Research Article

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Adherence to Dietary and Lifestyle Recommendations and Prostate Cancer Risk in the Prostate Testing for Cancer and Treatment (ProtecT) Trial

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Abstract

Background: The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) published eight recommendations for cancer prevention, but they are not targeted at prostate cancer prevention. We investigated whether adherence to the WCRF/AICR recommendations and a prostate cancer dietary index is associated with prostate cancer risk.

Methods: We conducted a nested case–control study of 1,806 prostate-specific antigen (PSA)–detected prostate cancer cases and 12,005 controls in the ProtecT trial. We developed a prostate cancer dietary index by incorporating three dietary factors most strongly associated with prostate cancer. Scores were computed to quantify adherence to the WCRF/AICR recommendations and the prostate cancer dietary index separately.

Results: The prostate cancer dietary index score was associated with decreased risk of prostate cancer [OR per 1 score increment: 0.91; 95% confidence interval (CI): 0.84–0.99; $P_{trend} = 0.04$] but the WCRF/AICR index score was not (OR: 0.99; 95% CI: 0.94–1.05; $P_{trend} = 0.71$). There was no heterogeneity in association by prostate cancer stage ($P = 0.81$) or grade ($P = 0.61$). Greater adherence to recommendations to increase plant foods (OR per 0.25 index score increment: 0.94; 95% CI: 0.89–0.99; $P_{trend} = 0.02$) and tomato products (OR adherence vs. nonadherence: 0.82; 95% CI: 0.70–0.97; $P = 0.02$) was inversely associated with overall prostate cancer risk.

Conclusions: Adherence to the prostate cancer–specific dietary recommendations was associated with decreased risk of prostate cancer. High intake of plant foods and tomato products in particular may help protect against prostate cancer.

Impact: Meeting the WCRF/AICR recommendations alone is insufficient for prostate cancer prevention. Additional dietary recommendations should be developed. *Cancer Epidemiol Biomarkers Prev; 23(10); 2066–77. ©2014 AACR.*

Introduction

Prostate cancer is the second most common cancer in men worldwide, with higher incidence and mortality observed in developed countries (1). Evidence from ecological and migrant studies suggests that the wide variation in international rates of prostate cancer may be attributed to a "Westernized" diet and lifestyle (2). Studies that examined diet and prostate cancer risk association traditionally focused on specific nutrients or food groups. However, there is growing interest in assessing overall dietary pattern, as it accounts for the mixed composition of diet and interactions between nutrients. Dietary and lifestyle index is frequently used to assess dietary pattern as it is usually developed based on dietary and lifestyle recommendations, which means the results can be interpreted with ease and have practical implications for public health policy (3).

In 2007, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) published eight recommendations on physical activity, diet, and body weight for cancer prevention (4). Whether adherence to these recommendations reduces prostate cancer risk is uncertain (5, 6). As prostate cancer is a clinically heterogeneous disease, the effects of dietary and lifestyle factors may differ in localized compared with more advanced cancers, or well- versus less-differentiated cancers (7). The large European Prospective Investigation into Cancer and Nutrition (EPIC) study reported that men who followed the WCRF/AICR recommendations did not have a lower prostate cancer risk, compared with

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those who did, although the authors did not examine the association by markers of advanced prostate cancer such as high grade or stage. Conversely, another study found that men who met these recommendations had a reduced risk of aggressive cancer (6).

Because the WCRF/AICR recommendations are not targeted at prostate cancer prevention, it may be useful to have prostate cancer–specific recommendations as an adjunct to the general WCRF/AICR recommendations that could be targeted at men or those at higher risk. The WCRF/AICR comprehensive systematic review found observational evidence that calcium is probably positively associated with prostate cancer risk, whereas selenium and foods containing lycopene are probably inversely associated (4). Therefore, additional dietary recommendations for prostate cancer prevention could include low consumption of calcium and high intake of selenium and foods containing lycopene.

In a nested case–control study, we investigated the association of prostate specific antigen (PSA)-detected prostate cancer with adherence to the WCRF/AICR recommendations for cancer prevention, and prostate cancer dietary index which we developed by incorporating three dietary factors most strongly associated with prostate cancer risk in the WCRF/AICR systematic review: calcium, selenium, and foods containing lycopene. We also investigated whether the associations differed by stage and grade of cancer.

Materials and Methods

Study population

The men included in this study were participants in the PSA-tested cohort of the ProtecT trial (8). ProtecT is a population-based randomized controlled trial investigating the effectiveness of treatments for localized prostate cancer. Approximately 227,300 men aged 50 to 69 years registered at general practices in nine UK cities were invited to attend a prostate check clinic between 2001 and 2009. More than 111,000 men had a PSA test after giving written consent. Of these, 11% of men with raised PSA ($\geq$3 ng/mL) were invited for repeated PSA test, digital rectal examination, and 10 core-transrectal ultrasound-guided biopsy. Uropathology specialists reviewed histologic materials obtained at biopsy and assigned Gleason score. For the purpose of this analysis, tumors with Gleason score of $\leq$6 were defined as low and $\geq$7 as high grade. Clinical staging was recorded using the tumor–node–metastasis system. Cases were classified as having localized (T1–T2, NX, M0) and advanced (T3–T4, N1, M1) prostate cancer. Study participants gave informed consent for the use of their data for research purposes. The Trent Multicentre Research Ethics Committee approved the ProtecT (MREC/01/4/025) and the associated ProMPT study (MREC01/4/061).

