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Dietary glycemic index, glycemic load, insulin index, fiber and whole grain intake, in relation to risk of prostate cancer

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Abstract

Objective—Insulin may play a role in prostate cancer tumorigenesis. Postprandial blood glucose and insulin responses of foods depend importantly on the carbohydrate quality and quantity, represented by glycemic index (GI), glycemic load (GL), fiber, and whole grain content, but are also influenced by intake of protein and other characteristics. The recently developed insulin index (II) quantifies the postprandial insulin secretion, also taking into account these additional characteristics.

Methods—We investigated the association between dietary GI, GL, II, fiber and whole grains and risk of total prostate cancer (n=5,112) and subgroups of prostate cancer as defined by stage or grade in 49,934 male participants of the Health Professionals Follow-up Study. Multivariate adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazards regression.

Results—Dietary GI, GL, II or fiber were not associated with risk of total or subgroups of prostate cancer. We observed a positive association between dietary intake of whole grains and total prostate cancer (HR highest versus lowest quintile 1.13, 95% CI 1.03–1.24), which was attenuated after restriction to PSA-screened participants (HR 1.03, 95% CI 0.91–1.17).

Conclusions—These results suggest that long-term exposure to a diet with a high insulin response does not affect prostate cancer incidence.

Keywords

glycemic index; glycemic load; insulin index; fiber; whole grains; prostate cancer

Introduction

During the 20th century, prostate cancer incidence rose dramatically in Western countries and incidence rates increase among migrants from Asian or African to Western countries [1, 2]. It has been proposed that these increases may be at least partly explainable by alterations in insulin metabolism related to Western diet and lifestyle. Circulating insulin has been

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shown to play a role in prostate cancer tumorigenesis by inhibiting apoptosis and stimulating cell proliferation [3]. In addition, insulin may alter tumor development through alterations in sex-hormone metabolism and by influencing the insulin-like growth factor (IGF) axis, i.e. increasing bioactivity of IGF-1, partly by reducing IGF binding protein levels [4, 5]. In two recent meta-analyses, high circulating IGF-1 was consistently associated with moderately increased risk of prostate cancer [6, 7]. In a recently published case-cohort analysis, fasting serum insulin was associated with increased prostate cancer risk [8]. Thus, elevated insulin levels may increase risk of prostate cancer, and could be potentially modifiable by dietary and life-style interventions.

Several dietary factors may affect levels of circulating insulin [4]. Carbohydrate restriction reduces serum insulin levels more effectively than fat restriction [9]. The effect of carbohydrates on blood glucose and insulin levels depends on the carbohydrate quality, which can be characterized by the diet's glycemic index (GI), glycemic load (GL), fiber or whole grain content. However, carbohydrates are not the only stimulus for insulin secretion. Especially in combination with carbohydrates, protein and fat act synergistically to enhance insulin secretion and reduce blood glucose concentrations [10]. The GI is a measure of carbohydrate quality that characterizes the carbohydrate in a food according to its relative effect on postprandial blood glucose levels, with the same amount of carbohydrate from glucose or white bread as the reference food. The GI concept does not allow testing for foods with low or no carbohydrate content. More recently, a food insulin index (II) has been suggested, which compares the postprandial insulin secretion (insulin response) of foods, including those with low or no carbohydrate content, to a reference food (analogous to the GI concept glucose or white bread) [10].

Epidemiological studies relating nutritional factors that determine the insulin response to the risk of prostate cancer have been inconclusive so far. In a case-control study, the odds ratios of prostate cancer were elevated in men with high average dietary GI or GL [11]. However, in a prospective investigation, no significant association between dietary GI or GL and risk of prostate cancer was observed [12]. Dietary fiber intake has been inconsistently related to the risk of prostate cancer in several case-control [13–15] and one cohort study [16]. The association between consumption of whole grains and prostate cancer has been investigated in two case-control studies [15, 17] with inconsistent results. No study so far has investigated the association of long-term dietary insulin demand represented by dietary II in relation to prostate cancer.

In this paper, we hypothesized that a diet characterized by high intake of rapidly absorbable carbohydrates represented by high GI/GL, and low intakes of fiber and whole grains, is associated with greater risk of prostate cancer. In addition, we investigated whether a high predicted dietary insulin demand represented by the newly developed II is associated with increased risk of prostate cancer. Because these dietary factors may also influence prostate cancer progression, we additionally examined advanced stage/fatal, organ-confined, low-grade and high-grade prostate cancer separately.

Materials and Methods

Study population

The Health Professionals Follow-up Study (HPFS) is an ongoing prospective cohort study to investigate the causes of chronic disease. The study was initiated in 1986 when 51,529 US male health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, veterinarians) aged between 40 and 75 years completed and returned a mailed health questionnaire ascertaining information on diet, anthropometric and lifestyle factors as well as medical history. Since study onset, the men completed biennial questionnaires to update

lifestyle factors and elicit new medical diagnoses. Follow-up questionnaires are sent to participants biannually to ascertain the onset of a variety of diseases and to update exposure information such as body weight, smoking status and physical activity. Follow-up rate exceeds 90%.

