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Dietary acrylamide and risk of prostate cancer

Kathryn M. Wilson[1,3], **Edward Giovannucci**[1,2,3], **Meir J. Stampfer**[1,2,3], and **Lorelei A. Mucci**[1,3,4]

[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA [2]Department of Nutrition, Harvard School of Public Health, Boston, MA [3]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[4]Centre for Public Health Sciences, University of Iceland, Reykjavik, Iceland

Abstract

Acrylamide has been designated by IARC as a "probable human carcinogen." High levels are formed during cooking of many commonly consumed foods including French fries, potato chips, breakfast cereal, and coffee. Two prospective cohort studies and two case-control studies in Europe found no association between acrylamide intake and prostate cancer. We examined this association in a large prospective cohort of 47,896 U.S. men in the Health Professionals' Follow-up Study, using updated dietary acrylamide intake from food frequency questionnaires in 1986, 1990, 1994, 1998, and 2002. From 1986 through 2006, we documented 5025 cases of prostate cancer, and 642 lethal cancers. We used Cox proportional hazards models to assess the association between acrylamide intake from diet and prostate cancer risk overall as well as risk of advanced or lethal cancer.

Acrylamide intake ranged from a mean of 10.5 mcg/day in the lowest quintile to 40.1 mcg/day in the highest quintile; coffee and potato products were largest contributors to intake. The multivariate-adjusted relative risk of prostate cancer was 1.02 (95% confidence interval: 0.92–1.13) for the highest versus lowest quintile of acrylamide intake (p-value for trend=0.90). Results were similar when restricted to never smokers and to men who had PSA tests. There was no significant association for dietary acrylamide and risk of lethal, advanced, or high-grade disease, or for different latency periods ranging from 0–4 years to 12–16 years. We found no evidence that acrylamide intake, within the range of U.S. diets, is associated with increased risk of prostate cancer.

Keywords

Acrylamide; diet; prostate cancer

Introduction

In 1994, the International Agency for Research on Cancer designated acrylamide as "a probable human carcinogen"(1) based primarily on the results of two animal studies that found increased risks of hormone-sensitive cancers in rats given acrylamide in drinking water; rates of thyroid adenomas and testicular mesotheliomas were significantly increased in male rats, and thyroid tumors, mammary gland fibroadenomas, and central nervous

Corresponding Author: Kathryn M. Wilson, Harvard School of Public Health, Department of Epidemiology 677 Huntington Avenue, Boston, MA 02115 Ph: 617-549-2006, Fax: 617-566-7805, kwilson@hsph.harvard.edu.

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system tumors were increased in female rats.(2, 3)The primary source of exposure in humans at that time was thought to be industrial use and tobacco, but in 2002, Tareke et al. discovered that acrylamide is formed naturally during high-temperature cooking of many foods.(4) Acrylamide is widespread in the food supply, with an estimated 38% of calories consumed in the U.S. coming from foods that contain acrylamide.(5) Potatoes, cold breakfast cereal, coffee, and baked goods are major sources of acrylamide among U.S. adults.(6) Given the prevalence of acrylamide in the human diet, it is of public health interest to determine the associations of dietary intake of acrylamide and cancer risk.

In humans, prospective studies of dietary acrylamide and risk of breast and colon cancer have consistently found no significant associations.(7–14) One cohort found a suggestion of increased risk of estrogen receptor positive (ER+) breast cancer among postmenopausal women (15), while another did not (11). Another study found a positive association between hemoglobin adducts of acrylamide, a biomarker of exposure, and ER+ cancer, particularly among smokers(16). Two prospective studies found suggestions of positive associations between acrylamide intake and risk of endometrial and ovarian cancer (8, 11), though another cohort found no association for these cancers (17, 18).

The positive findings have raised the possibility that acrylamide may act in part through a hormonal mechanism. Therefore, the relationship between acrylamide intake and prostate cancer is also of interest. Two case-control studies (19, 20) and two prospective cohort studies (21, 22) of acrylamide and prostate cancer found no association between acrylamide intake and overall risk of prostate cancer. The cohort studies, one in Sweden (22) and another in the Netherlands (21), reported a non-significant suggestion of decreased risk of advanced prostate cancer among never smoking men.

Dietary contributors to acrylamide intake vary across countries. Thus, we investigated the association between acrylamide and prostate cancer risk in a large, prospective study of U.S. men with multiple assessments of dietary intake over the course of 20 years. With a substantial number of advanced stage cancers in the cohort, we are able to address the previously reported inverse associations for advanced stage cancer.

