CRD summary
The authors concluded that daily aspirin reduced deaths from several common cancers across different study populations and benefits increased with longer treatment duration. The authors' conclusions reflected the evidence presented and, despite some reporting limitations, are likely to be reliable.

Authors' objectives
To evaluate the effect of daily aspirin on the long-term risk of death due to cancer.

Searching
PubMed, EMBASE and Cochrane Database of Systematic Reviews were searched without language restrictions from 2002 to March 2010. Search terms were reported. Published data were obtained from the Antithrombotic Trialists' (ATT) Collaboration. Anonymised data were requested from trial investigators.

Study selection
Randomised controlled trials (RCTs) that compared daily aspirin with control were eligible for inclusion in the review. Trials had to document at least four years' scheduled treatment and report a range beyond five years. The outcomes of interest were risk of fatal cancer and all-cause mortality.

The included trials were designed to evaluate the role of aspirin in the primary and secondary prevention of vascular disease. The included comparisons were: aspirin (any dose) versus no aspirin (and no other agent); and aspirin (any dose) versus no aspirin (with another antiplatelet or antithrombotic agent, provided this was administered in the same way in both study groups). Three trials that were conducted in the UK provided long-term follow-up data (20 years) using death certificate and cancer registration data and coded according to International Classification of Diseases (ICD). Mean age of included patients ranged from 51 years to 67 years; most were men. The proportion of smokers ranged from 16 to 53%. Median duration of scheduled treatment was between 4.2 and 8.2 years. Daily aspirin dose ranged from 75mg to 500mg. Most trials compared aspirin with placebo (unspecified).

The authors did not state how many reviewers carried out study selection.

Assessment of study quality
The authors did not state that they carried out a formal validity assessment, although some relevant aspects of study design were presented in the text and appendix. It was not reported whether there was any checking of individual patient data (IPD).

Data extraction
Data were collected for in-trial deaths to enable calculation of odds ratios (OR) and 95% confidence intervals (CI). Where possible for post-trial follow-up, IPD were obtained from trial investigators to enable calculation of hazard ratios (HR) and 95% confidence intervals. Data were analysed on an intention-to-treat basis.

Methods of synthesis
Odds ratios and 95% confidence intervals were pooled in a fixed-effect meta-analysis to evaluate the effects of aspirin on risk of death due to cancer and all-cause mortality during the period of the trial across all trials. Heterogeneity was reported as a p-value (P_{het}). IPD were pooled to estimate the cumulative risk of cancer death using Kaplan-Meier curves and the log-rank test (stratified by trial) and using hazard ratios derived from a Cox proportional hazards model (stratified by trial).

Subgroup analyses were carried out as follows: gastrointestinal tract cancers versus other solid cancers versus haematological cancer; for the period of five years since randomisation compared with thereafter; and for common
solid cancers (listed in the paper).

In trials with long-term follow-up, stratification by treatment duration (up to five years, five to 7.4 years and 7.5 years or longer) was carried out. Also in these trials, the effect of aspirin on 20-year risk of cancer death was stratified by type of cancer (above) and by follow-up (zero to 10 years versus 10 to 20 years).

Results of the review
Eight RCTs (n=25,570 participants) were included in the initial analysis. IPD were available for seven RCTs (n=23,535 participants), six of which were placebo-controlled and double-blind. Three trials (n=12,659 participants) provided an analysis of 20-year risk of cancer death.

Pooled data for all trials showed that daily aspirin was associated with a reduction in deaths due to cancer (OR 0.79, 95% CI 0.68 to 0.92; eight trials; 674 cancer deaths; non-significant heterogeneity). After five years' follow-up, pooled IPD revealed a significant benefit from daily aspirin on all cancers (HR 0.66, 95% CI 0.50 to 0.87; seven trials; 657 cancer deaths) and for gastrointestinal cancers (HR 0.46, 95% CI 0.27 to 0.77).

Pooled analysis of trials that assessed 20-year risk of cancer death showed significantly lower risk in patients who took aspirin in terms of all cancers (HR 0.78, 95% CI 0.70 to 0.87), all solid cancers (HR 0.80, 95% CI 0.72 to 0.88) and gastrointestinal cancers (HR 0.65, 95% CI 0.54 to 0.78). Subgroup analysis revealed that benefits significantly increased for all solid cancers and gastrointestinal cancers with extended scheduled treatment duration (7.5 years or longer). Further subgroup analyses revealed that the effect on deaths was observed only after around five years for oesophageal, pancreatic, brain and lung cancers. The time delay was greater for stomach, colorectal and prostate cancers. The greatest benefit in lung and oesophageal cancers was for adenocarcinomas after 20 years' follow-up (HR 0.66, 95% CI 0.56 to 0.77).

The effects of aspirin did not differ significantly by dose (over 75mg) and in relation to gender and smoking status. The absolute reduction in 20-year risk of cancer death was 7.08% (95% CI 2.42 to 11.74) in patients 65 years or older at randomisation.

Authors' conclusions
Daily aspirin reduced deaths from several common cancers across different study populations. Benefits increased with longer treatment duration.

CRD commentary
The review question was clear and this was supported by potentially reproducible inclusion criteria for all aspects apart from participants. The search strategy included some relevant sources and attempts were made to minimise language bias. Trial investigators were contacted for IPD. There appeared to be no formal validity assessment, although some relevant aspects of the included trials were reported. It was not reported whether or how the IPD were checked. Study characteristics were provided adequately, heterogeneity was assessed (although the method was not reported), and the chosen method of synthesis appeared to be appropriate. The analyses were conservative and could potentially underestimate the effect of aspirin. The authors proposed that the review findings may be generalisable given the consistency of results across the included trials. However, the applicability to under-represented populations (for example, females and non-smokers) or those not represented (for example, healthy people without known vascular risk factors) was less clear.

The authors presented a conclusion that reflected the evidence and acknowledged some potential limitations of the review. Overall, this was a well-conducted piece of research and, despite some reporting limitations, the authors' conclusions appear reliable.

Implications of the review for practice and research
Practice: The authors stated that patients who were eligible to receive long-term antiplatelet treatment were likely to benefit most from daily aspirin.

Research: The authors stated that further trials were needed to assess the effects of aspirin on incidence of cancer, and particularly in assessing the risk of female-related cancers. Follow-up beyond 20 years was warranted and it was also important to assess the short-term impact (within the first five years). The authors refered to ongoing data collection in
all these respects.

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