Calcium, magnesium, and whole-milk intakes and high-aggressive prostate cancer in the North Carolina–Louisiana Prostate Cancer Project (PCaP)

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ABSTRACT

Background: Calcium and dairy product intakes have been positively associated with prostate cancer risk. An imbalance in concentrations of calcium and magnesium has been associated with multiple chronic diseases, although few studies have examined the relation with prostate cancer aggressiveness.

Objective: The goal of this study was to examine the association between dietary intakes of calcium and magnesium, the calcium-to-magnesium ratio (Ca:Mg), and dairy products and prostate cancer aggressiveness.

Design: Dietary intake was assessed with the use of an interviewer-administered modified National Cancer Institute Diet History Questionnaire in 996 African American and 1064 European American men with a recent histologically confirmed diagnosis of prostate cancer from the North Carolina–Louisiana Prostate Cancer Project (PCaP). High-aggressive disease was defined as Gleason sum $\geq$8, or prostate-specific antigen (PSA) $>$20 ng/mL, or Gleason score $\geq$7 and clinical stage T3–T4. The comparison group was all other prostate cancer cases. Logistic regression was used to determine the adjusted ORs and 95% CIs for high-aggressive prostate cancer by tertile of diet and supplement exposures.

Results: There was a positive association across tertiles of dietary Ca:Mg intake, with odds of high-aggressive prostate cancer in the upper tertiles as follows—OR for tertile 2 compared with tertile 1: 1.38 (95% CI: 1.01, 1.88); OR for tertile 3 compared with tertile 1: 1.46 (95% CI: 1.06, 2.02). When stratified by race, the positive association was more pronounced in African American men (OR for tertile 3 compared with tertile 2: 1.62; 95% CI: 1.04, 2.53). Men who reported the highest daily consumption of whole-fat milk had a 74% increased odds of high-aggressive prostate cancer compared with non–whole-fat milk drinkers, which was attenuated after adjustment for potential mediating factors, such as saturated fat and Ca:Mg intake.

Conclusions: Among both African American and European American men diagnosed with prostate cancer, a higher Ca:Mg and whole-milk intake were associated with higher odds of high-aggressive prostate cancer. This study was registered at www.clinicaltrials.gov as NCT03289130. *Am J Clin Nutr* 2018;107:799–807.

Keywords: calcium, magnesium, dairy products, prostate cancer, racial disparities

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer mortality among American men (1). Prostate cancer risk factors include age, family history of the disease, and race/ethnicity. African American men have the highest rate of prostate cancer mortality in the world.

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PCaP data collection tools can be accessed at: https://pcap.bioinf.unc.edu/.

Supplemental Figure 1 and Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: Ca:Mg, ratio of calcium to magnesium; DHQ, Diet History Questionnaire; PCaP, North Carolina–Louisiana Prostate Cancer Project; PSA, prostate-specific antigen.

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This marked racial disparity may be the result of differences in access to and attitudes about screening and treatment, circulating androgens, genetics, environmental factors, socioeconomic factors, or diet, or a combination of these factors (2).

Calcium intake has been positively associated with a diagnosis of prostate cancer (3, 4), including a higher risk of more aggressive forms of prostate cancer (5–11), as well as localized or less aggressive disease (10, 12). A hypothesized mechanism for calcium's effect on prostate cancer is the suppression of 1,25-dihydroxyvitamin D, the biologically active form of vitamin D. Our group previously reported that calcium intake modified the association between plasma 25-hydroxyvitamin D concentrations and prostate cancer in the North Carolina–Louisiana Prostate Cancer Project (PCaP), from which the current study originates (13). The evidence related to dairy products and prostate cancer risk is less consistent, with some showing a nonsignificant inverse association with prostate cancer incidence (14–16) and others reporting significant increased risks of prostate cancer for the highest intakes of total dairy products (17, 18). The saturated fat content of dairy products has been suggested to be a possible explanatory factor in the positive associations. Higher odds of aggressive prostate cancer were associated with higher saturated fat intake in PCaP (19). However, few studies have examined associations between dairy products and prostate cancer aggressiveness while accounting for fat content.

Magnesium, the second-most abundant cation in the body, has been shown to regulate glucose metabolism, inflammation, and cell proliferation (20). When ingested, magnesium and calcium compete for absorption in the intestinal intraepithelial and reabsorption in the kidneys. Their concentrations in the body are regulated through a negative feedback mechanism (21), such that low concentrations of either could enhance the effects of the other. Dietary calcium and magnesium intakes have increased over the past decade, with a >2-fold increase observed in calcium intake (21). However, approximately half of the US population still consume less than the recommended daily requirement for magnesium (22). The ratio of calcium to magnesium (Ca:Mg) may be more strongly associated with disease risk than either mineral alone, although there are limited data in relation to prostate cancer in diverse populations (21, 23).

The current study examined the relation between intakes of calcium and magnesium and Ca:Mg and prostate cancer aggressiveness and investigated whether these relations differed by race. Furthermore, the relations between dairy product intakes, including whole-fat milk and non–whole-fat milk consumption, and prostate cancer aggressiveness were examined.

