Cancer Causes and Control (2006) 17:199–208
DOI 10.1007/s10552-005-0413-4

ORIGINAL PAPER

Diet after diagnosis and the risk of prostate cancer progression, recurrence, and death (United States)

June M. Chan · Crystal N. Holick · Michael F. Leitzmann · Eric B. Rimm · Walter C. Willett · Meir J. Stampfer · Edward L. Giovannucci

Received: 27 April 2005 / Accepted: 6 September 2005
© Springer-Verlag 2006

Abstract
Objective We examined post-diagnostic diet and risk of cancer progression in a cohort of men with prostate cancer from the Health Professionals Follow-up Study.
Methods We observed 392 progression outcomes among 1,202 men diagnosed with incident localized/regional prostate cancer between 1986 and 1996. Men completed prospective dietary surveys before and after diagnosis and were followed through 2000. We examined post-diagnostic consumption of red meat, grains, vegetables, fruits, milk, tomatoes, tomato sauce, and fish as predictors of progression using Cox proportional hazard regression models adjusted for total energy, age, clinical factors, and pre-diagnostic diet.
Results Men in the highest versus lowest quartile of post-diagnostic fish consumption had a multivariate hazard ratio (HR) of progression of 0.73 (95% CI 0.52–1.02); the comparable HR for tomato sauce was 0.56 (95% CI 0.38–0.82). We observed inverse linear relationships for fish and tomato sauce and risk of progression (HR = 0.83, p-value = 0.006 and HR = 0.80, p-value = 0.04 for a two serving/week increase of fish and tomato sauce, respectively). Milk and fresh tomato consumption were associated with small elevations in risk.
Conclusions These data suggest that diet after diagnosis may influence the clinical course of prostate cancer, and fish and tomato sauce may offer some protection against disease progression.

Key words Diet · Epidemiology · Progression · Prostate cancer · Survivors

Funding: University of California San Francisco Prostate Cancer SPORE P50 CA89520, Prostate Cancer Foundation, National Institute of Health grants CA 55075 and HL 35464 and Cancer Epidemiology Training Grant 5T 32 CA 09001-26 from the National Cancer Institute

J. M. Chan (✉)
Departments of Epidemiology & Biostatistics and Urology, University of California, Room A622, San Francisco, CA 94143-1695, USA
e-mail: june@uorg.ucsf.edu
Tel.: +1-415-885-3679
Fax: +1-415-885-7443

C. N. Holick · E. B. Rimm · W. C. Willett · M. J. Stampfer · E. L. Giovannucci
Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA, USA

M. F. Leitzmann
Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, USA

E. B. Rimm · W. C. Willett · M. J. Stampfer · E. L. Giovannucci
Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Introduction

In the United States approximately 1.5 million men live with a diagnosis of prostate cancer, and 25–40% of these men will experience a recurrence of their prostate cancer within 5 years [1–3]. Furthermore, a recent study suggests that men with early-stage apparently indolent disease at diagnosis may experience metastasis and death due to prostate cancer in the long term [4]. Many men alter their diet or lifestyle after a diagnosis of prostate cancer to delay

recurrence [5], but only limited data on the health effects of diet after prostate cancer diagnosis are available.

Several aspects of diet have been identified as possible risk factors or protective factors for incident prostate cancer. Vegetables, fruits, fish, and specific component nutrients of these foods have generally been associated with a lower risk of incident prostate cancer [6, 7]. Likewise, total and specific fats, meat, dairy products, and calcium have been positively associated with risk of developing prostate cancer [8–10]. Some of these nutritional factors were more strongly associated with metastatic or fatal prostate cancer risk, suggesting potential late-acting effects. Whether any of these dietary factors can affect the course of disease progression after diagnosis/treatment is unknown.

To address these issues in the Health Professionals Follow-up Study, we undertook an investigation of post-diagnostic diet and the risk of prostate cancer progression. This study prospectively assesses lifestyle and diet before and after diagnosis of prostate cancer and can directly address the question of whether these factors after diagnosis affect the risk of progression. In this report, we focus on major food groups and their associations with the risk of prostate cancer progression among men with incident prostate cancer.

Materials and methods

Study population

Details on the Health Professionals Follow-Up Study can be found elsewhere [11]. In brief, the study was initiated in 1986 to examine the associations between diet and lifestyle and the risk of cardiovascular disease and cancer among men. 51,529 male health professionals age 40–75 in 1986 were enrolled and asked to complete a semi-quantitative food frequency questionnaire (FFQ) every 4 years and a lifestyle survey every 2 years. Biennial follow-up rates in this cohort are approximately 94%, and we ascertain at least 98% of deaths in this cohort. Death and cause of death are identified through the postal system or next-of-kin in response to our follow-up questionnaires and the National Death Index for non-respondents. Study physicians assign cause of death following central review of medical records. This study and methods were approved by the Institutional Review Board of the Harvard School of Public Health.

Dietary assessment

Participants were asked to complete a semiquantitative FFQ in 1986, 1990, 1994, and 1998. The FFQ assessed consumption of approximately 130 food items plus vitamin and mineral supplement use, which collectively account for over 90% of a wide range of macro- and micro-nutrients [12]. For each food, a commonly used unit or portion size (*e.g.* a slice of bread) was specified, and participants were asked how often on average they consume that amount of each food. Intake of specific foods and nutrients were computed and analyzed as both continuous and categorical variables. The questionnaire also inquired about the types of fat used for frying, baking, and at the table, and there was an open-ended section for foods that were not pre-specified. In a validation study of this FFQ, 127 randomly selected male health professionals from this cohort provided two FFQs one year apart; during this interval they also completed two one-week diet records 6 months apart. Pearson correlation coefficients between the questionnaire and the average of the two one-week diet records for energy-adjusted nutrients were 0.61 for total fat, 0.71 for saturated fat, 0.67 for cholesterol, 0.64 for dietary fiber, and 0.53 for calcium [13]. The reproducibility and validity of assessment of individual food items were also considered [14]. The mean Pearson correlation coefficient reflecting reproducibility between food intakes from the two questionnaires was 0.59, and the mean Pearson correlation coefficient between questionnaire 2 and the average intake from the two diet records was 0.63, reflecting the validity of the questionnaire to assess food intake.

