Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials

Peter M Rothwell, F Gerald R Fowkes, Jill F F Belch, Hisao Ogawa, Charles P Warlow, Tom W Meade

Summary

Background Treatment with daily aspirin for 5 years or longer reduces subsequent risk of colorectal cancer. Several lines of evidence suggest that aspirin might also reduce risk of other cancers, particularly of the gastrointestinal tract, but proof in man is lacking. We studied deaths due to cancer during and after randomised trials of daily aspirin versus control done originally for prevention of vascular events.

Methods We used individual patient data from all randomised trials of daily aspirin versus no aspirin with mean duration of scheduled trial treatment of 4 years or longer to determine the effect of allocation to aspirin on risk of cancer death in relation to scheduled duration of trial treatment for gastrointestinal and non-gastrointestinal cancers. In three large UK trials, long-term post-trial follow-up of individual patients was obtained from death certificates and cancer registries.

Results In eight eligible trials (25 570 patients, 674 cancer deaths), allocation to aspirin reduced death due to cancer (pooled odds ratio [OR] 0·79, 95% CI 0·68–0·92, p=0·003). On analysis of individual patient data, which were available from seven trials (23 535 patients, 657 cancer deaths), benefit was apparent only after 5 years' follow-up (all cancers, hazard ratio [HR] 0·66, 0·50–0·87; gastrointestinal cancers, 0·46, 0·27–0·77; both p=0·003). The 20-year risk of cancer death (1634 deaths in 12 659 patients in three trials) remained lower in the aspirin groups than in the control groups (all solid cancers, HR 0·80, 0·72–0·88, p<0·0001; gastrointestinal cancers, 0·65, 0·54–0·78, p<0·0001), and benefit increased (interaction p=0·01) with scheduled duration of trial treatment (≥7·5 years: all solid cancers, 0·69, 0·54–0·88, p=0·003; gastrointestinal cancers, 0·41, 0·26–0·66, p=0·0001). The latent period before an effect on deaths was about 5 years for oesophageal, pancreatic, brain, and lung cancer, but was more delayed for stomach, colorectal, and prostate cancer. For lung and oesophageal cancer, benefit was confined to adenocarcinomas, and the overall effect on 20-year risk of cancer death was greatest for adenocarcinomas (HR 0·66, 0·56–0·77, p<0·0001). Benefit was unrelated to aspirin dose (75 mg upwards), sex, or smoking, but increased with age—the absolute reduction in 20-year risk of cancer death reaching 7·08% (2·42–11·74) at age 65 years and older.

Interpretation Daily aspirin reduced deaths due to several common cancers during and after the trials. Benefit increased with duration of treatment and was consistent across the different study populations. These findings have implications for guidelines on use of aspirin and for understanding of carcinogenesis and its susceptibility to drug intervention.

Funding None.

Lancet 2011; 377: 31–41

Published Online December 7, 2010 DOI:10.1016/S0140-6736(10)62110-1

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Stroke Prevention Research Unit, Department of Clinical Neurology, University of Oxford, Oxford, UK (Prof P M Rothwell FMedSci); **Wolfson Unit for Prevention of Peripheral Vascular Diseases, Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK** (Prof F G R Fowkes FRCPE); **The Institute of Cardiovascular Research, Vascular and Inflammatory Diseases Research Unit, University Division of Medicine and Therapeutics, Ninewells Hospital and Medical School, Dundee, UK** (Prof J F F Belch FRCP); **Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto City, Japan** (H Ogawa MD); **Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh, UK** (Prof C P Warlow FMedSci); **and London School of Hygiene and Tropical Medicine, University of London, London, UK** (Prof T W Meade FRS)

Correspondence to: Prof Peter M Rothwell, Stroke Prevention Research Unit, University Department of Clinical Neurology, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK **peter.rothwell@clneuro.ox.ac.uk**

Introduction

In the developed world, the lifetime risk of cancer is about 40%, and rates are increasing in the developing world.[1] In Europe, about 3·2 million new cancers present each year, with about 1·7 million deaths,[2] and there are more than 1·5 million new cases each year in the USA.[3] By contrast with treatment of cancer, there has been little progress in use of drugs in prevention of the disease. However, several lines of evidence suggest that long-term use of aspirin might reduce the risk of some cancers, particularly gastrointestinal tumours. Aspirin reduces incidence or growth rate, or both, of several cancers in animal models,[4–6] mediated at least in part by inhibition of the cyclo-oxygenase (COX) enzymes and reduced production of prostaglandins and other inflammatory mediators, but these findings might not be applicable to humans. Observational studies in humans also suggest that aspirin reduces risk of certain cancers,[5–8] but results have been conflicting, with more rigorous studies yielding weaker associations.[8] Moreover, observational studies have proved to be unreliable in determining risks and benefits of medications in the past,[9,10] and there is trial evidence that one antiplatelet drug might have adverse effects on cancer outcomes.[11]

Nevertheless, long-term follow-up of randomised trials has shown that aspirin does reduce the risk of colorectal cancer after a delay of several years,[12,13] probably by reducing precancerous adenomas,[14] possibly by inhibition of COX-2.[15] However, proof of an effect on other cancers is lacking. 10-year follow-up of the Women's Health Study, a randomised trial of 100 mg of aspirin on alternate days versus control, showed no reduction in incidence of cancer.[16] However, aspirin also failed to prevent colorectal adenomas in this study, which is consistent with observational studies suggesting that daily aspirin is required for

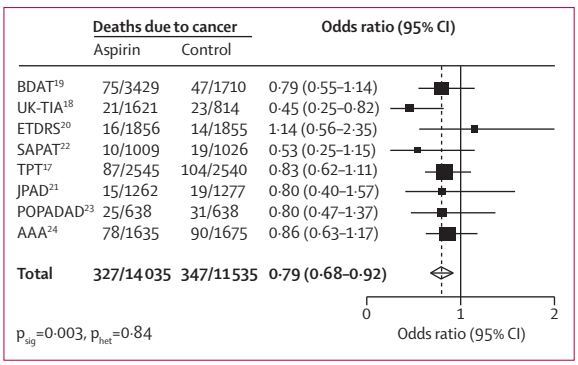

Figure 1: **Meta-analysis of the effect of aspirin on deaths due to cancer during all eligible randomised trials of aspirin versus control**
Data are n/N, where n=number of cancer deaths and N=number of trial participants in that treatment group. BDAT=British Doctors Aspirin Trial. UK-TIA=UK transient ischaemic attack trial. ETDRS=Early Treatment Diabetic Retinopathy Study. SAPAT=Swedish Angina Pectoris Aspirin Trial. TPT=Thrombosis Prevention Trial. JPAD=Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes. POPADAD=Prevention of Progression of Arterial Disease and Diabetes. AAA=Aspirin for Asymptomatic Atherosclerosis.

prevention of cancer.[5–8] Observational studies also suggest that use of aspirin for at least 5 years is required before reductions in risk of cancer are observed,[5–8] and the effect of aspirin on risk of colorectal cancer on follow-up of randomised trials was greatest in patients with duration of trial treatment of 5 years or longer.[12,13]

We therefore determined the effect of aspirin on risk of fatal cancer by analysis of individual patient data for deaths due to cancer during randomised trials of daily aspirin versus control (done originally for primary or secondary prevention of vascular events) in which the median duration of scheduled trial treatment was at least 4 years. We studied fatal cancers only, in the first instance, because cause of non-vascular deaths was reliably determined in most aspirin trials, and we also aimed to determine the effect of any reduction in cancer deaths on overall all-cause mortality. In three trials done in the UK,[17–19] we also determined any delayed effects of aspirin on the 20-year risk of death due to cancer by long-term post-trial follow-up.

