Type 2 diabetes mellitus, glycemic control, and cancer risk

Adedayo A. Onitilo[a,b,d], Rachel V. Stankowski[b], Richard L. Berg[b], Jessica M. Engel[c], Ingrid Glurich[b], Gail M. Williams[d] and Suhail A. Doi[d]

Type 2 diabetes mellitus is characterized by prolonged hyperinsulinemia, insulin resistance, and progressive hyperglycemia. Disease management relies on glycemic control through diet, exercise, and pharmacological intervention. The goal of the present study was to examine the effects of glycemic control and the use of glucose-lowering medication on the risk of breast, prostate, and colon cancer. Patients diagnosed with type 2 diabetes mellitus ($N=9486$) between 1 January 1995 and 31 December 2009 were identified and data on glycemic control (hemoglobin A1c, glucose), glucose-lowering medication use (insulin, metformin, sulfonylurea), age, BMI, date of diabetes diagnosis, insurance status, comorbidities, smoking history, location of residence, and cancer diagnoses were electronically abstracted. Cox proportional hazards regression modeling was used to examine the relationship between glycemic control, including medication use, and cancer risk. The results varied by cancer type and medication exposure. There was no association between glycemic control and breast or colon cancer; however, prostate cancer risk was significantly higher with better glycemic control (hemoglobin A1c $\leq$ 7.0%). Insulin use was associated with increased colon cancer incidence in women, but not with colon cancer in men or breast or prostate cancer risk. Metformin exposure was associated with reduced breast and prostate cancer incidence, but had no association with colon cancer risk. Sulfonylurea exposure was not associated with risk of any type of cancer. The data reported here support hyperinsulinemia, rather than hyperglycemia, as a major diabetes-related factor associated with increased risk of breast and colon cancer. In contrast, hyperglycemia appears to be protective in the case of prostate cancer. ***European Journal of Cancer Prevention*** **23:134–140 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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[a]Department of Hematology/Oncology, Marshfield Clinic Weston Center, Weston, [b]Marshfield Clinic Research Foundation, Marshfield, [c]Marshfield Clinic Cancer Care at St Michaels, Stevens Point, Wisconsin, USA and [d]School of Population Health, University of Queensland, Brisbane, Queensland, Australia

Correspondence to Adedayo A. Onitilo, MD, MSCR, Department of Hematology/Oncology, Marshfield Clinic Weston Center, 3501 Cranberry Boulevard, Weston, WI 54476, USA
Tel: +1 715 393 1400; fax: +1 715 393 1399;
e-mail: onitilo.adedayo@marshfieldclinic.org

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Introduction

Type 2 diabetes mellitus (DM) is a progressive disease characterized by prolonged hyperinsulinemia, development of insulin resistance, and eventual emergence of hyperglycemia. Hyperglycemia characterizes overt DM, and disease management is focused on glycemic control through a combination of diet, exercise, and pharmacological therapy. Serum glucose concentrations in patients with DM have been linked to promotion of tumor cell proliferation and migration *in vitro* (Masur *et al.*, 2011). However, recent evidence suggests that the hyperglycemia characteristic of DM may be less important in promoting cancer risk than the hyperinsulinemia characteristic of the prediabetes phase (Onitilo *et al.*, 2012).

Pharmaceutical modification of hyperinsulinemia and hyperglycemia further confounds the issue of DM and cancer risk. In support of the hyperinsulinemia hypothesis of carcinogenesis, glucose-lowering medications that increase circulating insulin levels, such as exogenous insulin, insulin analogs, and insulin secretagogues, have been reported to be associated with increased cancer risk. In contrast, drugs that decrease circulating insulin levels, such as metformin and thiazolidinediones, have been reported to reduce cancer risk (Onitilo *et al.*, 2012). Johnson and Bowker (2011) recently carried out a large meta-analysis to examine glycemic control independent of changes in insulin levels and observed no change in cancer risk with intensive glycemic control. The aim of the present study was to examine the interaction between glycemic control and use of insulin-modifying therapies as related to breast, prostate, and colon cancer risk in a well-defined cohort of adult patients with DM.

Patients and methods

The relationship between glycemic control and cancer risk in diabetic patients was assessed in a retrospective cohort study at the Marshfield Clinic, a large multispecialty group healthcare system in north–central Wisconsin. The study protocol and a waiver of informed consent were approved by the Marshfield Clinic Institutional Review Board.

