Asian Race and Risk of Prostate Cancer: Results from the REDUCE Study

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ABSTRACT

Background: Global prostate cancer incidence rates are lower in Asian men than Caucasian men. Whether this is the result of less screening in Asian men remains to be determined. We examined whether Asian race was associated with prostate cancer diagnosis in the Reduction by Dutasteride of Cancer Events (REDUCE) study.

Methods: REDUCE was a 4-year, multicenter, randomized trial of dutasteride versus placebo for prostate cancer prevention among men who underwent prostate-specific antigen (PSA)-independent biopsies at 2 and 4 years. Eligible men were ages 50 to 75 years, had PSA between 2.5 and 10 ng/mL, and a negative prestudy prostate biopsy. We tested the association between Asian and Caucasian race and prostate cancer diagnosis using logistic regression.

Results: Of 8,122 men in REDUCE, 5,755 (71%) were Caucasian and 105 (1.8%) were Asian. Asians had lower body mass index (24.8 vs. 26.9 kg/m^2, $P < 0.001$), had smaller prostate volume (35.0 vs. 43.5 cc, $P < 0.001$), and were less likely to have abnormal digital rectal exams ($P = 0.048$), but were similar in baseline age, PSA, family history of prostate cancer, and smoking status compared with Caucasian men (all $P \geq 0.164$). Asian men were equally likely to receive any on-study biopsy compared with Caucasian men ($P = 0.634$). After adjusting for potential confounders, Asian men were less likely to be diagnosed with prostate cancer during the 4-year study (OR = 0.49; 95% confidence interval, 0.28–0.88; $P = 0.016$), compared with Caucasian men.

Conclusions: In REDUCE, where all men underwent biopsies largely independent of PSA, Asian race was associated with lower prostate cancer diagnosis.

Impact: These findings suggest that lower prostate cancer risk in Asian men may be due to biological, genetic, and/or lifestyle factors.

Introduction

In the United States, compared with Caucasian men, prostate cancer incidence and mortality rates are higher in African American men (1, 2) and lower in Asian American men (3, 4). Furthermore, although prostate cancer incidence rates have been on the rise in Asian countries, prostate cancer incidence in Asian countries is still lower compared with Western countries (5). A study that compared data from the Prostate Biopsy Collaborative Group (PBCG, which includes cohorts from Europe and North America) and data from a Chinese cohort, found that the relationship between prostate-specific antigen (PSA) and prostate cancer risk differed between Chinese and Western populations, with an overall lower risk in the Chinese cohort at any given PSA level (6). Although genetic, social, and/or environmental factors may play a role in these observed disparities, differential rates of PSA screening may also be a factor. Indeed, PSA screening has been widely adopted in Western Countries, particularly in North America, but not in Asian countries (5). Furthermore, it has been long reported that PSA levels in Asian populations are lower compared with those of Western populations (7, 8), and this may affect prostate biopsy rates thereby impacting rates of prostate cancer diagnosis. For example, a study found Chinese men older than 50 years old had lower PSA values compared with other races (7). We therefore sought to assess prostate cancer incidence by race in a global dataset which included Asian men and where prostate biopsies were performed largely independent of PSA level.

The Reduction by Dutasteride of Cancer Events (REDUCE) study was a multinational randomized clinical trial designed to compare the effect of dutasteride vs. placebo on prostate cancer diagnosis among men with an elevated PSA (2.5–10 ng/mL) but a negative prestudy prostate biopsy (9). The men in the study were followed-up for 4 years and had two on-study biopsies. Thus, this study gathered the appropriate data to pose the question of whether Asian race predicts a prostate cancer diagnosis largely independent of PSA. We hypothesized that Asian men would be at lower risk of a prostate cancer diagnosis versus Caucasian men.