Dietary assessment

Dietary intake was ascertained by self-administered mailed food frequency questionnaires (FFQ) in 1986, 1990, 1994, 1998 and 2002. The semi-quantitative food frequency questionnaire contains a list of 131 food and beverage items for which commonly used units or portion sizes are specified. Participants are asked to report how often, on average, over the previous year, they consumed a serving of each food item with 9 possible response categories ranging from “never or less than once per month” to “6 or more times per day”. Daily nutrient intakes were calculated from FFQ data by multiplying the nutrient content per serving of each food by the indicated frequency of consumption (servings of that food per day) and summing over all foods.

The GI of a food is formally based on the incremental blood glucose area under the curve (AUC) over two hours after eating 50g carbohydrate from a test food divided by the AUC evoked by ingestion of the same amount of carbohydrates from a reference food [18]. A GI value for each carbohydrate-containing FFQ-item (with glucose as reference food) was assigned by using either published estimates [19] or values derived from direct testing of food items at the Nutrition Center of the University of Toronto (Prof. David J. Jenkins). The individual average GL during the past year was calculated by multiplying the carbohydrate content of each food item by its GI and the consumption frequency and summing values for all reported food items: $GL_{ave}=\sum_{a=1}^{n} GI_a \times CHO_a \times Frequency_a$; where n is the number of foods consumed, GI_a is the glycemic index for food a, CHO_a is the carbohydrate content per serving of food a, and $Frequency_a$ is the consumption frequency of one serving of food a during the past 12 months.

The average dietary GI was obtained by dividing the average GL by the total amount of carbohydrate intake:

$$GI_{ave}=\frac{\sum_{a=1}^{n}(GI_a \times CHO_a \times Frequency_a)}{\sum_{a=1}^{n}(CHO_a \times Frequency_a)}.$$

The II of a food is based on the incremental insulin AUC over two hours in response to consumption of a 1000 kJ portion of the test food divided by the AUC after ingestion of a 1000 kJ portion of the reference food. Analytical data on the food II of the FFQ items (with glucose as reference food) were provided by Prof. Jennie Brand Miller of the University of Sydney, Australia. US food items, selected to be representative for various FFQ items, were shipped to the laboratory in Sydney for testing. Food insulin indexes were assigned to the FFQ items using this newly analyzed data as well as previously published data [20]. The average dietary II was calculated by summing the product of food insulin index, energy content and consumption frequency over all FFQ items, divided by total energy intake:

$$II_{ave} = \frac{\sum_{a=1}^{n} (FII_a \times Energy_a \times Frequency_a)}{\sum_{a=1}^{n} (Energy_a \times Frequency_a)}$$; where *n* is the number of foods consumed, FII_a is the food II of food *a* and $Energy_a$ is the energy content of food *a* and $Frequency_a$ is the daily consumption frequency of one serving of food *a* during the past 12 months.

The calculation of whole grain intake has been described previously [21]. Using a specifically developed whole-grain database, whole grain content was assigned to all grain foods (rice, bread, pasta and breakfast cereals) according to the dry weight of whole-grain ingredients. Whole grains were considered in their intact and pulverized form containing the expected proportion of bran, germ and endosperm for the specific grain types. Ingredients in the database that were considered whole grains included whole wheat and whole wheat flour, whole oats and whole oat flour, whole cornmeal and whole corn flour, brown rice and brown rice flour, whole rye and whole rye flour, whole barley, bulgur, buckwheat, popcorn, amaranth, and psyllium. Dietary intake of fiber was calculated using data provided by the US Department of Agriculture [22].

Identification of prostate cancer

Participants reported a variety of diseases including prostate cancer on the biannual follow-up questionnaires. After each new report of prostate cancer, we sought written permission to obtain medical and pathology reports from the participant, or from the next-of-kin decedent in the event of death. By means of these records, study investigators blinded to the information from the questionnaire confirmed the diagnosis and ascertained information on stage at diagnosis and Gleason sum. Between baseline (1986) and January 31st 2007, 5112 incident cases of prostate cancer were documented. Of these, 860 were classified as advanced stage/fatal (T3b, T4, N1, M1 at diagnosis or had metastases during follow-up or died due to prostate cancer). We confirmed 3593 cases as organ-confined or limited extraprostatic extension (T1b, T1c, T2, T3a and N0 or Nx and M0), and the remainder could not be assigned a stage. For Gleason grade, 1932 cases were high-grade (Gleason sum ≥ 7) and 2119 low-grade (Gleason sum < 7), and for the remaining 21%, Gleason sum could not be determined with confidence.

Statistical analysis

We excluded men who reported cancer (other than non-melanoma skin cancer) at baseline (n=2,000) or did not return or not adequately fill in (70 or more items left blank) the food frequency questionnaire (n=1,597). Each of the remaining 49,934 individual's person-time was calculated from date of return of the baseline questionnaire to the date of prostate cancer diagnosis, date of death from any cause, or the end of follow-up (30th January 2007), whichever came first. All dietary variables except GI and II were energy-adjusted by the residual method. To reduce intra-individual variation and best represent long-term intake, cumulative updated average of dietary GI, GL, II, fiber and whole grain intakes were calculated and categorized into quintiles based on the total study population. Hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) adjusted for potential confounders were estimated using Cox proportional hazards regression for total prostate cancer, advanced/fatal prostate cancer, organ-confined prostate cancer, high-grade and low-grade prostate cancer. Models were stratified by period and age (in months) and adjusted for covariates that previously have been associated with risk of prostate cancer or are associated with one of the exposure variables. Covariates included BMI, height, history of diabetes, family history of prostate cancer, race/ethnicity (African, Caucasian, Asian, other), smoking (never or quit>10 years, current or quit ≤10 years and ≤15 cigarettes/day, current or quit