Selection of cases and controls

Cases were men aged 50 to 69 years with histologically confirmed prostate cancer, who had attended for PSA testing and had their PSA results recorded between 2001 and 2009. During this period, 2,939 cases were identified; 2,588 localized cases (88.7%) and 331 advanced cases (11.3%). The majority of advanced cases were T3 (73%), also defined here as locally advanced cases. All men within the ProtecT cohort who had no evidence of prostate cancer (PSA <3 ng/mL or raised PSA but with $\geq$1 negative biopsy) were eligible for random selection as controls: 20,781 controls were randomly selected for targeted data entry. Cases were frequency matched with controls by 5-year age band and recruiting general practice. Overall, 1,806 cases (61.4%) and 12,005 controls (57.8%) were included in our analyses (Supplementary Fig. S1). We excluded men who did not return the questionnaires ($n = 7,420$), men within the top or bottom 1% of the cohort distribution of the ratio of reported energy intake to energy requirements ($n = 302$), and men with missing data on physical activity ($n = 761$), body size ($n = 1,055$), waist circumference ($n = 151$), alcohol intake ($n = 79$), and dietary exposure variables ($n = 141$).

Data collection and dietary questionnaire

Before diagnosis, men filled out questionnaires on sociodemographic, medical and family history, anthropometry, lifestyle, and diet. Among the men included in the final analysis, the questionnaire was completed by 75.7% of controls ($n = 9,082$) and 71.6% of cases ($n = 1,293$), before receipt of the initial PSA test results.

Anthropometry. Trained nurses measured men's weight at the prostate check clinic according to standard protocol. If unavailable, self-reported weight was used (4.4% of men). Height was self-reported. Body mass index (BMI) was derived as weight over height squared (kg/m^2). We provided men with a tape measure and instructions for measuring their waist. Body size at age 20 years, 40 years, and at study baseline served as an indicator of body weight throughout adulthood. We asked men to select the figure that best reflected their body size using the Stunkard figure rating scale (9), which consists of nine body sizes in ascending order. We adapted a method recommended by Bulik and colleagues (10) to categorize men. Those who had selected figure 1–3 were categorized as normal weight and figure 4–9 as overweight/obese.

Physical activity. We used Godin Leisure Time Physical Activity questionnaire to assess physical activity (11). Men were asked on average how often they do strenuous, moderate, and mild physical activity for more than 15 minutes in a week. Physical activity was computed as number of times per week of moderate and strenuous exercise. Mild exercise was not included as it is not a strong contributor to health benefits (12) and was not cited in WCRF recommendations.

Alcohol and smoking. Alcohol intake was based on the number of spirits/wine/beer consumed and the amount of alcohol (g) per drink. We categorized men as never, former, and current smokers.

Dietary intake. Dietary intake in the past 12 months was assessed using a validated 114-item food frequency

questionnaire (FFQ) adapted from the UK arm of the EPIC study (13). Men reported frequency of intake for each food item across nine mutually exclusive categories, ranging from "never/less than once per month" to "six or more times per day." The assignment of portion size in grams for each food item was based on UK food portion sizes (14), food weights derived from a 7-day diet diary from a subsample of ProtecT participants, and data from the Carnegie survey of diet and health (15). Food intake was computed as the product of frequency of intake and portion size. Nutrient intake was derived by multiplying frequency of intake by the nutrient content per portion of food, using nutrient values from the composition tables of McCance and Widdowson, and its supplements (16).

WCRF/AICR index

To develop the WCRF/AICR index, we operationalized six of the eight recommendations (Table 1), as we did not have sufficient dietary information to translate the recommendations on "Preservation, Processing, Preparation" and "Dietary Supplements." We gave participants a score based on quantitative cutoffs provided in the WCRF/AICR recommendations. A score of 1, 0.5, and 0 was assigned for complete, partial, and nonadherence, respectively (Table 2). Where unspecified, *a priori* cutoffs were used for (i) waist circumference (17), (ii) red and processed meat intake (5), and (iii) dietary energy density (5). There are subrecommendations on "Body Fatness," "Food and Drinks that Promote Weight Gain," and "Plant Foods." The score for the main recommendation was derived as the average of the subrecommendation scores. We gave equal weight to each of the six main recommendations. The final score ranged from 0 to 6, and we further categorized men into quartiles of index score: 0–2, >2–<3, 3–<4, 4–6.

Foods and drinks that promote weight gain. Dietary energy density was computed as total energy intake from food divided by total food weight. We used energy density of the overall diet instead of energy-dense food intake to operationalize this recommendation, as it is based on evidence that a high energy density diet promotes weight gain, rather than consumption of specific energy-dense food items (18). We defined sugary drinks as nondiet soft drinks, fruit squash and fruit juice. For participants who consumed fruit juice only (no soft drink and fruit squash intake), 1 serving (150 g) per day was considered as meeting the recommendation (19).

Plant foods. In categorizing plant foods, we only included whole fruit and vegetable intake, and computed daily intake in grams. Potatoes, fruit, and vegetable juices were excluded.

Meat foods. Beef, lamb, and pork were included as red meat items and processed meat items included beef burgers, ham, bacon, sausages, luncheon meat, corned beef, "Spam," and savory pies. The recommended intake for processed meat is less than 20 g/day as a higher intake is associated with an increased risk of mortality (20). However, the WCRF/AICR advised abstinence, so a lower cutoff point of 3 g/day was used as meeting the recommendation (5).

