Research Article

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Geographic Differences in Baseline Prostate Inflammation and Relationship with Subsequent Prostate Cancer Risk: Results from the Multinational REDUCE Trial

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Abstract

Background: Prostate cancer incidence rates vary 25-fold worldwide. Differences in PSA screening are largely, but not entirely, responsible. We examined geographic differences in prevalence of histologic prostate inflammation and subsequent prostate cancer risk.

Methods: Seven thousand nonHispanic white men were enrolled in the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial from Europe ($n = 4{,}644$), North America ($n = 1{,}746$), South America ($n = 466$), and Australia/New Zealand ($n = 144$). Histologic inflammation in baseline negative prostate biopsies was classified as chronic (lymphocytes/macrophages) or acute (neutrophils). Multivariable logistic regression was used to examine associations between region and prostate inflammation, and between region and prostate cancer risk at 2-year biopsy.

Results: Prevalence of prostate inflammation varied across region, with broadly similar patterns for acute and chronic inflammation. Relative to Europe, prevalence of acute inflammation was higher in North America [odds ratio (OR), 1.77; 95% confidence interval (CI), 1.51–2.08] and Australia/New Zealand (OR, 2.07; 95% CI, 1.40–3.06). Men from these regions had lower prostate cancer risk than Europeans at biopsy. Among North Americans, prevalence of acute inflammation was higher in Canada versus the United States (OR, 1.40; 95% CI, 1.07–1.83), but prostate cancer risk did not differ between these regions. Among Europeans, prevalence of acute inflammation was lower in Northern and Eastern (OR, 0.79; 95% CI, 0.65–0.97 and OR 0.62; 95% CI, 0.45–0.87, respectively), relative to Western Europe, and these men had higher prostate cancer risk at biopsy.

Conclusions: Prevalence of histologic prostate inflammation varied by region. Geographic differences in prostate inflammation tracked inversely with geographic differences in prostate cancer risk.

Impact: Characterization of premalignant prostate biology and the relationship with subsequent prostate cancer risk could inform prostate cancer prevention efforts. *Cancer Epidemiol Biomarkers Prev; 27(7); 783–9. ©2018 AACR.*

Introduction

Prostate cancer incidence rates vary more than 25-fold worldwide and are highest in higher-resource countries (1). While much of this variation can be explained by differences in PSA screening, geographic variation in incidence rates was noted prior to the PSA screening era. Therefore, lifestyle factors associated with high-resource areas, including Westernized diet, physical inactivity, and obesity, may contribute to geographic variation in prostate cancer incidence rates (2). Identifying mechanisms contributing to geographic variation in incidence rates could inform prostate cancer prevention efforts.

Histologic evaluation of negative biopsies has revealed prostate inflammation in 60% to 80% of asymptomatic men undergoing a biopsy due to elevated PSA (3–6). Causes are not well understood, but a case–control study nested within the Prostate Cancer Prevention Trial (PCPT) reported that serum omega-3 and omega-6 fatty acid levels were associated with histologic prostate inflammation (3). Using data from the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial, we reported that current smokers were more likely to have histologic prostate inflammation than nonsmokers (7), while statin users were less likely to have histologic prostate inflammation than nonusers (8). Together, these studies suggest that lifestyle factors influence histologic prostate inflammation which, in turn, may affect prostate cancer risk (9).

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Herein, using data from the multinational REDUCE trial, we examined geographic differences in the prevalence of histologic inflammation in negative baseline prostate biopsies, and the relationship with prostate cancer risk at trial-mandated repeat biopsy. We hypothesized that the prevalence of histologic prostate inflammation would vary by geographic region. Further, given an etiologic role for inflammation in prostate cancer (9), we hypothesized that geographic differences in the prevalence of histologic prostate inflammation would be accompanied by geographic differences in prostate cancer risk.