Materials and Methods

The Health Professionals Follow-up Study (HPFS) is a prospective cohort study started in 1986 when 51,529 male health professionals aged 40–75 years responded to a mailed questionnaire on lifestyle and medical history. Follow-up questionnaires have been sent biennially to update information on lifestyle and health. We assessed diet in 1986 using a semi-quantitative food frequency questionnaire (FFQ) in 1986 and every four years thereafter.

Men who completed the baseline FFQ in 1986, excluding those who had implausible energy intake (<800 or >4200 kcal/day) or left more than 70 food items blank, form the study population for this analysis (N=49,894). We excluded men who reported a diagnosis of cancer at baseline (excluding non-melanoma skin cancer, N=1998). This left 47,896 men with baseline diet information for the analysis. This study is approved by the Human Subjects Committee at the Harvard School of Public Health.

Assessment of acrylamide intake

FFQs with over 130 food items were completed by men in 1986, 1990, 1994, 1998, and 2002. Participants were asked how frequently they had consumed a specified portion size of each item over the previous year with 9 possible responses, ranging from never or less than once a month to 6 or more times per day. The FFQ includes the major acrylamide

contributing foods according to US Food and Drug Administration surveys: French fries, cold breakfast cereal, potato chips, cookies, coffee, breads, baked goods, and snack foods. (FDA, 2006) We previously reported on the creation and validation of the acrylamide food composition database for the FFQ.(23) Briefly, data on acrylamide content of foods were taken from published U.S. FDA data along with additional analyses of U.S. food samples performed for us by the Swedish National Food Administration. We calculated daily acrylamide intake for each participant by multiplying the acrylamide content of one serving of food by the frequency of consumption of that food and summing across all food items on the questionnaire. Acrylamide intake from cold breakfast cereal was based on participants' reporting of the brand they used most often. Commonly consumed cereal brands were analyzed for the database, and for brands without analyzed values, we imputed a value based on cereals with similar grain composition and processing (e.g. puffs, flakes). We compared FFQ-assessed acrylamide intake with a biomarker of acrylamide intake, hemoglobin adducts of acrylamide and its genotoxic metabolite glycidamide, in a sample of 296 non-smoking women in the Nurses' Health Study II cohort.(23) The correlation was 0.34 ($p<0.0001$), adjusted for age, energy intake, BMI, and alcohol intake, and corrected for random within-person variation in the adduct measurement.

To reduce measurement error, and to provide an estimate of long-term dietary acrylamide over an extended period of time, for the primary analysis we used the cumulative average intake of acrylamide and high-acrylamide foods. That is, 1986 intake was used for the 1986–1990 follow-up period, the average of 1986 and 1990 intakes was used for the 1990–1994 follow-up period, the average of 1986, 1990, and 1994 was used for the 1994–1998 follow-up period, and so on. Data from the previous FFQ were carried forward to the next time period for participants with incomplete FFQ information after baseline.

We also used our repeated measures of diet to analyze the effect of latency time (time from exposure to cancer diagnosis) by relating each measure of acrylamide intake to prostate cancer incidence during specific time periods: 0–4 years, 4–8 years, 8–12 years, and 12–16 years after exposure.

Ascertainment and classification of prostate cancer cases

Study participants (or their next of kin) reported a new diagnosis of prostate cancer on the biennial questionnaires. We then asked permission to obtain medical records and pathology reports to obtain additional information, including stage and grade of disease. Deaths in the cohort were ascertained mostly through reports from family members and searches of the National Death Index. Underlying cause of death was assigned based on all available data including medical history, records, death certificates, registry information and death certificates. Follow-up for mortality is more than 98 percent complete. Eighty six percent of prostate cancer cases were documented by medical records; the remaining cases, based on confirmed self-reports or death certificates, were included because the reporting of prostate cancer by these health professionals is highly accurate among the men with available medical records.

We studied total prostate cancer incidence, but excluded stage T1a cancers – discovered incidentally, because these are especially prone to detection bias. In addition, given the considerable heterogeneity in the biologic potential of prostate cancer and previous findings for dietary acrylamide, we studied categories of disease based on stage and grade. Cases were categorized as lethal prostate cancer if they caused death or metastases to bone. Advanced cases included all lethal cases as well as men with stage T3b, T4, N1, or M1 cancers. Localized cancers were stage T1 or T2 and N0, M0. Cases were also categorized as high grade (Gleason sum at diagnosis 7–10) or low grade (Gleason sum 2–6).

