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Phosphodiesterase Type 5 Inhibitor Use and Disease Recurrence After Prostate Cancer Treatment

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Abstract

Background—Phosphodiesterase type 5 inhibitor (PDE5i) use is common for management of erectile dysfunction. Single-institution studies have reported conflicting data on the relationship between PDE5i use and biochemical recurrence of prostate cancer (BCR) after radical prostatectomy.

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Objective—To evaluate the association between PDE5i use and BCR after radical prostatectomy and radiation therapy in a nationwide population-based cohort.

Design, setting, and participants—This was a nested case-control study using the National Prostate Cancer Register of Sweden linked to the Prescribed Drug Register. Among men with localized prostate cancer who underwent primary radical prostatectomy or radiation therapy during 2006–2007 with 5 yr of follow-up, 293 had BCR after treatment (cases). For each case we identified 20 BCR-free controls (n = 5767) using incidence density sampling.

Outcome measurements and statistical analysis—Multivariable conditional logistic regression was used to examine the association between PDE5i use and BCR risk. Separate multivariable models including clinical variables for men undergoing prostatectomy or radiotherapy and including surgical pathology after prostatectomy were also analyzed.

Results and limitations—PDE5i use was not associated with BCR after radical prostatectomy (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.59–1.03) or radiation therapy (OR 0.98, 95% CI 0.49–1.97) after adjusting for marital status, education, income, prostate-specific antigen, clinical stage, Gleason score, and proportion of positive biopsies. Results were similar after additional adjustment for surgical pathology (OR 0.86, 95% CI 0.64–1.16). Men whose cumulative number of PDE5i pills was above the median had a slightly lower BCR risk after prostatectomy in the clinical model, and no difference in BCR risk after adjustment for pathologic tumor features.

Conclusions—Our results for a population-based cohort suggest that BCR risk is not higher among men using PDE5i after prostate cancer treatment.

Patient summary—Erectile dysfunction medications are not associated with a higher risk of disease recurrence after prostate cancer treatment.

Keywords

Phosphodiesterase inhibitors; Viagra; Erectile dysfunction; Prostate cancer; Recurrence

1. Introduction

Phosphodiesterase type 5 inhibitors (PDE5i) are recommended as first-line therapy for erectile dysfunction following prostate cancer (PCa) treatment [1]. On the basis of laboratory studies suggesting possible antineoplastic effects of PDE5i, Michl et al [2] examined whether they were associated with a reduction in the risk of PCa progression after radical prostatectomy. Among 4752 surgical patients from a tertiary referral center in Germany, there was a significantly lower progression-free survival rate among postoperative PDE5i users after multivariable adjustment [2]. A follow-up study by Gallina et al [3] including 2579 cases from a tertiary referral center in Italy found no difference in the 5-yr progression-free survival rate according to the number of PDE5i pills used postoperatively.

Given the frequency with which PDE5i medications are used, an association with PCa oncologic outcomes would have important consequences. The aim of the current study was to evaluate the relationship between PDE5i use and PCa biochemical recurrence (BCR)

using data from the population-based National Prostate Cancer Register (NPCR) and The Prescribed Drug Register of Sweden.

2. Patients and methods

The NPCR of Sweden includes 98% of prostate cancer cases nationwide, with detailed data on tumor characteristics and primary treatment. In the Prostate Cancer Data Base (PCBaSe), the NPCR is cross-linked to other health care registries and demographic databases [4]. Since 2005 this has included the Prescribed Drug Register, with data on all filled prescriptions in Sweden.

For cases diagnosed during 2003–2007, the NPCR performed a follow-up study of men aged ≤70 yr diagnosed with localized PCa (serum prostate-specific antigen [PSA] <20 ng/ml, clinical stages T1/T2). Since the Prescribed Drug Register started in 2005, we limited the current study to men in the follow-up study treated by radical prostatectomy or radiation therapy from 2006–2007.

Within this population, we identified 293 men with BCR after treatment, defined as two PSA measurements ≥0.2 ng/ml for men undergoing radical prostatectomy and two PSA measurements ≥2 ng/ml over the nadir for radiation therapy, with the date of the first such measurement considered the date of BCR. For each of these cases, we identified 20 controls who were BCR-free at the event date for the index case using incidence density sampling stratified by age at diagnosis and treatment type (n = 5767 controls). A man who had previously been selected as a control remained as a control in this case-control set even if he became a case at a later time point. To account for differences in exposure time between cases and controls, sensitivity analyses were performed with stratification according to exposure time.

