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The Association Between Phosphodiesterase Type-5 Inhibitors and Prostate Cancer: Results from the REDUCE Study

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Abstract

Purpose—Despite the routine use of phosphodiesterase type-5 inhibitors (PDE-5i) for treatment of erectile dysfunction, their role in prostate cancer (PC) chemoprevention remains unclear with only a few studies exploring the link between PDE-5i use and PC. We tested the association between PDE-5i use and PC risk in the REDUCE study.

Materials & Methods—REDUCE was a four-year multi-center study testing the effect of daily dutasteride on PC risk in men with a PSA of 2.5 to 10.0 ng/mL and a negative biopsy, with men undergoing study-mandated biopsies at 2- and 4-years. The association between PDE-5i use and overall PC risk and disease grade (Gleason 2–6 and 7–10) was examined using adjusted logistic and multinomial regression analysis. Secondary analysis was performed exploring the association between PDE-5i use and PC risk in North American men given the significantly higher use of PDE-5i among these subjects.

Results—PDE-5i inhibitor use was not associated with PC diagnosis (OR=0.90, 95%CI 0.68–1.20, $p=0.476$) or low- (OR=0.93, 95%CI 0.67–1.27, $p=0.632$) or high-grade disease (OR=0.85, 95%CI 0.51–1.39, $p=0.508$). An inverse trend was seen between PDE-5i use and PC diagnosis in North American men, but was not statistically significant (OR=0.67, 95%CI 0.42–1.07, $p=0.091$).

Conclusions—PDE-5i use was not associated with decreased PC diagnosis in post-hoc analysis of the REDUCE study. In North American men, who had a much higher baseline use of PDE-5i,

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use was associated with an inverse trend of PC diagnosis that approached, but did not reach, statistical significance.

Keywords

Prostate cancer; Prostate cancer chemoprevention; REDUCE; phosphodiesterase type-5 inhibitors

INTRODUCTION

Erectile dysfunction (ED) is a major problem with a prevalence of 20–40% in the 6th decade of life and approaching 75% in the 7th decade¹. Phosphodiesterase type-5 inhibitors (PDE-5i) were first introduced in 1998 and since then their durability, safety, and efficacy for treating ED have been clearly demonstrated^{2–4}.

In mouse models, PDE-5i have anti-neoplastic effects via down-regulating myeloid-derived suppressor cells (MDSCs)⁵. Given the routine use of PDE-5i for patients with ED after prostatectomy and the possibility that these agents may have anti-cancer activity, three recent studies examined PDE-5i use and biochemical recurrence (BCR) after prostatectomy and/or radiation with conflicting results: one found patients who routinely used PDE-5i post-operatively had a *higher* BCR rate⁶, while two others found no association between post-operative PDE-5i use and BCR^{7, 8}. Beyond prostatectomy patients, only one other study explored the association between PDE-5i use and diagnosis of prostate cancer (PC)⁹, finding that men on PDE-5i had a *lower* chance of being diagnosed with PC. The study was limited, however, in that all men had baseline ED, men did not have study-mandated biopsies, and there with significant differences in baseline characteristics such as PSA that influenced biopsy decisions.

We explored the association between PDE-5i use and PC diagnosis using the REDUCE dataset. REDUCE was a prospective, randomized controlled trial comparing the effect of dutasteride on PC diagnosis among men who had a negative pre-study biopsy. The strength of REDUCE is all men were required to undergo protocol-mandated biopsies at 2 and 4 years regardless of PSA and thus, cancer ascertainment was uniform in all men. Furthermore, we adjusted for exact PSA levels and other characteristics including erectile function as men in REDUCE had baseline potency data recorded. Based upon the basic science linking PDE-5i and anti-cancer activity, we hypothesized that PDE-5i would be associated with decreased PC detection.