Methods

Search strategy and selection criteria

We searched for randomised trials of aspirin versus control that had a mean or median scheduled trial treatment period of at least 4 years and a range extending beyond 5 years. Eligible trials had investigated the effects of randomised allocation to: aspirin (any dose) versus no aspirin in the absence of another agent; or aspirin (any dose) versus no aspirin in the presence of another antiplatelet agent or antithrombotic agent, if the other agent was used in the same way in the aspirin and no aspirin groups. Given the focus on cancer outcomes, no distinction was made between trials of aspirin in primary versus secondary prevention of vascular disease. In view of the availability of published data for all trials of antiplatelet agents from the Antithrombotic Trialists' (ATT) Collaboration, literature searches were confined to publications after the last ATT search (2002).[20,21] Trials were identified by searching for relevant systematic reviews in the Cochrane Collaboration Database of Systematic Reviews and by searches of PubMed and Embase (both last done on March 12, 2010) using the terms "aspirin" or "salicyl*" or "antiplatelet" with the term "randomised controlled trial". The searches were restricted to studies done in humans, but there was no restriction on language.

Procedure

The original investigators were contacted to determine whether anonymised data were available for the number of deaths in which cancer had been regarded as the main underlying cause, the time from randomisation to death, and the primary site of cancer. All cancer deaths had been coded according to the ninth or tenth revision of the International Classification of Diseases (ICD) and the designation of death due to cancer that had been made by the original trialists was used, unless specified otherwise. However, in three trials,[17–19] we reviewed the paper case-records of all deaths in patients with known incident cancer to check the designation of cause of death, with the aim of identifying any possible bias resulting from an increase in risk of vascular events due to withdrawal of aspirin treatment after diagnosis of cancer, which might reduce the number of deaths attributed to cancer in the aspirin groups.

Three eligible trials, all UK-based, had continued to obtain data for deaths due to cancer after completion of the trials via the national death certification and cancer registration systems—the Thrombosis Prevention Trial (TPT),[17] the British Doctors Aspirin Trial (BDAT),[19] and the UK transient ischaemic attack (UK-TIA) aspirin trial.[18] TPT[17] was a 2×2 factorial double-blind randomised trial of aspirin versus placebo and warfarin versus placebo in men aged 45–69 years at increased vascular risk. 135 000 patient records were reviewed in 108 UK primary care practices to exclude ineligible subjects, including those with a recent history of possible peptic ulceration or previous myocardial infarction or stroke. 5085 men with high vascular risk-factor scores were recruited from 1989 to 1992. 2545 were allocated to aspirin (75 mg daily controlled release) and 2540 to placebo. Men were reviewed by their family doctor each year and a research nurse searched their medical records. None were lost to follow-up before the trial end date (October, 1997). All trial participants were flagged in the National Health Service Central Register and notifications of cancer or death were obtained until September, 2009.

BDAT[19] recruited 5139 male doctors (4377 in 1978 and 762 in 1979) who were resident in the UK, born on or after 1900, had no contraindication to 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) versus no aspirin or products containing aspirin. Placebo tablets were not used. Treatment was continued until 1984. All participants were asked to complete a questionnaire every 6 months about their health and use of aspirin. 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.[12,13]

UK-TIA[18] recruited 2435 patients with a recent TIA or minor ischaemic stroke from 33 centres in the UK and Ireland between 1979 and 1985. Participants were older than 40 years, with no aspirin intolerance, alcoholism, chronic renal failure, or peptic ulceration. Randomisation was to 1200 mg aspirin daily versus 300 mg daily versus placebo, and treatment was double-blind. Patients were seen by a physician every 4 months until the end of the trial in 1986, and none were lost. Data for deaths and incident cancers notified during and after the trial until 2006 were obtained from national registries, as reported previously.[12,13]

Analysis of deaths during the trial period

The effects of allocation to aspirin on risk of death due to cancer and all-cause mortality during each trial were expressed as odds ratios (ORs; with 95% CIs). Pooled estimates were obtained by fixed-effects meta-analysis. After we assessed heterogeneity in effect of aspirin across trials, individual patient data were pooled. The cumulative effect of aspirin on risk of cancer death was estimated with Kaplan-Meier curves and log-rank test (stratified by trial) and by hazard ratios (HRs) obtained from a Cox proportional hazards model stratified by trial. All analyses were by intention to treat on the basis of treatment allocation in the original trials. The following stratified analyses were done: (1) for cancers of the gastrointestinal tract versus other solid cancers versus haematological cancers, given the prior expectation of greatest effects on gastrointestinal cancers (defined as primary site oesophagus, stomach, small intestine, colon, rectum, pancreas, biliary tract, gallbladder, and liver); (2) for the first 5 years after randomisation versus thereafter, given the expectation of greater effects after scheduled treatment and follow-up for at least 5 years; (3) for common specific solid cancers (oesophagus [with histological type], stomach, pancreas and biliary tract, colorectal, liver, lung [with histological type], prostate, bladder and kidney, and metastases with unknown primary [with histological type]).

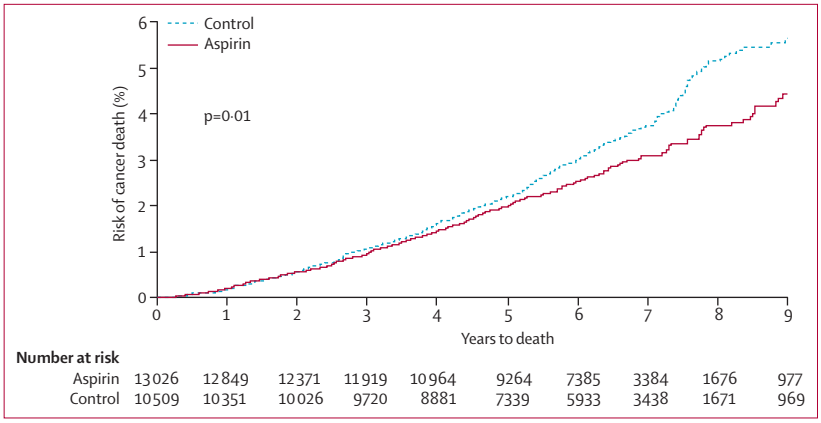

Figure 2: **Effect of allocation to aspirin versus control on risk of death due to cancer during the trial treatment periods in a pooled analysis of the 23 535 patients in seven trials[17-21,23,24]**

