Research Article

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Prostate Cancer Risk in Men with Baseline History of Coronary Artery Disease: Results from the REDUCE Study

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Abstract

Background: Coronary artery disease (CAD) and prostate cancer (PCa) are not only common diseases, but share many risk factors. To date, only a few studies have explored the relationship between CAD and PCa risk, with conflicting results.

Methods: The four-year REDUCE study tested dutasteride 0.5 mg daily for PCa risk reduction in men with prostate specific antigen (PSA) of 2.5 to 10.0 ng/mL and a negative biopsy. Among men who underwent at least one on-study biopsy ($n = 6{,}729$; 82.8%), the association between CAD and overall PCa risk and disease grade was examined with logistic and multinomial logistic regression adjusting for clinicopathologic features, respectively.

Results: Overall, 547 men (8.6%) had a history of CAD. Men with CAD were significantly older and had higher body mass index, PSA, and larger prostate volumes and were more likely to have diabetes, hypertension, and hypercholesterolemia and take aspirin and statins. On multivariate analysis, CAD was associated with a 35% increased risk of PCa diagnosis (OR = 1.35, 95% CI: 1.08–1.67, $P = 0.007$), while elevating risk of both low- (OR = 1.34, 95% CI: 1.05–1.73, $P = 0.02$) and high-grade disease (OR = 1.34, 95% CI: 0.95–1.88, $P = 0.09$).

Conclusions: In a post hoc hypothesis developing secondary analysis of the REDUCE study, CAD was significantly associated with increased PCa diagnosis.

Impact: If confirmed in other studies, this suggests CAD may be a novel PCa risk factor and suggests common shared etiologies. Whether lifestyle changes shown to reduce CAD risk (i.e., weight loss, exercise, cholesterol reduction, etc.) can reduce PCa risk, warrants further study. *Cancer Epidemiol Biomarkers Prev; 21(4); 576–81. ©2012 AACR.*

Introduction

The most common heart disease variant, coronary artery disease (CAD) remains a leading cause of morbidity and mortality (1). Likewise, prostate cancer (PCa) remains a major public health problem. When independently examined, CAD and PCa share several modifiable and nonmodifiable risk factors like age, race, family history, and possibly diet (2, 3). Prior studies suggest elevated serum cholesterol, a known CAD risk factor, may be associated with PCa risk and disease grade (4, 5). Furthermore, several recent studies found statins, which benefit men with CAD, may reduce overall PCa risk and disease recurrence (6, 7), though conflicting data exist (8). Only a few studies examined the relationship between CAD and PCa risk with mixed results (9–13). Moreover, prior studies may be biased, as men with chronic comorbidities (i.e., CAD) may be more likely to undergo cancer screening (14).

Given these observations, we carried out a post hoc hypothesis developing study investigating the relationship between CAD and overall PCa risk and disease grade using the REDUCE study, a 4-year placebo-controlled, randomized trial testing the chemopreventive properties of dutasteride, wherein dutasteride was shown to recude the risk of PCa by 23% but had no effect on the risk of Gleason 7–10 disease (15). Regardless of PSA level, all participants were required to undergo prostate biopsies at 2 and 4 years. This cohort grants a unique opportunity to test the association between CAD and PCa risk minimizing potential biases associated with prostate specific antigen (PSA) screening.

Materials and Methods

Study population

The design of the REDUCE study has been reported (15). Eligible men were aged 50 to 75 years, with a serum PSA of 2.5 to 10 ng/mL if aged 50 to 60 years, or 3 to 10 ng/mL if more than 60 years, and a single, negative prostate biopsy (6–12 cores) within 6 months prior to enrollment.

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Study design

REDUCE was a 4-year, multicenter, double-blind, placebo-controlled study. Eligible subjects were randomized to dutasteride 0.5 mg/d or placebo. Visits occurred every 6 months. Total serum PSA (Beckman Coulter Inc.) was assessed every 6 months, with doubled PSA values ($\pm$ 0.1 ng/mL) reported to investigators for men receiving dutasteride. Unscheduled PSA measurements were permitted if obtained through the central study laboratory.

Subjects underwent a 10-core transrectal ultrasound (TRUS)-guided biopsy at 2 and 4 years regardless of PSA levels ("protocol-dependent" biopsies); unscheduled biopsies were conducted if clinically indicated ("protocol-independent" biopsies). For cause biopsies obtained during months 19 to 24 and 43 to 48 replaced those scheduled for years 2 and 4 and were included in the definition of protocol-dependent biopsies.