Materials and Methods

Study population

REDUCE was a 4-year double-blind and placebo-controlled trial (10). Eligible men were 50 to 75 years of age, with a serum PSA of 2.5 to 10 ng/mL (if $\leq$60) or 3 to 10 ng/mL (if >60), and a single, negative biopsy (6–12 cores) within 6 months before enrollment (independent of trial). Baseline biopsies were centrally reviewed to confirm a negative prostate cancer diagnosis. Men were ineligible if they had more than one negative biopsy, a history of prostate cancer, high-grade prostatic intraepithelial neoplasia, atypical small acinar proliferation, a prostate volume >80 mL, had undergone previous prostate surgery, or had an International Prostate Symptom Score (IPSS) $\geq$25 or $\geq$20 while receiving α-blockers for treatment of benign prostatic hyperplasia. The REDUCE protocol was approved by the Institutional Review Boards at each site, and all participants provided written informed consent.

Data collection and variable definitions

At baseline, a detailed medical history was obtained including body mass index (BMI), smoking and alcohol use, medical comorbidities, and medication use. Prostate volume was measured by ultrasonography at the time of the baseline negative biopsy.

Histologic prostate inflammation was assessed by central review of baseline negative prostate biopsies stained with hematoxylin and eosin (H&E) by a single pathologist blinded to clinical data, using a standardized published method (11). Chronic histologic inflammation consisted mainly of lymphocytes and variable number of plasma cells and macrophages. Acute histologic inflammation consisted of neutrophils. Our primary analysis examined presence of any inflammation versus absence of inflammation, for chronic and acute inflammation separately. We also examined extent of chronic and acute inflammation across biopsy cores, categorized as none, moderate (>0%–<20%), and severe ($\geq$20% of biopsy cores), as previously described (8). In sensitivity analysis, we examined the extent of chronic and acute inflammation within individual biopsy cores, categorized as none, mild, moderate, and marked, as previously described (11).

Transrectal ultrasound (TRUS)-guided 10-core biopsies were performed at 2 years and 4 years after randomization using trial-specified protocols and were evaluated for prostate cancer by the central pathology facility.

Geographic region was categorized as Europe, North America, South America, and Australia/New Zealand. Europe was further subdivided into Western (France, Germany, Belgium, the Netherlands, Switzerland, and Austria), Northern (Ireland, the United Kingdom, Norway, Sweden, Finland, Denmark, Latvia, Lithuania, and Estonia), Southern (Italy, Spain, Portugal, Slovenia, Croatia, and Greece), and Eastern (Bulgaria, Belarus, Hungary, Poland, Romania, Russia, Slovakia, and Ukraine) regions, according the United Nations Statistics Division (http://unstats.un.org/unsd/methods/m49/m49regin.htm). North America was subdivided into the United States and Canada. Regions within South America (Argentina, Brazil, and Chile) contained too few participants for subdivision.

Statistical analysis

A total of 8,122 men were enrolled in the efficacy population of REDUCE. We excluded men with a baseline PSA outside the trial eligibility range ($n = 112$). Given that the prevalence of prostate inflammation varies by race/ethnicity (12, 13) and race/ethnicity varies by geographic region, we excluded nonwhite and Hispanic men ($n = 713$) to minimize this potential source of confounding. We also excluded men from Africa given the low number of white participants in this region ($n = 84$). Finally, we excluded men with missing data for covariates, including smoking ($n = 5$), BMI ($n = 109$), digital rectal exam (DRE) findings ($n = 9$), family history of prostate cancer ($n = 5$), and prostate volume ($n = 85$), resulting in $n = 7{,}000$ men in the present analysis.