MATERIALS AND METHODS

Study Design

REDUCE was a four-year multicenter, double-blind trial randomizing men to placebo or 0.5 mg of daily dutasteride¹⁰. Eligibility criteria included men 50–75 years old, PSA of 2.5–10.0ng/ml if 50–60 years or 3.0–10.0ng/ml if >60 years, and a single negative study-independent prostate biopsy (6–12) cores within 6 months prior to enrollment. Exclusion criteria included men with a past history of PC, prostate surgery, prostate volume >80ml, or IPSS >25 or >20 on alpha-blockers. Ten-core trans-rectal ultrasound (TRUS) guided prostate

biopsies were performed at 2- and 4-years post randomization regardless of PSA. A central pathologist reviewed all slides. Baseline prostate volume was obtained using the TRUS and digital rectal examination (DRE) findings were reported from the pre-study biopsy. PSA was obtained at enrollment and every six months thereafter. PDE-5i use including tadalafil, sildenafil, and vardenafil, medical history of coronary artery disease and diabetes, and height and weight were recorded at enrollment. Race was self-reported. Patients also completed questionnaires assessing sexual function using the PAS-SFI¹¹, with self-reported impotence assessed by the treating physician at baseline.

Participants

Among 8,122 men enrolled in the efficacy population of REDUCE, we excluded 1,391 who received no on-study biopsies. Of 6,731 men with at least one on-study biopsy, we further excluded men with missing baseline data for BMI (n=97), PSA (n=13), DRE (n=7), TRUS prostate volume (n=70), smoking history (n=3), CAD history (n=2), PC family history (n=4), diabetes (n=1) or baseline impotence (n=33) resulting in 6,501 men (Figure 1). There were no significant differences in baseline PSA, DRE, age, CAD, prostate volume, family history of PC, body mass index (BMI; kg/m²) or use of PDE-5i between men who received at least one biopsy during the study versus those who did not. Non-white race (p=0.001), North American location (p<0.001), current smokers (p=0.038), impotence (p=0.010), and being assigned to the placebo arm (p=0.008) were all predictive of not receiving any on-study biopsy.

Statistical Analysis

The association between baseline PDE-5i use and baseline clinical characteristics was examined using *t*-test, Wilcoxon rank-sum, or χ^2 for continuous normal, continuous non-normal and categorical variables, respectively. Logistic regression analysis was used to explore the relationship between PDE-5i use and PC diagnosis at any point during the study. Multivariable analyses were adjusted for age (continuous), race (white vs. non-white), geographic region (Europe, North America, other), baseline PSA (continuous), prostate volume (continuous), DRE findings (abnormal vs. normal), BMI (continuous), PC family history (yes/no), CAD (yes/no), smoking (current, former, and never), impotence (yes/no), diabetes (yes/no), and treatment group (placebo vs. dutasteride). Detailed questionnaires about sexual function (PAS-SFI) were available, but results were unchanged when adjusting for the numeric score from the questionnaire vs. the dichotomous impotence variable. As some men (n=555) were missing questionnaire data, we adjusted for the impotence variable instead.

To assess the association between PDE-5i use and disease grade we used a multinomial logistic regression with the outcomes of low-grade (Gleason 6 vs. no cancer) and high-grade (Gleason 7–10 vs. no cancer). Results were adjusted for the same variables as above. Given large geographic differences in PDE-5i use and potential difference due to dutasteride use, we tested whether region or randomization group (placebo vs. dutasteride) was an effect modifier on the association between PDE-5i use and PC by including both primary variables and a cross-product in the multivariable analysis with a Wald test to determine the p-value.

Given the possibility that PDE-5i use was related to biopsy compliance, which could affect PC detection, we explored the association between PDE-5i use and PC at the 2-year study-mandated biopsy.

Statistical significance was defined as $p < 0.05$. All analysis was performed using Stata v13.1 (StataCorp, College Station, TX USA).

RESULTS

Patient demographics

Of the 6,501 men, 364 (5.6%) used PDE-5i at baseline. Men on PDE-5i had higher BMIs ($p < 0.001$), lower PSAs ($p < 0.001$), and a higher rate of baseline diabetes ($p = 0.029$) (table 1). They were also more likely to have an abnormal DRE ($p = 0.001$), be impotent ($p < 0.001$) and be from North America ($p < 0.001$). No differences were observed between PDE-5i use and age, smoking, race, CAD, PC family history, prostate volume, or treatment arm (all p -values > 0.05).

