Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials

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Summary

Background **Daily aspirin reduces the long-term risk of death due to cancer. However, the short-term effect is less certain, especially in women, effects on cancer incidence are largely unknown, and the time course of risk and benefit in primary prevention is unclear. We studied cancer deaths in all trials of daily aspirin versus control and the time course of effects of low-dose aspirin on cancer incidence and other outcomes in trials in primary prevention.**

Methods **We studied individual patient data from randomised trials of daily aspirin versus no aspirin in prevention of vascular events. Death due to cancer, all non-vascular death, vascular death, and all deaths were assessed in all eligible trials. In trials of low-dose aspirin in primary prevention, we also established the time course of effects on incident cancer, major vascular events, and major extracranial bleeds, with stratification by age, sex, and smoking status.**

Results **Allocation to aspirin reduced cancer deaths (562 *vs* 664 deaths; odds ratio [OR] 0·85, 95% CI 0·76–0·96, p=0·008; 34 trials, 69 224 participants), particularly from 5 years onwards (92 *vs* 145; OR 0·63, 95% CI 0·49–0·82, p=0·0005), resulting in fewer non-vascular deaths overall (1021 *vs* 1173; OR 0·88, 95% CI 0·78–0·96, p=0·003; 51 trials, 77 549 participants). In trials in primary prevention, the reduction in non-vascular deaths accounted for 87 (91%) of 96 deaths prevented. In six trials of daily low-dose aspirin in primary prevention (35 535 participants), aspirin reduced cancer incidence from 3 years onwards (324 *vs* 421 cases; OR 0·76, 95% CI 0·66–0·88, p=0·0003) in women (132 *vs* 176; OR 0·75, 95% CI 0·59–0·94, p=0·01) and in men (192 *vs* 245; OR 0·77, 95% CI 0·63–0·93, p=0·008). The reduced risk of major vascular events on aspirin was initially offset by an increased risk of major bleeding, but effects on both outcomes diminished with increasing follow-up, leaving only the reduced risk of cancer (absolute reduction 3·13 [95% CI 1·44–4·82] per 1000 patients per year) from 3 years onwards. Case-fatality from major extracranial bleeds was also lower on aspirin than on control (8/203 *vs* 15/132; OR 0·32, 95% CI 0·12–0·83, p=0·009).**

Interpretation **Alongside the previously reported reduction by aspirin of the long-term risk of cancer death, the short-term reductions in cancer incidence and mortality and the decrease in risk of major extracranial bleeds with extended use, and their low case-fatality, add to the case for daily aspirin in prevention of cancer.**

Funding **None.**

Introduction

Cancer is the second most common cause of premature death worldwide and 5 million new cases are diagnosed each year in Europe and USA alone.[1–3] There is evidence that daily aspirin might prevent several common cancers,[4–8] with both case-control and cohort studies suggesting an association between daily aspirin use and reduced risk of cancer, particularly of the gastrointestinal tract.[4–8] Long-term follow-up of randomised trials of daily aspirin versus control in prevention of vascular events showed that aspirin reduced incidence and mortality due to colorectal cancer after a delay of 8–10 years,[9,10] and reduced deaths due to several other common cancers after 5–15 years.[11] However, several important questions remain. First, to maximise the potential to detect an effect, the recent study of effects of aspirin on long-term mortality was limited to trials with a mean duration of scheduled treatment of 4 years or more,[11] restricting statistical power to detect earlier effects on in-trial deaths. Second, the effect of aspirin on cancer incidence was not studied. Third, the two largest trials studied included only men and no data were reported for the effects of aspirin on risk of cancer in women.[9–11] Although 10-year follow-up of the Women's Health Study,[12] a randomised trial of alternate-day aspirin 100 mg versus control, did not show a reduction in overall cancer incidence in women, the rationale for alternate-day dosing (irreversible inhibition of COX-1 in platelets) might not be relevant to effects on cancers, and the importance of daily use has been emphasised in observational studies.[5–9] Fourth, the key clinical issue, the overall balance of risk and benefit of daily low-dose aspirin in primary prevention, was not addressed in the recent reports.[9–11] Finally, in view of the need to inform decisions about long-term use of aspirin in prevention of cancer, the evolution of risks and benefits with extended duration of use must be established.

We aimed to address these five areas of uncertainty. To increase reliability of estimates of early effects on cancer

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death, we studied all trials of daily aspirin versus control. To reduce biases due to selective availability of data or misclassification of cause of death, we also studied all non-vascular deaths. To establish the effect of aspirin on cancer incidence, we studied individual patient data from all trials of daily low-dose aspirin in primary prevention, also looking separately at effects in women. To estimate the likely balance of risk and benefit with extended use of aspirin, we established the time course of effects on cancer incidence, major vascular events, and major extracranial bleeds.

Methods

Search strategy and selection criteria

We identified trials from rigorous systematic reviews of randomised controlled trials of aspirin versus control in the Antithrombotic Trialists' (ATT) Collaboration,[13,14] and by formal searches of PubMed and Embase (last done on May 12, 2011) using the terms "aspirin" or "salicyl*" or "antiplatelet" with the term "randomised controlled trial", by searching for relevant systematic reviews on the Cochrane Collaboration Database of Systematic Reviews, and by review of other published systematic reviews of trials of antiplatelet agents. No additional search was made for any unpublished trials or abstracts of data presented at meetings that were not identified by these methods. There was no restriction on language of publication.

See Online for appendix

Trials were eligible if they randomly assigned participants to daily aspirin (any dose) versus no aspirin in the absence of another antiplatelet agent in either group. Trials done on a background of anticoagulation were eligible. Only trials of daily aspirin were eligible in view of evidence that less frequent use might be less effective in prevention of cancer,[5–9] and because daily use is the norm in clinical practice. Trials of short-term (≤90 days) treatment and trials in the treatment or secondary prevention of cancer or colonic polyps were excluded. Trials were classified as being in primary prevention if patients with previous ischaemic vascular events were excluded or were low in number, irrespective of whether eligibility required vascular risk factors (eg, diabetes, peripheral arterial disease).

	Trials* (n)	Deaths/participants		Pooled odds ratio (95% CI)	p_{sig}	p_{het}
		Aspirin	Control†			
High-dose aspirin trials	31	391/16 790	453/16 803‡	0·88 (0·76–1·01)	0·11	0·76
Low-dose aspirin trials	20	630/23 479	720/23 560	0·87 (0·78–0·97)	0·01	0·89
Primary prevention trials	12	623/22 019	710/22 049§	0·88 (0·78–0·98)	0·02	0·98
Secondary prevention trials	39	398/18 250	463/18 314¶	0·88 (0·74–1·02)	0·07	0·98
All trials	51	1021/40 269	1173/40 363‖	0·88 (0·78–0·96)	0·003	0·92

*See appendix pp 5–6 for classification of trials and numbers in individual trials. †Numbers in the control group have been multiplied by two in four trials of high-dose aspirin in which the control group was deliberately 50% smaller than the active treatment group, but the odds ratio, 95% CI, and statistical significance have been calculated on the basis of the actual numbers of events and patients; actual numbers were ‡335/13720, §638/20339, ¶417/16941, and ‖1055/37280.