At baseline, a detailed medical history was obtained including CAD, smoking history, medication use, and other medical comorbidities. Race was self-reported. Digital rectal examination (DRE) findings and TRUS prostate volume were reported from the prestudy biopsy.

Statistical analyses

Among the 8,122 men in the efficacy population, 6,729 had 1 or more on-study biopsy (82.8%). A significantly greater percentage of men with CAD did not receive any on-study biopsy (8.5% vs. 11.8%; x^2, $P < 0.001$). Men not undergoing a biopsy were similar aged, had similar baseline PSA, body mass index (BMI), and DRE findings (all $P > 0.05$), but were more likely to be black (3.9 vs. 1.9%; $P < 0.001$). Details of the biopsy population have been published (16). Of the 6,729 men who had 1 or more on-study biopsy, we excluded men with missing data for prestudy PSA ($n = 14$), BMI ($n = 205$), DRE ($n = 7$), TRUS volume ($n = 76$), alcohol intake ($n = 36$), smoking history ($n = 5$), or unknown hypercholesterolemia status ($n = 1$), resulting in a final population of 6,390 all with data on preenrollment CAD captured on the case-report forms at study enrollment via either self-report or from historical medical records. The distribution of CAD between arms was similar ($P = 0.81$). As treatment arm did not significantly modify the association between CAD and any outcomes, the placebo and dutasteride arms were combined ($P_{\text{interaction}} = 0.39$).

The association between CAD and baseline parameters was tested with rank sum for continuous variables and χ^2 for categorical variables. The OR associated with CAD for PCa risk was examined with logistic regression. For analysis predicting high-grade (Gleason $\geq$7) or low-grade PCa (Gleason <7) versus no cancer, a multinomial logistic regression was used. To explore whether the association between CAD and PCa risk changed with time, we examined overall PCa risk within the first and second 2-year time frames using logistic regression. Results were adjusted for clinical characteristics known to be associated with PCa risk including age (continuous), race (white, black, and other), baseline PSA (log-transformed and continuous), prostate volume (log-transformed and continuous), DRE findings (abnormal vs. normal), BMI (log-transformed, continuous), geographic region, and treatment arm (dutasteride vs. placebo). We also adjusted for other factors which have been shown to be related to PCa and/or CAD in other studies including alcohol intake in units/week (1 unit = $^1/_2$ pint of beer, 1 glass of wine, or 1 measure of alcohol; nondrinker: 0 units/wk vs. moderate drinker: $\leq$7 units/wk, vs. heavy drinker: >7 units/wk), aspirin use, statin use, smoking history (current, former, or never), diabetes status, history of hypertension, and history of hypercholesterolemia. Finally, we tested whether the association between CAD and PCa was modified by age by dividing patients into tertiles by age and testing for formal interactions. Of men with cancer, tumor volumes in microliters from the biopsy were known for 1,512 (99.7%; see REDUCE primary article for details of how tumor volume was determined; ref. 15). We tested the association between CAD and tumor volume (continuous and log-transformed) using linear regression adjusting for disease and patient characteristics. All analyses were conducted by Stata 11.1 (College Station, Texas, USA) with $P \leq 0.05$ for statistical significance.

Results

Study population and baseline characteristics

Overall, 547 (8.6%) men reported a preenrollment history of CAD (Table 1). Men with CAD were significantly older and had higher BMI, PSA, and TRUS values. In addition, these men were more likely to have diabetes, hypertension, and hypercholesterolemia as well as have taken either aspirin or a statin. A larger proportion of white men (8.8%) reported a positive history of CAD than men who reported their race as either black (7.7%) or other (4.7%, $P = 0.02$).

CAD and overall PCa risk, disease grade, and tumor volume

On univariate analysis, CAD was associated with a significant 45% increased PCa risk ($P < 0.001$; Table 2). After adjusting for potential confounders, though the association was slightly attenuated, CAD remained associated with a significant 35% increased PCa risk ($P = 0.001$). Within the first and second 2-year time frames, men with CAD were 24% (OR = 1.24, 95% CI: 0.96–1.59, $P = 0.09$) and 73% (OR = 1.73, 95% CI: 1.23–2.43, $P = 0.002$) more likely to be diagnosed with PCa versus men without CAD, respectively (Fig. 1)

When examining the association between CAD and disease grade, on univariate analysis, CAD was associated with a significant 36% (OR: 1.36, 95% CI: 1.08–1.71, $P = 0.008$; Table 3) and 66% (OR: 1.66, 95% CI: 1.23–2.25, $P = 0.001$) elevated risk of low- and high-grade disease, respectively. On multivariate analysis, CAD was associated with an equally increased risk of both low- and high-grade disease: 33% increased risk of low- (OR: 1.34, 95% CI: 1.05–1.73, $P = 0.02$), and 31% increased risk of high-grade disease (OR: 1.34, 95% CI: 0.95–1.88, $P = 0.09$).

