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Calcium channel blocker use and risk of prostate cancer by *TMPRSS2:ERG* gene fusion status

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Abstract

Background—Calcium channel blockers (CCBs) may affect prostate cancer (PCa) growth by various mechanisms including those related to androgens. The fusion of the androgen-regulated gene *TMPRSS2* and the oncogene *ERG* (*TMPRSS2:ERG* or *T2E*) is common in PCa, and prostate tumors that harbor the gene fusion are believed to represent a distinct disease subtype. We studied the association of CCB use with the risk of PCa, and molecular subtypes of PCa defined by *T2E* status.

Methods—Participants were residents of King County, Washington, recruited for population-based case–control studies (1993–1996 or 2002–2005). Tumor *T2E* status was determined by fluorescence *in situ* hybridization using tumor tissue specimens from radical prostatectomy. Detailed information on use of CCBs and other variables was obtained through in-person interviews. Binomial and polytomous logistic regression were used to generate odds ratios (ORs) and 95% confidence intervals (CIs).

Results—The study includes 1,747 PCa patients and 1,635 age-matched controls. A subset of 563 patients treated with radical prostatectomy had *T2E* status determined, of which 295 were *T2E* positive (52%). Use of CCBs (ever vs. never) was not associated with overall PCa risk. However, among European-American men, users had a reduced risk of higher-grade PCa (Gleason scores ≥ 7 : adjusted OR = 0.64; 95% CI: 0.44–0.95). Further, use of CCBs was associated with a reduced risk of *T2E* positive PCa (adjusted OR = 0.38; 95% CI: 0.19–0.78), but was not associated with *T2E* negative PCa.

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Conflict of interest

The authors declare that they have no conflict of interest.

Conclusions—This study found suggestive evidence that use of CCBs is associated with reduced relative risks for higher Gleason score and *T2E* positive PCa. Future studies of PCa etiology should consider etiologic heterogeneity as PCa subtypes may develop through different causal pathways.

INTRODUCTION

Prostate cancer (PCa) is the most frequently diagnosed solid tumor in men (1). There is substantial heterogeneity among primary prostate cancers, evident in the spectrum of its molecular alterations and in patients' variable prognosis (2,3). One of the most common somatic alterations in PCa is fusion of the androgen-regulated gene *TMPRSS2* with the oncogene *ERG* (4). The *TMPRSS2:ERG* (*T2E*) fusion is an early event in PCa that occurs in about half of all patients of European ancestry (5). An important consequence of the gene fusion is that the oncogene *ERG* becomes androgen-driven, leading to *ERG* overexpression (6). There is substantial evidence that *T2E* positive PCa represents a distinct disease subtype with different underlying oncogenic pathways (2,7–10). Several recent epidemiological studies have shown etiological differences by *T2E* status, and identified risk factors that were uniquely associated with *T2E* positive but not *T2E* negative disease (11–13).

Calcium channel blockers (CCBs) are used for the treatment of hypertension (14). Frequently prescribed CCBs include dihydropyridines (e.g., nifedipine), phenylalkylamines (e.g., verapamil), and benzothiazepines (e.g., diltiazem) (15,16). These drugs target calcium channels, which regulate calcium ion (Ca^{2+}) homeostasis (17,18), and may thereby alter cellular processes relevant to cancer including proliferation and apoptosis (18–20). Increased calcium channel activity has been associated with increased cellular proliferation and cancer growth (21,22).

Many studies have identified alterations in the expression of calcium channel genes in cancer, including PCa (18,21,23). Interestingly, androgens have been shown to increase intracellular calcium levels in PCa cells, and calcium may also affect androgen receptor (AR) expression (24). Different types of calcium channels have been implicated in prostate carcinogenesis including members of the ORAI, TRP, L-type and T-type family of channels (21,24–27). Further, there is some evidence of calcium channel genes being differentially expressed in prostate tumors that harbor the androgen-regulated *T2E* fusion (7,10,24,28–30).

A number of prior epidemiological studies have investigated the association of CCB use with PCa risk (31). Two of the studies reported an inverse association (32,33), six studies found no evidence of an association (34–39), and one study showed a positive association (40). These prior studies, however, did not comprehensively investigate the association of CCB use with features of more aggressive PCa; and no prior study has examined the association stratifying patients by *T2E* defined tumor molecular subtypes. In the present population-based case–control study we investigated the association between CCB use and PCa risk overall and more aggressive PCa features. We also performed analyses according to tumor *T2E* gene fusion status.