Materials and Methods

Study population

REDUCE was a 4-year, multicenter, randomized, double-blind, placebo-controlled study that assessed the effect of dutasteride (0.5 mg/day) versus placebo on prostate cancer incidence (9). Detailed methods and results from REDUCE have been previously published (8). Eligibility requirements included men who were 50–75 years old, had a serum PSA of 2.5 to 10.0 ng/mL if 50 to 60 years or 3.0 to 10.0 ng/mL if older than 60 years, and had a single, negative prostate biopsy (6–12 cores) within 6 months prior to study enrollment. Men

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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with past history of prostate cancer, prostate surgery, prostate volume >80 mL, or International Prostate Symptom Score (IPSS) >25 or >20 on α-blockers were excluded. The treatment group took 0.5 mg dutasteride daily, the control group received placebo. During the study, subjects' PSA tests were done every 6 months. Transrectal ultrasound was used to determine prostate volume. At 2 and 4 years, subjects underwent a 10-core transrectal ultrasound-guided biopsy independent of PSA or digital rectal exam (DRE) findings, as per protocol.

"Protocol-independent" biopsies were performed as clinically indicated. Body mass index (BMI) was calculated using height and weight (kg/m^2) measured at baseline. The primary endpoint was biopsy detectable prostate cancer at any time during the 4-year follow-up period.

Of the 8,122 men included in the efficacy population, 1,655 (20%) men did not undergo any on-study biopsy and were excluded from our analysis. The goal of our analysis was to determine whether Asian race was associated with lower prostate cancer diagnosis than Caucasian race. Black men ($n = 122$), Hispanic men ($n = 261$), and men with unknown race ($n = 63$) were therefore excluded. We also excluded 161 men with missing baseline data on BMI ($n = 77$), PSA ($n = 11$), DRE ($n = 7$), prostate volume ($n = 60$), family history of prostate cancer ($n = 3$), or smoking status ($n = 3$). A total of 5,860 subjects met the inclusion criteria (**Fig. 1**). Included men were categorized into two groups stratified by self-identified race: Asian or Caucasian. Of note, most Asian men in REDUCE were Japanese living in Japan (48%), followed by Asian American (26%) and Asian Canadian (12%), whereas the rest were Asian men living in Europe, Africa, and South America (Supplementary Table S1). Demographic information including age, BMI, and clinical information such as prostate volume, PSA, and DRE findings were recorded at baseline.

Statistical analysis

Comparison of baseline characteristics between Asian and Caucasian men was performed using chi-square and Wilcoxon rank sum tests for categorical and continuous variables, respectively. Logistic regression was used to evaluate the association between Asian race and prostate cancer diagnosis upon pathology review of prostate biopsies overall, at 2 and 4 years. The association between Asian race and prostate cancer aggressiveness (low, grade group 1 and high, grade group 2–5) was evaluated using multinomial logistic regression. Age-adjusted and multivariable models were fit. Multivariable models were adjusted for the baseline factors of age (continuous), PSA (continuous), prostate volume (continuous, log-transformed), DRE (abnormal vs. normal), BMI (continuous), family history of prostate cancer (yes or no), smoking status (current, former or nonsmoker), and treatment group (dutasteride or placebo). In sensitivity analyses we compared effect estimates for prostate cancer diagnosis in Asians living in Asia (i.e., Japanese living in Japan) versus Asians living outside Asia, relative to Caucasians.

Among men in the efficacy population of REDUCE, which included men who received study assigned medication and had negative baseline prostate biopsy results on central review, the association between Asian race and the likelihood of receiving any on-study biopsy, biopsy at 2 or 4 years was assessed using age-adjusted and multivariable logistic regression models. Multivariable models were adjusted for the same variables as above. A two-sided significance level