Table 1. Baseline characteristics of study population

	History of coronary artery disease		
	No	**Yes**	***P***
Number of patients, *n* (%)	5,843 (91.4)	547 (8.6)	
Median age at study enrollment, y	63 (58–67)	66 (62–70)	<0.001
Race, *n* (%)			0.02
White	5,349 (91.2)	519 (8.8)	
Black	108 (92.3)	9 (7.7)	
Other	386 (95.3)	19 (4.7)	
Geographic region, *n* (%)			0.006
North America	1,465 (92.7)	115 (7.3)	
South America	572 (92.3)	48 (7.7)	
Europe	3,520 (90.7)	362 (9.3)	
Australia/New Zealand	107 (87.7)	15 (12.3)	
Other (Japan, Tunisia, South Africa)	179 (96.2)	7 (3.8)	
BMI (kg/m^2)	26.8 (24.8–29.3)	27.2 (25.2–29.7)	0.003
Median PSA, ng/mL (IQR)	5.7 (4.4–7.3)	5.9 (4.6–7.5)	0.009
Median TRUS, cc (IQR)	43.3 (33.0–56.2)	45.1 (34.0–57.8)	0.08
PCa family history, *n* (%)	785 (13.4)	50 (9.1)	0.004
Abnormal digital rectal exam, *n* (%)	220 (3.8)	21 (3.8)	0.93
Assigned to Dutasteride arm, *n* (%)			0.77
No	2,970 (50.8)	281 (51.4)	
Yes	2,873 (49.2)	266 (48.6)	
Diabetes, *n* (%)			
No	5,523 (94.5)	494 (90.3)	<0.001
Yes	320 (5.5)	53 (9.7)	
Hypercholesterolemia, *n* (%)			0.003
No	5,138 (87.9)	404 (73.9)	
Yes	705 (12.1)	143 (26.1)	
Hypertension, *n* (%)			<0.001
No	4,521 (77.4)	288 (52.7)	
Yes	1,322 (22.6)	259 (47.3)	
Smoking history, *n* (%)			0.002
Never	2,700 (46.2)	223 (40.8)	
Current	856 (14.7)	67 (12.2)	
Former	2,287 (39.1)	257 (47.0)	
Alcohol intake, units per week (%)			0.002
None, 0 units	1,472 (25.2)	136 (24.9)	
Moderate drinker, <7 units	2,834 (48.5)	302 (55.2)	
Heavy drinker, ≥7 units	1,537 (26.3)	109 (19.9)	
Aspirin use, *n* (%)	1,682 (28.8)	363 (66.4)	<0.001
Statin use, *n* (%)	826 (14.1)	277 (50.6)	<0.001

However, due to the fewer number of men with high-grade disease, this latter association did not reach statistical significance.

Given a moderate attenuation in risk in the multivariate models relative to our univariate analyses, we explored which covariate(s) explained this attenuation in risk by adding each variable one at a time to the model. In so doing, adding age at study enrollment resulted in the greatest attenuation with respect to overall risk and high-grade disease. However, upon formal interaction testing, age (as tertiles) did not modify the association between CAD and PCa risk or grade ($P_{\text{interaction}} \geq 0.21$). Lastly, there was no significant association between CAD and tumor volume ($P = 0.33$).

Discussion

Beyond increased prevalence in industrialized countries, CAD and PCa share several risk factors. Given this, investigators have tested whether this is coincidental or if

Table 2. Overall PCa Risk in the REDUCE Study as a Function of Baseline CAD

	OR (95% CI)[b]	*P*
Univariate	1.45 (1.19–1.76)	<0.001
Multivariate[a]	1.35 (1.08–1.67)	0.007

[a]Multivariate logistic regression analyses adjusted for age, race, PCa family history, PSA, BMI, TRUS volume, hypertension, diabetes, hypercholesterolemia, aspirin use, statins use, alcohol intake, smoking history, geographic region, DRE findings, and treatment arm.
[b]Reference, men without history of CAD.

the 2 pathologies share common etiologies, however to date only limited and contradictory data exist (9–13). Furthermore, some studies are susceptible to screening/detection biases given increased cancer screening behavior in men with chronic conditions like CAD (14). To address these issues, we examined the association between CAD and PCa risk within the REDUCE study in which prostate biopsies were generally PSA independent. Herein, we observed that CAD was associated with elevated risk of both overall PCa and low- and high grade.