The Prescribed Drug Register was used to identify filled prescriptions for sildenafil, vardenafil, and tadalafil after PCa treatment. We examined overall PDE5i use, as well as cumulative counts of the number of filled pills.

Demographic data and tumor features were compared between cases and controls using the t test and χ^2 test. Multivariable conditional logistic regression was used to examine the relationship between overall PDE5i use and cumulative number of pills and BCR. For men undergoing radical prostatectomy and radiation therapy, we assessed clinical models adjusted for the following covariates: marital status (married vs not currently married), educational level (low, middle, high), income (per quartile), PSA (continuous in 1-ng/ml increments), clinical local stage (T2 vs ≤T1c), biopsy Gleason grade group [5] (increasing GGG 1, 2, 3, and combined 4–5 owing to low numbers), and proportion of positive biopsies (>33% vs ≤33%). Information on the level of education was obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) socioeconomic database, and was categorized as low (<10 yr, mandatory school), intermediate (10–12 yr, high school) or high (>12 yr, university or equivalent). For men undergoing radical prostatectomy, we also performed separate multivariable models adjusted for pathologic stage (non–organ-confined vs organ-confined), prostatectomy Gleason grade

group (increasing GGG 1, 2, 3, and 4–5), and surgical margin status (negative, positive, indeterminate). Multivariable models were also assessed after additional adjustment for adjuvant therapy, defined as use of androgen deprivation therapy within 1 yr or radiation therapy within 6 mo after radical prostatectomy. R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. The study was approved by the Research Ethics Board of Umeå University Hospital.

3. Results

The study population consisted of 293 men with BCR after PCa treatment and 5767 BCR-free controls, of whom 150 (51%) and 3334 (58%), respectively, used PDE5i pills after treatment. Table 1 shows demographic data for the study population stratified by treatment received, and Supplementary Table 1 shows cumulative pill counts for each PDE5i.

Table 2 shows multivariable conditional logistic regression models for BCR including clinical features and PDE5i use. PDE5i use was not associated with BCR in men who underwent radical prostatectomy (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.59–1.03) or radiation therapy (OR 0.98, 95% CI 0.49–1.97). Higher PSA and biopsy GGG were significant predictors of BCR after prostatectomy and radiation therapy. Clinical stage and >33% positive biopsy cores were also significant predictors of BCR after prostatectomy. In separate models additionally adjusted for pathology features (Supplementary Table 2), there was no significant association between PDE5i use and BCR. Non–organ-confined disease, increasing GGG, and positive or indeterminate surgical margins were significant predictors of BCR. The results were similar after additional adjustment for use of adjuvant therapy. On stratification by exposure time, there was no association between PDE5i exposure and BCR risk.

Finally, we examined whether a greater cumulative number of PDE5i pills was associated with the BCR risk after radical prostatectomy (Table 3). Men whose cumulative number of PDE5i pills was above the median had a slightly lower BCR risk in the clinical model (OR 0.68, 95% CI 0.48–0.96), and no difference in BCR risk after adjustment for prostatectomy features (OR 0.73, 95% CI 0.51–1.04).

4. Discussion

In this nested case-control study using a large nationwide, population-based registry, we found no significant relationship between PDE5i use with PCa recurrence after treatment. In fact, a greater number of cumulative PDE5i pills after treatment was associated with a slightly lower risk of recurrence, but this was no longer significant after adjusting for pathologic features.

These results conflict with the initial study by Michl et al [2] in which PDE5i use was associated with a significantly higher BCR risk after radical prostatectomy (hazard ratio [HR] 1.38, 95% CI 1.11–1.70; $p = 0.0035$). That study included a highly selected cohort of 4752 men who underwent bilateral nerve-sparing radical prostatectomy at a tertiary referral center in Germany, with binary data on PDE5i use (yes/no) after treatment. Proposed mechanisms for this unexpected association included a potential reduction in natural killer

cell activity or PDE5i stimulation of angiogenesis [6,7]. Notably, >85% of these patients had organ-confined disease. It is possible that a small biological impact of PDE5i is more likely to be detected in cases with favorable features. The advantages of the current study are a larger sample size of men undergoing radical prostatectomy or radiation therapy from a population-based registry, including detailed data on the cumulative number of PDE5i pills.

Our results corroborate the more recent findings of Gallina et al [3], who examined PDE5i use and BCR in 2579 patients who underwent nerve-sparing radical prostatectomy at a tertiary referral in Italy. Unlike the previous study by Michl et al [2] and more similar to our study, they examined the dose-response relationship using data on the number of pills taken, although this information was obtained from patient diaries. After adjusting for clinicopathologic features, the number of PDE5i pills taken was not significantly associated with BCR (HR 0.99, 95% CI 0.98–1.01; $p = 0.4$), similar to our finding of no association with the cumulative number of PDE5i pills using objective prescription registry data.