METHODS

Study population

The study used data from the PCaP, a population-based, case-only study designed to address racial differences in prostate cancer aggressiveness (24). Residents of the North Carolina and Louisiana study areas with a first diagnosis of histologically confirmed adenocarcinoma of the prostate were eligible to participate if they were 40–79 y old at diagnosis, could complete the study interview in English, did not live in an institution (nursing home), and were physically and mentally able to complete the study interview. Men self-identified as black/African American or white/Caucasian (European American) in response to the open-ended interview question on race (24). Patients eligible in North Carolina were identified by the Rapid Case Ascertainment Core Facility, a collaborative effort of the University of North Carolina–Lineberger Comprehensive Cancer Center and the North Carolina Central Cancer Registry. Patients eligible in Louisiana were identified by the Louisiana Tumor Registry in the School of Public Health at the Louisiana State University Health Sciences Center. Informed consent was obtained from all research participants. Research protocols were approved by the institutional review boards at the University of North Carolina, Louisiana State University Health Services Center, and the Department of Defense Prostate Cancer Research Program. The current analysis also was approved by the University of South Carolina Institutional Review Board as exempt. The study was registered at www.clinicaltrials.gov as NCT03289130.

Data collection

Research participants were visited in their home or other location of their choice by a trained registered nurse. The majority of visits were completed within 14 wk of diagnosis. Participants were asked to fast for 6 h before the study visit, which was scheduled in the morning whenever possible, and to gather all medications and supplements used in the 2 wk before the visit. The visit began by explaining the study and obtaining HIPAA (Health Insurance Portability and Accountability Act of 1996) authorization and formal written informed consent, after which biological samples and anthropometric measurements were collected and questionnaires administered. The structured questionnaires solicited information with regard to the following: background characteristics, occupation, family history, health status, health care, prostate cancer diagnosis and screening history, medication use, nonsteroidal anti-inflammatory drug use, and vitamin and supplement use. The 144-item Diet History Questionnaire (DHQ), developed by the National Cancer Institute, was modified by PCaP investigators to include Southern foods and interviewer-administered to research participants to ascertain intake frequency and usual portion sizes. Research participants were asked to recall their usual diet for the year before diagnosis. Questionnaire responses were linked to the updated DHQ Nutrient Database through the National Cancer Institute–developed Diet*Calc software to calculate average daily intakes of dietary calcium, magnesium, and other nutrients. Information on dietary supplement use, including multivitamins and single calcium and magnesium supplements, in the year before diagnosis was collected with the use of a validated questionnaire (25).

Medical records were requested from the diagnosing physician of consenting research participants. Trained staff abstracted information concerning prostate cancer diagnosis and treatment.

Outcome assessment

Information obtained from medical record abstraction was used to classify cases into 3 aggressiveness categories on the basis of clinical grade, clinical stage, and prostate-specific antigen (PSA) at diagnosis. High-aggressive cases had a Gleason score ≥8, a PSA >20 ng/mL, or a Gleason score ≥7 and clinical stage T3–T4. Low-aggressive cases had a Gleason score

<7 and were diagnosed at clinical stage T1–T2 and had a PSA <10 ng/mL at diagnosis. All other cases were considered intermediate aggressive. For the purpose of this study, cases were categorized as high-aggressive cases or low-intermediate-aggressive cases (comparison group).

Exposure assessment

Calcium, magnesium, and dairy products (milk, cheese, yogurt, and total dairy) served as the main exposures. Ca:Mg intakes were obtained by dividing calcium intake by magnesium intake. Three exposure variables were created for calcium, magnesium, and Ca:Mg: dietary, supplemental, and total (sum of dietary and supplemental intakes) intakes, which were categorized into tertiles by using cutoffs based on distributions among research participants in the comparison group. Average daily intakes of milk, cheese, yogurt, and total dairy were calculated with the use of the information on frequency of intakes and portion sizes obtained from the DHQ responses, and cutoffs for categorical variables were determined on the basis of the distributions among research participants with low-intermediate-aggressive prostate cancer. Research participants were asked on the DHQ what type of milk (whole; 2% fat; 1% fat; skim, nonfat, or 0.5% fat; soy; rice; or other) they usually consumed. Categories for whole-fat milk and non–whole-fat milk drinkers were created, and whole-fat milk drinkers were categorized further into 3 levels of intake on the basis of daily servings consumed. Non–whole-fat milk drinkers included research participants who reported either no milk consumption or who reported usually consuming any other milk besides whole-fat milk.