	n	0–5 years' follow-up		≥5 years' follow-up	
		HR (95% CI)	p value	HR (95% CI)	p value
Site of primary cancer*					
Gastrointestinal					
Oesophagus	23	0·78 (0·27–2·23)	0·64	0·43 (0·11–1·72)	0·23
Pancreas	45	0·88 (0·44–1·77)	0·73	0·25 (0·07–0·92)	0·04
Colorectal	54	0·78 (0·39–1·56)	0·48	0·41 (0·17–1·00)	0·05
Stomach	36	1·85 (0·81–4·23)	0·14	3·09 (0·64–14·91)	0·16
Other	24	0·67 (0·23–1·99)	0·47	0·20 (0·04–0·91)	0·04
All	182	0·96 (0·67–1·38)	0·81	0·46 (0·27–0·77)	0·003
Non-gastrointestinal					
Lung	198	0·92 (0·65–1·30)	0·65	0·68 (0·42–1·10)	0·11
Prostate	37	0·70 (0·29–1·73)	0·44	0·52 (0·20–1·34)	0·17
Bladder and kidney	31	1·04 (0·44–2·47)	0·93	1·28 (0·36–4·54)	0·70
Other solid	93	0·86 (0·52–1·44)	0·57	1·01 (0·51–1·98)	0·98
All	359	0·90 (0·69–1·16)	0·41	0·76 (0·54–1·08)	0·12
Unknown primary	36	0·56 (0·28–1·15)	0·12	0·56 (0·09–3·38)	0·53
All solid cancers	577	0·88 (0·72–1·08)	0·22	0·64 (0·49–0·85)	0·002
Histological type†					
Adenocarcinoma	247	0·86 (0·62–1·18)	0·34	0·53 (0·35–0·81)	0·003
Non-adenocarcinoma	224	0·89 (0·65–1·23)	0·48	0·79 (0·50–1·24)	0·30
Unknown	106	0·91 (0·58–1·44)	0·70	0·69 (0·34–1·43)	0·32
Haematological	50	0·82 (0·44–1·54)	0·53	0·34 (0·09–1·28)	0·11
All cancers*	627	0·88 (0·72–1·06)	0·17	0·62 (0·47–0·82)	0·001
All cancers including ETDRS‡	657	0·86 (0·71–1·04)	0·11	0·66 (0·50–0·87)	0·003

The numbers of cancer deaths included from each trial are those shown on webappendix p 3. n=number of cancer deaths. HR=hazard ratio. ETDRS=Early Treatment Diabetic Retinopathy Study. *Analysis confined to the six trials with site-specific cancer data follow-up.[17-19,21,23,24] †Analysis confined to solid (non-haematological) cancers. ‡Analysis included cancer deaths in ETDRS,[20] in which neither primary site nor histological type was known in any case.

Table 1: **Pooled analysis of the effect of allocation to aspirin on risk of death due to cancer during the seven trials from which individual patient data were available,[17-21,23,24] stratified by type of primary tumour and period of follow-up**

Analysis of long-term risk of cancer death

For long-term follow-up of the three UK trial cohorts,[17–19] all death certificate and cancer registration data relating to events occurring after the trials were also coded according to ICD 9 or 10 (masked to treatment

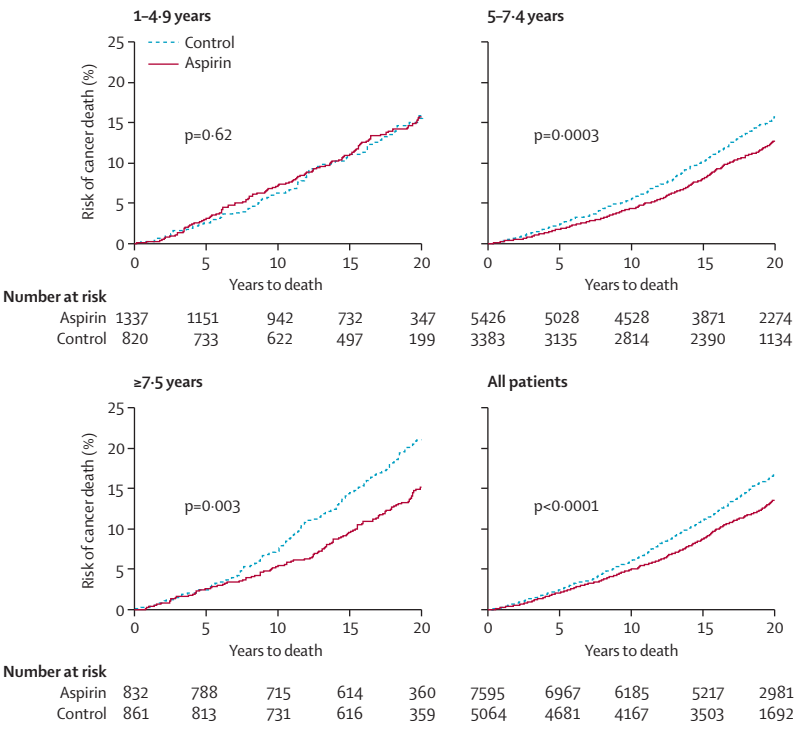

Figure 3: **Effect of allocation to aspirin versus control on 20-year risk of death due to any solid cancer stratified by scheduled duration of trial treatment in three trials with long-term follow-up[17–19]**
Continuous variable interaction, p=0·01.

See Online for webappendix

allocation). Fatal cancers were defined as those in which the cancer had been recorded as the primary underlying cause of death on the death certificate. After checking for heterogeneity between the trials in the absolute risk of cancer death during the trial and post-trial follow-up, which might confound a pooled analysis, and in the effect of allocation to aspirin on cancer death, we pooled individual patient data. Scheduled duration of trial treatment was 5 or 6 years in BDAT and ranged from 1 to 7 years in UK-TIA and from 4 to 9 years in TPT. The effect of scheduled duration of trial treatment on 20-year risk of cancer death was explored within each trial and in the pooled data with an interaction term in a Cox model with duration modelled as a continuous variable, and subsequent analyses were stratified accordingly (≤5 *vs* 5–7·4 *vs* ≥7·5 years). All analyses were done on an intention-to-treat basis, with scheduled duration of treatment simply defined as date of randomisation to date of the end of the trial, irrespective of compliance with treatment. The effect of aspirin on 20-year risk of cancer death was also stratified by category of cancers (gastrointestinal tract *vs* other solid *vs* haematological), by period of follow-up (0–10 *vs* 10–20 years), and was determined for deaths due to specific cancers (as defined above) in the 10 502 patients with more than 5 years' scheduled duration of trial treatment. In TPT, the effect of aspirin versus placebo was compared with that of warfarin versus placebo.

