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Research Article

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A Pooled Analysis of 15 Prospective Cohort Studies on the Association between Fruit, Vegetable, and Mature Bean Consumption and Risk of Prostate Cancer

Joshua Petimar[1,2], Kathryn M. Wilson[2,3], Kana Wu[1], Molin Wang[2,3,4], Demetrius Albanes[5], Piet A. van den Brandt[6], Michael B. Cook[5], Graham G. Giles[7], Edward L. Giovannucci[1,2,3,8], Gary E. Goodman[9], Phyllis J. Goodman[10], Niclas Håkansson[11], Kathy Helzlsouer[21], Timothy J. Key[13], Laurence N. Kolonel[14], Linda M. Liao[5], Satu Männistö[15], Marjorie L. McCullough[16], Roger L. Milne[7], Marian L. Neuhouser[9], Yikyung Park[17], Elizabeth A. Platz[12], Elio Riboli[18], Norie Sawada[19], Jeannette M. Schenk[9], Shoichiro Tsugane[19], Bas Verhage[6], Ying Wang[16], Lynne R. Wilkens[20], Alicja Wolk[11], Regina G. Ziegler[5], and Stephanie A. Smith-Warner[1,2]

Abstract

Background: Relationships between fruit, vegetable, and mature bean consumption and prostate cancer risk are unclear.

Methods: We examined associations between fruit and vegetable groups, specific fruits and vegetables, and mature bean consumption and prostate cancer risk overall, by stage and grade, and for prostate cancer mortality in a pooled analysis of 15 prospective cohorts, including 52,680 total cases and 3,205 prostate cancer–related deaths among 842,149 men. Diet was measured by a food frequency questionnaire or similar instrument at baseline. We calculated study-specific relative risks using Cox proportional hazards regression, and then pooled these estimates using a random effects model.

Results: We did not observe any statistically significant associations for advanced prostate cancer or prostate cancer mortality with any food group (including total fruits and vegetables, total fruits, total vegetables, fruit and vegetable juice, cruciferous vegetables, and tomato products), nor specific fruit and vegetables. In addition, we observed few statistically significant results for other prostate cancer outcomes. Pooled multivariable relative risks comparing the highest versus lowest quantiles across all fruit and vegetable exposures and prostate cancer outcomes ranged from 0.89 to 1.09. There was no evidence of effect modification for any association by age or body mass index.

Conclusions: Results from this large, international, pooled analysis do not support a strong role of collective groupings of fruits, vegetables, or mature beans in prostate cancer.

Impact: Further investigation of other dietary exposures, especially indicators of bioavailable nutrient intake or specific phytochemicals, should be considered for prostate cancer risk. *Cancer Epidemiol Biomarkers Prev; 26(8); 1276–87. ©2017 AACR.*

[1]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. [4]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland. [6]Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands. [7]Cancer Epidemiology Centre, Cancer Council Victoria, Carlton, Victoria, Australia. [8]Department of Medicine, Harvard Medical School, Boston, Massachusetts. [9]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington. [10]SWOG Statistical Center, Seattle, Washington. [11]Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [12]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. [13]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom. [14]Department of Public Health Sciences, University of Hawaii, Honolulu, Hawaii. [15]Department of Health, National Institute for Health and Welfare, Helsinki, Finland. [16]Epidemiology Research Program, American Cancer Society, Atlanta, Georgia. [17]Division of Public Health Sciences, Washington University School of Medicine, St. Louis, Missouri. [18]School of Public Health, Imperial College London, London, United Kingdom. [19]Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan. [20]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii. [21]Division of Cancer Control and Population Sciences, National Cancer Institute, NIH, Bethesda, Maryland.

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Corresponding Author: Joshua Petimar, Departments of Nutrition and Epidemiology, Harvard T.H. Chan School of Public Health, 665 Huntington Avenue, Boston, MA 02115. Fax: 617-432-2435; E-mail: jsp778@mail.harvard.edu, pooling@hsph.harvard.edu

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Introduction

Prostate cancer is the second most common cancer in men globally, accounting for 15% of all cancer cases and 7% of all cancer-related deaths in men (1). Although total prostate cancer has a high survival rate in developed countries (2), largely due to the high incidence of localized and regional prostate cancer as a result of widespread prostate-specific antigen (PSA) screening, metastatic prostate cancer has a markedly different prognosis (28% five-year survival in the United States; ref. 3). It is, therefore, important for epidemiologic studies to elucidate risk factors for prostate cancer with worse prognoses, including advanced prostate cancer and prostate cancer mortality.

Fruits, vegetables, and mature beans contain many nutrients hypothesized to prevent cancer, including dietary fiber, vitamins, minerals, carotenoids, and other phytochemicals (4, 5). Cruciferous vegetables and tomato products are of particular interest due to possible chemopreventive effects of indoles and isothiocyanates (6), and lycopene (7), respectively. However, epidemiologic studies that have examined fruit, vegetable, and mature bean intake and prostate cancer risk have been inconsistent, and the 2014 World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project report concluded that there was limited and inconclusive evidence regarding fruit, vegetable, and mature bean consumption on risk of prostate cancer (8). This may be due to the fact that prior studies have not defined advanced prostate cancer consistently, and that many studies may have had limited power to detect such associations. To clarify these relationships, we conducted pooled analyses of 15 prospective studies using harmonized participant-level data to examine associations between intakes of broad and specific fruit and vegetable groups, as well as mature beans (excluding soy) and risk of prostate cancer overall and by stage and grade. This approach provided a wide range of intake and sufficient power to detect associations for clinically relevant advanced disease, including prostate cancer mortality, as well as associations within subgroups in the population.

Methods

Study population

This study was conducted within the Pooling Project of Prospective Studies of Diet and Cancer (DCPP). Fifteen prospective cohorts (9–22) (Table 1) within this international consortium met the predefined criteria for inclusion: baseline assessment of usual diet, validation of the dietary assessment method used or a closely related instrument, at least one publication on an association between diet and cancer, and identification of at least 50 incident prostate cancer cases during follow-up. Each study received approval from the institutional review board of their institution.

Ascertainment of cases

Incident prostate cancer cases were identified in each study by follow-up questionnaires with subsequent review of medical records (20, 21), linkage to cancer registries (12–18, 23), or both (9–11, 22), with the exception of the Prostate Cancer Prevention Trial (PCPT), for which cases were limited to those diagnosed through biopsy performed because of an elevated PSA or suspicious digital rectal exam ("for cause") per trial protocol (19). Some studies also used mortality registries to identify prostate cancer deaths (10, 12, 14, 15, 17, 20, 22, 23). In addition to total prostate cancer, we examined localized (T1/T2 and N0M0 tumors), advanced (T4, N1, or M1 tumors, or prostate cancer mortality), advanced restricted (same as advanced prostate cancer, but excluding localized cases who died of prostate cancer during follow-up who had been diagnosed with localized cancer or those who had missing stage data), low-grade (Gleason score < 8, or being well or moderately differentiated), and high-grade (Gleason score ≥ 8, or being poorly differentiated/undifferentiated) prostate cancer, as well as prostate cancer mortality [cases where prostate cancer was determined to be the underlying cause of death; see appendix to Wu and colleagues (24) for more detail on harmonization of the outcome data]. Advanced restricted prostate cancer was considered to define a case group known to be advanced at diagnosis, as opposed to cases that might have progressed from a diagnosis of localized cancer to death.

Dietary assessment

Each study assessed at baseline usual diet during the past year (to assess long-term intake and account for seasonal variation) using self-administered food-frequency questionnaires (FFQ) with the exception of some centers in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, which used interviewer-administered dietary questionnaires (25). Food intake data were converted to grams consumed per day. We examined 8 food groups: total fruits and vegetables (including juice), total fruits (including fruit juice), total fruits excluding fruit juice, fruit and vegetable juice, total vegetables (including vegetable juice), cruciferous vegetables, tomato products, and mature beans (all beans excluding green beans and soy). Food group intakes were calculated as the sum of intakes of individual items in that group. Food group definitions were standardized, but each study's contribution to a food group depended on the foods assessed on that study's questionnaire. Results for total fruits (including fruit juice) and total fruits excluding fruit juice were similar; thus, only results for total fruits (including fruit juice) are presented. Potatoes were excluded from all food groups due to their high starch content, and pickled vegetables were excluded because of previous findings suggesting an increased risk of certain cancers (26, 27). Mature beans were excluded from vegetable groups because of their high protein content. Soybeans were excluded from the mature bean group because of the hypothesis that isoflavones reduce risk of prostate cancer (28, 29). We also analyzed associations with specific fruits and vegetables that were assessed in the majority of studies.

Although all studies conducted validation studies of their questionnaires, the validity of most food groups was not evaluated routinely. However, among the studies that evaluated the validity of total fruits or total vegetables (30–35), correlation coefficients for these food groups generally exceeded 0.35.