Statistical methods

PCaP enrolled a total of 2258 research participants. Participants were excluded for the following reasons: missing information on prostate cancer aggressiveness, energy intake <500 kcal/d or >6000 kcal/d, missing education or BMI data, or BMI (in kg/m^2) <18.5 (underweight; see research subject flow chart in **Supplemental Figure 1**). The final sample size was 2060 participants of whom 359 were high-aggressive and 1701 were low-intermediate-aggressive cases. Descriptive statistics were calculated as means ± SDs for continuous variables, and frequencies and percentages for categorical variables. Multivariable logistic regression was used to study the relations between each exposure and prostate cancer aggressiveness. A minimally adjusted model controlling only for age and energy intake was examined. Other covariates were selected with the use of the ≥10% change-in-estimate criterion that compares a model with and without the potential confounder (26) and also were identified through literature review on potential confounders and risk factors. A second multivariable model included age (continuous), energy intake (continuous), BMI [weight (kg)/height (m^2), categorized as normal (18.5–24.9), overweight (25.0–29.9), obese (30–39.9), or extremely obese (>40)], smoking status (nonsmoker, former smoker, or current smoker), previous screening (none, digital rectal exam only, PSA only, or PSA and digital rectal exam), study site (University of North Carolina or Louisiana State University), education (less than eighth grade or some high school, high school graduate or vocational/technical school, some college or college graduate, or some graduate training or graduate or professional degree), income (11 categories), and Charlson comorbidity index (0, 1–3, or ≥4). A third multivariable model (identified as the fully adjusted model) also included other dietary variables: alcohol intake (grams per day), lycopene intake (micrograms per day from both diet and supplements), and saturated fat intake (grams per day). The Ca:Mg intake was included in a fourth model in the whole-fat milk analyses to examine the potential mediating effects of this dietary factor. Results are presented for the entire study population and stratified by race. In the race-stratified analyses, race-specific cutoffs for exposure variables were determined by using the distribution among the low-intermediate-aggressive cases for each race.

Analyses were conducted with the use of SAS version 9.4 (SAS Institute), and significance was set at $\alpha = 0.05$.

RESULTS

Research participants with high-aggressive prostate cancer were more likely to be African American, past or current smokers, and older and have a higher BMI, lower educational attainment, fewer prostate cancer screenings, and higher daily total energy, saturated fat, and alcohol intakes than participants with low-intermediate-aggressive prostate cancer (**Table 1**). Calcium and magnesium intakes were higher in European Americans than in African Americans. Research participants with high-aggressive prostate cancer had higher average daily intakes of dietary, supplemental, and total calcium and milk and total dairy and a higher Ca:Mg than low-intermediate-aggressive cases (**Supplemental Table 1**).

There were no associations between calcium intake, either from food alone or supplements, and prostate cancer aggressiveness (**Table 2**). Higher dietary intakes of magnesium were associated with reduced odds of aggressive prostate cancer in the highest tertile (OR for tertile 3 compared with tertile 1: 0.60; 95% CI: 0.39, 0.94) for all research participants combined, although the association was attenuated with further adjustment for other dietary variables (OR for tertile 3 compared with tertile 1: 0.71; 95% CI: 0.45, 1.12) (**Table 3**).

In the fully adjusted model, higher dietary and total Ca:Mgs were significantly associated with increased odds of high aggressive prostate cancer (dietary—OR for tertile 2 compared with tertile 1: 1.38; 95% CI: 1.01, 1.88; OR for tertile 3 compared with tertile 1: 1.46; 95% CI: 1.06, 2.02; and total intake—OR for tertile 2 compared with tertile 1: 1.63; 95% CI: 1.19, 2.24; OR for tertile 3 compared with tertile 1: 1.65; 95% CI: 1.19, 2.28) (**Table 4**). When stratified by race, associations for total (diet+supplement) Ca:Mg intake were more pronounced for African Americans (OR for tertile 3 compared with tertile 1: 1.80; 95% CI: 1.16, 2.80) than for European Americans (OR for tertile 3 compared with tertile 1: 1.35; 95% CI: 0.84, 2.17).

In the fully adjusted models, no significant relations were detected between intakes of milk, cheese, yogurt, or total dairy and prostate cancer aggressiveness (**Supplemental Table 2**). In the analysis of prostate cancer aggressiveness among whole-fat milk and non–whole-fat milk drinkers, research participants who reported consuming ≥1.25 servings of whole-fat milk/d had a 74% increased odds of high-aggressive prostate cancer when compared with non–whole-fat milk drinkers (OR: 1.74; 95% CI: 1.16, 2.62) (**Table 5**). The association was attenuated (OR: 1.37; 95% CI: 0.89, 2.11) after further adjustment for other dietary variables

TABLE 1
Distribution of demographic and lifestyle factors by prostate cancer aggressiveness and by race in the PCaP[1]

