Inverse Association between Prostate Cancer and the Use of Calcium Channel Blockers

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Abstract

Calcium channel blockers block calcium signal-mediated apoptosis. It is hypothesized that the use of these drugs may be associated with the development of cancer. This study investigated the association between daily use of calcium channel blockers and prostate cancer in a community-based cohort of men who participated in a longitudinal study of lower urinary tract symptoms. Study subjects were men ages 40 to 79 years by January 1, 1990, and were randomly selected from Olmsted County in Minnesota. At baseline, participants underwent an interview to determine all medications taken on a daily basis, including calcium channel blockers and to elicit a family history of prostate cancer. During follow-up, all men with a histological diagnosis of prostate cancer were identified through patient self-report and by a review of the complete medical record. Over 12,668 person years of follow-up, 15 (6.8%) of 220 calcium channel blocker users and 120 (10.5%) of 1142 nonusers developed prostate cancer ($P = 0.09$; odds ratio, 0.62; 95% confidence interval, 0.36–1.10). With adjustment for age and family history of prostate cancer, the risk (odds ratio, 95% confidence interval) of prostate cancer was 0.55 (0.31–0.97) in calcium channel blocker users compared with nonusers. In analyses stratified by family history of prostate cancer, the risk of prostate cancer was 0.45 (0.23–0.88) in men without a family history and 2.64 (0.82–8.47) in men with a family history of prostate cancer ($P = 0.006$). These findings suggest an association between prostate cancer and daily use of calcium channel blockers that varies by family history of prostate cancer.

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Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer in males in occidental countries and the second leading cause of cancer death, affecting primarily those over 65 years old (1). Family history, diet, and pharmaceutical drugs such as nonsteroidal anti-inflammatory drugs, lipoxygenase inhibitors, and isoflavones have been associated with PCa (2, 3). Because calcium channel blockers alter calcium signals and thereby interfere with cellular apoptosis, the relationship between the use of these drugs and cancer of the prostate and other organs is of interest (4–6). Pahor *et al.* (4) found an increased risk of a number of cancers with the use of calcium channel blocker, but reported no specific data for PCa. In another study, Jick (5) analyzed the General Practice Research Database in the United Kingdom, and found a nonsignificant positive association between calcium-channel blockers and the risk of cancer (adjusted relative risk, 1.27). The authors stated that the difference was too small to suggest that the medications were associated with an increased risk of developing cancer. Vezina *et al.* (6) assessed the association between calcium-channel blockers and PCa in a cohort of men younger than 70 years old but observed no increased risk of PCa in men using calcium-channel blockers.

The rationale for an association between calcium channel blocker use and cancer is based on the hypothesis that calcium channel blockers block calcium signal-mediated apoptosis and thereby increase the risk of cancer. Recent studies on cellular models, however, have shown that calcium-channel blockers inhibit PCa cell proliferation (7–9). Rybalchenko *et al.* showed that extracellular application of verapamil inhibits proliferation of the human PCa cell line LNCaP (8). On the other hand, Jan *et al* (7). demonstrated that fendiline induces internal calcium release, one of the proposed mechanisms for apoptosis induction, in PC3 cells. Thus, we sought to determine whether the antiproliferative effects of calcium channel blockers on cancer cells observed *in vitro*, are exhibited in the population setting. The purpose of this study was to evaluate the relationship between calcium-channel blocker use and the risk of PCa in a population-based cohort of men in Olmsted County, Minnesota.