There are many examples of adverse drug-related effects detected long after the initial clinical trials and regulatory approval, leading to increasing recognition of the importance of pharmacovigilance through postauthorization safety studies [8,9]. Such studies are extremely important for detection of possible adverse effects of widely used drugs for which replication studies are required. In this case, the data from our study and that of Gallina et al [3] have failed to replicate the initial findings of Michl et al [2], indicating that a change in clinical practice regarding PDE5i use after PCa treatment is not needed.

PDE5i use was also recently investigated for a possible link to melanoma. Li et al [10] reported a significant association between self-reported sildenafil use and risk of melanoma among US men in the Health Professionals Follow-Up Study. Using comprehensive data from the Swedish Melanoma Register and the Prescribed Drug Register, we found that although there is an association between PDE5i use and melanoma, there was no dose-response relationship (ie, no higher risk with more filled prescriptions or longer-acting drugs) and no relationship to biologic aggressiveness, suggesting the absence of a causal relationship [11]. These studies highlight the importance of independent replication studies for findings on adverse drug-related events, preferably in large population-based cohorts with sufficient numbers of cases to allow pertinent subgroup analyses and minimize the risk of selection bias.

A limitation of the study is that PDE5i use was assessed using records for filled prescriptions. We chose a case-control design to minimize pitfalls in exposure classification and to facilitate a computationally efficient analysis of a dose-response relationship. Nevertheless, a previous US study reported that a minority of men obtain PDE5i online without a prescription [12], which might also occur in Sweden, leading to some misclassification of exposure [13]. In addition, the sample size was insufficient to examine the relationship between cumulative PDE5i pills and BCR after radiation therapy, and the event rate was low because of the inclusion criteria of PSA <20 ng/ml and clinical stage T1/T2 for the follow-up study. Finally, data on pretreatment PDE5i use were not available for the study population since the Prescribed Drug Register started in 2005. However, Plym

et al [14] reported that approximately 9% of Swedish men diagnosed with PCa use PDE5i during the year before diagnosis.

The strengths of our study include the availability of population-based data from health care registries and demographic databases in Sweden, which are real-world data of high quality. Comprehensive linkages provide complete and detailed data, including PCa treatment outcomes, exact cumulative PDE5i exposure, and information on putative confounders including socioeconomic factors.

5. Conclusions

Our results suggest against an association between PDE5i use and BCR after PCa treatment. In addition, men with greater cumulative PDE5i pills did not have a higher BCR risk after radical prostatectomy. A change in clinical practice regarding PDE5i use after PCa treatment is not warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics for men with prostate cancer who underwent radical prostatectomy or radiotherapy during 2006–2007 with 5-yr follow-up data [a]

	Radical prostatectomy		Radiotherapy	
	Cases (*n* = 248)	**Controls (*n* = 4886)**	**Cases (*n* = 45)**	**Controls (*n* = 881)**
Age, yr	64 (60–67)	63 (60–66)	65 (61–68)	65 (62–68)
Marital status				
Not married	75 (30)	1218 (25)	9 (20)	287 (33)
Married	173 (70)	3668 (75)	36 (80)	594 (67)
Educational level [b]				
Low	78 (32)	1510 (31)	17 (38)	304 (35)
Middle	104 (42)	2008 (41)	18 (40)	386 (44)
High	65 (26)	1356 (28)	10 (22)	186 (21)
Annual income [c]				
Quartile 1	51 (21)	724 (15)	9 (20)	175 (20)
Quartile 2	51 (21)	1145 (23)	13 (29)	266 (30)
Quartile 3	65 (26)	1282 (26)	18 (40)	246 (28)
Quartile 4	81 (33)	1733 (35)	5 (11)	189 (22)
Prostate-specific antigen, ng/ml	9.0 (6.3–12.2)	6.4 (4.7–9.2)	9.0 (6.5–15.0)	7.5 (5.6–11.0)
Clinical stage				
T1	127 (51)	3467 (71)	20 (44)	526 (60)
T2	121 (49)	1419 (29)	25 (56)	355 (40)
Biopsy Gleason grade group [d]				
GGG 1	129 (52)	3308 (68)	11 (24)	490 (56)
GGG 2	64 (26)	991 (20)	13 (29)	210 (24)
GGG 3	31 (12)	333 (7)	7 (16)	75 (9)
GGG 4	17 (7)	192 (4)	9 (20)	63 (7)
GGG 5	5 (2)	56 (1)	5 (11)	43 (5)
Missing data	2 (1)	6 (0)	0 (0)	0 (0)
Proportion of positive biopsies				
≤33%	91 (37)	2508 (51)	12 (27)	339 (38)
>33%	120 (48)	1699 (35)	23 (51)	388 (44)
Missing data	37 (15)	679 (14)	10 (22)	154 (17)
PDE5i use				
No	111 (45)	1825 (37)	32 (71)	608 (69)
Yes	137 (55)	3061 (63)	13 (29)	273 (31)
Pathologic stage				
<pT3	113 (46)	3364 (69)		
pT3+	113 (46)	926 (19)		
Missing data	22 (9)	596 (12)		