Study compliance

PDE-5i use was not significantly predictive of receiving any on-study biopsy over the entire study period. However, among men with a negative 2-year biopsy, PDE-5i users were more likely to receive the 4-year biopsy after adjusting for clinical and demographic features (OR=1.57, 95%CI 1.11–2.22, $p = 0.011$).

PDE-5i use and PC

The rate of PC diagnosis during the study was 19.5% (71/364) for men on PDE-5i vs. 22.7% (1,391/6,137) for men not on PDE-5i. Though PDE-5i use was associated with lower PC detection, this did not reach statistical significance on univariable (OR=0.83, 95%CI 0.63–1.08, $p = 0.161$) or multivariable analysis (OR=0.90, 95%CI 0.68–1.20, $p = 0.478$). When examined by grade, PDE-5i use was unrelated to both low-grade and high-grade cancer on univariable and multivariable analysis (all $p > 0.05$, table 2). Results were unchanged whether high-grade was defined as Gleason $\geq 7(4+3)$ or ≥ 8 (data not shown).

Interaction between PDE-5i use and region for predicting PC

Given the significantly higher PDE-5i use in North American, subset analysis was performed comparing North American men with other regions. Among North American men, those on PDE-5i tended to have a lower risk of overall PC that approached but did not reach significance (multivariable OR=0.67, $p = 0.091$; table 3). When stratified by disease grade, the inverse association between PDE-5i use was stronger for high-grade (OR=0.42, $p = 0.076$) than low-grade (OR=0.78, $p = 0.351$), though neither association reached statistical significance on univariable or multivariable analysis. The interaction between region and PDE-5i use was not significant for either overall PC risk ($p = 0.101$), or when stratified by grade ($p = 0.217$). Among non-North American patients, PDE-5i use was unrelated to all outcomes (all $p > 0.6$; table 3).

Interaction between PDE-5i use and treatment arm for predicting PC

As dutasteride use may influence the effect of PDE-5i use on PC risk, we explored whether results were similar in men treated with placebo or dutasteride. We found treatment arm (placebo vs. dutasteride) was not a significant effect modifier ($p=0.974$) meaning results were similar in both arms.

PDE-5i use and PC on 2-year biopsy

As men on PDE-5i were slightly more likely to receive a 4-year biopsy, we tested the association between PDE-5i and PC at the 2-year study-mandated biopsy to eliminate any bias present from higher biopsy rates among PDE-5i users. Results were similar to the overall cohort: no significant association between PDE-5i use and overall PC or high-grade/low-grade disease (table 4).

DISCUSSION

PDE-5i have anti-cancer effects *in-vitro* via mediation of apoptosis^{12, 13} and modulation of MDSCs⁵. However, in humans, data are mixed with some studies showing PDE-5i use associated with increased BCR⁶, no change in BCR⁷, longer PSA doubling time after BCR¹⁴ and lower PC diagnosis⁹. Herein, we investigated the association between PDE-5i use and PC detection in REDUCE, wherein men with a negative baseline biopsy underwent study-mandated biopsies at 2- and 4-years. We found PDE-5i use was not associated with PC diagnosis. While there was a suggestion of an inverse association in North American men, this did not reach statistical significance. While these findings do not support PDE-5i for PC chemoprevention, they do not demonstrate any increased PC diagnosis associated with PDE-5i use.

PDE-5i were first introduced in 1998, quickly gaining widespread popularity due to their efficacy and minimal side effects⁴. Given data that other commonly used medicines may be associated with lower PC risk^{15, 16} and the high frequency of PDE-5i use in older men (i.e. those at greatest risk for PC), several studies examined the relationship between PDE-5i use and PC with conflicting results. Among 4,752 patients treated with radical prostatectomy, post-operative PDE-5i use was associated with increased BCR risk (HR=1.38; 95%CI: 1.11–1.70)⁶. In contrast, a similar study of 2,579 patients showed no significant association between PDE-5i use and BCR after prostatectomy, even after adjusting for number of pills taken or treatment type (on demand use vs. prophylactic daily use) (HR=1.18, 95%CI: 0.85–1.63)⁷. Similarly no association was seen between overall PDE-5i use and BCR in a recent case-control series matching 293 patients who had BCR after prostatectomy or radiation to BCR-free controls. Limitations of these studies include the retrospective nature of analysis and potential inherent differences between patient's requiring PDE-5i post operatively vs. those who do not (i.e. differences in extent of nerve sparing dissection dictated by tumor aggressiveness). Also, these studies evaluated PC progression, not cancer diagnosis and some drugs may work better to block progression vs. cancer development¹⁷.