Materials and Methods

Subject Selection. Study subjects were participants of the Olmsted County Study of Urinary Symptoms and Health Status among Men, a prospective cohort study designed to evaluate long-term outcomes of lower urinary tract symptoms. Details have been published elsewhere (10). Briefly, in 1989, a sampling frame of all Olmsted County male residents ages 40 to 79 years by January 1, 1990 was constructed using the resources of the Rochester Epidemiology Project. From this frame, a random sample was selected, and medical records were reviewed for exclusion criteria: a history of PCa, prostate surgery, urethral stricture or surgery, bladder cancer or surgery, or any medical condition known to affect voiding other than benign prostatic

hyperplasia. A total of 2115 men agreed to participate at baseline (55% participation rate). From this cohort, a random sample of 25% of the cohort (clinical cohort) was invited to participate in a clinical portion of the study. In the 1992 and 1994 follow-up evaluations, 332 men were randomly selected from the community using the same criteria and protocol as at baseline, to replace men who had died or were lost to follow-up.

Measurements. At the baseline evaluation, study participants completed a previously validated self-administered questionnaire that assessed medical history, urinary tract symptoms and sociodemographic characteristics. Structured interviews were conducted by trained research assistants to elicit information on current daily medications and family history of PCa. Each participant was asked to report all prescribed and over-the-counter medications that were taken on a daily basis. All types of calcium channel blockers were taken into account. The duration of use of calcium channel blockers was not assessed directly. At baseline and biennially, thereafter, men in the clinical cohort underwent a detailed urological work-up including a digital rectal examination, serum prostate-specific antigen (PSA) determination, and transrectal sonographic imaging of the prostate. In addition medication use was re-ascertained during the 2000 follow-up evaluation.

For ascertainment of a diagnosis of PCa, active follow-up was performed every 2 years through the clinical examination and from patient self-report. Passive follow-up of each subject was also performed by a review of the complete community medical record through the Rochester Epidemiology Project. Only men with a histological diagnosis of PCa during a median follow-up of 127 months from baseline (from 1990 through 2002), were considered to have PCa in this study. Because of the low incidence of PCa among men ages 40 to 49 years at baseline (only 17 of 1089 developed PCa), these men were excluded from the analyses presented in this study. Therefore, of the 2451 men recruited to the study at baseline ($n = 2115$) and during follow-up ($n = 332$), 1362 men ages 50 to 79 years at study entry were included in the analyses for this study.

Statistical Analyses. The risk of PCa in men who reported taking calcium channel blockers at the onset of the study was assessed using logistic regression analyses and proportional hazards models. Age-adjusted and age-stratified analyses were performed to evaluate confounding or effect modification by age. Men with a father, half- or full-brother with a family history of PCa were categorized as having a family history of PCa. The effect of family history of PCa on the association between PCa and the use of calcium channel blockers was assessed by stratification on the presence or absence of a family history of PCa. To differentiate the association between PCa and the use of calcium channel blockers from hypertension effects, or antihypertensive medication in general, the association between PCa and the use of β-adrenergic receptor blockers was examined.

Results

Of the 1362 subjects under study, 220 reported using calcium channel blockers on a daily basis (Table 1), and 135 (9.9%) men developed PCa during 12,668 person-years of follow-up. Men who reported using calcium channel blockers were older [median (25th, 75th percentile age was 65.0 (58.3, 71.3) years in calcium channel blocker users and 60.5 (54.6, 67.8) in nonusers ($P = 0.001$)] and had more digital rectal examinations (4 *versus* 3, $P < 0.001$) and serum PSA determinations (3 *versus* 2, $P < 0.02$) in the year before enrollment through follow-up, compared with men who did not report using calcium blockers at baseline. Calcium channel blocker users had a higher prevalence of benign prostatic hyperplasia, diabetes, other malignancy besides PCa, stroke, and heart disease than nonusers. There was no significant difference between calcium

Table 1 Characteristics of study cohort at baseline and follow-up by exposure status