Role of the funding source

The study was unfunded and was independent of any pharmaceutical company or other commercial interest. 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

Trials

Of eight eligible randomised trials of aspirin versus control (webappendix p 1) with a mean duration of scheduled treatment before the end of the trial of 4 years or more, two had been done in primary prevention of vascular disease,[17,19] one in secondary prevention after recent vascular events,[18] and five in groups with increased vascular risk without previous vascular events (type 1 or 2 diabetes;[20] type 2 diabetes;[21] stable angina;[22] diabetes with asymptomatic peripheral arterial disease;[23] low ankle brachial index[24]). Data for the number of deaths due to cancer were available from all eight trials. Individual patient data were available from seven trials, but all records of one trial had been destroyed (Juul-Moller S, University Hospital, Malmo, Sweden, personal communication).[22]

In-trial deaths

During the eight trials there were 674 deaths due to cancer among 25 570 patients. The proportion of all deaths that were due to cancer varied (p<0·0001), ranging from 4·2% in the young diabetic population in the Early Treatment Diabetic Retinopathy Study (ETDRS),[20] 12·8% and 15·4% in the patients with symptomatic vascular disease in the 1980s in UK-TIA[18] and the Swedish Angina Pectoris Aspirin Trial,[22] to 28·7% (Prevention of Progression of Arterial Disease and Diabetes [POPADAD] study),[23] 29·2% (BDAT),[19] 45·4% (TPT),[17] 46·4% (Aspirin for Asymptomatic Atherosclerosis [AAA] trial),[24] and 47·9% (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes [JPAD] study)[21] in lower vascular risk or more recently recruited cohorts. However, there was very little heterogeneity between trials (figure 1; p_{het}=0·84) in the effect of allocation to aspirin on risk of death due to cancer (OR 0·79, 95% CI 0·68–0·92, p=0·003, overall; 0·81, 0·68–0·97, p=0·03, in trials of aspirin 75–100 mg daily). Reclassification of cause of death in a small number of cases in UK-TIA and TPT had little effect on the pooled estimate (686 deaths; OR 0·80, 0·69–0·93, p=0·004, webappendix p 3). The reduction in cancer deaths on aspirin during the trials resulted in lowered in-trial all-cause mortality (10·2% *vs* 11·1%, OR 0·92, 0·85–1·00, p=0·047, webappendix p 4), even though other deaths were not reduced (0·98, 0·89–1·07, p=0·63).

In our analysis of individual patient data for time to death, which were available for seven trials (657 cancer

	n	0–10 years' follow-up		10–20 years' follow-up		0–20 years' follow-up	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Solid cancers							
Gastrointestinal							
Oesophagus	62	0·53 (0·24–1·18)	0·12	0·36 (0·18–0·71)	0·003	0·42 (0·25–0·71)	0·001
Pancreas	77	0·82 (0·41–1·67)	0·59	0·79 (0·44–1·42)	0·43	0·81 (0·51–1·26)	0·34
Colorectal	179	0·79 (0·49–1·26)	0·32	0·51 (0·35–0·74)	0·0005	0·60 (0·45–0·81)	0·0007
Stomach	71	1·36 (0·64–2·90)	0·43	0·42 (0·23–0·79)	0·007	0·69 (0·43–1·10)	0·11
Other	18	0·68 (0·14–3·36)	0·64	1·97 (0·53–7·27)	0·31	1·33 (0·50–3·54)	0·57
All	409	0·80 (0·59–1·08)	0·14	0·56 (0·44–0·72)	<0·0001	0·65 (0·53–0·78)	<0·0001
Non-gastrointestinal							
Lung	326	0·68 (0·50–0·92)	0·01	0·75 (0·55–1·02)	0·07	0·71 (0·58–0·89)	0·002
Prostate	210	0·83 (0·47–1·46)	0·52	0·80 (0·58–1·09)	0·15	0·81 (0·61–1·06)	0·12
Bladder and kidney	94	0·75 (0·41–1·37)	0·35	0·90 (0·52–1·57)	0·72	0·83 (0·55–1·25)	0·37
Other solid	128	0·68 (0·39–1·17)	0·16	1·28 (0·80–2·05)	0·31	0·98 (0·69–1·39)	0·91
All	757	0·71 (0·56–0·88)	0·002	0·85 (0·71–1·03)	0·10	0·79 (0·69–0·91)	0·001
Unknown primary	89	1·19 (0·58–2·42)	0·63	0·95 (0·56–1·61)	0·84	1·03 (0·67–1·57)	0·90
All solid cancers	1251	0·76 (0·63–0·90)	0·002	0·75 (0·65–0·87)	0·0001	0·75 (0·67–0·84)	<0·0001
Histological type*							
Adenocarcinoma	648	0·70 (0·54–0·91)	0·008	0·64 (0·53–0·77)	<0·0001	0·66 (0·56–0·77)	<0·0001
Non-adenocarcinoma	302	1·04 (0·72–1·52)	0·83	0·74 (0·55–0·98)	0·04	0·87 (0·70–1·08)	0·21
Unknown	331	0·66 (0·49–0·90)	0·01	1·12 (0·83–1·52)	0·46	0·84 (0·67–1·05)	0·13
Haematological cancers	126	1·31 (0·69–2·50)	0·41	1·00 (0·65–1·54)	0·99	1·09 (0·76–1·56)	0·65
All cancers	1378	0·79 (0·66–0·93)	0·005	0·77 (0·67–0·89)	0·0002	0·78 (0·70–0·87)	<0·0001

Analysis limited to patients with scheduled duration of trial treatment or 5 years or longer. n=number of cancer deaths. HR=hazard ratio. *Analysis confined to solid (non-haematological) cancers.

Table 2: **Pooled analysis of the effect of allocation to aspirin on the 20-year risk of death due to cancer during and after the trial treatment periods in the 10 502 patients with scheduled treatment duration of 5 years or longer in the three trials with long-term follow-up,[17–19] stratified by type of primary tumour and period of follow-up**

deaths in 23 535 patients based on data in web-appendix p 3),[17–21,23,24] aspirin reduced deaths due to cancer (HR 0·82, 0·70–0·95, p=0·01, figure 2), due mainly to fewer deaths after five years (0·66, 0·50–0·87, p=0·003; table 1), but had no effect on other deaths (n=1871; 1·03, 0·94–1·13, p=0·54). Data were available for the site of the primary cancer in six trials (627 cancer deaths in 19 824 patients).[17–19,21, 23,24] Aspirin reduced deaths due to gastrointestinal cancers and deaths due to non-gastrointestinal solid cancers (table 1), with most benefit again seen after 5 years of scheduled trial treatment (gastrointestinal cancers, HR 0·46, 0·27–0·77, p=0·003; non-gastrointestinal solid cancers, 0·76, 0·54–1·08, p=0·12), and including significant reductions in colorectal and pancreatic cancer deaths (table 1).

