

# INPLASY PROTOCOL

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The authors declare no conflict of interest.

## Antidiabetic Medications and the Risk of Prostate Cancer in Patients with Diabetes Mellitus: A Systematic Review and Meta-analysis

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**Review question / Objective:** To evaluate the relationship between antidiabetic medications and the risk of prostate cancer among patients with diabetes by performing a systematic review and meta-analysis.

**Condition being studied:** Multiple epidemiological studies and meta-analyses suggested that diabetes was associated with a decreased risk of prostate cancer. A recent study has suspected that the protective effects of prostate cancer may not be only related to diabetes. Instead, the use of antidiabetic medications, such as metformin, thiazolidinediones, sulfonylureas, insulin, incretin-based therapies and sodium-glucose cotransporter 2 inhibitors may also modify the incidence of prostate cancer. However, the existing studies showed inconsistent results. Additionally, there is no available study that provides a simultaneous and comprehensive assessment of the impacts of all conventional antidiabetic medications on risk modification of prostate cancer.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 June 2020 and was last updated on 30 June 2020 (registration number INPLASY202060113).

### INTRODUCTION

**Review question / Objective:** To evaluate the relationship between antidiabetic medications and the risk of prostate cancer among patients with diabetes by

performing a systematic review and meta-analysis.

**Rationale:** Antidiabetic medications may modify the incidence of prostate cancer in patients with diabetes.

**Condition being studied:** Multiple epidemiological studies and meta-analyses suggested that diabetes was associated with a decreased risk of prostate cancer. A recent study has suspected that the protective effects of prostate cancer may not be only related to diabetes. Instead, the use of antidiabetic medications, such as metformin, thiazolidinediones, sulfonylureas, insulin, incretin-based therapies and sodium-glucose cotransporter 2 inhibitors may also modify the incidence of prostate cancer. However, the existing studies showed inconsistent results. Additionally, there is no available study that provides a simultaneous and comprehensive assessment of the impacts of all conventional antidiabetic medications on risk modification of prostate cancer.

## METHODS

**Search strategy:** A systematic literature search was conducted by two researchers using Embase, PubMed, and Cochrane Library (up to April 2020) for all relevant studies investigating the associations between antidiabetic medications administration and prostate cancer risk in diabetics. Medical Subject Headings search terms are given below: “hypoglycemic agents”, “metformin”, “thiazolidinediones”, “insulin”, “sulfonylurea compounds”, “dipeptidyl-peptidase IV inhibitors”, “glucagon-like peptide-1 receptor agonists”, “sodium-glucose cotransporter 2 inhibitors” combined with “neoplasms”. Additionally, the references lists of retrieved papers and relevant systematic reviews were manual-searched to identify other potential series.

**Participant or population:** Patients with type 2 diabetes who take conventional antidiabetic medications, and report the risk of prostate cancer.

**Intervention:** Administration of metformin, thiazolidinediones, insulin, sulfonylureas dipeptidyl-peptidase IV inhibitors, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter 2 inhibitors.

**Comparator:** 1) Placebo; 2) no intervention; 3) lifestyle intervention; 4) other antidiabetic medications (besides the index agent).

**Study designs to be included:** Observational studies and randomized controlled trials with follow-up over 2 years.

**Eligibility criteria:** Studies were included when they fulfilled all of the following criteria: 1) have subjects treated for diabetes with antidiabetic medications ; 2) studies reported risk of prostate cancer in diabetics; 3) studies reported hazard ratio, relative risk or odds ratio with its 95% confidence intervals (CIs) or provided sufficient data for their calculation.

**Information sources:** We searched PubMed, Embase and Cochrane library from inception to April 2020 by using medical subject headings, Emtree, and text word with no language limitations. The full electronic search strategy of PubMed, Embase and Cochrane library was according to the Biondi-Zoccai’s methods. Moreover, the references of relevant studies, reviews, editorials, and letters were also searched manually. The eligibility was based on the full text and supplement files. Any inconsistency will be sent to a third reviewer (Guixia Wang) for final decision.

**Main outcome(s):** Risk of prostate cancer.

**Quality assessment / Risk of bias analysis:** The quality assessment was determined with the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Collaboration’s tool for randomized controlled trials by two independent authors (Haiying Cui and Shuo Yang). Any disagreements were resolved by discussion or consensus with a third reviewer (Guixia Wang).

**Strategy of data synthesis:** Dichotomous data were calculated as odds ratio (OR), with 95% confidence intervals (CI). All tests were two-tailed and a P value less than 0.05 was deemed statistically significant.

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All analyses and calculations were completed in Stata version 12 (StataCorp, College Station, TX, USA).

**Subgroup analysis:** Subgroup analysis was performed based on the following predefined criteria: study design; study location; study setting and whether the study adjusted for the concomitant use of other antidiabetic medications besides the index agent.

**Sensibility analysis:** Sensitivity analysis was conducted by examining the combined estimate depended on the effect size from certain study.

**Language:** English.

**Country(ies) involved:** China.

**Keywords:** Prostate cancer; antidiabetic medications; meta-analysis; risk.

**Contributions of each author:**

Author 1 - Haiying Cui.

Author 2 - Yao Wang.

Author 3 - Shuo Yang.

Author 4 - Guangyu He.

Author 5 - Zongmiao Jiang.

Author 6 - Xiaokun Gang.

Author 7 - Guixia Wang.