Data were collected electronically from the Marshfield Clinic electronic medical record (EMR) and cancer registry. Data validation was performed in an iterative fashion and included both electronic screening (e.g. graphical review of laboratory results, identification of apparent discrepancies between laboratory values and diagnoses) and manual

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review. Manually reviewed patients included two sequential random samples (90 and 84 cases) with selection stratified electronically with respect to prevalence of diabetes and cancer, calendar year, and location of residence. These samples were manually validated by searching the patient medical record for the presence and incident dates of diagnosis for diabetes and cancer through utilization of text records, diagnosis description codes, pathology reports, and review of diabetes-related laboratory tests and medications. Validation results were used to refine cohort definitions, as described below.

Patients diagnosed with DM between 1 January 1995 and 31 December 2009 were eligible for the study. All patients were required to be at least 30 years old by the end of the study period and could not have any diabetes-related diagnoses before the study start date. To ensure adequate follow-up within the Marshfield Clinic system and accurate determination of date of diagnosis, all patients were required to have at least one nondiabetes diagnosis or electronic code documenting a well-visit from a Marshfield Clinic provider in at least one of the three calendar years before diagnosis of diabetes. Observation times were censored before any gap of 4 or more consecutive calendar years in the EMR.

Patients with DM were identified using a combination of clinical and laboratory data. Patients were included if they had at least one diagnosis of DM by International Classification of Diseases, Ninth Revision (ICD-9) code in the EMR (250.00 or 250.02), at least two elevated hemoglobin A1c (HbA1c) or glucose tests within 3 years before or after DM diagnosis, and at least one normal HbA1c or glucose test before the abnormal test, but within 3 years before DM diagnosis. Laboratory values were defined using American Diabetes Association criteria for diabetic patients (HbA1c $\geq$ 6.5%, fasting glucose $\geq$ 126 mg/dl, or random glucose $\geq$ 200 mg/dl) or normal (HbA1c $<$ 6.5%, fasting glucose $<$ 126 mg/dl, or random glucose $<$ 200 mg/dl) (American Diabetes Association, 2010). Date of DM onset was defined as the earliest of the first DM diagnosis by ICD-9 diagnostic code or the second elevated diabetes-related laboratory value. All dates of diagnosis fell within the 15-year study period from 1995 through 2009, but follow-up extended through 2011.

Diagnosis of breast, prostate, or colon cancer was determined by examining the EMR for ICD-9 diagnostic codes representative of each specific cancer type, requiring at least two documented diagnoses in the patient's medical record. The first date a cancer ICD-9 code was used was considered the date of cancer diagnosis. The cancer registry was also searched for cancer diagnoses, and the two lists were merged to validate the date if diagnosis was obtained from the EMR. Patients with a history of breast, prostate, or colon cancer at the time of DM onset were excluded.

Glycemic control in diabetic patients was estimated based on observed HbA1c values and HbA1c values predicted based on glucose measurements. Although HbA1c is the gold standard for clinical management of patients with diabetes, the Marshfield Clinic EMR contains many more glucose than HbA1c results. After finding good correlation between system-wide HbA1c and glucose levels ($\sim$0.6), we followed the example of Nathan *et al.* (2008) and incorporated both HbA1c and glucose levels into our assessment of glucose control. Glucose results were modeled to develop a prediction equation for HbA1c such that observed glucose measurements could be converted to a predicted HbA1c result and combined with observed HbA1c measurements. To account for greater accuracy of observed versus predicted HbA1c measurements, observed HbA1c values were applied to a period of up to 120 days (ending on the day of measurement), accounting for the lifespan of the red blood cell, whereas predicted HbA1c values were applied to the single day of measurement, weighting the measure of glycemic control highly toward observed HbA1c results. The final regression model predicts log(HbA1c) from a cubic spline function of log(glucose), with separate functions for random and fasting glucose. To determine glycemic control in a given time period, we calculated the simple day-weighted mean over that period. Baseline HbA1c was calculated using all observed and predicted HbA1c measurements available in