METHODS

Study population

Study participants were residents of King County, Washington, who participated in population-based case-control studies (41,42). Incident cases diagnosed with histologically confirmed adenocarcinoma of the prostate were identified via the Seattle-Puget Sound Surveillance, Epidemiology, and End Results cancer registry. Cases from the first study (ages: 40 to 64 years) were diagnosed with PCa from 1993 through 1996 and cases from the second study (ages: 35 to 74 years) were diagnosed between 2002 and 2005. In total, 1,754 interviewed patients were available for these analyses, including 984 patients who underwent radical prostatectomy. Data on Gleason score, diagnostic prostate-specific antigen (PSA) level, and tumor stage were collected from the cancer registry. Population-based controls without a history of PCa (n = 1,645) were identified using random digit telephone dialing, recruited evenly throughout the ascertainment periods for cases, and frequency-matched to cases by five-year age groups. All participants signed informed consent for participation, and cases were asked for consent to obtain tumor tissues; the studies were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Use of calcium channel blockers

Information on lifetime use of CCBs was obtained during a detailed in-person interview. Medication show cards were used to obtain information on the type of CCB used. Seven cases and ten controls had missing data on CCB use and were excluded from the analysis. In addition, data on duration of use, date or age of first use, and current vs. former use were available for the subset of men in the second study, but not for men in the first study. Current use was defined as use within the year prior to the reference date (i.e., date of diagnosis for cases and a similar, randomly preassigned date for controls that approximated the distribution of diagnosis dates for cases). Information on demographic and lifestyle factors, personal and family medical history, and other cancer-related factors was collected during the interview.

Determination of *TMPRSS2:ERG* gene fusion status

Formalin-fixed, paraffin-embedded tumor tissue blocks from radical prostatectomy specimens were used to make hematoxylin and eosin stained slides. In total, 563 radical prostatectomy patients had tumor tissue available. These slides were reviewed by a prostate pathologist, who marked areas containing ~75% tumor tissue. From these areas, two 1-mm cores were taken and embedded in recipient paraffin blocks for the creation of tumor tissue microarrays (TMAs). Fluorescence *in situ* hybridization (FISH) 'break-apart' assays were used to determine *T2E* status for patients represented on the TMAs. A two-color FISH technique was used as described previously (11).

Statistical data analysis

Logistic regression was used to calculate the odds ratio (OR) as an estimate of the relative risk and 95% confidence interval (CI) for the association between ever vs. never use of

CCBs and PCa. Polytomous logistic regression was used for analyses stratifying patients by tumor *T2E* status and Gleason score (<7 vs. 7). Statistical models were adjusted for age (five-year age groups) and race (African-American, European-American). Other variables were also considered as potential confounders: education, body mass index, lifetime alcohol consumption, aspirin and other NSAIDs use, recent exercise frequency, history of diabetes mellitus, and history of hypertension. We investigated the effect of adding these variables to the model, one by one, on the OR for the association of CCB use with PCa risk. Only body mass index (continuous) and history of hypertension (no, yes) changed the OR for CCB use by at least 5%, and these variables were therefore additionally included in the final model. Associations were also evaluated in the subgroup of European-American men. African-American patients were not considered separately because the numbers were too small. All *P*-values were two-sided and a *P*-value of less than 0.05 was considered to be statistically significant. All statistical analyses were conducted using R.

RESULTS

The study population included 1,747 PCa patients and 1,635 controls (Table 1). As expected, patients were more likely to have a first-degree family history of PCa compared to controls. Tumor tissue was collected for the patients who had radical prostatectomy and these samples were used to determine *T2E* status. Of the 563 patients with *T2E* data, 295 (52%) had tumors that were *T2E* gene fusion-positive. Positive fusion status was associated with younger ages at diagnosis, European-American ancestry, and lower Gleason score tumors.

Almost all CCB users in the study used medications from the following three drug classes: dihydropyridines (52.9%), phenylalkylamines (24.8%), and benzothiazepines (21.8%). As expected, most men that reported CCB use also reported having a history of hypertension (Supplementary Table 1).