≤10 years and >15 cigarettes/day), vigorous physical activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/week), energy intake (kcal/day, quintiles), alcohol intake (g/day, quintiles), calcium intake (500–749, 750–999, 1000–1499, 1500–1999, ≥2000 mg/day), alpha-linolenic acid (g/day, quintiles), tomato sauce (never, 0–0.5, 0.5–1, >1 servings/week). We ran models with and without adjusting for dietary intake variables (energy, alcohol, calcium, alpha-linolenic acid and tomato sauce intake), but due to similar results, only the fully adjusted models are presented. We tested for linear trend over quintiles by assigning the median value to each category and entering this variable as continuous variable to the model.

To investigate whether introduction of PSA screening influenced our results, we repeated all analyses in a study population restricted to subjects who reported having had a PSA test by 1994 (the first year that we asked about PSA-screening in the follow-up questionnaire), 1996, 1998, 2000, 2002, or 2004, and began follow-up in 1994 or in the year of the first reported PSA-screening (after 1994). Through this analysis, we exclude prevalent cases at baseline and because once men in the cohort received their initial PSA screening, their subsequent screening rate was uniformly high, we reduce the potential for detection bias.

Because the influence of high GI or II diets may be accentuated in men who are insulin resistant, we ran models stratified by BMI (a surrogate of insulin resistance), and diabetes (at baseline or during follow-up). We further stratified by age at diagnosis (<65 years/≥ 65 years), as associations with BMI, energy intake and physical activity in this cohort tended to differ by age [23–25]. We formally tested for interaction by creating cross-product terms and evaluating these using the Wald-test.

All P-values are based on two-sided tests. Statistical analyses were performed using SAS release 8.2 (SAS Institute, Cary, NC).

Results

BMI, height, family history of prostate cancer, Caucasian ethnicity, and diabetes at baseline or during follow-up did not vary remarkably across quintiles of GI, GL, II, fiber or whole grains intake (Table 1). Men in the upper quintiles of GL, II, fiber and whole grains intake were less likely to be current smokers. Participants in the upper quintiles of fiber and whole grains intake reported more regular vigorous physical activity (≥ 10.5 MET hours/week). Men in the upper quintiles of all exposure variables had a lower intake of alcohol and total fat and a higher intake of carbohydrates.

The top three FFQ items (% contribution) contributing to total intake were mashed potatoes (7%), cold cereals (6%) and dark bread (5%) for glycemic load, mashed potatoes (6%), cold cereals (5%) and beef (5%) for overall dietary insulin demand (insulin load), cold cereals (34%), dark bread (18%) and pasta (8%) for fiber, and cold cereals (39%), brown rice (16%) and dark bread (15%) for whole grain intake (figures derived from 1986 FFQ). Spearman correlation coefficients between the GI, GL and II were as follows: GIxGL, r=0.52; GIxII, r=0.46; GLxII, r=0.75; (all p-values <0.0001).

No significant associations were observed for GI, GL, or II with total prostate cancer or subgroups of prostate cancer (Table 2). There was a weak positive association between average dietary GI and risk of low-grade prostate cancer (HR comparing highest versus lowest quintile 1.15, 95% CI 0.99–1.34, p-trend=0.09). Dietary fiber was not associated with total, advanced/fatal, organ-confined or low-grade prostate cancer, but marginally associated with high-grade prostate cancer (HR highest versus lowest quintile 1.22, 95% CI 1.04–1.44, p-trend=0.07). We observed a statistically significant positive association between whole-grain intake and risk of total prostate cancer (HR highest versus lowest quintile 1.13, 95%

CI 1.03–1.24, p-trend=0.001) as well as for organ-confined, high-grade and low-grade prostate cancer, but not for advanced prostate cancer.

When the cohort was restricted to men who had at least one PSA screening test by 2004, dietary GI was significantly positively associated with low-grade prostate cancer (HR highest versus lowest quintile 1.24, 95% CI 1.02–1.50, p-trend=0.05). Apart from this finding, no association was observed between GI, GL or II and total or subtypes of prostate cancer. Dietary fiber intake was unrelated to total prostate cancer, and subtypes of prostate cancer, including high-grade prostate cancer in this screened sub-cohort. Dietary intake of whole grains was unrelated to total, advanced, and low-grade prostate cancer among men who had undergone at least one PSA-screening test, while a non-significant positive association persisted with organ-confined and high-grade prostate cancer.

In an additional analysis, we compared combined tertiles of GL and fiber or whole grain intake with respect to risk of prostate cancer. Men with high GL and low fiber intake had a non-significantly decreased risk of total prostate cancer compared to men with low GL/high fiber intake (HR 0.90, 95% CI 0.74–1.08). When comparing men with high GL and low whole grain intake to men with low GL and high whole grain intake HR was 0.91 (95% CI 0.77–1.08). These results were not altered after restriction to screened men.