	Daily calcium channel blocker use[a]				*P*
	Yes ($n = 220$)		No ($n = 1142$)		
	n	%	*n*	%	
Prostate cancer diagnosis[b]	15	6.8	120	10.5	0.09
Age, yr[a]					<0.001
50–59	67	30.4	553	48.4	
60–69	91	41.4	373	32.7	
70–79	62	28.2	216	18.9	
Family history of prostate cancer	20	9.1	116	10.2	0.63
Urologic diagnoses[c]					
BPH[d]	139	63.2	552	48.3	<0.001
Prostatitis	15	6.8	104	9.1	0.27
Renal/ureteric stones	14	6.4	58	5.1	0.4
UTI	39	17.7	196	17.2	0.08
Comorbidities[c]					
Diabetes	31	14.1	61	5.3	<0.001
Malignancy	25	11.4	84	7.4	0.04
Stroke	11	5	31	2.71	0.07
Heart disease	99	45	165	14.4	<0.001
Number of DREs[e]	4	2.3, 6.0	3	2.0, 5.0	<0.001
Number of PSAs[e]	3.0	1.0, 5.0	2.0	1.0, 4.0	0.02

[a] Self-reported daily use of calcium channel blockers at baseline, age at baseline.
[b] Biopsy proven prostate cancer diagnosis during follow-up.
[c] Urologic diagnoses and comorbidities at baseline and during follow-up.
[d] BPH, benign prostatic hyperplasia; UTI, urinary tract infection.
[e] Median (25th, 75th percentile) number of digital rectal examinations (DREs) and prostate-specific antigen (PSA) determinations in the year prior to enrollment through follow-up.

channel blocker users and nonusers regarding a family history of PCa ($P = 0.63$).

There was a trend toward an inverse association between self-reported use of calcium channel blockers at baseline and a diagnosis of PCa. Of the 220 calcium channel blocker users, 15 (6.8%) developed PCa and of the 1142 nonusers, 120 (10.5%) developed PCa ($P = 0.09$). The relative odds (95% CI) of PCa in calcium channel blocker users decreased with increasing age among men ages 50 to 59 years, 60 to 69 years, and 70 to 79 years at baseline: 1.16 (0.44–3.06), 0.50 (0.22–1.15), and 0.3 (0.09–1.03), respectively (P for interaction = 0.19; Table 2). In bivariate analyses, men who reported using calcium channel blockers were less likely to develop PCa compared with nonusers [odds ratio (OR), 0.62; 95% confidence interval (CI), 0.36–1.10; Table 3). After adjustment for age and family history, the relative odds of PCa in calcium channel blocker users decreased to 0.55 (95% CI, 0.31–0.97), and the CI no longer included 1.

In stratified analyses, the association between calcium channel blocker use and PCa varied significantly by family history, but not by age. Among men with no family history of PCa, calcium channel blocker users had a lower likelihood of PCa compared with nonusers (OR, 0.45; 95% CI, 0.23–0.88; Table 4). However, among men with a family history of PCa, calcium channel blocker users were more likely to have a diagnosis of PCa (OR, 2.64,;95% CI, 0.82–8.47) compared with nonusers (P for interaction = 0.006). To investigate possible surveillance bias among men with a family history, the difference in the number of PSA determinations and digital rectal examinations from enrollment through follow-up between calcium channel blocker users and nonusers was investigated, stratified by family history of PCa. Among men with a family history of PCa, the difference in the number of PSA determinations (3.5 and 3.0; $P = 0.29$) or digital rectal examinations (5 and 4; $P = 0.11$) between calcium channel blocker users and nonusers, respectively, was not statistically significant. Among men with no history of PCa however, the difference in number of PSA determinations (3 and 2; $P = 0.03$) and digital rectal examinations (4 and 3; $P = 0.0001$) was statistically significantly different between calcium channel blocker users and nonusers, respectively. The results based on proportional hazards methods were similar to logistic regression methods (results not shown).

Table 2 Association between calcium channel blocker use and prostate cancer stratified by age[a]

Age, yr	Calcium channel blocker use	OR[b] (95% CI)
50–59	Yes	1.16 (0.44–3.06)
	No	1.0
60–59	Yes	0.50 (0.22–0.86)
	No	1.0
70–79	Yes	0.30 (0.09–1.03)
	No	1.0

[a] The Breslow-Day test of the homogeneity of the odds ratio was 0.19, indicating that the difference in the association across age groups was not statistically significant.
[b] OR, odds ratio; CI, confidence interval.