Table 1 Baseline characteristics of diabetic patients

	Diabetic patients (N=9486)
Mean baseline HbA1c (IQR) (%)	7.0 (6.2–7.2)
Mean overall HbA1c (IQR) (%)	6.9 (6.3–7.2)
Sex [*N* (%)]	
Male	4956 (52.2)
Female	4530 (47.8)
Mean age (IQR) (years)	61.7 (52.3–71.1)
Smoking status [*N* (%)]	
Ever	6333 (66.8)
Never	3153 (33.2)
DM diagnosis period [*N* (%)]	
1995–1999	2070 (21.8)
2000–2004	3937 (41.5)
2005–2009	3479 (36.7)
MESA residency [*N* (%)]	
No	7643 (80.6)
Yes	1843 (19.4)
Mean BMI (IQR) (kg/m^2)	33.7 (28.7–37.4)
Have insurance [*N* (%)]	7436 (78.4)
Median observation time (IQR) (years)	7.1 (4.6–10.1)
Hypoglycemic medications [*N* (%)][a]	
Insulin	2882 (30.4)
Metformin	5679 (59.9)
Sulfonylurea	886 (9.3)
None of the above	3113 (32.8)
Cancer [*N* (%)][b]	
Breast (women only)	181 (4.0)
Prostate (men only)	237 (4.8)
Colon	
Male	56 (1.1)
Female	50 (1.1)

DM, type 2 diabetes mellitus; HbA1c, hemoglobin A1c; IQR, interquartile range; MESA, Marshfield Epidemiologic Study Area.
[a]Medication use at any time during study period.
[b]*N* (%) of men or women, as indicated, diagnosed with the cancer listed during study period.

the 3 year time period before DM onset, followed by determination of annual means after diagnosis date.

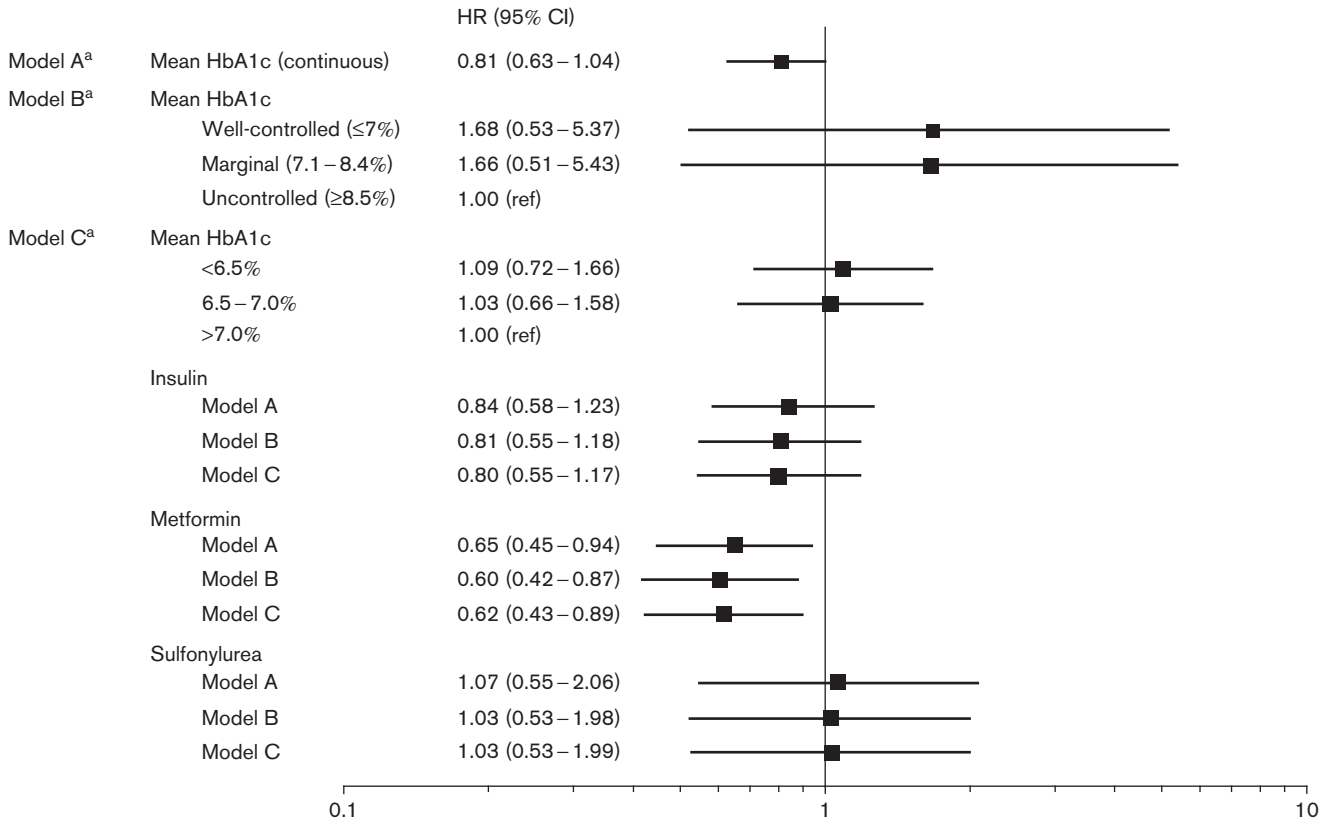
Because glycemic control and use of hypoglycemic medication are inextricably linked, we also examined use of three classes of diabetes medications, including insulin, metformin, and sulfonylurea drugs. In time-varying analyses, patients were considered unexposed until evidence of pharmacological exposure in the EMR, after which patients were classified as 'exposed'. Data with regard to several additional covariates with the potential to influence cancer risk were also extracted including comorbidities and clinical risk factors. Comorbidities of interest included myocardial infarction, coronary heart disease, peripheral vascular disease, cardiovascular disease, chronic pulmonary disease, rheumatic heart disease, and renal insufficiency/renal failure, which were summarized using a modified Charlson score (indicator for comorbidities other than diabetes and cancer). Comorbidities were established by examining the EMR for relevant diagnostic codes, requiring at least two documented diagnoses. Additional data collected from the EMR included BMI, smoking history, location of residence, and insurance status.