Logistic regression was used to generate age-adjusted and multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) to examine geographic differences in the prevalence of acute and chronic histologic inflammation (presence vs. absence, for each type of inflammation separately) in baseline negative prostate biopsies. In secondary analysis, we used multinomial logistic regression to examine geographic differences in the prevalence of chronic inflammation only, acute inflammation only, and both types of inflammation, treating men with neither type of inflammation as the reference group. We also examined geographic differences in the extent of acute and chronic histologic inflammation (classified as <20% and $\geq$20% vs. 0% of cores, and as mild or moderate/marked vs. none, for each type of inflammation separately) using multinomial logistic regression. Multivariable models were adjusted for baseline characteristics, including age (continuous), BMI (continuous), statin use (no, yes), nonsteroidal anti-inflammatory drug (NSAID) use (no, yes), smoking status (never, former, current), family history of prostate cancer (no, yes), DRE findings (abnormal, normal/enlarged), prostate volume (grams; continuous), and PSA (ng/mL; continuous). We further adjusted for IPSS in sensitivity analysis, but this did not substantially change our results and so these findings are not presented. We did not adjust models for chronic prostatitis symptom index (CPSI) as this was previously shown to be unrelated to prostate inflammation in REDUCE (14). We stratified analyses of associations between geographic region and prostate inflammation by baseline PSA ($\geq$median vs. <median), smoking status (current vs. never/former), NSAID (yes vs. no), and statin use (yes vs. no) to test each of these factors as potential effect modifiers of the association between geographic region and prostate inflammation. We tested for interaction between each of these factors and geographic region in association with prostate inflammation by incorporating a cross product term into the logistic regression model, and testing its significance using the Wald test. We explored geographic differences in prostate inflammation at the 2-year biopsy using the same approach as described for baseline biopsies, with models additionally adjusted for treatment arm.

We also used logistic regression to examine differences in prostate cancer risk at trial-mandated 2-year repeat biopsy across

geographic regions. These multivariable models were adjusted for the aforementioned covariates in addition to treatment arm (placebo, dutasteride). In sensitivity analysis, we explored further adjusting prostate cancer risk models for acute and chronic histologic prostate inflammation, and we also performed analyses stratified by treatment arm. We also stratified analyses of associations between regions and prostate cancer risk by family history of prostate cancer (yes vs. no), obesity status (BMI $\geq$30 vs. <30 kg/m^2), NSAID, and statin use. We had a reduced sample size with which to examine geographic differences in prostate cancer risk at 4-year repeat biopsy and, given that findings were similar to those at 2-year repeat biopsy, they are not presented. We did not examine geographic differences in prostate cancer risk stratified by Gleason grade given low numbers of high-grade prostate cancers.

Statistical analysis was performed using Stata, version 13.0 (Stata Corp.).

Results

Baseline characteristics of REDUCE participants by geographic region

Of 7,000 men, Europeans formed the majority (66%), followed by North Americans (25%), South Americans (7%), and Australian/New Zealanders (2%). There were slight differences in age and PSA by region (Table 1). North Americans and Australian/New Zealanders were more likely to have an abnormal DRE than Europeans and South Americans (8% and 6% vs. 2% and 1%, respectively). Relative to other regions, North Americans were more likely to have a family history of prostate cancer (23% vs. 10% in Europe, 11% in South America, and 15% in Australia/New Zealand).

The prevalence of obesity, defined as BMI $\geq$30 kg/m^2, was highest in North America (28%), followed by Australia/New Zealand (24%), South America (20%), and Europe (18%; Table 1). Prevalence of diabetes was similar across geographic regions, affecting 6% to 9% of men. Alcohol use was highest in Australia/New Zealand and Europe, where 37% and 31% of men consumed at least 7 units per week, respectively. Smoking rates were relatively similar across regions, with 12% to 16% current smokers. Finally, NSAID and statin use was highest in North America (56% and 33%, respectively), relative to Europe (19% and 13%), South America (24% and 6%), and Australia/New Zealand (28% and 13%; Table 1).

Prevalence of acute and chronic prostate inflammation across geographic regions

Overall, 1,070 men (15%) had acute inflammation in their baseline negative prostate biopsy. Chronic inflammation was more prevalent, affecting 5,409 men (77%); 14% had both types of inflammation and 22% had neither type of inflammation. Less than 1% had acute inflammation only, while 63% had chronic inflammation only. We observed significant differences in the prevalence of acute and chronic inflammation across geographic regions in REDUCE (Table 2). We describe results for acute inflammation in detail, noting broadly similar patterns for chronic inflammation. Overall, geographic differences observed in age-adjusted analyses remained similar in multivariable analyses. Relative to Europe, North America and Australia/New

Table 1. Baseline demographic and prostate characteristics of REDUCE participants by geographic region