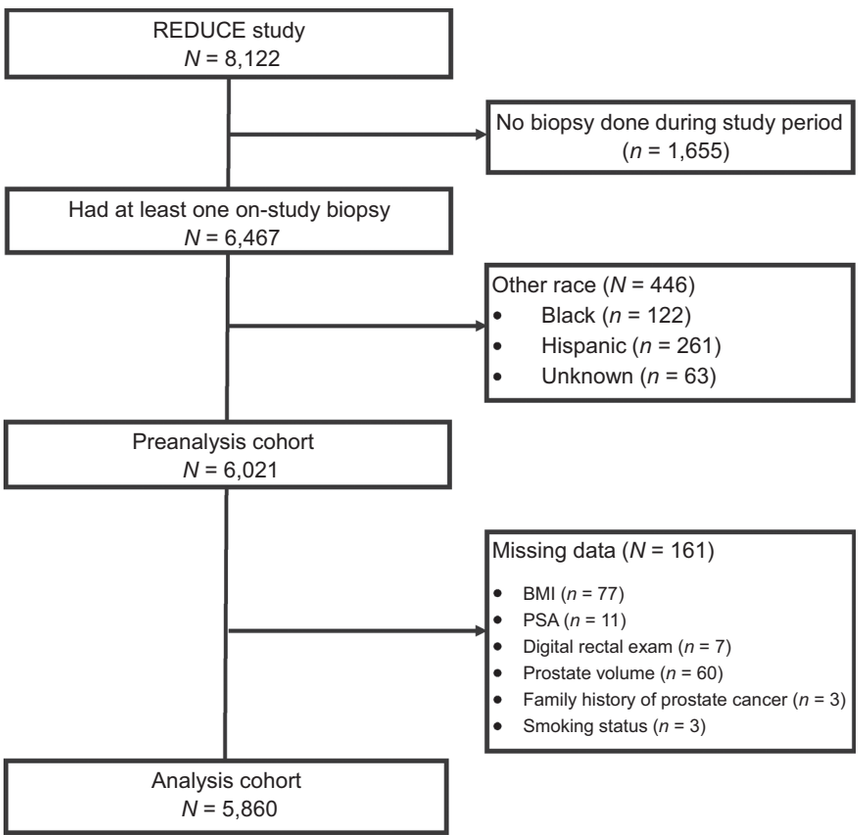

Figure 1.
Consort diagram showing patient selection. After excluding men who did not undergo a biopsy, men who were not either white or Asian, and those with missing data, the analysis cohort comprised 5,860 men.

Table 1. Baseline clinical characteristics for men with complete data enrolled in the REDUCE trial, $n = 5{,}860$.

	Asian ($N = 105$)	Caucasian ($N = 5{,}755$)	*P* value
Age (years), median (IQR)	63 (57, 67)	63 (58, 67)	0.996[a]
BMI (kg/m^2), median (IQR)	24.8 (23.0, 26.5)	26.9 (24.8, 29.3)	<0.001[a]
Prostate volume (cc), median (IQR)	35.0 (27.7, 46.6)	43.5 (33.2, 56.3)	<0.001[a]
PSA (ng/mL), median (IQR)	5.5 (4.1, 6.9)	5.7 (4.4, 7.3)	0.202[a]
Abnormal DRE, *n* (%)	0 (0.0%)	206 (3.6%)	0.048[b]
Positive PC family history, *n* (%)	11 (10.5%)	763 (13.3%)	0.404[c]
Smoking status, *n* (%)			0.164[c]
Never	40 (38.1%)	2636 (45.8%)	
Former	44 (41.9%)	2285 (39.7%)	
Current	21 (20.0%)	834 (14.5%)	
Treatment arm, *n* (%)			0.789[c]
Placebo	52 (49.5%)	2926 (50.8%)	
Dutasteride 0.5 mg	53 (50.5%)	2829 (49.2%)	

[a]Wilcoxon rank sum test.
[b]Fischer exact test.
[c]Chi-square test.

of 0.05 was considered for all tests. All analyses were performed using SAS 9.4 (SAS Institute, Inc.).