Table 1: **Summary results of meta-analyses of the effect of aspirin on risk of non-vascular death during 51 trials of aspirin versus control in prevention of vascular events stratified by dose of aspirin (<300 mg *vs* ≥300 mg) and the indication (primary *vs* secondary prevention)**

Procedures

Published data for vascular and non-vascular deaths during the trials were extracted from the main trial report and any subsequent reports. For trials included in previous ATT reports,[13] numbers were crossreferenced and the ATT data used if they were discrepant. For other trials, data from the main trial reports were used. For all eligible trials, individual patient data for cancer deaths during the trials (primary site, time from randomisation to death, randomised treatment allocation, cancer diagnosis before randomisation) were obtained from the trialists, if available. If not, any data for cancer deaths were extracted from the original trial reports or subsequent publications.

For trials of daily low-dose (<300 mg) aspirin in primary prevention of vascular events, individual patient data were obtained for all cancers during trial follow-up (primary site, time from randomisation to diagnosis or notification, randomised treatment allocation, cancer diagnosis before randomisation). The methods of trial follow-up and ascertainment of cancer data that were used in these trials are summarised on appendix p 3. Individual patient data for age, sex, smoking status at baseline, and for major vascular events, major extracranial bleeds, and date and cause of all deaths during trial follow-up were also obtained for all participants in these trials.

Statistical analysis

SPSS (version 20) was used for all analyses. For the analysis of mortality data, four fatal outcomes were studied in all eligible trials: death due to cancer (as coded by the original triallists); all non-vascular death (including death due to cancer); vascular death (using the same definition as the ATT—ie, including fatal haemorrhages[13]); and all deaths. All analyses were by intention to treat based on the randomised treatment allocation. For each outcome, odds ratios (ORs) were calculated for aspirin versus control in each trial and pooled estimates were obtained by fixed-effects meta-analysis (Mantel-Haenszel-Peto method). Heterogeneity was calculated with the χ^2 test. To allow direct comparison of the effects of aspirin on vascular and non-vascular deaths in the same trials, small trials with no non-vascular deaths during follow-up were not included in analyses. To reduce bias in estimation of the effect of aspirin on cancer deaths due to unavailability of cancer data from some small trials, analysis was also done including all non-vascular deaths in such trials. Using individual patient data for cancer deaths, we stratified analyses by years from randomisation to death (<3, 3·00–4·99, ≥5 years), by dose of aspirin (<300 mg *vs* ≥300 mg), and by site of primary cancer. Analyses were also done excluding cancers diagnosed before randomisation.

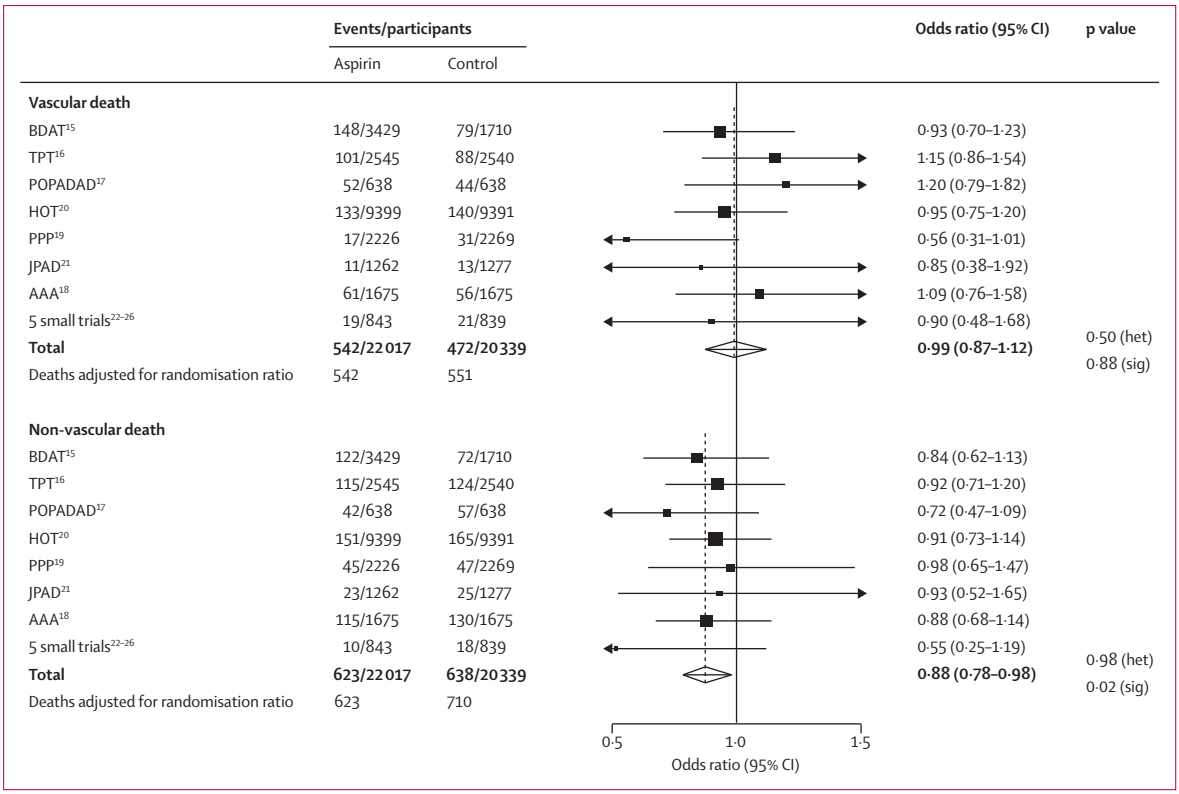

Figure 1: **Meta-analysis of the effect of aspirin on risk of vascular death and non-vascular death during 12 randomised trials of daily aspirin versus control in primary prevention of vascular events**

Numbers of deaths are also given after adjustment for the 2:1 randomisation ratio in BDAT. BDAT=British Doctors Aspirin Trial. TPT=Thrombosis Prevention Trial. POPADAD=Prevention of Progression of Arterial Disease and Diabetes. HOT=Hypertension Optimal Treatment. PPP=Primary Prevention Project. JPAD=Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes. AAA=Aspirin for Asymptomatic Atherosclerosis.