Prostate cancer dietary index

To develop the prostate cancer dietary index, we included calcium, selenium, and foods rich in lycopene in the index (Table 2), as these dietary components were strongly associated with prostate cancer incidence in the WCRF/AICR systematic review in their second expert report (4). Fresh tomato and tomato product intake were used as an indicator of lycopene intake as they are rich sources of lycopene. Tomato products include tomato juice, tomato sauce, pizza, and baked beans. Participants received a score of 1 for complete adherence and 0 for nonadherence. The cutoff criteria were derived from the WCRF/AICR second expert report (4) for calcium, studies by Hurst and colleagues (21, 22) for selenium, and the Health Professionals Study (23) for tomato and tomato products. Each recommendation contributed equally to the total score, with a maximum score of three. We categorized men into tertiles of index score 0 and 1, 2, and 3.

Statistical analysis

We estimated ORs and 95% confidence intervals (CI) for associations of the index score with risk of prostate cancer using conditional logistic regression, matched by 5-year age band and center of recruitment, and further adjusted for age (continuous variable). We used multinomial unconditional logistic regression to assess the associations of index score with prostate cancer risk by stage and grade subtypes. We ran two separate analyses, each with the outcome variable grouped into three categories: (i) controls, localized cases (T1–T2, NX, M0), and locally advanced cases (T3–T4, N1, M1) and (ii) controls, low-grade cases (Gleason score $\leq$6), and high-grade cases (Gleason score $\geq$7). The models were adjusted for age (continuous variable) and the study center in which the recruiting general practice was based. In case-only analyses, we used unconditional logistic regression to estimate associations of the index scores with cancer stage (locally advanced vs. localized) and grade (high vs. low); both models adjusted for age (continuous variable) and the study center where the recruiting general practice was based. The effect estimates of the associations are expressed as relative risk ratios (RRR). To test for linear trend for associations of index scores with prostate cancer risk, we modeled the index scores as continuous variables.

We compared the basic logistic regression models with the models additionally adjusted for the following confounding factors identified *a priori*: family history of prostate cancer (yes/no), self-reported diabetes (yes/no), ethnicity (White/others), occupational class (managerial/intermediate/routine), smoking status (never/former/current), and total energy intake (kcal/day). For each of the confounding factors that we adjusted for, we grouped men with missing data into a separate category, except for total energy intake that has complete data. Diabetes,

Table 1. WCRF/AICR recommendations for cancer prevention and scoring criteria

WCRF/AICR recommendations	Personal recommendations	Operationalization	Score	Cases ($n = 1{,}806$) %	Controls ($n = 12{,}005$) %
1. Body fatness. Be as lean as possible without becoming underweight.	1a. Ensure that body weight throughout childhood and adolescent growth projects toward the lower end of the normal BMI range at the age of 21 years.	Insufficient information	NA		
	1b. Maintain body weight within the normal range from the age of 21 years.	Lean at aged 20, 40, and trial entry	1	21.7	21.4
		Lean at 2 timepoints	0.5	31.1	30.4
		Overweight at aged 20, 40, and trial entry	0	47.2	48.2
	1c. Avoid weight gain and increases in waist circumference throughout adulthood.	WC <94 cm	1	41.5	41.3
		WC ≥94 to <102 cm	0.5	37.1	36.1
		WC ≥102 cm	0	21.4	22.6
2. Physical activity. Be physically active as part of your everyday life.	2a. Be moderately physically active, equivalent to brisk walking for 30 minutes every day.	PA ≥7 times/wk	1	28.1	27.1
		PA 3 to <7 times/wk	0.5	33.8	32.9
		PA <3 times/wk	0	38.1	40.0
	2b. As fitness improves, aim for 60 minutes of moderate or for 30 minutes of vigorous physical activity every day.	Insufficient information available	NA		
	2c. Limit sedentary habits such as watching television.	No information available	NA		
3. Foods and drinks that promote weight gain. Limit consumption of energy-dense foods; avoid sugary drinks.	3a. Consume energy-dense foods sparingly.	DED ≤125 kcal·100 g^{-1}·d^{-1}	1	16.2	18.0
		DED >125 to ≤175 kcal·100 g^{-1}·d^{-1}	0.5	63.1	62.0
		DED >175 kcal/100·100 g^{-1}·d^{-1}	0	20.7	20.0
	3b. Avoid sugary drinks.[a]	No sugary drinks or ≤1 fruit juice	1	45.1	44.5
		≤250 g/day sugary drinks or >1 to ≤2 fruit juice	0.5	36.7	35.8
		>250 g/day sugary drinks or >2 fruit juice	0	18.2	19.7
	3c. Consume fast foods sparingly, if at all.	Insufficient information available			
4. Plant foods. Eat mostly foods of plant origin.	4a. Eat 5 portions/servings (400 g) of a variety of nonstarchy vegetables and of fruit every day.	F&V ≥400 g/day	1	53.3	56.3
		F&V ≥200 to <400 g/day	0.5	37.2	34.6
		F&V <200 g/day	0	9.5	9.1
	4b. Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal.	NSP ≥18 g/day	1	63.3	65.0
		NSP ≥ 10 to <18 g/day	0.5	33.2	31.8
		NSP <10 g/day	0	3.5	3.2
	4c. Limit refined starchy foods.	Insufficient information available			
	4d. People who consume starchy roots or tubers as staples should also ensure sufficient intake of non starchy vegetables, fruit, and pulses (legumes).	Not applicable to our study population			