Results

Patient demographics

In our cohort ($n = 5{,}860$), 5,755 (98.2%) were Caucasian men and 105 (1.8%) were Asian men. Men of Asian race were less likely to have an abnormal DRE at baseline (0.0% vs. 3.6 %, $P = 0.048$), more likely to have lower prostate volume (35 vs. 43.5 cc, $P < 0.001$), and lower BMI (24.8 vs. 26.9 kg/m^2, $P < 0.001$) compared with Caucasian men. There were no statistically significant differences between races in regard to age ($P = 0.996$), PSA level ($P = 0.202$), family history of prostate cancer ($P = 0.404$), smoking status ($P = 0.164$) or treatment group ($P = 0.789$; **Table 1**).

The efficacy population likelihood of receiving biopsy

Among men in the efficacy population, on age-adjusted analyses, Asian men were no more or less likely to receive biopsy during the entire study period ($P = 0.707$; **Table 2**) compared with Caucasian men. Similarly, there was no difference in the likelihood of receiving biopsy for Asian men compared with Caucasian men at 2 years ($P = 0.950$) or 4 years ($P = 0.787$). Again, after multivariable adjustment, there remained no difference in the likelihood of receiving biopsy during the entire study period, at 2 or 4 years for Asian men compared with Caucasian men (all $P \geq 0.634$).

Asian race and prostate cancer diagnosis

On age-adjusted analyses, Asian race was associated with lower odds of prostate cancer diagnosis during the entire study period (OR = 0.53; 95% confidence interval [CI], 0.31–0.98; **Table 3**). Although not statistically significant, the magnitude and direction of the association between Asian race and prostate cancer diagnosis at 2-year biopsy (OR = 0.54; 95% CI, 0.27–1.07) and 4-year biopsy (OR = 0.60; 95% CI, 0.24–1.50) were similar to findings for the entire study period. On multivariable analysis, Asian race remained statistically significantly associated with lower odds of prostate cancer diagnosis, (OR = 0.49; 95% CI, 0.28–0.88), during the entire study period. At 2-year biopsy, the multivariable-adjusted association between Asian race and prostate cancer reached statistical significance (OR = 0.49; 95% CI, 0.24–0.97; **Table 4**) but not at 4 years (OR = 0.53; 95% CI, 0.21–1.34), although the magnitude and direction of these associations remained inverse. In sensitivity analyses, relative to Caucasians, we found a similar magnitude and direction of associations for Japanese living in Japan as we did for Asians living outside Asia though effect estimates were imprecise due to the small number of events (Supplementary Tables S2 and S3).

Table 2. Associations of Asian race as a predictor of receiving: (a) any on-study biopsy, $n = 7{,}296$; (b) year 2 on-study biopsy, $n = 7{,}296$; (c) year 4 on-study biopsy among men with negative year 2 biopsy, $n = 5{,}004$.

			Age-adjusted		Multivariable	
	N	*n*	OR (95% CI)	*P*	OR (95% CI)	*P*
On study ($N = 7{,}296$)						
Caucasians	7,165	5,992	ref	0.707	ref	0.634
Asians	131	108	0.92 (0.58–1.44)		0.90 (0.57–1.41)	
Year 2 biopsy ($N = 7{,}296$)						
Caucasians	7,165	5,755	ref	0.950	ref	0.921
Asians	131	105	0.99 (0.64–1.52)		0.98 (0.63–1.51)	
Year 4 biopsy ($N = 5{,}004$)						
Caucasians	4,908	4,091	ref	0.787	ref	0.743
Asians	96	81	1.08 (0.62–1.88)		1.10 (0.63–1.93)	

Note: Models adjusted for baseline age, PSA, BMI, DRE, log-prostate volume, treatment group, family history of prostate cancer, and smoking status.
Abbreviations: *N*, number of men within each category; *n*, number of men who had biopsy; *P*, *P*-value.

Table 3. Age-adjusted associations of Asian race as a predictor of prostate cancer (PC), PC aggressiveness (low-, high- grade PC) on: (a) any on-study biopsy, $n = 5{,}860$; (b) year 2 on-study biopsy, $n = 5{,}860$; (c) year 4 on-study biopsy among men with negative year 2 biopsy, $n = 4{,}172$.