The frequency of any CCB use among controls was 8.6% (Table 2; Supplementary Table 1). Use of CCBs was not associated with the relative risk of overall, lower-grade (Gleason <7), or higher-grade (Gleason 7) PCa, with adjusted ORs of 0.87 (95% CI: 0.67–1.13), 0.99 (95% CI: 0.73–1.33), and 0.74 (95% CI: 0.53–1.04), respectively (Table 2). Because African-American men have a higher incidence of PCa compared to European-American men; and in our control population there was a difference in the frequency of calcium channel blocker use in African (14%) versus European-American men (8%), we repeated the analysis focusing on European-American men only. In this subgroup, use of CCBs was inversely associated with risk of higher-grade PCa (adjusted OR = 0.64; 95% CI: 0.44–0.95). The association was more pronounced for patients with Gleason scores of 7 that had pattern 4 as the predominant pattern (4+3) or higher (adjusted OR = 0.53; 95% CI: 0.29–0.98). Results were similar when using a definition of more aggressive PCa based on a combination of clinical-pathological parameters (i.e., Gleason score, stage, and diagnostic PSA level; results not shown). One of the variables included in the multivariable-adjusted model was a history of hypertension (yes vs. no) because it was significantly associated with overall PCa risk in the study population (age-adjusted OR = 1.22, 95% CI: 1.05–1.41; multivariable-adjusted OR = 1.47, 95% CI: 1.09–1.98).

There was no evidence suggesting that the associations differed substantially by type of CCB (results not shown). For a subset of men, data were available on current vs. former use, duration of use, and time since first use of CCBs. No significant associations were found according to these detailed exposure measures (Table 3). In the subgroup of European-American men, however, current use of CCBs was associated with a significantly lower relative risk of higher-grade PCa (adjusted OR = 0.44; 95% CI: 0.23–0.83).

Table 4 shows the results for the association between CCB use and PCa risk stratified by *T2E* status. Use of CCBs was associated with a significantly reduced risk of *T2E* positive PCa, with an adjusted OR of 0.38 (95% CI: 0.19–0.78). Of the patients with *T2E* positive PCa who used CCBs, 78% (7 out of 9) had lower-grade disease (Gleason scores ≤ 6). No association was observed for *T2E* negative PCa (adjusted OR = 1.05; 95% CI: 0.65–1.69). A test for the difference in the OR for *T2E* positive versus *T2E* negative PCa was significant (P-value = 0.01). The association of CCB use with fusion-positive PCa was slightly more pronounced when the analysis was restricted to European-American men (adjusted OR = 0.33; 95% CI: 0.15–0.73). Among the subset of European-American men, all *T2E* positive PCa patients who used CCBs (n = 7) had low grade disease (Gleason scores ≤ 6).

DISCUSSION

This case–control study showed that ever use of CCBs was associated with a decreased relative risk of *T2E* gene fusion positive PCa, which is an important molecular subtype of the disease. No associations were observed between CCB use and risk of *T2E* negative PCa. In the larger study population there was no association between CCB use and overall PCa risk, however, there was suggestive evidence that CCB use is associated with a lower risk of higher-grade tumors among European-American men.

Although prior studies have not investigated the association between CCB use and PCa risk in patients stratified by tumor *T2E* status, at least nine observational studies of CCBs and overall PCa risk have been conducted (31,34,39). Of these, two small prospective studies found an inverse association. The first study by Fitzpatrick et al. included 2,442 men (151 PCa patients), and found that CCB users had a relative risk of PCa of 0.6 (95% CI: 0.4–0.9) (32). The second study by Debes et al. included 1,362 men (135 PCa patients), and showed that CCB use was associated with a relative risk of 0.55 (95% CI: 0.31–0.97) (33). The majority of studies, however, found no association between CCB use and PCa risk. These investigations include three cohort studies (2 prospective and 1 retrospective study) (34,36,39), including a prospective cohort study with 3,031 incident PCa patients (36), and four case–control studies (35,37,38,40). Only one previous observational study specifically investigated CCB use in relation to more aggressive PCa features, and that study found no association (36). Based on our results showing an inverse association between CCB use and higher-grade PCa, further studies are needed to examine whether CCBs might be associated with a reduced risk of developing more clinically aggressive forms of the disease. Our study also showed novel evidence that CCBs may reduce the risk of developing *T2E* positive PCa. Given that this is the first study to examine the association, further molecular epidemiological studies focused on CCB use in patients stratified by *T2E* tumor subtypes are needed.