Assessment of nondietary risk factors

Information was collected on nondietary factors at baseline. Age, height, and weight were either measured or collected by self-report in all studies. Body mass index [BMI, calculated as weight(kg)/height(m)^2] was calculated on the basis of height and weight at baseline. Most studies assessed smoking habits, physical activity, education, race, marital status, multivitamin use, and history of diabetes. The percent of data missing for these covariates was low (generally <8%).

Statistical analysis

In addition to the study-specific exclusion criteria, we excluded from our analyses (i) participants with a prior history of cancer except nonmelanoma skin cancer at baseline and (ii) those whose energy intakes were outside 3 SDs from the study-specific $\log_e$-transformed mean energy intake. The latter was done to exclude individuals who might have filled out their questionnaire incorrectly.

For all outcomes except prostate cancer mortality, participants contributed person-years of follow-up time from the date of the baseline questionnaire to the date of diagnosis with prostate cancer, death, loss to follow-up, if available, or administrative end of follow-up, whichever came first. For analyses of prostate cancer mortality, participants contributed person-years of follow-up time from the date of the baseline questionnaire to the date of death, loss to follow-up, if available, or administrative end of follow-up, whichever came first. The Netherlands Cohort Study was analyzed as a case–cohort study, as required by their study design (36).

We conducted analyses using the Statistical Analysis System (SAS) version 9.3. Intakes of food groups were categorized by study-specific quantiles based on the distribution in the subcohort for the Netherlands Cohort Study and the full cohort for all other studies. Additional analyses were conducted in which intakes were categorized using common absolute cut-off points. If there were no cases in the highest intake category in a study, the relative risk (RR) of that category could not be calculated, and the person-time and noncases in the highest category were included in the second highest category.

A two-stage method was used to estimate pooled RRs. In the first stage, study-specific RRs and 95% confidence intervals (CI) between each food group or food and risk of each prostate cancer outcome were estimated using the Cox proportional hazards model (37). We stratified the baseline hazard by age at baseline (years), year of questionnaire return, and center (only for EPIC). This is equivalent to a left-truncated survival analysis with age as the time scale, and allowed the baseline incidence rates to vary jointly by age at enrollment and calendar year. We also conducted analyses in which we adjusted for energy intake known and suspected confounders (see footnote a, Table 2). If a study had more than 200 cases of the prostate cancer endpoint of interest, all covariates were included in the model. If a study had fewer than 200 such cases, we adjusted for confounding using the propensity score method (38–40). For each study for each confounding variable that was measured, we included missing indicator variables for missing data, if needed. We tested for linear trends in the associations by assigning the median value of each exposure category, modeling that variable as a continuous variable, and testing the coefficient using the Wald test. Individual studies were excluded from analyses of a specific prostate cancer subtype if they did not contribute at least 50 cases of that subtype.

In the second stage, we combined the study-specific $\log_e$ RRs, weighted by the inverse of their variance and the estimated between-studies variance component (41). We tested for heterogeneity between studies using the Q statistic (41, 42). We calculated two-sided 95% CIs for all statistical tests.

We assessed whether associations for all food groups and risk of total, advanced, advanced restricted, and high-grade prostate cancer, as well as prostate cancer mortality, were consistent with linearity by examining nonparametric regression curves using restricted cubic splines (43, 44). These analyses combined all studies into a single dataset, stratified by age, the year that the questionnaire was returned, and study, and adjusted for the same confounding variables as in the categorical analyses. We excluded participants in the top 1% of intake in each study to reduce the influence of extreme values. The model with linear and cubic spline terms, selected by a stepwise regression procedure, was compared to the model fit with only the linear term using the likelihood ratio test. If associations were consistent with linearity, we then conducted analyses in which intakes were modeled continuously.

We tested for the presence of effect modification by age at diagnosis (<65 vs. ≥65 years), BMI (<25 vs. ≥25 kg/m^2), follow-up time (<5 vs. ≥5 years) and geographic region of study (United States vs. other) using a mixed effects meta-regression model (45). Geographic region was included because we could not directly test for effect modification by PSA screening, but we hypothesized that PSA screening was more prevalent and began earlier in the United States compared with other regions of the world (46). This was of concern due to enhanced detection of indolent prostate cancer in countries where PSA screening was commonplace. We tested for differences between prostate cancer outcomes for all food groups using a contrast test (47).

Results

In the pooled cohort of 842,149 participants, followed for a maximum of 9 to 22 years across studies, 52,680 cases of incident prostate cancer were identified (Table 1). There were 38,475 cases of localized prostate cancer, 4,934 advanced cases, 3,115 advanced restricted cases, and 3,205 prostate cancer deaths. By grade, there were 37,556 low-grade and 9,753 high-grade cases (Supplementary Table S1). Median total fruit and vegetable intake (Table 1), as well as the number of fruit and vegetable questions on the FFQs, varied 6- to 7-fold across studies.

Because the age- and multivariable-adjusted results were similar, we only report associations for multivariable models. When intakes were modeled using study-specific quantiles, we observed no statistically significant associations for intakes of total fruits and vegetables, total fruits, and total vegetables, and risk of any prostate cancer endpoint; pooled multivariable RRs comparing the highest versus lowest quantile ranged from 0.89 to 1.09 (Table 2). In general, there was no between-studies heterogeneity for any association. For fruit and vegetable juice, a statistically significant association was only observed for localized prostate cancer; however, risk increased by only 4% comparing the highest versus lowest tertile (pooled multivariable RR = 1.04, 95% CI, 1.01–1.06).

When food group intakes were modeled as categorical variables defined using common absolute cut-off points across studies (Table 3), no statistically significant associations were observed for total fruit and vegetable, total fruit, total fruit and vegetable juice, or total vegetable consumption with risk of total, localized, advanced, advanced restricted, low-grade prostate cancer, and high-grade prostate cancer, as well as prostate cancer mortality; pooled multivariable RRs comparing the highest versus lowest intake categories for each food group ranged from 0.89–1.16. In general, there was no between-studies heterogeneity for any association.

Table 1. Characteristics of the cohort studies included in the pooled analyses of fruit, vegetable, and mature bean consumption and prostate cancer risk

Study	Follow-up	Baseline cohort size	Age range, years	Number of prostate cancer cases	Total fruit (g/day) Median (10th–90th percentile)	Total vegetables (g/day) Median (10th–90th percentile)
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)	1985–2002	26,987	50–69	1,316	122 (28–299)	82 (31–178)
Beta-Carotene and Retinol Efficacy Trial (CARET)	1985–2005	10,474	50–69	736	197 (44–523)	190 (88–373)
CLUE II: Campaign Against Cancer and Heart Disease (CLUE-II)	1989–2009	5,926	18–90	461	153 (25–409)	148 (56–313)
Cancer Prevention Study-II Nutrition Cohort (CPS-II)	1992–2005	65,923	50–74	6,943	182 (44–394)	201 (92–385)
Cohort of Swedish Men (COSM)	1998–2008	45,338	45–79	3,011	171 (52–409)	134 (52–272)
European Prospective Investigation into Cancer and Nutrition (EPIC)	1991–2006	142,195	20–97	2,727	222 (56–535)	148 (54–382)
Health Professionals Follow-up Study (HPFS)	1986–2008	47,781	40–75	5,536	300 (97–621)	228 (112–424)
The Japan Public Health Center-Based Study Cohort I (JPHC-I)	1990–2004	20,161	40–59	135	70 (27–168)	119 (53–216)
The Japan Public Health Center-Based Study Cohort II (JPHC-II)	1993–2004	24,116	40–69	167	40 (10–132)	24 (8–57)
Melbourne Collaborative Cohort Study (MCCS)	1990–2006	14,824	27–75	910	363 (104–841)	200 (85–381)
Multiethnic Cohort Study (MEC)	1993–2004	84,297	45–75	5,583	258 (58–711)	205 (81–464)
The Netherlands Cohort Study (NLCS)	1986–2007	58,279	55–69	2,416	153 (43–333)	154 (82–268)
The NIH-AARP Diet and Health Study (NIH-AARP)	1995–2006	250,065	50–71	18,889	293 (74–731)	178 (70–395)
Prostate Cancer Prevention Trial (PCPT)	1994–2003	15,620	55–86	853	224 (55–541)	320 (131–674)
The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)	1993–2008	30,163	55–74	2,997	281 (80–630)	259 (121–506)
Total		842,149		52,680		

We did not find any statistically significant associations between intakes of cruciferous vegetables or all tomato products combined and any prostate cancer endpoint (Tables 2 and 3). However, except for pizza, (which generally includes tomato paste or sauce and was assessed in 11 cohorts), the vast majority of studies did not assess sources of bioavailable lycopene (i.e., cooked tomatoes, tomato sauce, pasta with tomato sauce, pizza, and lasagna), which likely resulted in our tomato product variable not being a good measure of intake of bioavailable lycopene. Of note, pizza intake was associated with a statistically significantly reduced risk of prostate cancer mortality (2,262 cases among eight cohorts; pooled multivariable RR = 0.46, 95% CI, 0.23–0.89 for a 120 g/day increase in consumption, which is roughly equivalent to one slice of pizza).

