Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials

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CRD summary
The review concluded that, as well as reducing the long-term risk of some cancers, aspirin may also prevent distant cancer metastasis. Despite a lack of reporting of some aspects of the review and the restriction to UK trials, the authors' conclusions appear likely to be reliable.

Authors' objectives
To examine the effect of daily aspirin on the risk of cancer metastasis.

Searching
The authors used search results from two previous studies. PubMed and EMBASE (2002 to May 2011) and Cochrane Database of Systematic Reviews were searched. Search terms were reported. There were no language restrictions. Studies prior to 2002 were identified from the Antithrombotic Trialists Collaboration. Published systematic reviews were examined for further studies.

Study selection
Randomised controlled trials (RCTs) of any dose of aspirin versus no aspirin in the absence of another antiplatelet agent and trials of any dose of aspirin versus no aspirin in the presence of another antithrombotic agent (if balanced in the aspirin and no-aspirin groups) for the prevention of vascular events were eligible for inclusion. Studies had to be conducted in the UK. Trials with fewer than 10 incident cancers recorded during follow-up, trials of short-term (≤90 days) treatment of acute vascular events and trials in the treatment or secondary prevention of cancer or colonic polyps were excluded.

Included studies were conducted for primary prevention of vascular disease, secondary prevention after recent vascular events and in patients with asymptomatic peripheral arterial disease. Two studies included only male patients. Mean ages ranged from 57.5 to 62 years. Between 31% and 53% of participants were smokers. Daily aspirin doses ranged from 75mg to 1,200mg. Mean/median treatment durations ranged from 4.4 to 8.2 years. Trial completion years ranged from 1984 to 2008. All studies were placebo-controlled except one for which control treatment details were not presented.

The authors did not state how many reviewers selected studies.

Assessment of study quality
The authors reported neither any data checking procedures used nor whether a study quality assessment was made.

Data extraction
Individual patient data for the intention-to-treat populations were extracted on primary and metastatic cancer incidence in order to calculate hazard ratios (HR) and odds ratios (OR) with 95% confidence intervals (CIs). Metastasis was categorised into four groups (details defined in the paper). Haematological and brain cancer data were both excluded from analyses of metastasis.

Methods of synthesis
Meta-analyses using a fixed-effect model were used to pool odds ratios where there was no evidence of statistical heterogeneity. Tests for statistical heterogeneity were used and results were presented as p values (no method details were provided).

Hazard ratios were calculated for the risk of cancer with definite distant metastasis (with stratification by site) and for the risk of cancer with potentially distant metastasis using Cox regression stratified by trial. For all participants who developed incident cancer, hazard ratios were calculated for: the effect of aspirin on the proportion of cancers that had
metastases (distant or site-unspecified) at presentation or follow-up versus local disease only (stratified by site); risk of metastasis during follow-up (time from diagnosis of cancer to diagnosis of metastasis) in participants in whom no metastases were evident at initial diagnosis or less than one year after; and survival (for death due to cancer and for any death) after diagnosis of cancer.

Subgroup analyses also explored the effect of type of cancer (adenocarcinoma versus non-adenocarcinoma) age, sex, aspirin dose and current smoking status.

Results of the review

Five RCTs were eligible (17,285 participants; 987 had a new solid cancer diagnosed during mean in-trial follow-up of 6.5 years). Four RCTs were placebo-controlled and double-blinded.

Aspirin treatment reduced risk of cancer with definite distant metastasis (all cancers HR 0.64, 95% CI 0.48 to 0.84). The result remained statistically significant for adenocarcinoma (HR 0.54, 95% CI 0.38 to 0.77), but not for other solid cancers (HR 0.82, 95% CI 0.53 to 1.28). Aspirin increased the risk of cancer with local disease only (HR 1.24, 95% CI 1.01 to 1.53).

Aspirin reduced the risk of adenocarcinoma with metastasis at initial diagnosis (HR 0.69, 95% CI 0.50 to 0.95) and the risk of metastasis on subsequent follow-up in patients without initial metastasis (HR 0.45, 95% CI 0.28 to 0.72), particularly in patients with colorectal cancer (HR 0.26, 95% CI 0.11 to 0.57) and patients who remained on trial treatment up to or after diagnosis (HR 0.31, 95% CI 0.15 to 0.62, all adenocarcinomas).

Aspirin treatment reduced death due to cancer in patients who developed adenocarcinoma, especially in patients without metastasis at diagnosis (HR 0.50, 95% CI 0.34 to 0.74) and reduced the overall risk of fatal adenocarcinoma (HR 0.65, 95% CI 0.53 to 0.82), but not the risk of other fatal cancers (HR 1.06, 95% CI 0.84 to 1.32). The effects were independent of age, sex and smoking status. Low doses of aspirin were as effective as higher doses.

Further results were reported.

Authors’ conclusions

The findings provide the first proof that, as well as reducing the long-term risk of some cancers, daily aspirin also prevents distant cancer metastasis. This suggests that aspirin might help in treatment of some cancers and provides proof of principle for pharmacological intervention specifically to prevent distant metastasis.

CRD commentary

The review question was clear and was supported by appropriate inclusion criteria. Attempts to identify relevant UK studies in any language were undertaken by searching electronic databases, although the possibility of missing unpublished studies could not be ruled out. It was unclear whether methods (such as use of independent duplicate procedures) were employed to reduce the risks of reviewer error and bias during study selection. Neither an assessment of study quality nor details of data checking procedures were reported, although most of the trials had large sample sizes and formed part of the Antithrombotic Trialists Collaboration. Sufficient study details were provided and appropriate methods were used to synthesise data.

Despite a lack of reporting of some aspects of the review and the restriction to UK trials, the authors’ conclusions appear likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that their findings suggested that daily aspirin can reduce metastasis when started soon after a diagnosis. Stopping aspirin after a diagnosis of cancer (common in routine clinical practice) could be detrimental. The authors added that there was a possibility that more intensive platelet inhibition with combination treatment might be even more effective.

Research: The authors stated a need for more randomised trials of aspirin or other antiplatelet drugs in the treatment of cancer (they noted that two new trials had started).

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Other publications of related interest


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