

Metformin Use and Risk of Prostate Cancer: Results from the REDUCE Study

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Abstract

The role of metformin in prostate cancer chemoprevention remains unclear. REDUCE, which followed biopsy-negative men with protocol-dictated PSA-independent biopsies at 2- and 4-years, provides an opportunity to evaluate the link between metformin use and prostate cancer diagnosis with minimal confounding from screening biases. In diabetic men from REDUCE, we tested the association between metformin use, use of other antidiabetic medications, versus no antidiabetic medication use, and prostate cancer diagnosis as well as prostate cancer grade (low-grade Gleason 4–6 and high-grade Gleason 7–10) using logistic regression. Of the 540 diabetic men with complete data, 205 (38%) did not report use of any antidiabetic medications, 141 (26%) reported use of at least one antidiabetic medication other than metformin, and 194 (36%) reported use of metformin. During the 4-year study, 122 men (23%) were diagnosed with

prostate cancer. After adjusting for various clinical and demographic characteristics, we found that metformin use was not significantly associated with total (OR, 1.19; $P = 0.50$), low- (OR, 1.01; $P = 0.96$), or high-grade (OR, 1.83; $P = 0.19$) prostate cancer diagnosis. Likewise, there was no significant association between the use of non-metformin antidiabetic medications and prostate cancer risk in both crude (OR, 1.02; $P = 0.95$) and multivariable analysis (OR, 0.85; $P = 0.56$). Furthermore, the interactions between antidiabetic medication use and BMI, geographic location, coronary artery disease, smoking, and treatment group were not significant (all $P > 0.05$). Among diabetic men with a negative prestudy biopsy who all underwent biopsies largely independent of PSA, metformin use was not associated with reduced risk of prostate cancer diagnosis. *Cancer Prev Res*; 8(11); 1055–60. ©2015 AACR.

Introduction

Aside from skin cancer, prostate cancer is the most commonly diagnosed cancer among men in the Western world and the second most common cause of cancer-related death among men (1). It is estimated that about 1 in 6 men in the United States will be diagnosed with prostate cancer during their lifetime and 1 in 36 will die from this disease. Prostate cancer is also a heterogeneous disease and may take decades for a subclinical cancer to progress into a potentially clinically detectable disease of medical consequence. Given its prevalence and its slow progression, prevention of prostate cancer, especially aggressive disease, would have significant benefits in reducing its enormous burden to public health.

Chemoprevention for prostate cancer involves reducing the risk of disease not only in otherwise healthy men, but also in those with subclinical disease with the goal of halting or slowing disease

progression. To date, lifestyle modifications, dietary supplements, and pharmacologic agents have all been studied as potential chemoprevention strategies for prostate cancer; however, none other than the 5 alpha-reductase inhibitors have shown any promise (2). However, there have been concerns raised about potential increased risk of high-grade disease with these agents (3), and they are not FDA approved for prostate cancer chemoprevention.

Metformin, 1,1-dimethylbiguanide hydrochloride, is the oral hypoglycemic agent most widely prescribed to patients with type 2 diabetes. Its primary action is the inhibition of hepatic glucose production through the LKB1/AMPK-mediated mechanism, and thus acts to reduce insulin resistance (4). Studies have demonstrated that metformin use was associated with reduced overall cancer incidence (5–8) and decreased cancer-specific mortality among individuals with diabetes relative to insulin use (9, 10). Preclinical studies have also shown the beneficial effects of metformin on prostate cancer cells via a variety of mechanisms, including cell-cycle arrest (11), mTOR inhibition (12), and growth inhibition (13). However, epidemiologic studies have yielded conflicting results. Although some indicated metformin may be associated with decreased incidence (14–16), others have reported a lack of association between metformin therapy and prostate cancer risk in diabetic patients (17–20). Thus, the role of metformin in prostate cancer chemoprevention remains unclear.

We investigated whether the use of metformin or other antidiabetic medications were associated with overall, low- and high-grade prostate cancer risk in REDUCE. REDUCE was a randomized clinical trial designed to compare the effect of

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dutasteride on prostate cancer diagnosis, among men with a negative prestudy biopsy and at least one on-study biopsy. All men underwent a protocol-mandated biopsy at 2 and 4 years after enrollment regardless of PSA level, thus eliminating the confounding effect of the influence of antidiabetic medications and insulin levels on PSA levels and cancer detection.

We hypothesized that the use of metformin would be associated with overall decreased prostate cancer risk relative to diabetic patients not taking any antidiabetic medications.