Standard descriptive statistics were used to summarize patient characteristics. Three models were developed using Cox proportional hazards regression to examine the relationship between glycemic control, including use of hypoglycemic medications, and the time from DM onset to diagnosis of cancer in diabetic patients. All models included mean HbA1c and medication exposure (insulin, metformin, and sulfonylurea) with adjustment for covariates including BMI, age, DM diagnosis date, insurance status, comorbidities, smoking history, and location of residence. In model A, mean HbA1c was treated as a continuous variable. In models B and C, HbA1c was treated as a categorical variable, with more stringent cut points in model C. Medication use was treated as a time-varying covariate in all models. Results are reported as hazard ratio (HR) with 95% confidence interval (CI).

Results

Characteristics of the 9486 diabetic patients eligible for study participation are shown in Table 1. Median follow-up time was 7.1 years (interquartile range 4.6–10.1 years). Baseline HbA1c met American Diabetes Association

Fig. 1



Forest plot showing effects of glycemic control and hypoglycemic medication exposure on breast cancer risk in women using three different statistical models. Values greater than 1 indicate increased breast cancer risk and less than 1 indicate decreased breast cancer risk. [a]Adjusted for BMI, age, date of diagnosis, insurance status, comorbidities, smoking history, and location of residence. Diabetes medication use: time varying. HbA1c, hemoglobin A1c; HR, hazard ratio; 95% CI, 95% confidence interval.

criteria for DM. Crude incidence of breast cancer in women was 533.6/100 000 person years. Crude incidence of prostate cancer in men was 664.8/100 000 person years. Crude incidence of colon cancer in men and women combined was 149.0/100 000 person years.