(Continued on the following page)

Table 1. WCRF/AICR recommendations for cancer prevention and scoring criteria (Cont'd)

WCRF/AICR recommendations	Personal recommendations	Operationalization	Score	Cases ($n = 1,806$) %	Controls ($n = 12,005$) %
5. Animal foods. Limit intake of red meat and avoid processed meat.	5a. People who eat red meat should consume <500 g/wk and very few, if any, processed meats.	Red and processed meat <500 g/wk and processed meat <3 g/day	1	3.6	5.0
		Red and processed meat <500 g/wk and processed meat ≥3 g/day to ≤20 g/day	0.5	28.3	26.1
		Red and processed meat ≥500 g/wk or processed meat >20 g/day	0	68.1	68.9
6. Alcoholic drinks. Limit alcoholic drinks.	6a. If alcoholic drinks are consumed, limit consumption to 2 drinks/day for men and 1 drink/day for women.	Alcohol ≤20 g/day	1	54.7	53.9
		Alcohol >20 g/day to ≤30 g/day	0.5	14.3	14.9
		Alcohol >30 g/day	0	31.0	31.2

Abbreviations: DED, dietary energy density; F&V, fruits and vegetables; NSP, nonstarch polysaccharides; PA, physical activity; WC, waist circumference.

[a]Sugary drinks include nondiet soft drink, fruit squash and fruit juice. Fruit juice cutoffs apply to men who consumed fruit juice only.

ethnicity, and occupational class were subsequently excluded from the fully adjusted models as they did not confound the observed associations between index score and prostate cancer risk. Cases with missing stage ($n = 10$) or grade ($n = 6$) were included in the analyses of overall prostate cancer risk but omitted from stage- or grade-specific analyses. For analyses based on the prostate cancer dietary index, two controls with missing score were excluded.

We also examined the associations of the individual components in each index with prostate cancer risk separately. For the WCRF/AICR index, we adjusted for all other components in the index except for dietary energy density, as total energy intake was included as a covariate in the models. We modeled index scores as a continuous variable to test for linear trend across index score for each component. For the prostate cancer dietary index, we ran the models with and without BMI and physical activity, but the estimates did not differ appreciably.

To assess the possibility of recall bias, we repeated the analyses restricted to men who completed the questionnaire before receiving their initial PSA test results. To investigate whether the association for body weight recommendation differs when BMI is used as an indicator of body weight, we repeated the analyses using BMI at baseline instead of body size and waist measurement. Finally, we repeated analyses for the plant food recommendation, but restricted it to fruit and vegetable intake only to avoid double counting due to the close relationship of dietary fiber and fruit and vegetable intake. All statistical analyses were performed using Stata v12.1 (StataCorp).

Results

The baseline characteristics of cases and controls were largely similar (Table 3) but more cases than controls reported having family history of prostate cancer and

Table 2. Prostate cancer–specific dietary recommendations and scoring criteria

Dietary component	Operationalization	Score	Cases ($n = 1,806$) %	Controls ($n = 12,005$) %
Calcium	Calcium intake <1,500 mg/day	1	89.2	89.1
	Calcium intake ≥1500 mg/day	0	10.8	10.9
Tomato and tomato products[a]	Tomato and products >10 servings/wk	1	11.0	13.0
	Tomato and products ≤10 servings/wk	0	89.0	87.0
Selenium	Selenium intake ≥105 to ≤200 μg/day	1	26.3	27.4
	Selenium intake <105 or >200 μg/day	0	73.7	72.6

[a]Tomato products include tomato juice, tomato sauce, pizza, and baked beans.

Table 3. Baseline characteristics of participants

	Controls (maximum, $n = 12{,}005$)		Cases (maximum, $n = 1{,}806$)	
Characteristics	***n***	**Mean (SD) or %**	***n***	**Mean (SD) or %**
Age, y	12,005	61.6 (5.0)	1,806	62.0 (5.0)
Body mass index (kg/m^2)	11,901	27.4 (3.9)	1,787	27.1 (3.6)
Total energy intake (kcal/day)	12,005	2408 (681)	1,806	2398 (679)
Ethnicity				
White	11,843	98.7	1,775	98.3
Others	88	0.7	21	1.2
Missing	74	0.6	10	0.5
Family history of prostate cancer				
Yes	608	5.1	139	7.7
No	10,179	84.8	1,470	81.4
Missing	1,218	10.1	197	10.9
Diabetes				
Yes	884	7.4	111	6.1
No	10,448	87.0	1,580	87.5
Missing	673	5.6	115	6.4
Occupational class				
Managerial	5,843	48.7	851	47.1
Intermediate	1,814	15.1	272	15.1
Working	4,152	34.6	656	36.3
Missing	196	1.6	27	1.5
Smoking status				
Never	4,068	33.9	686	38.0
Past	6,296	52.4	880	48.7
Current	1,585	13.2	239	13.2
Missing	56	0.5	1	0.1
Dietary supplement intake				
Yes	6,027	50.2	938	51.9
No	5,740	47.8	829	45.9
Missing	238	2.0	39	2.2
Stage				
Localized	—	—	1,612	89.3
Locally advanced	—	—	184	10.2
Missing	—	—	10	0.5
Gleason grade				
Low (2–6)	—	—	1,204	66.7
High (7–10)	—	—	596	33.0
Missing	—	—	6	0.3

never-smoking. Conversely, the prevalence of diabetes was lower in cases, as previously published (24). Overall, 50.2% controls and 51.9% cases reported taking dietary supplements. Of these, only a small proportion (17.3% controls, 16.0% cases) provided details on the types of supplement, dosage, and frequency of intake. Four controls and no cases specifically stated that they took lycopene, and 38 controls and four cases took selenium. When the characteristics of controls were compared with WCRF/AICR index scores, men in the highest index score quartiles had lower BMI and total energy intake and were more likely to be non-smokers and of higher occupational class, than those in the lowest quartiles (Supplementary Table S1).