	Geographic region			
	Europe	**North America**	**South America**	**Australia/New Zealand**
Participants, n	4,644	1,746	466	144
Age, mean (SD)	63.3 (5.9)	61.5 (6.3)	62.9 (6.1)	62.0 (6.2)
Prostate volume, median (IQR)	32.6 (42.9–55.8)	33.8 (43.6–56.2)	35.5 (49.2–62.0)	34.6 (46.9–55.0)
PSA (ng/mL), median (IQR)	5.9 (4.6–7.5)	5.1 (4.0–6.6)	5.7 (4.3–7.2)	6.0 (4.8–7.4)
DRE findings, *n* (%)				
Normal/enlarged	4,548 (98)	1,610 (92)	461 (99)	135 (94)
Abnormal	96 (2)	136 (8)	5 (1)	9 (6)
Family history of prostate cancer, *n* (%)				
No	4,200 (90)	1,348 (77)	416 (89)	123 (85)
Yes	444 (10)	398 (23)	50 (11)	21 (15)
BMI, *n* (%)				
Normal	1,321 (28)	334 (19)	128 (27)	43 (30)
Overweight	2,507 (54)	928 (53)	247 (53)	66 (46)
Obese	816 (18)	484 (28)	91 (20)	35 (24)
Diabetes, *n* (%)				
No	4,283 (92)	1,593 (91)	431 (92)	136 (94)
Yes	361 (8)	153 (9)	35 (8)	8 (6)
Alcohol intake (units/week)[a], *n* (%)				
None	974 (21)	560 (32)	146 (31)	12 (8)
$\leq$7	2,236 (48)	872 (50)	205 (44)	79 (55)
>7	1,419 (31)	306 (18)	113 (24)	53 (37)
Smoking status, *n* (%)				
Never	2,223 (48)	716 (41)	182 (39)	64 (44)
Former	1,670 (36)	816 (47)	216 (46)	62 (43)
Current	751 (16)	214 (12)	68 (15)	18 (13)
NSAID use, *n* (%)				
No	3,760 (81)	769 (44)	355 (76)	103 (72)
Yes	884 (19)	977 (56)	111 (24)	41 (28)
Statin use, *n* (%)				
No	4,018 (87)	1,162 (67)	440 (94)	125 (87)
Yes	626 (13)	584 (33)	26 (6)	19 (13)

[a]Alcohol intake missing for $n = 25$ men.

Table 2. Geographic differences in the presence of acute and chronic prostate inflammation in REDUCE

	Acute prostate inflammation				Chronic prostate inflammation			
	None *N* (%)	Any *N* (%)	OR[a] (95% CI)	OR[b] (95% CI)	None *N* (%)	Any *N* (%)	OR[a] (95% CI)	OR[b] (95% CI)
Overall	5,930 (85)	1,070 (15)			1,591 (23)	5,409 (77)		
Global region								
Europe	4,012 (86)	632 (14)	1 (ref)	1 (ref)	1,145 (25)	3,499 (75)	1 (ref)	1 (ref)
North America	1,372 (79)	374 (21)	1.69 (1.46–1.95)	1.77 (1.51–2.08)	324 (19)	1,422 (81)	1.50 (1.30–1.72)	1.55 (1.33–1.81)
South America	437 (94)	29 (6)	0.42 (0.29–0.62)	0.42 (0.29–0.62)	100 (21)	366 (79)	1.21 (0.96–1.52)	1.15 (0.91–1.45)
Australia/NZ	109 (76)	35 (24)	2.00 (1.36–2.96)	2.07 (1.40–3.06)	22 (15)	122 (85)	1.87 (1.18–2.96)	1.89 (1.19–3.00)
North American region								
United States	1,048 (80)	264 (20)	1 (ref)	1 (ref)	256 (20)	1,056 (80)	1 (ref)	1 (ref)
Canada	324 (75)	110 (25)	1.36 (1.05–1.76)	1.40 (1.07–1.83)	68 (16)	366 (84)	1.28 (0.96–1.72)	1.30 (0.96–1.77)
European region								
Western	1,430 (85)	261 (15)	1 (ref)	1 (ref)	390 (23)	1,301 (77)	1 (ref)	1 (ref)
Northern	1,378 (87)	208 (13)	0.81 (0.66–0.98)	0.79 (0.65–0.97)	404 (25)	1,182 (75)	0.91 (0.77–1.06)	0.90 (0.77–1.06)
Southern	710 (87)	110 (13)	0.84 (0.66–1.07)	0.84 (0.66–1.07)	226 (28)	594 (72)	0.80 (0.66–0.96)	0.77 (0.63–0.93)
Eastern	421 (90)	47 (10)	0.63 (0.45–0.87)	0.62 (0.45–0.87)	106 (27)	362 (77)	0.99 (0.78–1.27)	0.96 (0.75–1.22)