	Low-intermediate aggressive ($n = 1701$)		High aggressive ($n = 359$)	
Characteristics	AA ($n = 798$)	EA ($n = 903$)	AA ($n = 198$)	EA ($n = 161$)
Age, y	62 ± 8[2]	64 ± 8	63 ± 8	67 ± 8
Total energy intake, kcal/d	2588 ± 1144	2320 ± 867	2827 ± 1211	2346 ± 959
Total lycopene intake, μg/d	5669 ± 7725	6938 ± 8163	5611 ± 8433	5941 ± 5310
Saturated fat intake, g/d	29 ± 16	29 ± 14	33 ± 17	31 ± 15
Alcohol intake, g/d	16 ± 38	13 ± 26	18 ± 46	16 ± 30
Income, *n* (%)				
Missing/don't know	69 (9)	77 (9)	25 (13)	15 (9)
<$5000	29 (4)	3 (0.3)	11 (6)	3 (2)
$5001–$10,000	60 (8)	17 (2)	32 (16)	5 (3)
$10,001–$20,000	133 (17)	53 (6)	34 (17)	15 (9)
$20,001–$30,000	100 (12)	88 (10)	35 (18)	16 (10)
$30,001–$40,000	106 (13)	91 (10)	15 (8)	17 (11)
$40,001–$50,000	79 (10)	70 (8)	12 (6)	11 (7)
$50,001–$60,000	53 (7)	83 (9)	8 (4)	12 (7)
$60,001–$70,000	39 (5)	63 (7)	4 (2)	14 (9)
$70,001–$80,000	31 (4)	60 (7)	8 (4)	6 (4)
>$80,000	99 (12)	298 (33)	14 (7)	47 (29)
BMI (kg/m^2), *n* (%)				
Normal (18.5–24.9)	160 (20)	151 (17)	39 (20)	20 (12)
Overweight (25–29.9)	325 (41)	425 (47)	75 (38)	64 (40)
Obese (30–39.9)	281 (35)	300 (33)	66 (33)	69 (43)
Extremely obese (≥40)	32 (4)	27 (3)	18 (9)	8 (5)
Study site, *n* (%)				
UNC	380 (48)	440 (49)	86 (43)	72 (45)
LSU	418 (52)	463 (51)	112 (57)	89 (55)
Education, *n* (%)				
Less than eighth grade or some high school	237 (30)	77 (9)	80 (41)	26 (16)
High school graduate or vocational/technical school	270 (34)	257 (28)	62 (31)	36 (22)
Some college or college graduate	232 (29)	372 (41)	50 (25)	70 (44)
Some graduate school or graduate/professional degree	59 (7)	197 (22)	6 (3)	29 (18)
Screening history, *n* (%)				
None/missing/don't know	126 (16)	56 (6)	62 (31)	19 (12)
DRE only	168 (21)	88 (10)	49 (25)	19 (12)
PSA only	27 (3)	36 (4)	9 (5)	10 (6)
PSA and DRE	477 (60)	723 (80)	78 (39)	113 (70)
Smoking status, *n* (%)				
Missing/nonsmoker	269 (34)	330 (36)	39 (20)	58 (36)
Past smoker	384 (48)	494 (55)	102 (51)	86 (53)
Current smoker	145 (18)	79 (9)	57 (29)	17 (11)
Charlson comorbidity index, *n* (%)				
0	375 (47)	491 (54)	86 (43)	79 (49)
1–3	367 (46)	361 (40)	97 (49)	69 (43)
≥4	56 (7)	51 (6)	15 (8)	13 (8)

[1]Prostate cancer aggressiveness was defined by a combination of Gleason score, clinical stage, and PSA concentration at diagnosis and classified as follows—high aggressive: Gleason score ≥8, PSA >20 ng/mL or Gleason score ≥7 and clinical stage T3–T4; low-intermediate aggressive: all other cases. AA, African American; DRE, digital rectal exam; EA, European American; LSU, Louisiana State University; PCaP, North Carolina–Louisiana Prostate Cancer Project; PSA, prostate-specific antigen; UNC, University of North Carolina.

[2]Mean ± SD (all such values).

that may mediate the association, such as saturated fat and the Ca:Mg intake.

DISCUSSION

In this population-based study of determinants of racial differences in aggressive prostate cancer, the dietary intake Ca:Mg was positively associated with aggressive prostate cancer, whereas calcium intake alone had no association. Dietary intake of magnesium was modestly inversely associated with aggressive prostate cancer. In addition, men who reported usually consuming whole-fat milk were at increased odds of aggressive prostate cancer compared with non-milk drinkers or those who consume usually other types of milk, whereas dairy product intake showed no association.

Few studies have examined Ca:Mg and cancer outcomes. Previously, modifying effects have been reported, such that higher intakes of magnesium and calcium were associated with reduced risk of 2 intermediate premalignant endpoints, colorectal adenoma (27) and Barrett esophagus (28), with more pronounced

TABLE 2
ORs (95% CIs) for aggressive prostate cancer by calcium intake for all participants, stratified by race, in the PCaP[1]