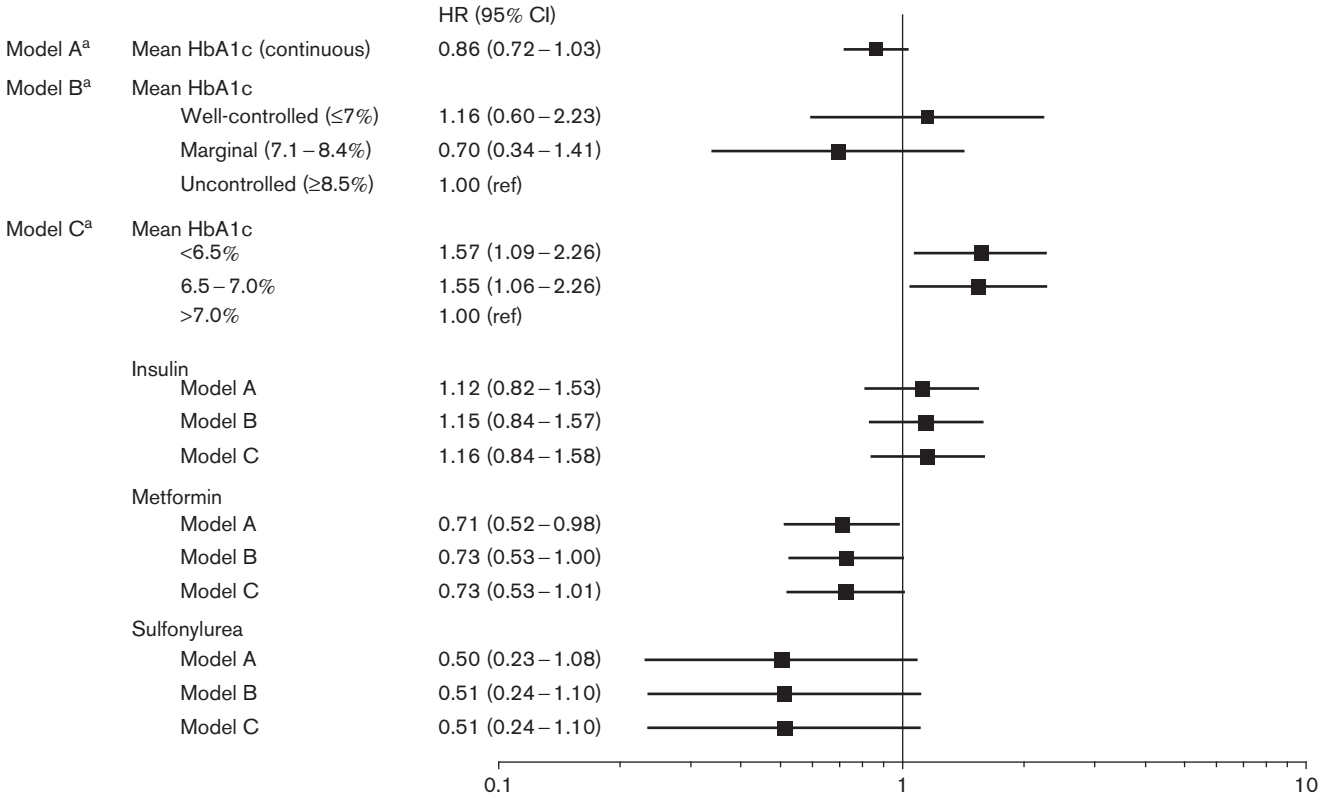
Figures 1–4 demonstrate the association between glycemic control and glucose-lowering medication use with incidence of breast cancer in women, prostate cancer in men, colon cancer in women, and colon cancer in men, respectively. Regardless of the model used, there was no significant association between glycemic control and incidence of breast (Fig. 1) or colon cancer (Figs 3 and 4). In men, the incidence of prostate cancer was significantly greater with better glycemic control (HbA1c $\leq$ 7.0%) (Fig. 2). Use of certain hypoglycemic medications was associated with either increased or decreased risk, depending on the medication and the cancer. Insulin use was significantly associated with increase in the risk of colon cancer in women (Fig. 3). Although the trend was similar in men, the effect was not significant (Fig. 4). Insulin showed no significant association with breast cancer in women (Fig. 1) or prostate cancer in men (Fig. 2). Metformin use was significantly associated with reduction in the risk of breast cancer in women (Fig. 1) and prostate cancer in men (Fig. 2). In contrast, there was no significant association between metformin and colon cancer risk for either sex (Figs 3 and 4). Sulfonylurea exposure was not significantly associated with risk of any cancer in our study.

Discussion

Glycemic control and the medications used to achieve control vary among patients with DM. Similarly, the association between glycemic control and cancer risk appears to vary by both cancer type and glucose-lowering medication(s) used. Previous studies suggest that, in general, tighter glycemic control does not reduce cancer risk (Johnson and Bowker, 2011), and that the effects of glucose-lowering medications are more likely to be the result of influence on levels of circulating insulin (Onitilo *et al.*, 2012). Our results are consistent with these findings, but vary by cancer type.