Few studies explored the relationship between heart disease and PCa risk with no consensus. Within retirement community residents, Henderson and colleagues observed a 2-fold increased PCa risk in men with heart disease—an observation echoed in a case–control study by Neugut and colleagues (10, 11). Similarly, Thompson and colleagues found men with heart disease, defined as a history of hospitalization for either a heart attack or heart failure, were 1.9 times more likely to be diagnosed with PCa versus those without heart disease, though this was not significant (17). Notably, however, the authors concluded this observed risk likely resulted from detection bias in men with heart disease. A more contemporary nested case–control study within the Physicians Health Study found men with CAD were nearly 25% less likely to be diagnosed with PCa (9). Unfortunately, these studies are limited in using racially and economically homogenous populations (e.g., upper middle class white men or a cohort of physicians), small number of PCa cases, and/or focus on general heart disease or surrogates thereof (e.g., hospitalization after heart attack or heart failure) and not solely CAD. Moreover, as CAD is strongly linked with obesity, previous investigations may be additionally burdened by detection/screening biases associated with obesity such as PSA hemodilution, anecdotally more difficult DREs, and larger prostates (18, 19). In our study, wherein screening biases were minimized, we observed a significant 35% increased PCa diagnosis among men with CAD, which was true for both low- and high-grade disease, though the strength of the association was modest versus prior studies showing an approximately 2-fold increased risk (14, 15). Furthermore, the strength of the association between CAD and PCa risk seemed to increase from the first to the second 2-year time frame. Although this may suggest that CAD more strongly influences future PCa risk as opposed to near-term risk, this requires validation in future prospective studies.

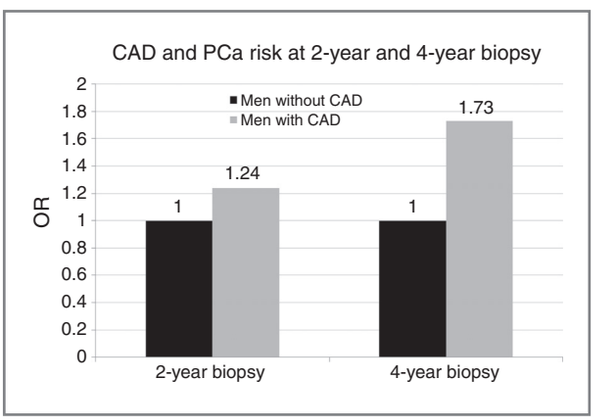

Figure 1. Overall risk of PCa in men with CAD at 2- and 4-year biopsy.

There are multiple mechanisms why CAD may be associated with increased PCa risk. First, CAD is linked with hypercholesterolemia and may serve as a surrogate of long-standing elevated serum cholesterol. Indeed, several studies found men with high cholesterol are at increased PCa risk (4, 20). In addition, data suggest increased serum cholesterol plays a role in not only tumorgenesis but in progression and development of aggressive disease (5, 21). Herein, we found the link between CAD and PCa risk was unchanged after adjusting for hypercholesterolemia. Furthermore, after adjusting for statins, which some studies suggested are associated with reduced PCa risk, the results remained unchanged, though, in prior analyses from REDUCE, statins were unrelated to PCa risk (22). However, hypercholesterolemia is a crude measure of cholesterol. Also, given the long latency of PCa, serum cholesterol levels years prior rather than current levels (or a current diagnosis of hypercholesterolemia) may be more important for PCa risk. Moreover, we observed a higher percentage of men reporting stain use than history of hypercholesterolemia. Thus, we suspect hypercholesterolemia was likely underreported. Thus, though these observations suggest CAD may be linked with PCa independent of cholesterol, more study is needed to better understand the link between cholesterol and PCa.