In the current investigation, we examined the following food groups: red meat, milk, fruits, vegetables, tomato sauce, fresh tomato products, grains, and fish. We separated tomato sauce and fresh tomato products because previous studies indicated that tomato sauce was more strongly related to lower risk [15, 16] and to higher circulating lycopene levels [17]. Red meat included beef, pork, or lamb as a main dish or mixed dish, bacon, hot dogs, hamburger, salami/bologna, and other processed meats. Milk included skim milk, 2% milk, and whole milk. Fruits included raisins, prunes, bananas, cantaloupe, apples/pears, oranges, apple juice, orange juice (with and without calcium), grapefruit, grapefruit juice, other fruit juices, strawberries, blueberries, peaches/apricots/plums, avocado, watermelon, and applesauce. Vegetables included string beans, mushrooms, broccoli, sauerkraut, coleslaw, cabbage, cauliflower, brussels sprouts, alfalfa sprouts, raw and cooked carrots, corn, peas/lima beans, mixed vegetables, beans, eggplant, yams/sweet potatoes, raw spinach, cooked spinach, kale, iceberg lettuce, romaine lettuce, celery, yellow squash, orange squash, green pepper, garlic, onions, beets, and tofu. Grains included breakfast cereal, cooked oatmeal, other cooked breakfast cereal, white bread, dark bread, English muffins/bagels/rolls, muffins/biscuits, brown rice, white rice, pasta, other grains, pancakes/waffles, tortillas, and crackers. Fresh tomato products included tomatoes, tomato juice, and salsa; tomato sauce

included regular sauce and sauce from pizza. Fish included canned tuna fish, dark meat fish, and other fish.

Clinical data collection and follow-up

Incident cases of prostate cancer were identified in the cohort through participant self-report on biennial follow-up questionnaires or death certificates indicating prostate cancer as cause of death. For each newly reported diagnosis, we requested and reviewed the relevant medical and pathology records to confirm and characterize the case (*e.g.* diagnostic PSA, Gleason score, and stage), after obtaining written permission from the participant or his next of kin. The response rate among nonfatal cases was 96%, and we estimated that we ascertained 98% of incident fatal cases.

In addition to our ongoing follow-up of incident prostate cancer, we conducted post-diagnostic clinical follow-up on men diagnosed with prostate cancer during a ten-year period (1986–1996) to record secondary prostate cancer outcomes. In 2000, these participants were asked to complete surveys regarding their clinical course and current status with prostate cancer since initial diagnosis. We obtained permission from participants to contact their treating physicians and collect additional clinical data via surveys to the physicians or medical record review. We attempted to contact men and their physicians up to three times. We contacted 1,295 living participants, and received 1,046 surveys and 1,054 consent forms to contact physicians. We mailed surveys to the physician(s) of these 1,054 participants, and received clinical data from the physicians on 866 men.

Using the medical records and follow-up surveys from participants and their physicians, we assessed Gleason score at diagnosis, prostate specific antigen (PSA) level at diagnosis, clinical stage at diagnosis, pathologic stage subsequent to surgery, and primary treatment(s). To collect data on our main outcome, we asked physicians and patients directly on the surveys whether or not the prostate cancer had recurred or progressed (i.e. ''Since your/the patient's initial diagnosis/treatment, has your/the patient's prostate cancer recurred or progressed?'' Yes or No checkbox response). We also obtained data on the nature of the progression (i.e. rising PSA, metastasis to lymph nodes, bone, or other organs). All surveys and medical records from participants and the physicians were reviewed by study investigators (JMC and MFL). Information on important primary clinical variables such as Gleason score, PSA level, tumor stage, and primary treatment were abstracted according to a specific standardized hierarchy system. For analysis, data taken from the medical records or the treating doctor's questionnaire were considered first, and only in cases where such information was missing did we use patient's self-reported values.

If medical records were provided in addition to or in lieu of the physician questionnaire and there was any ambiguity regarding the occurrence of recurrence/progression from the physician response, we used the following criteria to define outcome: (1) two or more successive PSA rises of 0.2 ng/ml or more above the post-surgery nadir, or of 0.5 ng/ml or more above the post-radiation/hormonal therapy nadir, or of 1 ng/ml or more above the post-diagnosis nadir if no treatment selected, or (2) documentation in the medical notes that a PSA rise occurred (criteria based on clinical standards at the time of review [18, 19]). In instances where date of recurrence was not given, we also used any provided medical chart information to assign date of progression as the earliest of the following events: (1) initiation of second therapy, (2) date of first PSA rise given there was a successive trend of rises based on the criteria above, or (3) date of positive scans for metastasis.