History of diabetes was included as covariate in all models presented in tables 2 and 3. Exclusion of this variable from the model did not change the results appreciably. In addition, results remained stable after exclusion prevalent and incident diabetes cases (n=4,688) from analysis. In previous studies on diabetes [26–28], glycemic load and cereal fiber intake negatively confounded each other. When we ran the models for GI, GL and II with additional adjustment for cereal fiber intake, risk estimates changed only marginally. Also, risks of prostate cancer were not increased for the combination of a high glycemic load and a low cereal fiber intake compared with the opposite extreme.

We did not observe major modification of risk estimates after stratification by BMI, diabetes and age at diagnosis and all p-values for interaction were >0.05 (data not shown).

Discussion

Our findings suggest that there is no strong association between dietary GI, GL, II, fiber or whole grains intake in relation to prostate cancer. We observed a weak positive association between dietary GI and low-grade prostate cancer, which was slightly stronger after restriction to men who have had a PSA test. In contrast, the observed significant positive association between dietary intake of whole grains and prostate cancer did not persist when the cohort was restricted to PSA-screened men.

Few studies have related dietary factors that are likely specifically to influence insulin levels to prostate cancer incidence. Our observation of no overall association between GI or GL and risk of total prostate cancer is in agreement with results from a large cohort study of 262,642 men aged 50–71 years at baseline (15,949 prostate cancer cases) [12]. However, one case-control study reported significant positive associations with both GI and GL in relation to prostate cancer [11]. Neither of these two studies investigated subgroups of prostate cancer as defined by stage or grade. We observed a weak positive association between GI but not GL and risk of low-grade prostate cancer, which persisted after restriction to men with PSA-screening. Although this might be a chance finding, it is noteworthy that in several nested case-control studies [29–31], including one within HPFS [30], IGF-1 was more strongly associated with low-grade than with high-grade prostate cancer.

Dietary II was unrelated to risk of total prostate cancer and subgroups of prostate cancer. In most studies relating dietary GI or GL to cancer risk the underlying hypothesis was modulation of the insulin and IGF axes. The dietary GI is based on the postprandial increase in blood glucose levels, while the II is directly based on the postprandial insulin response. Since the increase in blood glucose levels is not always proportional to the insulin response, the II seems to be the more relevant measure to test this hypothesis. The II of mixed meals predicted the insulin response better than GL in a small group (n=11) of lean young healthy men [10]. At the current stage of research, further studies on the validity, reproducibility and usefulness of the food II with respect to clinical settings as well as to epidemiological research are warranted. Our results suggest that long-term exposure to high postprandial insulin responses is not associated with risk of prostate cancer incidence or progression. This finding needs to be confirmed in other studies.

Dietary fiber was not associated with total prostate cancer in our study, which is in agreement with several case-control studies [13, 14, 32] and one cohort study [16]. In contrast, a recent case-control study found a significant inverse association between dietary fiber and prostate cancer risk [15]. We observed a significant positive association between fiber intake and high-grade prostate cancer, which, however, disappeared after restriction to men with PSA-screening.

We found whole grain intake to be significantly positively associated with total prostate cancer, but this finding was largely attenuated in the analysis limited to men who had PSA screening. A significant positive association between grain intake and prostate cancer has been observed in an case-control study [15]. In this study, however, the definition of grains did not distinguish between whole grains and refined grains, so that it remains unclear whether this result is driven by whole grains. Another case-control study observed no association between consumption of whole grain foods (essentially whole grain bread or pasta) and prostate cancer [17].

In light of the overall null results of this study, the ability to validly estimate dietary exposures by means of semi-quantitative FFQs is crucial. The repeated measurement of dietary intake by FFQs every 4 years reduces measurement error and is suitable to best reflect long-term dietary intake. Validation studies relating dietary intake assessed by FFQ to metabolic biomarkers, as surrogate markers to test for validity have been performed [33–35].In the Nurses' Health Study (NHS), high dietary GI/GL assessed by FFQ were associated with lower plasma HDL cholesterol (percentage difference between highest and lowest quintile of both GI and GL minus 11%) and higher fasting plasma triacylglycerol (percentage difference plus 75% for GI and plus 18% for GL) [34] and were positively associated with plasma C-peptide (percentage difference 16% for GL) [35], a marker of insulin secretion. In addition, cereal fiber (in HPFS, percentage difference minus 15.6%) [35] as well as whole grain intakes (in HPFS and NHS, percentage difference minus 14%) [33] were inversely associated with plasma C-peptide. The dietary II was positively associated with fasting plasma triacylglycerol in a subgroup of the current study population (percentage difference plus 26%, unpublished data). Dietary GI and GL have been positively associated with type 2 diabetes [26–28] and inverse associations have been observed between dietary intake of fiber [26, 27] and whole grains [36], and type 2 diabetes. These studies demonstrate the ability to measure the here investigated dietary exposure variables by means of FFQ. The dietary variables investigated here tended to be associated with a healthier lifestyle reflected by less smoking and higher vigorous physical activity. Although it is possible that measurement error in exposure or residual confounding may have contributed to the observed null-associations, it is rather unlikely that a substantial association would have been missed. However, we cannot rule out a small association.