Table 3 Association of age, family history, and/or calcium channel blocker use with prostate cancer

	Unadjusted OR[a] (95% CI)	Adjusted[b] OR (95% CI)
Age, yr		
50–59	1.0	1.0
60–69	2.10 (1.38–3.18)	2.18 (1.43–3.31)
70–79	1.97 (1.22–3.18)	2.07 (1.27–3.35)
Family history[c]		
No	1.0	1.0
Yes	1.45 (0.85–2.46)	1.36 (0.80–2.35)
Calcium channel blocker use		
No	1.0	1.0
Yes	0.62 (0.36–1.10)	0.55 (0.31–0.97)

[a] OR, odds ratio; CI, confidence interval.
[b] Adjusted for other variables in column 1.
[c] Family history of prostate cancer.

Table 4 Association between calcium channel blocker use and prostate cancer stratified by family history of prostate cancer[a]

	Family history OR[b] (95% CI)	No family history OR (95% CI)
Calcium channel blocker use		
Yes	2.64 (0.82–8.47)	0.45 (0.23–0.88)
No	1.0	1.0

[a] The Breslow-Day test of the homogeneity of the odds ratio was 0.0058, indicating a difference in the association by family history status.
[b] OR, odds ratio; CI, confidence interval.

Discussion

These findings demonstrate an inverse association between the daily use of calcium channel blockers and a diagnosis of PCa after adjustment for age. Interestingly, the stratified analyses demonstrated an inverse association between PCa and calcium channel blocker use in men with no family history of PCa but a positive association in men with a family history of PCa. The variation in risk of PCa based on family history of PCa is intriguing, but the reasons for this variation are not clear. One possibility is increased surveillance and, therefore, increased PCa detection in calcium channel blocker users. The older age, greater number of digital rectal examinations and PSA determinations, and greater comorbidity among calcium channel blocker users would suggest a greater likelihood of detection among calcium channel blocker users because of more frequent contact with the medical system or a greater risk of PCa because of age, in these men. On the contrary, a reduced risk of PCa was observed in calcium channel blocker users, suggesting that the association was not because of increased surveillance among calcium channel blocker users.

Another possible explanation is that greater surveillance among men with a family history of PCa may explain the variation in risk. The lack of statistically significant differences in the number of PSA determinations and number of digital rectal examinations between calcium channel blocker users and nonusers in men with a family history of PCa, relative to the statistically significant higher numbers among calcium channel blocker users with no family history, however, suggests that surveillance bias among men with a family history is unlikely to explain the observed association. These findings raise the question that the observed risk estimates may actually be biased toward the null.

The difference in risk could also be associated with genetic differences in the metabolism of calcium channel blockers. PCa has been shown to have a familial component, and a number of PCa susceptibility genes have been identified. The study findings raise interesting questions about PCa susceptibility genes that may be related to calcium channel physiology or to the

metabolism of calcium channel blockers. Men with a family history of PCa may have genes that are associated with an increased metabolism of calcium channel blockers or decreased action of the drug, with the reverse occurring in men without a family history of PCa. The pathophysiology of this variation in risk of PCa in calcium channel blocker users deserves further study.

A number of hypotheses have been proposed to explain the association between calcium channel blocker use and PCa. Calcium channel blockers have been associated with apoptosis. The association however, is complex because both increased and decreased intracellular levels of calcium have been associated with apoptosis (11, 12). Calcium-channel blockers alter calcium transport at the cellular level and increase calcium release into the cytoplasm. This has been proposed as a mechanism for the induction of cellular apoptosis (7). Laboratory studies suggest that calcium channel blockers induce regression and inhibition of vascular wall growth (13) and also inhibit angiogenic growth factors (14) through increased apoptosis. Calcium channel blockers have also been associated with inhibition of tumor growth and metastases (12, 15). It has been hypothesized that increased sympathetic activity may stimulate androgen-mediated prostatic growth and thereby promote PCa (16). Consequently, antihypertensive medication may decrease androgen-mediated prostatic growth. Therefore, the effects on PCa cells of decreased sympathetic activity, inhibition of angiogenic growth factors, and induction of apoptosis by calcium channel blockers, may decrease the risk of PCa.