In regards to PDE-5i use and cancer risk, several studies have shown an association between PDE-5i use and increased risk of melanoma; however these associations may be due to

shared lifestyle factors as PDE-5i users may be more likely have a lifestyle placing them at higher risk for melanoma^{18, 19}. Specific to PC risk, only one study to date has examined this issue. Among 4,974 men with baseline ED seen between 2000 and 2006 in the US, the authors found men on PDE-5i had a 60% reduced risk of PC during the study (OR=0.4; 95% CI: 0.3–0.5)⁹. However analysis was limited as men on PDE-5i had significantly lower PSAs, not all men received biopsies, and results were not adjusted for PSA. Furthermore, PDE-5i use was lower in 2000 than in 2006 creating concerns about differential follow-up in that PDE-5i users may not have been followed long enough. To overcome these limitations, we examined the association between PDE-5i use and PC diagnosis among men who all had negative baseline biopsies and underwent study-mandated biopsies at 2- and 4-years in REDUCE. Furthermore, we adjusted for key baseline differences between the groups, including PSA. In so doing, we found no association between PDE-5i use and overall PC diagnosis or low- or high-grade disease.

Despite the negative primary findings, a key secondary finding was that North American men were more likely to take PDE-5i, and among these men, there was a suggestion that PDE-5i use may be associated with lower risk of PC diagnosis, though this did not reach statistical significance. It is speculative to assume that there is an association between PDE-5i use and PC, however if future studies show a geographic difference in the association between PDE-5i use and PC risk the exact reasons are unclear; though other drugs have been shown to be associated with lower PC risk in some geographic regions and not others²⁰. One possible explanation may be derived from the more common and perhaps liberal use of PDE-5i use in North American men as opposed to non-North American men, thus men outside of North America may have had a stronger indication for PDE-5i use (severe ED) as opposed to North-American men. Given that risk factors for ED include smoking, CAD, and obesity, which in themselves have been associated with PC^{21–23}, PDE-5i use in non-North American men may be linked tighter to these risks factors (as opposed to North American men), thereby negating any potential “protective” effect of PDE-5i.

Despite our overall null findings, pre-clinic research suggests PDE-5i have anti-cancer properties, including anti-PC^{24, 25}. Mechanistically, PDE-5i prevent the cleavage of cGMP to 5'-GMP by PDE-5, with elevated cGMP mediating apoptosis via cGMP- dependent protein kinase¹². PDE-5i also modulate MDSCs, which overexpress inducible nitric oxide synthase and arginase-1, arginine metabolizers. Arginine depletion leads to T-cell downregulation, however PDE-5i inhibit nitric oxide synthase and arginase-1 resulting in an improved anti-tumor immune response⁵. Despite this, mouse models of sildenafil vs. placebo on PC growth and metastasis show no difference in tumor weight, nodal, or distant metastasis²⁶. Unfortunately, the REDUCE study design did not allow us to examine the association between PDE-5i and disease progression.

Our study has several strengths. All men underwent 1 on-study protocol-mandated biopsy independent of PSA, minimizing any confounding effect of PDE-5i on PSA and biopsy indication. REDUCE included a large multi-national prospective cohort with central pathology review.

The main limitations of our study are that PDE-5i use was not randomly assigned. Moreover, PDE-5i use was low. As all men had a baseline negative biopsy, it is possible that PDE-5i are linked to PC, but by excluding men with PC prior to enrollment we were unable to detect this association. Furthermore PDE-5i use was self-reported at enrollment; men may have started or stopped during study. Data for PDE-5i dosage and frequency were unavailable, and thus we were unable to control for these factors. Our results are limited to Caucasians and it is unclear whether PDE-5i have different effects on other ethnicities. Finally, our study period was limited to 4 years. Thus, we cannot comment on PDE-5i and PC diagnosis over longer durations or on disease progression.