Race and tertile	Calcium intake, mg/d	High aggressive/ low-intermediate aggressive, *n/n*	OR (95% CI)[2]	OR (95% CI)[3]	OR (95% CI)[4]
Dietary intake					
All ($n = 2060$)					
T1	<625.64	112/567	1 (ref)	1 (ref)	1 (ref)
T2	625.64–966.50	113/568	0.85 (0.63, 1.16)	0.99 (0.72, 1.37)	1.01 (0.73, 1.41)
T3	>966.50	134/566	0.80 (0.55, 1.17)	1.00 (0.67, 1.49)	1.03 (0.68, 1.55)
EA ($n = 1064$)					
T1	<707.83	60/301	1 (ref)	1 (ref)	1 (ref)
T2	707.83–1014.48	44/302	0.64 (0.40, 1.00)	0.66 (0.41, 1.05)	0.72 (0.46, 1.15)
T3	>1014.48	57/300	0.77 (0.46, 1.31)	0.80 (0.47, 1.39)	0.92 (0.52, 1.61)
AA ($n = 996$)					
T1	<549.41	47/266	1 (ref)	1 (ref)	1 (ref)
T2	549.41–914.62	69/267	1.35 (0.87, 2.08)	1.53 (0.96, 2.42)	1.52 (0.95, 2.42)
T3	>914.62	82/265	1.35 (0.77, 2.36)	1.43 (0.79, 2.58)	1.37 (0.74, 2.55)
Supplement intake					
All ($n = 2060$)					
T1	0	203/909	1 (ref)	1 (ref)	1 (ref)
T2	≤200	60/348	0.78 (0.57, 1.08)	0.95 (0.68, 1.32)	0.96 (0.69, 1.33)
T3	>200	96/444	0.91 (0.70, 1.20)	1.16 (0.87, 1.55)	1.19 (0.89, 1.60)
EA ($n = 1064$)					
T1	0	68/414	1 (ref)	1 (ref)	1 (ref)
T2	≤200	38/194	1.19 (0.77, 1.84)	1.33 (0.84, 2.11)	1.35 (0.84, 2.15)
T3	>200	55/295	1.05 (0.71, 1.55)	1.19 (0.79, 1.81)	1.29 (0.84, 1.96)
AA ($n = 996$)					
T1	0	135/495	1 (ref)	1 (ref)	1 (ref)
T2	≤200	22/154	0.53 (0.33, 0.87)	0.68 (0.41, 1.14)	0.67 (0.40, 1.12)
T3	>200	41/149	0.97 (0.65, 1.45)	1.17 (0.76, 1.79)	1.16 (0.76, 1.78)
Total intake					
All ($n = 2060$)					
T1	<729.52	110/567	1 (ref)	1 (ref)	1 (ref)
T2	729.52–1122.57	115/568	0.90 (0.66, 1.21)	1.10 (0.79, 1.52)	1.16 (0.83, 1.61)
T3	>1122.57	134/566	0.86 (0.61, 1.22)	1.19 (0.82, 1.74)	1.23 (0.84, 1.82)
EA ($n = 1064$)					
T1	<825.9	54/301	1 (ref)	1 (ref)	1 (ref)
T2	825.9–1211.58	49/302	0.85 (0.54, 1.32)	0.91 (0.58, 1.45)	1.00 (0.62, 1.59)
T3	>1211.58	58/300	0.95 (0.58, 1.55)	1.06 (0.63, 1.78)	1.19 (0.70, 2.02)
AA ($n = 996$)					
T1	<617.97	50/266	1 (ref)	1 (ref)	1 (ref)
T2	617.97–1009.39	70/267	1.24 (0.81, 1.90)	1.45 (0.92, 2.28)	1.44 (0.91, 2.28)
T3	>1009.39	78/265	1.12 (0.66, 1.89)	1.30 (0.75, 2.26)	1.26 (0.71, 2.23)

[1]AA, African American; EA, European American; PCaP, North Carolina–Louisiana Prostate Cancer Project; ref, reference; T, tertile.
[2]Adjusted for age and energy intake.
[3]Adjusted for age, energy intake, race, BMI, smoking. previous screening, study site, education, income, and Charlson comorbidity index, with the exception of race in the race-stratified analyses.
[4]Adjusted for all variables in footnote 3 and intakes of alcohol, lycopene, and saturated fat.

associations among those with lower Ca:Mg intake. A significant interaction between Ca:Mg intake and transient receptor potential melastatin 7 (*TRPM7*) polymorphism was observed in relation to risk of colorectal adenoma (27). In a recent study on serum calcium and magnesium concentrations, elevated serum Ca:Mg was significantly associated with an increased risk of high-grade prostate cancer, and a higher serum Ca:Mg was observed among non–European American participants than in European American participants (23). Another study observed a higher serum Ca:Mg in participants with prostate cancer than in age-matched controls without prostate cancer (29). High calcium intake may reduce the absorption of both calcium and magnesium (28, 30). In the present study, a higher dietary Ca:Mg intake was associated with increased odds of high-aggressive prostate cancer. The results suggest that the concentrations of calcium relative to magnesium intakes may have an impact on prostate cancer aggressiveness, whereas calcium intake alone may not be as influential. In support of this finding, secondary analyses of a clinical trial of calcium supplements found no increased risk of prostate cancer after an average of 10.3 y of follow-up among men randomly assigned to receive 1200 mg Ca for 4 y (31).