Analysis of effect of aspirin on cancer incidence (excluding non-melanoma skin cancers) was done in trials of daily low-dose aspirin in primary prevention of vascular events. Meta-analysis of effects in individual trials was done with stratification by time to diagnosis or first notification during trial follow-up (<3, 3·00–4·99, ≥5 years). Individual patient data were then pooled and Kaplan-Meier curves (1–proportion free of incident cancer) generated for time to diagnosis or first notification of cancer during trial follow-up. We determined statistical significance using the log-rank test stratified by trial. Any interaction between the effect of randomised treatment on incidence of cancer and time from randomisation was assessed with an interaction term in a Cox model with time expressed as a continuous variable. The absolute reduction in cancer incidence per 1000 patient-years was determined during each period of trial follow-up with stratification by sex, age (<60 *vs* ≥60 years), and smoking status (current smoker).

In view of the small numbers of specific cancers, primary sites were grouped into several categories: gastrointestinal tract (oesophagus, stomach, pancreas, biliary tract, liver, small bowel, colon, and rectum); urinary tract (kidney, ureter, bladder, prostate, or urethra); respiratory tract (lung, pleura, larynx, pharynx, or nasopharynx); female reproductive (breast, endometrium, ovary, cervix, and vagina); haematological (lymphoma, leukaemia, and myeloma); other solid (all other solid cancers); and unknown (including metastasis with unknown primary).

	Number of deaths		Odds ratio (95% CI)	p
	Aspirin	Control		
Cancer death only*				
0–2·9 years	292	325	0·90 (0·76–1·06)	0·18
3·0–4·9 years	161	173	0·93 (0·75–1·16)	0·51
≥5 years	92	145	0·63 (0·49–0·82)	0·0005
Unknown	17	21	..	..
Total	562	664	0·85 (0·76–0·96)	0·008
Cancer death or non-vascular deaths if cancer data were unavailable†				
0–2·9 years	322	364	0·88 (0·76–1·03)	0·10
3·0–4·9 years	161	173	0·93 (0·75–1·16)	0·51
≥5 years	92	145	0·63 (0·49–0·82)	0·0005
Unknown	39	46	..	..
Total	614	728	0·85 (0·76–0·95)	0·005

*Cancer deaths available from 34 trials of aspirin versus control (69 224 participants). †Data for cancer deaths were unavailable from 17 small trials (8325 patients); all non-vascular deaths from these trials were therefore added to the data for cancer deaths from the other trials.

Table 2: **Pooled analysis of the effect of aspirin on cancer deaths in 51 trials (77 549 participants) of aspirin versus control in prevention of vascular events, stratified by years to death**

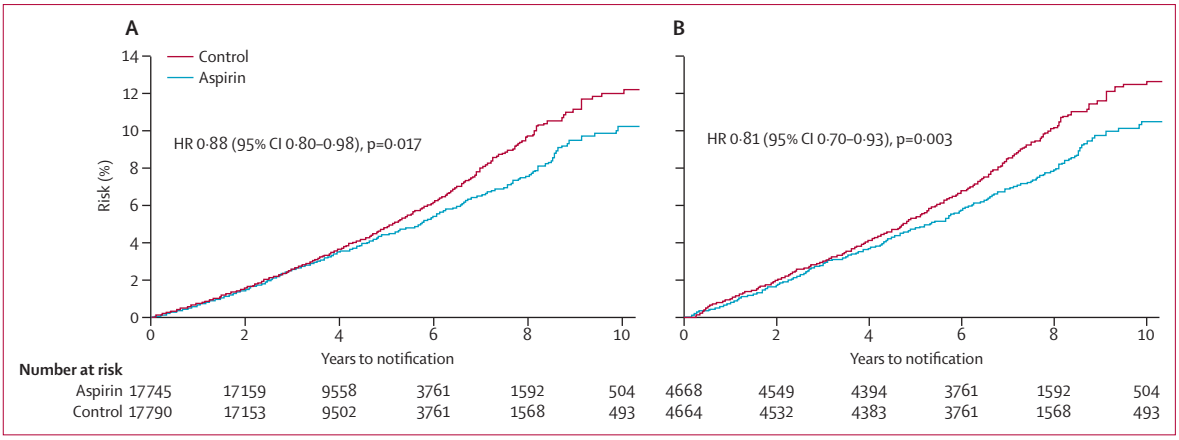

Figure 2: **Pooled analysis of effect of allocation to aspirin on incidence of cancer during six randomised trials of daily low-dose (75–100mg daily) aspirin versus placebo in primary prevention of vascular events[16–21]**
(A) All patients. (B) All patients with scheduled duration of trial treatment of at least 5 years . HR=hazard ratio.

	Number of cancers		Odds ratio (95% CI)*	p*	Absolute reduction per 1000 patient-years (95% CI)†
	Aspirin	Control			
All patients					
<3 years	445	442	1·01 (0·88 to 1·15)	0·92	–0·06 (–1·15 to 1·04)
≥3 years	324	421	0·76 (0·66 to 0·88)	0·0003	3·13 (1·44 to 4·82)
Men					
<3 years	269	284	0·94 (0·80 to 1·12)	0·49	0·60 (–0·98 to 2·18)
≥3 years	192	245	0·77 (0·63 to 0·93)	0·008	3·09 (0·85 to 5·33)
Women					
<3 years	176	158	1·13 (0·91 to 1·40)	0·28	–0·83 (–2·38 to 0·72)
≥3 years	132	176	0·75 (0·59 to 0·94)	0·01	3·19 (0·61 to 5·77)
Age <60 years					
<3 years	115	141	0·83 (0·65 to1·07)	0·14	0·92 (–0·41 to 2·25)
≥3 years	105	149	0·72 (0·56 to 0·93)	0·01	2·74 (0·69 to 4·78)
Age ≥60 years					
<3 years	330	301	1·08 (0·92 to 1·27)	0·32	–0·75 (–2·46 to 0·96)
≥3 years	219	272	0·77 (0·65 to 0·93)	0·006	3·68 (1·03 to 6·33)
Non-smokers					
<3 years	317	320	0·99 (0·85 to 1·16)	0·95	0·01 (–1·20 to 1·22)
≥3 years	202	272	0·74 (0·61 to 0·89)	0·001	3·07 (1·18 to 4·97)
Smokers					
<3 years	128	122	1·05 (0·81 to 1·35)	0·72	–0·18 (–2·90 to 2·53)
≥3 years	122	149	0·79 (0·62 to 1·02)	0·07	3·34 (–0·20 to 6·88)

*Derived from meta-analysis of individual trials by Mantel-Haenszel-Peto method. †Derived from pooled analysis of individual patient data.