Tables 1 and 2 show the scoring criteria and the proportion of cases and controls who met each of the WCRF/AICR and prostate cancer dietary recommendations, respectively. Adherence to the WCRF/AICR recommendations was similar between cases and controls, although the proportion of controls who met WCRF/AICR recommendations for fruit and vegetable (56.3% vs. 53.3%) and red and processed meat (5.0% vs. 3.6%) intake was slightly higher than that of cases. Adherence to the prostate cancer–specific dietary recommendations was similar in cases and controls (Table 2), but fewer cases (11%) had more than 10 servings of tomato and tomato products per week compared with controls (13%).

Table 4. Associations of WCRF/AICR index score with prostate cancer risk

	WCRF/AICR index score				Dose response	
	0–2	>2 to <3	3 to <4	4–6	(per 1 unit score)	P_{trend}[d]
Controls, *n*	1,983	3,178	4,658	2,186		
Overall cases, *n*	294	479	688	345		
Model 1[a]	1	1.02 (0.87–1.19)	0.99 (0.85–1.14)	1.05 (0.88–1.24)		
Model 2	1	1.01 (0.86–1.18)	0.96 (0.83–1.11)	1.01 (0.85–1.19)	0.99 (0.94–1.05)	0.71
Localized cases[b], *n*	257	429	626	300		
Model 1	1	1.04 (0.88–1.22)	1.02 (0.87–1.19)	1.04 (0.87–1.24)		
Model 2	1	1.02 (0.87–1.21)	0.99 (0.84–1.16)	0.99 (0.83–1.19)	0.99 (0.93–1.05)	0.72
Locally advanced cases[b], *n*	34	48	59	43		
Model 1	1	0.90 (0.57–1.40)	0.73 (0.47–1.12)	1.13 (0.71–1.78)		
Model 2	1	0.90 (0.57–1.40)	0.73 (0.48–1.13)	1.16 (0.72–1.84)	1.00 (0.85–1.18)	0.97
Locally advanced vs. localized[c], *n*	34/257	48/429	59/626	43/300		
Model 1	1	0.86 (0.54–1.38)	0.70 (0.44–1.09)	1.06 (0.65–1.73)		
Model 2	1	0.87 (0.54–1.41)	0.75 (0.47–1.19)	1.17 (0.71–1.94)	1.02 (0.86–1.22)	0.81
Low-grade cases[b], *n*	188	331	465	220		
Model 1	1	1.10 (0.91–1.33)	1.06 (0.89–1.27)	1.07 (0.87–1.32)		
Model 2	1	1.08 (0.90–1.31)	1.02 (0.85–1.22)	1.00 (0.81–1.24)	1.00 (0.93–1.07)	0.93
High-grade cases[b], *n*	106	146	220	124		
Model 1	1	0.84 (0.65–1.09)	0.83 (0.66–1.06)	0.99 (0.75–1.29)		
Model 2	1	0.85 (0.66–1.10)	0.84 (0.66–1.07)	1.00 (0.76–1.31)	0.97 (0.89–1.07)	0.55
High vs. low grade[c], *n*	106/188	146/331	220/465	124/220		
Model 1	1	0.76 (0.55–1.03)	0.79 (0.59–1.05)	0.93 (0.67–1.30)		
Model 2	1	0.74 (0.54–1.01)	0.79 (0.58–1.06)	0.96 (0.68–1.34)	0.97 (0.87–1.09)	0.61

NOTE: Model 1 for cancer subtypes: adjusted for age (continuous variable) and recruitment center; and Model 2: adjusted for family history of prostate cancer, smoking status, and total energy intake (continuous variable). For definitions of localized, locally advanced, and low- and high-grade cancer, please refer to Materials and Methods.

[a]ORs and 95% CIs from conditional logistic regression, matched by 5-year age band and recruitment center, and adjusted by age (continuous variable).

[b]RRRs and 95% CIs from multinomial logistic regression.

[c]RRRs and 95% CIs from logistic regression.

[d]P_{trend} for the association of prostate cancer risk per 1 unit increment in index score.

Table 4 shows the associations of WCRF/AICR index score with prostate cancer risk. In the adjusted models, the WCRF/AICR index score was not associated with overall prostate cancer risk (OR per 1 score increment: 0.99; 95% CI: 0.94–1.05; $P_{trend} = 0.71$). There was no heterogeneity in the association of index score and cancer stage ($P_{trend} = 0.81$) or grade ($P_{trend} = 0.61$). Conversely, adherence to the WCRF/AICR recommendation on plant foods was inversely associated with overall prostate cancer risk and risk of localized prostate cancer (Table 5). A one-quintile increment in the score was associated with 6% reduction in overall prostate cancer risk (OR: 0.96; 95% CI: 0.89, 0.99; $P = 0.02$), and localized prostate cancer (95% CI: 0.89, 0.99; $P = 0.02$). There was no evidence of heterogeneity comparing associations with localized versus locally advanced cancer ($P = 0.81$) or high versus low grade cancer (Supplementary Table S2). When we restricted our analyses for plant recommendation to fruit and vegetable intake only, the inverse association of plant food intake with prostate cancer risk remained (results not shown).