The interdependence of calcium and magnesium could explain the inconsistencies observed in previous epidemiologic studies of calcium alone and prostate cancer, and explain the interactive

TABLE 3
ORs (95% CIs) for aggressive prostate cancer by magnesium intake for all participants, stratified by race, in the PCaP[1]

Race and tertile	Magnesium intake, mg/d	High aggressive/ low-intermediate aggressive, *n/n*	OR (95% CI)[2]	OR (95% CI)[3]	OR (95% CI)[4]
Dietary intake					
All ($n = 2060$)					
T1	<306.02	125/567	1 (ref)	1 (ref)	1 (ref)
T2	306.02–435.55	113/568	0.71 (0.52, 0.96)	0.81 (0.59, 1.11)	0.88 (0.64, 1.22)
T3	>435.55	121/566	0.49 (0.33, 0.74)	0.60 (0.39, 0.94)	0.71 (0.45, 1.12)
EA ($n = 1064$)					
T1	<323.15	63/301	1 (ref)	1 (ref)	1 (ref)
T2	323.15–445.08	49/302	0.64 (0.41, 1.00)	0.69 (0.43, 1.10)	0.79 (0.49, 1.28)
T3	>445.08	49/300	0.48 (0.26, 0.88)	0.53 (0.28, 1.01)	0.72 (0.37, 1.40)
AA ($n = 996$)					
T1	<282.62	52/266	1 (ref)	1 (ref)	1 (ref)
T2	282.62–428.18	74/267	1.17 (0.76, 1.79)	1.44 (0.92, 2.28)	1.49 (0.93, 2.37)
T3	>428.18	72/265	0.79 (0.44, 1.45)	0.96 (0.50, 1.82)	1.00 (0.52, 1.96)
Supplement intake					
All ($n = 2060$)					
T1	0	213/961	1 (ref)	1 (ref)	1 (ref)
T2	≤50	108/560	0.84 (0.65, 1.08)	1.08 (0.82, 1.42)	1.10 (0.83, 1.45)
T3	>50	38/180	0.95 (0.65, 1.40)	1.08 (0.72, 1.61)	1.15 (0.77, 1.72)
EA ($n = 1064$)					
T1	0	72/445	1 (ref)	1 (ref)	1 (ref)
T2	≤50	72/363	1.15 (0.80, 1.65)	1.32 (0.90, 1.93)	1.42 (0.96, 2.09)
T3	>50	17/95	1.06 (0.60, 1.90)	1.15 (0.63, 2.10)	1.36 (0.74, 2.51)
AA ($n = 996$)					
T1	0	141/516	1 (ref)	1 (ref)	1 (ref)
T2	≤50	36/197	0.66 (0.44, 0.99)	0.85 (0.55, 1.30)	0.83 (0.54, 1.28)
T3	>50	21/85	0.94 (0.56, 1.57)	1.03 (0.59, 1.80)	1.05 (0.60, 1.82)
Total intake					
All ($n = 2060$)					
T1	<331.79	127/567	1 (ref)	1 (ref)	1 (ref)
T2	331.79–470.06	108/568	0.68 (0.50, 0.92)	0.80 (0.58, 1.10)	0.86 (0.62, 1.19)
T3	>470.06	124/566	0.56 (0.39, 0.82)	0.71 (0.47, 1.07)	0.83 (0.54, 1.26)
EA ($n = 1064$)					
T1	<351.88	58/301	1 (ref)	1 (ref)	1 (ref)
T2	351.88–482.24	55/302	0.83 (0.54, 1.28)	0.90 (0.57, 1.41)	1.03 (0.65, 1.64)
T3	>482.24	48/300	0.59 (0.33, 1.04)	0.64 (0.35, 1.17)	0.89 (0.48, 1.67)
AA ($n = 996$)					
T1	<302.77	59/266	1 (ref)	1 (ref)	1 (ref)
T2	302.77–450.67	62/267	0.88 (0.58, 1.35)	1.03 (0.66, 1.62)	1.08 (0.68, 1.70)
T3	>450.67	77/265	0.82 (0.48, 1.43)	1.03 (0.57, 1.85)	1.07 (0.58, 1.97)

[1] AA, African American; EA, European American; PCaP, North Carolina–Louisiana Prostate Cancer Project; ref, reference; T, tertile.
[2] Adjusted for age and energy intake.
[3] Adjusted for age, energy intake, race, BMI, smoking. previous screening, study site, education, income, and Charlson comorbidity index, with the exception of race in the race-stratified analyses.
[4] Adjusted for all variables in footnote 3 and intakes of alcohol, lycopene, and saturated fat.

role of calcium and magnesium in the development of high-aggressive disease. A suggested biological mechanism has been proposed in experimental studies in which activation of *TRPM7* due to an imbalance in Ca:Mg may stimulate prostate cancer cell proliferation (29). Although no inverse association was observed for magnesium supplements, the use of magnesium supplements was likely too low to assert a definitive effect, particularly among African-Americans. Most research participants who consumed supplemental magnesium also consumed supplemental calcium (338 African-Americans and 534 European-Americans compared with only 1 African-American and 13 European-Americans who consumed supplemental magnesium and not supplemental calcium), and the Ca:Mg in supplement users was higher than in non-supplement users (average Ca:Mg of 2.55 compared with 2.36, respectively).