Materials and Methods

Study population

REDUCE was a 4-year, multicenter, randomized, double-blind, placebo-controlled study and details are described elsewhere (21). Eligibility requirements were men who were 50 to 75 years old, had a serum PSA of 2.5 to 10.0 ng/mL if 50 to 60 years or 3.0 to 10.0 ng/mL if older than 60 years, and had a single, negative prostate biopsy (6–12 cores) within 6 months prior of enrollment independent of the study. Men with history of prostate cancer, prostate surgery, prostate volume >80 mL, or IPSS >25 or >20 on alpha-blockers were excluded. Subjects were randomized to 0.5 mg dutasteride daily or placebo. Prostate volume was determined by transrectal ultrasound and PSA was measured at baseline and every 6 months. Total serum PSA was doubled when reported to investigators for men in the treatment arm to maintain the blinded nature of the study. Subjects underwent a "protocol-dependent" 10-core transrectal ultrasound-guided biopsy at 2 and 4 years regardless of PSA or DRE findings. "Protocol-independent" biopsies were performed as clinically indicated. Diabetes status was self-reported at enrollment and was not updated during the study period. Body mass index (BMI) was calculated using height and weight (kg/m²) measured at baseline. Metformin and other antidiabetic medication use were recorded at the time of randomization. The primary end-point was biopsy-detectable prostate cancer at any time during the 4-year period, including the 2- and 4-year study mandated biopsies as well as protocol-independent biopsies.

Self-reported diabetic status was available for all 8,122 men included in the efficacy population. We identified 693 men with diabetes at time of enrollment. A total of 130 (19%) men did not undergo any on-study biopsy and were excluded. We also excluded men with missing data on BMI ($n = 7$), prostate volume ($n = 12$), PSA ($n = 2$), and DRE findings ($n = 2$), resulting in a final study population of 540. These men were then categorized into three mutually exclusive groups according to medication use of no antidiabetic medications, any antidiabetic medication other than metformin, and metformin (with or without other antidiabetic medications). Demographic information, including age, race, BMI, prostate volume, PSA, and DRE findings, was recorded at baseline.

Statistical analysis

Comparison between baseline characteristics among the three medication categories was performed using χ^2 and Kruskal-Wallis tests for categorical and continuous variables. Logistic regression was used to evaluate the association between metformin and other antidiabetic medication use on prostate cancer diagnosis (upon pathology review of prostate biopsies during the study). Multinomial regression was used to model the outcomes of low-grade (Gleason 4–6) versus no prostate cancer and high-

grade disease (Gleason 7–10) versus no prostate cancer. The small sample size and few men diagnosed with Gleason 8–10 during the study ($n = 8$) precluded us from separately analyzing the risk of metformin on Gleason 8–10 prostate cancer. All multivariable analyses were adjusted for factors at baseline that are known to be correlated with prostate cancer risk in REDUCE or potential confounders, including age (continuous), race (black, white, or other), geographic region by continent (North America, Europe, or other), PSA (continuous), prostate volume (continuous), digital rectal examination findings (abnormal vs. normal), BMI (continuous), family history of prostate cancer (yes or no), coronary artery disease (yes or no), smoking (smoker or non-smoker), aspirin use (yes or no), NSAIDs use (yes or no), statin use (yes or no), and treatment group (dutasteride or placebo).

Secondary analyses were conducted to test for interactions between antidiabetic medication use and BMI, geographic location, coronary artery disease, smoking, and treatment group. Cross product terms of medication use and the variable of interest were included in the multivariable models along with the main effects, and likelihood ratio tests between the models with and without the interaction terms were used to determine whether the interaction was significant.

All P values were two-sided and alpha was <0.05 for statistical significance. All analyses were performed using Stata 13.0 (Stata Corp.).

Comparison of study sub-population to REDUCE overall

REDUCE had 670 diabetic men. Our inclusion criteria were for diabetic men to have at least one on-study biopsy. To confirm that no bias was created in selecting our study population, we examined whether any demographic or clinical differences existed among diabetic men in our study population ($n = 540$ diabetic men with at least one on-study biopsy) versus diabetic men who did not receive any on-study biopsy ($n = 130$). Among 670 diabetic men in REDUCE, no differences in age, BMI, PSA, prostate volume, and DRE finding were observed between men who did not receive an on-study biopsy versus those who had one or more on-study biopsy (our study population). There was an association between race and receiving one or more on study biopsy ($P = 0.03$).