Table 3: **Pooled analysis of the effect of allocation to aspirin versus control on the risk of all incident cancer during trial follow-up in the six trials of low-dose aspirin in primary prevention of vascular disease,[16–21] by years to notification**

To increase statistical power, analyses of effects of aspirin on these cancer groups were done for all incident cancers from trials of low-dose aspirin in primary prevention plus all fatal cancers from all other eligible trials.

We also analysed the time course of risk and benefits. To estimate the effect of any effect on cancer incidence on the balance of risks and benefits of daily low-dose aspirin in primary prevention, we did four analyses: (1) meta-analyses of individual trials to establish the effects of aspirin on incident cancer, major vascular events (based on ATT definition[13,14]—ie, including all stroke, myocardial infarction, other coronary death, or intracranial bleed), and major extracranial bleeds (based on ATT definition[13,14]—ie, fatal or requiring blood transfusion); (2) these same meta-analyses stratified by period of follow-up (<3 years from randomisation *vs* ≥3 years; chosen to provide similar numbers of patient-years of follow-up in both periods); (3) pooled analysis of individual patient data to establish the effect of aspirin on the absolute number of events prevented per 1000 patients per year for incident cancer, major vascular events, and major extracranial bleeding events stratified by period of trial follow-up; and (4) pooled analysis to establish the effect of aspirin on two composite outcomes (major vascular events, incident cancer, and fatal extracranial bleeds; major vascular events, incident cancer, and all major extracranial bleeds).

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

Trial inclusion

The 2009 ATT Collaboration report[14] included data from 20 trials of daily aspirin versus control in primary or secondary prevention of vascular disease, 19 of which (54037 patients) included one or more non-vascular deaths and were therefore included in our analyses (appendix pp 5–6). A further 20 eligible trials (13296 patients) included in previous reports of the ATT[13] were also included (appendix pp 5–6). The search strategy identified

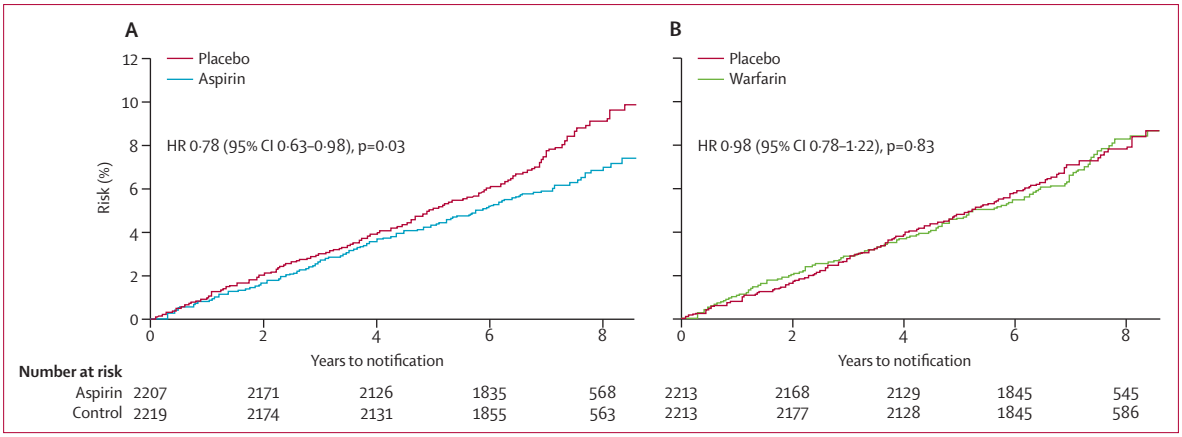

***Figure 3*: Effect of allocation to aspirin versus placebo (A) and warfarin versus placebo (B) on the incidence of cancer during the Thrombosis Prevention Trial[16]**
Analysis limited to patients with scheduled duration of trial treatment of at least 5 years. HR=hazard ratio.

19 additional trials (appendix pp 5–6), mainly published in the past 5 years, 12 (10 216 patients) of which were eligible and had one or more non-vascular deaths, resulting in inclusion of a total of 51 trials (77 549 patients; 40 269 randomly assigned to aspirin and 37 280 to control; appendix pp 5–6).

Deaths

Allocation to aspirin reduced the risk of non-vascular death in the 51 trials (1021 *vs* 1173 deaths; OR 0·88, 95% CI 0·78–0·96, p=0·003; 152 deaths avoided in 40 269 participants allocated aspirin; table 1). The proportion of deaths classed as non-vascular varied (heterogeneity p<0·0001), ranging from 10–20% in early, predominantly high-dose trials in patients with ischaemic heart disease to about 70% in predominantly low-dose trials in primary prevention (data not shown). In 12 trials in primary prevention (figure 1),[15–26] aspirin reduced non-vascular death (OR 0·88, 95% CI 0·78–0·98, p=0·02; 87 deaths avoided), but not vascular death (OR 0·99, 95% CI 0·87–1·12, nine deaths avoided), such that the effect on all-cause mortality was non-significant (1165 *vs* 1261 deaths; OR 0·92, 95% CI 0·85–1·00, p=0·06).

The number of cancer deaths by treatment group were available from 34 trials, which included 69 224 (89%) participants in the 51 eligible trials. In these trials, 1226 (58%) non-vascular deaths were due to cancer. In the remaining 17 small trials (8325 patients), only data for unspecified non-vascular death were available (appendix pp 5–6). Allocation to aspirin resulted in fewer deaths due to cancer compared with control (OR 0·85, 95% CI 0·76–0·96, p=0·008; appendix p 1, table 2). This treatment effect remained after inclusion of data for non-vascular deaths from trials without cancer data (OR 0·85, 95% CI 0·76–0·95, p=0·005; appendix p 1, table 2). Results were also similar after exclusion, where data were available, of cancers diagnosed before randomisation (OR 0·84, 95% CI 0·75–0·94, p=0·002; appendix p 1). Numbers of specific cancers were small, but allocation to aspirin did reduce deaths due to colorectal cancer (38 *vs* 65 deaths; OR 0·58, 95% CI 0·38–0·89, p=0·008) and lymphoma (14 *vs* 27; OR 0·52, 95% CI 0·26–1·00, p=0·04). The 39% reduction in deaths due to female reproductive cancers did not reach statistical significance (24 *vs* 39; OR 0·61, 95% CI 0·36–1·05, p=0·058).

Data for time from randomisation to cancer death were available from 32 trials, which included 65 973 (85%) patients in the 51 eligible trials (appendix pp 5–6). Stratification by time to death showed that most benefit occurred after 5 years' follow-up (OR 0·63, 95% CI 0·49–0·82, p=0·0005; table 2), but cancer deaths were also reduced during the first 3 years in trials of high-dose aspirin (OR 0·69, 95% CI 0·51–0·92, p=0·01; appendix p 2). This apparent dose-related effect was therefore assessed in the Dutch-TIA trial,[27] the only large randomised trial of high-dose (283 mg) versus low-dose (30 mg) aspirin in prevention of vascular events, revealing a non-significant reduction in cancer deaths on the higher dose (32/1576 *vs* 44/1555; OR 0·71, 95% CI 0·44–1·15, p=0·15).

