

Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials



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Summary

Background High-dose aspirin (≥ 500 mg daily) reduces long-term incidence of colorectal cancer, but adverse effects might limit its potential for long-term prevention. The long-term effectiveness of lower doses (75–300 mg daily) is unknown. We assessed the effects of aspirin on incidence and mortality due to colorectal cancer in relation to dose, duration of treatment, and site of tumour.

Methods We followed up four randomised trials of aspirin versus control in primary (Thrombosis Prevention Trial, British Doctors Aspirin Trial) and secondary (Swedish Aspirin Low Dose Trial, UK-TIA Aspirin Trial) prevention of vascular events and one trial of different doses of aspirin (Dutch TIA Aspirin Trial) and established the effect of aspirin on risk of colorectal cancer over 20 years during and after the trials by analysis of pooled individual patient data.

Results In the four trials of aspirin versus control (mean duration of scheduled treatment 6.0 years), 391 (2.8%) of 14 033 patients had colorectal cancer during a median follow-up of 18.3 years. Allocation to aspirin reduced the 20-year risk of colon cancer (incidence hazard ratio [HR] 0.76, 0.60–0.96, $p=0.02$; mortality HR 0.65, 0.48–0.88, $p=0.005$), but not rectal cancer (0.90, 0.63–1.30, $p=0.58$; 0.80, 0.50–1.28, $p=0.35$). Where subsite data were available, aspirin reduced risk of cancer of the proximal colon (0.45, 0.28–0.74, $p=0.001$; 0.34, 0.18–0.66, $p=0.001$), but not the distal colon (1.10, 0.73–1.64, $p=0.66$; 1.21, 0.66–2.24, $p=0.54$; for incidence difference $p=0.04$, for mortality difference $p=0.01$). However, benefit increased with scheduled duration of treatment, such that allocation to aspirin of 5 years or longer reduced risk of proximal colon cancer by about 70% (0.35, 0.20–0.63; 0.24, 0.11–0.52; both $p<0.0001$) and also reduced risk of rectal cancer (0.58, 0.36–0.92, $p=0.02$; 0.47, 0.26–0.87, $p=0.01$). There was no increase in benefit at doses of aspirin greater than 75 mg daily, with an absolute reduction of 1.76% (0.61–2.91; $p=0.001$) in 20-year risk of any fatal colorectal cancer after 5-years scheduled treatment with 75–300 mg daily. However, risk of fatal colorectal cancer was higher on 30 mg versus 283 mg daily on long-term follow-up of the Dutch TIA trial (odds ratio 2.02, 0.70–6.05, $p=0.15$).

Interpretation Aspirin taken for several years at doses of at least 75 mg daily reduced long-term incidence and mortality due to colorectal cancer. Benefit was greatest for cancers of the proximal colon, which are not otherwise prevented effectively by screening with sigmoidoscopy or colonoscopy.

Funding None.

Introduction

Colorectal cancer is the second most common cancer in developed countries, with a lifetime risk of 5% and about 1 million new cases and 600 000 deaths worldwide each year.¹ Most colorectal cancers develop from adenomas,^{1,2} and trials have shown that aspirin^{3–7} and cyclooxygenase-2 (COX-2) inhibitors^{8–10} reduce the recurrence by about 20%. However, with a mean follow-up of only 2–3 years these trials were unable to establish any effect on colorectal cancer. Prevention with COX-2 inhibitors is not feasible because of an increased risk of vascular events, but long-term use of aspirin is feasible.¹¹ On long-term follow-up of two large trials of high-dose aspirin (≥ 500 mg daily) versus control for prevention of vascular events, daily aspirin for about 5 years reduced risk of colorectal cancer after a latent period of about 10 years.¹² However, the greater risk of bleeding complications in patients on high-dose aspirin¹¹ might limit its potential for primary prevention of colorectal cancer.

The risk of major bleeding on aspirin is dose-dependent,¹¹ but the effect of dose on risk of colorectal cancer is uncertain. First, although 81–325 mg daily is effective in secondary prevention of adenomas,^{3–7} the likelihood of malignant transformation of adenomas that develop despite these doses is uncertain. Second, there is evidence that aspirin reduces the development of tumours by inhibition of COX-2,^{13–16} which needs higher doses than inhibition of COX-1.¹⁷ Third, most observational studies have only shown strong associations with high-dose aspirin.^{12,18} Finally, two large trials of low-dose alternate day aspirin (100 mg and 325 mg)^{19,20} in primary prevention of vascular disease showed no effect on risk of colorectal cancer during 10-year follow-up. Given the delay from early development of an adenoma to presentation with colorectal cancer,^{21,22} follow-up might have been insufficient. However, aspirin also failed to prevent colorectal adenomas in the Women's Health Study,¹⁹

Published Online

October 22, 2010

DOI:10.1016/S0140-

6736(10)61543-7

See Online/Comment

DOI:10.1016/S0140-

6736(10)61509-7

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suggesting that the dose might have been insufficient or that giving it on alternate days is ineffective.

We therefore did long-term follow-up of three large trials of daily low-dose aspirin (75–300 mg) in prevention of vascular events,^{23–25} and pooled these data with our previously reported long-term follow-up of two trials of high-dose aspirin,^{12,26,27} to establish the effects of aspirin on incidence and mortality due to colorectal cancer in relation to dose and duration of trial treatment. Given evidence that aspirin might have a greater effect on cancer of the proximal colon than on cancer of the distal colon or rectum,^{28–31} which would have implications for combination with sigmoidoscopic screening,³² we also stratified our analyses by site of cancer.