We also investigated associations between mature bean intake and prostate cancer endpoints. We excluded soybeans from the mature bean group because of an isoflavone hypothesis in cancer, but noted that soy intake was negligible in most studies, except for the Japan Public Health Center-Based Study Cohorts I (JPHC-I) and II (JPHC-II), and the Multiethnic Cohort Study (MEC). However, JPHC-I and JPHC-II were not included in analyses of advanced prostate cancer, advanced restricted prostate cancer, or prostate cancer mortality because they had few cases of these outcomes. We found statistically significant inverse associations between mature bean intake and risk of total, localized, low-grade, and high-grade prostate cancer, while nonsignificant positive associations were observed for advanced and advanced restricted prostate cancer, as well as prostate cancer mortality.

For all food groups evaluated, we compared the results between localized and advanced prostate cancer, localized and advanced restricted prostate cancer, low-grade and high-grade prostate cancer, and localized prostate cancer and prostate cancer mortality when fruit and vegetable intake was modeled as categories based on common absolute cut-off points. We observed only one statistically significant difference (between advanced and localized prostate cancer for mature bean consumption, $P = 0.03$; other results not shown).

Nonparametric regression analyses indicated that all associations between intake of each food group and risk of total, advanced, advanced restricted, and high-grade prostate cancer, and prostate cancer mortality were linear ($P_{\text{nonlinearity}} > 0.05$), with the exception of tomato product consumption and risk of total prostate cancer. We therefore conducted analyses in which food groups were modeled as continuous variables (except for tomato product consumption and risk of total, localized, or low-grade prostate cancer, due to the nonlinear association observed for total prostate cancer). Among all the food groups and prostate cancer endpoints evaluated, statistically significant associations were only present for mature bean intake and risk of total, localized, low-grade, and high-grade prostate cancer (Supplementary Table S2).

In examination of specific fruits and vegetables, we observed few statistically significant associations (Table 4). While we observed a statistically significant positive association for corn intake and risk of advanced prostate cancer (pooled multivariable RR = 1.53, 95% CI, 1.12–2.07) and prostate cancer mortality (pooled multivariable RR = 1.49, 95% CI, 1.01–2.20), other significant associations for individual food items and prostate cancer outcomes were small in magnitude or did not follow a discernible pattern.

There was no evidence of effect modification by follow-up time, age at diagnosis, or geographic region for the associations between all food groups and each prostate cancer endpoint ($P_{interaction} > 0.10$, results not shown), and only one statistically significant association for effect modification by BMI. Because many analyses were conducted, the latter result was likely due to chance.

Discussion

In this pooled analysis of 15 prospective cohort studies, we did not find any statistically significant associations between intakes

Table 2. Pooled multivariable RRs[a] and 95% CI for study-specific quantiles of fruit and vegetable consumption and prostate cancer risk

	Quantiles						
	Q1	Q2	Q3	Q4	Q5	P_{trend}	*P* for between-studies heterogeneity[b]
Total fruits and vegetables							
Total	1.00	1.04 (1.01–1.07)	1.02 (0.99–1.05)	1.00 (0.97–1.04)	1.01 (0.98–1.04)	0.59	0.51
By stage							
Localized	1.00	1.04 (1.00–1.07)	1.03 (0.98–1.08)	1.00 (0.97–1.03)	1.01 (0.97–1.05)	0.57	0.28
Advanced[c]	1.00	1.00 (0.91–1.10)	0.98 (0.89–1.08)	1.02 (0.92–1.12)	0.96 (0.87–1.07)	0.78	0.63
Advanced restricted[d]	1.00	1.02 (0.91–1.16)	1.05 (0.93–1.19)	1.09 (0.96–1.23)	0.99 (0.85–1.15)	0.60	0.26
Prostate cancer mortality[e]	1.00	0.95 (0.84–1.07)	0.92 (0.81–1.03)	0.98 (0.87–1.11)	0.92 (0.81–1.04)	0.37	0.70
By grade							
Low	1.00	1.04 (0.99–1.08)	1.03 (0.98–1.08)	0.99 (0.96–1.03)	0.99 (0.95–1.03)	0.15	0.39
High[f]	1.00	1.02 (0.96–1.09)	1.03 (0.96–1.10)	1.04 (0.97–1.13)	1.02 (0.94–1.11)	0.81	0.38
Total fruits							
Total	1.00	1.01 (0.98–1.04)	1.01 (0.98–1.03)	1.03 (0.99–1.07)	1.01 (0.98–1.04)	0.83	0.69
By stage							
Localized	1.00	1.01 (0.97–1.06)	1.01 (0.96–1.06)	1.03 (0.98–1.09)	1.01 (0.97–1.06)	0.56	0.26
Advanced[c]	1.00	1.00 (0.91–1.10)	0.94 (0.85–1.03)	1.02 (0.93–1.12)	0.99 (0.90–1.10)	0.94	0.70
Advanced restricted[d]	1.00	0.99 (0.88–1.12)	0.94 (0.83–1.06)	1.05 (0.93–1.18)	0.99 (0.87–1.12)	0.64	0.73
Prostate cancer mortality[e]	1.00	0.97 (0.86–1.09)	0.92 (0.82–1.04)	1.02 (0.87–1.19)	0.98 (0.86–1.11)	0.86	0.77
By grade							
Low	1.00	1.01 (0.98–1.05)	1.01 (0.97–1.04)	1.01 (0.98–1.05)	0.99 (0.96–1.03)	0.50	0.74
High[f]	1.00	1.00 (0.94–1.07)	1.00 (0.93–1.07)	1.06 (0.95–1.17)	1.01 (0.94–1.09)	0.79	0.43
Fruit and vegetable juice							
Total	1.00	1.02 (1.00–1.04)	1.03 (1.00–1.06)			0.10	0.30
By stage							
Localized	1.00	1.02 (0.98–1.06)	1.04 (1.01–1.06)			0.10	0.83
Advanced[c]	1.00	1.02 (0.95–1.10)	1.05 (0.98–1.13)			0.43	0.55
Advanced restricted[d]	1.00	1.02 (0.93–1.13)	1.08 (0.98–1.19)			0.20	0.97
Prostate cancer mortality[e]	1.00	1.00 (0.91–1.10)	1.04 (0.94–1.13)			0.89	0.45
By grade							
Low	1.00	1.01 (0.98–1.05)	1.02 (0.99–1.04)			0.29	0.49
High[f]	1.00	1.04 (0.97–1.13)	1.05 (0.98–1.13)			0.36	0.19
Total vegetables							
Total	1.00	1.02 (0.99–1.05)	1.01 (0.98–1.04)	1.01 (0.97–1.05)	0.99 (0.96–1.02)	0.38	0.55
By stage							
Localized	1.00	1.03 (1.00–1.07)	1.01 (0.98–1.05)	1.01 (0.97–1.05)	0.99 (0.95–1.04)	0.35	0.29
Advanced[c]	1.00	1.01 (0.91–1.12)	0.95 (0.86–1.05)	0.98 (0.86–1.12)	0.95 (0.86–1.05)	0.51	0.47
Advanced restricted[d]	1.00	1.01 (0.90–1.13)	0.98 (0.87–1.11)	1.06 (0.92–1.23)	0.95 (0.84–1.08)	0.96	0.64
Prostate cancer mortality[e]	1.00	0.98 (0.84–1.13)	0.92 (0.82–1.03)	0.92 (0.80–1.06)	0.95 (0.84–1.08)	0.52	0.70
By grade							
Low	1.00	1.03 (1.00–1.07)	1.01 (0.98–1.04)	1.01 (0.97–1.05)	0.98 (0.94–1.03)	0.14	0.31
High[f]	1.00	1.04 (0.97–1.12)	1.07 (1.01–1.15)	1.03 (0.97–1.11)	1.04 (0.97–1.11)	0.42	0.67
Cruciferous vegetables							
Total[g]	1.00	1.05 (1.01–1.09)	1.03 (0.98–1.07)	1.02 (0.98–1.06)	1.02 (0.99–1.05)	0.87	0.41
By stage							
Localized[g]	1.00	1.05 (1.00–1.09)	1.03 (0.98–1.07)	1.03 (0.99–1.06)	1.02 (0.99–1.06)	0.84	0.55
Advanced[c]	1.00	1.03 (0.93–1.13)	1.01 (0.92–1.12)	0.98 (0.89–1.08)	0.94 (0.86–1.04)	0.20	0.88
Advanced restricted[d]	1.00	1.09 (0.97–1.23)	1.06 (0.94–1.20)	1.04 (0.92–1.18)	1.01 (0.89–1.15)	0.79	0.94
Prostate cancer mortality[e]	1.00	0.94 (0.83–1.05)	0.90 (0.80–1.01)	0.90 (0.80–1.01)	0.90 (0.79–1.04)	0.28	0.27
By grade							
Low[g]	1.00	1.05 (1.00–1.10)	1.04 (0.99–1.08)	1.02 (0.98–1.06)	1.01 (0.98–1.05)	0.57	0.75
High[f]	1.00	1.11 (1.01–1.23)	1.07 (1.00–1.14)	1.09 (0.99–1.19)	1.09 (0.99–1.19)	0.16	0.19
Tomato products[h]							
Total[i]	1.00	0.99 (0.96–1.02)	0.99 (0.95–1.03)	1.00 (0.96–1.04)	0.96 (0.91–1.02)	0.22	0.007
By stage							
Localized[i]	1.00	0.99 (0.96–1.02)	1.00 (0.97–1.03)	0.99 (0.95–1.04)	0.96 (0.92–1.01)	0.01	0.19
Advanced[c]	1.00	0.94 (0.85–1.04)	0.99 (0.88–1.12)	1.01 (0.92–1.11)	0.93 (0.82–1.06)	0.49	0.14
Advanced restricted[d]	1.00	0.95 (0.83–1.09)	0.99 (0.84–1.18)	1.01 (0.90–1.14)	0.93 (0.78–1.11)	0.51	0.08
Prostate cancer mortality[e]	1.00	0.89 (0.78–1.01)	0.93 (0.79–1.09)	0.97 (0.86–1.08)	0.89 (0.75–1.06)	0.38	0.06

