CRD summary
The review found that observational studies indicated that aspirin had a beneficial role in relation to digestive tract cancers and may reduce the risk of breast and prostate cancer. However, evidence of a cause-effect relationship was unclear. The authors' cautious conclusions appropriately reflect limitations in the evidence including suboptimal study design, possible publication bias and differences between the studies.

Authors' objectives
To assess the effect of aspirin on cancer risk.

Searching
MEDLINE was searched to September 2011. Search terms were reported. Reference lists of articles retrieved were checked for additional studies. The search was restricted to published studies in English.

Study selection
Case-control or cohort studies of the association between regular aspirin use and cancer were eligible for inclusion. The reviewers excluded randomised controlled trials (RCTs), studies that did not consider aspirin separately from other non-steroidal anti-inflammatory drugs and studies of selected patients with specific diseases. One study that included low-dose aspirin only was excluded.

Study populations in the included studies differed according to cancer site and few participant characteristics were reported in the review. Definitions of frequency of aspirin use varied widely across the included studies. The studies reported incidence or mortality rates for 12 cancer sites. Most of the studies were based in North America or Europe.

The authors did not state how many reviewers selected the studies.

Assessment of study quality
The authors did not state that they assessed validity. They stated that they did not assign quality scores to studies and did not exclude studies on the basis of design or data quality.

Data extraction
The reviewers extracted data on aspirin use and event rates for each group in each study and calculated risk ratios (RRs), which were approximated from odds ratios in case-control studies. The main comparison was between regular aspirin use (at least one to two tablets weekly) and never use. Regularity of use was estimated from frequency or duration of use data if necessary. Data were categorised by study design (case-control or cohort) and estimates adjusted for potential confounders were used where possible.

Two reviewers independently reviewed and cross-checked the data and resolved disagreements by consensus.

Methods of synthesis
Data were combined to calculate pooled estimates of the risk ratio and 95% confidence interval (CI) for each type of cancer, stratified by study design. The results of random-effects models were presented. Statistical heterogeneity was assessed using the $\chi^2$ test ($p<0.10$ defined as significant) and $I^2$ value. Subgroup analyses were conducted to examine the effect of aspirin dose (low dose versus regular strength), frequency of use (regular versus ever) and duration of use (more or less than about five years) and of clinical differences within specific groups of studies (such as smoking status, hormone-receptor status, cancer grade). In a sensitivity analysis, studies based on prescription databases were excluded. Publication bias was assessed with funnel plots and Egger's and Begg's tests.

Results of the review
The review included 139 case-control and cohort (including nested case-control) studies.
Aspirin users had a significantly reduced risk of digestive tract cancers, including colorectal cancer (RR 0.73, 95% CI 0.67 to 0.79; 30 studies), squamous cell/not otherwise specified (NOS) oesophageal cancer (RR 0.61, 95% CI 0.50 to 0.76; 11 studies), oesophageal and gastric cardia adenocarcinoma (RR 0.64, 95% CI 0.52 to 0.78; 11 studies) and gastric cancer (RR 0.67, 95% CI 0.54 to 0.83; 13 studies). For all these analyses there was statistically significant heterogeneity ($X^2$ p-values ranged from 0.060 to <0.001). For outcomes other than colorectal cancer, risk reductions were not significant when analysis was restricted to cohort studies. There was evidence of publication bias for studies of colorectal cancer (p=0.003) and squamous cell/NOS oesophageal cancer (p<0.001).

Aspirin users had a significantly reduced risk of lung cancer (RR 0.91, 95% CI 0.84 to 0.99; 20 studies), breast cancer (RR 0.90, 95% CI 0.85 to 0.95; 32 studies) and prostate cancer (RR 0.90, 95% CI 0.85 to 0.96; 24 studies), with significant heterogeneity (p<0.001). There was no significant difference between users and non-users for the outcomes of pancreatic cancer (10 studies), ovarian cancer (15 studies), bladder cancer (nine studies) and kidney cancer (10 studies).

There was significant heterogeneity (p 0.060 to <0.001) for analyses of all outcomes except pancreatic, endometrial, bladder and kidney cancer. There was evidence of significant publication bias for analyses of colorectal cancer (Egger's test p=0.003), squamous cell/NOS oesophageal cancer (p<0.001), lung cancer (p<0.003) and breast cancer (p<0.032).

Results of subgroup analyses were reported in the review.

**Authors' conclusions**
Observational studies indicated that aspirin has a beneficial role in relation to digestive tract cancers and may reduce the risk of breast and prostate cancer. However, evidence of a cause-effect relationship was unclear.

**CRD commentary**
The objectives and inclusion criteria of the review were clear in most respects but the rationales for excluding RCTs and for excluding a study of low dose aspirin were not fully explained. Only one database was searched and the search was restricted by language and publication status, so the review was at risk of missing studies. Statistical evidence of publication bias was found for several outcomes. Steps were taken to minimise the risk of reviewer bias and error in the process of data extraction; it was unclear whether this also applied to study selection and it did not appear that study quality was systematically assessed. These factors made it difficult to determine the reliability of the data presented. There were some discrepancies between the text and the study tables with regard to sample numbers.

The methods used to combine data, assess heterogeneity and explore differences between the studies appeared appropriate in most respects. However, it appeared that data on cancer incidence were pooled with data on cancer mortality in some analyses and this may not have been appropriate.

As the authors acknowledged, their findings were limited by high levels of heterogeneity and by failure to demonstrate a dose-risk or duration-risk relationship. Their cautious conclusions appropriately reflect limitations in the evidence including suboptimal study design, possible publication bias and differences between the studies.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.