Methods

Trials

We studied trials of aspirin versus control in the UK or Sweden in the 1980s and early 1990s, because these two countries had centralised death certification established by the 1980s (and cancer registration in the UK) making these data available for research. Eligible trials had to have recruited at least 1000 participants and to have a median scheduled treatment period of at least 2·5 years (since the effect of aspirin on risk of colorectal cancer increased with treatment duration at the high doses).¹² Five trials fulfilled these criteria,^{23,24,26,27,33} but records of one had been destroyed (Juul-Moller S, University Hospital, Malmo, Sweden, personal communication).³³ We therefore followed up four randomised trials of aspirin versus control in primary (Thrombosis Prevention Trial

[TPT],²³ British Doctors Aspirin Trial [BDAT]²⁷) and secondary (Swedish Aspirin Low Dose Trial [SALT],²⁴ UK-TIA Aspirin Trial [UK-TIA]²⁶) prevention of vascular. Long-term follow-up data on cause of death were also available from the Dutch TIA trial.²⁵

Procedure

TPT was a 2×2 factorial trial of aspirin versus placebo and warfarin versus placebo in men aged 45–69 years at increased risk of vascular events.²³ We only report the aspirin comparison. 135 000 patient records were reviewed in 108 UK primary care practices to exclude ineligible participants, which included those with a recent history of possible peptic ulceration, previous myocardial infarction or stroke, and drugs incompatible with trial treatment. Potential participants were then invited to screening clinics (61 422 attended) at which a vascular risk-factor score was calculated. 10 557 men within the top quintile of risk within each practice were eligible for the trial, of whom 5085 were recruited from 1989 to 1992. 2545 men were allocated to aspirin (75 mg daily controlled-release formulation) and 2540 to placebo. Treatment allocation was double-blind. Men were reviewed by their family doctor each year and a research nurse searched their medical records. No patients were lost to follow-up before the trial end date (October, 1997). All men in the trial were flagged in the UK National Health Service Central Register and all notifications of cancer or death were obtained until September, 2009.

SALT was a double-blind randomised trial of aspirin 75 mg daily (film-coated tablets) versus placebo

	Thrombosis Prevention Trial	Swedish Aspirin Low Dose Trial	Dutch TIA Aspirin Trial*	UK-TIA Aspirin Trial	British Doctors Aspirin Trial
Aspirin comparison	75 mg daily vs placebo	75 mg daily vs placebo	283 mg vs 30 mg daily	300 mg vs 1200 mg daily vs placebo	500 mg daily vs control
Patients (active/control)	2545/2540	676/684	1231/1224	811/821/817	3429/1710
Placebo controlled and double-blind	Yes	Yes	Yes	Yes	No
Recruitment period	1989–92	1984–89	1986–89	1979–85	1978–79
Year original trial completed	1997	1990	1990	1986	1984
Median (range) duration of scheduled treatment in original trial (years)	6·9 (4·3–8·6)	2·7 (1·0–5·3)	2·6 (1·0–4·3)	4·4 (1·0–7·1)	6·0 (5·0–6·0)
Patients with scheduled duration of trial treatment ≥2·5 years (active/control)	2545/2540	444/468	648/639	684/653/702	3429/1710
Patients with scheduled duration of trial treatment ≥5 years (active/control)	2207/2219	10/9	0/0	321/312/316	3429/1710
Patients informed of treatment allocation at end of original trial	Yes	Yes	Yes	No	Open throughout
Methods of post-trial follow-up	Death certification, cancer registration	Death certification	Death certification, record review, patient contact ³⁴	Death certification, cancer registration	Death certification, cancer registration
Year post-trial follow-up extended to	2009	2007	2003	2006	2002
Mean (SD) age at randomisation (years)	57·5 (6·7)	66·9 (7·1)	65·3 (10·1)	60·3 (9·0)	61·6 (7·0)
Proportion male	100·0%	65·8%	65·0%	73·0%	100·0%
Proportion of current smokers at randomisation	41·2%	27·0%	45·5%	53·0%	31·0%

*LILAC substudy cohort.³⁴

Table 1: Characteristics of trials studied and details of post-trial follow-up

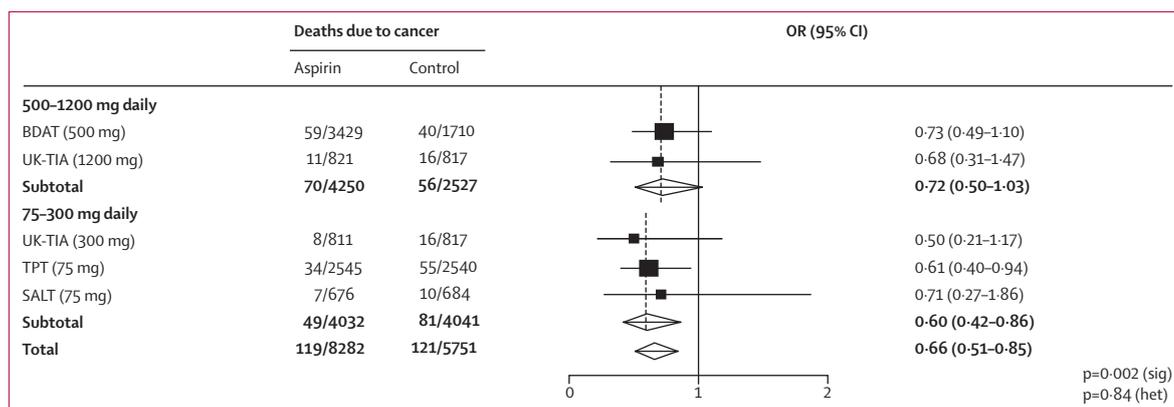


Figure 1: Meta-analysis of effect of aspirin on long-term risk of death due to colorectal cancer in randomised trials of aspirin versus control

All randomised patients are included, irrespective of scheduled duration of trial treatment. The overall pooled estimate is adjusted to correct for double-counting of the control group of the UK-TIA Aspirin Trial, which is included in both of the separate aspirin-dose subanalyses. BDAT=British Doctors Aspirin Trial. TPT=Thrombosis Prevention Trial. SALT=Swedish Aspirin Low Dose Trial.

1–4 months after a transient ischaemic attack or a minor ischaemic stroke.²⁴ Patients were enrolled from 17 hospital centres in Sweden from December, 1984, to January, 1989. After a 3–5 week active treatment run-in period, 676 patients were randomly assigned to aspirin and 684 to placebo. Follow-up was done every 4 months by study physicians until the end of the trial in January, 1990 (median duration 32 months, range 12–63). After additional ethics approval, all death certificates were obtained from the Swedish Medical Board for deaths up to September, 2007. No data were available on incidence of non-fatal cancers.