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Table 2. Pooled multivariable RRs[a] and 95% CI for study-specific quantiles of fruit and vegetable consumption and prostate cancer risk (Cont'd)

	Quantiles						
	Q1	Q2	Q3	Q4	Q5	P_{trend}	*P* for between-studies heterogeneity[b]
By grade							
Low[i]	1.00	0.98 (0.95–1.02)	0.98 (0.93–1.04)	0.99 (0.94–1.04)	0.95 (0.89–1.02)	0.12	0.007
High[f]	1.00	1.00 (0.90–1.11)	1.00 (0.91–1.11)	1.02 (0.91–1.15)	0.98 (0.88–1.09)	0.83	0.10

Abbreviations: NIH-AARP, NIH-AARP Diet and Health Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CARET, Beta-Carotene and Retinol Efficacy Trial; CI, confidence interval; CLUE-II, CLUE II: Campaign Against Cancer and Heart Disease; CPS-II, Cancer Prevention Study-II Nutrition Cohort; COSM, Cohort of Swedish Men; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; JPHC-I, Japan Public Health Center-Based Study Cohort I; JPHC-II, Japan Public Health Center-Based Study Cohort II; MCCS, Melbourne Collaborative Cohort Study; MEC, Multiethnic Cohort Study; NLCS, Netherlands Cohort Study; PCPT, Prostate Cancer Prevention Trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR, relative risk. "Advanced": defined as T4, N1, or M1 tumors or prostate cancer mortality; "Advanced restricted": same as advanced prostate cancer but excluding those who died of prostate cancer during follow-up who had been diagnosed with localized cancer or had missing stage data; "High grade": Gleason score ≥8 or poorly differentiated/undifferentiated; "Localized": defined as T1/T2 and N0M0 tumors, that is, cancers confined within the prostate; "Low grade": Gleason score <8 or well/moderately differentiated.

[a]All models adjusted for marital status [married (ref), never married, widowed, divorced], race [Caucasian (ref), African-American, Asian, Hispanic, other], education [<high school (ref), high school, >high school], body mass index [BMI, kg/m^2; <23 (ref), 23–<25, 25–<30, ≥30], height [meters; <1.70 (ref), 1.70–<1.75, 1.75–<1.80, 1.80–<1.85, ≥1.85; in JPHC-I and JPHC-II: <1.60 (ref), 1.60–<1.65, 1.65–<1.70, 1.70–<1.75, ≥1.75), alcohol [g/day; 0 (ref), >0–<5, 5–<15, 15–<30, ≥30], multivitamin use [no (ref), yes], total energy intake (kcal/d, as continuous variable), smoking status [never (ref), past smoker <15 packyears, past smoker ≥15 packyears, current smoker <40 packyears, current smoker ≥40 packyears], prostate cancer family history [no (ref), yes], physical activity [low (ref), medium, high], history of diabetes [no (ref), yes]. Age in years and year of questionnaire return were included as stratification variables. We additionally stratified the baseline hazard by center for EPIC.

[b]*P* value for between-studies heterogeneity for highest category.

[c]JPHC-I, JPHC-II, and PCPT were excluded from this analysis because these cohorts each had fewer than 50 cases of advanced prostate cancer.

[d]CARET, CLUE-II, JPHC-I, JPHC-II, MCCS, and PCPT were excluded from this analysis because these cohorts each had fewer than 50 cases of advanced restricted prostate cancer.

[e]CARET, CLUE-II, JPHC-I, JPHC-II, and PCPT were excluded from this analysis because these cohorts each had fewer than 50 cases of prostate cancer mortality.

[f]JPHC-I and JPHC-II were excluded from this analysis because these cohorts each had fewer than 50 cases of high-grade prostate cancer.

[g]JPHC-I and JPHC-II were excluded from this analysis because the variable for cruciferous vegetables was too discrete. There were too few values for the number of categories.

[h]The tomato product food group included tomatoes (raw, cooked, and unknown), tomato sauce (with meat, without meat, and unknown), tomato juice, pizza, and lasagna. A fraction was applied to estimate tomato consumption for foods that consisted of tomatoes with other ingredients.

[i]JPHC-I was excluded from analyses of tomato product intake because this study did not assess tomato consumption. JPHC-II was excluded from this analysis because of a limited intake distribution of tomato products in this study.

of total fruits and vegetables, total fruits, total vegetables, cruciferous vegetables, and most specific fruits and vegetables and risk of prostate cancer overall, for subtypes defined by stage or grade, or for prostate cancer mortality regardless of whether intakes were modeled as quantiles, categories based on common absolute cut-off points, or continuously. While some case–control studies have suggested an inverse association between vegetable intake and prostate cancer risk (48–52) and a positive association between fruit intake and total prostate cancer risk (53, 54), other case–control studies (55, 56) and cohort studies (57–59) that did not participate in these analyses have shown null results. Our results similarly suggest no clear benefit (or harm) of total fruit and/or vegetable intake on risk of prostate cancer (total or subtypes). While we observed some statistically significant associations for fruit and vegetable juice intake and risk of total and localized prostate cancer, and for a few specific fruits and vegetables, most associations were weak and likely statistically significant due to the very large sample size. Moreover, the large number of tests we conducted, and our lack of *a priori* hypotheses about most associations with prostate cancer, suggests they may be due to chance.

The inverse associations we observed between mature bean intake and risk of total, localized, low-grade, and high-grade prostate cancer are consistent with findings from other epidemiologic investigations (51, 53, 60, 61), although these findings have not been consistent across all studies (49, 52, 62). Although these inverse associations have been attributed to the high dietary fiber content of mature beans (63), the association between dietary fiber intake and prostate cancer has been inconsistent (63–67). In addition, many fruits and vegetables have high fiber content, and yet we did not observe any inverse associations for fruit and vegetable intake. The associations for mature bean consumption and risk of indolent prostate cancer may therefore be due to chance or to residual confounding. This is supported by an observed nonsignificant increased risk of advanced prostate cancer and prostate cancer mortality with increasing mature bean intake.

Despite, an *a priori* hypothesis for a protective role of tomatoes on prostate cancer risk, we did not find inverse associations between tomato product intake and risk of any prostate cancer outcome. This could be due to the lack of assessment in most cohorts of sources of bioavailable lycopene, the potential cancer-preventive agent in tomatoes. However, we observed a statistically significant inverse association for prostate cancer mortality and pizza intake, which was the only source of bioavailable lycopene that was assessed in the majority of studies included. We also may not have observed an association due to the fact that we only used data on overall tomato product intake, which does not account for the absorption, distribution, or metabolism of lycopene. In fact, correlation coefficients between dietary intake of lycopene and circulating lycopene are generally less than 0.30 (68–70). Inverse associations between circulating lycopene levels, which better reflect bioavailable lycopene, and prostate cancer risk have been observed in previous studies (71, 72), and for risk of advanced prostate cancer in a recent large pooled analysis (73).