Table 6 shows the associations of prostate cancer dietary index score with prostate cancer risk. A one-point increment in the score was associated with a risk reduction of 9% for overall prostate cancer (95% CI: 0.84–0.99; $P = 0.04$). In analyses of the association between individual components of the index and prostate cancer (Supplementary Table S3), there was an 18% lower risk of prostate cancer associated with adherence to the tomato intake recommendation (eating more than 10 servings per week). When analyzed by cancer stage, the inverse association was observed in localized prostate cancer only (OR: 0.82; 95% CI: 0.70–0.97; $P = 0.02$). There was no evidence of heterogeneity comparing localized and locally advanced prostate cancer ($P = 0.82$).

Discussion

Prostate cancer dietary index score, but not the WCRF/AICR index score, was associated with a decreased risk of overall prostate cancer. There was also some evidence that

Table 5. Associations of the components of WCRF/AICR index score and prostate cancer risk by cancer stage[a]

		Overall prostate cancer			Localized			Locally advanced			Locally advanced vs. localized	
Score	**Control, *n***	***N***	**OR (95% CI)**	**P_{trend}[d]**	***n***	**OR (95% CI)**	**P_{trend}**	***n***	**OR (95% CI)**	**P_{trend}**	**OR (95% CI)**	**P_{trend}**
Body fatness												
0–0.25	5,007	747	1		679	1		65	1		1	
0.5	2,928	448	1.02 (0.90–1.16)		390	0.97 (0.84–1.10)		52	1.37 (0.95–1.99)		1.38 (0.93–2.05)	
0.75	1,998	293	0.96 (0.83–1.11)		264	0.95 (0.81–1.10)		29	1.16 (0.74–1.81)		1.18 (0.73–1.90)	
1	2,072	318	1.00 (0.87–1.16)		279	0.96 (0.82–1.11)		38	1.48 (0.98–2.24)		1.58 (1.01–2.45)	
Dose response[b]			1.01 (0.97–1.05)	0.73		1.00 (0.96–1.04)	0.85		1.11 (0.99–1.24)	0.08	1.11 (0.99–1.26)	0.08
Physical activity												
0	4,796	688	1		602	1		80	1		1	
0.5	3,956	610	1.08 (0.96–1.21)		559	1.13 (1.00–1.28)		47	0.71 (0.49–1.03)		0.62 (0.42–0.93)	
1	3,253	508	1.10 (0.97–1.24)		451	1.11 (0.97–1.27)		57	1.03 (0.72–1.46)		0.96 (0.65–1.41)	
Dose response[c]			1.05 (0.98–1.12)	0.14		1.06 (0.99–1.13)	0.09		1.00 (0.83–1.20)	0.96	0.96 (0.79–1.18)	0.71
Foods and drinks that promote weight gain												
0–0.25	2,948	438	1		386	1		51	1		1	
0.5	4,005	607	1.01 (0.88–1.15)		545	1.03 (0.90–1.19)		60	0.85 (0.58–1.24)		0.79 (0.52–1.20)	
0.75	3,890	606	1.04 (0.91–1.20)		545	1.07 (0.92–1.23)		54	0.79 (0.53–1.17)		0.75 (0.49–1.15)	
1	1,162	155	0.91 (0.74–1.12)		136	0.91 (0.73–1.12)		19	1.02 (0.58–1.78)		1.06 (0.58–1.95)	
Dose response[b]			1.00 (0.95–1.06)	0.96		1.00 (0.95–1.06)	0.97		0.99 (0.85–1.15)	0.86	0.98 (0.83–1.16)	0.81
Plant foods												
0–0.25	1,063	165	1		145	1		18	1		1	
0.5	2,456	398	1.04 (0.85–1.27)		355	1.04 (0.84–1.28)		41	1.06 (0.60–1.87)		0.99 (0.54–1.83)	
0.75	2,547	403	1.00 (0.82–1.22)		357	0.99 (0.80–1.22)		44	1.10 (0.62–1.95)		1.02 (0.55–1.90)	
1	5,939	840	0.87 (0.72–1.06)		755	0.87 (0.71–1.06)		81	0.88 (0.51–1.54)		0.95 (0.52–1.74)	
Dose response[b]			0.94 (0.89–0.99)	0.02		0.94 (0.89–0.99)	0.02		0.94 (0.81–1.09)	0.45	0.98 (0.83–1.15)	0.81
Animal foods												
0	8,277	1,230	1		1,094	1		130	1		1	
0.5	3,129	511	1.09 (0.97–1.22)		458	1.10 (0.98–1.24)		50	1.01 (0.72–1.42)		0.94 (0.65–1.35)	
1	599	65	0.73 (0.56–0.96)		60	0.76 (0.58–1.01)		4	0.43 (0.16–1.19)		0.61 (0.22–1.74)	
Dose response[c]			0.98 (0.89–1.07)	0.61		0.99 (0.90–1.09)	0.84		0.86 (0.65–1.14)	0.28	0.88 (0.65–1.20)	0.43
Alcohol												
0	3,745	559	1		500	1		55	1		1	
0.5	1,788	259	0.97 (0.83–1.14)		232	0.96 (0.82–1.14)		26	1.02 (0.64–1.65)		1.16 (0.70–1.94)	
1	6,472	8	1.00 (0.90–1.13)		880	1.00 (0.88–1.12)		103	1.10 (0.78–1.55)		1.12 (0.77–1.62)	
Dose response[c]			1.00 (0.95–1.06)	0.89		1.00 (0.94–1.06)	0.98		1.05 (0.89–1.25)	0.58	1.05 (0.88–1.26)	0.58

[a]Adjusted for age (continuous variable), recruitment center, family history of prostate cancer, smoking status, and total energy intake (kcal/day). All components were mutually adjusted for each other except for the "foods and drinks that promote weight gain" component.