Furthermore, given the possibility that metformin use may be related to on-study biopsy compliance, we examined whether metformin and other antidiabetic medication use influenced those associations. We found that among 670 diabetic men with complete data on crude analysis, metformin users were more likely to receive at least one on-study biopsy versus those not on any antidiabetic medication (OR, 1.66; $P = 0.04$). After adjusting for demographic and disease characteristics, metformin use remained significantly associated with an increased risk of receiving at least one on-study biopsy (OR, 1.84; $P = 0.02$) versus no receiving on-study biopsies. However, there was no difference in the likelihood of having a protocol-independent biopsy between metformin and non-antidiabetic medication users ($P = 0.531$). Moreover, of 426 men who received a first on-study biopsy with no cancer detected, metformin users were equally likely to receive a second biopsy relative to men not on antidiabetic medications on both crude (OR, 0.80; $P = 0.47$) and multivariable analysis (OR, 0.79; $P = 0.46$). Thus, even though metformin use may have affected our eligibility criteria, the use of metformin did not influence the receipt of on-study biopsies. Hence, we conclude that our eligibility criteria would not affect our results on the

Table 1. Baseline characteristics of $n = 540$ diabetic patients

Variable	None anti-diabetic medications	Non-metformin anti-diabetic medications	Metformin	P^a
Total patients (%)	205 (38)	141 (26)	194 (36)	
Age at study entry				0.014
Median (IQR)	63 (58-68)	65 (61-70)	64 (59-68)	
Ethnic group (%)				0.065 ^b
White	182 (89)	119 (84)	168 (87)	
Black	4 (2)	12 (9)	13 (7)	
Other	19 (9)	10 (7)	13 (7)	
Body mass index				<0.001
Median (IQR)	27.4 (25.5-30.3)	27.6 (25.5-30.1)	29.0 (26.2-32.7)	
PSA				0.524
Median (IQR)	5.7 (4.5-7.3)	5.6 (4.2-6.6)	5.5 (4.4-6.8)	
Prostate volume				0.283
Median (IQR)	45.4 (34.7-58.0)	42.4 (33.0-56.4)	46.1 (34.5-61.1)	
Abnormal DRE	8 (4)	7 (5)	4 (2)	0.338 ^b

Abbreviations: IQR, interquartile range; PSA, prostate specific antigen; SD, standard deviation.

^a P value by Kruskal-Wallis, except where noted.

^b P value by χ^2 .

associations between metformin use and prostate cancer diagnosis at the 2- and 4-year study biopsies.

Results

Patient demographics

Of the 8,122 men randomized in REDUCE, 693 had diabetes. Of these, 540 had at least one on-study biopsy and complete data and constitute the study population. Of these men, 205 (38%) were not on any antidiabetic medications, 141 (26%) were on an antidiabetic medication other than metformin, and 194 (36%) were on metformin (Table 1). Metformin users had higher BMIs ($P < 0.001$) compared with the other two groups. Diabetics on other antidiabetic medications tended to be older in age ($P = 0.01$). All other baseline characteristics among the three patient groups were similar (all $P > .05$).

Metformin use and prostate cancer

During the 4-year study, 122 (23%) men were diagnosed with prostate cancer. Relative to nondiabetic medication users, the risk

of prostate cancer diagnosis on any on-study biopsy at 4 years follow-up was not significantly different among metformin users ($P = 0.31$) or other antidiabetic medication users ($P = 0.95$) on crude analysis (Table 2). Results were unchanged after adjusting for various clinical and demographic characteristics, including age, race, geographic region, PSA levels, digital rectal examination findings, BMI, prostate volume, and family history of prostate cancer.

When analyzed by grade, both metformin and other antidiabetic medication use were unrelated to low-grade and high-grade disease in both crude and multivariable analysis relative to no antidiabetic drug use ($P > 0.05$). The OR for metformin for predicting high-grade prostate cancer was 1.83 on multivariable analysis, but this was not significant ($P = 0.19$).

To account for prostate cancer risk factors that may have influenced these associations, we tested for interactions between antidiabetic medication use and BMI, geographic location, coronary artery disease, smoking, and treatment group. No significant interactions were found (all $P > 0.05$).