Analysis population and exclusions

The current analysis includes only men who were free of any cancer diagnosis (except non-melanoma skin cancer) at baseline in 1986, were subsequently diagnosed with localized or regional prostate cancer between 1986 and 1996, and who had completed at least one pre- and one post-diagnostic dietary survey (n = 1,445). We did not include 128 men with metastatic (stage D) cancer at diagnosis because we hypothesized that diet after diagnosis was most likely to affect prostate cancer progression among men with local/regional disease. We subsequently excluded 143 men for whom we had unknown stage data, 85 men for whom we had no post-diagnostic clinical follow-up data, and 15 participants on whom we had the report of a recurrence/progression event but no date for the event. There were 1,202 men included in this analysis (i.e. 1,445−143−85−15 = 1,202); of those 778 had both patient and physician follow-up surveys, 187 had patient surveys only, 26 had only doctor surveys/medical records, and 211 men had died without survey information but we knew their cause of death and initial diagnostic features from their medical records.

We identified 392 outcomes among these 1,202 men, and 94% of these were PSA recurrences (n = 312) or cases of metastases (n = 7) reported in response to the recurrence questions on the surveys (or in a minority of cases based on review of medical charts provided by the physician), or prostate cancer deaths confirmed by adjudication of medical records (n = 50). We also considered there to be evidence of progression if a man pursued watchful waiting (i.e. no indication of treatment for at least 18 months after diagnosis) and then initiated treatment (n = 14); or underwent a second treatment at least six months after an initial treatment given within the first year after diagnosis (n = 9).

Date of recurrence/progression was the earliest date for any of the above events. We hereafter refer to these collective outcomes as ''progression.''

Statistical methods

We used Cox proportional hazards models to analyze the associations between post-diagnostic food consumption and time to prostate cancer progression. Follow-up time was from the date of diagnosis until the earliest of the following events – progression, non-prostate cancer death, or end of follow-up (August 2000). The hazard ratio (HR) and its 95% confidence intervals (CI) were used as an estimate of the relative risk of progression. Dietary data were available from the 1986, 1990, 1994, and 1998 surveys. Initial dietary exposure at the time of diagnosis was taken from the survey closest in time and before the date of diagnosis. Dietary exposure was updated with post-diagnostic survey data until the participant was censored (due to non-prostate cancer death or end of follow-up) or he experienced progression. Men had to have at least one pre- and one post-dietary survey to be included in this analysis. If a participant was missing any additional dietary surveys or had missing dietary data on his survey, his most recent previous dietary survey responses were used.

We examined patterns of food consumption before and after diagnosis, stratified by prognostic risk group. We categorized change in consumption after versus before diagnosis as ''less,'' ''same,'' ''more,'' using the following definitions: for grains, vegetables, fruits, and milk, ''less'' equated to a decrease in consumption of serving/day or more; ''same'' meant eating within $\pm$ serving/day; and ''more'' equated to an increase in consumption of serving/day or greater. Similar definitions were applied for red meat, fish, tomato sauce, and fresh tomatoes; however we used a cut-off value of 1 serving/week, taking into consideration that these foods are generally consumed less frequently.

We considered four primary multivariate models. The first model included only age at diagnosis and post-diagnostic total energy consumption as continuous variables, and indicator variables for quartiles of the post-diagnostic food group of interest. In a second model, we additionally adjusted for prognostic risk group and primary treatment. Risk groups were defined as follows – low risk: PSA <10 and Gleason sum ≤ 6 and stage ≤ 2; high risk: PSA ≥ 20 or Gleason sum ≥ 8 or stage = 3; and intermediate risk: all others (based on modified D'Amico classification [20]). The primary treatment groups were radical prostatectomy, radiation therapy, hormonal therapy, other, and unknown. In the third model, we adjusted for age, post-diagnostic total energy, and other post-diagnostic food groups (quartile index variables for each food group). Lastly, we considered a model adjusted for age, post-diagnostic total energy, other post-diagnostic food groups, and pre-diagnostic diet (i.e. continuous variables for each food group and total energy consumption from the 1986 questionnaire). In addition, we investigated the linear relationships between consumption of each food group and the risk of progression using continuous variables for each food group (i.e. servings/day).

Models were additionally adjusted for smoking habits, exercise level, body mass index, family history of prostate cancer, and race. There was little evidence of confounding by these factors, and they were not included in the primary multivariate analyses.

Results

We identified 392 cases of prostate cancer progression through August 2000 among 1,202 men diagnosed with prostate cancer between 1986 and 1996. Socio-demographic and clinical diagnostic characteristics of this population for analysis are provided in Table 1. The mean age at diagnosis was 68 years, the population was predominantly Caucasian, and about 15% of men had a family history of prostate cancer. Men were evenly distributed across the clinical prognostic groups, and the most common therapy received was radical prostatectomy, followed by radiation therapy. The associations between clinical parameters and the risk of progression were as expected (data not shown). For example, men pursuing radiation therapy had a greater risk of progression compared to men who underwent radical prostatectomy (multivariate HR = 1.97, 95% CI 1.52–2.54, adjusted for food groups, age, total energy, and prognostic risk group), likely reflecting the usage of radiation therapy for both localized patients as well as those with more advanced disease. Similarly, men in the intermediate or high prognostic risk group at diagnosis had a greater relative hazard of progression compared to those classified as low risk (HR = 1.26, 95% CI 0.96–1.65 for intermediate risk; HR = 2.30, 95% CI 1.80–2.95 for high risk).

In Table 2, we present data on mean food group intake in 1986 (i.e. before diagnosis), and change in food group consumption after diagnosis, stratified by prognostic risk group. These data show that the majority of men consumed less red meat and more grains, fruits, and vegetables after diagnosis relative to before. The majority of men consumed about the same amounts of milk, fish, tomato sauce, and fresh tomato products before and after diagnosis. Dietary changes appeared to be similar across prognostic risk groups.