Post-trial follow-up

Follow-up was obtained to 20 years in TPT, BDAT, and UK-TIA (1634 cancer deaths in 12 659 patients, webappendix p 2).[17–19] Aspirin reduced the 20-year risk of death due to all solid cancers (HR 0·80, 0·72–0·88, p<0·0001) and gastrointestinal cancer (0·65, 0·54–0·78, p<0·0001), but not haematological cancer (1·03, 0·74–1·43, p=0·87). However, in both TPT and UK-TIA, in which duration of trial treatment varied, the effect on 20-year risk of solid cancer increased with duration of scheduled treatment (interaction: p=0·016 in TPT, p=0·08 in UK-TIA). This interaction remained (p=0·01) in the pooled analysis with BDAT (figure 3), with no reduction in solid cancers in patients with scheduled treatment for 1–4·9 years (HR 1·06, 0·82–1·39, p=0·62), significant benefit with 5–7·4 years (0·79, 0·70–0·90, p=0·0003), and greatest benefit with 7·5 years or longer (solid cancers, 0·69, 0·54–0·88, p=0·003; gastrointestinal cancers, 0·41, 0·26–0·66, p=0·0001). Results given below therefore refer to the 10 502 patients (1378 cancer deaths) with scheduled duration of 5 years or longer unless otherwise specified.

In patients with scheduled duration of trial treatment of 5 years or more (table 2), allocation to aspirin reduced the 20-year risk of death due to both gastrointestinal (HR 0·65, 0·53–0·78, p<0·0001) and non-gastrointestinal solid (0·79, 0·69–0·91, p=0·001) cancers. There was no significant heterogeneity in effect of aspirin across the different gastrointestinal cancers (p=0·26), but effects were greatest for oesophageal and colorectal cancers (table 2, figure 4). As expected, there was a latent period before any effect was observed, with reductions in risk of death due to oesophageal and pancreatic cancer evident from 5 years onwards and reductions in deaths due to stomach and colorectal cancer not evident until about

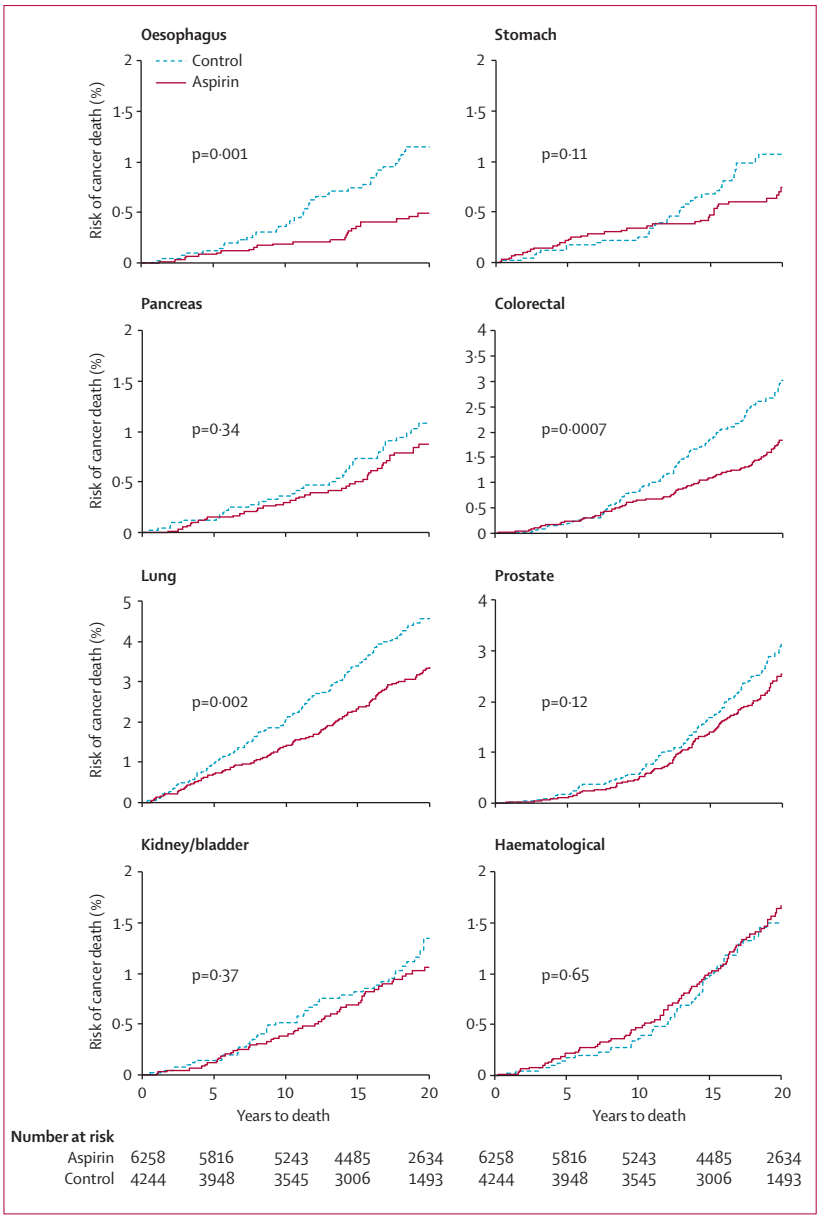

Figure 4: **Effect of allocation to aspirin versus control on the 20-year risk of death due to the most common fatal cancers in the 10 502 patients with scheduled treatment duration of 5 years or longer in the three trials with long-term follow-up[17–19]**

The eight most common cancer types are shown.

10 years (tables 1 and 2). The effect of aspirin on death due to pancreatic cancer was only significant at 20-year follow-up in patients with scheduled duration of trial treatment longer than 7·5 years (HR 0·28, 0·08–1·00, p=0·04). Overall, the absolute risk of death due to gastrointestinal cancer was reduced by 2·18% (1·14–3·22) at 20-year follow-up.

The effect of aspirin on 20-year risk of death due to non-gastrointestinal solid cancer (table 2) was attributable mainly to a reduction in deaths due to lung cancer and a non-significant late reduction in deaths due to prostate cancer (figure 4), particularly in patients with scheduled duration of trial treatment of 7·5 years or longer (HR 0·52, 0·24–1·10, p=0·08). Aspirin also reduced deaths due to primary brain tumours during the first 10 years of follow-up (5/6258 in the aspirin groups *vs* 12/4244 in the control groups; HR 0·31, 0·11–0·89, p=0·03) and mean time from randomisation to death from brain tumour remained longer in the aspirin group than in the control group at 20 years (p=0·018, webappendix p 5). Overall, the absolute risk of death due to non-gastrointestinal solid cancer was reduced by 1·88% (0·57–3·19) at 20-year follow-up.