In BDAT, 5139 British male doctors resident in the UK and born on or after 1900 were recruited in 1978 (4377 individuals) or 1979 (762).²⁷ Eligible participants were required to have no contraindication to the use of aspirin; no regular aspirin use; and no history of peptic ulcer disease, stroke, or myocardial infarction. Randomisation (2:1 ratio) was to daily aspirin unless some contraindication developed (500 mg ordinary, soluble, or effervescent aspirin, as desired, or, if subsequently requested, 300 mg enteric coated aspirin) versus no aspirin or products containing aspirin unless some specific indication developed. Placebo tablets were not used. Treatment continued for 5–6 years (until 1984). All participants were asked to complete a questionnaire every 6 months about their health and recent use of aspirin or other antiplatelet drugs. At the end of the trial a further questionnaire was completed by 99% of all surviving participants. Participants were flagged with the National Cancer Registry and the Office of the Registrar General and all notifications of cancer and death were collected until 2001.¹²

The UK-TIA trial recruited 2449 patients with a recent transient ischaemic attack or minor ischaemic stroke from 33 centres in the UK and Ireland between 1979 and 1985.²⁶ Participants were older than 40 years, with no history of aspirin intolerance, alcoholism, chronic renal

failure, or peptic ulceration. Randomisation to 1200 mg aspirin daily versus 300 mg daily versus placebo was by random numbers within each centre and treatment was double-blind. Patients were followed up by a physician every 4 months until the end of the trial in 1986 and none were lost. After obtaining ethics approval, data on deaths and all incident cancers notified during and after the trial until 2006 were obtained from national registries.¹²

Dutch TIA trial was a double-blind randomised trial of 30 mg versus 283 mg aspirin daily for secondary prevention up to 3 months after a transient ischaemic attack or minor ischaemic stroke. A subset of patients were also randomised to atenolol versus placebo. 3131 patients were assigned to the aspirin groups during 1986–89 and had hospital follow-up every 4 months until 1990 (median duration 2.6 years, range 1.0–4.3), with no patients lost.²⁵ After additional ethics approval, post-trial follow-up (median 10.1 years) was obtained for patients in the 24 largest centres—accounting for 2473 (78.5%) of the original trial cohort—by contact with the trial physicians, primary care physicians, and the patient or a relative.³⁴ Follow-up was complete in 2447 (99%) patients.³⁴

Statistical analysis

For long-term follow-up of each trial cohort, colorectal cancers were identified (blind to treatment allocation) from death certificate and cancer registration data—coded according to the 9th or 10th revision of the International Classification of Diseases.¹² Data on death due to colorectal cancer (defined as those in which the cancer had been recorded as the primary underlying cause of death on the death certificate) were available from all trials. Incidence of colorectal cancer was assessed in TPT, BDAT, and UK-TIA.

All analyses were by intention to treat, which we defined as treatment allocation in the original trials. We established the effect of randomisation to aspirin on risk

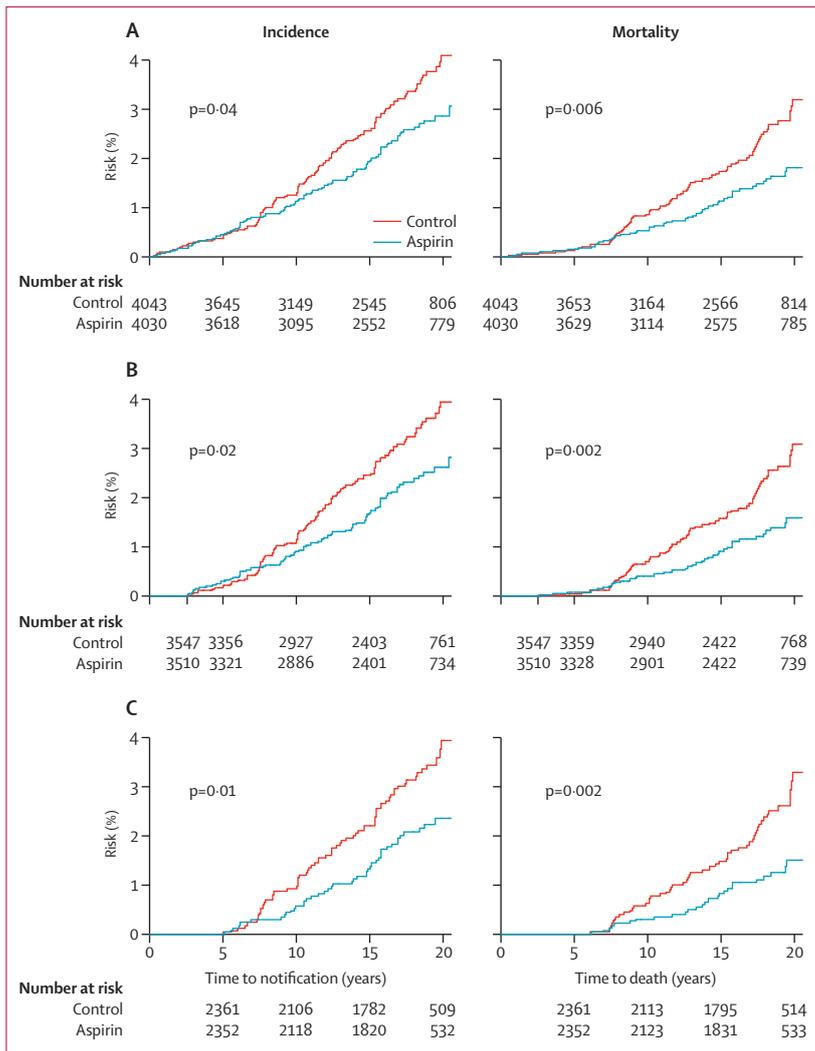


Figure 2: Pooled analysis of the effect of low-dose (75–300 mg) aspirin versus control
 The effect on subsequent incidence and mortality due to colorectal cancer in all randomised patients (A) in the Thrombosis Prevention Trial, the Swedish Aspirin Low Dose Trial, and the UK-TIA Aspirin Trial (lower-dose aspirin versus control); in those with scheduled duration of trial treatment ≥ 2.5 years (B); and in those with scheduled duration of trial treatment ≥ 5 years (C).

of death due to colorectal cancer during and after the trials as an odds ratio for each trial. A pooled estimate from the four trials of aspirin versus control was obtained by fixed-effects meta-analysis (Peto method). The same analysis was used for incidence of colorectal cancer in TPT, BDAT, and UK-TIA.

