Diabetes Medication Use and Cancer Risk: Protocol for a Systematic Review

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Protocol

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Abstract

Background: Cancer is a growing public health challenge. Innovative approaches to prevent the future burden of cancer are needed. Diabetes medications may help to decrease the risk of cancers, however, a better understanding of relationships by cancer site and diabetes medication class are essential to guide future clinical trials. However, there is not adequate knowledge synthesis on different types of diabetes medications and cancer types. We aim to provide an integrated view of diabetes medications' role and site-specific cancers.

Methods: This systematic review will include observational studies (cohort, nested case-control, case-cohort, and case-control) and randomized controlled trials in human adults in which the effect of diabetes medication use on breast, lung, colorectal, prostate, liver, and pancreatic cancers was evaluated. The former four are among the most common cancer types, while liver and pancreatic cancer are of interest due to the biological roles of the liver and pancreas in blood glucose regulation. MEDLINE, Embase, Web of Science Core Collection, and Cochrane CENTRAL will be searched using a comprehensive and sensitive search strategy. The reference list of identified studies and relevant systematic reviews will be manually screened. Two reviewers will independently screen studies, extract data, and assess quality. Random-effect models will be employed to obtain overall pooled estimates of associations and corresponding 95% confidence intervals (CIs). This systematic review and meta-analyses will be reported following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Results will be reported as specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Discussion: Findings of this review will help to clarify relationships between diabetes medication and cancer, which is critical for future efforts to improve cancer prevention. Further, challenges and limitations identified in this review will foster opportunities to refine design and analysis procedures in future studies.

Systematic review registration: The systematic review protocol was registered on Open Science Framework (https://osf.io/frg5z) and on PROSPERO (registration number CRD42021239348).

Background

Rationale

Cancer is recognized as a major public health problem. It is estimated that 20% of people would be diagnosed with cancer during their lifetime worldwide (1), although estimates are greater in many high-income countries (e.g., 44% in Canadians) (2). As the most common cancers, breast, lung, colorectal, and prostate cancers constitute 41% of new cases for both sexes of adults aged 20 and above (1). Cancers of liver and pancreas are less common but have high fatality rates. An estimated 0.91 million new liver cancer cases and 0.83 million liver cancer deaths occurred in both sexes, and pancreatic cancer was responsible for 0.50 million new cancer cases and 0.47 million deaths (1). The global cost of treating

people diagnosed with cancer was US $285.8 billion in 2009, and the annual indirect cost due to productivity loss and premature death was estimated to be US $1.16 trillion (3).

The number of people living with diabetes continues to rise every year. The projected worldwide prevalence of diabetes for adult populations is projected to reach 10.2% in 2030 from 9.3% in 2019 (4). In addition to lifestyle management, metformin is the first-line medication for treating moderate to severe type 2 diabetes (T2D), hereafter referred to as diabetes. Second-line medications will subsequently be added to the treatment regimen if monotherapy fails (5).

Diabetes and cancer have several shared risk factors, like aging, male sex, race/ethnicity, excess body fat, physical inactivity, unbalanced diet, excess alcohol consumption, and smoking (6) that may contribute to observed relationships. Nevertheless, several mechanisms provide biologic plausibility for the effect of diabetes on cancer risk. Diabetes may impact cancer formation through hyperinsulinemia, hyperglycemia, and chronic inflammation (6). The activity of insulin and insulin-like growth factor axis, bidirectional promotion effect of diabetes and obesity, and metabolic symbiosis may lead to cancer development in people with hyperglycemia. Endoplasmic reticulum stress and autophagy are additional potential cellular mechanisms linking increased insulin production and hyperglycemia with cancer development. For example, cellular response to endoplasmic reticulum stress facilitates tumor growth (7, 8). Quality control of protein in cancer cells is encumbered with autophagy defects and autophagy inhibition accelerates tumor progression (7).

Diabetes medication-cancer links may be specific to different cancer sites and medication classes, namely biguanide, incretin-based medicines, sodium-glucose cotransporter 2 inhibitors, alpha-glucosidase inhibitors, insulin secretagogues, thiazolidinediones, and insulin. Medications that reduce insulin resistance have been hypothesized to reduce cancer risk (9). Metformin indirectly suppresses tumor cells by lowering glucose, insulin, and insulin-like growth factor 1 levels. Metformin may also directly inhibit carcinogenesis by reducing the production of pro-inflammatory cytokines (10). Elevated pancreatic cancer risk may reflect pancreatic inflammation and proliferation of pancreatic cells induced by incretin-based medicines (11). The antitumor effect of canagliflozin, a type of sodium-glucose cotransporter 2 inhibitors, might be via inhibition of mitochondrial respiration (12). Alpha-glucosidase inhibitors may play a role in colon cancer through their effect on the digestive system. For instance, higher butyrate production induced by acarbose might be related to a lower risk of colon cancer (13). Sulfonylureas, the first kind of insulin secretagogues, may lower cancer risk by promoting cell apoptosis and inhibiting proliferation (14). Hypothesized mechanisms of thiazolidinediones on neoplasia include the induction of apoptosis, arrest of cancer cell proliferation, and promotion of cellular differentiation (15). Owing to the growth promotion mechanisms of insulin therapy, this group of medications may be regarded as a risk factor for cancers (16). Finally, glucose-lowering medications may play a role in the occurrence of pancreatic and liver cancer due to their role in regulating blood glucose levels via insulin and glucagon.