Cancer incidence

Individual patient data for all fatal and non-fatal cancers were available from five of the six trials of daily low-dose aspirin versus control in primary prevention (32 996 participants),[16–20] and for fatal cancers in the other trial[21] (2539 participants; appendix p 3). Pooled analysis of individual patient data showed that aspirin reduced risk of cancer during trial follow-up (hazard ratio [HR] 0·88, 95% CI 0·80–0·98, p=0·017; figure 2). No effect was noted during the first 3 years of follow-up in the pooled analysis (figure 2), or in the individual trials, but benefit became apparent with increasing follow-up thereafter (interaction with duration of follow-up, p=0·04; 0–2·9 years, HR 1·00, 95% CI 0·88–1·15, p=0·94; 3–4·9 years, HR 0·81, 95% CI 0·67–0·98, p=0·03; ≥5 years, HR 0·71, 95% CI 0·57–0·89, p=0·003). Overall benefit was therefore most evident in patients with a scheduled duration of trial treatment

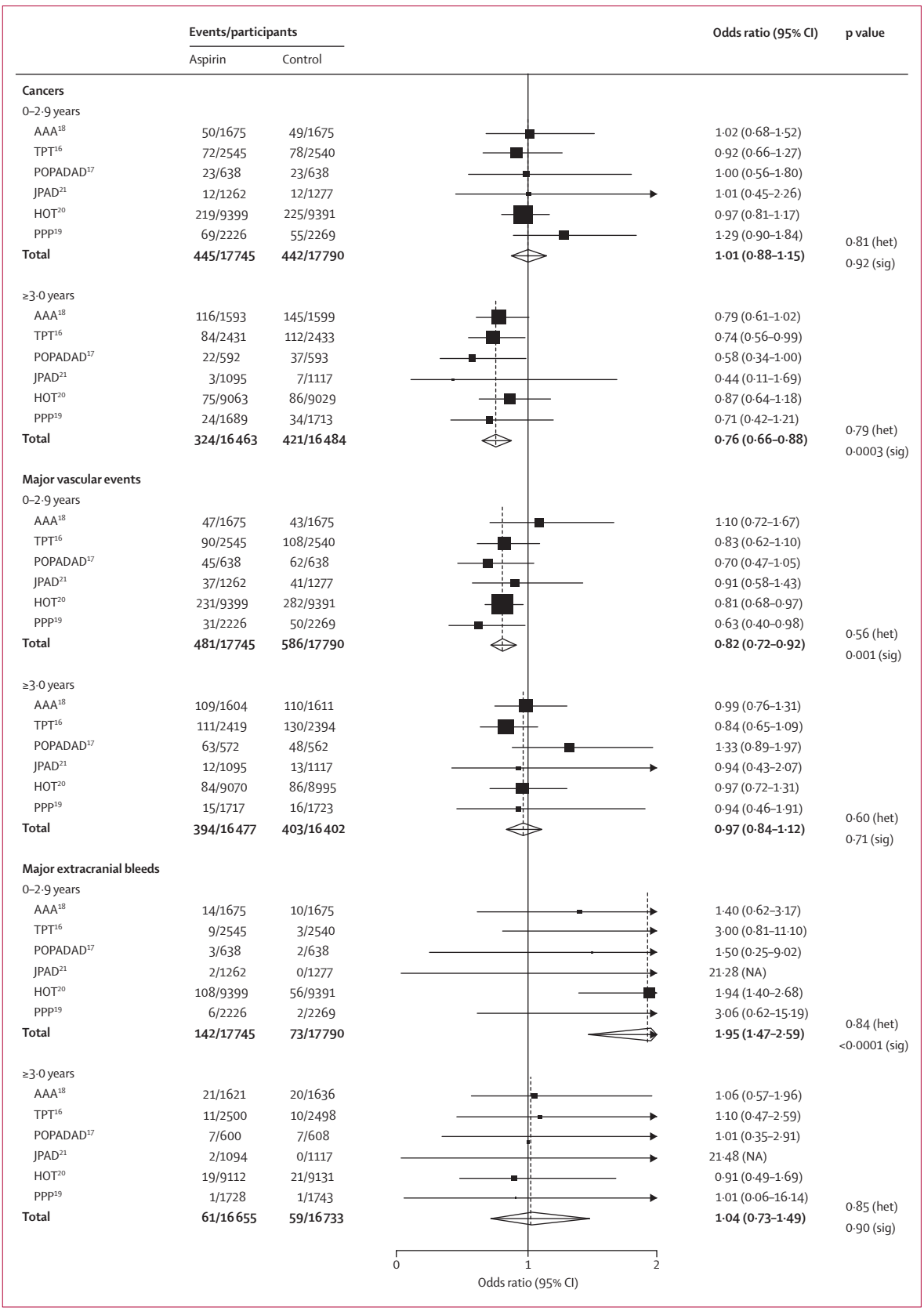

Figure 4: **Meta-analysis of the effect of aspirin on the risks of incident cancer, major vascular events, and major extracranial bleeds during six randomised trials of daily low-dose aspirin versus control in primary prevention of vascular events[16–21] stratified by period of trial follow-up (0–2·9, ≥3·0 years)**

The number of participants at the start of the ≥3-year period is based on the number of individuals surviving free of the relevant outcome event, such that only first events of each type are included. Statistical significance of differences in effect of aspirin between 0–2·9 versus ≥3·0 years: cancer, p=0·006; major vascular events, p=0·06; major extracranial bleeds, p=0·006. NA=not available. AAA=Aspirin for Asymptomatic Atherosclerosis. TPT=Thrombosis Prevention Trial. POPADAD=Prevention of Progression of Arterial Disease and Diabetes. JPAD=Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes. HOT=Hypertension Optimal Treatment. PPP=Primary Prevention Project.