After checking for any heterogeneity in the absolute risks of colorectal cancer during follow-up between the trials, which might confound pooled analysis of individual patient data, and any heterogeneity between trials in the effect of allocation aspirin, individual patient data from the four trials of aspirin versus control were pooled. Data on date of deaths from causes other than colorectal cancer were available for all trials, which allowed actuarial analyses of risks of colorectal cancer. Kaplan-Meier analysis was used for survival curves and log-rank tests

were used to assess significance. Cox regression was used to establish hazard ratios for the incidence of colorectal cancer and risk of death.

These analyses were stratified by the dose categories used in the Antithrombotic Trialists' Collaboration:¹¹ 75–300 mg versus 500–1200 mg. The 75–300 mg category was the dose range used in previous adenoma trials.^{4,7} The analyses were also stratified by duration of treatment during the initial trial period. Based on observational studies and our previous analysis of UK-TIA and BDAT,¹² the extent of any delayed reduction by aspirin in the risk of colorectal cancer was expected to increase with the duration of the previously scheduled treatment. Scheduled duration of trial treatment was at least 5 years in all patients in BDAT and for almost all patients in TPT, but varied from 1 year to 7 years in UK-TIA, from 1 year to 5 years in the SALT, and from 1 year to 4 years in the Dutch TIA trial. Analyses were therefore done on all patients and on those with at least 2.5 years or 5.0 years of scheduled trial treatment. Each of these analyses was done on an intention-to-treat basis, scheduled duration of treatment being determined simply as the time from randomisation to the end of the trial, irrespective of actual duration of compliance with treatment. Analyses were also stratified by site of cancer in predefined categories:^{28–31} colon proximal to the splenic flexure versus distal colon (splenic flexure, descending colon, sigmoid colon, and rectosigmoid junction) versus rectum.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the baseline clinical characteristics of patients at randomisation in the five trials studied, and gives details of scheduled treatment and of post-trial follow-up. A total of 14033 patients were randomly assigned to aspirin or control in TPT, SALT, UK-TIA, and BDAT.

Duration of follow-up was extended to 17–20 years in TPT, 21–27 years in UK-TIA, 18–23 years in SALT, and 22–23 years in BDAT. Follow-up to 17 years had been done in the Dutch TIA trial. 391 patients (172 in BDAT, 141 in TPT, 61 in UK-TIA, and 17 in SALT) had 397 colorectal cancers during and after the four trials of aspirin versus control. A further seven patients had a past history of colorectal cancer at randomisation, none of whom had a recurrence on follow-up. Ascertainment of cancers via the UK cancer registration system was reliable in UK-TIA and BDAT.¹² Of 42 cancers identified during the TPT, only three were notified on the basis of death certificate only; all others were confirmed on histology. The absolute risks of colorectal cancer during follow-up and the time-course of risk were also very

	Incidence of colorectal cancer				Mortality due to colorectal cancer			
	n/N	HR (95% CI)	ARR (95% CI)	p	n/N	HR (95% CI)	ARR (95% CI)	p
All patients	196/8073	0.75 (0.56–0.97)	1.21% (0.19–2.22)	0.02	130/8073	0.61 (0.43–0.87)	1.36% (0.44–2.28)	0.005
Scheduled treatment \geq 2.5 years	185/7383	0.69 (0.51–0.93)	1.33% (0.30–2.36)	0.003	119/7383	0.54 (0.36–0.80)	1.49% (0.55–2.43)	0.001
Scheduled treatment \geq 5 years	135/5077	0.62 (0.43–0.94)	1.55% (0.34–2.76)	0.003	91/5077	0.48 (0.30–0.77)	1.76% (0.61–2.91)	0.001

Pooled analyses of trials of low-dose aspirin (75–300 mg daily) stratified according to the duration of scheduled treatment during the initial trial period. Data are hazard ratios (HR) from a Cox model and absolute reductions in 20-year risk (ARR) derived from life-tables. The p values are taken from the Cox model stratified by study and the analysis of patients with longer scheduled trial treatments includes all events from the time of randomisation. The p values therefore differ slightly from those obtained from the log-rank test in analyses from different timepoints in figure 2.

Table 2: Effect of low-dose (75–300 mg) aspirin versus control on subsequent long-term incidence and mortality due to colorectal cancer

similar in the four trials of aspirin versus control (heterogeneity $p=0.34$; webappendix p 2), as were the case-fatality rates.

Meta-analysis of the effect of allocation to aspirin versus control on long-term risk of death due to colorectal cancer showed no heterogeneity (figure 1), with reductions in mortality on 75 mg daily, 300 mg daily, and 500–1200 mg daily. Results were similar (odds ratio [OR] 0.64, 95% CI 0.49–0.83; $p=0.001$) with the addition of seven cases in which the underlying cause of death was not colorectal cancer, but in which the patient died within 1 year of notification of the cancer diagnosis, and after exclusion of patients with treatment duration of less than 2.5 years (OR 0.61, 0.47–0.80; $p<0.0001$; webappendix p 3). In TPT, UK-TIA, and BDAT, meta-analysis also showed no heterogeneity ($p=0.91$) in the effect of aspirin on incidence of colorectal cancer (OR 0.75, 0.61–0.92; $p=0.007$).

In the Dutch TIA trial cohort (excluding one death due to colorectal cancer diagnosed before randomisation), there were 12 deaths due to colorectal cancer in patients assigned to aspirin 30 mg daily versus six deaths in those assigned to 283 mg daily (OR 2.02, 0.70–6.05; $p=0.15$).