Table 3 displays results on quartiles of post-diagnostic food group consumption and the risk of prostate cancer progression. There was little evidence of any association

Table 1 Socio-demographic and clinical features of 1,202 men with prostate cancer in the Health Professionals Follow-up Study

Characteristic	Means ± standard deviations or percents
Age at diagnosis (years)	68 ± 6.3
African-Americans	1%
Family history of prostate cancer (father or brother)	15%
Body mass index in 1986 (kg/m^2)	25.3 ± 2.8
Follow-up time (months)	77 ± 34
Smoking habits in 1986	
Never smoker	43%
Past smoker	47%
Current smoker	7%
Missing	3%
Prostate specific antigen at diagnosis (ng/ml)	8.9 ± 14.5
Gleason score 2–5	38%
Gleason score 6–7	53%
Gleason score 8–10	9%
Clinical stage at diagnosis	
1 = local, PSA detected only	12%
2 = local, palpable	65%
3 = regional	23%
Primary treatment	
Radical prostatectomy	46%
Radiation therapy	23%
Hormonal therapy	2%
Other	1%
Unknown	28%
Clinical risk group at diagnosis[a]	
Low risk	36%
Intermediate risk	32%
High risk	32%

[a] Risk group categorization defined as follows- low: $0 \leq PSA < 10$ and Gleason sum ≤ 6 and stage ≤ 2; high: $PSA \geq 20$ or Gleason sum ≥ 8 or stage = 3; intermediate risk: all others

for grains, fruits, and red meat and the risk of prostate cancer progression. There was some suggestion of a small-elevated risk associated with the middle quartiles of vegetable intake, however there was no evidence for a linear trend or dose response. Men in the highest versus lowest quartile of milk consumption had a slight elevation in risk, but the results were not statistically significant. Fish consumption was modestly inversely associated with the risk of progression, but these results were also not statistically significant. There was a strong and statistically significant inverse association for tomato sauce consumption, whereby men in the highest versus lowest quartile of consumption had an approximate 40% reduced risk of prostate cancer progression. In contrast, men in the highest versus lowest quartile of fresh tomato product consumption had up to a 58% increased risk of progression. There was little to moderate variation in results across the four primary multivariate models considered. Overall, the clinical variables did not appear to alter the estimates and were not retained in subsequent models. Adjustment for other post-diagnostic dietary food groups and additional adjustment for pre-diagnostic diet each slightly strengthened any observed associations (Table 3).

In Table 4, we present the hazard ratios for a one serving per day increase in post-diagnostic consumption of each food group as a reflection of linear trends. Effects were slightly stronger with additional adjustment for pre-diagnostic diet and other post-diagnostic food groups. Increasing post-diagnostic consumption of fish or tomato sauce by one serving per day was associated with an approximate 50% lower risk of progression, independent of pre-diagnostic diet and other post-diagnostic foods (p-value = 0.006 for fish and 0.04 for tomato sauce). In contrast, small positive linear associations were observed for milk and fresh tomato products. There was no evidence of association for red meat, vegetables, grains, or fruits. The more modest results for a two serving/week increase, which better reflects the more likely changes for less commonly eaten foods, were 1.00, 1.01, 0.99, 0.97, 1.03, 0.83, 0.80, and 1.07 for grains, vegetables, fruits, red meat, milk, fish, tomato sauce, and fresh tomatoes, respectively (p-values same as those in Table 4; adjusted for age, total energy, pre- and post-diagnostic diet).

There were 93 men who experienced progression before returning their first post-diagnostic dietary survey. In the primary analysis, information regarding their post-diagnostic dietary exposure was based on their most recent pre-diagnostic dietary survey, and they were censored before their dietary exposure could be updated with their first post-diagnostic survey. We reran the main analysis models excluding these men, and the results were essentially the same. We also examined associations within strata of known treatment groups (i.e. surgery, radiation, or hormones), prognostic risk group (i.e. low, intermediate, or high), and date of diagnosis (before or after June 1991); point estimate results were similar, although confidence intervals were wide. We examined individual results for processed meat (i.e. hot dogs, bacon, salami/bologna or other processed meat) and fresh tomatoes, and results were essentially the same as those presented in Table 3 for total red meat and total fresh tomato products (including salsa and tomato juice), respectively.

Discussion

To our knowledge, this is the first prospective investigation of pre-and post-diagnostic diet and the risk of prostate cancer progression in a cohort of men with prostate cancer. We observed that post-diagnostic fish and tomato sauce intake were inversely associated with risk of prostate cancer progression, while fresh tomato products and milk consumption appeared to slightly increase the risk of

Table 2 Pre-diagnostic mean food group intake and change in consumption after diagnosis of prostate cancer, by prognostic risk group, among 1,202 men with prostate cancer

Food Group	Prognostic Risk Group[a]											
	Low (n = 432)				Intermediate (n = 385)				High (n = 385)			
	Servings per day 1986	Less[b] (%)	Same[b] (%)	More[b] (%)	Servings per day 1986	Less (%)	Same (%)	More (%)	Servings per day 1986	Less (%)	Same (%)	More (%)
Grains	2.9	29	28	43	2.8	30	30	40	2.9	30	31	38[c]
Vegetables	2.9	29	25	46	2.9	29	33	38	3.1	28	30	42
Fruits	2.5	28	31	41	2.5	27	29	44	2.5	25	35	40
Red Meat	0.9	50	25	25	0.9	42	30	28	1.0	51	25	24
Milk	0.9	16	66	18	1.0	19	61	20	1.1	19	60	21
Fish	0.4	33	55	12	0.3	30	53	17	0.3	31	55	14
Tomato Sauce	0.2	11	72	17	0.2	12	68	20	0.2	14	72	14
Fresh Tomato Products	0.5	30	40	30	0.5	37	32	31	0.5	31	37	31[c]