Statistical analysis

Each participant contributed person-time from the date of return of the baseline questionnaire in 1986 until prostate cancer diagnosis, death, or the end of the study period, January 31, 2006. Prostate cancer death and metastases among cases were recorded through January 31, 2008, and this information was used in defining lethal and advanced cases. Participants were divided into quintiles of acrylamide intake, and relative risks of prostate cancer were calculated as the incidence rate for a given quintile of intake divided by the rate in the lowest quintile.

We used Cox proportional hazards regression to adjust for potential confounding by other prostate cancer risk factors. We stratified the analysis jointly by age in months at the start of each follow-up period and by calendar year. We used multivariable models to adjust for the following factors: race, height (quartiles), BMI at age 21 (<20, 20–<22.5, 22.5–<25, ≥25), current BMI (<21, 21–<23, 23–<25, 25–<27.5, 27.5–<30, ≥30), vigorous physical activity (quintiles), smoking (never, former quit >10 yrs ago, former quit <10 yrs ago, current), diabetes (yes/no), family history of prostate cancer in father or brother (yes/no), multivitamin use (yes/no), intakes of red meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, and alcohol intake (all quintiles), energy intake (continuous), and history of PSA testing (yes/no, lagged by one period to avoid counting diagnostic PSA tests as screening; collected from 1994 on). All covariates except race, height, BMI at age 21, and family history of prostate cancer were updated in each questionnaire cycle.

To test for a linear trend across categories of intake, we modeled acrylamide intake as a continuous variable using the median intake for each category.

We repeated our analyses for the major acrylamide-contributing foods and food groups in the cohort. Because cigarette smoking is a major contributor to acrylamide exposure, we repeated our analyses restricted to men who had never smoked to assess the association of dietary acrylamide in men with low background levels of exposure. In addition, to reduce the potential for detection bias due to PSA testing, we repeated our analyses among the subgroup of men in each time period who reported having a PSA test in the previous two years. Follow-up for this subgroup was from 1996 to 2006.

Results

From 1986 to 2006 we documented 5025 cases of prostate cancer, including 642 lethal cases (defined as prostate cancer death or bone metastatses). The characteristics of the study population according to acrylamide intake in 1986 are shown in Table 1. Estimated intake of acrylamide from diet ranged from a mean of 10.5 mcg/day in the lowest quintile to 40.1 mcg/day in the highest quintile of intake. Men in the highest quintile of acrylamide consumption were younger, more likely to smoke, and less physically active than men in the lowest quintile. Men in the middle quintiles were slightly more likely to report having a PSA test in 1994 and 2004. Men with higher acrylamide consumption consumed less calcium and alcohol and more alpha-linolenic acid.

The major food contributors to acrylamide intake in 2002 were French fries (26%), coffee (14%), cold breakfast cereal (13%), potato chips (6%), and bagels/English muffins/rolls (6%). Baked or fried potatoes overall contributed 36% of acrylamide intake, and baked goods overall contributed 15% of acrylamide intake.

There was no association between acrylamide intake and risk of total prostate cancer in the full cohort or among never-smokers.(Table 2) In the full cohort, the adjusted relative risk of prostate cancer for men in the highest versus lowest quintile was 1.02 (95% CI: 0.92–1.13,

p-trend=0.90). Among never-smokers the relative risk was 1.01 (CI: 0.85–1.19, p-trend=0.68).

Acrylamide intake from diet was not associated with subtypes of prostate cancer defined by stage (lethal, advanced, or localized), or Gleason score in analyses among all men or those limited to never smokers. (Table 2) Compared to the lowest quintile of intake, the relative risk for men in the highest quintile was 0.98 (0.75–1.27, p-trend=0.72) for lethal disease, 0.98 (0.79–1.23, p-trend=0.81) for advanced disease and 1.09 (0.96–1.23, p-trend=0.55) for localized disease. For high grade disease (Gleason sum 7–10), the relative risk was 1.04 (0.88–1.23, p-trend=0.97), and for low grade disease (Gleason sum 2–6), the relative risk was 1.08 (0.93–1.25, p-trend=0.45). Among never smokers, the relative risk for the highest quintile was 0.90 (0.56–1.45, p-trend=0.61) for lethal cancer, 0.91 (0.62–1.33, p-trend=0.52) for advanced cancer, and 1.09 (0.88–1.34, p-trend>0.99) for localized disease. For high grade disease the relative risk was 1.02 (0.78–1.32, p-trend=0.85), and for low grade disease the relative risk was 1.09 (0.85–1.40, p-trend=0.80) among never smokers.