In view of the similar risks of colorectal cancer across the four trials of aspirin versus control (webappendix p 2) and the similar effects of randomised treatment allocation (figure 1), data from all 14033 patients in the four trials were pooled. The median duration of scheduled treatment was 6.0 years and median follow-up from assignment to death or end of follow-up was 18.3 years. As expected, the reduction in risk of colorectal cancer in the aspirin versus control groups increased with scheduled treatment duration ($p=0.04$ for mortality; $p=0.05$ for incidence), but there was no evidence of earlier diagnosis in the aspirin versus control group of those colorectal cancers that presented during the trials (webappendix p 4). Figure 2 shows a pooled analysis of the effect of low-dose (75–300 mg) aspirin versus placebo on subsequent incidence and mortality due to colorectal cancer in all randomised patients and in those with durations of scheduled trial treatment. Table 2 shows an equivalent Cox-regression analysis (stratified by trial) and the absolute reductions in 20-year risk.

In a pooled analysis of the four trials of aspirin versus control, aspirin at any dose, with a mean duration of

	All patients			Scheduled treatment duration \geq 5 years		
	Events	Hazard ratio (95% CI)	p	Events	Hazard ratio (95% CI)	p
All cancers	397	0.76 (0.63–0.94)	0.01	316	0.68 (0.54–0.87)	0.002
Proximal colon	69	0.45 (0.28–0.74)	0.001	61	0.35 (0.20–0.63)	<0.0001
Distal colon	100	1.10 (0.73–1.64)	0.66	75	1.14 (0.69–1.86)	0.61
Colon (site unspecified)	109	0.74 (0.51–1.07)	0.11	93	0.81 (0.52–1.25)	0.34
All colon	278	0.76 (0.60–0.96)	0.02	229	0.75 (0.58–0.97)	0.03
Rectum	119	0.90 (0.63–1.30)	0.58	87	0.58 (0.36–0.92)	0.02
Fatal cancers	240	0.66 (0.52–0.86)	0.002	193	0.57 (0.42–0.78)	<0.0001
Proximal colon	41	0.34 (0.18–0.66)	0.001	37	0.24 (0.11–0.52)	<0.0001
Distal colon	44	1.21 (0.66–2.24)	0.54	30	1.24 (0.58–2.65)	0.58
Colon (site unspecified)	89	0.61 (0.40–0.94)	0.02	75	0.71 (0.44–1.17)	0.18
All colon	174	0.65 (0.48–0.88)	0.005	142	0.63 (0.45–0.87)	0.006
Rectum	70	0.80 (0.50–1.28)	0.35	54	0.47 (0.26–0.87)	0.01

Numbers differ slightly from those quoted for case-fatality in the main text because of inclusion of data from SALT. Stratified by site of tumour and by scheduled duration of treatment allocated in the initial randomised trial in a pooled analysis (Cox regression, stratified by trial) of the Thrombosis Prevention Trial, the Swedish Aspirin Low Dose Trial (SALT), the UK-TIA Aspirin Trial, and the British Doctors Aspirin Trial. The p values are taken from a Cox model stratified by study and the analysis of patients with longer scheduled trial treatments includes all events from the time of random assignment. The p values therefore differ slightly from those obtained from the log-rank test in analyses from different timepoints in figure 2. Two colorectal cancers at different sites are included in four patients in whom it was not possible to establish which cancer was responsible for death.

Table 3: Effect of aspirin (75–1200 mg) versus control on long-term risk of colorectal cancer

scheduled treatment of 5.8 years (range 1.0–8.5), reduced long-term risk of colon cancer, but not rectal cancer (table 3). The effect on colon cancer was similar in an analysis limited to patients allocated 75 mg versus placebo in TPT and SALT (incidence HR 0.76, 0.52–1.10, $p=0.15$; mortality 0.61, 0.38–0.98, $p=0.04$).

Further stratification by site of cancer (figures 3 and 4; table 3; webappendix p 1) showed that the effect of aspirin on risk of colon cancer was due to a reduction in risk of cancer of the proximal colon, with no effect on cancer of the distal colon. This difference was statistically significant for both incidence ($p=0.04$) and mortality ($p=0.01$). Again, the effect on proximal colon cancer was similar in an analysis limited to patients allocated 75 mg versus placebo in TPT and SALT (incidence HR 0.49, 95% CI 0.23–1.06, $p=0.06$; mortality 0.29, 0.09–0.87, $p=0.03$). In patients with a scheduled duration of trial treatment of 5 years or longer, allocation to aspirin reduced subsequent risk of proximal colon cancer by about 70% and also reduced incidence of rectal cancer