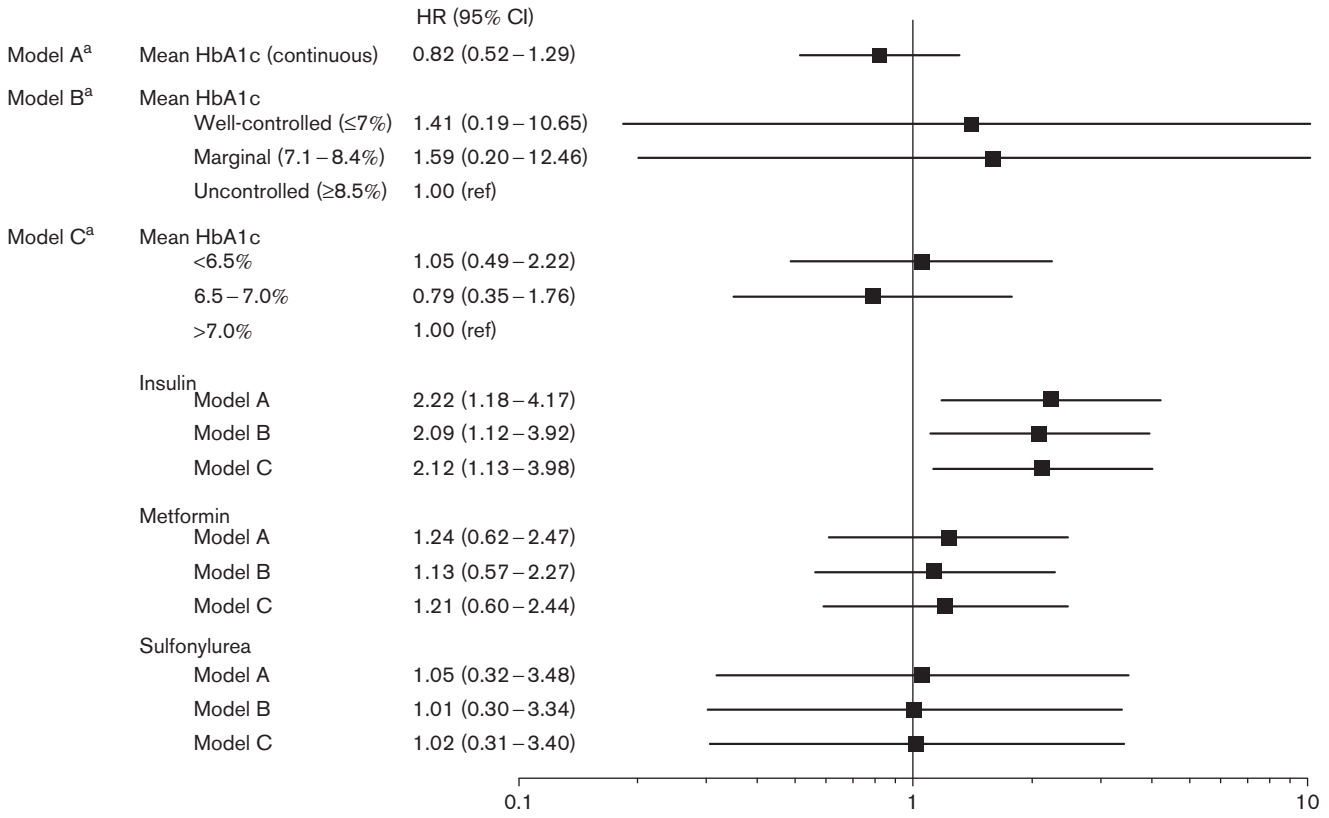
The concentration of glucose present in the blood stream of patients with DM is sufficient to promote increased tumor cell proliferation and migration *in vitro*

Fig. 2



Forest plot showing effects of glycemic control and hypoglycemic medication exposure on prostate cancer risk in men using three different statistical models. Values greater than 1 indicate increased prostate cancer risk and less than 1 indicate decreased prostate cancer risk. [a]Adjusted for BMI, age, date of diagnosis, insurance status, comorbidities, smoking history, and location of residence. Diabetes medication use: time varying. HbA1c, hemoglobin A1c; HR, hazard ratio; 95% CI, 95% confidence interval.