[a] Risk group categorization defined as follows- low: $0 \leq PSA < 10$ and Gleason sum ≤ 6 and stage ≤ 2; high: $PSA \geq 20$ or Gleason sum ≥ 8 or stage = 3; intermediate risk: all others

[b] For grains, vegetables, fruits, and milk: ''less'' = a negative change of serving/day or greater, after diagnosis compared to before; ''same'' = eating $\pm$ serving/day; ''more'' = a positive change of serving/day or greater. For red meat, fish, tomato sauce, and fresh tomatoes: ''less'' = a negative change of one serving/week or greater, after diagnosis compared to before; ''same'' = eating $\pm$ one serving/week; ''more'' = a positive change of one serving/week or greater

[c] Percents may not sum to 100 due to rounding

progression. We found little evidence for any associations for grains, red meat, or fruits.

Previous studies have demonstrated an inverse association between the risk of developing cancer, in particular prostate cancer, and consumption of tomatoes, tomato based products, or lycopene [15]. Lycopene is a carotenoid which is highly concentrated in the prostate gland and has antioxidant properties; tomatoes are the primary source of lycopene in typical American diets. In a previous investigation examining predictors of incident prostate cancer in this cohort, men consuming two or more servings of tomato sauce per week experienced an approximate 20–35% lower risk of developing prostate cancer [16]. Our findings extend these results and suggest that tomato sauce consumption *after diagnosis* independently predicts risk of recurrence or progression, among men with prostate cancer. The lack of evidence of an inverse association for fresh tomato products in this study may partially be explained by previous observations that tomato sauce is the best source of bioavailable lycopene [15, 17]. A meta-analysis of tomato products and lycopene for the prevention of prostate cancer also observed a slightly stronger effect of cooked versus raw tomato products when compared to non-frequent consumption of overall tomato products (relative risk = 0.89, 95% CI 0.80–1.00 for raw and 0.81, 95% CI 0.71–0.92 for cooked, comparing extreme quintiles of intake) [21]. The modest elevation in risk observed for fresh tomato products was unexpected, however, and further research is warranted to reconcile this association.

These findings for post-diagnostic tomato sauce consumption and progression risk are consistent with a few small intervention studies that reported on potential benefits of a tomato sauce or lycopene supplemented diet, among men with prostate cancer. In one study, 32 men with localized prostate cancer received a tomato sauce-based pasta dish daily for 3 weeks prior to radical prostatectomy; reductions in leukocyte and prostate tissue oxidative DNA damage were observed when compared to levels assessed prior to the intervention (leukocyte) or in a small control group (tissue) [22]. In another study, 26 men with newly diagnosed localized prostate cancer were randomly assigned to either a 15 mg lycopene supplement (n = 15) or no supplement (n = 11) for 3 weeks prior to surgery. The men on intervention experienced an 18% decrease in PSA level compared to a 14% increase experienced by the control group (p = 0.25) [23].

The association of post-diagnostic fish intake with lower risk of prostate cancer recurrence, progression, or death is consistent with previous results for pre-diagnostic diet and risk of incident prostate cancer from a large Swedish cohort study [24] and this cohort [25]. In the Swedish study, men who rarely consumed fish had a threefold greater risk of prostate cancer death compared to men who reported consuming fish moderately often [24]. A unique nutritional component of fish is the marine omega-3 fatty acids, and some experimental studies suggest that marine omega-3 fatty acid alone or a greater ratio of omega-3 to omega-6 fatty acid may decrease prostate cancer cell growth *in vitro* [26]. Hypothesized mechanisms of action include effects on cancer cell proliferation and inflammatory pathways that influence cancer growth. Growth of DU-145 (an aggressive human prostate cancer cell line) xenografts was inhibited in nude mice fed a diet rich in marine omega-3 fatty acids [docosahexaenoic (DHA) + eicosapentaenoic

Table 3 Post-diagnostic food group consumption and the risk of prostate cancer progression (392 outcomes) among 1,202 men with prostate cancer from the Health Professionals Follow-up Study