See Online for webappendix

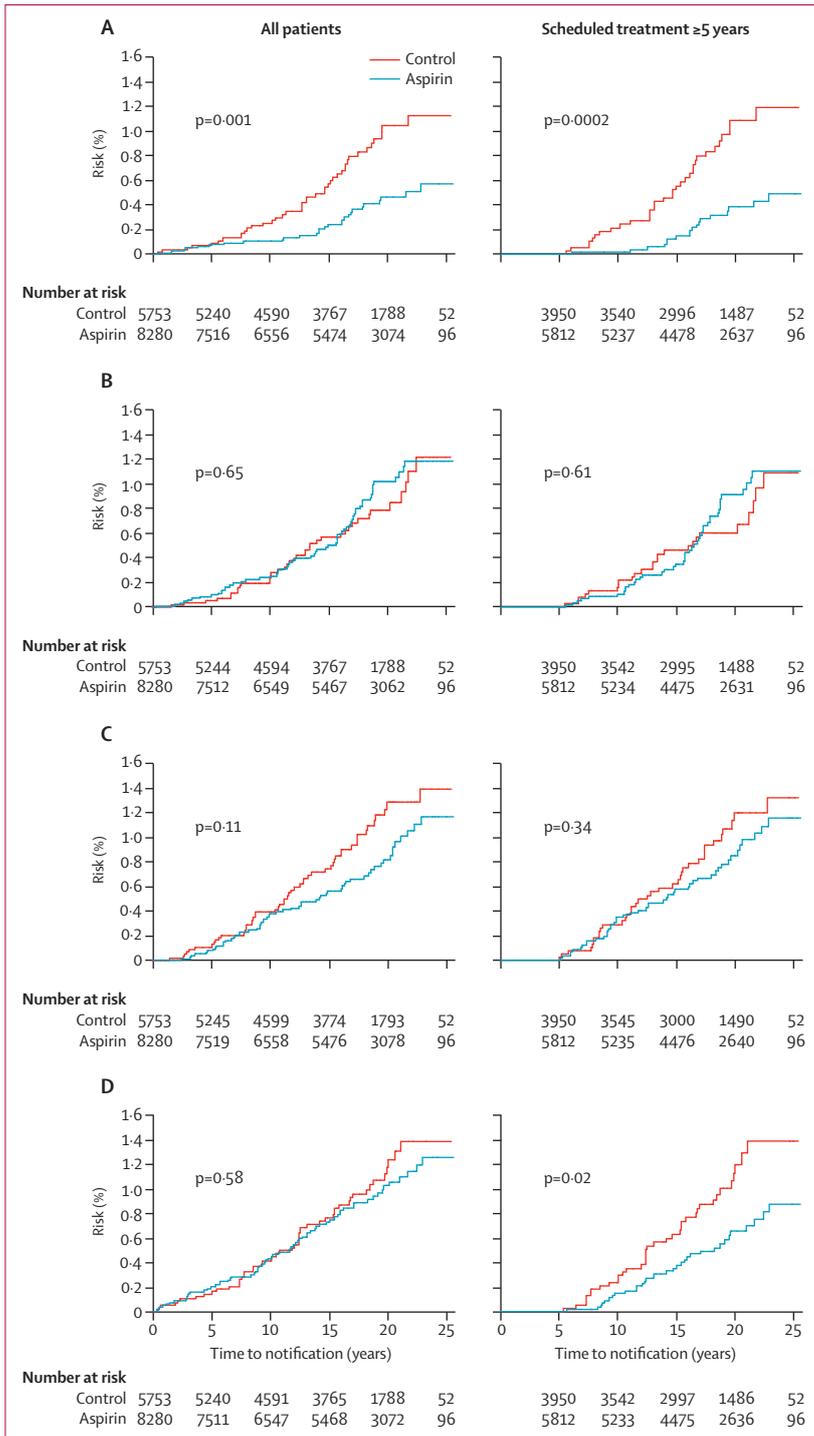


Figure 3: Pooled analysis of the effect of aspirin (75–1200 mg) versus control on incidence of colorectal cancer. Pooled analysis is by cancer site: proximal colon (A), distal colon (B), unspecified colon site (C), and rectum (D). Statistical significance is given by the log-rank test.

(figures 3 and 4; table 3; webappendix p 1), but there was no effect on distal colon cancer.

In the three trials in which both fatal and non-fatal events were recorded, case-fatality rates for colorectal

cancer were similar (89 of 141 in TPT, 35 of 61 in UK-TIA, and 99 of 172 in BDAT; heterogeneity $p=0.56$). In a pooled analysis of these trials, case fatality was higher for cancers of the proximal versus distal colon (table 3; relative risk [RR] 1.37, 95% CI 1.02–1.84; $p=0.04$) and was intermediate for rectal cancer (64 [57%] of 113). Case fatality overall might be lower in patients allocated to aspirin versus control (112 of 203 vs 111 of 171; 0.85, 0.72–1.00; $p=0.056$); the difference was greatest for proximal colon tumours (14 of 28 vs 27 of 41; 0.76, 0.49–1.17; $p=0.19$), absent for distal colon tumours (25 of 60 vs 16 of 37; 0.96, 0.60–1.55; $p=0.88$), and intermediate for rectal tumours (33 of 64 vs 31 of 49; 0.82, 0.59–1.12; $p=0.21$). However, in cases of fatal colorectal cancer, time from notification of cancer to death did not differ between the aspirin (mean 1.75 years) and control groups (1.92) when stratified by site of cancer ($p=0.67$). There was also no effect of aspirin on time to death of any cause after a diagnosis of colorectal cancer.

Discussion

In a previous report of data from UK-TIA and BDAT,¹² we showed that the 20-year incidence of colorectal cancer was reduced by about 30% by treatment with high-dose aspirin for about 5 years. Our new report adds several important observations. First, we have shown the same effect for 75–300 mg doses of aspirin, with 75 mg daily being as effective as higher doses. Second, we had statistical power to show this effect of aspirin more reliably than previously and particularly to show a statistically robust and clinically important reduction in death due to colorectal cancer (only data on incidence were published previously¹²). Third, we showed that this reduction in fatal colorectal cancer tended to be greater than the reduction in incidence. Fourth, we showed in the Dutch-TIA trial that very low doses of aspirin (ie, 30 mg daily) might not be effective in prevention of colorectal cancer. Finally, we showed that the reductions in incidence and death due to colorectal cancer were greater for proximal colon tumours than distal colon or rectal tumours.

The reduction in the long-term incidence of colorectal cancer by lower-dose aspirin (table 2) was larger than the 17% reduction in colorectal adenomas noted in short-term trials of aspirin,⁷ but consistent with the 28% reduction in more advanced adenomas reported in these trials.⁷ However, the 40–50% reduction in 20-year risk of death due to colorectal cancer in the low-dose aspirin groups (table 2) was larger than expected. Yet, our analyses were conservative in several respects. First, although all of the trials of low-dose aspirin were double-blind, there were high rates of drop-outs from the active treatment groups and of open treatment with aspirin in the placebo groups. The proportion of patients withdrawing from trial treatment at 1 year follow-up in TPT was 14%, at 3 years was 29%, and at 5 years was 42%. In BDAT, 19% of those allocated to take aspirin