Participants with a healthier lifestyle (i.e., those with higher fruit and vegetable consumption) may have better access to healthcare, be more likely to undergo PSA screening, and be more likely to be diagnosed with indolent prostate cancer (74, 75). Most studies in the United States in this pooled analysis (8 studies)

Table 3. Pooled multivariable RRs[a] and 95% CI for categories of fruit, vegetable, and mature bean consumption and prostate cancer risk

	Pooled multivariable RR (95% CI)					P_{trend}	*P* for between-studies heterogeneity[b]
Total fruits and vegetables							
Intake category, g/day	**<200**	**200–<400**	**400–<600**	**600–<800**	**≥800**		
Total[c]	1.00	1.07 (1.02–1.11)	1.04 (0.99–1.08)	1.01 (0.97–1.05)	1.05 (0.99–1.11)	0.72	0.21
By stage							
Localized[d]	1.00	1.08 (1.03–1.14)	1.06 (1.00–1.12)	1.03 (0.99–1.08)	1.07 (0.99–1.15)	0.99	0.11
Advanced[e]	1.00	0.97 (0.88–1.07)	0.96 (0.86–1.07)	0.94 (0.82–1.08)	0.98 (0.84–1.14)	0.78	0.65
Advanced restricted[f]	1.00	0.99 (0.88–1.12)	1.03 (0.86–1.23)	1.02 (0.85–1.21)	1.02 (0.80–1.30)	0.63	0.24
Prostate cancer mortality[g]	1.00	1.00 (0.89 -1.13)	0.89 (0.78–1.02)	0.92 (0.78–1.09)	0.89 (0.74–1.07)	0.39	0.86
By grade							
Low[c]	1.00	1.07 (1.02–1.12)	1.04 (1.00–1.08)	1.01 (0.96–1.06)	1.02 (0.97–1.08)	0.22	0.80
High[h]	1.00	1.08 (0.97–1.20)	1.11 (0.99–1.25)	1.04 (0.91–1.18)	1.16 (0.95–1.42)	0.33	0.01
Total fruits							
Intake category, g/day	**<100**	**100–<200**	**200–<300**	**300–<400**	**≥400**		
Total[c]	1.00	1.01 (0.98–1.04)	1.02 (0.99–1.05)	0.99 (0.96–1.02)	1.00 (0.97–1.03)	0.76	0.81
By stage							
Localized[c]	1.00	1.01 (0.97–1.06)	1.04 (1.00–1.07)	1.00 (0.96–1.03)	1.01 (0.97–1.05)	0.76	0.38
Advanced[e]	1.00	0.90 (0.82–0.98)	0.95 (0.86–1.04)	0.94 (0.85–1.05)	0.93 (0.84–1.03)	0.82	0.57
Advanced restricted[f]	1.00	0.89 (0.79–0.99)	0.97 (0.86–1.09)	1.04 (0.91–1.20)	0.99 (0.86–1.14)	0.54	0.80
Prostate cancer mortality[g]	1.00	0.89 (0.80–0.99)	0.99 (0.87–1.12)	0.92 (0.80–1.06)	0.90 (0.76–1.06)	0.66	0.22
By grade							
Low[c]	1.00	1.02 (0.99–1.06)	1.03 (0.99–1.06)	1.00 (0.96–1.04)	0.99 (0.96–1.03)	0.27	0.92
High[h]	1.00	0.96 (0.90–1.03)	1.04 (0.97–1.11)	0.99 (0.92–1.07)	1.01 (0.94–1.09)	0.60	0.81
Fruit and vegetable juice							
Intake category, g/day	**<25**	**25–<75**	**75–<150**	**150–<250**	**≥250**		
Total	1.00	1.03 (1.00–1.06)	1.04 (1.00–1.08)	1.02 (0.99–1.05)	1.03 (0.99–1.07)	0.26	0.31
By stage							
Localized	1.00	1.04 (0.99–1.09)	1.04 (0.99–1.09)	1.03 (1.00–1.06)	1.03 (0.99–1.06)	0.08	0.58
Advanced[e]	1.00	1.03 (0.93–1.15)	1.04 (0.95–1.15)	1.03 (0.93–1.15)	1.09 (0.95–1.25)	0.31	0.36
Advanced restricted[f]	1.00	1.08 (0.95–1.22)	1.04 (0.92–1.18)	1.10 (0.96–1.26)	1.14 (0.97–1.33)	0.06	0.75
Prostate cancer mortality[g]	1.00	1.05 (0.94–1.19)	1.02 (0.90–1.14)	1.01 (0.89–1.15)	1.01 (0.86–1.19)	0.75	0.39
By grade							
Low	1.00	1.02 (0.97–1.06)	1.03 (0.99–1.08)	1.01 (0.98–1.05)	1.01 (0.96–1.05)	0.75	0.35
High[h]	1.00	1.14 (1.01–1.27)	1.08 (1.01–1.16)	1.04 (0.97–1.11)	1.08 (0.96–1.22)	0.88	0.17
Total vegetables							
Intake category, g/day	**<100**	**100–<200**	**200–<300**	**300–<400**	**≥400**		
Total[i]	1.00	1.02 (1.00–1.05)	1.01 (0.98–1.05)	1.01 (0.97–1.05)	0.99 (0.95–1.04)	0.28	0.67
By stage							
Localized[j]	1.00	1.03 (1.00–1.06)	1.02 (0.98–1.06)	1.02 (0.98–1.07)	0.98 (0.94–1.03)	0.35	0.56
Advanced[e]	1.00	0.98 (0.90–1.07)	0.95 (0.86–1.06)	0.96 (0.84–1.10)	0.98 (0.84–1.14)	0.47	0.82
Advanced restricted[k]	1.00	1.03 (0.93–1.15)	0.96 (0.82–1.14)	1.00 (0.84–1.19)	0.98 (0.81–1.20)	0.58	0.47
Prostate cancer mortality[g]	1.00	0.94 (0.85–1.04)	0.90 (0.79–1.02)	0.92 (0.77–1.08)	0.94 (0.78–1.13)	0.57	0.89
By grade							
Low[l]	1.00	1.02 (0.99–1.06)	1.02 (0.98–1.05)	1.01 (0.97–1.06)	0.98 (0.92–1.04)	0.13	0.33
High[h]	1.00	1.08 (1.00–1.18)	1.07 (0.97–1.18)	1.05 (0.97–1.15)	1.08 (0.94–1.24)	0.73	0.21
Cruciferous vegetables							
Intake category, g/day	**<10**	**10–<30**	**30–<50**	**50–<70**	**≥70**		
Total[m]	1.00	1.03 (1.00–1.06)	1.01 (0.97–1.05)	1.00 (0.96–1.04)	1.02 (0.96–1.09)	0.94	0.08
By stage							
Localized[m]	1.00	1.03 (0.99–1.07)	1.00 (0.95–1.06)	1.00 (0.95–1.05)	1.02 (0.96–1.09)	0.80	0.17
Advanced[e]	1.00	1.05 (0.95–1.17)	1.05 (0.89–1.24)	0.91 (0.77–1.09)	0.98 (0.83–1.17)	0.47	0.97
Advanced restricted[f]	1.00	1.05 (0.95 -1.17)	1.05 (0.89–1.25)	0.90 (0.75–1.08)	0.98 (0.82–1.16)	0.45	0.94
Prostate cancer mortality[g]	1.00	0.92 (0.83–1.02)	0.94 (0.82–1.08)	0.84 (0.71–1.00)	0.89 (0.75–1.05)	0.28	0.48
By grade							
Low[m]	1.00	1.02 (0.98–1.06)	1.00 (0.95–1.06)	1.00 (0.95–1.04)	1.02 (0.97–1.06)	0.58	0.50
High[h]	1.00	1.09 (1.01–1.19)	1.05 (0.97–1.14)	1.11 (0.97–1.27)	1.13 (0.95–1.36)	0.25	0.01
Tomato products[n]							
Intake category, g/day	**<10**	**10–<25**	**25–<50**	**50–<100**	**≥100**		
Total[o]	1.00	1.00 (0.97–1.03)	0.99 (0.94–1.04)	1.00 (0.96–1.04)	0.95 (0.89–1.02)	0.09	0.17
By stage							
Localized[o]	1.00	1.00 (0.96–1.04)	1.00 (0.96–1.04)	1.00 (0.96–1.04)	0.95 (0.90–1.01)	0.02	0.47
Advanced[e]	1.00	1.00 (0.90–1.12)	1.05 (0.93–1.19)	1.05 (0.88–1.25)	0.99 (0.83–1.18)	0.73	0.67
Advanced restricted[p]	1.00	0.96 (0.85–1.09)	1.05 (0.88–1.25)	0.99 (0.79–1.23)	0.89 (0.70–1.13)	0.43	0.34
Prostate cancer mortality[q]	1.00	0.98 (0.85–1.15)	1.02 (0.89–1.17)	1.05 (0.85–1.29)	0.99 (0.80–1.23)	0.84	0.65
By grade							
Low[o]	1.00	0.99 (0.95–1.03)	0.99 (0.94–1.04)	1.01 (0.95–1.07)	0.93 (0.87–1.00)	0.02	0.38
High[r]	1.00	1.09 (1.01–1.18)	1.01 (0.90–1.14)	1.06 (0.97–1.15)	1.04 (0.93–1.17)	0.61	0.79