The effect of aspirin on risk of death due to gastrointestinal cancer did not differ by age at randomisation (figure 5; interaction: relative effect, p=0·44; absolute effect, p=0·96), but the effect on death due to non-gastrointestinal solid cancers increased with age (relative effect, p=0·056; absolute effect, p=0·001). For the 20-year risk of death due to any cancer, the reductions in absolute risk in the aspirin groups were 1·41% (–0·74 to 3·56) at age less than 55 years, 4·53% (2·06–6·99) at age 55–64 years, 7·08% (2·42–11·74) at age 65 years or older, and 3·49% (1·85–5·13) at all ages combined. Relative and absolute effects were similar in smokers and non-smokers (data not shown).

Where data for histological type were available, aspirin had no effect on the 20-year risk of death due to small-cell (HR 0·85, 0·52–1·39, p=0·56) or squamous-cell (1·26, 0·73–2·18, p=0·49) lung cancers, but reduced the risk of death due to adenocarcinoma of lung (0·55, 0·33–0·94, p=0·04). The reduction in deaths due to oesophageal cancer was also confined to adenocarcinoma (HR 0·36, 0·21–0·63, p=0·0001), although the number of squamous-cell cancers was small (9/6258 in the aspirin groups *vs* 2/4244 in the control groups). Indeed, across all cancers (tables 1 and 2, webappendix p 6), aspirin only reduced deaths due to either histologically proven adenocarcinomas or primary cancers in which adenocarcinoma predominates (stomach, small bowel, pancreas, bile duct, colon, rectum, breast, uterus, ovary, and prostate). This effect on adenocarcinoma was consistent across the three trials (webappendix p 7) and for different doses of aspirin (webappendix p 6), but was not seen in the comparison of warfarin versus placebo in TPT (figure 6).

In patients with scheduled duration of trial treatment of 5 years or longer, all-cause mortality was reduced at 15 years' follow-up (HR 0·92, 0·86–0·99, p=0·03), due entirely to fewer cancer deaths, but this effect was no longer seen at 20 years (0·96, 0·90–1·02, p=0·37). However, the effect on post-trial deaths was diluted by a transient increase in risk of vascular death in the aspirin groups during the first year after completion of the trials (75 observed *vs* 46 expected, OR 1·69, 1·08–2·62, p=0·02), presumably due to withdrawal of trial aspirin.

Discussion

We showed previously that treatment with aspirin for longer than 5 years reduced the long-term risk of colorectal cancer.[12,13] In analyses of nearly 2000 cancer deaths, we now show that aspirin also reduces deaths due to several other common cancers (panel). First, we showed by meta-analysis that aspirin reduced the risk of death due to cancer by about 20% during the trials. Second, by analysis of individual patient data we showed that this benefit was due mainly to a delayed reduction of about 30–40% in deaths after 5 years of treatment. Third, by long-term follow-up of three large trials we showed that the reduction in deaths due to solid cancers was maintained for 20 years, only becoming apparent for some cancers after completion of the trials. Fourth, these effects were consistent across trials, despite the very different populations, suggesting that the findings will be generalisable. Fifth, as shown for colorectal cancer,[12,13] the effect of aspirin increased with duration of scheduled trial treatment. Sixth, the effect was limited to certain cancers, most particularly adenocarcinomas. Seventh, the effect did not appear to increase at aspirin doses greater than 75 mg daily. Eighth, the absolute reduction in death due to cancer increased with age, within the range of patients entered into the trials. Finally, the effect of aspirin on risk of fatal cancers resulted in a small reduction in all-cause mortality.

Our analyses were conservative in several respects. First, although all but one of the trials we studied were double-blind, there were high rates of drop-outs from randomised treatment. In the trials in which we obtained long-term follow-up, about 40% of patients in the aspirin groups had stopped treatment by the end of the trial periods.[17–19] Nevertheless, to reduce bias we restricted our analyses to intention to treat. Second, since the effect of aspirin increased with scheduled duration of trial treatment, but the trials were of finite length, it is likely that we underestimated the benefit of long-term treatment on deaths due to cancer. The difference in aspirin use between the treatment groups was already limited by the end of BDAT, many patients in the TPT control group went on to aspirin after the trial,[25] and post-trial aspirin use would not have differed much between the treatment groups in UK-TIA because trial treatment allocation was never revealed.

The trials that we studied were randomised, but could our findings have been due to bias? First, the trials were not designed to study cancer. However, cancer deaths were recorded during the trials, and long-term follow-up via UK cancer registration achieves high rates of ascertainment and accuracy,[26–28] as we found previously for colorectal cancer.[12,13] Attribution of cause of death during the trials was masked to treatment allocation, as was coding of the cause of post-trial deaths. Attribution was usually based on death certification, supported by any previous cancer registration, which has been shown previously to agree well with expert committee review.[29–31] Second, lack of knowledge among the trial investigators that data might later be used to study the effect of aspirin on risk of cancer will have limited any potential investigator bias. Third, investigation of side-effects of aspirin, such as anaemia and bleeding, might have resulted in earlier diagnosis of cancers and hence a reduction in later deaths. However, analysis of time to incidence of colorectal cancer showed no evidence of earlier diagnosis,[13] and the very low cure rates of cancers such as oesophageal cancer would limit any bias due to earlier diagnosis. The only evidence of a possible effect of increased investigation in the aspirin groups was a transient increase in risk of deaths attributed to stomach cancer during the trials, and a transient reduction in deaths attributed to cancers with unknown primary site (table 1). Moreover, the complete lack of any effect of warfarin on cancer deaths in TPT suggests that