		Cancer vs. no cancer			Low-grade vs. no cancer			High-grade vs. no cancer		
	N	*n*	OR (95% CI)	*P*	*n*	OR (95% CI)	*P*	*n*	OR (95% CI)	*P*
On study ($N = 5{,}860$)										
Caucasians	5,755	1,243	ref	0.041	883	ref	0.051	360	ref	0.393
Asians	105	14	0.53 (0.31–0.98)		9	0.50 (0.25–1.00)		5	0.67 (0.27–1.67)	
Year 2 biopsy ($N = 5{,}860$)										
Caucasians	5,755	847	ref	0.078	589	ref	0.120	258	ref	0.361
Asians	105	9	0.54 (0.27–1.07)		6	0.52 (0.23–1.19)		3	0.58 (0.18–1.86)	
Year 4 biopsy ($N = 4{,}172$)										
Caucasians	4,091	396	ref	0.275	294	ref	0.230	102	ref	0.884
Asians	81	5	0.60 (0.24–1.50)		3	0.49 (0.15–1.57)		2	0.90 (0.22–3.73)	

Abbreviations: *N*, number of men within each category; *n*, number of men with cancer (overall, low-grade, or high-grade) within each category; *P, P*-value.

Asian race and prostate cancer aggressiveness

On age-adjusted analyses, there were inverse directions of association, not reaching statistical significance, between Asian race and low-grade prostate cancer throughout the study period (OR = 0.50; 95% CI, 0.25–1.00), at 2-years (OR = 0.52; 95% CI, 0.23–1.19), and at 4-years (OR = 0.49; 95% CI, 0.15–1.57; **Table 3**). After multivariable adjustment, the association between Asian race and low-grade prostate cancer during the entire study period became statistically significant (OR = 0.46; 95% CI, 0.23–0.92) and the nonstatistically significant inverse directions of association between Asian race and low-grade prostate cancer at 2- and 4-year biopsies were similar to results from age-adjusted models (**Table 4**). In general, Asian race was similarly inversely related to high-grade prostate cancer in both age-adjusted (OR ≤ 0.52) and multivariable (OR ≤ 0.86) analyses, although, the associations did not reach statistical significance ($P \geq 0.243$) at any time point studied. In sensitivity analyses, relative to Caucasians, we found a similar magnitude and direction of associations for Japanese living in Japan and as we did for Asians living outside Asia though, again, effect estimates were imprecise due to the low number of events (Supplementary Tables S2 and S3).

Discussion

Globally, prostate cancer incidence rates are lower in Asian compared with Western countries (5). Asian men in Asia still show an approximately 17% lower prostate cancer risk compared with Caucasian men in Western countries (5). Therefore, in addition to racial differences in prostate cancer incidence rates potentially linked to lifestyle and/or biological factors, lower PSA screening and lower PSA levels in Asian men have also been suggested to contribute (5, 7, 8). To test whether prostate cancer diagnosis differs by race in a largely PSA-independent context, we investigated the relationship between Asian race and prostate cancer diagnosis in REDUCE, where all men had a negative pre-study biopsy and an elevated PSA level (2.5–10 ng/mL) at baseline, and received up to two on-study biopsies largely independent of PSA. As we hypothesized, after accounting for various clinical and demographic characteristics, we found that Asian men were significantly less likely than Caucasian men to be diagnosed with prostate cancer during the 4-year study. These results suggest that the lower prostate cancer risk in Asian men could be linked to biological, genetic, and/or lifestyle factors.

