use of aspirin after completion of the trials. However, no continued difference in aspirin use between treatment groups would be expected after

the UK-TIA trial because neither patients nor physicians were told what the randomised treatment allocation had been. Thus, the reduction in colorectal cancer after 10 years follow-up in the UK-TIA trial (ie, about 5 years after the end of scheduled trial treatment) can only have been due to a delayed effect of the previous trial treatment. By contrast, some difference in aspirin use between the randomised treatment groups is likely to have been maintained in the British Doctors Aspirin Trial, which was not blinded. This continued difference in aspirin use could explain the trend towards a reduction in risk of colorectal cancer 15 years after randomisation (table 3), which was most marked in the British Doctors Aspirin Trial, although this could simply indicate variation between individuals in the latency of the effect of aspirin.

The randomised studies had some potential limitations. First, neither trial was designed to study colorectal cancer. However, data for cancers were obtained during both trials, and we were fortunate that reliable long-term follow-up was possible via the UK cancer registration system. Studies of this registration system have documented high rates of ascertainment and accuracy for cancer in general,^{70,71} and for colorectal cancer specifically.^{72,73} Moreover, under-ascertainment of cancers would, if anything, have attenuated any treatment effect and would not have introduced any systematic bias. Second, treatment allocation in the British Doctors Aspirin Trial was not blind. However, diagnostic bias is unlikely to have arisen in the 1970s and 1980s when there was little to suggest that aspirin had any effect on cancer. Moreover, any diagnostic bias would have tended to increase diagnosis of gastrointestinal cancers in the aspirin treated groups during the trial because of the likely increased rate of upper and lower gastrointestinal imaging in the investigation of adverse effects—eg, anaemia, bleeding, dyspepsia, and constipation—which were more common in the aspirin treatment groups.^{68,69} Low rates of colonoscopy in the UK in the early 1980s mean that bias is unlikely to have arisen due to excess removal of polyps from the aspirin groups during the trials. Similarly, any bias due to the small reduction in risk of fatal cardiovascular events on aspirin would have tended to increase the likelihood of survival to diagnosis of any cancer. Third, the trials predated colonoscopic screening, which might today have prevented some cancers.

Observational studies reported consistent associations between use of aspirin or NSAID and a reduced risk of colorectal cancer only when analyses were stratified by extent and duration of use, indicating the importance of detailed definition of exposure. The evidence of a duration-of-use effect in both case-control and cohort studies was consistent with the 10-year latency of effect in the trials, and those studies that stratified analyses by both regularity of use and duration of use reported 50–70% reductions in odds of colorectal cancer associated with use of medium-high dose aspirin for more than 10 years.^{17,44,45,47,57} Our use

of overall rates of use of aspirin in case-control studies as a surrogate marker for the likely rigorousness of definition and true extent of use might be appropriate in studies of other exposures. The initial finding of apparently stronger risk associations in smaller studies (figure 3), with a significantly asymmetrical funnel plot, might otherwise be misinterpreted as evidence of publication bias. Here, the finding seems to indicate a more discriminating definition of use of aspirin or NSAID in smaller studies.

Thus, the results of the observational studies were sufficiently consistent with the randomised studies to be used to address outstanding issues, and had sufficient statistical power to do so. The randomised studies had only 215 colorectal cancers during follow-up, whereas the case-control studies included data for more than 20 000 patients with colorectal cancer and the cohorts studies included more than 1 million individuals with nearly 6000 colorectal cancers during follow-up. First, we found that the effects of aspirin and NSAID seemed to be similar in terms of size and duration-of-use effect. There was also no evidence of any differences in effect between various individual NSAIDs. Second, there was no consistent difference in the apparent effect on colon cancer and rectal cancer and no difference in relation to the site of colon cancer, which is of relevance to the mode and frequency of screening and surveillance for adenomas. Third, the effect did not seem to differ in relation to age, sex, race, or country in which the study was done, although these are all factors that affect the rate of colorectal cancer.¹ Fourth, and of particular importance, the effect was present equally in individuals with and without a family history of colorectal cancer. Family history of colorectal cancer in a first degree relative increases life-time risk 2–4 fold and is one of the factors sometimes used to target colonoscopy screening.^{1,9,74} Fifth, there was no evidence of any lesser effect of aspirin in cases of particularly aggressive colorectal cancer or in studies confined to fatal cases. Finally, observational data suggest that long-term continuous treatment with aspirin or NSAID is not associated with a fall-off in benefit or a late rebound effect, with strengthening risk associations for use up to at least 20 years.^{47,50}