Abbreviation: NZ, New Zealand.
[a]Adjusted for age.
[b]Adjusted for age, BMI, statin use, NSAID use, smoking status, family history of prostate cancer, DRE findings, prostate volume, PSA level.

Zealand had higher prevalence of acute inflammation while South America had lower prevalence. We observed similar, albeit slightly attenuated, results for chronic inflammation, with the exception of South America where the prevalence of chronic inflammation was higher than Europe. Results were similar when men with acute inflammation were omitted from analyses of chronic inflammation, and vice versa, although estimates for acute inflammation in the absence of chronic inflammation were imprecise due to small numbers (Supplementary Table S1). We also observed differences in the prevalence of prostate inflammation within North American and European regions, although these were not as pronounced as differences between these regions. Relative to the United States, the prevalence of acute inflammation was higher in Canada; this difference was similar in magnitude and direction for chronic inflammation, though not statistically significant. Relative to Western Europe, the prevalence of acute inflammation was lower in Northern and Eastern Europe, while the prevalence of chronic inflammation was lower in Southern Europe (Table 2). Geographic differences in extent of inflammation were similar to geographic differences in the presence of inflammation, with no strong suggestion of a dose–response relationship (Supplementary Table S2). Geographic patterns of acute and chronic prostate inflammation within global, North American, and European regions were similar within strata defined by median baseline PSA (all P interactions ≥ 0.43), smoking status (all P interactions ≥ 0.07), NSAID (all P interactions ≥ 0.24) and statin use (all P interactions > 0.30). The only interaction that approached statistical significance was for smoking and chronic inflammation in association with region within Europe (P interaction $= 0.07$). Among men who received the 2-year biopsy, geographic differences in the prevalence of inflammation at the 2-year biopsy were similar to those at baseline, albeit with attenuated differences between Europe and North America, and between Western and Eastern Europe (Supplementary Table S3).

Geographic differences in prostate cancer risk

Overall, 833 men (15%) were diagnosed with prostate cancer at the 2-year biopsy. Prior findings from REDUCE showed that acute and chronic histologic inflammation in a negative baseline prostate biopsy were inversely associated with prostate cancer risk upon subsequent biopsy (11). Herein, our distinct yet complementary analysis tested geographic differences in risk of prostate cancer diagnosis in REDUCE. As summarized in Fig. 1, we found that regions with higher prevalence of inflammation had lower risk of prostate cancer and vice versa. Specifically, North Americans and Australian/New Zealanders had higher prevalence of inflammation (Table 2) but lower prostate cancer risk than Europeans (OR, 0.43; 95% CI, 0.23–0.91; Table 3). Within Europe, Northern and Eastern regions had lower prevalence of prostate inflammation (Table 2) but higher prostate cancer risk than Western Europe (OR, 1.29; 95% CI, 1.04–1.61 and OR, 1.78; 95% CI, 1.32–2.40, respectively). There were no differences in prostate cancer risk between Southern and Western Europeans, or between men from Canada and the United States (Table 3). Geographic differences in prostate cancer risk were similar in placebo and dutasteride arms (Supplementary Table S4). Geographic differences in prostate cancer risk within global, North American, and European regions were similar within strata defined by family history of prostate cancer (all P interactions ≥ 0.43), obesity status (all P interactions ≥ 0.12), NSAID (all P interactions ≥ 0.44), and statin use (all P interactions ≥ 0.27). Adjusting our models for chronic and acute inflammation produced similar results (Supplementary Table S5).