Previous studies showed prostate cancer in Asian populations may be missed if based on PSA values alone. Indeed, the use of optimal age-specific PSA cutoff values in Asian populations may be more accurate to predict prostate cancer among this group (7). A study of 9,374 Chinese men who underwent PSA determination during a 3-year period (7), was compared with four other studies in Korean (10), Japanese (11, 12), and Asian American men (13). Comparison between PSA 95th percentile values in Chinese, Korean, Japanese, and Asian

Table 4. Multivariable adjusted associations of Asian race as a predictor of prostate cancer, prostate cancer aggressiveness (low-, high-grade prostate cancer) on: (a) any on-study biopsy, $n = 5{,}860$; (b) year 2 on-study biopsy, $n = 5{,}860$; (c) year 4 on-study biopsy among men with negative year 2 biopsy, $n = 4{,}172$.

		Cancer vs. no cancer			Low-grade vs. no cancer			High-grade vs. no cancer		
	N	*n*	OR (95% CI)	*P*	*n*	OR (95% CI)	*P*	*n*	OR (95% CI)	*P*
On study ($N = 5{,}860$)										
Caucasians	5,755	1,243	ref	0.016	883	ref	0.028	360	ref	0.255
Asians	105	14	0.49 (0.28–0.88)		9	0.46 (0.23–0.92)		5	0.59 (0.23–1.47)	
Year 2 biopsy ($N = 5{,}860$)										
Caucasians	5,755	847	ref	0.042	589	ref	0.088	258	ref	0.243
Asians	105	9	0.49 (0.24–0.97)		6	0.48 (0.21–1.12)		3	0.50 (0.16–1.60)	
Year 4 biopsy ($N = 4{,}172$)										
Caucasians	4,091	396	ref	0.182	294	ref	0.161	102	ref	0.834
Asians	81	5	0.53 (0.21–1.34)		3	0.43 (0.14–1.39)		2	0.86 (0.20–3.62)	

Abbreviations: *N*, number of men within each category; *n*, number of men with cancer (overall, low-grade, or high-grade) within each category; *P* = *P*-value. Models adjusted for baseline age, PSA, BMI, DRE, log-prostate volume, treatment group, family history of prostate cancer, and smoking status.

American men showed consistently that above 50 years old, Asian men living in Asia (age 50–59: 2.87 ng/mL; age 60–69: 4 ng/mL; age 70–79: 5.46 ng/mL) had significantly lower PSA values compared with Asian Americans living in the United States (age 50–59: 4.50 ng/mL; age 60–69: 5.50 ng/mL; age 70–79: 6.80 ng/mL; ref. 7). Although, in China, the most commonly used age-specific PSA cut points are higher than the above-mentioned 95th percentile values (14), meaning that more patients would get biopsies and more prostate cancers would be detected, at the cost of more negative biopsies. In a large PSA screening study in China, among patients with PSA 4 to 10 ng/mL, only 11% had prostate cancer (15), even fewer cases than the study that compared a Chinese cohort (25%) to the PBCG cohort (40%; ref. 6). In the REDUCE study, men were eligible to participate if PSA values ranged from 2.5 to 10 ng/mL. In the present analysis, although PSA values were slightly lower in Asian men [median 5.5 ng/mL; interquartile range (IQR) = 4.1–6.9], they were not statistically significantly different compared with those of Caucasian men (median 5.7 ng/mL; IQR = 4.4–7.3). Analyses were age-adjusted, and all men underwent prostate biopsies regardless of PSA, thus supporting a statistically significant lower risk of prostate cancer diagnosis in Asian men, compared with Caucasian men.