Food Group	Quartile	Multivariate hazard ratio (95% Confidence Interval, CI)							
		Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
Grains	1	1.00		1.00		1.00		1.00	
	2	1.09	(0.82–1.45)	1.13	(0.85–1.51)	1.12	(0.83–1.52)	1.16	(0.86–1.57)
	3	1.12	(0.84–1.50)	1.14	(0.85–1.52)	1.15	(0.85–1.56)	1.19	(0.87–1.62)
	4	0.83	(0.60–1.15)	0.88	(0.63–1.22)	0.86	(0.61–1.20)	0.93	(0.65–1.31)
Vegetables	1	1.00		1.00		1.00		1.00	
	2	1.39	(1.03–1.86)	1.40	(1.04–1.88)	1.48	(1.07–2.04)	1.50	(1.09–2.08)
	3	1.31	(0.97–1.78)	1.28	(0.95–1.74)	1.41	(1.00–1.99)	1.44	(1.02–2.03)
	4	1.14	(0.83–1.57)	1.18	(0.86–1.62)	1.23	(0.85–1.78)	1.26	(0.85–1.87)
Fruits	1	1.00		1.00		1.00		1.00	
	2	1.21	(0.91–1.60)	1.20	(0.91–1.59)	1.20	(0.90–1.61)	1.19	(0.88–1.59)
	3	0.90	(0.67–1.21)	0.93	(0.69–1.26)	0.88	(0.64–1.22)	0.86	(0.62–1.20)
	4	0.98	(0.73–1.33)	0.98	(0.73–1.33)	0.94	(0.67–1.31)	0.90	(0.62–1.28)
Red Meat	1	1.00		1.00		1.00		1.00	
	2	0.99	(0.74–1.32)	1.06	(0.80–1.42)	1.00	(0.75–1.34)	1.02	(0.76–1.38)
	3	1.05	(0.78–1.40)	1.12	(0.84–1.51)	1.03	(0.76–1.38)	1.06	(0.78–1.45)
	4	1.01	(0.74–1.39)	1.08	(0.79–1.47)	0.98	(0.71–1.34)	1.03	(0.72–1.46)
Milk	1	1.00		1.00		1.00		1.00	
	2	1.14	(0.84–1.53)	1.16	(0.86–1.56)	1.17	(0.86–1.59)	1.18	(0.86–1.60)
	3	1.00	(0.76–1.32)	1.02	(0.77–1.35)	1.04	(0.78–1.39)	1.04	(0.78–1.40)
	4	1.26	(0.94–1.70)	1.25	(0.93–1.69)	1.27	(0.94–1.71)	1.30	(0.93–1.83)
Fish	1	1.00		1.00		1.00		1.00	
	2	1.03	(0.78–1.36)	1.01	(0.77–1.33)	1.04	(0.78–1.38)	1.01	(0.76–1.35)
	3	1.02	(0.76–1.36)	1.02	(0.76–1.37)	1.02	(0.75–1.38)	0.94	(0.69–1.29)
	4	0.86	(0.64–1.15)	0.88	(0.66–1.18)	0.85	(0.62–1.17)	0.73	(0.52–1.02)
Tomato Sauce	1	1.00		1.00		1.00		1.00	
	2	0.81	(0.61–1.07)	0.86	(0.65–1.13)	0.78	(0.58–1.05)	0.78	(0.58–1.05)
	3	0.98	(0.74–1.29)	0.99	(0.75–1.32)	0.94	(0.69–1.27)	0.91	(0.67–1.24)
	4	0.63	(0.44–0.89)	0.67	(0.47–0.95)	0.59	(0.41–0.86)	0.56	(0.38–0.82)
Fresh Tomato Products	1	1.00		1.00		1.00		1.00	
	2	1.29	(0.96–1.74)	1.29	(0.96–1.74)	1.45	(1.06–1.99)	1.46	(1.06–2.01)
	3	1.28	(0.95–1.71)	1.31	(0.98–1.76)	1.44	(1.04–1.99)	1.48	(1.06–2.06)
	4	1.35	(1.00–1.82)	1.32	(0.98–1.78)	1.55	(1.11–2.17)	1.58	(1.10–2.25)

[a] Adjusted for age and total energy

[b] Adjusted for age and total energy, prognostic risk group, and primary treatment modality (surgery, radiation, hormonal therapy, other, unknown)

[c] Adjusted for age, total energy and all other post-diagnostic diet food groups (quartile indicators)

[d] Adjusted for age, total energy, pre-diagnostic diet (continuous variables), and all other post-diagnostic food groups (quartile indicators)

(EPA)] [27]. Chung *et al*. has reported that DHA + EPA inhibited androgen-stimulated LNCaP prostate cancer cell growth [28]. It has been demonstrated, in a mouse squamous cell carcinoma model, that EPA induces partial depletion of intracellular Ca^{2+} stores, which inhibits translation initiation and leads to cell cycle arrest in G_1 [29]. We previously reported that pre-diagnostic EPA + DHA intake in this cohort was related to lower risk of incident advanced prostate cancer (relative risk = 0.74, 95% CI 0.49–1.08, when comparing the highest versus lowest quintile of consumption) [30]. Fish is also one of the few natural sources of vitamin D, a hypothesized beneficial factor for prostate cancer [10]. The current results suggest that fish consumption *after* diagnosis may have a similar beneficial effect on protecting against the risk of prostate cancer progression, independent of pre-diagnostic consumption levels.

The suggestion of a slight positive association between post-diagnostic milk consumption and the risk of prostate cancer progression is consistent with prior evidence (including an investigation from this cohort) that dairy products, milk, or calcium intake may increase risk of developing incident prostate cancer, in particular metastatic and fatal disease [10, 31–35]. We have hypothesized that high calcium consumption, from supplements or calcium-rich products (*e.g.* milk), may lead to higher circulating calcium levels, which reduces production of 1,25 dihydroxyvitamin D_3, a vitamin D metabolite that suppresses prostate cancer tumor growth *in vitro* and *in vivo* [10]. Although milk in the United States is fortified with

Table 4 Linear trends between post-diagnostic food group consumption and the risk of prostate cancer progression (392 outcomes), among 1,202 men with incident prostate cancer from the Health Professionals Follow-up Study

Food Group	Hazard Ratio for one serving/day increase(p-value)	
	Adjusted for age and total energy[a]	Also adjusted for pre- and post-diagnostic diet[a,b]
Grain	0.96 (0.20)	0.98 (0.61)
Vegetables	1.01 (0.63)	1.04 (0.14)
Fruits	0.98 (0.44)	0.96 (0.23)
Red Meat	0.92 (0.32)	0.89 (0.24)
Milk	1.09 (0.06)	1.12 (0.04)
Fish	0.73 (0.12)	0.52 (0.006)
Tomato Sauce	0.52 (0.06)	0.46 (0.04)
Fresh Tomato Products	1.12 (0.12)	1.27 (0.02)

[a] Model adjusts for age at diagnosis and post-diagnostic total energy consumption

[b] Model adjusts for all pre-and post-diagnostic food group consumption as continuous variables

vitamin D, the overall influence of milk is to lower 1,25 dihydroxyvitamin D_3 because of its high calcium content. Men with greater milk intake have also been shown to have higher levels of circulating insulin like growth factor-I [36–38], a hormone linked to greater risk of advanced stage incident prostate cancer [39]. In contrast, secondary results from a randomized clinical trial for the prevention of colorectal adenomas suggested that there is a null or even inverse association between calcium supplements and the risk of incident prostate cancer [40]. These apparently conflicting findings warrant further research, especially given that men with prostate cancer on hormonal therapy are often recommended to take supplemental calcium to prevent bone loss.

