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


CRD summary
This meta-analysis used mainly individual patient data on people treated with low-dose daily aspirin for primary prevention of vascular events. The authors found a short-term reduction in cancer incidence and mortality and a decrease in major extracranial bleeds with extended use of aspirin. Despite being based on a subset of included trials, the findings appear reliable.

Authors' objectives
To establish the effects of daily aspirin on cancer incidence, mortality and non-vascular death and analyse the time course of risks and benefits.

Searching
Trials were identified from: systematic reviews undertaken by the Antithrombotic Trialists' Collaboration; searching PubMed and EMBASE to May 2011 (search terms reported); searching Cochrane Database of Systematic Reviews; and reviewing other published systematic reviews of trials of antiplatelet agents. No language restrictions were applied. The authors did not search for unpublished trials or abstracts of conference presentations.

Study selection
Randomised controlled trials (RCTs) of daily aspirin (any dose) versus no aspirin were eligible. Neither group should have another antiplatelet agent. Trials in which both groups received anticoagulants were eligible. Trials of short-term (90 days or less) treatment and trials for treatment or secondary prevention of cancer or colonic polyps were excluded.

Included trials were of low-dose (40mg to 200mg daily) and high-dose (300mg to 1,500mg daily) aspirin and primary and secondary prevention of vascular disease. Trials of low-dose aspirin for primary prevention were completed between 1997 and 2008. Mean age of participants ranged from 57.5 to 64.5 years. The proportion of men ranged from 28.5% to 100%. The proportion of smokers at baseline ranged from 14.8% to 41.2%.

The authors did not report how trials were selected for inclusion.

Assessment of study quality
The authors did not report that they assessed risk of bias in included trials. They also did not report whether individual patient data (IPD) were checked for integrity and queries resolved with trial investigators.

Data extraction
Data for vascular and non-vascular deaths were extracted from trial reports to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for aspirin versus control. IPD for cancer deaths were obtained for all eligible trials where available, otherwise data were extracted from published reports. IPD for trials of daily low-dose aspirin in primary prevention were obtained for all cancers during trial follow-up (primary site, time from randomisation to diagnosis or notification, randomised treatment and cancer diagnosis before randomisation) and for age, sex, smoking status at baseline, major vascular events, major extracranial bleeds and date and cause of all deaths. All analyses were done on an intention-to-treat basis.

The authors did not report how data were extracted from published reports.

Methods of synthesis
Pooled odds ratios for mortality outcomes were obtained by fixed-effect meta-analysis. Heterogeneity was assessed using the X² test. Analyses of IPD for cancer deaths were stratified by time from randomisation to death, dose of aspirin and site of primary cancer. Further analyses excluded cancers that were diagnosed before randomisation. For cancer incidence, meta-analysis of effects in individual trials was done with stratification by time to diagnosis or first
notification. IPD were then pooled and Kaplan-Meier curves generated for time to diagnosis or first notification of cancer. Statistical significance was determined using the log-rank test stratified by trial. Interaction between the effect of randomised treatment on cancer incidence and time from randomisation was assessed with an interaction term in a Cox model. Cancers were grouped into categories by primary site. The authors also performed several analyses at the individual trial and IPD level to assess the effect of any effect on cancer incidence on the balance of benefits and harms of daily low-dose aspirin for primary prevention (details in the paper).

**Results of the review**

Fifty-one trials (77,549 participants) were included: six trials (35,535 participants) were of low-dose daily aspirin for primary prevention. Follow-up ranged from 0.5 to 8.2 years for low-dose aspirin trials and from one to five years for high-dose trials.

Across all trials aspirin significantly reduced cancer deaths (OR 0.85, 95% CI 0.76 to 0.96; 34 trials) and resulted in significantly fewer non-vascular deaths overall (OR 0.88, 95% CI 0.78 to 0.96; 51 trials).

In trials of daily low-dose aspirin for primary prevention, aspirin reduced cancer incidence from three years onwards (OR 0.76, 95% CI 0.66 to 0.88). This effect was seen in both women and men. A reduced risk of major vascular events in the aspirin group was initially offset by an increased risk of major bleeding. Effects on both outcomes decreased over time, leaving only a reduced risk of cancer (absolute reduction 3.13 cases per 1,000 patients per year, 95% CI 1.44 to 4.82) from three years onwards. Fatality in cases of major extracranial bleeding was significantly lower on aspirin than control treatments (OR 0.32, 95% CI 0.12 to 0.83). Where reported, there was no evidence of significant statistical heterogeneity. Results of other analyses were reported in the paper and appendix.

**Authors’ conclusions**

The short-term reduction in cancer incidence and mortality and the decrease in major extracranial bleeds with extended use, together with their low case fatality, add to the case for daily aspirin in the prevention of cancer.

**CRD commentary**

The research questions and inclusion criteria were complex but generally clear. The search for studies covered a range of relevant sources but was confined to published trials, so some relevant trials may have been omitted. The limited reporting of details of study selection and quality assessment made it difficult to assess these aspects of the meta-analysis. Limited details of included trials were reported.

Methods of synthesis involved a mixture of sophisticated trial-level and IPD analyses and appeared to be appropriate. The authors’ conclusions reflect the evidence presented, although the main conclusions were based on a subset of the included trials. Despite this and some limitations in reporting, the conclusions regarding the effects of aspirin are likely to be reliable. Any decision on whether to take aspirin would need to balance potential benefits against adverse effects.

**Implications of the review for practice and research**

**Practice:** The authors stated that long-term use of daily aspirin could be of value for cancer prevention in middle age.

**Research:** The authors stated a need for further research into the effects of aspirin on specific cancers, on the most important mechanisms of action of aspirin for prevention of cancer and into the effects of co-prescription of a proton-pump inhibitor or eradication of *Helicobacter pylori* infection on risk of bleeding.

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