stopped doing so in the first year, increasing to 29% by 3 years and 40% by 5 years. Although we therefore found the largest reductions in incidence of colorectal cancer in on-treatment analysis in our previous report of trials of high-dose aspirin,¹² we restricted our current analyses to intention-to-treat to estimate what might be achieved in routine practice and to reduce any bias. Second, although our previous report also showed a greater reduction in incidence of colorectal cancer with increasing duration of scheduled trial treatment with aspirin (interaction $p=0.004$),¹² we included patients with short durations of scheduled trial treatment in many of the current analyses. Third, the small reduction in fatal cardiovascular events on aspirin would increase the likelihood of survival to diagnosis cancer in the aspirin groups. Fourth, loss of any difference between the treatment groups in use of aspirin after completion of the trials probably underestimated the benefits of long-term use of aspirin. Patients were not told about their trial allocation at the end of the UK-TIA trial and so any difference thereafter in treatment between the initial randomised treatment groups is unlikely. Although patients were told at the end of the SALT and TPT trials, subsequent differences in use between the groups were small in TPT,³⁵ and patients were advised to go on to aspirin at the end of the SALT trial. Thus, we essentially established the delayed effect of an average period of allocation to low-dose aspirin versus placebo of about 6 years (an average period of actual use of aspirin vs placebo of 4–5 years in an on-treatment sense). This allocation resulted in a reduction in incidence of colorectal cancer that started after a latent period of 7–8 years and lasted for about the same period as the initial treatment. It is reasonable to postulate that the difference between the treatment groups would have continued to increase had the difference in aspirin use been maintained.

None of the trials that we followed up were designed to study colorectal cancer. However, data on cancers were collected during all five trials and reliable long-term follow-up was possible (table 1). The UK-based trials contributed more than 90% of the cancer outcomes and studies of the UK cancer registration system have documented very high rates of ascertainment and accuracy for cancer,^{36,37} and for colorectal cancer specifically.^{38,39} Indeed, the 4% absolute risk of colorectal cancer during the 20-year follow-up was consistent across the trials (webappendix p 2) and corresponds with the expected rate on the basis of a life-time risk of about 5%.^{1,2} Moreover, underascertainment of cancers would have attenuated the absolute treatment effect and should not have introduced any bias. In fact, the lack of any foreknowledge among the trial investigators that the data might subsequently be used to study the effect of aspirin on the risk of cancer will have limited any potential investigator-related bias.

Our study does have some potential limitations. First, it is possible that patients assigned to aspirin would have

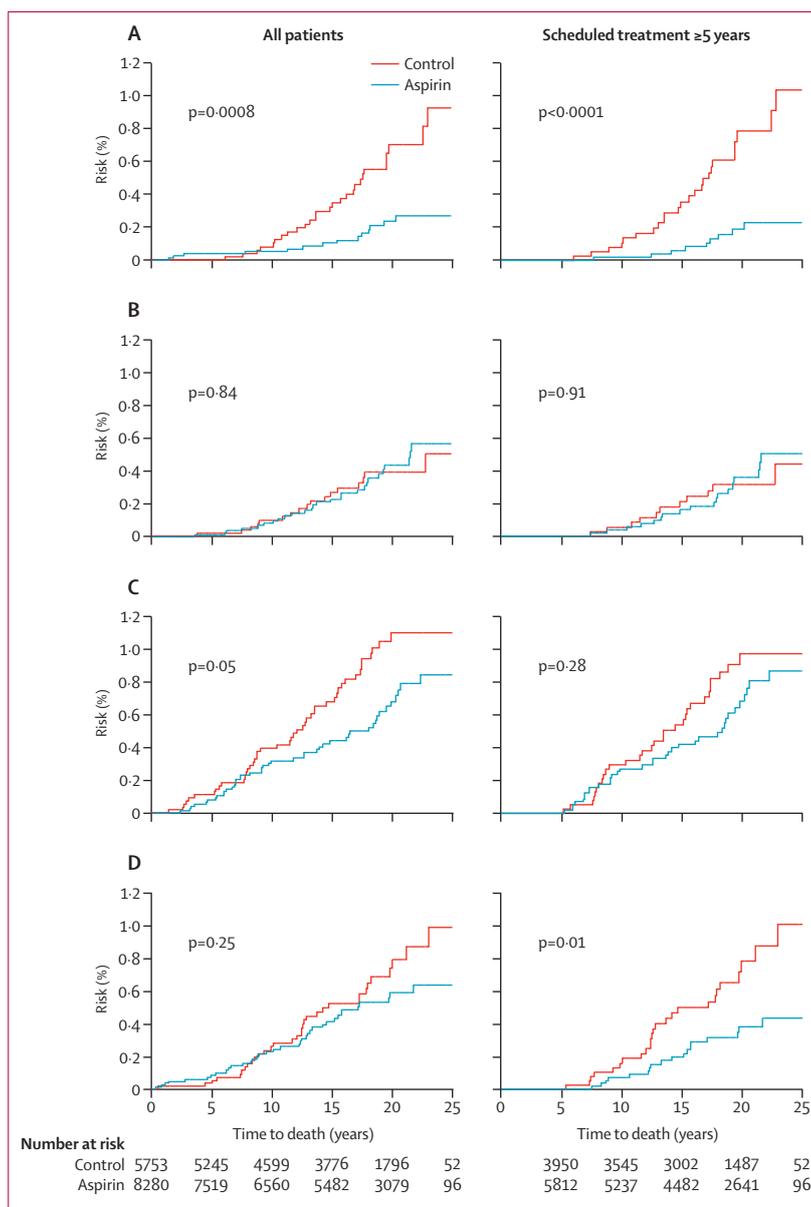


Figure 4: Pooled analysis of the effect of aspirin (75–1200 mg) versus control on risk of death due to colorectal cancer

Pooled analysis is by cancer site: proximal colon (A), distal colon (B), unspecified colon site (C), and rectum (D). Statistical significance is given by the log-rank test.