Table 2. Association between metformin and other anti-diabetic medication use and prostate cancer risk

Variable	None anti-diabetic medications	Non-metformin anti-diabetic medications		Metformin	
	OR	OR (95% CI)	P	OR (95% CI)	P
Overall prostate cancer risk					
No. with cancer/total	43/205	30/141		49/194	
Univariable	Referent	1.02 (0.60-1.72)	0.946	1.27 (0.80-2.03)	0.311
Multivariable ^a	Referent	0.85 (0.48-1.48)	0.560	1.19 (0.72-1.99)	0.495
Disease grade, low grade ^d					
No. with cancer/total ^b	33/195	20/131		31/176	
Univariable	Referent	0.88 (0.48-1.62)	0.691	1.05 (0.61-1.80)	0.860
Multivariable ^a	Referent	0.79 (0.42-1.49)	0.463	1.01 (0.57-1.81)	0.961
Disease grade, high grade ^d					
No. with cancer/total ^c	10/172	10/121		18/163	
Univariable	Referent	1.46 (0.59-3.62)	0.415	2.01 (0.90-4.50)	0.089
Multivariable ^a	Referent	1.23 (0.46-3.26)	0.678	1.83 (0.75-4.46)	0.185

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for age, race, geographic region, prostate specific antigen levels, digital rectal examination findings, body mass index, prostate volume, family history of prostate cancer, coronary artery disease, smoking status, NSAIDs, statins, aspirin, and treatment group.

^bNumbers reflect men included in the analysis: those with low-grade disease and those without cancer.

^cNumbers reflect men included in the analysis: those with high-grade disease and those without cancer.

^dMultinomial regression was used to model the outcomes of low vs. no prostate cancer and high grade disease vs. no prostate cancer.

Discussion

Given the enormous burden to public health and the nature of the disease, chemoprevention has the potential to decrease the morbidity and mortality associated with prostate cancer. While various agents have been tested, none are approved by the FDA for reducing prostate cancer risk. Metformin seems to be a promising agent given its anticancer effects *in vitro* and in experimental animal models (11–13). However, in humans, although metformin was associated with decreased risk of prostate cancer in multiple epidemiologic studies (14–16), other studies have shown no effect (17, 18). To test this, we investigated the relationship between metformin and prostate cancer risk in the REDUCE trial. Contrary to our hypothesis, we found that in diabetic men, metformin use, as well as use of other antidiabetic medications, was not associated with a reduced risk of prostate cancer. Moreover, our results were similar for low- and high-grade cancers in terms of no significant associations with antidiabetic medication use. These findings do not support the role of metformin as chemoprevention for prostate cancer among men with a prior negative biopsy.

Prior epidemiologic studies examining the association of metformin use and prostate cancer risk have yielded conflicting results. Wright and colleagues (15) in a population-based case-control study of 1,001 cases and 942 controls found a 44% risk reduction for prostate cancer in Caucasian men who reported use of metformin [adjusted OR, 0.56; 95% confidence interval (CI), 0.32–1.00] whereas no effect was seen in African-American men. A larger population study of 24,723 men from the national Finnish registry found similar protective effects of metformin (OR, 0.80; 95% CI 0.73–0.88; ref. 14). However, this study did not control for PSA. As diabetes may be associated with lower PSA levels (22, 23), this could alter the detection rate of prostate cancer, and thus offers an alternative explanation for the reduced prostate cancer risk. A more recent population-based study that did control for PSA and severity of diabetes showed that metformin users had a 16% reduced risk of prostate cancer (OR, 0.84; 95% CI, 0.74–0.96), and this risk reduction was greatest in men with the longest duration of use and the highest cumulative dose of metformin (16). However, all of those studies included the general population rather than limiting their study cohort to men with diabetes. As men with diabetes have a reduced risk of prostate cancer in general (24, 25), the reported reduced risk in men on metformin in these studies may actually be due to the effect of diabetes, not metformin *per se*.

In contrast with the above studies, multiple other studies, which limited their populations to diabetic men, found no association between metformin use and prostate cancer risk (17, 18). Specifically, two large nested case-control studies from the UK and Canada limited their cohorts to men with incident diabetes, thus controlling for the confounding effect of diabetes on prostate cancer risk (17, 18). The UK cohort included 63,049 incident users of antidiabetic medications, in which 739 cases of prostate cancer were matched to 7,359 controls, whereas the Canadian cohort included 119,315 men with diabetes in which 5,306 cases of prostate cancer were matched to 26,530 controls (17, 18). Neither study found an association between metformin use and prostate cancer risk (OR, 1.23; 95% CI, 0.99–1.52; OR, 1.03; 95% CI, 0.96–1.1, respectively). Consistent with these negative studies, we also found no association between metformin use and risk of prostate cancer diagnosis. Moreover, we found

no association between metformin use and prostate cancer grade, also consistent with the Canadian study, which showed that metformin was unrelated to both high- and low-grade disease (17). We report an OR of 1.83 for metformin for predicting high-grade prostate cancer on multivariable analysis, suggesting a possible link between metformin and greater risk of high-grade disease, but this was not significant. Future studies are needed to evaluate the possibility that metformin may be linked with an increased risk of high-grade disease.

