Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis

CRD summary
The review concluded that metformin appeared to reduce subsequent cancer risk, especially risk of pancreatic and colorectal cancer, in patients with diabetes but sulphonylurea did not. The uncertain quality of the evidence base, differences across studies and potential for biases and confounding limit the reliability of the pooled results and hence the authors’ conclusions.

Authors’ objectives
To determine the association of metformin and sulphonylurea with the risk of cancer in patients with type 2 diabetes.

Searching
MEDLINE was searched to May 2011 for articles published in English. Search terms were reported. Reference lists of reviews and meta-analyses were handsearched.

Study selection
Eligible studies were cohort or case control studies that assessed exposure to metformin or sulphonylurea and the risk of all cancer (primary outcome) or risk of cancer at specific sites (secondary outcome) in patients with type 2 diabetes. Studies of recurrent cancers or prevalent cancer were excluded. Studies had to report sufficient data to enable calculation or estimation of the association between exposure and outcome.

The included studies investigated the risk of cancer associated with metformin and sulfonylurea and metformin alone. Studies examined cancer at any site, colon and rectum cancer, prostate cancer, pancreatic cancer, breast cancer and other specified site cancers. Studies were conducted in various countries that included UK, other European countries, USA, Canada, China and Taiwan. Studies were published between 2004 and 2011.

Two reviewers independently undertook study selection. Disagreements were resolved by discussion.

Assessment of study quality
The authors did not state whether they assessed study quality.

Data extraction
Two reviewers extracted data on risk of cancer (all and specific sites) and used these data to calculate relative risks (RR) and 95% confidence intervals (CI). Adjusted data were used where possible; otherwise raw data were used to calculate relative risks.

Methods of synthesis
Fixed effect meta-analysis was used to calculate pooled relative risks and 95% CI. Random-effects meta-analysis with DerSimonian and Laird model was used where there was evidence of substantial statistical heterogeneity. $I^2$ and $X^2$ statistics were used to assess statistical heterogeneity. Use of adjusted versus unadjusted data were explored.

Publication bias was assessed using funnel plots and Egger’s test. Subgroup analysis was presented on the basis of study type (case control and cohort study). Sensitivity analysis was undertaken for several study characteristics and by exclusion of each study at a time.

Results of the review
Seventeen studies were included in the review (37,632 cancers): 11 studies looked at both treatments and six studies looked at metformin alone. Seven studies looked at cancer at any site (3,931 cancers) and 10 studies looked at specific cancer sites (33,701). Study sample sizes ranged from 112 to 24,723 cancers.
Compared with control, metformin was associated with statistically significantly reduced risk of all cancers (RR 0.61, 95% CI 0.54 to 0.70; I²=84%), colorectal cancer (RR 0.64, 95% CI 0.54 to 0.76; five studies; I²=19%) and pancreatic cancer (HR 0.38, 95% CI 0.14 to 0.91; four studies; I²=89%). There was no evidence that metformin was associated with risk of breast or prostate cancer. Sulphonylurea was not associated with risk of cancer at any site (RR 0.97, 95% CI 0.82 to 1.14; I²=0%).

There was evidence of publication bias with metformin.

**Authors' conclusions**
Metformin appeared to reduce subsequent cancer risk, especially risk of pancreatic and colorectal cancer, in patients with diabetes but sulphonylurea did not.

**CRD commentary**
Inclusion criteria for the review were clearly defined. The search was limited to one relevant database. Only articles in English were included so language bias was possible. Publication bias was assessed and was detected. Attempts were made to reduce reviewer error and bias throughout the review. The authors did not state whether they undertook quality assessment and this made it difficult to assess the reliability of the evidence base. The authors noted that the study populations were clinically heterogeneous.

Data were combined using meta-analysis. There was evidence of substantial heterogeneity in some of the analyses. The authors noted that it was not possible to rule out potential for confounding to have given rise to the protective effect of metformin on cancer.

The uncertain quality of the evidence base, differences across studies and potential for biases and confounding limit the reliability of the pooled results and hence the authors' conclusions. Many of these factors are a consequence of the need to assess a long-term outcome, where randomised studies are unlikely to be relevant, but the authors' recommendation for further higher quality research appears appropriate.

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

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that better designed studies on the interaction between diabetes, diabetes therapies and cancer were needed urgently. The potential protective effect of sulphonylurea on hepatocellular cancer needed further exploration.

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