The inflammatory response is essential to the initiation and progression of atherosclerotic plaque. Similarly, inflammation may play a role in PCa development (23). Indeed, inflammatory markers such as C-reactive protein (CRP) and Il-6 have been linked with both CAD progression and poorer PCa outcomes (24, 25). Unfortunately, CRP levels or any other marker of systemic inflammation were not available in the current study. We did adjust for aspirin use, a known anti-inflammatory, which in itself

Table 3. Risk of low- and high-grade disease and history of coronary artery disease[a,b]

	Gleason score <7		Gleason score ≥7	
Overall	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Univariate				
Positive CAD	1.36 (1.08–1.71)	0.008	1.66 (1.23–2.25)	0.001
Multivariate[a]				
Positive CAD	1.34 (1.05–1.73)	0.02	1.34 (0.95–1.88)	0.09

[a]Multivariate multinomial logistic regression model adjusted for age, race, PCa family history, PSA, BMI, TRUS volume, hypertension, diabetes, hypercholesterolemia, aspirin use, statins use, alcohol intake, smoking history, geographic region, DRE findings, and treatment arm.

[b]Reference, men without history of CAD.

has been linked to reduced PCa risk, and found no appreciable difference in CAD's association with PCa risk (26, 27). However, this does not exclude the possibility that inflammation mediates at least in part the link between CAD and PCa diagnosis and therefore further study may be necessary.

Interestingly, when adjusting for the aforementioned factors and other comorbidities, lifestyle factors and medications, CAD continued to be positively associated with PCa risk. Of note, we did find an appreciable reduction in the magnitude of risk attributed to CAD when controlling for age at study enrollment. This was expected considering CAD, like PCa, is a disease associated with advancing age. However, adjusting for age did not fully explain the link between CAD and PCa. Moreover, on formal interaction testing, age did not modify the significant association between CAD and PCa risk.

Ultimately, it is unlikely that CAD itself causes PCa. Rather we suspect that if confirmed in future studies, our findings suggest CAD may share etiologies with PCa. From a clinical perspective, the association between CAD and PCa is modest. As such, when considering the greatest overall threat to a patient's life, CAD should be given much greater weight as heart disease is the number one cause of death of men. Rather these observations shed light on the possible etiologies of PCa and suggest future avenues of research and novel approaches for PCa prevention.

We do acknowledge several limitations. First, we did not have available data such as markers of systemic inflammation, physical activity level, diet, nor serial body weight measurements over the course of the study, which are all proposed factors important in both PCa and CAD (28). Second, this is an investigation examining proximal PCa outcomes (i.e., overall risk and disease grade) and did not explore CAD's role in disease progression. Third, all men in this study had an initial negative biopsy. How CAD influences the risk of PCa in general or among men undergoing initial biopsy requires further study. Fourth, REDUCE enrolled men with an elevated PSA who were felt to be at high risk for PCa. To what degree these results can be generalized to other populations is unclear. Fifth, there were no data available on the severity of CAD and thus we were unable to explore a "dose relationship." Sixth, as this was a post hoc exploratory analysis, it is more susceptible to a type I error. Finally, there may have been some misclassification with both over- and under-reporting of CAD. As misclassification tends to bias the results to the null, the current study may have underestimated the association between CAD and PCa risk. Despite these limitations, we feel this study has several strengths. In a multinational cohort, we could account for numerous potential confounders thought to be important for both CAD and PCa biology and examine CAD independent of their influence. Moreover, this study is unique in that men underwent biopsies regardless of PSA allowing us to test the association between CAD and PCa risk while reducing the effect of detection/screening bias.

Conclusion

Among men who all underwent biopsy largely independent of PSA in the REDUCE study, CAD was an independent predictor of overall PCa risk and both low- and high-grade disease grade. Moreover, the association between CAD and PCa diagnosis seemed to be stronger with longer follow-up. As CAD reflects a confluence of many other separate risk factors (i.e., diet, cholesterol, etc.), if this association is confirmed in future studies, then further study of this relationship and the potential biological mechanisms by which CAD mediates this elevation in PCa risk are warranted. Ultimately, if the relationship between CAD and PCa risk is confirmed, then measures proven to reduce CAD, may theoretically also reduce PCa risk.

Disclosure of Potential Conflicts of Interest

Drs. Freedland and Andriole are paid consultants to GSK. Drs. Freedland and Andriole have research support from GSK. Dr. Rittmaster is an employee of GSK. Views and opinions of, and endorsements by the author or authors do not reflect those of the U.S. Army or the Department of Defense.

Authors' Contributions

Drs. J.-A. Thomas and S.J. Freedland had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the sponsor

The role of the funding sources was to provide the data to Drs. Freedland and J.F. Thomas for analysis and cover salary support for the investigators.

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