Despite our negative findings, this does not rule out the possibility that metformin may have a role in prostate cancer management. Prostate cancer is a slow growing disease and may take decades to manifest as a clinically significant cancer. Rather than reducing the risk of cancer diagnosis, metformin may have an effect on disease progression. Preclinical studies have shown that metformin's role in cancer prevention may relate to the AMPK pathway in reducing hyperinsulinemia (4). Because elevated systemic levels of insulin before prostate cancer diagnosis have been associated with prostate cancer mortality (26), it is possible that the insulin-lowering property of metformin may protect against prostate progression. Moreover, metformin has been shown to have antiproliferative effects on prostate cancer cells via AMPK-independent pathways via mTOR inhibition, cell-cycle arrest, and autophagy (12, 27). All of these mechanisms suggest that metformin may inhibit cancer progression rather than initiation. Such preclinical results have led to the investigation of metformin on prostate cancer mortality, with some promising data. Margel and colleagues (28) in a large population-based retrospective cohort showed a decrease in both all-cause and prostate cancer-specific mortality in diabetic men with increased metformin exposure. However, there are also some less supportive data for metformin's role in delaying prostate cancer progression. Specifically, in a separate study of diabetic men undergoing radical prostatectomy, we previously found no association between metformin use and progression risk (29). Unfortunately, the REDUCE study design did not allow us to study the association between metformin use and disease progression.

Our study has many strengths, including use of a large dataset with almost no missing data, and REDUCE being a multicenter study with central pathology review. The REDUCE dataset allowed us to explore the association between metformin use and the risk of high- and low-grade prostate cancer in addition to overall cancer risk in an overall relatively healthy population of men being studied for prostate cancer chemoprevention. Because we limited our cohort to diabetics, we eliminated any confounding effect of diabetes status on the risk of prostate cancer. Furthermore, all men underwent at least one on-study protocol-mandated biopsy after enrollment regardless of PSA level, thus removing any influence of antidiabetic medication on PSA and potential detection bias.

The main limitations of our study are its observational nature and selection bias. Diabetic treatment was not randomly assigned, and the study excluded patients with prostate cancer at baseline; therefore, it is possible that metformin may be associated with prostate cancer, but by excluding men with prostate cancer on their initial biopsy, we were unable to observe this. Our observed null association may also be due to our relatively small sample size. Furthermore, diabetes status and medication use were self-reported on enrollment and were not updated throughout the study; however, past studies have shown over a 97% concordance rate between self-reported information and actual disease status

(30) and baseline characteristics in the different groups were similar. Moreover, we do not have information on the distribution of type 1 versus 2 diabetes, although epidemiologic data suggest that more than 95% of diabetics are likely type 2 (31). The lack of data on dietary factors and exercise precludes us from considering these as potential confounding factors with metformin use. Furthermore, our results are limited to primarily Caucasian patients with diabetes, and it is unknown whether metformin may have different effects on prostate cancer in men without diabetes and in men of other ethnicities. Finally, our study period was limited to 4 years based on biopsy results; thus, we cannot make any comments on the effect of metformin on prostate cancer diagnosis over longer durations or on prostate cancer progression.

In summary, in the REDUCE trial, the use of metformin or other antidiabetic medications was not associated with lower prostate cancer risk, but rather with equal risk of overall prostate cancer as well as low-grade disease; and if anything with a higher risk of high-grade disease, although none of the associations were statistically significant. Though our findings do not support the chemoprevention effects of metformin on prostate cancer risk among men with a prior negative biopsy, future studies with longer follow-up may be beneficial in determining the role of metformin in prostate cancer progression.

Disclosure of Potential Conflicts of Interest

R. Castro-Santamaria has ownership interest (including patents) in GSK. G.L. Andriole reports receiving other commercial research support from John-

son & Johnson, Medivaion, and Traxsson and is a consultant/advisory board member for Augmenix, Bayer, Blue Earth Diagnostics, Genomic Health, and Myriad Genetics. No potential conflicts of interest were disclosed by the other authors.

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