Diabetes medications may also be prescribed for off-label use. For instance, metformin is used in adults to treat pre-diabetes, gestational diabetes, and to manage antipsychotic-induced weight gain (17). For women with polycystic ovary syndrome, metformin prevents ovarian hyperstimulation syndrome (18) and treats oligomenorrhea (19). A considerable number of people are on diabetes medication because of the high prevalence of diabetes and the versatility of the drugs. The relatively high prevalence of exposure to diabetes medications indicates a critical opportunity to prevent cancer.

Although the literature on the diabetes-cancer association is rapidly growing, few studies have synthesized the associations between different diabetes medications and cancer sites. The growing utilization of newer medications demands an updated understanding of long-term benefits and harms. Based on recent evidence from 2011 onwards, we aim to conduct a systematic review of studies on the associations between diabetes medications and site-specific cancers.

Objectives

This systematic review aims to evaluate the association between diabetes medication use in adult populations and cancer risk. For this reason, the proposed systematic review will address the following query: when compared with nonusers, do users of diabetes medication vary with respect to risk of breast, lung, colorectal, prostate, liver, and pancreatic cancers? Meta-analyses will be conducted to estimate pooled measures of association between different diabetes medication classes and cancers of interest if sample size permits.

Methods/design

The protocol was developed and described following the PRISMA-P checklist (Additional file 1) (20, 21). The systematic review and meta-analysis will be reported following Meta-analysis of Observational Studies in Epidemiology (MOOSE) (22) for observational studies and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (23) statement for experimental studies. Following the guidelines, our systematic review protocol was registered on Open Science Framework (https://osf.io/frg5z) and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on March 29, 2021 (registration number CRD42021239348).

Inclusion and Exclusion Criteria

As a systematic review of epidemiological studies, eligibility criteria specified the study design, participants/population, intervention (or exposure for observational studies), comparators, and outcomes.

Study design: We will include original observational and experimental studies that evaluate the associations between diabetes medications and cancer (breast, lung, prostate, colorectal, pancreatic, and liver cancers). Cross-sectional designs will not be considered due to limited ability to confirm temporality. Retrospective and prospective cohort studies, case-control studies within a pre-existing cohort (i.e., nested

case-control and case-cohort studies), and randomized controlled trials (RCTs) will be included in this review.

Participants/population: We will include male and female adult participants for cancer of shared anatomic sites (lung, colon and rectum, liver, and pancreas). For breast and prostate cancer, the study population will be restricted to females and males, respectively. People with existing cancer or a previous history of cancer will be excluded from the study. No other restrictions applied to participants based on demographic and medical characteristics.

Intervention/exposure: For cohort studies, ascertainment of exposure to diabetes medication should be determined by written measurements, medical records, pharmacy prescription, or insurance claims database. The same criteria apply to case-control, nested case-control, and case-cohort studies. Diabetes mediations in RCTs will not be restricted to monotherapy.

Comparator(s)/control: Use of active comparator is not required in cohort studies, case-control studies, and variants of the case-control design. For a diabetes medication of interest, people on other diabetes medication(s) are also considered eligible as controls. For RCTs, people receiving no treatment, placebo, or active comparator are considered as controls. Population- and hospital-based controls are sources of control groups in cohort studies, nested case-control studies, case-cohort studies, and classic case-control studies and RCTs.

Outcome: Cancer incidence and cancer mortality should be ascertained through national recording system, cancer registry, or death certificates. Eligible effect measure includes standardized mortality ratio (SMR), standardized incidence ratio (SIR), odds ratio (OR), relative risk (RR), and hazard ratio (HR). External controls from local, regional, or national general populations are needed to obtain SMR or SIR. Computing OR, RR, and HR requires internal controls.

Publication characteristics: To assess and synthesize current evidence, eligible studies will be limited to a publication date from January 2011 onwards. Published journal articles will be considered. No language restrictions will be imposed. After titles/abstracts screening, full-text of selected studies in a language other than English will be translated using Google Translate. Searches will be re-run before the final analysis if necessary.

Search Strategy

The research team will carry out the search strategies with the assistance of an expert librarian. We will systematically search MEDLINE (Ovid), Embase (Ovid), Web of Science Core Collection, and Cochrane CENTRAL (Ovid). We will identify additional studies from reference lists of extracted studies and previous systematic reviews. Search terms included controlled vocabulary and keywords terms related to various diabetes medications and cancer at multiple sites. Details of the search strategy for MEDLINE (Ovid) are provided in an additional file (Additional file 2).