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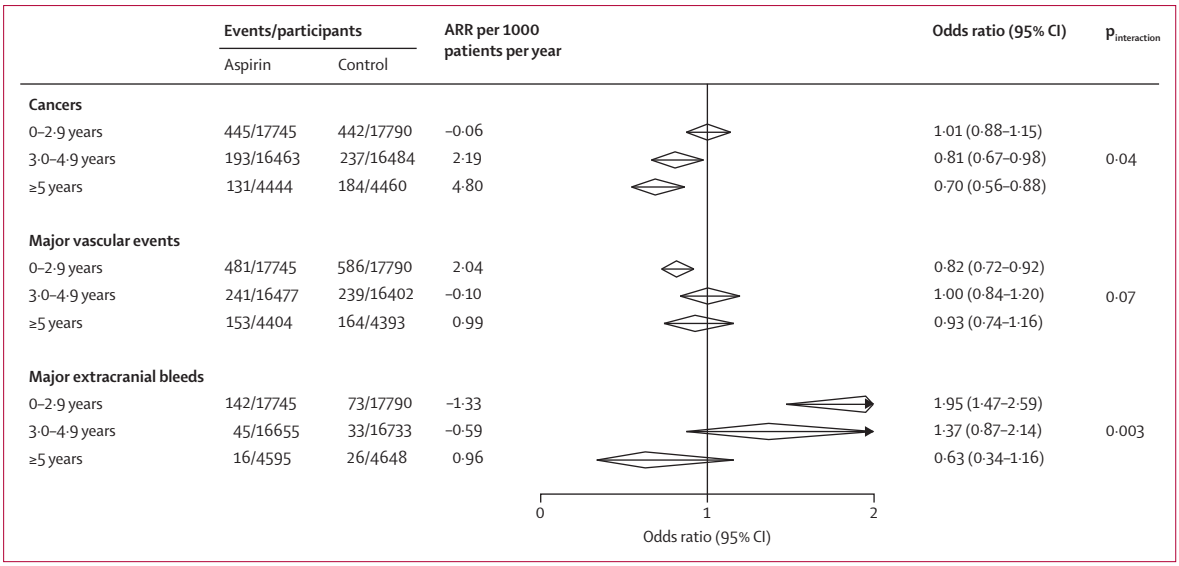

Figure 5: **Summary of meta-analyses of the effect of aspirin on risks of incident cancer, major vascular events, and major extracranial bleeds during six randomised trials of daily low-dose aspirin versus control in primary prevention of vascular events[16–21] stratified by period of trial follow-up (0–2·9, 3·0–4·9, ≥5 years)**
The number of participants at the start of each period was based on the number of individuals surviving free of the relevant outcome event at the start of the period, such that only first events of each type were included. The statistical significance of the interaction between the treatment effect and the period of follow-up was derived from a Cox model in which time was included as a continuous variable. ARR=absolute reduction in risk.

(ie, time of randomisation to end of trial) of 5 years or more (HR 0·81, 95% CI 0·70–0·93, p=0·003; figure 2).

The reduced cancer incidence from 3 years onwards (324 *vs* 421 cases; OR 0·76, 95% CI 0·66–0·88, p=0·0003) was independent of age, sex, and smoking status (table 3), but cancer deaths were only reduced from 5 years onwards (66 *vs* 104 deaths; OR 0·63, 95% CI 0·47–0·86, p=0·004). In TPT,[16] which had a 2×2 factorial design, allocation to aspirin versus placebo reduced cancer incidence, but allocation to warfarin versus placebo did not (figure 3).

The number of cancers in the six trials was too small to reliably establish effects of aspirin on specific cancer types. Combined analysis with data for fatal cancers from the other 26 trials in which primary site of cancers was known showed that risk of non-fatal or fatal cancer was reduced from 3 years onwards (407 *vs* 514 cases; OR 0·79, 95% CI 0·70–0·90, p=0·0004; appendix p 4), the reduction being greatest for cancers of the female reproductive organs (34 *vs* 63; OR 0·54, 95% CI 0·36–0·82, p=0·003), with trends towards fewer cancers of the uterus (zero *vs* nine; p=0·003, Fisher exact test), ovary (six *vs* 12; p=0·16), and breast (27 *vs* 42; p=0·07). Across all of follow-up, there were also reductions in risks of lymphoma (25 *vs* 45 cases; p=0·017) and sarcoma (one *vs* 11; p=0·007), but no significant increase in incidence of any cancer.

Overall balance of risk and benefit

We assessed the overall balance of risk and benefit of low-dose daily aspirin in primary prevention. Analyses of major vascular events, incident cancer, and major extracranial bleeds in each of the six trials stratified by period of follow-up showed consistent effects of aspirin (figure 4). However, by contrast with cancer incidence, for which the effect of aspirin increased with duration of trial follow-up, effects on major vascular events and major extracranial bleeding diminished.

The effect of aspirin on the absolute numbers of major outcomes per 1000 patients treated per year was calculated by time period in a pooled intention-to-treat analysis of individual patient data from the six trials (figure 5). The interaction between time from randomisation (expressed as a continuous variable) and the effect of allocation to aspirin was significant for incident cancer (p=0·04) and for major extracranial bleeds (p=0·003), but not for major vascular events (p=0·07). When analysis was restricted to individuals who remained on allocated trial treatment up until the event, the time course of effect of aspirin was similar for risk of major extracranial bleeds (p=0·04) and stronger for major vascular events (p=0·03).

There was no significant heterogeneity in the absolute annual risks of any of the main outcomes across the six trials or in the effects of aspirin on these risks after stratification by period of follow-up, and so the evolution of the overall balance of risk and benefit throughout follow-up was assessed by analyses of pooled individual patient data (figure 6). Aspirin reduced the risk of the composite outcome of major vascular events, cancer, or fatal extracranial bleeds (HR 0·88, 95% CI 0·82–0·94, p=0·0002) and benefit remained when non-fatal extracranial bleeds were added (HR 0·92, 95% CI 0·86–0·98, p=0·01). The proportion of major extracranial bleeds that were fatal was lower in patients allocated aspirin versus those on placebo (8/203 *vs* 15/132; OR 0·32, 95% CI

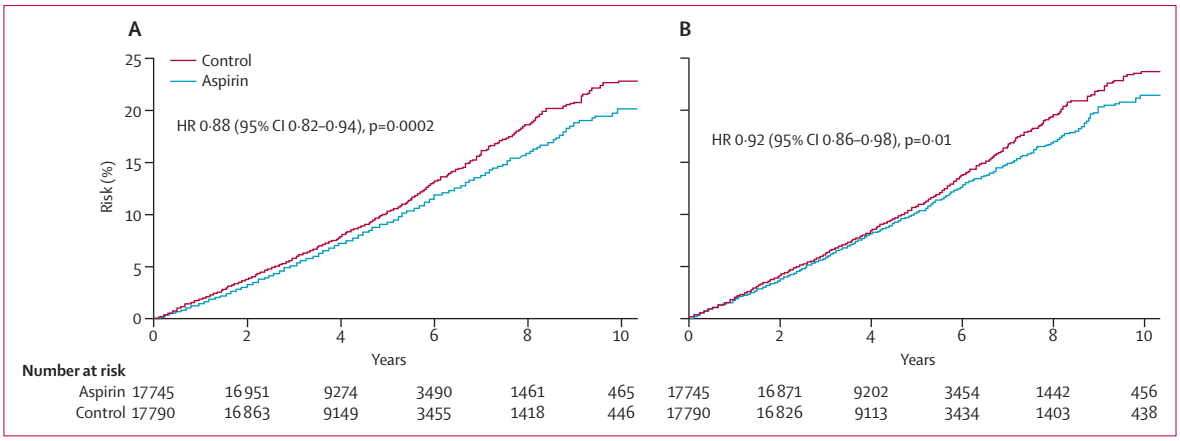

Figure 6: **Pooled analyses of the six randomised trials of daily low-dose (75–100 mg daily) aspirin versus placebo in primary prevention of vascular events[16–21] showing the effect of allocation to aspirin on (A) the composite outcome of major vascular events, cancer, or fatal extracranial haemorrhage and (B) major vascular events, cancer, or any extracranial haemorrhage**

All intracranial haemorrhages were included as major vascular events.

