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

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Purpose: Despite routine use of phosphodiesterase type 5 inhibitor to treat erectile dysfunction the role in prostate cancer chemoprevention remains unclear. Only a few studies have explored the link between phosphodiesterase type 5 inhibitor use and prostate cancer. We tested the association between phosphodiesterase type 5 inhibitor and prostate cancer risk in the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial.

Materials and Methods: REDUCE was a 4-year multicenter study testing the effect of daily dutasteride on prostate cancer risk in men with prostate specific antigen 2.5 to 10.0 ng/ml and negative biopsy who underwent study mandated biopsies at 2 and 4 years. The association of phosphodiesterase type 5 inhibitor with overall prostate cancer risk and disease grade (Gleason 2-6 and 7-10) was examined using adjusted logistic and multinomial regression analysis. Secondary analysis was performed to explore the association between phosphodiesterase type 5 inhibitor and prostate cancer risk in North American men, given the significantly higher use of phosphodiesterase type 5 inhibitor in these subjects.

Results: Phosphodiesterase type 5 inhibitor was not associated with prostate cancer diagnosis (OR 0.90, 95% CI 0.68−1.20, p = 0.476), low grade disease (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 phosphodiesterase type 5 inhibitor and prostate cancer diagnosis in North American men but this was not statistically significant (OR 0.67, 95% CI 0.42−1.07, p = 0.091).

Conclusions: Phosphodiesterase type 5 inhibitor use was not associated with decreased prostate cancer diagnoses on post-hoc analysis of REDUCE. In North American men, who had much higher baseline use of phosphodiesterase type 5 inhibitor, this treatment was associated with an inverse trend of prostate cancer diagnosis that approached but did not reach statistical significance.

Abbreviations and Acronyms

BCR = biochemical recurrence
BMI = body mass index
CAD = coronary artery disease
cGMP = cyclic GMP
DRE = digital rectal examination
ED = erectile dysfunction
GMP = guanosine monophosphate
MDSC = myeloid-derived suppressor cell
PC = prostate cancer
PDE-5i = phosphodiesterase type 5 inhibitor
PSA = prostate specific antigen
TRUS = transrectal ultrasound

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ERECTILE dysfunction is a major problem with a prevalence of 20% to 40% in the sixth decade of life and approaching 75% in the seventh decade.[1] Since PDE-5is were first introduced in 1998, the durability, safety and efficacy for treating ED have been clearly demonstrated.[2–4]

In mouse models PDE-5is have antineoplastic effects via down-regulating MDSCs.[5] Given the routine use of PDE-5i in patients with ED after prostatectomy and the possibility that these agents may have anticancer activity, 3 recent studies examined PDE-5i use, and BCR after prostatectomy and/or radiation with conflicting results.[6–8] One study showed that patients who routinely received PDE-5i postoperatively had a higher BCR rate[6] while 2 others demonstrated no association between postoperative PDE-5i use and BCR.[7,8] Beyond post-prostatectomy only 1 other group has explored the association between PDE-5i and PC diagnosis, which showed that men on a PDE-5i had a lower chance of being diagnosed with PC.[9] However, that study was limited in that all men had baseline ED, they did not undergo study mandated biopsies and there were 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 data set. REDUCE was a prospective, randomized, controlled trial comparing the effect of dutasteride on PC diagnosis among men who had a negative prestudy 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 on the basic science linking PDE-5i and anticancer activity we hypothesized that PDE-5i would be associated with decreased PC detection.

MATERIALS AND METHODS

Study Design

REDUCE was a 4-year multicenter, double-blind trial randomizing men to placebo or 0.5 mg daily dutasteride.[10] Eligibility criteria included age 50 to 75 years, PSA 2.5 to 10.0 ng/ml if age 50 to 60 years or 3.0 to 10.0 ng/ml if older than 60 years, and a single negative study-independent 6 to 12-core prostate biopsy within 6 months before enrollment. Exclusion criteria included a history of PC, prostate surgery, prostate volume greater than 80 ml, or I-PSS (International Prostate Symptom Score) greater than 25 or greater than 20 while on α-blockers. Ten-core TRUS guided prostate biopsies were performed 2 and 4 years after randomization regardless of PSA. A central pathologist reviewed all slides. Baseline prostate volume was obtained using TRUS and DRE findings from the prestudy biopsy. PSA was determined at study enrollment and every 6 months thereafter. PDE-5i use, including tadalafil, sildenafil and vardenafil, a medical history of CAD and diabetes, and height and weight were recorded at enrollment. Race was self-reported. Patients also completed the PAS-SFI (Problem Assessment Scale of the Sexual Function Index) questionnaire assessing sexual function[11] and self-reported impotence was assessed by the treating physician at baseline.

Participants

Of the 8,122 men enrolled in the efficacy population of REDUCE we excluded 1,391 who underwent no on-study biopsies. Of 6,731 men with at least 1 on-study biopsy we further excluded those with missing baseline data, including BMI in 97, PSA in 13, DRE in 7, TRUS prostate volume in 70, smoking history in 3, CAD history in 2, PC family history in 4, diabetes in 1 and baseline impotence in 33, resulting in 6,501 men who were included in analysis (see figure). There were no significant differences in baseline PSA, DRE, age, CAD, prostate volume, family history of PC, BMI in kg/m^2 or PDE-5i use between men who underwent at least 1 biopsy during the study vs those who did not. Nonwhite race ($p = 0.001$), North American location ($p < 0.001$), current smoking ($p = 0.038$), impotence ($p = 0.010$) and assignment to the placebo arm ($p = 0.008$) were predictive of not undergoing an on-study biopsy.

Statistical Analysis

The association between baseline PDE-5i use and baseline clinical characteristics was examined using the t-test, the Wilcoxon rank-sum test and the chi-square test for continuous normal, continuous nonnormal and categorical variables, respectively. Logistic regression analysis was done 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 nonwhite), geographic region (Europe, North America and 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 questions about sexual function on PAS-SFI were available but results were unchanged when adjusting for the numerical score from the questionnaire vs the dichotomous impotence variable. Because 555 men were missing questionnaire data, we adjusted for the impotence variable instead.