Study Selection

All titles and abstracts will be imported to Covidence (www.covidence.org), a web-based software platform. Covidence will streamline the processes of screening, study selection, and identifying discrepancies between two reviewers. The study selection will be conducted in two stages: titles/abstracts screening and full-text screening. First, all titles and abstracts will be screened by reviewers (YC, FM, and SS) for potentially relevant papers in accordance with inclusion and exclusion criteria. Studies declined by two reviewers will be excluded. Second, full texts of all potentially relevant studies will be retrieved and screened independently for eligibility by two reviewers. We will resolve any disagreement through discussion, or if required, we will consult a senior reviewer (RAM). Reasons for exclusion will be documented at the full-text screening. We will identify and collate multiple reports of the same study. Duplicates will be excluded, and each study will be counted once. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data Extraction

Two reviewers will extract relevant data independently from all selected studies into a standardized data collection form using Covidence. Before full data extraction, necessary amendments will be made based on a pilot test of twenty studies. Discrepancy respecting extracted data will be resolved by discussion or consensus with a third reviewer. All data in languages other than English will be translated. The lead reviewer will be responsible for primary data extraction and the second reviewer will verify extracted data.

The extracted information will include:

Administrative details: author(s); year of publication, year in which study was conducted;

Details of the study: location(s) of study; study design; duration of follow-up; loss to follow-up (%);

Details of participants: age (range, mean, and standard deviation); sex (% male); sample size;

Details of intervention/exposure: medication name(s); dose, frequency and/or duration of use;

Details of control group: medication name(s), dose, frequency, and/or duration of use if any;

Details of outcomes: cancer identification through national recording system, cancer registry, death certificates, or others.

Details of data analysis: reported numbers for outcome; whether employing an intention-to-treat analysis for RCTs; potential confounders adjusted in observational studies.

Quality Assessment

The methodological quality of observational studies and RCTs will be examined by two reviewers independently using the Newcastle-Ottawa scale (NOS) (24) and Cochrane Collaboration's tool for assessing the risk of bias (25). NOS assesses three domains for case-control and cohort studies:

selection of study group, comparability of groups, and ascertainment of exposure or outcome of interest. The latter comprises selection, performance, detection, attrition, reporting, and other bias.

Data Synthesis

We will conduct a narrative synthesis first to summarize the findings of selected studies following the Centre for Reviews and Dissemination (26). Textual description and/or tabulation will compare and contrast potential differences. When two or more studies evaluating the same drug class and cancer site with similar study designs are identified, we will employ a random-effects model to pool the data (27). We will use Cochran's Q to test statistical heterogeneity across included studies with significance level $P = 0.1$ for chi-squared (28). Heterogeneity will be quantified using the I^2 statistic (29): < 25% and > 75% as low and high heterogeneity, respectively. Possible sources of between-study heterogeneity can be attributed to different diabetes medication types, cancer sites, study designs, participants' characteristics, etc. Primary analyses will be performed at drug class level for each of the seven broad classes. We will perform subgroup analyses and meta-regression to explore the sources of heterogeneity if possible.

Meta-bias: Funnel plot will be used to visually inspect potential publication bias. If the number of included studies is greater than 10, Egger's test for asymmetry of the funnel plot may be performed (30).

Confidence in cumulative evidence: To evaluate certainty of the body of evidence, we will use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (31).

Differences between the protocol and the review: We will document unforeseeable changes and report them in the final manuscript (32).

Discussion

Several systematic reviews and meta-analyses on diabetes medication use and cancer risk association have been published (33–40). But previous reviews did not investigate proposed cancer sites (33) or only evaluated associations with well-established medications (34, 36–40). Based on recent evidence, this systematic review will evaluate the role of various diabetes medications in site-specific cancers (breast, lung, colorectal, prostate, liver, and pancreatic cancers). Specifically, we will identify, examine, and synthesize the available research evidence from published observational studies and randomized controlled trials addressing the effects of diabetes medication use on the development of the aforementioned cancers.

Given the various study designs, medications, and cancer types to be included, we anticipate potential challenges and limitations for this review. The risk of bias may vary considerably across studies. The number of eligible studies for subgroup analyses may be small due to insufficient homogeneity in quantitative data. Because cancer takes a long time to develop, sparse cancer cases or deaths will be obtainable in the relatively short follow-up. Besides, observed effects of diabetes medication are more likely cancer-promoting than initiating if positive associations are observed. Despite the limitations, this

review intends to integrate findings from recent studies and advance understanding of cancer risk among diabetes medication users.

Abbreviations

Cochrane CENTRAL: Cochrane Central Register of Controlled Trials; EMBASE: Excerpta Medica DataBase; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HR: hazard ratio

MEDLINE: Medical Literature Analysis and Retrieval System Online; MOOSE: Meta-Analysis of Observational Studies in Epidemiology; NOS: Newcastle-Ottawa scale; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols; PROSPERO: Prospective Register of Systematic Reviews; RCT: randomized controlled trial; RR: relative risk; 95% CI: 95% confidence interval.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare no competing interests.

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Authors’ contributions

YC and RAM contributed to the initial research question and created the study design. YC drafted the initial protocol. FM, SS and RAM provided critical comments on the protocol. All authors read and approved the final manuscript.

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- Additionalfile2.MEDLINESearchStrategy.docx