Discussion

Geographic differences in prostate cancer screening drive much of the international variation in prostate cancer incidence rates, but differences in lifestyle factors across geographic regions may also contribute (1). Using data from 7,000 men in the multinational REDUCE trial, we report geographic differences in the prevalence of acute and chronic histologic inflammation in negative prostate biopsies. Moreover, we found that geographic variation in the prevalence of prostate inflammation in REDUCE tracked inversely with geographic differences in prostate cancer risk upon subsequent biopsy. Despite some conflicting data regarding the association between histologic prostate inflammation and prostate cancer risk, given an etiologic role for inflammation in prostate cancer (9), further study is required to determine whether prostate inflammation could contribute to international variation in prostate cancer incidence rates.

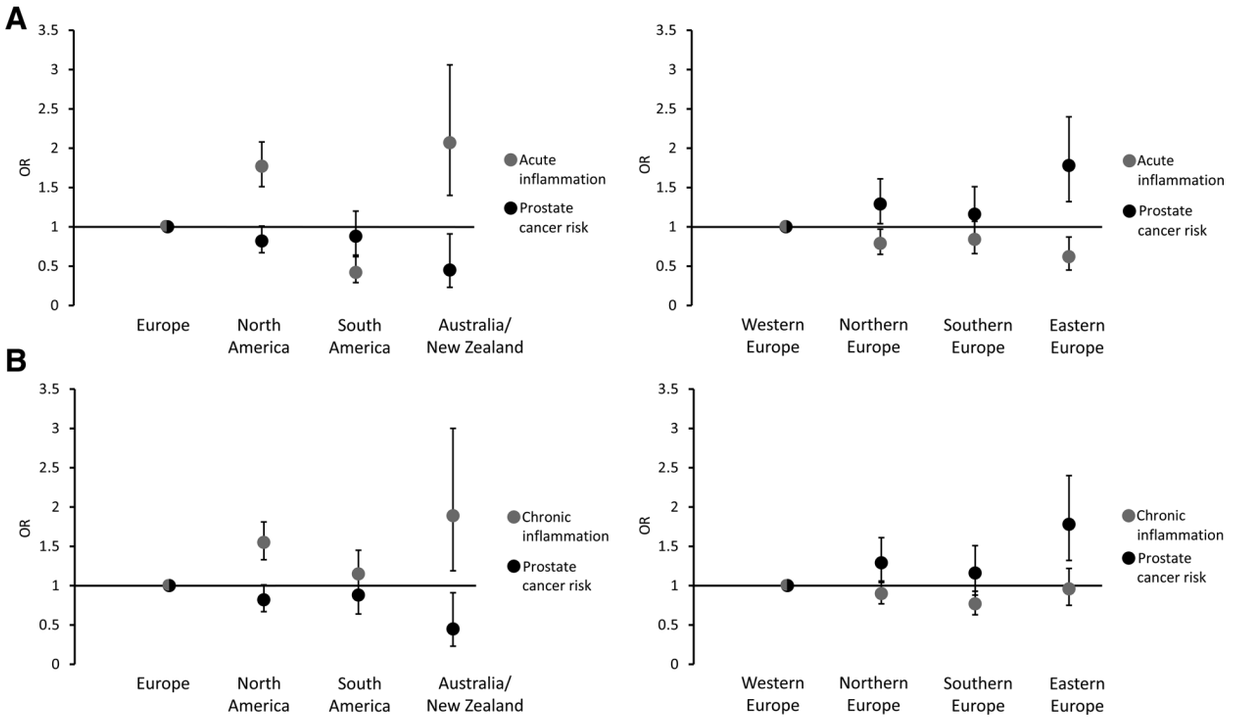

Figure 1.
Summary of geographic differences in the prevalence of (**A**) acute histologic prostate inflammation (gray circles) (**B**) chronic histologic prostate inflammation (gray circles) and geographic differences in prostate cancer risk at repeat biopsy (black circles). Men from geographic regions with a higher prevalence of inflammation had lower prostate cancer risk, and vice versa.