Studies investigating the association between PCa risk and antihypertensive medication use have yielded inconsistent results. Some studies have observed an inverse association between the risk of PCa and use of calcium channel blockers or other antihypertensives (17, 18), whereas others have observed no significant association (3, 4, 19, 20). The findings from the present study are consistent with findings from the Cardiovascular Health Study, a cohort study in which calcium channel blocker users had a 40% reduced risk of PCa (17), similar to the present study. In a prospective study of elderly persons, Pahor *et al.* (4) found a nonsignificant but increased risk of PCa (OR, 1.99) in subjects using calcium channel blockers compared with nonusers. However, the findings may have been biased by age-related factors because the median age of study subjects was 79 years. In a nested case–control study, Jick (5) observed a nonsignificant increased risk of PCa in calcium channel blockers users compared with β blocker users (relative risk, 1.27). No comparison was made with subjects who were not taking an antihypertensive medication; thus, the generalizability of the findings may be limited. Similarly, Hole *et al.* (20) found no significant association when calcium channel blocker users were compared with noncalcium channel blocker users or population controls. In a case–control study conducted in men 70 years old or younger, Vezina *et al.* (6) observed no significant association. The findings may be biased by not including men over 70 years old. The present community-based cohort of men ages 50 to 79 years at baseline, provided the opportunity to assess the association over a broad age group of men and over an extended period of time (median, 10.5 years).

In our study, a number of potential limitations should be kept in mind. We did not directly assess the duration of use of calcium channel blockers; therefore, we could not evaluate the association with duration of use or of cumulative dose. We also did not determine whether the medication was used continuously over the duration of the study, and some men may have discontinued using calcium channel blockers during follow-up. However, among the 740 men who provided information on calcium channel blocker use at baseline and in 2000, the age-adjusted estimates of the association between calcium channel blocker use and PCa were in the same direction but closer to the null (OR, 0.7; 95% CI, 0.3, 1.8). In this group of men, 578 men (78.1%) did not use calcium channel blocker at baseline or during follow-up, 136 (18.4%) reported calcium channel blocker use at baseline or during follow up, and 26 (3.5%) reported calcium channel blocker use at baseline but not at follow-up.

It is possible that the association could be related to hypertension or an antihypertensive effect. When the association between PCa and β-blocker use was examined, there was no significant association (OR, 0.81;95% CI, 0.50–1.32), and the estimates were unchanged after adjustment for age and family history. Nonsteroid anti-inflammatory drugs have also been inversely associated with PCa in this cohort (21). Adjustment for β-blocker use or nonsteroid anti-inflammatory drug use did not alter the association between calcium channel blockers and PCa overall, nor when stratified by family history. The lack of availability of finasteride at the onset of the study in 1990 precluded our ability to determine if the use of finasteride could partially explain our findings, in light of the recently reported results of finasteride in the Prostate Cancer Primary Prevention trial (22). The baseline response rate of 55% for the entire cohort suggests a potential for nonparticipation bias. Although participants were slightly older and had slightly more urological conditions than nonparticipants (23), these baseline differences have had no impact on long-term urological outcomes, such as acute urinary retention (24) or the prevalence of prostatitis (25) between participants and nonparticipants during follow-up. Finally, the study was conducted on a community of middle-class white men, and, therefore, caution should be used in extrapolation of these findings to subjects not represented in this cohort.

In summary, these findings suggest an inverse association between PCa and daily use of calcium channel blockers, which differed according to a family history of PCa. The findings from this study should stimulate further laboratory and epidemiological research directed at understanding a possible role of calcium channel blockers in the pathogenesis of PCa.

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