Our analysis of observational studies also suggested that for both aspirin and NSAID, daily use had most effect, with consistent evidence of an association with aspirin 300 mg daily, but diminishing associations with less frequent or lower doses. In the UK-TIA Aspirin Trial, we saw no evidence of greater protection with high-dose (1200 mg) versus medium-dose (300 mg), although the number of cancers was too small to draw reliable conclusions. Aspirin is thought to affect the development of tumours via inhibition of COX-2,^{1,75} which is found at high concentrations in colorectal neoplasia,⁷⁶ although there is also evidence that COX-1 inhibition might also be important.^{77,78} Inhibition of COX-2 requires higher doses of aspirin than does inhibition of COX-1.⁷⁹ The randomised trials of aspirin in secondary prevention of adenomas, the

findings of which might or might not extrapolate to effects on colorectal cancer, are conflicting with respect to dose of daily aspirin, showing variously that both 160 mg and 300 mg were effective,⁵ that 325 mg was effective,⁴ and that 81 mg a day was about as effective as 325 mg a day.³

Further follow-up of other large randomised trials of aspirin could help assess whether lower or less frequent doses, or both, protect against colorectal cancer. The Physicians Health Study (325 mg on alternate days for about 5 years in primary prevention) reported no effect up to 10 years after randomisation, but a non-significant trend towards a reduced risk was seen at 10–12 years.⁶⁵ The Women's Health Study (100 mg on alternate days for about 10 years in primary prevention) also found no effect during 10 years' follow-up.¹⁰ Although the dose of aspirin in the Women's Health Study could well be too low to affect the incidence of colorectal cancer, further follow-up is necessary. If higher oral doses of aspirin are most effective, further research on the direct local effects of low dose colonic-release preparations might be worthwhile.⁸⁰

We did not attempt to model the effect of the reduction in risk of colorectal cancer on the balance of risk and benefit of long-term use of aspirin. Such determinations will be complex and will need to be individualised, depending on the absolute risks of ischaemic vascular events, of bleeding complications, and of colorectal cancer. The incidence of colorectal cancer varies with age, sex, race, country, family history, and history of adenomas.¹⁹ Chemoprevention with aspirin might be cost-effective in certain high-risk groups, perhaps in combination with risk-based colonoscopic screening.^{9,74} However, further research is needed to establish the balance of risk and benefit in different clinical settings, with particular consideration of the substantial cumulative risk of major bleeding with long-term use of 300 mg or more of aspirin,^{81,82} the effectiveness of existing colonoscopic screening programmes,⁸³ and potential pharmacogenetic issues.⁸⁴

In conclusion, randomised trials show that regular use of at least 300 mg aspirin daily for about 5 years seems to be effective in the primary prevention of colorectal cancer with a latency of about 10 years. Observational studies show a negative association between colorectal cancer and regular use of aspirin (at least 300 mg) and other NSAID with the same latency as in the trials, with no heterogeneity in relation to clinical characteristics. Lower or less frequent doses of aspirin might be less effective, but long-term follow-up of randomised trials of low dose aspirin is needed.

Contributors

PMR conceived the study, planned and supervised the analysis, searched the published work, and wrote the paper. EF collated the data, searched the published work, did analyses, and commented on drafts of the paper.

Conflict of interest statement

PMR has received honoraria for talks, advisory boards and clinical trial committees from several pharmaceutical companies with an interest in antithrombotic agents, including Sanofi-BMS, Servier, Bayer, and

AstraZeneca. However, this study was completely independent of any pharmaceutical company or any other commercial interest. EF declares that he has no conflict of interest.

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The paper is dedicated to Richard Doll, who died shortly before the preliminary results were available.

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