Histologic chronic and/or acute inflammation of benign prostate tissue is common, found in 60% to 80% of men undergoing prostate biopsy (11). An autopsy study found a similar prevalence of histologic prostate inflammation in Asians and Caucasians (15), but other studies reported racial differences in prevalence of histologic prostate inflammation (12, 13). Gene expression profiling revealed upregulation of inflammatory signaling pathways in resected tumors from African Americans versus European Americans (16, 17), suggesting that the prevalence of prostate inflammation differs across distinct populations in the United States. In limiting our analysis to nonHispanic white men, this study is the first, to our knowledge, to report geographic differences in the prevalence of prostate inflammation independent of race. Causes of histologic prostate inflammation are not well understood, but may include exposure to infectious agents, urinary reflux and physical trauma (9). We and others also reported that lifestyle factors, including smoking, serum fatty acid levels and statin use, influence both acute and chronic histologic prostate inflammation (3, 7, 8). Lifestyle factors such as these, which influence prostate inflammation and which differ by

Table 3. Geographic differences in risk of prostate cancer at 2-year repeat biopsy in REDUCE

	Negative[a]	Positive[a]		
	N	*N* (%)	OR[b] (95% CI)	OR[c] (95% CI)
Overall	4,820 (85)	833 (15)		
Global region				
Europe	3,174 (84)	597 (16)	1 (ref)	1 (ref)
North America	1,192 (87)	176 (13)	0.84 (0.70–1.01)	0.82 (0.67–1.01)
South America	344 (87)	51 (13)	0.80 (0.59–1.09)	0.88 (0.64–1.20)
Australia/New Zealand	110 (92)	9 (8)	0.46 (0.23–0.90)	0.45 (0.23–0.91)
North American region				
United States	873 (87)	127 (13)	1 (ref)	1 (ref)
Canada	319 (87)	49 (13)	1.02 (0.71–1.46)	1.06 (0.72–1.54)
European region				
Western	1,186 (86)	193 (14)	1 (ref)	1 (ref)
Northern	1,095 (83)	220 (17)	1.30 (1.05–1.61)	1.29 (1.04–1.61)
Southern	553 (85)	100 (15)	1.13 (0.87–1.47)	1.16 (0.88–1.51)
Eastern	283 (78)	81 (22)	1.66 (1.24–2.23)	1.78 (1.32–2.40)

[a]"Negative" and "Positive" refer to prostate cancer status based on 2-year biopsy results.
[b]Adjusted for age.
[c]Adjusted for age, BMI, statin use, NSAID use, smoking status, family history of prostate cancer, DRE findings, prostate volume, PSA level, treatment arm.

geographic region, may contribute to geographic variation in the prevalence of histologic prostate inflammation. Given a role for prostate inflammation in benign prostate disease (15, 18) and prostate cancer (9), identifying modifiable causes of prostate inflammation could inform prevention efforts for both these prostate conditions.

Though inflammation is proposed to play an etiologic role in prostate cancer (9), epidemiologic studies examining associations between histologic prostate inflammation and prostate cancer risk have reported mixed findings. A nested case–control study within the PCPT showed that histologic inflammation of benign prostate tissue was positively associated with concomitant high-grade prostate cancer (19), and similar results were seen in another small US biopsy study (20). A prospective analysis of PCPT participants who were subsequently enrolled in the SELECT trial also showed that the presence of prostate inflammation in benign biopsy tissue was positively associated with prostate cancer diagnosis on subsequent biopsy (21). By contrast, results from REDUCE showed an inverse association between histologic inflammation in a negative prostate biopsy and prostate cancer risk upon subsequent PSA-independent biopsy (11). A number of other epidemiologic studies also reported inverse associations between histologic inflammation in negative prostate biopsies and subsequent prostate cancer risk (4, 6, 22, 23). In patients with a negative biopsy performed due to elevated PSA, either undetected cancer or subclinical prostatitis (if histologic evidence of inflammation is present) may serve as plausible explanations for the high PSA. Thus, men with an elevated PSA caused by inflammation may be at lower risk for prostate cancer detection upon rebiopsy, versus their counterparts with elevated PSA caused by occult prostate cancer. Alternatively, immune cell infiltration may provide an immune surveillance function, thereby lowering the risk of prostate cancer. These competing mechanisms are challenging to tease apart as histologic assessment does not reveal the type of immune cell nor the activation state (e.g. $CD4^+$ vs. $CD8^+$ T cell). Going forward, molecular assessment of inflammation using gene expression or immunohistochemistry analyses will be required to appropriately classify this complex biologic pathway which can exert protumor and antitumor effects (9). Integrating molecular and histologic assessment of inflammation could shed light on the role of inflammation in prostate cancer and inform follow-up biopsy strategies in men with histologic inflammation in a prostate biopsy that was negative for cancer. Regardless of the reason for the inverse association between prostate inflammation and prostate cancer risk in REDUCE, our data show that geographic differences in the prevalence of histologic inflammation track inversely with geographic differences in prostate cancer risk. If confirmed, our findings could guide future studies to integrate molecular data in the context of multinational cohorts to understand mechanistic drivers of risk factor associations. These future efforts should focus on the identification of molecular biomarkers to inform prostate cancer prevention efforts and clinical decision-making.