0·12–0·83, p=0·009) and this difference remained when analysis was restricted to individuals who were still on allocated trial treatment at the time of the bleed (8/178 *vs* 12/97; OR 0·33, 95% CI 0·12–0·92, p=0·016).

Discussion

Long-term post-trial follow-up of three large trials of daily aspirin versus control in prevention of vascular events with mean duration of 4 years or more showed previously that aspirin reduced 20-year cancer mortality by 20–30%, due mainly to fewer deaths after completion of the trials.[11] Although data were also included from five other trials of similar duration,[11] numbers of in-trial cancer deaths were too small to reliably identify short-term effects of aspirin, effects on non-fatal cancers were not reported, and the effect of cancer prevention on the balance of risks and benefits in primary prevention was not established. Our new analyses addressed each of these issues (panel).

First, by collating cancer deaths from about 90% of participants in all trials of daily aspirin versus control, and non-vascular deaths from all trials, we have largely avoided selection bias and have more reliably established the short-term effects of aspirin. Aspirin reduced in-trial cancer deaths by nearly 40% after a delay of about 5 years. There was some evidence of an earlier reduction in cancer deaths in trials of high-dose aspirin, which might suggest an effect on cancers that would have been present, albeit clinically occult, at randomisation. Daily high-dose aspirin does not improve survival from small-cell lung cancer,[28] but has been associated with reduced case-fatality in observational studies in colorectal cancer and breast cancer.[29,30] Our finding was based on few events, but it should encourage trials of aspirin in the treatment of cancer.

Second, aspirin reduced the risk of all non-vascular death, suggesting that the effect on cancer death was unlikely to be due to bias in attribution or reporting of cause of death. Non-vascular deaths were excluded from previous analyses of the balance of risks and benefits of aspirin,[13] but should be considered in future. The absence of effect of aspirin on vascular death in primary prevention trials is likely to be due, at least in part, to open use of aspirin after non-fatal vascular events.[31] However, this behaviour reflects routine clinical practice.

Third, aspirin also reduced the incidence of cancer. We restricted this analysis to trials in primary prevention because the overall balance of risk and benefit is uncertain in this group and to trials of low-dose aspirin because high-dose treatment is of less current clinical relevance. Some data for non-fatal cancers were also available from four other trials of daily aspirin versus control (three in secondary prevention[32–34] and one of high-dose aspirin in primary prevention[15]). Meta-analysis of the effect of aspirin on cancer incidence in these four trials yielded a very similar effect size (OR 0·89, 95% CI 0·72–1·11, data not shown) to that we noted in the six trials of low-dose aspirin in primary prevention (OR 0·88, 95% CI 0·78–0·98), and so there has been no inclusion bias. Aspirin reduced the incidence of cancer by about 25% after a delay of about 3 years of follow-up, with consistency across the trials. This finding is important because it was otherwise possible that early diagnosis and treatment of cancers identified during investigation of side-effects of aspirin, such as anaemia and bleeding, might account for the subsequent reduction in cancer deaths. We showed previously that aspirin reduced long-term incidence of colorectal cancer,[9,10] and that it also substantially reduced mortality due to some cancers with very low cure rates, such as carcinoma of the oesophagus,[11] which could only really be due to reduced incidence. However, the absence in the present study of any excess of incident cancers early after randomisation to aspirin, the overall reduction in cancer incidence as well as mortality, and the effect of aspirin but not warfarin in TPT all provide further evidence against diagnostic bias.

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Fourth, we showed that aspirin reduced cancer incidence in women. Our previous evidence of the effect of aspirin on the long-term risk of cancer was based mainly in men,[9–11] whereas 15726 participants in the six trials of low-dose aspirin in primary prevention analysed here were female. Although the numbers of cancers of the female reproductive organs was small, we noted a trend towards fewer deaths and a significant reduction in fatal or non-fatal events from 3 years onwards. The reduction in numbers of uterine cancers (zero *vs* nine, p=0·003) is also consistent with a recent trial of aspirin versus placebo in patients with Lynch syndrome (5/427 *vs* 13/434, p=0·06).[35]

Fifth, having established the effects of low-dose aspirin on cancer incidence, we were able to assess the overall balance of risks and benefits in the primary prevention setting. Addition of the more recent trials did not change the conclusions of previous ATT analyses that the reduced risk of major vascular events on aspirin is substantially offset by the increased risk of major bleeding.[14] However, in view of the need to inform decisions about long-term use of aspirin, we assessed how effects on all major outcomes evolved with time from randomisation. Meta-analysis undertaken without regard to duration of study would underestimate the reduction in risk of cancer, for example, because two of the largest trials had mean follow-up of little over 3 years and no follow-up beyond 5 years.[19,20] By stratification of analyses by period of follow-up, we showed that the reduced cancer incidence on aspirin accounted for most major events prevented after 3 years. Since vascular death was not reduced and fatal extracranial bleeds were not increased, the reduction in total mortality reflected the reduction in fatal cancers.

We also showed evolution of the effects of aspirin on the risks of major vascular events and major extracranial bleeding. Some trends would be expected because of withdrawal from trial treatment in the aspirin groups and open use of aspirin in the placebo groups, although such trends would still be important because they would also be expected with a policy of aspirin use in routine clinical practice. However, the reduction in effect of aspirin on risk of major vascular events with increasing duration of use was greatest in individuals who remained compliant, and there is evidence of a similar timecourse of effect in trials in secondary prevention (PMR, personal communication). The reduction in effect of aspirin on risk of major extracranial bleeding events with increasing follow-up was due to a fall in risk in the aspirin group rather than to an increase in risk in the placebo group, and might be due, at least in part, to a fall in the proportion of susceptible individuals because of treatment withdrawal after more minor gastrointestinal intolerance or other side-effects. This time-trend remained significant in on-treatment analysis, suggesting that it was not simply an artifact due to widespread treatment withdrawal. Further insights might come from analysis of the two large trials of alternate-day aspirin,[12,36] but the finding that daily aspirin might be used long term in prevention of cancer without a persisting increase in risk of major extracranial bleeding in those who can tolerate it is important. We should stress, however, that our preliminary finding of the reduction in effect of aspirin on major vascular events after a few years does not imply that aspirin should then be stopped in secondary prevention.