Detection bias due to PSA screening is critical when participation in PSA-screening is associated with the exposure of interest. This was not the case for GI, GL and II, but PSA-screening seemed to be slightly more frequent in men with high intake of fiber and whole grains in our study population. Thus, the positive association between dietary fiber and high-grade prostate cancer, as well as whole grain intake and total prostate cancer observed in the total cohort may be biased by more frequent PSA-screening among men with high intake of fiber or whole grains, respectively. Supporting this assumption, these positive associations disappeared in a cohort restricted to men who reported to have participated in at least one PSA-test by 2004. In contrast, results for GI, GL, and II remained unchanged after this restriction for PSA screening.

We had hypothesized that the group of dietary exposure variables investigated in this study might be related to incidence of prostate cancer via alterations in fasting circulating insulin levels. Insulin may affect cancer development by both exerting mitogenic effects itself and by decreasing IGF binding proteins (IGFBPs) thereby increasing the bioactivity of IGF-1, which is a generally stronger mitogen than insulin [37]. Although not entirely consistent, several studies have shown that fasting insulin [8, 38, 39], or plasma C-peptide [40, 41] were associated with prostate cancer incidence or mortality. In addition, a large body of epidemiological evidence is in favor of a moderate positive association between circulating IGF-1 and risk of prostate cancer, which is supported by two recent meta-analyses [6, 7]. The fact that we did not observe any strong associations between dietary factors that are likely to influence insulin response, and risk of prostate cancer does not necessarily negate the insulin hypothesis, because absolute long-term insulin exposure is additionally influenced by anthropometric factors, physical activity, genetic and epigenetic factors, dietary factors influencing insulin resistance (which differ from those that influence secretion), and beta-cell depletion. However, our findings suggest that in the context of the many factors that influence insulin levels, dietary factors specifically related to the insulin response are unlikely to be major determinants of prostate cancer risk.

A meta-analysis suggested an overall direct positive association between GI and GL and colorectal and endometrial cancer [42]. The present study, however, suggests that for prostate cancer, GI and GL are not strong predictors of incidence or mortality. It is notable that BMI, which causes hyperinsulinemia, is a strong risk factor for those cancers, whereas it is not for total prostate cancer; hence our data are consistent with these observations. In summary, the findings of this study do not support the hypothesis that dietary GI, GL, II, fiber and whole grains are related to the risk of prostate cancer.

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Table 1

Lifestyle and dietary characteristics (at baseline unless otherwise indicated) according to the lowest, middle and highest quintiles (Q) of glycemic index, glycemic load, insulin index, fiber and whole grain intake in US men in the Health Professionals Follow-Up Study (HPFS)

	Glycemic index (index/day)			Glycemic load (load/day)			Insulin index (index/day)			Fiber (g/day)			Whole grains (g/day)		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
	≤50.39	52.49–54.12	≥55.96	≤103	118–130	≥145	≤36.52	39.59–41.97	≥44.65	≤15.4	18.6–21.6	≥26.0	≤6.5	13.3–21.4	≥34.3
Number of men	9993	9949	9974	10085	10440	10233	9989	9990	9985	9875	9983	9903	9965	9962	10002
Age (y)	54.9	53.6	52.7	54.3	53.5	53.7	54.8	53.4	53.2	51.7	53.4	55.9	53.5	53.3	54.8
BMI (kg/m^2)	25.8	25.6	25.2	26.1	25.6	24.8	25.8	25.7	25.1	25.8	25.7	25.0	25.8	25.7	24.8
Height (inches)	70.0	70.1	69.9	70.1	70.1	69.9	70.1	70.0	70.0	70.1	70.1	70.0	69.9	70.1	70.1
Family history (%)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Current smokers (%)	11	9	9	16	8	5	16	8	5	19	8	4	17	9	4
Caucasian (%)	92	91	89	92	91	88	91	91	90	91	91	90	89	91	91
Diabetes at baseline (%)	4	3	3	4	3	2	4	3	3	2	3	4	3	3	4
Diabetes at baseline or during follow up (%)	8	7	7	8	7	5	8	7	6	6	7	7	7	7	7
Ever PSA screening by 2004 (%)	81	81	80	79	82	80	79	82	81	77	82	82	78	81	83
Vigorous physical activity ≥10.5 METs/week (%)	28	28	23	22	28	30	24	28	29	19	27	35	20	27	34
Dietary intake of Energy (kcal/day)	1870	2005	2031	1959	2027	1933	1902	2011	2018	1950	2021	1954	1980	2051	1865
Alcohol (g/day)	16	11	8	23	9	4	26	8	4	19	11	7	14	11	8
Total fat (g/day)	73	72	69	82	73	58	76	73	63	77	73	61	76	73	63
Protein (g/day)	97	93	87	100	93	83	96	94	87	90	93	94	90	93	94
Carbohydrates (g/day)	218	235	250	179	235	291	191	237	275	205	232	273	217	231	262
Fructose (g/day)	24	25	27	16	25	36	19	26	30	21	24	32	24	25	27
Calcium (mg/day)	1044	887	767	868	908	907	814	890	980	846	877	990	789	900	1001
α-Linolenic acid (gm/day)	1.06	1.09	1.06	1.12	1.09	0.99	1.12	1.09	0.99	1.04	1.09	1.06	1.08	1.09	1.03
Tomato sauce (servings/day)	0.14	0.14	0.11	0.12	0.14	0.14	0.13	0.14	0.13	0.09	0.14	0.18	0.13	0.14	0.13
Skimmed milk (servings/day)	0.95	0.75	0.49	0.64	0.80	0.72	0.45	0.75	0.98	0.74	0.74	0.74	0.55	0.78	0.86
Glycemic index	48	53	58	50	53	56	50	53	55	53	53	53	53	53	54
Glycemic load	104	125	144	89	124	161	96	125	151	108	123	143	114	122	141
Insulin index	37	41	44	35	41	46	33	41	48	38	41	42	39	40	43