Fig. 3



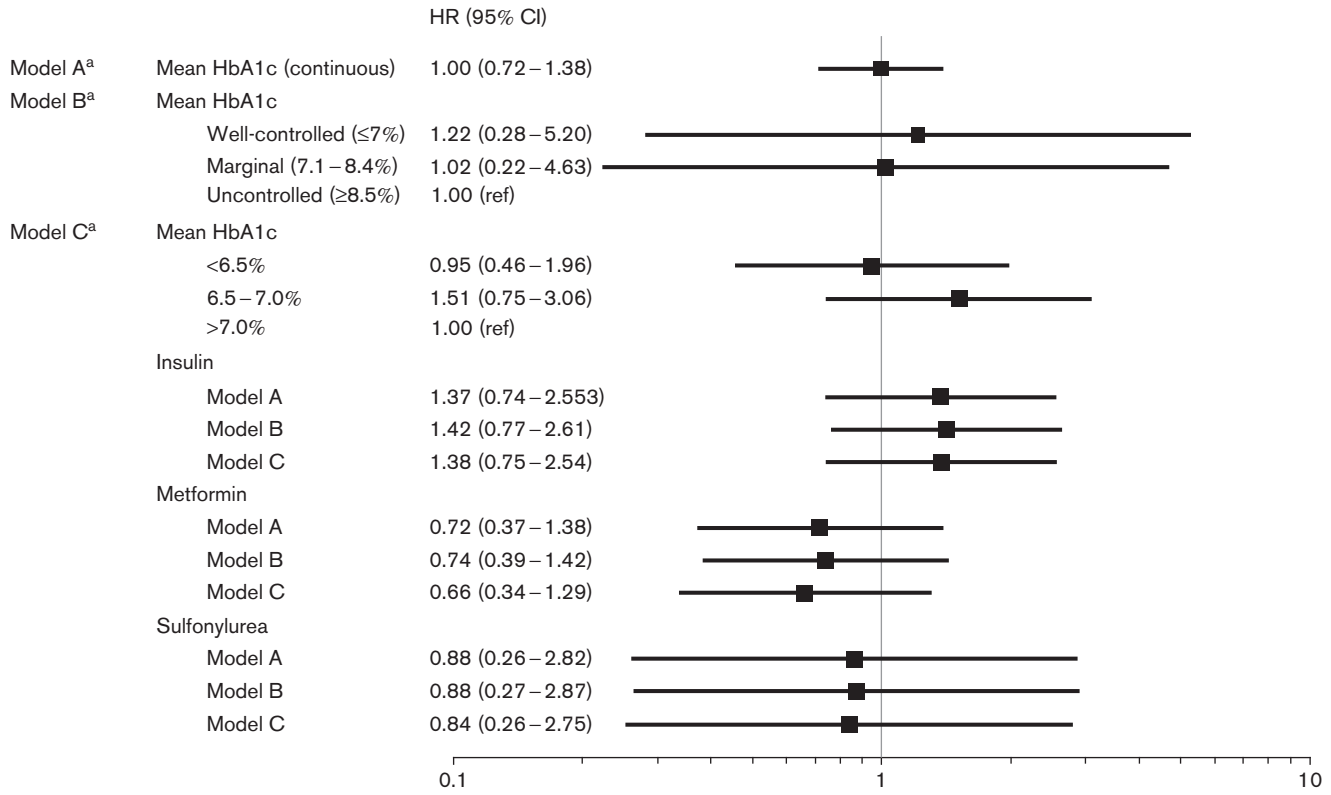
Forest plot showing effects of glycemic control and hypoglycemic medication exposure on colon cancer risk in women using three different statistical models. Values greater than 1 indicate increased colon cancer risk and less than 1 indicate decreased colon cancer risk. [a]Adjusted for BMI, age, date of diagnosis, insurance status, comorbidities, smoking history, and location of residence. Diabetes medication use: time varying. HbA1c, hemoglobin A1c; HR, hazard ratio; 95% CI, 95% confidence interval.

(Masur *et al.*, 2011). However, tumors continue to use high amounts of glucose regardless of blood glucose concentrations, suggesting that external glucose concentration may not be a limiting factor in tumor growth (Taubes, 2012). In the present study, we found no significant association between glycemic control and breast cancer incidence in any of the models examined (Fig. 1). Similarly, colon cancer risk was not associated with glycemic control in either men or women (Figs 3 and 4). These findings are consistent with the recent meta-analysis by Johnson and Bowker (2011), who examined cancer risk in patients with improved glycemic control and found a pooled risk ratio for cancer incidence of 0.91 (95% confidence interval 0.79–1.05), but did not account for differences by cancer type or sex.