The moderate positive association for post-diagnostic intermediate levels of vegetable consumption and the risk of prostate cancer progression is inconsistent with previous studies suggesting that total and specific vegetable intakes are associated with slight reductions in or no influence on the risk of developing prostate cancer [7, 41–44]. This unclear association for vegetables may be due partially to the heterogeneity of this food group. The category of ''vegetables'' contained the most items (up to 26 specific vegetables were assessed in any given questionnaire year), and it is possible that different specific vegetables have opposing effects on risk of prostate cancer progression.

There are several limitations of this study to consider. Details on prostate cancer clinical follow-up came from physician and, to a lesser degree, patient reports of past events. While we cannot overlook the potential for measurement error in assessing our outcome, for 67% of the men we had data from their physician(s); for 18% we had medical record data because the men died during follow-up; and for only 16% of the cohort did we rely solely on patient self-report of secondary outcomes. Our main outcome was heterogeneous, combining biochemical relapses, second treatment, progression to metastatic disease, and prostate cancer death. We conducted an analysis excluding the 23 cases identified based on initiation of second treatment after primary therapy or initiation of first treatment among watchful waiters, and the results were unchanged. There were too few prostate cancer deaths ($n = 50$) and cases of metastases ($n = 7$) to examine these outcomes independently, although we acknowledge that these may be the most relevant clinical events. We combined these outcomes primarily to maximize statistical power, but also because no previous data suggested the biological mechanism for diet would be different for these events. These events are likely somewhat inter-related, as biochemical recurrence and metastasis predict prostate cancer death. With additional follow-up, we will focus on metastasis/death as primary outcomes in the future.

We did not comprehensively collect details on adjuvant or neoadjuvant therapies, complications during treatment, repeated measurements of PSA indicating the rise/velocity, or medical charts or pathology reports for every post-diagnostic clinical visit. However, the main baseline diagnostic and treatment variables (i.e. diagnostic Gleason score, PSA, and stage, and primary therapy) were not correlated with dietary habits, so these should not be serious confounding variables.

The study also had several strengths, including repeated prospective assessments of diet before and after prostate cancer diagnosis, an average of 6 years and up to 14 years of post-diagnosis follow-up based primarily on physician surveys and medical chart death data, and reasonable details on tumor characteristics at diagnosis and primary treatment. We also were able to consider the potential confounding effects of body size, exercise, family history, smoking, and race; although there was little ethnic diversity in this population.

To our knowledge, this is the first report to examine post-diagnostic diet and risk of prostate cancer progression, with consideration for pre-diagnostic diet and other clinical and lifestyle factors. We observed suggestive inverse associations for tomato sauce and fish consumption and the risk of prostate cancer progression, and a possible positive association for milk and fresh tomato products. These results are preliminary and should be interpreted cautiously. Nonetheless, they support the hypothesis that post-diagnostic diet could influence the progression of prostate cancer, at least among men diagnosed before macro-metastases are detected. That little evidence of confounding by clinical and other lifestyle factors on the association between diet and risk of progression was apparent here may be an important consideration for other

studies that have collected longitudinal nutritional data but less detailed clinical data. These results may be useful in the development of secondary prevention intervention studies. Further research is warranted to examine these findings in settings with larger populations of patients and more detailed comprehensive clinical follow-up.

Acknowledgements We would like to thank the participants, without whom this research could not be done; and Mira Kaufman, Jason Salter, and Anne Que for their invaluable help in data management and project coordination.