We also found no association when we limited our analysis to the more homogenous subgroup of screened men who reported having a PSA test in the two years prior to the questionnaire. Following these men from 1996 through 2006, the relative risk of prostate cancer for the highest versus lowest quintile was 1.00 (0.85–1.18, p-trend=0.78, n cases=2077). Acrylamide intake was not associated with any subtypes of prostate cancer in this screened group (data not shown).

In the latency analysis, acrylamide intake remained unassociated with prostate cancer risk 0–4 years, 4–8 years, 8–12 years, or 12–16 years after exposure. (Table 3)

We then assessed the association between prostate cancer risk and the individual major food contributors of acrylamide intake. We found no association of intake of total potatoes, baked goods, potato chips, and bagels/English muffins/rolls with prostate cancer. (Table 4) French fries and coffee were both inversely associated with prostate cancer risk, while breakfast cereal was associated with increased risk. (Table 4) These associations were unchanged when acrylamide intake was included in the models (data not shown), suggesting that the associations are not related to the acrylamide content of these foods. The associations for French fries and for cereal were statistically significant only for localized, and not for lethal or advanced cancers, which suggests associations may be due to detection bias due to differences in PSA testing.(Table 4) Indeed, PSA testing was inversely associated with consumption of French fries and positively associated with cereal (data not shown). In an analysis restricted to men with PSA tests in 1994 and 1996, with follow-up through 2006, the associations between French fries and cereal and total prostate cancer were attenuated and no longer statistically significant. In contrast, the inverse association between coffee and prostate cancer was strongest for lethal and advanced disease and appeared unrelated to PSA testing (24). (Table 4)

Discussion

We found no association between dietary acrylamide intake and prostate cancer risk in a large, prospective study of U.S. men with updated dietary information. We also found no association for aggressive cancer, defined by lethal, advanced, or high-grade disease. There was also no indication of an association for overall prostate cancer or any of these subtypes in never smoking men, which is important to consider as smokers have acrylamide adduct levels apporximately three times higher than never smokers. (20, 23) Using our multiple FFQs administered over 20 years, we saw no association between acrylamide intake and cancer risk in any time period from 0–4 years to 12–16 years after exposure.

These results are consistent with two previous prospective studies (21, 22) and two previous case-control studies (19, 20), none of which found an association between acrylamide intake calculated by FFQ and risk of total prostate cancer. Intakes in our cohort were similar to those in the Dutch study (21), whereas intakes were higher among men in the two Swedish studies (20, 22). One case-control study in Swedish men (20) also found no association between acrylamide adducts of hemoglobin, a biomarker of exposure, and prostate cancer risk. However, in that study blood was collected at the time of, or just after, diagnosis, so the biomarker did not specifically measure diet in the years before diagnosis.

We found statistically significant inverse associations between coffee and French fries and risk of prostate cancer, and a positive association between breakfast cereal and prostate cancer. These associations persisted after adjustment for acrylamide intake, suggesting that some other aspect of these foods – or perhaps some other attribute of more frequent consumers of these foods – is responsible for the association. Indeed, detection bias due to differences in use of PSA testing appeared to explain the observed associations for French fries and cereal. That is, high consumers of French fries were less likely to have PSA tests, making them less likely to be diagnosed with localized prostate cancer; high consumers of breakfast cereal were more likely to have PSA tests, increasing their risk of diagnosis with localized prostate cancer. However, the association for coffee persisted even among the PSA-tested subgroup, and was strongest for lethal and advanced prostate cancer, not localized cancer.

Both previous prospective cohort studies found a suggestion of a statistically non-significant inverse association for advanced cancer among never smoking men. Comparing extreme quantiles, Hogervorst et al. (21), reported a hazard ratio of 0.57 (95% CI: 0.27–1.17, p-trend=0.10, 117 cases) for advanced cancer, defined by high stage. Larsson et al. (22), found a relative risk of 0.75 (CI: 0.51–1.10, p-trend=0.15, 351 cases) for advanced cancer defined by high stage or high grade. We found no significant inverse association of lethal or advanced cancer among never smoking men, with an RR of 0.90 (CI: 0.56–1.45, p-trend=0.61, 237 cases) for lethal cancer and 0.91 (CI: 0.62–1.33, p-trend=0.52, 344 cases) for advanced cancer (defined by stage). While a hormonal mechanism of acrylamide has been hypothesized (8), the association between sex hormones and prostate cancer risk is complex and still not entirely clear (25), and there is presently no clear biological explanation for an inverse association between acrylamide and advanced prostate cancer. In addition, the role of chance in the previous findings should not be overlooked, as the suggestion of an inverse association was not statistically significant and was seen only for a subset of prostate cancer cases in a subgroup of the population.