	Glycemic index (index/day)			Glycemic load (load/day)			Insulin index (index/day)			Fiber (g/day)			Whole grains (g/day)		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
	≤50.39	52.49–54.12	≥55.96	≤103	118–130	≥145	≤36.52	39.59–41.97	≥44.65	≤15.4	18.6–21.6	≥26.0	≤6.5	13.3–21.4	≥34.3
Fiber (g/day)	21	21	20	17	21	26	19	21	23	13	20	32	17	20	27
Whole grains (g/day)	17	23	26	13	21	34	16	22	29	9	20	40	3	17	53

NOTE: All variables (except age) are age-standardized; mean values unless indicated otherwise

Q=quintile; BMI=body mass index; PSA=prostate specific antigen;

Table 2

Multivariate HR (95% CI) of prostate cancer and subgroups of prostate cancer in relation to dietary glycemic index, glycemic load, insulin index, fiber and whole grains in the Health Professionals Follow-Up Study, 1986-January 2007

	Q1	Q2	Q3	Q4	Q5	p_{trend}
Glycemic index (index/day)	≤50.39	50.40–52.48	52.49–54.12	54.13–55.97	≥55.98	
Total Prostate Cancer (n=5112)	1.00	1.05 (0.96, 1.14)	1.09 (1.00, 1.19)	1.12 (1.02, 1.23)	1.00 (0.91, 1.10)	0.38
Advanced/fatal (n= 860)	1.00	1.12 (0.91, 1.39)	1.19 (0.96, 1.48)	1.26 (1.01, 1.57)	1.05 (0.83, 1.33)	0.34
Organ-confined (n=3593)	1.00	1.08 (0.98, 1.20)	1.12 (1.01, 1.24)	1.15 (1.04, 1.28)	1.02 (0.91, 1.14)	0.32
High-grade (Gleason ≥ 7) (n=1932)	1.00	1.09 (0.94, 1.25)	1.08 (0.93, 1.24)	1.19 (1.02, 1.37)	0.95 (0.81, 1.12)	0.80
Low-grade (Gleason < 7) (n= 2119)	1.00	1.14 (1.00, 1.31)	1.17 (1.02, 1.35)	1.12 (0.97, 1.30)	1.15 (0.99, 1.34)	0.09
Glycemic load (load/day)	≤103	104–117	118–130	131–144	≥145	
Total Prostate Cancer (n=5112)	1.00	1.08 (0.99, 1.18)	1.02 (0.93, 1.12)	1.09 (0.99, 1.20)	1.04 (0.94, 1.16)	0.46
Advanced/fatal (n= 860)	1.00	1.07 (0.86, 1.33)	0.98 (0.78, 1.24)	0.97 (0.76, 1.23)	1.09 (0.86, 1.40)	0.73
Organ-confined (n=3593)	1.00	1.15 (1.03, 1.28)	1.08 (0.97–1.21)	1.12 (1.00–1.26)	1.04 (0.92–1.18)	0.74
High-grade (Gleason ≥ 7) (n=1932)	1.00	1.16 (1.00–1.35)	1.17 (1.01–1.37)	1.17 (1.00–1.37)	1.07 (0.90–1.27)	0.51
Low-grade (Gleason < 7) (n= 2119)	1.00	1.11 (0.96–1.27)	0.97 (0.84–1.12)	1.07 (0.92, 1.25)	1.00 (0.85–1.17)	0.83
Insulin index (index/day)	≤36.52	36.53–39.58	39.59–41.97	41.98–44.64	≥44.65	
Total Prostate Cancer (n=5112)	1.00	0.96 (0.88, 1.05)	1.09 (0.99, 1.20)	1.05 (0.95, 1.17)	1.03 (0.92, 1.14)	0.34
Advanced/fatal (n= 860)	1.00	1.00 (0.80, 1.26)	1.12 (0.89, 1.42)	1.07 (0.84, 1.37)	1.06 (0.82, 1.37)	0.60
Organ-confined (n=3593)	1.00	0.98 (0.88, 1.09)	1.11 (0.99, 1.24)	1.05 (0.93, 1.18)	1.06 (0.93, 1.21)	0.28
High-grade (Gleason ≥ 7) (n=1932)	1.00	0.99 (0.86, 1.15)	1.09 (0.93, 1.28)	1.08 (0.91, 1.27)	1.01 (0.85, 1.20)	0.72
Low-grade (Gleason < 7) (n= 2119)	1.00	0.95 (0.82, 1.10)	1.15 (0.99, 1.34)	1.05 (0.90, 1.24)	1.08 (0.91, 1.27)	0.26
Fiber (g/day)	≤15.4	15.5–18.5	18.6–21.6	21.7–25.9	≥26.0	
Total Prostate Cancer (n=5112)	1.00	1.03 (0.94, 1.13)	1.01 (0.92, 1.12)	1.09 (0.99, 1.19)	1.01 (0.92, 1.12)	0.70
Advanced/fatal (n= 860)	1.00	1.18 (0.94, 1.49)	1.00 (0.79, 1.27)	1.11 (0.88, 1.40)	1.02 (0.80, 1.30)	0.81
Organ-confined (n=3593)	1.00	1.06 (0.95, 1.19)	1.05 (0.94, 1.18)	1.08 (0.96, 1.21)	1.03 (0.91, 1.16)	0.81
High-grade (Gleason ≥ 7) (n=1932)	1.00	1.24 (1.06, 1.45)	1.18 (1.00, 1.38)	1.23 (1.05, 1.44)	1.22 (1.04, 1.44)	0.07
Low-grade (Gleason < 7) (n= 2119)	1.00	0.94 (0.81, 1.09)	1.00 (0.86, 1.15)	1.03 (0.89, 1.19)	0.91 (0.78, 1.06)	0.37
Whole grains (g/day)	≤6.5	6.6–13.2	13.3–21.4	21.5–34.2	≥34.3	
Total Prostate Cancer (n=5112)	1.00	1.02 (0.92, 1.12)	1.08 (0.99, 1.19)	1.17 (1.06, 1.28)	1.13 (1.03, 1.24)	0.001
Advanced/fatal (n= 860)	1.00	1.04 (0.83, 1.31)	1.02 (0.81, 1.28)	1.23 (0.99, 1.54)	1.11 (0.88, 1.40)	0.22
Organ-confined (n=3593)	1.00	1.06 (0.94, 1.19)	1.19 (1.06, 1.33)	1.31 (1.17, 1.47)	1.18 (1.05, 1.33)	0.001