In contrast to breast and colon cancer, risk of prostate cancer was significantly increased in patients with stricter glycemic control (Fig. 2). Reports in the literature consistently demonstrate a protective effect of DM on prostate cancer risk (Bansal *et al.*, 2013). While the exact mechanism responsible for such protection is unclear, it is hypothesized that decreased levels of testosterone as a result of hyperglycemia may play a role in reducing prostate cancer risk (Grossmann *et al.*, 2008; Kasper *et al.*, 2008). In men with better glycemic control, testosterone levels may be closer to normal than in those with uncontrolled hyperglycemia, which may account for the increased risk we observed in men with HbA1c level less than 7.0%.

As with hyperglycemia, glucose-lowering medications for the treatment of DM also influence different types of cancers in different ways. In general, medications that increase circulating insulin, such as exogenous insulin, insulin analogs, and insulin secretagogues, tend to increase the risk of cancer. Medications that decrease circulating insulin levels, such as metformin and thiazolidinediones, tend to decrease cancer risk (Onitilo *et al.*, 2012). Consistent with these patterns, we found that metformin exposure was associated with a significant decrease in the incidence of breast cancer in women (Fig. 1) and a trend toward decreased risk of prostate cancer in men (Fig. 2). We did not observe any association between metformin and colon cancer in men or women (Figs 3 and 4). Several studies have identified a protective

Fig. 4



Forest plot showing the effects of glycemic control and hypoglycemic medication exposure on colon cancer risk in men using three different statistical models. Values greater than 1 indicate increased colon cancer risk and less than 1 indicate decreased colon cancer risk. [a]Adjusted for BMI, age, date of diagnosis, insurance status, comorbidities, smoking history, and location of residence. Diabetes medication use: time varying. HbA1c, hemoglobin A1c; HR, hazard ratio; 95% CI, 95% confidence interval.

role of metformin in cancer development, without differentiating by cancer type (Currie *et al.*, 2009; Libby *et al.*, 2009; Baur *et al.*, 2011). In cancer-specific studies, metformin use has been associated with reduced risk of colorectal, pancreatic, and ovarian cancer (Currie *et al.*, 2009; Bodmer *et al.*, 2011, 2012a) and reduced risk of mortality or increased survival in breast, liver, ovarian, and prostate cancer (Jiralerspong *et al.*, 2009; Azoulay *et al.*, 2011; Currie *et al.*, 2012; He *et al.*, 2012). The evidence presented here supports a role for metformin in reducing the risk of breast and prostate cancer, but not colon cancer. Further study to clarify these discrepancies is needed.

Medications that increase circulating insulin levels, including exogenous insulin and sulfonylureas, are generally associated with an increased risk of cancer (Onitilo *et al.*, 2012). In the present study, we did not observe any association between sulfonylurea use and breast, prostate, or colon cancer incidence. Similarly, insulin use was not significantly associated with breast or prostate cancer incidence. However, exposure to exogenous insulin was associated with a significant increase in the incidence of colon cancer in women (Fig. 3), but not men (Fig. 4). A previous study by Bodmer *et al.* (2012b) found no association between insulin use and colorectal cancer risk, but did not stratify by sex. Sex differences in colon cancer risk have been described previously and appear to be related to hormonal effects on oncogenic processes (Niv *et al.*, 2008; Nguyen *et al.*, 2009). How insulin exposure may further influence sex-specific colon cancer risk warrants further study.

The present study was limited by its retrospective nature as data were collected during routine clinical care and not in the context of a systematic research study. Additionally, time-varying analysis of exposure to glucose-lowering medications was limited to first signs of exposure, after which point patients were considered 'exposed', even after medication discontinuation or change to a different medication. Despite these limitations, the study is strengthened by consideration of each cancer type separately, careful adjustment for confounding factors, and simultaneous evaluation of both glycemic control and glucose-lowering medication use.

Achievement of glycemic control is the overarching goal of diabetes management. To achieve glycemic control, a combination of diet, exercise, self-management, and

medications are used. The three classes of glucose-lowering drugs examined here, including exogenous insulin, metformin, and sulfonylureas, function by modifying levels of circulating insulin. The absence of any association between glycemic control and cancer risk, as observed here and reported previously (Johnson and Bowker, 2011), and findings of increased cancer risk following exposure to medications that increase circulating insulin and decreased cancer risk following exposure to medications that reduce circulating insulin suggest that hyperinsulinemia, rather than hyperglycemia, is the major diabetes-related factor associated with increased cancer risk. Additionally, therapy with metformin appears to be a promising intervention for not only achieving glycemic control but also decreasing cancer risk in patients with diabetes.

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Conflicts of interest

There are no conflicts of interest.

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