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Table 3. Pooled multivariable RRs[a] and 95% CI for categories of fruit, vegetable, and mature bean consumption and prostate cancer risk (Cont'd)

	Pooled multivariable RR (95% CI)				P_{trend}	*P* for between-studies heterogeneity[b]
Mature beans[s]						
Intake category, g/day	**<15**	**15–<50**	**50–<100**	**≥100**		
Total[t]	1.00	0.99 (0.97–1.01)	0.95 (0.92–0.98)	0.86 (0.78–0.95)	0.003	0.06
By stage						
Localized[u]	1.00	0.97 (0.95–1.00)	0.93 (0.90–0.97)	0.88 (0.82–0.95)	<0.001	0.37
Advanced[u]	1.00	1.08 (1.00–1.16)	1.01 (0.89–1.14)	1.10 (0.91–1.34)	0.72	0.72
Advanced restricted[v]	1.00	1.07 (0.95–1.20)	1.02 (0.87–1.20)	1.06 (0.82–1.36)	0.77	0.94
Prostate cancer mortality[w]	1.00	1.07 (0.97–1.17)	1.02 (0.88–1.19)	1.12 (0.89–1.42)	0.49	0.77
By grade						
Low[t]	1.00	0.98 (0.95–1.01)	0.94 (0.91–0.98)	0.89 (0.82–0.97)	0.003	0.28
High[x]	1.00	1.00 (0.93–1.08)	0.99 (0.92–1.07)	0.86 (0.76–0.97)	0.02	0.41

Abbreviations: NIH-AARP, NIH-AARP Diet and Health Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CARET, Beta-Carotene and Retinol Efficacy Trial; CI, confidence interval; CLUE-II, CLUE II: Campaign Against Cancer and Heart Disease; CPS-II, Cancer Prevention Study-II Nutrition Cohort; COSM, Cohort of Swedish Men; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; JPHC-I, Japan Public Health Center-Based Study Cohort I; JPHC-II, Japan Public Health Center-Based Study Cohort II; MCCS, Melbourne Collaborative Cohort Study; MEC, Multiethnic Cohort Study; NLCS, Netherlands Cohort Study; PCPT, Prostate Cancer Prevention Trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; "Advanced": defined as T4, N1, or M1 tumors or prostate cancer mortality; "Advanced restricted": same as advanced prostate cancer, but excluding those who died of prostate cancer during follow-up who had been diagnosed with localized cancer or had missing stage data; "High grade": Gleason score ≥8 or poorly differentiated/undifferentiated; "Localized": defined as T1/T2 and N0M0 tumors, i.e., cancers confined within the prostate; "Low grade": Gleason score <8 or well/moderately differentiated.

[a]All models adjusted for marital status [married (ref), never married, widowed, divorced], race [Caucasian (ref), African-American, Asian, Hispanic, other], education [<high school (ref), high school, >high school], body mass index [BMI, kg/m^2; <23 (ref), 23–<25, 25–<30, ≥30], height [meters; <1.70 (ref), 1.70–<1.75, 1.75–<1.80, 1.80–<1.85, ≥1.85; in JPHC-I and JPHC-II: <1.60 (ref), 1.60–<1.65, 1.65–<1.70, 1.70–<1.75, ≥ 1.75), alcohol [g/day; 0 (ref), >0–<5, 5–<15, 15–<30, ≥30], multivitamin use [no (ref), yes], total energy intake (kcal/d, as continuous variable), smoking status [never (ref), past smoker <15 packyears, past smoker ≥15 packyears, current smoker <40 packyears, current smoker ≥40 packyears], prostate cancer family history [no (ref), yes], physical activity [low (ref), medium, high], history of diabetes [no (ref), yes]. Age in years and year of questionnaire return were included as stratification variables. We additionally stratified the baseline hazard by center for EPIC.

[b]*P* value for between-studies heterogeneity for highest category.

[c]JPHC-II was excluded from the top two levels of intake because there were no cases in these levels. The participants in this study who were in these categories and were not cases were included in the next highest category.

[d]JPHC-I was excluded from the highest level of intake and JPHC-II was excluded from the two highest levels of intake because there were no cases in these levels. The participants in these studies who were in these categories and were not cases were included in the next highest category.

[e]JPHC-I, JPHC-II, and PCPT were excluded from this analysis because each had fewer than 50 cases of advanced prostate cancer.

[f]CARET, CLUE-II, JPHC-I, JPHC-II, MCCS, and PCPT were excluded from this analysis because each study had fewer than 50 cases of advanced restricted prostate cancer.

[g]CARET, CLUE-II, JPHC-I, JPHC-II, and PCPT were excluded from this analysis because each study had fewer than 50 cases of prostate cancer mortality.

[h]JPHC-I and JPHC-II were excluded from this analysis because each had fewer than 50 cases of high-grade prostate cancer.

[i]JPHC-I was excluded from the highest two levels of intake and JPHC-II was excluded from the highest three levels of intake because there were no cases in these levels. The participants in these studies who were in these categories and were not cases were included in the next highest category.

[j]JPHC-I was excluded from the highest two levels of intake, JPHC-II was excluded from the highest three levels of intake, and ATBC was excluded from the highest level of intake because there were no cases in these levels. The participants in these studies who were in these categories and were not cases were included in the next highest category.

[k]JPHC-I, JPHC-II, PCPT, CARET, CLUE-II, and MCCS were excluded from this analysis because each study had fewer than 50 cases of this subtype; ATBC was excluded from the highest two levels of intake because there were no cases in these levels. The participants in ATBC who were in these categories and were not cases were included in the next highest category.

[l]JPHC-II was excluded from this analysis because all cases were in the reference group; JPHC-I was excluded from the highest two levels of intake and ATBC was excluded from the highest level of intake because there were no cases in these levels. The participants in JPHC-I and ATBC who were in these categories and were not cases were included in the next highest category.

[m]JPHC-I and JPHC-II were excluded from the highest two levels of intake because there were no cases in these levels. The participants in these studies who were in these categories and were not cases were included in the next highest category.

[n]The tomato product food group included tomatoes (raw, cooked, and unknown), tomato sauce (with meat, without meat, and unknown), tomato juice, pizza, and lasagna. A fraction was applied to estimate tomato consumption for foods that consisted of tomatoes with other ingredients. JPHC-I was excluded from all analyses of tomato product intake because this study did not assess tomato consumption.

[o]JPHC-II was excluded from the highest level of intake because there were no cases in this level. The participants in this study who were in this category and were not cases were included in the next highest category.

[p]CARET, CLUE-II, JPHC-II, MCCS, and PCPT were excluded from this analysis because each study had fewer than 50 cases of advanced restricted prostate cancer.

[q]CARET, CLUE-II, JPHC-II, and PCPT were excluded from this analysis because each study had fewer than 50 cases of prostate cancer mortality.

[r]JPHC-II was excluded from this analysis because this study had fewer than 50 cases of high-grade prostate cancer.

[s]ATBC and JPHC-II were excluded from all analyses of mature bean intake because these studies did not assess mature bean consumption.

[t]JPHC-I was excluded from the highest two levels of intake and CARET was excluded from the highest level of intake because there were no cases in these levels. The participants in these studies who were in these categories and were not cases were included in the next highest category.

[u]JPHC-I and PCPT were excluded from this analysis because each study had fewer than 50 cases of this subtype; CARET, CLUE-II, CPS-II, and NLCS were excluded from the highest level of intake because there were no cases in this level. The participants in CARET, CLUE-II, CPS-II, and NLCS who were in this category and were not cases were included in the next highest category.

[v]JPHC-I, PCPT, CARET, CLUE-II, and MCCS were excluded from this analysis because each study had fewer than 50 cases of this subtype; CPS-II, and NLCS were excluded from the highest level of intake because there were no cases in this level. The participants in CPS-II and NLCS who were in these categories and were not cases were included in the next highest category.

[w]JPHC-I, PCPT, CARET, and CLUE-II were excluded from this analysis because each study had fewer than 50 cases of this subtype; CPS-II, NLCS, and PLCO were excluded from the highest level of intake because there were no cases in this level. The participants in CPS-II, NLCS, and PLCO who were in this category and were not cases were included in the next highest category.

[x]JPHC-I was excluded from this analysis because this study had fewer than 50 cases of this subtype; CARET, CLUE-II, and NLCS were excluded from the highest level of intake because there were no cases in this level. The participants in CARET, CLUE-II, and NLCS, who were in this category and were not cases, were included in the next highest category.

