Diabetes and Risk of Cancer:
A Retrospective Cohort Study among the Veteran Affairs Population

Clinical Incentive Grant

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Principal Investigator
LeAnn Norris, PharmD, BCPS, BCOP
Clinical Assistant Professor
Department of Clinical Pharmacy and Outcomes Sciences
South Carolina College of Pharmacy – USC Campus
(803) 777-7888
BACKGROUND

Diabetes mellitus (DM) is a group of metabolic diseases characterized by high glucose levels (hyperglycemia). It is estimated that approximately 100 million people have diabetes mellitus worldwide, with forecasts suggesting that this number will triple by the year 2025. Information from the Center for Disease Control and Prevention (CDC) indicates that diabetes affects 25.8 million people or 8.3% of the U.S. population. About 11.3% of people aged 20 or older have diabetes and the prevalence of diabetes increases to 26.9% among people 65 years or older. Diabetes is responsible for 3% of deaths, and ranked the 7th most frequent cause of death in the U.S. in 2007. The economic burden of diabetes is also heavy. The estimated total cost of diabetes in 2007 was $174 billion.

Epidemiologic studies demonstrate that patients with either type 1 or type 2 diabetes have an increased risk of cancer. For instance, type 2 diabetes mellitus is associated with an increased mortality risk from colon, breast and pancreatic cancers. Literature documents that type 2 diabetes carries a 50% increased risk for pancreatic cancer, 30% for colon cancer, and 20% for breast cancer. Similarly, type 1 diabetes carries a 20% increased risk for cancer overall. Specifically, type I DM increases the risk of stomach cancer (SIR = 2.3, 95% CI = 1.1 to 4.1), cervix cancer (SIR = 1.6, 95% CI = 1.1 to 2.2), and endometrial cancer (SIR = 2.7, 95% CI = 1.4 to 4.7).

Recently, a few studies report that metformin (an antidiabetic drug used alone or with other medications, including insulin, to treat type 2 diabetes) might lower the risk of cancer among diabetics. Literature also documents that other antidiabetic drugs, such as actos (thiazolidinediones / TZDs) or insulin, are associated with an increased risk of cancer. However, the majority of the studies have a small sample size which does not allow enough power to detect a statistically significant association, or, have a short study period, whereas cancer needs a long time to develop. In addition, most of these studies are subject to biased results because they failed to control for important confounders such as patients’ co-morbidities, and particularly, disease severity. Controlling for disease severity is particularly important because metformin is often used for patients with less severe diabetes who already have a lower cancer risk; thus the lower risk of cancer found in patients with metformin treatment may not
necessarily because metformin can lower the risk. Studies to separate this effect (termed “confounding by indication”) by controlling for diabetes severity are needed to compare the effectiveness of metformin use on the risk of cancer in people with and without metformin treatment. **This Comparative Effectiveness Research (CER), therefore, defines the literature gap by providing evidence on the link between diabetes, antidiabetic drugs and the risk of cancer.**

**METHODS**

**Study Design:**
Our objectives were to explore the association between diabetes and cancer and to examine the association between the use of antidiabetic drugs and the risk of cancer among diabetes.

We proposed a retrospective cohort study design to examine the risk of cancer associated with diabetes alone and antidiabetic drugs. Logistic and/or Cox regression models were performed for research questions. SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used for data analysis. Patients were included if they were enrolled in the VA health-care system between January 1997 and December 2005. Patients were excluded if patients were less than 18 years of age at the time of diabetes diagnosis and/or the first time use of antidiabetic medications, patients with existing cancer prior to diagnosis of diabetes or index date, Medicare/VA or Medicaid VA dual-eligible patients. Diabetes status was a dummy variable to indicate whether a person has or does not have diabetes. Incident cancers were a dummy dependent variable. We controlled covariates in the model, including use of antidiabetic and antihypertensive medications, demographics, comorbidities, types of diabetes, and diabetes control.

**Data Source:**
Data for this analysis was obtained from the Veteran’s Administration Health Care System (VAHCS) Electronic Medical record, which included clinical and utilization information from 153 medical centers across all 50 states, Puerto Rico and the District of Columbia. The VAHCS operates more than 1,400 sites of care, including 909 ambulatory care and community-based outpatient clinics, 135 nursing homes, 47 residential rehabilitation treatment programs, 232 Veterans Centers and 108 comprehensive home-care programs. Veteran’s Administration (VA) health care facilities provide a broad spectrum of medical, surgical and rehabilitative care.
RESULTS

In a database of 2,145,452 observations, the majority of these patients were male and over the age of 70. Logistic progression models found a statistically significant association (defined as $p < 0.05$) with diabetes and the following cancers including breast, pancreatic, bladder, colon, lung, and tumors classified as “other” in the VA database. There was no association of liver, brain, ovarian, uterine, cervical, lymphoma, kidney, and stomach cancer with diabetes. Metformin use was found to be protective for the following tumor types including breast, liver, bladder, brain, cervical, lymphoma, colon, kidney, lung, stomach, and “other” types of cancer. Metformin use was not protective in pancreatic, ovarian, and uterine cancer. TZD therapy was also shown to be protective in pancreatic, bladder, and lymphoma. TZD therapy was found to be non-protective in breast, liver, brain, uterine, colon, kidney, lung, and stomach cancer.

DISCUSSION

The association found in this study between multiple tumor types and diabetes was not surprising. The majority of these tumor types are indeed solid tumors where other confounding factors such as diet, obesity, and metabolic syndrome has been associated with an increased risk in multiple tumor types. Metformin, as studies suggest, has a protective effect in several tumor types including those types that are the leading causes of cancer death such as lung, breast, and colon. TZD therapy was also shown to be protective in pancreatic, bladder, and lymphoma. This finding contradicts our hypothesis and recent data showing an increased risk or association with bladder cancer and TZD use. Ongoing analysis of this large database continues. Once analyses are completed, article submission is planned for publication in the Spring to a reputable journal.

BUDGET

The majority of our budget was utilized for personal services, contractual services, and data processing via the WJB Dorn VA Hospital and the Dorn Research Institute. The data collection was prolonged due to IRB submission and approval and national VINCI approval.
REFERENCES