In the analysis of dairy products, ORs tended to be >1.0 for higher intakes of milk and cheese, although CIs included the null value. However, when comparing whole-fat milk drinkers with non–whole-fat milk drinkers, participants who consumed the most whole-fat milk (≥1.25 servings/d) had significantly higher odds of high-aggressive prostate cancer. Results were attenuated after adjustment for saturated fat and other dietary factors. Results were attenuated further after adjustment for Ca:Mg intake. These results suggest a potentially mediating effect of

TABLE 4
ORs (95% CIs) for aggressive prostate cancer by Ca:Mg intake for all participants, stratified by race, in the PCaP[1]

Race and tertile	Ca:Mg	High aggressive/ low-intermediate aggressive, *n/n*	OR (95% CI)[2]	OR (95% CI)[3]	OR (95% CI)[4]
Dietary intake					
All ($n = 2060$)					
T1	<1.90	89/573	1 (ref)	1 (ref)	1 (ref)
T2	1.90–2.40	127/572	1.35 (1.00, 1.81)	1.41 (1.04, 1.92)	1.38 (1.01, 1.88)
T3	>2.40	143/556	1.52 (1.13, 2.03)	1.59 (1.17, 2.15)	1.46 (1.06, 2.02)
EA ($n = 1064$)					
T1	<1.97	38/305	1 (ref)	1 (ref)	1 (ref)
T2	1.97–2.50	61/301	1.63 (1.05, 2.53)	1.56 (0.99, 2.45)	1.54 (0.97, 2.46)
T3	>2.50	62/297	1.67 (1.07, 2.59)	1.55 (0.98, 2.46)	1.39 (0.85, 2.67)
AA ($n = 996$)					
T1	<1.82	47/280	1 (ref)	1 (ref)	1 (ref)
T2	1.82–2.27	61/265	1.23 (0.81, 1.87)	1.32 (0.84, 2.05)	1.29 (0.82, 2.02)
T3	>2.27	90/263	1.77 (1.19, 2.64)	1.70 (1.12, 2.59)	1.62 (1.04, 2.53)
Supplement intake					
All ($n = 2060$)					
T1	<4.20	281/1338	1 (ref)	1 (ref)	1 (ref)
T2	4.20–4.40	55/253	0.99 (0.72, 1.36)	1.20 (0.86, 1.68)	1.22 (0.87, 1.71)
T3	>4.40	23/110	0.96 (0.60, 1.54)	1.31 (0.80, 2.16)	1.40 (0.85, 2.31)
EA ($n = 1064$)					
T1	<4.20	110/654	1 (ref)	1 (ref)	1 (ref)
T2	4.20–4.40	32/157	1.14 (0.74, 1.76)	1.23 (0.78, 1.94)	1.28 (0.80, 2.03)
T3	>4.40	19/92	1.16 (0.68, 1.99)	1.28 (0.73, 2.26)	1.43 (0.80, 2.55)
AA ($n = 996$)					
T1	<2.96	162/612	1 (ref)	1 (ref)	1 (ref)
T2	2.96–4.40	32/168	0.71 (0.46, 1.07)	0.90 (0.58, 1.40)	0.89 (0.57, 1.38)
T3	>4.40	4/18	0.84 (0.28, 2.54)	1.19 (0.36, 3.91)	1.23 (0.37, 4.01)
Total intake					
All ($n = 2060$)					
T1	<2.02	86/577	1 (ref)	1 (ref)	1 (ref)
T2	2.02–2.54	129/558	1.50 (1.11, 2.02)	1.65 (1.21, 2.25)	1.63 (1.19, 2.24)
T3	>2.54	144/566	1.57 (1.17, 2.10)	1.77 (1.30, 2.41)	1.65 (1.19, 2.28)
EA ($n = 1064$)					
T1	<2.15	41/306	1 (ref)	1 (ref)	1 (ref)
T2	2.15–2.74	57/300	1.39 (0.90, 2.15)	1.37 (0.87, 2.14)	1.39 (0.87, 2.20)
T3	>2.74	63/297	1.53 (1.00, 2.35)	1.50 (0.96, 2.35)	1.35 (0.84, 2.17)
AA ($n = 996$)					
T1	<1.89	46/267	1 (ref)	1 (ref)	1 (ref)
T2	1.89–2.36	58/267	1.18 (0.77, 1.81)	1.25 (0.80, 1.95)	1.23 (0.78, 1.93)
T3	>2.36	94/264	1.89 (1.27, 2.81)	1.87 (1.23, 2.85)	1.80 (1.16, 2.80)

[1]AA, African American; Ca:Mg, calcium-to-magnesium ratio; EA, European American; PCaP, North Carolina–Louisiana Prostate Cancer Project; ref, reference; T, tertile.

[2]Adjusted for age and energy intake.

[3]Adjusted for age, energy intake, race, BMI, smoking. previous screening, study site, education, income, and Charlson comorbidity index, with the exception of race in the race-stratified analyses.

[4]Adjusted for all variables in footnote 3 and intakes of alcohol, lycopene, and saturated fat.

saturated fat and could help explain the mixed results obtained in previous studies of calcium and milk intakes on prostate cancer aggressiveness (8, 32–35). In addition, men who consume whole-fat milk frequently may be less health-conscious, less likely to be screened, and more likely to be diagnosed with aggressive disease. However, the association was maintained when previous screening history was included as a covariate in our models to account for this potential confounder.