Our study does have potential limitations. First, our findings only apply to use of daily aspirin. The Women's Health Study,[12] a trial of aspirin 100 mg on alternate days versus control, did not show a reduction in cancer incidence, and the only other large trial of alternate-day aspirin did not report a reduction in non-vascular death.[36] Second, the trials we studied had not focused on cancer outcomes. However, cancer deaths were recorded and attribution of cause of death was done blind to treatment allocation. Attribution was usually based on death certification, supported by clinical records, which has been shown to agree well with expert committee review.[37–39] In the trials of daily low-dose aspirin in primary prevention, data for non-fatal cancers were derived mainly from patient-reported diagnosis at face-to-face follow-up, usually supported by review of medical records. In TPT,[16] which also used cancer registration, the risk of cancer during follow-up and the effect of aspirin were similar to those in the other trials. Finally, our analyses of the overall balance of risks and benefits of low-dose aspirin using composite outcomes were simplistic. Many people would deem a non-fatal gastrointestinal bleed to be less serious,

***Panel:* Research in context**

Findings

Using all available individual patient data from randomised trials of daily aspirin versus no aspirin in prevention of vascular events, we showed that aspirin reduces the risk of non-vascular death, due mainly to fewer cancer deaths after 5 years. Using individual patient data from all randomised trials of daily low-dose aspirin in primary prevention of vascular events, we showed that aspirin also reduces cancer incidence, both in men and women and in smokers and non-smokers. The effects of aspirin on other major outcomes evolve with duration of treatment, the initial reduction in risk of major vascular events and the increase in risk of major extracranial bleeding diminishing with time, such that the reduced risk of cancer is the only significant effect from 3 years onwards.

Interpretation

Previous systematic reviews and analyses of the risks and benefits of aspirin have not considered effects of aspirin on cancer incidence, mortality, or non-vascular death and have assumed that the relative effects of aspirin on major vascular events and major bleeding will be independent of duration of use. Our findings, taken with previous evidence that aspirin also reduces long-term post-trial cancer deaths, suggest that extended use of aspirin will be safer than previously supposed and will be of value in prevention of cancer.

for example, than a stroke or a cancer. Analyses based on disability and death would be preferable, but disability data were not obtained in the trials. However, even when non-fatal extracranial bleeds are given the same weight as other outcomes, low-dose aspirin was still of modest overall benefit.

Our findings should also be interpreted alongside those in the two accompanying reports.[40,41] First, the consistency of the findings on the long-term effects of aspirin on cancer incidence and mortality in case-control studies, cohort studies, and randomised trials, when they are performed and analysed appropriately,[41] is strong evidence of the validity and generalisability of the effects observed during and after the trials. Second, the two accompanying reports show that aspirin also reduces distant cancer metastasis in the shorter-term and will explain, at least in part, the reduction in cancer deaths that we observed during trials of aspirin versus control. The metastasis finding could also explain the apparent early reduction in cancer incidence on aspirin that we found during the six primary prevention trials if prevention of metastasis delayed diagnosis of some cancers until after the trials were completed. Although there is good evidence that aspirin reduces the long-term incidence of some cancers on post-trial follow-up,[9–11] the long latency of that effect is consistent with prevention of the very early cancer development, whereas the apparent reduction in cancer incidence after only 3 years would be more consistent with an effect of aspirin on growth or metastasis of cancers that were already present, albeit occult, at randomisation.

Our findings supercede those of a recent meta-analysis that found only a non-significant trend towards fewer cancer deaths during trials of aspirin versus control.[42] That report included data from fewer trials (nine *vs* 51), combined estimates from trials of daily aspirin and trials of alternate-day aspirin, and did not have access to individual patient data or to any post-trial follow-up data in order to identify the substantial delayed effects of aspirin on long-term cancer incidence and mortality.[9–11] Setting aside any long-term effects of aspirin, as we have shown in the current report and previously,[11] individual patient data are essential to determine the time course of effects on risk of cancer and other outcomes during trials. Crude meta-analyses of overall numbers of events from trials of different lengths without stratification by period of follow-up will be of limited value.

Addition of data from new trials and from further post-trial follow-up of previous trials through the Non-Vascular Outcomes on Aspirin [NOVA] Collaboration will increase the reliability of estimates of effects on specific cancers. More data from appropriately conducted observational studies would also be informative.[41] Research is also needed into which mechanisms of action of aspirin are most important in prevention of cancer, as well as into the effects of co-prescription of a proton-pump inhibitor[43,44] or eradication of *Helicobacter pylori* infection[45] on risk of bleeding. In the meantime, we have shown that daily aspirin reduces cancer incidence and mortality. Alongside the previously reported reductions in post-trial cancer deaths,[9–11] the demonstration of overall benefit from aspirin in the shorter-term, and the finding that the increased risk of major extracranial bleeding does not persist with extended use add to the case for long-term use of aspirin for cancer prevention in middle age in addition to appropriate dietary and lifestyle interventions.[46] In view of the very low rates of vascular events in recent and ongoing trials of aspirin in primary prevention, prevention of cancer could become the main justification for aspirin use in this setting, although more research is required to identify which individuals are likely to benefit most. Future analyses of previous trials and design of new trials should take into account the effects of aspirin on non-vascular outcomes and the time course of effects.

Contributors

PMR conceived and coordinated the project, did literature searches, obtained and collated published and unpublished data, planned and undertook analyses, and wrote the report. MW checked and extracted unpublished data from some trials and ZM helped with analyses. Other authors were the principal investigators and data managers of the trials of aspirin in primary prevention of vascular events from which data on fatal and non-fatal cancers were obtained: AAA trial (FGRF and JFP); POPADAD trial (JFFB and RL); PPP trial (MCR and GT); HOT trial (AZ); and TPT trial (TWM). All authors commented on drafts of the report.

Collaborators

A Algra; J Boreham; M G Bousser; G Boysen; E Chew; J G Cleland; R Cote; H C Diener; C-E Elwin; P Elwood; M Goulding; R G Hart; C Knottenbelt; P J Koudstaal; R Landolfi; R Marchioli; T Morimoto; B Norrving; H Ogawa; B Peterson; R Peto; I S Posada; A Rudnicka; C P Warlow; I Warnold.

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, and is on the executive committee of the ARRIVE Trial. FGRF has received research support and honoraria from AstraZeneca, Bayer, and Sanofi-Aventis/Bristol-Myers Squibb.

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