Strengths of our study include large case numbers, including 642 lethal and 896 advanced cases, and multiple FFQs which allow us to capture diet over time. In addition, the acrylamide database used for this analysis has previously been shown to perform reasonably well when validated against a biomarker of acrylamide intake.(23)

The wide variation in acrylamide content of foods, and lack of information in our population on cooking methods and food preparation techniques contributes to misclassification of acrylamide intake in our study. It is likely that this measurement error is non-differential with respect to cancer outcomes, which would tend to bias results towards no association. In addition, confounding by other dietary or lifestyle factors is also a possibility, although we have controlled for several of the proposed prostate cancer risk factors.

In summary, we found no evidence that acrylamide in levels typically consumed in the diets of U.S. men is associated with prostate cancer risk. This adds to previous case-control and

prospective studies suggesting that dietary acrylamide intake is not a risk factor for prostate cancer incidence or progression.

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Table 1

Age-adjusted characteristics of the HPFS study population by acrylamide intake, 1986

	Quintile of energy-adjusted acrylamide intake				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Participants (N)	12413	9229	8408	8001	9845
Acrylamide intake, (micrograms/day)	10.5	16.7	20.8	25.7	40.1
Age (years)	57	56	54	53	51
BMI, (kg/m^2)	25	25	25	26	26
BMI at age 21	23	23	23	23	23
Height (inches)	70	70	70	70	70
Current smokers (%)	8%	9%	9%	10%	13%
Top quintile of physical activity (%)	19%	16%	15%	15%	12%
Diabetes (%)	3%	3%	3%	3%	3%
Family history of PCa (%)	12%	12%	12%	13%	12%
Multivitamin use (%)	45%	43%	41%	41%	39%
Had PSA test*, 1994 (%)	35%	39%	40%	40%	36%
Had PSA test*, 2004 (%)	58%	66%	67%	68%	63%
Nutrient intakes (per day)					
Energy (kcal)	1995	2068	1990	1898	1951
Calcium (mg)	970	913	894	872	823
Alpha-linolenic acid (g)	1.03	1.07	1.08	1.09	1.11
Alcohol (g)	11.8	12.1	11.8	10.6	9.9
Supplemental vitamin E (mg)	46.7	39.2	35.1	34.4	32.2
Food intakes (servings)					
Processed meat (/wk)	2.1	2.5	2.7	2.6	2.9
Tomato sauce (/wk)	1.0	1.0	0.9	0.8	0.8
French Fries (/wk)	0.1	0.4	0.5	0.7	1.9
Coffee (/day)	1.0	1.6	2.0	2.4	2.7
Breakfast cereal (/wk)	2.1	2.6	2.9	3.2	3.4
Potato chips (/wk)	0.3	0.7	0.9	1.2	1.7
Bagels/Eng muffins/rolls (/wk)	1.3	1.4	1.3	1.3	1.2

	Quintile of energy-adjusted acrylamide intake				
	Q1	Q2	Q3	Q4	Q5
All potatoes (/wk)	2.7	3.3	3.6	4.0	5.7
Baked goods (/day)	2.0	2.5	2.6	2.6	2.6

All variables (except age) are standardized to the age distribution of the cohort in 1986.

*Reported having a PSA test in the two years prior to the questionnaire date.

Table 2

Relative risk (and 95% confidence intervals) of prostate cancer by quintile of energy-adjusted acrylamide intake in the full cohort and among never-smoking men