[b]ORs/RRRs and 95% CIs per 0.25 score increment.

[c]ORs/RRRs and 95% CIs per 0.5 score increment.

[d]P_{trend} were calculated by modeling components of WCRF/AICR score as a continuous variable.

Table 6. Associations of prostate cancer dietary index score with prostate cancer risk

	Prostate Cancer Dietary Index score			Dose response (per 1 unit score)	P_{trend}[d]
	0 to 1	2	3		
Controls, *n*	8,436	3,120	447		
Overall cases, *n*	1,311	437	58		
Model 1[a]	1	0.90 (0.80–1.01)	0.82 (0.62–1.08)		
Model 2	1	0.90 (0.80–1.02)	0.82 (0.61–1.09)	0.91 (0.84–0.99)	0.04
Localized cases[b], *n*	1,165	398	49		
Model 1	1	0.92 (0.82–1.04)	0.78 (0.58–1.06)		
Model 2	1	0.92 (0.81–1.04)	0.78 (0.57–1.06)	0.93 (0.85–1.01)	0.10
Locally advanced cases[b], *n*	138	37	9		
Model 1	1	0.71 (0.49–1.02)	1.18 (0.60–2.34)		
Model 2	1	0.71 (0.49–1.04)	1.17 (0.58–2.36)	0.79 (0.61–1.03)	0.08
Locally advanced vs. localized[c], *n*	138/1,165	37/398	9/49		
Model 1	1	0.81 (0.54–1.19)	1.45 (0.68–3.06)		
Model 2	1	0.84 (0.56–1.25)	1.48 (0.68–3.19)	0.90 (0.69–1.19)	0.46
Low-grade cases[b], *n*	873	292	39		
Model 1	1	0.90 (0.79–1.04)	0.84 (0.60–1.17)		
Model 2	1	0.89 (0.77–1.03)	0.82 (0.59–1.16)	0.93 (0.84–1.03)	0.15
High-grade cases[b], *n*	433	144	19		
Model 1	1	0.89 (0.73–1.08)	0.80 (0.50–1.28)		
Model 2	1	0.92 (0.75–1.12)	0.83 (0.51–1.34)	0.90 (0.78–1.04)	0.16
High vs. low grade[c], *n*	433/873	144/292	19/39		
Model 1	1	0.99 (0.78–1.25)	1.06 (0.60–1.88)		
Model 2	1	1.04 (0.81–1.33)	1.13 (0.63–2.03)	0.98 (0.82–1.18)	0.86

NOTE: Model 1 for cancer subtypes: adjusted for age (continuous variable) and recruitment center; and Model 2: further adjusted for family history of prostate cancer, smoking status, and total energy intake (continuous variable).

[a]ORs and 95% CIs from conditional logistic regression, matched by 5-year age band and recruitment center, and adjusted by age (continuous variable).

[b]RRRs and 95% CIs from multinomial logistic regression.

[c]RRRs and 95% CIs from logistic regression.

[d]P_{trend} for the association of prostate cancer risk per 1 unit increment in index score.

following the WCRF/AICR plant recommendation and eating more than 10 servings of tomato and tomato products per week was associated with a reduced risk of overall and localized prostate cancer.

Our findings of a null association between overall prostate cancer risk and adherence to WCRF/AICR recommendations is consistent with the large EPIC cohort study (5). There is only one study that examined the association by cancer stage and grade (6). In that case-only study, an inverse relationship between WCRF/AICR index score and risk of aggressive prostate cancer was reported (OR per 1 increment in score: 0.87; 95% CI: 0.79–0.96). However, differences in definition of cancer subtypes and scoring system for operationalization preclude us from directly comparing our results.

We were able to assess changes in body size throughout adulthood instead of a single measurement of BMI around the time of diagnosis. We also had waist measurements of participants, albeit around the time of diagnosis only, to operationalize the WCRF/AICR body fatness recommendation. Using recalled body size might result in nondifferential misclassification and bias the result to null. However, recalled body size has been shown to have a moderate correlation with measured body mass index at childhood and adolescence (25). Adherence to the body fatness recommendation, based on men's BMI around the time of diagnosis, was also not associated with prostate cancer risk in our study (results not shown).

Meeting the recommendation on plant foods have a dose-dependent inverse relationship with overall ($P_{trend} = 0.02$) and localized prostate cancer ($P_{trend} = 0.02$). There was also a risk reduction of similar magnitude for locally advanced cases, although the confidence interval was wide. Plant foods contain a variety of nutrients and phytochemicals; cruciferous vegetables in particular have been linked to decreased risk of prostate cancer incidence and progression (26, 27). Despite this, evidence on the plant food–prostate cancer association is inconsistent. This may be due to differences in methodology (quantification and definition), small range of intake, and residual confounding of healthy lifestyle behaviors (28, 29). It is plausible that the beneficial effect of plant food intake

observed in our study is due to a wider range of fruit and vegetable and dietary fiber intake in our participants as compared with other large cohort studies (30, 31). We also defined dietary fiber as nonstarch polysaccharides rather than using the Association of Analytical Communities' definition.