	Q1	Q2	Q3	Q4	Q5	p_{trend}
High-grade (Gleason ≥ 7) (n=1932)	1.00	1.09 (0.93, 1.28)	1.20 (1.02, 1.40)	1.31 (1.12, 1.53)	1.32 (1.13, 1.54)	<0.001
Low-grade (Gleason < 7) (n= 2119)	1.00	1.02 (0.88, 1.18)	1.10 (0.95, 1.28)	1.22 (1.05, 1.41)	1.15 (1.00, 1.34)	0.02

NOTE: Multivariate HRs are hazard ratios stratified on period and age (months), adjusted for BMI (<21, 21–22.9, 23–24.9, 25–27.4, 27.5–29.9, 30+ kg/m^2), height (<66, 66–67, 68–70, ≥71 inch), history of diabetes (no diabetes, Diabetes ≤5y, 5.1–10 y, >10 y), family history of prostate cancer, race/ethnicity (African, Caucasian, Asian, other), smoking (never or quit>10 years, current or quit ≤10 years and ≤15 cigarettes/day, current or quit ≤10 years and >15 cigarettes/day), vigorous physical activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/day), energy intake (kcal/day, quintiles), alcohol intake (g/day, quintiles), calcium intake (500–749, 750–999, 1000–1499, 1500–1999, ≥2000 mg/day), alpha-linolenic acid (g/day, quintiles), tomato sauce (never, 0–0.5, >0.5–1, >1 servings/week).

Table 3

Multivariate HR (95% CI) of prostate cancer and subgroups of prostate cancer in relation to dietary glycemic index, glycemic load, insulin index, fiber and whole grains in the Health Professionals Follow-Up Study, among men who were screened by 2004, follow-up 1994 - January 2007