Quintile (median intake)	Full Cohort			Never Smokers		
	N Cases	Age-adjusted RR*	Fully-adjusted RR*	N Cases	Age-adjusted RR*	Fully-adjusted RR*
All Cases						
Q1 (12 mcg/d)	1027	1.00	1.00	421	1.00	1.00
Q2 (17 mcg/d)	1150	1.14 (1.05–1.24)	1.10 (1.01–1.20)	468	1.09 (0.95–1.25)	1.07 (0.93–1.23)
Q3 (21 mcg/d)	1081	1.12 (1.03–1.23)	1.08 (0.99–1.18)	440	1.16 (1.01–1.33)	1.12 (0.97–1.29)
Q4 (26 mcg/d)	999	1.11 (1.01–1.21)	1.06 (0.97–1.16)	341	1.01 (0.87–1.17)	0.97 (0.84–1.13)
Q5 (35 mcg/d)	768	1.04 (0.94–1.14)	1.02 (0.92–1.13)	255	1.04 (0.88–1.22)	1.01 (0.85–1.19)
p-trend		0.82	0.90		0.99	0.68
Lethal Cases[1]						
Q1 (12 mcg/d)	181	1.00	1.00	71	1.00	1.00
Q2 (17 mcg/d)	159	1.03 (0.83–1.28)	1.01 (0.81–1.26)	61	0.97 (0.68–1.38)	0.93 (0.64–1.34)
Q3 (21 mcg/d)	97	0.74 (0.57–0.95)	0.72 (0.56–0.93)	37	0.71 (0.47–1.06)	0.69 (0.45–1.06)
Q4 (26 mcg/d)	109	0.94 (0.74–1.20)	0.95 (0.74–1.22)	40	0.96 (0.64–1.44)	0.94 (0.61–1.43)
Q5 (35 mcg/d)	96	0.98 (0.76–1.27)	0.98 (0.75–1.27)	28	0.96 (0.61–1.51)	0.90 (0.56–1.45)
p-trend		0.66	0.72		0.73	0.61
Advanced Cases[1]						
Q1 (12 mcg/d)	237	1.00	1.00	101	1.00	1.00
Q2 (17 mcg/d)	212	1.04 (0.86–1.25)	1.00 (0.83–1.21)	85	0.96 (0.71–1.29)	0.93 (0.68–1.26)
Q3 (21 mcg/d)	147	0.82 (0.66–1.01)	0.79 (0.64–0.98)	58	0.78 (0.56–1.09)	0.76 (0.54–1.08)
Q4 (26 mcg/d)	161	1.00 (0.81–1.22)	0.97 (0.79–1.20)	56	0.91 (0.65–1.28)	0.89 (0.62–1.26)
Q5 (35 mcg/d)	139	1.01 (0.82–1.26)	0.98 (0.79–1.23)	44	0.99 (0.68–1.42)	0.91 (0.62–1.33)
p-trend		0.96	0.81		0.77	0.52
Localized cases[1]						
Q1 (12 mcg/d)	581	1.00	1.00	242	1.00	1.00
Q2 (17 mcg/d)	733	1.24 (1.11–1.39)	1.17 (1.05–1.31)	331	1.29 (1.08–1.53)	1.23 (1.03–1.46)
Q3 (21 mcg/d)	736	1.27 (1.14–1.42)	1.17 (1.05–1.31)	307	1.32 (1.11–1.58)	1.23 (1.03–1.47)
Q4 (26 mcg/d)	672	1.22 (1.09–1.36)	1.12 (1.00–1.26)	241	1.15 (0.96–1.38)	1.06 (0.88–1.29)

Quintile (median intake)	Full Cohort			Never Smokers		
	N Cases	Age-adjusted RR*	Fully-adjusted RR*	N Cases	Age-adjusted RR*	Fully-adjusted RR*
Q5 (35 mcg/d)	499	1.11 (0.98–1.26)	1.09 (0.96–1.23)	177	1.14 (0.93–1.40)	1.09 (0.88–1.34)
p-trend		0.31	0.55		0.56	>0.99
High Grade Cases[2]						
Q1 (12 mcg/d)	346	1.00	1.00	157	1.00	1.00
Q2 (17 mcg/d)	451	1.29 (1.12–1.49)	1.23 (1.06–1.41)	181	1.12 (0.90–1.39)	1.09 (0.87–1.36)
Q3 (21 mcg/d)	413	1.22 (1.06–1.41)	1.15 (0.99–1.33)	175	1.19 (0.95–1.49)	1.15 (0.92–1.44)
Q4 (26 mcg/d)	400	1.25 (1.08–1.45)	1.17 (1.01–1.36)	130	1.03 (0.81–1.31)	0.99 (0.78–1.27)
Q5 (35 mcg/d)	282	1.07 (0.91–1.25)	1.04 (0.88–1.23)	101	1.05 (0.81–1.36)	1.02 (0.78–1.32)
p-trend		0.80	0.97		0.96	0.85
Low Grade Cases[2]						
Q1 (12 mcg/d)	415	1.00	1.00	172	1.00	1.00
Q2 (17 mcg/d)	465	1.13 (0.99–1.29)	1.06 (0.92–1.21)	214	1.20 (0.97–1.47)	1.14 (0.92–1.40)
Q3 (21 mcg/d)	472	1.17 (1.02–1.34)	1.07 (0.94–1.23)	201	1.26 (1.02–1.55)	1.17 (0.94–1.44)
Q4 (26 mcg/d)	432	1.13 (0.98–1.29)	1.04 (0.90–1.20)	167	1.14 (0.91–1.42)	1.04 (0.83–1.30)
Q5 (35 mcg/d)	350	1.12 (0.96–1.29)	1.08 (0.93–1.25)	124	1.16 (0.91–1.48)	1.09 (0.85–1.40)
p-trend		0.23	0.45		0.39	0.80