CONCLUSIONS

In summary, we found PDE-5i use in REDUCE was not associated with PC diagnosis. On secondary analysis, among North American men, there was an inverse association between PDE-5i use and PC diagnosis, which approached, but did not reach statistical significance. Future studies with longer follow-up and larger study populations are warranted to determine the association between PDE-5i and PC.

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Abbreviation Key

ED	Erectile dysfunction
PDE-5i	Phosphodiesterase type-5 inhibitor
MDSCs	Myeloid-derived suppressor cells
BCR	Biochemical recurrence
PC	Prostate cancer

TRUS	Trans-rectal ultrasound
DRE	Digital rectal exam
CAD	Coronary artery disease
PSA	Prostate specific antigen
BMI	Body mass index

Figure 1.

Assembly of study population from REDUCE

BMI = Body mass index, PC=prostate cancer; TRUS=transrectal ultrasound; PSA=prostate specific antigen; CAD = coronary artery disease; DRE=digital rectal exam

Table 1

Baseline Characteristics of study population

Variable	On PDE-5 inhibitors	Not on PDE-5 inhibitors	P value*
Total patients (%)	364 (5.6)	6,137 (94.4)	
Age at study entry			0.747 [†]
Mean (SD)	62.6 (5.9)	62.7 (6.0)	
Ethnic group (%)			0.541
White	337 (92.6)	5,626 (91.7)	
Non-white	27 (7.4)	511 (8.3)	
Body mass index			<0.001 ^{††}
Median (IQR)	27.7 (25.6–30.4)	26.8 (24.8–29.2)	
PSA			<0.001 ^{††}
Median (IQR)	5.3 (4.1–6.8)	5.7 (4.4–7.3)	
Prostate volume			0.0496 ^{††}
Median (IQR)	45.6 (34.3–59.1)	43.4 (33.0–56.2)	
Abnormal DRE (%)			0.001
Yes	25 (6.9)	217 (3.5)	
No	339 (93.1)	5,920 (96.5)	
History of CAD (%)			0.396
Yes	25 (6.9)	498 (8.1)	
No	339 (93.1)	5,639 (91.9)	
Family history of prostate cancer (%)			0.074
Yes	59 (16.2)	795 (13.0)	
No	305 (83.8)	5,342 (87.0)	
Smoking history (%)			0.141
Never	152 (41.8)	2,824 (46)	
Former	162 (44.5)	2,412 (39.3)	
Current	50 (13.7)	901 (14.7)	
Region (%)			<0.001
North America	176 (48.4)	1,429 (23.3)	
Europe	133 (36.5)	3,842 (62.6)	
Other	55 (15.1)	866 (14.1)	
Impotence (%)			<0.001
Yes	263 (72.3)	1,533 (25.0)	
No	101 (27.7)	4,604 (75.0)	

Variable	On PDE-5 inhibitors	Not on PDE-5 inhibitors	P value*
Treatment (%)			0.491
Placebo	179 (49.2)	3,132 (51.0)	
Dutasteride	185 (50.8)	3,005 (49.0)	
Diabetes (%)			0.029
Yes	41 (11.3)	493 (8.0)	
No	323 (88.7)	5,644 (92.0)	

Abbreviations: PSA (prostate specific antigen), SD (standard deviation), IQR (interquartile range), DRE (digital rectal exam), CAD (coronary artery disease), PDE-5 (phosphodiesterase type-5 inhibitor)

* P value by χ^2 , except where noted.