Table 4. Pooled multivariable RRs and 95% CI for specific food items and prostate cancer risk

Item	Increment unit[a]	Total prostate cancer	Local prostate cancer	Advanced prostate cancer	Advanced restricted prostate cancer	Prostate cancer mortality	Low-grade prostate cancer	High-grade prostate cancer
Apples, pears, & applesauce	138 g/day	0.99[b,c] (0.97–1.02)	1.00[b,c] (0.97–1.02)	0.97[b,c,d,e] (0.87–1.08)	1.03[b,c,d,e,f,g,h] (0.88–1.20)	0.97[b,c,d,e,f,g] (0.86–1.09)	1.00[b,c] (0.97–1.03)	0.98[b,c,d] (0.92–1.04)
Bananas	114 g/day	1.01[c,d,g,i,j,k,] (0.96–1.07)	1.03[c,d,g,i,j,k] (0.97–1.09)	0.91[c,d,e,g,i,j,k] (0.80–1.03)	0.90[c,d,e,f,g,h,j,k,] (0.77–1.05)	0.91[c,d,e,f,g,i,j,k] (0.76–1.09)	1.01[c,d,g,i,j,k] (0.95–1.07)	1.02[c,d,g,i,j,k] (0.96–1.10)
Broccoli	78 g/day	1.07[b,c,d,l] (0.99–1.17)	1.09[b,c,d,l] (1.00–1.18)	0.90[b,c,d,e,l] (0.73–1.10)	0.96[b,c,d,e,f,g,h,l] (0.76–1.22)	0.78[b,c,d,e,f,g,l] (0.59–1.03)	1.08[b,c,d,l] (0.99–1.17)	1.05[b,c,d,l] (0.96–1.16)
Cabbage	68 g/day	0.97[c,d,e,h,k,l] (0.92–1.03)	0.99[c,d,e,h,k,l] (0.92–1.06)	0.83[c,d,e,h,k,l] (0.68–1.01)	0.89[c,d,e,f,g,h,k,l,] (0.69–1.15)	0.82[c,d,e,f,g,h,k,l] (0.64–1.04)	0.95[c,d,e,h,k,l] (0.89–1.02)	1.04[c,d,e,h,k,l] (0.89–1.21)
Cantaloupe	134 g/day	1.03[b,c,d,j,l,m] (0.89–1.19)	1.00[b,c,d,j,l,m] (0.82–1.22)	0.80[b,c,d,e,j,l,m] (0.52–1.22)	0.64[b,c,d,e,f,g,h,j,l,m] (0.33–1.22)	0.71[b,c,d,e,f,g,h,j,l,m] (0.28–1.80)	1.05[b,c,d,j,l,m] (0.86–1.29)	1.01[b,c,d,j,l,m] (0.78–1.30)
Carrots	57 g/day	1.00[b,c] (0.97–1.04)	0.99[b,c] (0.93–1.05)	0.95[b,c,d,e] (0.85–1.06)	0.97[b,c,d,e,f,g,h] (0.84–1.12)	0.90[b,c,d,e,f,g,n] (0.76–1.06)	0.99[b,c] (0.93–1.04)	1.02[b,c,d] (0.95–1.10)
Corn	82 g/day	0.98[b,c,d,g,i,j,l,m] (0.90–1.06)	0.92[b,c,d,g,i,j,l,m] (0.84–1.02)	1.53[b,c,d,e,g,i,j,l,m] (1.12–2.07)	1.53[b,c,d,e,f,g,h,i,j,l,m] (0.95–2.46)	1.49[b,c,d,e,f,g,h,i,j,l,m] (1.01–2.20)	0.92[b,c,d,g,i,j,l,m] (0.83–1.02)	1.22[b,c,d,g,i,j,l,m] (0.98–1.51)
Mixed greens	100 g/day	1.06[b,j,l,m,n] (0.90–1.25)	0.94[b,j,l,m,n] (0.74–1.19)	1.68[b,c,d,e,j,l,m,n] (0.96–2.96)	1.81[b,c,d,e,f,g,h,j,l,m,n] (0.88–3.73)	1.66[b,c,d,e,f,g,h,j,l,m,n] (0.80–3.43)	0.98[b,j,l,m,n] (0.80–1.20)	1.18[b,c,d,j,l,m,n] (0.84–1.64)
Grapefruit	120 g/day	0.99[b,c,d,e,j,l,m] (0.96–1.03)	1.01[b,c,d,e,j,l,m] (0.97–1.05)	0.97[b,c,d,e,j,l,m] (0.84–1.11)	0.92[b,c,d,e,f,g,h,j,l,m,n] (0.76–1.12)	0.95[b,c,d,e,f,g,h,j,l,m,n] (0.80–1.13)	0.99[b,c,d,e,j,l,m] (0.94–1.04)	0.96[b,c,d,e,j,l,m] (0.88–1.04)
Orange & grapefruit juice	186 g/day	1.01[c,d,m,n] (1.00–1.02)	1.02[c,d,m,n] (1.01–1.04)	1.00[c,d,e,m,n] (0.94–1.06)	1.05[c,d,e,f,g,h,m,n] (0.98–1.13)	0.98[c,d,e,f,g,m,n] (0.91–1.06)	1.00[c,d,m,n] (0.99–1.02)	1.01[c,d,m,n] (0.98–1.04)
Lettuce	56 g/day	0.99[b,c,d] (0.96–1.02)	1.00[b,c,d] (0.96–1.03)	0.91[b,c,d,e] (0.85–0.98)	0.92[b,c,d,e,f,g,h] (0.84–1.01)	0.86[b,c,d,e,f,g,n] (0.78–0.94)	1.00[b,c,d] (0.97–1.03)	1.01[b,c,d] (0.97–1.05)
Oranges	131 g/day	1.00[b,c,d,e,j,m] (0.97–1.04)	1.00[b,c,d,e,j,m] (0.97–1.04)	1.03[b,c,d,e,j,m] (0.94–1.13)	1.00[b,c,d,e,f,g,h,j,m] (0.88–1.13)	1.06[b,c,d,e,f,g,j,m] (0.94–1.18)	1.00[b,c,d,e,j,m] (0.96–1.04)	1.05[b,c,d,e,j,m] (0.94–1.17)
Peppers	138 g/day	0.78[b,c,d,g,i,o] (0.56–1.08)	0.75[b,c,d,g,i,o] (0.54–1.04)	1.01[b,c,d,e,g,i,o] (0.53–1.92)	1.08[b,c,d,e,f,g,h,i,o] (0.45–2.58)	1.31[b,c,d,e,f,g,i,o] (0.63–2.73)	0.68[b,c,d,g,i,o] (0.46–0.99)	1.77[b,c,d,g,i,o] (0.66–4.74)
String beans	68 g/day	1.01[b,c,d,g,i,j,o] (0.89–1.14)	1.00[b,c,d,g,i,j,o] (0.89–1.12)	1.03[b,c,d,e,g,i,j,o] (0.86–1.24)	0.97[b,c,d,e,f,g,h,i,j,o] (0.72–1.31)	1.11[b,c,d,e,f,g,i,j,o] (0.86–1.43)	0.99[b,c,d,g,i,j,o] (0.88–1.12)	1.05[b,c,d,g,i,j,o] (0.93–1.18)
Vegetable soup	244 g/day	1.02[b,c,d,h,j,k,l,m,o] (0.95–1.10)	0.97[b,c,d,h,j,k,l,m,o] (0.86–1.09)	1.27[b,c,d,e,h,j,k,l,m,o] (0.94–1.71)	1.36[b,c,d,e,f,g,h,j,k,l,m,o] (0.91–2.03)	1.16[b,c,d,e,f,g,h,j,k,l,m,o] (0.78–1.73)	1.02[b,c,d,h,j,k,l,m,o] (0.93–1.11)	0.99[b,c,d,h,j,k,l,m,o] (0.83–1.19)
Spinach	80 g/day	1.00[b,c,d,e,h,o] (0.95–1.06)	1.10[b,c,d,e,h,o] (0.89–1.36)	1.25[b,c,d,e,h,o] (0.85–1.84)	1.03[b,c,d,e,f,g,h,o] (0.78–1.37)	1.38[b,c,d,e,f,g,h,o] (0.94–2.03)	1.00[b,c,d,e,h,o] (0.93–1.08)	1.25[b,c,d,e,h,o] (0.93–1.69)
Tomatoes	122 g/day	0.97[b,c,e,n,p] (0.86–1.10)	0.97[b,c,e,n,p] (0.88–1.07)	0.98[b,c,e,n,p] (0.82–1.18)	0.91[b,c,d,e,f,g,h,n,p] (0.65–1.27)	0.97[b,c,d,e,f,g,n,p] (0.78–1.20)	0.98[b,c,e,n,p] (0.84–1.14)	0.99[b,c,d,e,n,p] (0.85–1.14)
Yams	128 g/day	0.98[b,c,d,h,j,l,m] (0.81–1.18)	1.01[b,c,d,h,j,l,m] (0.81–1.27)	1.28[b,c,d,e,h,j,l,m] (0.48–3.41)	1.44[b,c,d,e,f,g,h,j,m,] (0.68–3.07)	0.74[b,c,d,e,f,g,h,j,l,m] (0.22–2.51)	0.88[b,c,d,h,j,l,m] (0.68–1.12)	1.54[b,c,d,h,j,l,m] (0.59–4.03)