*Age-adjusted model adjusted for age and calendar time. Multivariable model additionally adjusted for: race, height (quartiles), BMI at age 21 (4 categories), current BMI (6 categories), vigorous physical activity (quintiles), smoking (never, former quit >10 yrs ago, former quit <10 yrs ago, current), diabetes, family history of prostate cancer, multivitamin use, intakes of red meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, and alcohol intake (all quintiles), energy intake (continuous), and PSA testing in the prior period (yes/no).

[1]Lethal cases: prostate cancer death or bone metastases; Advanced: Lethal, or Stage T3b or T4, or N1 or M1; Localized: T1 or T2, and N0, M0.

[2]High Grade: Gleason sum 7–10. Low Grade: Gleason sum 2–6.

Table 3

Relative risks (and 95% confidence intervals) of prostate cancer by quintile of energy-adjusted acrylamide intake for various latency periods between exposure and cancer diagnosis

	Quintile of energy-adjusted acrylamide intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P-Trend**
0–4 YEAR LATENCY						
N Cases	893	900	880	830	733	
MV-adjusted RR	1.00	1.07 (0.97–1.17)	1.09 (0.99–1.20)	1.07 (0.97–1.18)	1.05 (0.95–1.16)	0.43
4–8 YEAR LATENCY						
N Cases	857	836	790	836	679	
MV-adjusted RR	1.00	1.04 (0.94–1.14)	1.01 (0.91–1.11)	1.11 (1.01–1.22)	1.02 (0.92–1.13)	0.47
8–12 YEAR LATENCY						
N Cases	662	635	648	623	516	
MV-adjusted RR	1.00	0.98 (0.88–1.09)	1.00 (0.90–1.12)	0.99 (0.88–1.11)	0.89 (0.79–1.00)	0.06
12–16 YEAR LATENCY						
N Cases	417	449	438	455	397	
MV-adjusted RR	1.00	1.07 (0.93–1.23)	1.05 (0.91–1.20)	1.08 (0.94–1.24)	1.00 (0.87–1.16)	0.93

Multivariable model adjusted for: age, calendar time, race, height (quartiles), BMI at age 21 (4 categories), current BMI (6 categories), vigorous physical activity (quintiles), smoking (never, former quit >10 yrs ago, former quit <10 yrs ago, current), diabetes, family history of prostate cancer, multivitamin use, intakes of red meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, and alcohol intake (all quintiles), energy intake (continuous), and PSA testing in the prior period (yes/no).

Table 4

Relative risks (and 95% confidence intervals) for the association between intake of quartile or quintile of high-acrylamide foods and risk of prostate cancer