References

1. Graefen M, Karakiewicz PI, Cagiannos I et al. (2002) International validation of a preoperative nomogram for prostate cancer recurrence after radical prostatectomy. J Clin Oncol 20:3206–3212
2. Winkler MH, Khan FA, Hoh IM et al. (2004) Time trends in case selection, stage and prostate-specific antigen recurrence after radical prostatectomy: a multicentre audit. BJU Int 93:725–729
3. Khuntia D, Reddy CA, Mahadevan A, Klein EA, Kupelian PA (2004) Recurrence-free survival rates after external-beam radiotherapy for patients with clinical T1–T3 prostate carcinoma in the prostate-specific antigen era: what should we expect? Cancer 100:1283–1292
4. Johansson JE, Andren O, Andersson SO et al. (2004) Natural history of early, localized prostate cancer. JAMA 291:2713–2719
5. Patterson RE, Neuhouser ML, Hedderson MM, Schwartz SM, Standish LJ, Bowen DJ (2003) Changes in diet, physical activity, and supplement use among adults diagnosed with cancer. J Am Diet Assoc 103:323–328
6. Giovannucci E (2002) A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. Exp Biol Med (Maywood) 227:852–859
7. Chan JM, Giovannucci EL (2001) Vegetables, fruits, associated micronutrients, and risk of prostate cancer. Epidemiol Rev 23:82–86
8. Nelson WG, De Marzo AM, Isaacs WB (2003) Prostate cancer. N Engl J Med 349:366–381
9. Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC, Giovannucci E (2001) A prospective study on intake of animal products and risk of prostate cancer. Cancer Causes Control 12:557–567
10. Chan JM, Giovannucci EL (2001) Dairy products, calcium, and vitamin D and risk of prostate cancer. Epidemiol Rev 23:87–92
11. Rimm EB, Giovannucci EL, Willett WC et al. (1991) Prospective study of alcohol consumption and risk of coronary disease in men. Lancet 338:464–468
12. Willett WC, Reynolds RD, Cottrell-Hoehner S, Sampson L, Browne ML (1987) Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. J Am Diet Assoc 87:43–47
13. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC (1992). Reproducibility and validity of a expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 135:1114–1126
14. Feskanich D, Rimm EB, Giovannucci EL et al. (1993) Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 93:790–796
15. Giovannucci E (1999) Tomatoes, tomato-based products, lycopene, and cancer:review of the epidemiologic literature. J Natl Cancer Inst 91:317–331
16. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC (2002) A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst 94:391–398
17. Allen CM, Schwartz SJ, Craft NE, Giovannucci EL, De Groff VL, Clinton SK (2003) Changes in plasma and oral mucosal lycopene isomer concentrations in healthy adults consuming standard servings of processed tomato products. Nutr Cancer 47:48–56
18. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC (1999) Natural history of progression after PSA elevation following radical prostatectomy. JAMA 281:1591–1597
19. Consensus statement:guidelines for PSA following radiation therapy (1997) American Society for Therapeutic Radiology and Oncology Consensus PanelInt. J Radiat Oncol Biol Phys 37:1035–1041
20. D'Amico AV, Whittington R, Malkowicz SB et al. (2002) Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era. Cancer 95:281–286
21. Etminan M, Takkouche B, Caamano-Isorna F (2004) The role of tomato products and lycopene in the prevention of prostate cancer:a meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev 13:340–345
22. Chen L, Stacewicz-Sapuntzakis M, Duncan C et al. (2001) Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. J Natl Cancer Inst 93:1872–1879
23. Kucuk O, Sarkar FH, Sakr W et al. (2001) Phase II randomized clinical trial of lycopene supplementation before radical prostatectomyCancer. Epidemiol Biomarkers Prev 10:861–868
24. Terry P, Lichtenstein P, Feychting M, Ahlbom A, Wolk A (2001) Fatty fish consumption and risk of prostate cancer. Lancet 357:1764–1766
25. Augustsson K, Michaud DS, Rimm EB et al. (2003) A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomarkers Prev 12:64–67
26. Rose DP, Connolly JM (1991) Effects of fatty acids and eicosanoid synthesis inhibitors on the growth of two human prostate cancer cell lines. Prostate 18:243–254
27. Karmali RA (1987) Fatty acids:inhibition. Am J Clin Nutr 45(Suppl 1):225–229
28. Chung BH, Mitchell SH, Zhang JS (2001) Effects of docosahexaenoic acid and eicosapentaenoic acid on androgen-mediated cell growth and gene expression in LNCaP prostate cancer cells. Carcinogenesis 22:1201–1206
29. Palakurthi SS, Fluckiger R, Aktas H, et al. (2000) Inhibition of translation initiation mediates the anticancer effect of the n-3 polyunsaturated fatty acid eicosapentaenoic acid. Cancer Res 60:2919–2925
30. Leitzmann MF, Stampfer MJ, Michaud DS et al. (2004) Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. Am J Clin Nutr 80:204–216
31. Rodriguez C, McCullough ML, Mondul AM et al. (2003) Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. Cancer Epidemiol Biomarkers Prev 12:597–603
32. Bosetti C, Micelotta S, Dal Maso L et al. (2004) Food groups and risk of prostate cancer in Italy. Int J Cancer 110:424–428
33. Chan JM, Giovannucci E, Andersson S-O, Yuen J, Adami H-O, Wolk A (1998) Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer. Cancer Causes Control 9:559–566

34. Chan JM, Stampfer MJ, Ma J, Gann PH, Gaziano JM, Giovannucci EL (2001) Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. Am J Clin Nutr 74:549–554
35. Giovannucci E, Rimm EB, Wolk A et al. (1998) Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 58:442–447
36. Giovannucci E, Pollak M, Liu Y et al. (2003) Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. Cancer Epidemiol Biomarkers Prev 12:84–89
37. Heaney R, McCarron D, Dawson-Hughes B et al. (1999) Dietary changes favorably affect bone remodeling in older adults. J Am Diet Assoc 99:1228–1233
38. Holmes MD, Pollak MN, Willett WC, Hankinson SE (2002) Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev 11:852–61
39. Chan JM, Stampfer MJ, Ma J et al. (2002) Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. J Natl Cancer Inst 94:1099–1106
40. Baron JA, Beach M, Wallace K et al. (2005) Risk of prostate cancer in a randomized clinical trial of calcium supplementation. Cancer Epidemiol Biomarkers Prev 14:586–589
41. Sonoda T, Nagata Y, Mori M et al. (2004) A case–control study of diet and prostate cancer in Japan:possible protective effect of traditional Japanese diet. Cancer Sci 95:238–242
42. Hodge AM, English DR, McCredie MR et al. (2004) Foods, nutrients and prostate cancer. Cancer Causes Control 15:11–20
43. Hsing AW, Chokkalingam AP, Gao YT et al. (2002) Allium vegetables and risk of prostate cancer:a population-based study. J Natl Cancer Inst 94:1648–1651
44. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC (2003) A prospective study of cruciferous vegetables and prostate cancer. Cancer Epidemiol Biomarkers Prev 12:1403–1409