Our study had strengths and weaknesses. First, although repeat biopsies in REDUCE were conducted independent of PSA, the baseline prostate biopsies, in which we assessed inflammation, were largely performed due to elevated PSA. However, any selection bias introduced by the trial design would affect all REDUCE sites, and therefore should not affect our ability to detect differences in prevalence of inflammation and in prostate cancer risk across sites. Indeed, common trial eligibility criteria across REDUCE sites minimized the contribution of regional differences in clinical characteristics to regional differences in the prevalence of prostate inflammation. Second, REDUCE recruited men with an elevated PSA but had various exclusion criteria that, while increasing the homogeneity of the sample, may limit the generalizability of our results. Thus, our results from REDUCE may not be generalizable to the general population in these geographic regions. As such, rather than comparing absolute region-specific prostate cancer incidence rates, our data highlight the relationship between patterns of histologic prostate inflammation and prostate cancer risk across geographic regions. Third, we were unable to examine within-country or urban–rural differences, as country-level data were the smallest unit of geographic data available in REDUCE. Finally, we did not have access to data regarding the prostate zone sampled and were therefore unable to assess the effect of prostate zone on patterns of histologic inflammation across different geographic regions. Study strengths include the large, multinational population in REDUCE, and central pathology review of all biopsy tissues. Moreover, we adjusted our analysis for lifestyle factors that vary by region and that may affect inflammation, including smoking, obesity, NSAID, and statin use, thereby reducing this potential source of confounding, though we lacked information on other lifestyle factors such as diet and exercise, as well as other factors potentially related to prostate inflammation such as sexually transmitted diseases. Finally, an additional strength was that histologic inflammation was centrally reviewed by a single pathologist in biopsies negative for prostate cancer, whereas prior studies evaluated inflammation in benign regions of the prostate adjacent to tumor (19, 22). Although some men may have had prostate cancer that was missed in the baseline biopsy, the REDUCE study design enables us to determine the effect of histologic prostate inflammation on prostate cancer risk while limiting the effect of inflammation as a response to the tumor.

In conclusion, a critical barrier to developing new approaches for cancer prevention is the lack of understanding of mechanisms driving tumor initiation and development (24). Leveraging data from REDUCE, a multinational chemoprevention trial in men at high risk of prostate cancer, our findings highlight geographic differences in the prevalence of histologic inflammation in negative prostate biopsies. Moreover, we find that patterns of histologic inflammation track inversely with prostate cancer risk on subsequent biopsy in REDUCE. Characterization of premalignant prostate histology and the relationship with subsequent prostate cancer risk will improve methods for risk stratification and could inform prostate cancer prevention efforts.

Disclosure of Potential Conflicts of Interest

G.L. Andriole reports receiving commercial research support from Blue Earth Diagnostics, Medivation, and Progenics and is a consultant/advisory board member for 3D Biopsy, Augmenix, and Tolmar Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

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Conception and design: E.H. Allott, G.L. Andriole, S.J. Freedland
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