Calcium channels regulate Ca^{2+} homeostasis and are involved in several important cellular mechanisms (18,21). Altered expression of calcium channel genes is common in cancer, and increased calcium channel activity can increase cellular proliferation and may promote PCa growth (23). Overexpression of specific calcium channel genes may also protect PCa cells from apoptosis (25,43). Although the precise biological mechanisms through which CCBs may reduce risk of *T2E* positive PCa are unclear, a likely mechanism is via inhibition of voltage-dependent calcium channels on the plasma membrane that would then limit Ca^{2+} influx and activity of downstream Ca^{2+} regulated signaling pathways. The Ca^{2+} channel CaV1.3 , encoded by *CACNA1D* (44), is of particular interest as this gene is known to be highly overexpressed in *T2E* positive PCa (7,10,24,28–30,45). Previous evidence from our group showed that this increase in *CACNA1D* correlates with aberrant DNA methylation of the gene (10). *CACNA1D* encodes the calcium-channel, voltage-dependent, L-type, α 1D subunit, CaV1.3 (44). This L-type calcium channel is a target of the most commonly prescribed CCBs including dihydropyridines, phenylalkylamines, and benzothiazepines (15,16). The ability of LNCaP PCa cells to exhibit 5α -DHT-stimulated Ca^{2+} transients that were sensitive to the CCBs nifedipine (dihydropyridine), verapamil (phenylalkylamine) or diltiazem (benzothiazepine) indicates expression of functional channels (46). Further, it has been shown that suppression of *CACNA1D* inhibits androgen-stimulated Ca^{2+} transients, androgen receptor transactivation, and PCa cell growth (24). Additional mechanistic studies are needed to fully understand the potential link between use of CCBs and development of *T2E* positive tumors, and the potential involvement of the *CACNA1D* gene. Finally, vitamin D can increase calcium influx (47). Epidemiologic studies have reported inconsistent associations of vitamin D with PCa risk (48). Given the role of vitamin D in calcium homeostasis, however, additional investigations are needed to examine the potential role of vitamin D in the link between calcium, CCB use, and PCa.

Calcium channel blockers are commonly prescribed drugs for the treatment of hypertension. Hypertension has been associated with a higher risk of PCa (49), which we confirmed in the present analysis. The OR for hypertension increased after including calcium channel blocker use in the multivariable model, which could be explained by the subset of hypertensive patients who were not treated with calcium channel blockers.

Strengths of this study include its population-based design, availability of data on many potential confounding variables, and data on tumor *T2E* gene fusion status determined using fluorescence *in situ* hybridization, which is considered the ‘gold standard’ for assessing this somatic alteration. Because of the retrospective study design, the possibility of recall bias in relation to medication use cannot be ruled out. However, because patients are expected to have better recall of medication use compared to controls, recall bias would not explain the observed inverse association of CCB use with PCa risk. Further, we would not expect recall to vary by tumor molecular subtype, which is therefore unlikely to have impacted our findings related to *T2E* status. There was no evidence that the associations were substantially different for men with a longer duration of CCB use or time since first use. However, there were limited numbers of long-term users or users who initiated CCB use over five years ago, which may have limited power for assessing these details of exposure. Another potential limitation is that tumor *T2E* status was only available for the subset of patients who chose radical prostatectomy for primary treatment. However there was no

evidence that the frequency of CCB use differed by primary treatment groups. Finally, although we adjusted for many potential confounders, residual confounding might be a problem. For example, use of CCBs is associated with treatment of hypertension, which is also linked to obesity and cardio-metabolic abnormalities that may increase cancer incidence. That would, however, not explain the reduced relative risks observed in our study.

In conclusion, the present study showed that CCB use was associated with a lower risk of an important molecular subtype of PCa, *T2E* gene fusion-positive disease. If confirmed, our results suggest that CCBs, which are commonly used for the treatment of hypertension, may also reduce the risk of developing *T2E* positive PCa, a molecular subtype that represents approximately half of all prostate tumors diagnosed in men of European ancestry. This molecular epidemiological study of PCa highlights the importance of examining exposures that may alter cancer risk in patients with specific tumor molecular subtypes of PCa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Selected characteristics of prostate cancer (PCa) cases and controls