Although our findings support a biological contribution to the lower risk of prostate cancer in Asian relative to Caucasian men, the potential contributing mechanisms are not well defined, although differences in prostate inflammation could hold a clue. In the REDUCE study, prostate biopsies were reviewed by a single pathologist who graded them systematically for inflammation (9). Analyzing negative biopsies from 6,238 men in REDUCE who had a subsequent biopsy, we previously found the presence of inflammation at baseline, either acute or chronic, was associated with a 35% to 40% lower odds of prostate cancer diagnosis on a biopsy taken 2 years later (16). However, only baseline acute inflammation was associated with reduced prostate cancer diagnosis on the 4-year biopsy (16). These findings suggest that acute inflammation in a benign biopsy may portend a lower future prostate cancer risk, and inflammation of the prostate has also been associated with lower prostate cancer risk by several other studies (17, 18). Thus, in a follow-up study, we analyzed whether inflammation varied by race (19). We found that compared with Caucasian men, African American men were less likely and Asian men more likely to have acute prostatic inflammation in their negative biopsies (19). No associations were found between chronic prostatic inflammation and race (19), in line with a previously published study (20). If confirmed, these findings suggest that racial differences in acute prostatic inflammation may contribute, in part, to racial differences in prostate cancer risk, especially among Asian men. As we observed in our previous REDUCE study (19), whether acute inflammation is protective against prostate cancer in Asian men requires validation. Further studies are needed to determine if differences in the prevalence of prostate inflammation may be due to host differences in genetics and/or lifestyle, which could in turn affect the prostate microenvironment (20). We previously reported geographic differences in the prevalence of prostate inflammation among Caucasian men, supporting a role for lifestyle on the prostate microenvironment (21). Moreover, studies are needed to test by race whether certain immune cell phenotypes are protective whereas others are protumor (22).

This subanalysis of the REDUCE study had key strengths: large samples of subjects, centrally and systematically read pathology, and data available on key confounding variables including age, PSA, prostate size, smoking status, BMI, DRE, prostate volume, and family history of prostate cancer. Although the REDUCE study was large, the number of Asian men was modest ($n = 105$), and therefore the analyses stratified by tumor aggressiveness included a small sample size. There is evidence that Asian men living in Western countries have a higher prostate cancer incidence than Asian men living in Asia (23). Although we did not see any evidence that our findings differed between Asians living outside Asia and Japanese living in Japan, our sample size was limited and may not be large enough to fully explore this research question. This study is also limited in that it included men previously biopsied, and of the prostate cancers detected during the course of follow-up, few were aggressive prostate cancers. Furthermore, no data were available for cancer localization in the prostate. Asian men are more likely to have cancer in the transition-zone of the prostate, compared with Caucasian men, which may be more likely to be missed at biopsy (24). As such, we cannot rule out a possibility of a greater number of missed cancers in Asian men contributing to our findings. However, although one autopsy study found that the prevalence of latent prostate cancer was not significantly different between Asian Japanese and Caucasian Russian men (25), a meta-analysis of autopsy studies concluded that prevalence of latent prostate cancer was lower in Asians versus Caucasians (26), suggesting that any potential differences in localization of tumors by race is unlikely to explain our findings. Moreover, no data on lifestyle and long-term outcomes were available. As noted, a key strength of this study is that prostate biopsies were performed largely independent of PSA. However, in REDUCE, all men were required to have had a negative 6 to 12 core biopsy within 6 months of enrollment as well as an elevated PSA; thus, results from this study may not apply to the general population. Despite this, the findings from our study may help to inform follow-up protocols in men with a negative prostate biopsy.

In summary, in REDUCE where all men underwent biopsies largely independent of PSA, Asian race was associated with lower PC diagnosis. These data suggest lower prostate cancer risk among Asian men may be due to biological, genetic, and/or lifestyle factors.

Disclosure of Potential Conflicts of Interest

R. Castro-Santamaria reports other from GlaxoSmithKline (GlaxoSmithKline sponsored the REDUCE study) during the conduct of the study and other from GlaxoSmithKline (employee) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

A.C. Vidal: Conceptualization, supervision, investigation, methodology, writing–original draft, writing–review and editing. **T. Oyekunle:** Formal analysis. **T. Feng:** Conceptualization and formal analysis. **A.R. Freedland:** Conceptualization and formal analysis. **D. Moreira:** Conceptualization and formal analysis. **R. Castro-Santamaria:** Resources, funding acquisition, writing–review and editing. **G.L. Andriole:** Writing–review and editing. **S.J. Freedland:** Conceptualization, resources, supervision, investigation, writing–review and editing. **E.H. Allott:** Methodology, writing–review and editing.

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