Few studies have attempted to compare the effects of full-fat with low- or no-fat dairy products on cancer risk or prognosis. Whole-fat milk intake was positively associated with fatal prostate cancer in the Physicians' Health Study, whereas skim/low-fat milk intake was positively associated with low-grade, early-stage, and screen-detected prostate cancers (36). In a recent study from Sweden, men diagnosed with localized prostate cancer who drank ≥3 servings of high-fat milk/d were at increased risk of prostate cancer mortality, whereas low-fat milk drinkers had a borderline reduction in prostate cancer deaths (37). Similar results have been reported for breast cancer, another hormonally driven cancer. The Life After Cancer Epidemiology (LACE) Study reported that the intake of high-fat dairy, but not low-fat dairy, was associated with higher mortality after a breast cancer diagnosis (38), whereas an Italian study reported no association between high-fat dairy or low-fat dairy and mortality

TABLE 5
ORs (95% CIs) for aggressive prostate cancer by whole-fat milk intake in the PCaP[1]

		Whole-fat milk drinkers		
	Non–whole-fat milk drinkers[2]	Tertile 1: 0.07–0.56 servings/d	Tertile 2: 0.57–1.24 servings/d	Tertile 3: ≥1.25 servings/d
High aggressive, *n*	255	26	29	49
Low-intermediate aggressive, *n*	1369	111	111	110
OR (95% CI)[3]	1 (ref)	1.35 (0.86, 2.12)	1.36 (0.88, 2.11)	2.07 (1.40, 3.05)
OR (95% CI)[4]	1 (ref)	1.03 (0.64, 1.67)	1.08 (0.68, 1.71)	1.74 (1.16, 2.62)
OR (95% CI)[5]	1 (ref)	1.00 (0.61, 1.61)	1.01 (0.64, 1.62)	1.49 (0.97, 2.29)
OR (95% CI)[6]	1 (ref)	1.04 (0.64, 1.70)	0.93 (0.58, 1.49)	1.37 (0.89, 2.11)

[1]PCaP, North Carolina–Louisiana Prostate Cancer Project; ref, reference.
[2]Non–whole-fat milk drinkers include nonmilk drinkers and men who reported usually consuming milk that is 2% fat, 1% fat, skim, nonfat, 0.5% fat, soy, rice, or other milk.
[3]Adjusted for age and energy intake.
[4]Adjusted for age, energy intake, race, BMI, smoking, previous screening, study site, education, income, and Charlson comorbidity index.
[5]Adjusted for all variables in footnote 4 and intakes of alcohol, lycopene, and saturated fat.
[6]Adjusted for all variables in footnote 5 and calcium-to-magnesium intake ratio.

among women diagnosed with breast cancer, although there was a marginally significant increased risk among milk drinkers (the study did not distinguish between whole-fat and low- or no-fat milk) (39). Mechanisms by which high-fat milk may affect prostate cancer include deleterious effects of saturated fat, increasing C-peptide concentrations, or higher insulin-like growth factor I (36). Future research in large prospective studies that compare full-fat milk with other types of milk is warranted to confirm the current findings.

There are several advantages to PCaP. First, the case ascertainment was based on cancer registry records, medical records, and pathology reports, thereby minimizing outcome misclassification bias. Second, the study used information on a wide range of potential confounders, such as age, race, BMI, energy intake, education, family history of prostate cancer, history of PSA screening, smoking status, income, and Charlson comorbidity index. Third, the food-frequency questionnaire used to estimate nutrient intakes was modified to assess intakes of Southern foods, which may decrease information bias due to measurement error of the exposure. Fourth, a relatively large sample size ($n = 2060$) was used and was representative of the population of men with prostate cancer in 2 states, Louisiana and North Carolina; therefore, it has a good potential for the detection of small differences and for generalizability of the results. Fifth, in this study, 2 populations of interest, European Americans and African Americans, are equally well represented ($n = 1064$ and 996, respectively), which allows comparisons in prostate cancer aggressiveness by race that, to our knowledge, had not been done before.

Limitations also should be noted. First, because PCaP is a case-only study, the comparison or control group consisted of men with low-intermediate-aggressive prostate cancer. Although utilization of this control group allows important comparisons between low-intermediate and high-aggressive prostate cancers, it does not allow comparison of effects of risk factors in men who are cancer-free. Second, the DHQ elicited information about usual food intakes during the year preceding the diagnosis of prostate cancer. Intakes in the more distant past could have been different and have a higher impact than more recent diet, because prostate cancer may take decades to develop. Third, knowledge of disease status may have biased DHQ responses by the participants. Fourth, although all of the variables and analyses were planned a priori, and it has been suggested that there is no need for multiple testing adjustment in this situation (40), there is still a possibility of false-positive conclusions. Finally, although multiple confounders were included in the model, unmeasured or residual confounding is possible in observational studies.

The current study suggests that a high Ca:Mg intake and whole-fat milk consumption are associated with higher prostate cancer aggressiveness. Future studies are warranted to explore the effect-modifying role of race on relations between nutrients, such as calcium and magnesium, and prostate cancer aggressiveness, and the interaction between calcium and magnesium in the pathogenesis and progression of prostate cancer.

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