NOTE: "Advanced": defined as T4, N1, or M1 tumors or prostate cancer mortality; "Advanced restricted": same as advanced prostate cancer, but excluding those who died of prostate cancer during follow-up who had been diagnosed with localized cancer or had missing stage data; "High grade": Gleason score ≥8 or poorly differentiated/undifferentiated; "Localized": defined as T1/T2 and N0M0 tumors, that is, cancers confined within the prostate; "Low grade": Gleason score <8 or well/moderately differentiated. All models adjusted for marital status [married (ref), never married, widowed, divorced), race [Caucasian (ref), African-American, Asian, Hispanic, other), education [<high school (ref), high school, >high school], body mass index [BMI, kg/m^2; <23 (ref), 23–<25, 25–<30, ≥30], height [meters; <1.70 (ref), 1.70–<1.75, 1.75–<1.80, 1.80–<1.85, ≥1.85; in JPHC-I and JPHC-II: <1.60 (ref), 1.60–<1.65, 1.65–<1.70, 1.70–<1.75, ≥1.75], alcohol [g/day; 0 (ref), >0–<5, 5–<15, 15–<30, ≥30], multivitamin use [no (ref), yes], total energy intake (kcal/d, as continuous variable), smoking status [never (ref), past smoker <15 packyears, past smoker ≥15 packyears, current smoker <40 packyears, current smoker ≥40 packyears], prostate cancer family history [no (ref), yes], physical activity [low (ref), medium, high], history of diabetes [no (ref), yes]. Age in years and year of questionnaire return were included as stratification variables. We additionally stratified the baseline hazard by center for EPIC.

[a]Increments were chosen to reflect a serving size of each individual item (e.g., generally 1 cup for lettuce and soup, $^1/_2$ cup or 1 medium for most other fruits and vegetables, 6 oz for juice).

[b]Excludes European Prospective Investigation into Cancer and Nutrition (EPIC).

[c]Excludes The Japan Public Health Center-Based Study I (JPHC-I).

[d]Excludes The Japan Public Health Center-Based Study II (JPHC-II).

[e]Excludes Prostate Cancer Prevention Trial (PCPT).

[f]Excludes Beta-Carotene and Retinol Efficacy Trial (CARET).

[g]Excludes CLUE II: Campaign Against Cancer and Heart Disease (CLUE-II).

[h]Excludes Melbourne Collaborative Cohort Study (MCCS).

[i]Excludes Cancer Prevention Study-II Nutrition Cohort (CPS-II).

[j]Excludes Cohort of Swedish Men (COSM).

[k]Excludes Health Professionals Follow-Up Study (HPFS).

[l]Excludes Netherlands Cohort Study (NLCS).

[m]Excludes Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC).

[n]Excludes NIH-AARP Diet and Health Study (NIH-AARP).

[o]Excludes Multiethnic Cohort (MEC).

[p]Excludes Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO).

were conducted in the post-PSA era, which saw a dramatic increase in prostate cancer incidence in the 1990s (76, 77), and may therefore be affected. We were unable to separately examine cases diagnosed in the "pre-PSA" versus "post-PSA" era because too few cases were diagnosed in the pre-PSA era, or exclude cases diagnosed by PSA screening because the majority of studies did

not have information on PSA screening available. We alternatively tested associations between all food groups and prostate cancer risk separately in the US and other regions, since PSA screening started earlier in the US than in other countries, but found no significant differences in associations by region. However, the extent to which PSA screening popularity in Europe, Asia, and Oceania lagged behind that in the United States, and current differences in screening between regions, are unclear (78). Thus, we cannot exclude the possibility that healthier lifestyle and diet choices among men who undergo PSA screening in North America may explain our observed associations. However, it should be noted that we adjusted for multiple factors associated with lifestyle choices, including BMI, physical activity, multivitamin use, and smoking habits.

An important strength of this study is its inclusion of many studies (most of which have not previously published on these associations) across different populations and geographic regions, which allowed us to observe a wide range of fruit and vegetable intake (7-fold difference in median intake across studies). The exposure, endpoint, and covariate data from each study were harmonized, standardized definitions were applied to each of the fruit and vegetable groups, and there was little evidence of heterogeneity in the results between studies. This allowed us to pool these studies, which greatly increased our power to detect associations for prostate cancer subtypes. This is especially important for analyses for advanced prostate cancer and prostate cancer mortality, which are underpowered in most cohort studies. This study's large size also enabled us to test for effect modification by BMI, follow-up time, age at diagnosis, and geographic region. Finally, because all included studies used a prospective cohort design, there is a lower risk of recall bias, which is problematic in retrospective nutritional epidemiologic investigations.

Despite these strengths, this study has several limitations. Diet was measured with error due to both within-person random and systematic variation (79, 80), and we could not apply techniques that have been developed to adjust for these errors (80–82) because most studies did not assess the validity of fruit, vegetable, and mature bean intake in their questionnaires. If there are any true associations between fruit and vegetable intake and prostate cancer risk, this measurement error could have attenuated them and led us to report a nonsignificant association. In addition, we only had a single measure of intake at baseline, and therefore could not assess changes in diet over time or test for potentially different etiologically relevant exposure time periods. It is also possible that some noncases were actually undiagnosed cases, which would most likely attenuate the associations observed. However, we expect this to be less problematic for the results for advanced prostate cancer and prostate cancer mortality, which are less likely to be misclassified than localized prostate cancer, and are less likely to be increased due to screening. Although we harmonized these data and used standardized criteria for defining exposures and covariates across studies, there is still heterogeneity in dietary evaluation, data collection, sampling procedures, and other aspects of study design. However, the prospective nature of each study reduced the risk of differential measurement error between cases and noncases, and the tests for between-studies heterogeneity in the risk estimates were nonsignificant across most associations evaluated. Because we only included data on confounding variables measured at study enrollment in our regression models, there could be residual confounding by time-varying covariates. However, our results showed little evidence of confounding between the age-adjusted and multivariable analyses. Our analyses were also limited due to our lack of data on PSA screening, although we observed no difference in results between studies conducted in the United States compared with studies in other regions where PSA screening is likely less common. Finally, we were unable to assess effect modification by race/ethnicity due to a low number of cases in racial and ethnic groups other than Caucasians.

In summary, this large pooled analysis of prospective studies does not support a strong role of fruit and vegetable consumption and risk of prostate cancer. This appears to be true for intake of both broad and more specific fruit and vegetable groupings. While we did observe inverse associations for mature bean consumption (excluding soy) and risk of some prostate cancer subtypes, the low consumption and narrow distribution of intake among participants suggests we may have missed any associations involving higher mature bean intake and prostate cancer outcomes. These associations should therefore be examined in other populations with higher levels of mature bean intake in future studies. In addition, while overall tomato intake was not associated with prostate cancer risk, further study of cooked tomato products that provide bioavailable lycopene is warranted. Although not strongly associated with prostate cancer risk or mortality in our study, fruit, vegetable, and bean intake remain important for reducing risk of obesity (83), cardiovascular disease, and all-cause mortality (84).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J. Petimar, K. Wu, D. Albanes, G.G. Giles, E.L. Giovannucci, Y. Park, A. Wolk, S.A. Smith-Warner

Development of methodology: M. Wang, S.A. Smith-Warner

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Albanes, P.A. van den Brandt, G.G. Giles, E.L. Giovannucci, G.E. Goodman, N. Håkansson, K. Helzlsouer, T.J. Key, L.N. Kolonel, S. Männistö, M.L. McCullough, M.L. Neuhouser, Y. Park, N. Sawada, S. Tsugane, B.A.J. Verhage, Y. Wang, L.R. Wilkens, A. Wolk, R.G. Ziegler, S.A. Smith-Warner

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Petimar, K.M. Wilson, K. Wu, P.A. van den Brandt, R.L. Milne, Y. Park, S.A. Smith-Warner

Writing, review, and/or revision of the manuscript: J. Petimar, K.M. Wilson, K. Wu, D. Albanes, P.A. van den Brandt, M.B. Cook, G.G. Giles, E.L. Giovannucci, G.E. Goodman, P.J. Goodman, N. Håkansson, K. Helzlsouer, T.J. Key, L.N. Kolonel, L.M. Liao, S. Männistö, M.L. McCullough, R.L. Milne, M.L. Neuhouser, Y. Park, E.A. Platz, E. Riboli, N. Sawada, J.M. Schenk, S. Tsugane, B.A.J. Verhage, Y. Wang, L.R. Wilkens, A. Wolk, R.G. Ziegler, S.A. Smith-Warner

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Petimar, N. Håkansson, L.M. Liao, R.L. Milne, E.A. Platz, N. Sawada

Study supervision: S.A. Smith-Warner

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