had more investigations because of adverse effects such as anaemia, dyspepsia, gastrointestinal bleeding, and constipation, potentially resulting in earlier diagnosis of colorectal adenoma or cancer. However, there was no evidence of earlier diagnosis of colorectal cancer in any of the trials (webappendix p 4), and any such effect would be greatest for distal colon and rectal cancers. Second, our analysis of the long-term follow-up of the Dutch TIA trial suggested that 30 mg daily was ineffective or at least less effective than 300 mg daily, but the number of cancers was too small to be certain. Further follow-up of

the Women's Health Study (aspirin 100 mg alternate days vs placebo) could provide more data, but lack of an effect of aspirin on rates of patient-reported colorectal adenomas¹⁹ suggests that a substantial reduction in risk of colorectal cancer is unlikely. Third, we might have overestimated the latent period duration before an effect of aspirin on death due to colorectal cancer. The number of deaths due to colorectal cancer during the first few years of follow-up was small, partly because patients with a recent diagnosis of cancer were ineligible for inclusion in any of the trials, so we cannot confirm or exclude a reduction in mortality by aspirin in patients with established colorectal cancer.¹⁵ Fourth, our results cannot be generalised to less frequent use of aspirin. Although alternate-day aspirin seems to be as effective as daily aspirin in prevention of vascular events, because of the irreversible inhibition of COX-1 in platelets, irreversible inhibition would not be expected in other tissues, and observational studies have highlighted the importance of daily aspirin for reducing the incidence of colorectal cancer.^{12,14,18} All trials of aspirin in secondary prevention of adenomas have also used daily doses.⁷

Our results do however differ from those of observational studies in two important respects. First, several case-control and cohort studies reported no reduction in risk of colorectal cancer with 75 mg, but showed stronger associations with increasing doses of aspirin.¹² Second most observational studies have found no consistent differences in associations between aspirin use and risks of colon cancer versus rectal cancer, and reports of differences in effect by site of colon cancer have been inconsistent.¹² However, the only randomised trial of aspirin in prevention of recurrent adenomas to report results by site did report a 40–50% reduction in proximal colonic adenomas with aspirin and no reduction in distal adenomas.²⁸ In our study, the difference in effect of aspirin between proximal and distal colon cancers was significant for both incidence and mortality, and was present in all four trials of aspirin versus control and at all doses of aspirin (data not shown). Moreover, differences in effects of other treatments on proximal versus distal colon tumours are widely accepted,⁴⁰ and there are many differences in normal physiology between the proximal and distal colon,^{41,42} due partly to their different embryological origins, and in risk factors for cancers in the two sites, in mechanisms of carcinogenesis, and in the molecular and genetic characteristics of the cancers.^{41–44} Of particular relevance, expression of COX-2 tends to be greater in tumours of the distal colon and rectum than those of the proximal colon,^{43,45,46} aspirin therefore perhaps achieves less complete inhibition of COX-2 in distal tumours. Nevertheless, we cannot exclude a clinically important reduction in risk of distal colon cancer in view of the wide CI around our estimate of effect (table 3). A pooled analysis of all previous trials of aspirin, and possibly also of COX-2 inhibitors, in secondary prevention of colonic adenomas with

stratification by site of recurrent polyps might provide further useful insights.

We also showed that aspirin reduced mortality due to colorectal cancer more than it reduced incidence and more than expected by its effect on recurrent adenomas in previous trials. A change in the opposite direction would be expected because of dilution of the effect on incidence by other causes of death. The lower case fatality of cancers in the aspirin groups in the absence of any evidence of earlier diagnosis suggests a genuine difference in the aggressiveness of the cancers in the two groups. Designation of whether the colon cancer was the cause of death was masked to original treatment allocation in the trials and different methods of making this distinction have been shown to produce similar results.^{32,47}

The roughly 1.5% reduction in long-term absolute risk of colorectal cancer after treatment with aspirin for about 5 years has implications for clinical practice. In patients with an established indication for long-term antiplatelet treatment, such as in secondary prevention of vascular disease, this additional benefit will favour treatment with aspirin over other antiplatelet drugs, assuming that other drugs do not afford similar benefit. Although we did not model the effect of the reduction in deaths due to colorectal cancer on the overall balance of risk and benefit of long-term use of aspirin in healthy individuals, the reduction in risk of ischaemic vascular events and the increase in risk of major bleeding have been finely balanced in recent analyses,^{48,49} and so additional benefits of aspirin will tip the balance in favour of treatment. The five trials we studied all predated endoscopic screening for adenomas, which also reduces colorectal cancer incidence and mortality,^{32,50} and might therefore reduce the absolute benefit of aspirin. However, the suggestion of a particular effect of aspirin on more aggressive and rapidly growing tumours might allow less frequent screening, and the prevention of proximal colonic cancers by aspirin, which would not be identified by sigmoidoscopy screening and for which colonoscopy screening is only partly effective,⁵¹ is clearly important. Indeed, the very substantial reduction in proximal colon cancers on aspirin might be due in part to an effect on non-polypoid of de novo cancers, which tend to be flat and are easily missed at colonoscopy, but which tend to be aggressive and to occur in the proximal colon.^{51,52} It is therefore probable that these two approaches to prevention of colorectal cancer will be synergistic.

Contributors

PMR conceived and coordinated the project, obtained long-term follow-up data for the UK-TIA Aspirin Trial cohort, planned and did all analyses, and wrote the paper; MW collated the follow-up data from the TPT; CPW was primary investigator in the UK-TIA Aspirin Trial. AA was co-primary investigator in the Dutch TIA Aspirin Trial and the Lilac Study. BN was primary investigator in SALT. C-EE was co-primary investigator on SALT and obtained long-term death certificate follow-up data from the Swedish Medical Board. TWM was primary investigator on the TPT and obtained long-term follow-up data. All authors commented on drafts of the paper.

Conflicts of interest

PMR and BN have received honoraria for talks, advisory boards and clinical trial committees from several pharmaceutical companies with an interest in antiplatelet agents, including AstraZeneca, Bayer, Boehringer Ingelheim, Sanofi-BMS, and Servier. AA has received honoraria for advisory boards and research funding from Boehringer Ingelheim. The other authors declare no conflicts of interest.

Acknowledgments

We thank Richard Peto and Jill Boreham for access to data from the British Doctors Aspirin Trial; Christine Knottenbelt and Marilyn Goulding for their help in accessing long-term follow-up data from the TPT cohort; Birgit Peterson for help in collating data on causes of deaths in the SALT trial cohort; and Ziyah Mehta for help with analysis and production of graphs. The cost of cancer registry and death certificate follow-up of the UK-TIA Aspirin Trial was met by unrestricted research funds from the Stroke Prevention Research Unit, Oxford, UK. PMR is in receipt of an NIHR Senior Investigator Award.

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