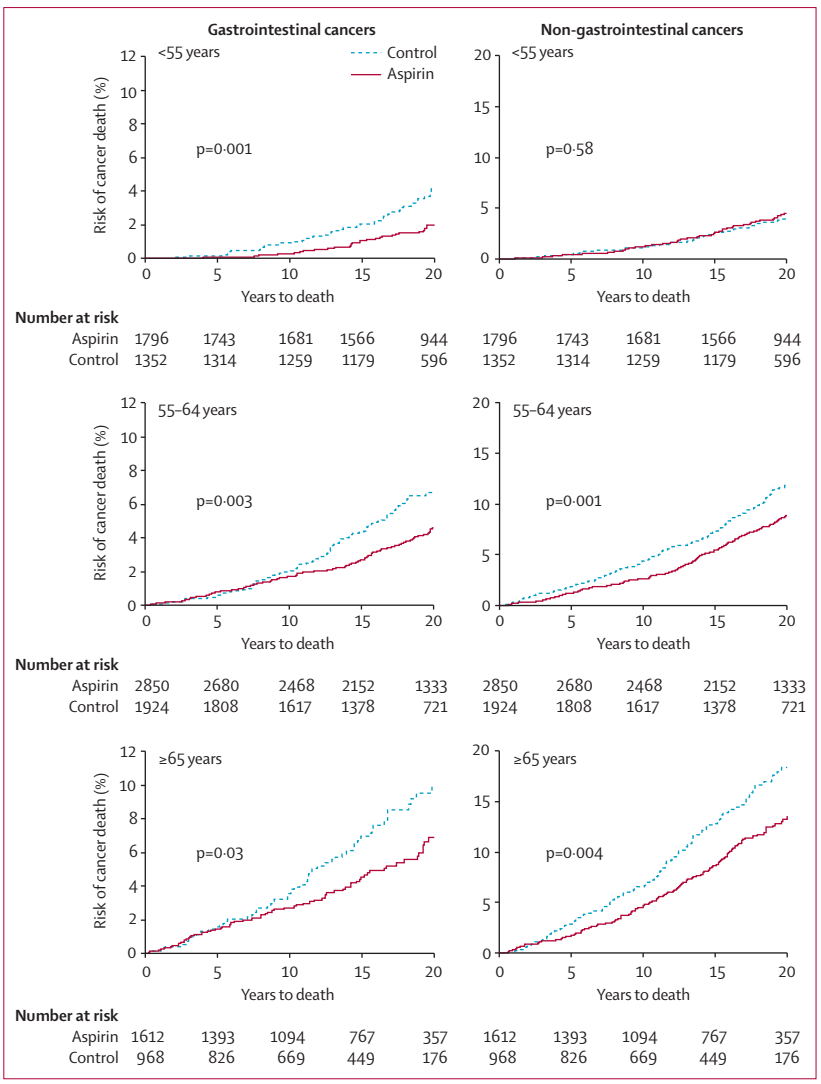

Figure 5: **Effect of allocation to aspirin versus control on risk of death due to cancers of the gastrointestinal tract and other solid cancers in the 10 502 patients with scheduled treatment duration of 5 years or longer, stratified by age at randomisation in three trials with long-term follow-up[17–19]**

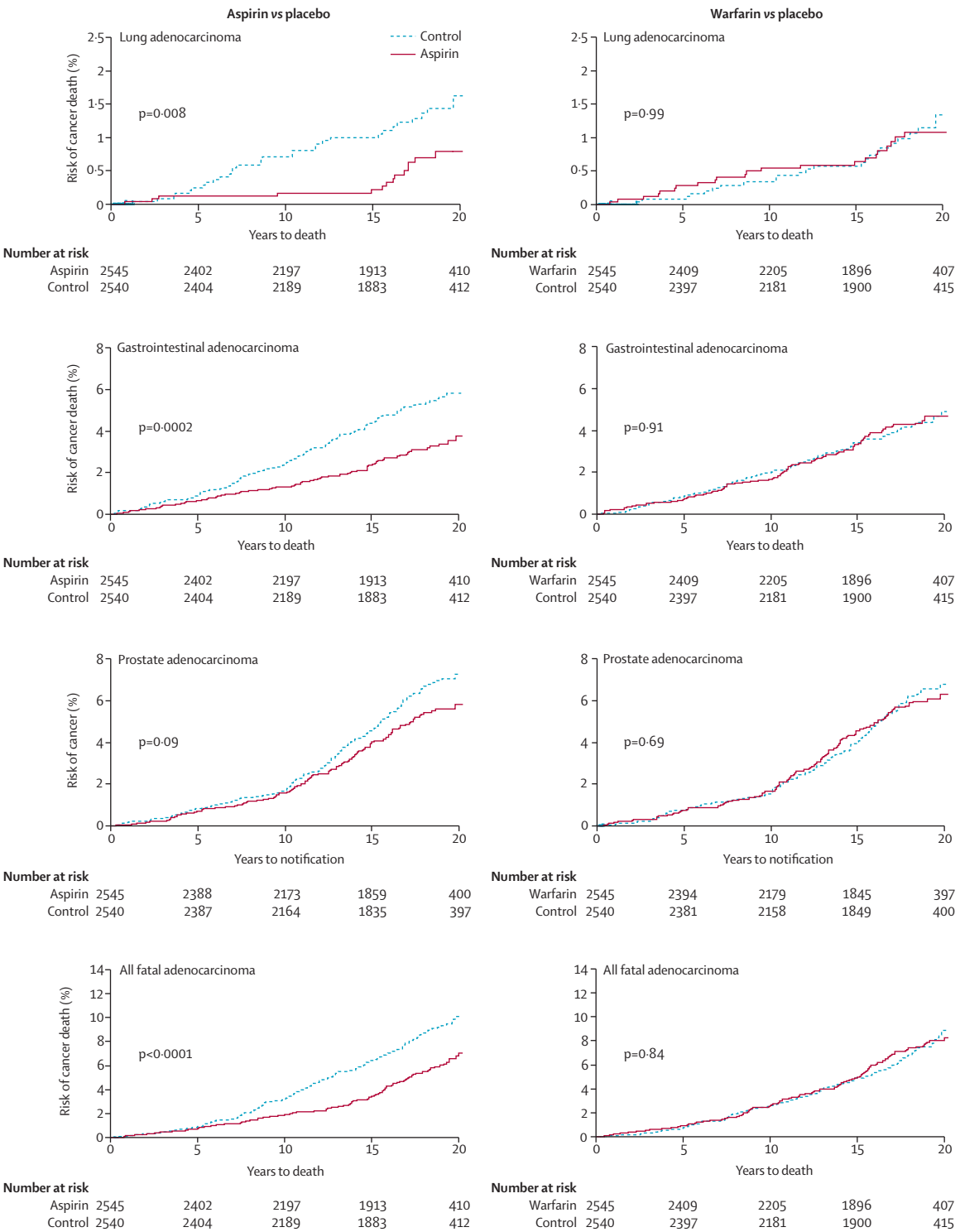

Figure 6: **Comparison of effect of allocation to aspirin or warfarin versus placebo on risk of death due to adenocarcinoma during long-term follow-up of the Thrombosis Prevention Trial[17]**

Analysis includes all patients, irrespective of scheduled duration of trial treatment. Analysis of prostate cancer also includes non-fatal cancers because of the small numbers of fatal cancers in the single trial.

Panel: **Research in context**

Findings

Using individual patient data from all randomised trials of daily aspirin versus no aspirin with mean duration of scheduled trial treatment longer than 4 years, we showed that aspirin reduced risk of death due to cancer by about 20% in the trials, due mainly to a 34% reduction in cancer deaths after 5 years. By long-term post-trial follow-up of patients in three of these trials, we showed that the 20-year risk of cancer death remained about 20% lower in the aspirin groups, and that benefit increased with scheduled duration of treatment in the original trial. The latent period before an effect on deaths was about 5 years for oesophageal, pancreatic, brain, and lung cancer, but was more delayed for stomach, colorectal, and prostate cancer. For lung and oesophageal cancer, benefit was confined to adenocarcinomas.