	Q1	Q2	Q3	Q4	Q5	p_{trend}
Glycemic index (index/day)	≤50.39	50.40–52.48	52.49–54.12	54.13–55.97	≥55.98	
Total Prostate Cancer (n=3024)	1.00	1.11 (0.99, 1.25)	1.17 (1.04, 1.31)	1.14 (1.01, 1.29)	1.08 (0.95, 1.23)	0.13
Advanced/fatal (n=311)	1.00	1.15 (0.79, 1.67)	1.22 (0.84, 1.77)	1.29 (0.88, 1.89)	1.33 (0.89, 2.00)	0.12
Organ-confined (n=2378)	1.00	1.13 (0.99, 1.29)	1.16 (1.02, 1.33)	1.16 (1.01, 1.32)	1.10 (0.95, 1.27)	0.13
High-grade (Gleason ≥ 7) (n=1202)	1.00	1.15 (0.96, 1.38)	1.12 (0.93, 1.35)	1.21 (1.00, 1.46)	1.03 (0.83, 1.27)	0.49
Low-grade (Gleason < 7) (n=1349)	1.00	1.14 (0.96, 1.36)	1.23 (1.03, 1.47)	1.10 (0.92, 1.33)	1.24 (1.02, 1.50)	0.05
Glycemic load (load/day)	≤103	104–117	118–130	131–144	≥145	
Total Prostate Cancer (n=3024)	1.00	1.15 (1.02, 1.30)	1.09 (0.96, 1.24)	1.08 (0.95, 1.23)	1.02 (0.89, 1.17)	0.82
Advanced/fatal (n=311)	1.00	1.03 (0.70, 1.52)	1.22 (0.83, 1.80)	1.11 (0.74, 1.67)	1.00 (0.65, 1.55)	0.95
Organ-confined (n=2378)	1.00	1.23 (1.07, 1.41)	1.15 (0.99, 1.32)	1.09 (0.94, 1.27)	1.04 (0.89, 1.22)	0.74
High-grade (Gleason ≥ 7) (n=1202)	1.00	1.21 (1.00, 1.47)	1.28 (1.05, 1.57)	1.17 (0.95, 1.44)	1.06 (0.85, 1.33)	0.86
Low-grade (Gleason < 7) (n=1349)	1.00	1.11 (0.93, 1.33)	0.93 (0.77, 1.13)	1.01 (0.83, 1.22)	0.95 (0.77, 1.16)	0.38
Insulin index (index/day)	≤36.52	36.53–39.58	39.59–41.97	41.98–44.64	≥44.65	
Total Prostate Cancer (n=3024)	1.00	0.92 (0.82, 1.05)	1.11 (0.98, 1.26)	1.05 (0.91, 1.20)	0.98 (0.84, 1.13)	0.78
Advanced/fatal (n=311)	1.00	0.81 (0.54, 1.21)	1.17 (0.79, 1.73)	1.00 (0.65, 1.52)	0.85 (0.54, 1.34)	0.73
Organ-confined (n=2378)	1.00	0.95 (0.83, 1.09)	1.14 (0.98, 1.31)	1.08 (0.93, 1.26)	1.06 (0.90, 1.24)	0.26
High-grade (Gleason ≥ 7) (n=1202)	1.00	1.01 (0.82, 1.23)	1.19 (0.97, 1.46)	1.22 (0.98, 1.51)	1.07 (0.85, 1.36)	0.28
Low-grade (Gleason < 7) (n=1349)	1.00	0.86 (0.71, 1.03)	1.06 (0.88, 1.28)	0.97 (0.79, 1.19)	0.99 (0.80, 1.23)	0.75
Fiber (gm/day)	≤15.4	15.5–18.5	18.6–21.6	21.7–25.9	≥26.0	
Total Prostate Cancer (n=3024)	1.00	1.01 (0.89, 1.14)	0.99 (0.87, 1.12)	1.06 (0.93, 1.20)	0.94 (0.82, 1.07)	0.37
Advanced/fatal (n=311)	1.00	1.28 (0.86, 1.92)	1.12 (0.74, 1.68)	1.34 (0.90, 2.00)	0.90 (0.58, 1.39)	0.40
Organ-confined (n=2378)	1.00	1.08 (0.93, 1.24)	1.03 (0.89, 1.19)	1.09 (0.94, 1.26)	0.98 (0.84, 1.13)	0.55
High-grade (Gleason ≥ 7) (n=1202)	1.00	1.19 (0.97, 1.46)	1.17 (0.96, 1.44)	1.18 (0.96, 1.45)	1.09 (0.88, 1.36)	0.84
Low-grade (Gleason < 7) (n=1349)	1.00	0.96 (0.79, 1.15)	0.93 (0.77, 1.11)	1.00 (0.83, 1.20)	0.86 (0.71, 1.05)	0.19
Whole grains (gm/day)	≤6.5	6.6–13.2	13.3–21.4	21.5–34.2	≥34.3	
Total Prostate Cancer (n=3024)	1.00	0.98 (0.86, 1.11)	1.00 (0.88, 1.14)	1.08 (0.95, 1.22)	1.03 (0.91, 1.17)	0.33
Advanced/fatal (n=311)	1.00	1.02 (0.68, 1.51)	0.89 (0.59, 1.33)	1.18 (0.80, 1.73)	1.00 (0.67, 1.50)	0.79
Organ-confined (n=2378)	1.00	1.05 (0.91, 1.22)	1.14 (0.98, 1.32)	1.24 (1.07, 1.43)	1.12 (0.96, 1.30)	0.09

	Q1	Q2	Q3	Q4	Q5	p_{trend}
High-grade (Gleason ≥ 7) (n=1202)	1.00	1.06 (0.86, 1.30)	1.02 (0.83, 1.26)	1.23 (1.01, 1.51)	1.15 (0.93, 1.41)	0.09
Low-grade (Gleason < 7) (n=1349)	1.00	0.93 (0.76, 1.13)	1.06 (0.88, 1.28)	1.14 (0.94, 1.37)	1.07 (0.88, 1.30)	0.17

NOTE: Multivariate HRs are hazard ratios stratified on period and age (months), adjusted for BMI (<21, 21–22.9, 23–24.9, 25–27.4, 27.5–29.9, 30+ kg/m^2), height (<66, 66–67, 68–70, ≥71 inch), history of diabetes (no diabetes, Diabetes ≤5y, 5.1–10 y, >10 y), family history of prostate cancer, race/ethnicity (African, Caucasian, Asian, other), smoking (never or quit>10 years, current or quit ≤10 years and ≤15 cigarettes/day, current or quit ≤10 years and >15 cigarettes/day), vigorous physical activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/day), energy intake (kcal/day, quintiles), alcohol intake (g/day, quintiles), calcium intake (500–749, 750–999, 1000–1499, 1500–1999, ≥2000 mg/day), alpha-linolenic acid (g/day, quintiles), tomato sauce (never, 0–0.5, >0.5–1, >1 servings/week).