CRD summary
The authors concluded that addition of bevacizumab to chemotherapy or biological therapy increased treatment-related mortality compared to chemotherapy alone. Given methodological limitations with the review process, variability in trial populations and trial findings and the quality of the trials, the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess the effects of bevacizumab on rates of fatal adverse events in patients with cancer.

Searching
PubMed, EMBASE and Web of Science databases were searched from 1966 to October 2010. Search terms were reported. Abstracts and conference meetings from the American Society of Clinical Oncology were searched.

Study selection
Phase II or III randomised controlled trials (RCTs) that compared bevacizumab in combination with chemotherapy (or biological therapy) versus a control (placebo or best supportive care in combination with chemotherapy or biological therapy) in the treatment of cancer patients were eligible for inclusion. The outcome of interest was incidence of fatal adverse events (defined as deaths related to adverse events according to version two or three of the National Cancer Institute's Common Terminology Criteria for Adverse Events).

Included trials were of patients with colorectal cancer, non-small cell lung cancer, breast cancer, renal cell carcinoma, pancreatic cancer and prostate cancer. Patients were required to have adequate hepatic, renal and haematologic functions. Patients received 2.5mg/kg or 5mg/kg bevacizumab per week along with any of the following treatments (regimens unknown): irinotecan, fluorouracil, leucovorin, oxaliplatin, capecitabine, paclitaxel, carboplatin, cisplatin, gemcitabine, docetaxel, pemetrexed, interferon alpha and erlotinib.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Trial quality was assessed according to the Jadad scale of randomisation, blinding and withdrawals. Trials received a score between zero and 5 (5 denoted highest quality).

The authors did not state how many reviewers performed the assessment.

Data extraction
Three reviewers independently extracted the number of fatal adverse events in each treatment group to calculate the proportion of patients with fatal adverse events in each group ultimately to calculate relative risks (RRs) and 95% confidence intervals (CIs). Primary authors and pharmaceutical manufacturers were contacted for further relevant data where necessary. Discrepancies were resolved by consensus.

Methods of synthesis
A fixed-effect model was used to pool relative risks and 95% confidence intervals; a random-effects model was used where there was evidence of statistical heterogeneity. Statistical heterogeneity was assessed using the Cochran Q and $I^2$ statistics.

Subgroup analyses were undertaken by treatment dose (low dose 2.5, 5, or 7.5mg/kg per schedule, equivalent to a weekly dose of 2.5mg/kg versus high dose 10 or 15mg/kg per schedule, equivalent to a weekly dose of 5mg/kg), trial date, tumour type and chemotherapy regimens (platinums or taxanes versus non-platinum or non-taxanes). Findings were assessed by quality score (≤3 versus >3).
Sensitivity analysis was performed by excluding trials of patients with squamous cell histology of lung cancer as these patients were no longer treated with bevacizumab.

**Results of the review**

Sixteen RCTs (10,216 patients, calculated from the table) were included in the review: four phase II trials and 12 phase III trials. Trial quality ranged from 1 to 4 (fair quality); four trials scored 4 and seven scored 3. Where reported, median follow-up durations ranged from 6.7 to 28 months.

There was a statistically significant increased risk of fatal adverse events with the addition of bevacizumab to chemotherapy or biological agent (RR 1.33, 95% CI 1.02 to 1.73; I²=26.62%; 16 RCTs).

Subgroup analysis showed no statistically significant difference in risk of fatal adverse events between patients who received high- or low-dose bevacizumab. However, there was a statistically significantly increase in risk in patients who received high doses (RR 1.98, 95% CI 1.20 to 3.27; eight RCTs). There was no statistically significant variation in risk of fatal adverse events by tumour type, although one RCT showed increased risk with bevacizumab in patients with prostate cancer.

Subgroup analysis by chemotherapy regimen showed increased risk of fatal adverse events in patients who received bevacizumab with platinum or taxane chemotherapy agents (RR 3.49, 95% CI 1.82 to 6.66; five RCTs), but not in patients who received bevacizumab with non-platinum or non-taxanes (three RCTs); this difference was statistically significant (p=0.006).

Sensitivity analysis did not significantly alter the findings. There was no significant association with year of trial. Findings by quality score showed no significant differences for those who scored 3 or less versus those who scored more than 3.

There was a statistically significantly increased risk of specific adverse events, such as haemorrhage and pulmonary haemorrhage, in patients who received additional bevacizumab. Other findings were reported in the review.

**Authors' conclusions**

Addition of bevacizumab to chemotherapy or biological therapy increased treatment-related mortality compared to chemotherapy alone.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The literature search was adequate, but it was unclear whether there were any language restrictions. Publication bias was not formally assessed. The authors used previously published criteria to assess study quality, which were deemed to be of fair quality. The authors stated that data extraction was undertaken in duplicate; it was unclear whether this was the case for study selection and quality assessment, so reviewer error and bias could not be ruled out.

The authors highlighted the wide variation in tumour type and concurrent chemotherapy. Subgroup analyses further highlighted the difference in findings. Therefore, pooling of trials may not have been appropriate. Only a small number of events occurred in some trials. It was unclear how treatment arms with zero events were handled. It was unclear from the forest plots how much weighting each trial contributed to the overall findings. The authors acknowledged that fatal adverse events were not the primary outcome in the included studies and it was unclear how this may have affected the findings.

Given methodological limitations with the review process, variability in trial populations and trial findings and the quality of the trials, the authors' conclusions should be interpreted with caution.

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

**Practice:** The authors stated that healthcare professionals and patients needed to recognise risks as well as benefits associated with bevacizumab. Patients should be monitored closely to identify and treat serious adverse events. The authors stated that the findings were in patients with adequate major organ function and may not have been generalisable to the general patient population.
Research: The authors stated that further research was needed to identify the risk factors of major haemorrhage, neutropenia and gastrointestinal tract perforation and unspecified causes of fatal adverse events associated with bevacizumab. Further studies were needed to further investigate risk in patients with different tumour types.

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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.