	Radical prostatectomy		Radiotherapy	
	Cases (*n* = 248)	**Controls (*n* = 4886)**	**Cases (*n* = 45)**	**Controls (*n* = 881)**
Positive margins				
No	89 (36)	3204 (66)		
Yes	101 (41)	793 (16)		
Indeterminate	44 (18)	536 (11)		
Missing data	14 (6)	353 (7)		
Pathological Gleason grade group [d]				
GGG 1	72 (29)	2279 (47)		
GGG 2	75 (30)	1588 (33)		
GGG 3	61 (25)	543 (11)		
GGG 4	16 (6)	130 (3)		
GGG 5	12 (5)	47 (1)		
Missing data	12 (5)	299 (6)		

Cases experienced biochemical recurrence of prostate cancer, while controls did not. Data are presented as median (interquartile range) for continuous variables and as *n* (%) for categorical variables.

[a] Only available for men with PSA <20 ng/ml and T1–2, not N1/M1.

[b] Educational levels: low = compulsory school (<10 yr); middle = upper secondary school (10–12 yr); high = college or university (>12 yr).

[c] Quartiles are based on a background male population free from prostate cancer, matched for year of birth and county of residence.

[d] Gleason grade groups: GGG 1 = Gleason score ≤6; GGG 2 = Gleason score 3 + 4; GGG 3 = Gleason score 4 + 3; GGG 4 = Gleason score 8; GGG 5 = Gleason score 9–10. GGG was considered to be missing for men with Gleason score 7 but indeterminate Gleason grades.

Table 2

Risk of biochemical recurrence of prostate cancer in relation to phosphodiesterase type 5 inhibitor (PDE5i) exposure on multivariable conditional regression

	Odds ratio (95% confidence interval)	
	Radical prostatectomy	**Radiotherapy**
PDE5i use		
No	1.00 (reference)	1.00 (reference)
Yes	0.78 (0.59–1.03)	0.98 (0.49–1.97)
Married		
No	1.00 (reference)	1.00 (reference)
Yes	0.79 (0.59–1.06)	2.10 (0.98–4.51)
Educational level		
Low	1.00 (reference)	1.00 (reference)
Middle	0.98 (0.72–1.34)	0.80 (0.38–1.68)
High	1.08 (0.75–1.54)	1.09 (0.46–2.59)
Annual income (per quartile)	0.93 (0.82–1.06)	0.99 (0.71–1.39)
PSA (per 1 ng/ml)	1.14 (1.10–1.17)	1.08 (1.00–1.15)
Clinical T2 (reference T1)	2.08 (1.59–2.72)	1.41 (0.74–2.68)
Biopsy Gleason grade group	1.28 (1.11–1.46)	1.68 (1.30–2.18)
Proportion of positive biopsies		
≤33%	1.00 (reference)	1.00 (reference)
>33%	1.46 (1.11–1.93)	0.99 (0.50–1.98)

PSA = prostate-specific antigen.

Table 3

Risk of biochemical recurrence of prostate cancer after radical prostatectomy and cumulative number of phosphodiesterase type 5 inhibitor (PDE5i) pills prescribed according to multivariable conditional regression

Cumulative PDE5i pills	Odds ratio (95% confidence interval)	
	Diagnostic variables [a]	RP variables [b]
None	1.00 (reference)	1.00 (reference)
Below median	0.88 (0.64–1.21)	0.99 (0.71–1.38)
Above median	0.68 (0.48–0.96)	0.73 (0.51–1.04)

RP = radical prostatectomy.

[a] Model adjusted for marital status, education, income, prostate-specific antigen, clinical stage, biopsy Gleason grade group, and proportion of positive biopsies.

[b] Model adjusted for marital status, education, income, prostate-specific antigen, pathologic stage, prostatectomy Gleason grade group, and surgical margin status.