Interpretation

These findings provide the first proof in man that aspirin reduces deaths due to several common cancers. Benefit was consistent across the different trial populations, suggesting that the findings are likely to be generalisable.

early diagnosis due to bleeding is unlikely to have been a major source of bias. Fourth, many patients would probably have stopped taking their trial drug if they developed cancer. Stopping aspirin could in some cases have triggered a fatal vascular event that might have resulted in an underlying cancer not being diagnosed or at least not being listed on the death certificate as the underlying cause of death. However, there was no evidence of any excess of non-fatal vascular events during the year before death due to cancer in the aspirin groups (data not shown), and most of the reduction in cancer deaths occurred after the trials. Finally, we had long-term post-trial follow-up from only three of the trials, but this factor was determined simply by the country in which the trials were done and the era. Moreover, the effect of aspirin on in-trial cancer deaths was no greater in these trials than in the others (figure 1).

These results therefore provide the first reliable evidence that aspirin prevents non-colorectal cancer in humans, which is consistent with previous predictions of effects on cancers of the oesophagus, stomach, pancreas, lung, prostate,[7] and possibly brain.[32,33] However, more work is required. Effects of aspirin on incidence of cancer must be determined, both for cancers that are less commonly fatal and to determine whether the latent period before an effect is shorter than for death. More trial data are required for the effect of aspirin on risk of breast and other cancers of women. Follow-up beyond 20 years is necessary to identify any late rebound in cancer deaths. The estimate of effect of aspirin on death due to cancer in the first 5 years of the trials does not exclude a clinically important short-term benefit for cancers that would probably have already been present at randomisation, and so pooled analysis of trials with shorter follow-up is also required. To address each of these issues, the Non-Vascular Outcomes on Aspirin Collaboration is collating all available data from trials of aspirin (Rothwell, personal communication) and will report further results in 2011.

Our study does have several potential limitations. First, we included only trials of daily aspirin. Alternate-day aspirin was used in other trials in prevention of vascular events because aspirin irreversibly inhibits COX-1 in platelets, but this effect would not be irreversible in other tissues, and observational studies have highlighted the importance of daily aspirin in associations with reduced incidence of cancer.[5–8,12] 10-year follow-up of the Women's Health Study, a randomised trial of aspirin 100 mg on alternate days versus control, did show a possible reduction in incidence of lung cancer, but there was no reduction in other cancers or in overall cancer incidence.[16] Second, although there was no evidence of any sex-related difference in the effect of aspirin on deaths due to cancer during the trials (data not shown), or in previous observational studies, we had too few women in the trials with long-term follow-up to allow us to determine the effects of aspirin on breast or gynaecological cancers. Third, analysis of effect of aspirin on adenocarcinoma overall was data-dependent, although analysis of histological subtype of lung and oesophageal cancers was prespecified. Fourth, we were unable to determine the effect of long-term (eg, 20–30 years) continued aspirin use on cancer death or all-cause mortality because of the finite duration of the trials. The transient increase in risk of vascular deaths in the aspirin groups after the trials, consistent with studies of aspirin withdrawal,[34,35] also diluted the effect that we did observe on long-term mortality. Finally, the benefits of aspirin may be less in populations with a high dietary intake of salicylates.

Our results have implications for clinical practice. Since other antiplatelet drugs do not reduce risk of cancer death in randomised trials (Rothwell, unpublished data), patients with an indication for long-term antiplatelet treatment are likely, on average, to benefit most from aspirin. Although the reduction in risk of ischaemic vascular events on aspirin in healthy individuals is partly offset by a small increase in risk of non-fatal bleeding complications,[36–38] the balance of risk and benefit will now be altered by the reduction in cancer deaths after 5 years' treatment. Our analyses show that taking aspirin daily for 5–10 years would reduce all-cause mortality (including any fatal bleeds) during that time by about 10% (relative risk reduction). Subsequently, there would be further delayed reductions in risk of cancer death, but no continuing excess risk of bleeding. In terms of cost-effectiveness,[39] such benefit would exceed that of established initiatives such as screening for breast or prostate cancer, potentially justifying added costs to reduce bleeding complications, such as co-prescription of a proton-pump inhibitor,[40,41]

treatment to eradicate *Helicobacter pylori* infection,[42] and further development of potentially more effective derivatives of aspirin.[43] Moreover, since the effect of aspirin on risk of cancer death increased with scheduled duration of trial treatment, the roughly 30% reduction in 20-year risk of cancer deaths observed in patients with scheduled trial treatment of 7·5–10 years may well underestimate the benefit that would result from longer-term treatment (eg, from age 50–75 years). Indeed, a late rebound in cancer deaths in the aspirin group at 10–20 years' follow-up is clearly present for some cancers (figures 4 and 6, webappendix p 5). Finally, our results have implications for understanding of carcinogenesis, particularly for adenocarcinoma, and they demonstrate the potential for drug intervention in the prevention of cancer. Although the effect of aspirin may be mediated in part by inhibition of COX-2, more research is required, other pro-apoptotic effects early in the development of tumours perhaps also being important.[43,44]

Contributors

PMR conceived and coordinated the project, obtained long-term follow-up of the UK-TIA trial, collated all data, planned and performed all analyses, and wrote the report. FGRF was principal investigator on the AAA trial. JFFB was principal investigator on the POPADAD trial. HO was principal investigator on the JPAD trial. CPW was principal investigator on the UK-TIA aspirin trial. TWM was principal investigator on the TPT and obtained long-term follow-up data. All authors commented on drafts of the report.

Conflicts of interest

This study was completely independent of any pharmaceutical company or other commercial interest. However, PMR has 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-Aventis/Bristol-Myers Squibb, and Servier. FGRF has had research support, honoraria, and travel expenses from Bayer and Sanofi-Aventis/Bristol-Myers Squibb. JFFB has received payment for board membership from Roche Pharmaceuticals and Sanofi-Aventis. HO has received speakers' fees from Astellas, AstraZeneca, Banyu, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Eisai, Guidant Japan, Japan Lifeline, Kowa, Kyowa Hakko Kirin, Novartis, Otsuka, Pfizer, Sanofi-Aventis, Schering-Plough, and Takeda. CPW has received speakers' fees from Bayer for a talk about aspirin. TWM has received an honorarium and travel expenses from Bayer.

Collaborators

Emily Chew (ETDRS; National Eye Institute, Bethesda, MD, USA); Takeshi Morimoto (JPAD trial; Kyoto University Graduate School of Medicine, Kyoto, Japan); Richard Peto (BDAT; University of Oxford, Oxford, UK).

Acknowledgments

The study received no specific funding. Funding of the original trials was as reported previously.[17–19,22–26] The cost of coordination of the project and collation and analysis of data was met by unrestricted research funds from the Stroke Prevention Research Unit, Oxford. PMR is in receipt of an NIHR Senior Investigator Award. We thank Jill Boreham for help with access to data from the BDAT; Christine Knottenbelt and Marilyn Goulding for their help in accessing long-term follow-up data from TPT and Michelle Wilson for help in coding these data; Izzy Butcher for help with data from AAA; and Robert Lee for help with data from POPADAD. We thank Ziyah Mehta for help with analysis and production of graphs.

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