Variables	Controls (n = 1,635)			Overall PCa cases (n = 1,747)			T2E negative PCa cases (n = 268)			T2E positive PCa cases (n = 295)		
	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%
Age (years)	59.2 (7.2)	-	-	59.8 (7.0)	-	-	59.3 (6.9)	-	-	56.9 (6.6)	-	-
Race												
African-American	-	114	7.0%	-	205	11.7%	-	30	11.2%	-	15	5.1%
European-American	-	1,521	93.0%	-	1,542	88.3%	-	238	88.8%	-	280	94.9%
First-degree family history of PCa												
No	-	1,457	89.1%	-	1,381	79.0%	-	204	76.1%	-	232	78.6%
Yes	-	178	10.9%	-	366	21.0%	-	64	23.9%	-	63	21.4%
Body mass index (kg/m ²)	27.2 (4.2)	-	-	27.1 (4.1)	-	-	26.9 (3.7)	-	-	26.7 (3.7)	-	-
Smoking status												
Never	-	690	42.2%	-	705	40.4%	-	112	41.8%	-	128	43.4%
Former	-	713	43.6%	-	808	46.3%	-	133	49.6%	-	135	45.8%
Current	-	232	14.2%	-	234	13.4%	-	23	8.6%	-	32	10.9%
History of hypertension												
No	-	1,125	68.9%	-	1,122	64.2%	-	175	65.3%	-	206	69.8%
Yes	-	508	31.1%	-	625	35.8%	-	93	34.7%	-	89	30.2%
Gleason score												
6	-	-	-	-	983	56.5%	-	117	43.7%	-	161	54.6%
7(3+4)	-	-	-	-	478	27.5%	-	96	35.8%	-	100	33.9%
7(4+3)	-	-	-	-	113	6.5%	-	32	11.9%	-	15	5.1%
8-10	-	-	-	-	165	9.5%	-	23	8.6%	-	19	6.4%
Disease stage												
Local	-	-	-	-	1,366	78.2%	-	186	69.4%	-	200	67.8%
Regional	-	-	-	-	334	19.1%	-	81	30.2%	-	95	32.2%
Distant	-	-	-	-	47	2.7%	-	1	0.4%	-	0	0.0%
PSA (ng/mL) at diagnosis												
<4	-	-	-	-	227	14.1%	-	33	13.2%	-	54	19.4%

Variables	Controls (n = 1,635)			Overall pCa cases (n = 1,747)			T2E negative pCa cases (n = 268)			T2E positive pCa cases (n = 295)		
	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%
4<10	-	-	-	-	970	60.2%	-	156	62.2%	-	176	63.3%
10-<20	-	-	-	-	250	15.5%	-	45	17.9%	-	31	11.2%
20	-	-	-	-	163	10.1%	-	17	6.8%	-	17	6.1%
Primary treatment												
Radical prostatectomy	-	-	-	-	984	56.1%	-	268	100.0%	-	295	100.0%
Radiation with or without ADT	-	-	-	-	508	29.0%	-	-	-	-	-	-
ADT only	-	-	-	-	91	5.2%	-	-	-	-	-	-
Active surveillance	-	-	-	-	164	9.4%	-	-	-	-	-	-
Other	-	-	-	-	7	0.4%	-	-	-	-	-	-

Note: ADT: androgen-deprivation therapy; pCa, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation; T2E, *TMPS2:ERG*.

Table 2

Odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between calcium channel blocker use and risk of overall, lower-grade, and higher-grade prostate cancer

	Calcium channel blocker use		
	No	Yes	
	OR (ref)	OR	(95% CI)
<i>All men</i>			
No. controls	1,495	140	
Overall PCa			
No. cases	1,598	149	
Age-adjusted	1.00	0.97	(0.76, 1.24)
Multivariable-adjusted ^a	1.00	0.87	(0.67, 1.13)
Gleason score <7			
No. cases	896	87	
Age-adjusted	1.00	1.05	(0.79, 1.39)
Multivariable-adjusted ^a	1.00	0.99	(0.73, 1.33)
Gleason score ≥ 7			
No. cases	695	61	
Age-adjusted	1.00	0.78	(0.57, 1.08)
Multivariable-adjusted ^a	1.00	0.74	(0.53, 1.04)
<i>European-American men</i>			
No. controls	1,397	124	
Overall PCa			
No. cases	1,426	116	
Age-adjusted	1.00	0.91	(0.70, 1.19)
Multivariable-adjusted ^b	1.00	0.84	(0.63, 1.12)
Gleason score <7			
No. cases	810	75	
Age-adjusted	1.00	1.08	(0.80, 1.46)
Multivariable-adjusted ^b	1.00	1.00	(0.72, 1.38)
Gleason score ≥ 7			
No. cases	611	40	
Age-adjusted	1.00	0.69	(0.48, 1.00)
Multivariable-adjusted ^b	1.00	0.64	(0.44, 0.95)

Note: CI, confidence interval; OR, odds ratio; PCa, prostate cancer.

^aModels were adjusted for age (five-year age groups), race (African-American, European-American), body mass index (continuous), and history of hypertension (no, yes).

^bModels were adjusted for age (five-year age groups), body mass index (continuous), and history of hypertension (no, yes).