$\dagger$ P value by *t*-test

$\dagger\dagger$ P value by Wilcoxon rank-sum

Table 2

Association between PDE-5 inhibitor use and prostate cancer risk

Variable	No PDE-5 inhibitor use	PDE-5 inhibitor use		
	OR	OR	95% CI	P-value
Overall prostate cancer risk				
No. with cancer/total (%)	1,391/6,137 (22.7)		71/364 (19.5)	
Univariable	Referent	0.83	0.63–1.08	0.161
Multivariable *	Referent	0.90	0.68–1.20	0.478
Disease grade, low grade				
No. with cancer/total **	969/5,715 (17.0)		52/345 (15.1)	
Univariable	Referent	0.87	0.64–1.18	0.365
Multivariable *	Referent	0.93	0.67–1.27	0.634
Disease grade, high grade				
No. with cancer/total ***	422/5,168 (8.2)		19/312 (6.1)	
Univariable	Referent	0.73	0.45–1.17	0.192
Multivariable *	Referent	0.85	0.51–1.39	0.509

OR, odds ratio

CI, confidence interval

* Adjusted for age, race, geographic region, prostate specific antigen levels, body mass index, prostate volume, baseline digital rectal exam, family history of prostate cancer, coronary artery disease, smoking status, baseline impotence, diabetes and treatment group

** Numbers reflect men included in the analysis: those with low-grade disease and those without cancer

*** Numbers reflect men included in the analysis: those with high-grade disease and those without cancer

Table 3

Association between PDE-5 inhibitor use and prostate cancer risk stratified by region

Variable	North American patients				Non North American patients			
	No PDE-5 inhibitor use	OR	95% CI	P-value	No PDE-5 inhibitor use	OR	95% CI	P-value
Overall prostate cancer risk								
No. with cancer/total (%)	292/1,429 (20.4)		25/176 (14.2)		1,099/4,708 (23.3)		46/188 (24.5)	
Univariable	Referent	0.64	0.41–1.00	0.052	Referent		1.06	0.76–1.49
Multivariable*	Referent	0.67	0.42–1.07	0.091	Referent		1.09	0.76–1.55
Disease grade, low grade								
No. with cancer/total**	208/1,345 (15.5)		20/171 (11.7)		761/4370 (17.4)		32/174 (18.4)	
Univariable	Referent	0.72	0.44–1.18	0.196	Referent		1.07	0.72–1.58
Multivariable*	Referent	0.78	0.46–1.31	0.351	Referent		1.05	0.70–1.58
Disease grade, high grade								
No. with cancer/total***	84/1,221 (6.9)		5/156 (3.2)		338/3,947 (8.6)		14/156 (9.0)	
Univariable	Referent	0.45	0.18–1.12	0.087	Referent		1.05	0.60–1.84
Multivariable*	Referent	0.42	0.16–1.10	0.076	Referent		1.16	0.65–2.09

OR, odds ratio

CI, confidence interval

* Adjusted for age, race, geographic region, prostate specific antigen levels, body mass index, prostate volume, baseline digital rectal exam, family history of prostate cancer, coronary artery disease, smoking status, baseline impotence, diabetes and treatment group

** Numbers reflect men included in the analysis: those with low-grade disease and those without cancer

*** Numbers reflect men included in the analysis: those with high-grade disease and those without cancer

Table 4

Association between PDE-5 inhibitor use and prostate cancer risk at 2 year biopsy

Variable	No PDE-5 inhibitor use	PDE-5 inhibitor use		
	OR	OR	95% CI	P-value
Overall prostate cancer risk				
No. with cancer/total (%)	875/5,891 (14.9)		44/355 (12.4)	
Univariable	Referent	0.81	0.59–1.12	0.205
Multivariable *	Referent	0.86	0.62–1.21	0.402
Disease grade, low grade				
No. with cancer/total **	598/5,614 (10.7)		33/344 (9.8)	
Univariable	Referent	0.89	0.62–1.29	0.536
Multivariable *	Referent	0.94	0.64–1.38	0.733
Disease grade, high grade				
No. with cancer/total ***	256/5,152 (5.0)		10/314 (3.2)	
Univariable	Referent	0.64	0.35–1.18	0.155
Multivariable *	Referent	0.71	0.37–1.33	0.283

OR, odds ratio

CI, confidence interval

* Adjusted for age, race, geographic region, prostate specific antigen levels, body mass index, prostate volume, baseline digital rectal exam, family history of prostate cancer, coronary artery disease, smoking status, baseline impotence, diabetes and treatment group

** Numbers reflect men included in the analysis: those with low-grade disease and those without cancer

*** Numbers reflect men included in the analysis: those with high-grade disease and those without cancer