To our knowledge, this is the first study to develop a prostate cancer dietary index based on dietary risk factors for prostate cancer. This index score was inversely associated with prostate cancer risk in a dose-dependent nature. Although the evidence for heterogeneity comparing localized versus locally advanced prostate cancer was weak ($P = 0.08$), risk reduction was higher in locally advanced prostate cancer. Epidemiologic evidence suggests that selenium and tomato exert a higher risk reduction effect on advanced or aggressive prostate cancer than localized cancer (32). Conversely, risk of advanced and fatal prostate cancer is higher in men with high calcium intake (33, 34). To maintain bone health, men in the United Kingdom are still advised to meet the recommended calcium intake of 750 mg/day, as the increase in prostate cancer risk was only apparent at intake above 1,500 mg/day (4).

The association between prostate cancer risk and the prostate cancer dietary index score was largely driven by high consumption of tomato and tomato products. The effect estimate for the association of tomato intake and overall prostate cancer risk is consistent with a risk reduction of about 20% to 30% reported in a meta-analysis (32). It has been postulated that the protective effect is conferred by lycopene, the major carotenoid in tomato, although epidemiologic evidence remained controversial (32, 35). While lycopene is more bioavailable in tomato products as a result of food processing and preparation, men should consume pizza, tomato sauce, and baked beans in moderation due to their high salt, sugar, and fat content. The lack of association observed for calcium and selenium with prostate cancer risk in our study might be due to misclassification of men by their intakes. This is because we did not have sufficient information on the types, dosage, and frequency of supplement intakes, so the true intakes of these nutrients might be underestimated. Nonetheless, men should obtain these nutrients from dietary sources as much as possible and avoid taking high-dose supplements as there is no evidence that supplements have beneficial effects on prostate cancer.

In our study, the risk reduction was higher for locally advanced than localized prostate cancer in men with optimal dietary selenium intake (29% vs. 3%), but the confidence interval was wide. A recent observational study conducted in a low selenium status population reported 63% risk reduction of advanced prostate cancer for men in the highest quintile of toenail selenium concentration compared with the lowest quintile (36). We included selenium to the index, despite the fact that the Selenium and Vitamin E Cancer Prevention Trial (SELECT) reported a null effect of selenium supplementation on prostate cancer risk. Some argued that participants of SELECT were selenium-replete at baseline, so supplementation would not provide additional benefit (37, 38).

Strengths of our study include its relatively large sample size and population-based, prospective design. Detection bias was minimized, as case finding was part of the trial design and there were accurate records of cancer stage and grade, allowing stratification of associations by cancer stage and grade. It is possible that men with vague symptoms might be more likely to participate in our study. However, we believe that this is marginal and unlikely to bias our results, as a characteristic of PSA-detected prostate cancers is that they are largely small, organ confined, and asymptomatic. We also assessed potential recall bias among men who filled in their questionnaire after receiving their initial PSA test results. As an elevated PSA may be indicative of prostate cancer, men who completed their questionnaire after knowing their PSA test result may report their diet, health, and lifestyle differently from those who did not. The effect estimates for the associations did not differ appreciably (results not shown).

Although we used validated and detailed questionnaires, there might still be measurement errors and misclassification of exposures. Compared with food diaries, FFQ is prone to a greater degree of misclassification, but the effect is likely to be nondifferential as most of the questionnaires (80.3%) were filled out before the receipt of initial PSA test results. Thus, the true effect of adherence to WCRF/AICR recommendations and prostate cancer dietary guidelines on prostate cancer risk might be underestimated. While FFQ is not the gold standard for assessing selenium intake, a recent review showed that compared with diet records they gave acceptable values for selenium over the long term (39). In addition, a study in New Zealand found that selenium intakes assessed by diet records were very similar to those measured by chemical analysis in duplicate diets. Thus, the available literature suggests some validity for dietary methods (40).

We were unable to operationalize WCRF/AICR recommendations on "dietary supplements" and "preservation, processing, preparation." Evidence remains inconclusive on the association between dietary supplements and prostate cancer incidence (4, 41). There is currently no evidence to suggest that the latter recommendation, which advocates lower salt intake, is a risk factor for prostate cancer (4). Inclusion of these recommendations in the index score could have biased the results toward null. We cannot rule out chance findings due to multiple testing. To minimize this error, we had decided *a priori* on the variables to be tested and used a strength of evidence approach to interpret our results (42).

In conclusion, the prostate cancer dietary index but not the WCRF/AICR index was associated with decreased risk of prostate cancer. Adherence to WCRF/AICR recommendations alone is insufficient for prostate cancer prevention. In addition to meeting the optimal intake for the three dietary factors associated with prostate cancer, men

should maintain a healthy weight and an active lifestyle to reduce risk of developing prostate cancer, cardiovascular diseases, and diabetes (43). The prostate cancer dietary index requires validation, and additional dietary recommendations to prevent prostate cancer should be developed. High intake of plant foods and tomato products in particular may help protect against prostate cancer, which warrants further investigations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The views expressed in this study are those of the authors and do not necessarily reflect those of Cancer Research UK, the NHS, the NIHR, or the Department of Health.

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