	Cumulative average intake					
	Quantile of high-acrylamide foods					
	Q1	Q2	Q3	Q4	Q5	P- Trend
ALL POTATOES[1]						
Median intake (serv/d)	0.1	0.3	0.5	0.7	1.0	
N cases	983	1084	1044	1063	851	
MV adjusted RR	1.00	1.07 (0.98–1.17)	1.01 (0.92–1.11)	1.08 (0.98–1.18)	1.07 (0.96–1.19)	0.25
BAKED GOODS[2]						
Median intake (serv/d)	0.9	1.5	2.1	2.9	4.5	
N cases	888	1035	1059	1033	1010	
MV adjusted RR	1.00	1.05 (0.96–1.15)	1.03 (0.94–1.14)	1.02 (0.92–1.13)	1.01 (0.90–1.13)	0.77
POTATO CHIPS (quartiles)						
Median intake (serv/wk)	0	0.5	0.9	2.4		
N cases	1338	1712	828	1147		
MV adjusted RR	1.00	1.03 (0.96–1.11)	1.09 (0.99–1.20)	1.07 (0.98–1.17)		0.18
ENGLISH MUFFINS, ROLLS, BAGELS (quartiles)						
Median intake (serv/wk)	0	0.5	1.1	3.0		
N cases	1309	1186	1346	1184		
MV adjusted RR	1.00	0.99 (0.91–1.07)	1.06 (0.98–1.15)	1.01 (0.93–1.10)		0.75
FRENCH FRIES (quartiles)						
Median intake (serv/wk)	0	0.2	0.5	1.4		
N cases	1389	1255	1587	794		
MV adjusted RR (all cases)	1.00	1.02 (0.94–1.11)	1.04 (0.96–1.12)	0.88 (0.80–0.98)		0.005
MV RR for lethal cancer* (n=642)	1.00	1.05 (0.83–1.34)	1.00 (0.81–1.24)	1.03 (0.79–1.33)		0.89
MV RR for advanced cancer* (n=896)	1.00	1.08 (0.88–1.32)	0.99 (0.83–1.19)	1.03 (0.83–1.28)		0.90
MV RR for localized cancer* (n=3221)	1.00	0.98 (0.88–1.08)	1.04 (0.94–1.15)	0.85 (0.75–0.96)		0.006
Among men with PSA testing* (n=2077)	1.00	1.05 (0.92–1.18)	1.08 (0.94–1.23)	0.89 (0.76–1.05)		0.06
CEREAL (quartiles)						

	Cumulative average intake					
	Quantile of high-acrylamide foods					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P- Trend**
Median intake (serv/d)	0	0.2	0.4	0.9		
N cases	1103	1196	1366	1360		
MV adjusted RR (all cases)	1.00	1.03 (0.94–1.12)	1.11 (1.02–1.20)	1.12 (1.03–1.22)		0.004
MV RR for lethal cancer * (n=642)	1.00	1.00 (0.78–1.26)	0.95 (0.76–1.19)	0.96 (0.77–1.21)		0.72
MV RR for advanced cancer * (n=896)	1.00	0.97 (0.79–1.18)	0.97 (0.80–1.18)	1.01 (0.83–1.23)		0.81
MV RR for localized cancer * (n=3221)	1.00	1.03 (0.93–1.15)	1.14 (1.03–1.27)	1.14 (1.03–1.28)		0.008
Among men with PSA testing * (n=2077)	1.00	0.93 (0.81–1.07)	1.04 (0.91–1.20)	1.06 (0.92–1.23)		0.10
COFFEE						
Median intake (serv/d)	0	0.8	1.6	2.3	4.5	
N cases	892	1036	1260	926	911	
MV adjusted RR (all cases)	1.00	0.92 (0.84–1.01)	0.96 (0.88–1.05)	0.92 (0.83–1.01)	0.89 (0.81–0.99)	0.05
MV RR for lethal cancer * (n=642)	1.00	0.75 (0.59–0.97)	0.81 (0.63–1.05)	0.70 (0.53–0.91)	0.73 (0.56–0.96)	0.07
MV RR for advanced cancer * (n=896)	1.00	0.85 (0.69–1.05)	0.81 (0.65–1.00)	0.76 (0.61–0.95)	0.74 (0.58–0.93)	0.02
MV RR for localized cancer * (n=3221)	1.00	0.94 (0.84–1.06)	0.98 (0.87–1.09)	0.94 (0.83–1.06)	0.96 (0.85–1.09)	0.70
Among men with PSA testing * (n=2077)	1.00	0.95 (0.82–1.11)	1.01 (0.88–1.16)	0.91 (0.78–1.07)	0.92 (0.79–1.08)	0.26

Multivariable model adjusted for: age, calendar time, race, height (quartiles), BMI at age 21 (4 categories), current BMI (6 categories), vigorous physical activity (quintiles), smoking (never, former quit >10 yrs ago, former quit <10 yrs ago, current), diabetes, family history of prostate cancer, multivitamin use, intakes of red meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamin E, and alcohol intake (all quintiles), energy intake (continuous), and history of PSA testing.

*Models for specific case types and among men with PSA tests in the previous period to investigate possible detection bias, see text for details. Lethal cases: prostate cancer death or bone metastases; Advanced: Lethal, or Stage T3b or T4, or N1 or M1; Localized: T1 or T2, and N0, M0.

[1]All potatoes: sum of potato chips, French fries, and baked/mashed/boiled potatoes.

[2]Baked goods: sum of bread, English muffins/rolls/bagels, muffins, pancakes, cookies, brownies, donuts, cake, pie, and sweet rolls.