Odds ratios (ORs) and 95% confidence interval (CIs) for prostate cancer risk by categories of calcium channel blocker use^a**Table 3**

		All men						European-American men					
		No. controls	No. cases	OR	(95% CI)	No. controls	No. cases	OR	(95% CI)	No. controls	No. cases	OR	(95% CI)
<i>Overall PCa</i>													
Use													
Never (ref.)		844	901	1.00		757	768	1.00					
Former		31	35	1.00	(0.60, 1.66)	29	31	1.00	(0.59, 1.70)				
Current		67	65	0.82	(0.56, 1.19)	58	44	0.71	(0.47, 1.09)				
Duration of use, years													
<5		37	41	0.97	(0.61, 1.56)	31	34	1.02	(0.61, 1.70)				
5		54	56	0.87	(0.58, 1.31)	49	38	0.73	(0.47, 1.15)				
Time since first use, years													
<5		28	27	0.84	(0.48, 1.45)	23	23	0.93	(0.51, 1.69)				
5		60	67	0.94	(0.64, 1.38)	56	46	0.76	(0.51, 1.17)				
<i>Gleason score <7</i>													
Use													
Never (ref.)		844	469			757	407	1.00					
Former		31	18	1.03	(0.56, 1.89)	29	15	0.94	(0.49, 1.81)				
Current		67	38	0.99	(0.64, 1.53)	58	30	0.93	(0.58, 1.51)				
Duration of use, years													
<5		37	27	1.27	(0.75, 2.15)	31	23	1.32	(0.74, 2.34)				
5		54	27	0.88	(0.54, 1.45)	49	20	0.75	(0.43, 1.31)				
Time since first use, years													
<5		28	19	1.18	(0.64, 2.16)	23	17	1.32	(0.69, 2.55)				
5		60	35	1.03	(0.66, 1.63)	56	26	0.84	(0.51, 1.40)				
<i>Gleason score ≥7</i>													
Use													
Never (ref.)		844	428			757	359	1.00					
Former		31	17	0.99	(0.53, 1.84)	29	16	1.06	(0.56, 2.01)				
Current		67	26	0.63	(0.39, 1.03)	58	13	0.44	(0.23, 0.83)				

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All men		European-American men					
	No. controls	No. cases	OR	(95% CI)	No. controls	No. cases	OR (95% CI)
Duration of use, years							
<5	37	14	0.66	(0.34, 1.25)	31	11	0.70 (0.34, 1.43)
5	54	28	0.86	(0.53, 1.41)	49	17	0.68 (0.38, 1.21)
Time since first use, years							
<5	28	8	0.49	(0.22, 1.10)	23	6	0.52 (0.21, 1.29)
5	60	31	0.85	(0.53, 1.37)	56	19	0.65 (0.37, 1.13)

Note: CI, confidence interval; OR, odds ratio; PCa, prostate cancer.

^aModels were adjusted for age (five-year age groups), race (African-American, European-American), body mass index (continuous), and history of hypertension (no, yes).

Table 4

Odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between calcium channel blocker use and risk of prostate cancer stratified by *TMPRSS2:ERG* gene fusion status

	Calcium channel blocker use		
	No	Yes	
	OR (ref)	OR	(95% CI)
<i>All men</i>			
No. controls	1,495	140	
<i>T2E positive PCa</i>			
No. cases	286	9	
Age-adjusted	1.00	0.40	(0.20, 0.79)
Multivariable-adjusted ^a	1.00	0.38	(0.19, 0.78)
<i>T2E negative PCa</i>			
No. cases	243	25	
Age-adjusted	1.00	1.11	(0.71, 1.75)
Multivariable-adjusted ^a	1.00	1.05	(0.65, 1.69)
<i>European-American men</i>			
No. controls	1,397	124	
<i>T2E positive PCa</i>			
No. cases	273	7	
Age-adjusted	1.00	0.36	(0.16, 0.78)
Multivariable-adjusted ^b	1.00	0.33	(0.15, 0.73)
<i>T2E negative PCa</i>			
No. cases	219	19	
Age-adjusted	1.00	1.00	(0.60, 1.66)
Multivariable-adjusted ^b	1.00	0.99	(0.58, 1.71)

Note: CI, confidence interval; OR, odds ratio; PCa, prostate cancer; *T2E*, *TMPRSS2:ERG*.

^aModels were adjusted for age (five-year age groups), race (African-American, European-American), body mass index (continuous), and history of hypertension (no, yes).

^bModels were adjusted for age (five-year age groups), body mass index (continuous), and history of hypertension (no, yes).