Title

Mediterranean Diet and Prostate Cancer Risk and Mortality in the Health Professionals Follow-up Study

Journal

European Urology, 65(5)

ISSN

0302-2838

Authors

Kenfield, Stacey A
DuPre, Natalie
Richman, Erin L
et al.

Publication Date

2014-05-01

DOI

10.1016/j.eururo.2013.08.009

Peer reviewed

Published in final edited form as:
Eur Urol. 2014 May ; 65(5): 887–894. doi:10.1016/j.eururo.2013.08.009.

Mediterranean Diet and Prostate Cancer Risk and Mortality in the Health Professionals Follow-up Study

Stacey A. Kenfield[1,2,3,*], **Natalie DuPre**[1], **Erin L. Richman**[4], **Meir J. Stampfer**[1,2,5], **June M. Chan**[3,4,†], and **Edward L. Giovannucci**[1,2,5,†]

[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

[2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

[3]Department of Urology, University of California, San Francisco, San Francisco, CA, USA

[4]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

[5]Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

Abstract

Background—Prostate cancer (PCa) mortality rates are lower in the Mediterranean countries compared with northern Europe. Although specific components of the Mediterranean diet (Med-Diet) may influence PCa risk, few studies have assessed the traditional Med-Diet pattern with the risk of incident advanced or lethal PCa or with disease progression among men diagnosed with nonmetastatic PCa.

[*]Corresponding author. Helen Diller Family Cancer Research Building Room HD389 1450 3rd Street, University of California, San Francisco, San Francisco, CA 94158-9001, USA. Tel: +1 617 953 7375; Fax: +1 415 514 4927. KenfieldS@urology.ucsf.edu.
[†]Shared senior authorship.

Author contributions: Stacey A. Kenfield had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kenfield, Dupre, Stampfer, Giovannucci.
Acquisition of data: Stampfer, Giovanucci, Chan.
Analysis and interpretation of data: Kenfield, Dupre, Richman, Stampfer, Chan, Giovannucci.
Drafting of the manuscript: Kenfield.
Critical revision of the manuscript for important intellectual content: Kenfield, Dupre, Richman, Stampfer, Chan, Giovannucci.
Statistical analysis: Kenfield.
Obtaining funding: Giovannucci, Stampfer.
Administrative, technical, or material support: Kenfield, Richman.
Supervision: Stampfer, Chan, Giovannucci.
Other (specify): None.

Financial disclosures: Stacey A. Kenfield certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Objective—To determine whether the traditional Med-Diet pattern is associated with risk of incident advanced or lethal PCa and with PCa-specific and overall mortality among men with PCa.

Design, setting, and participants—We prospectively followed 47 867 men in the Health Professionals Follow-up Study followed from 1986 to 2010. The case-only analysis included 4538 men diagnosed with nonmetastatic PCa, followed from diagnosis to lethal outcome or to January 2010.

Outcome measurements and statistical analysis—We used Cox proportional hazards models to examine traditional and alternative Med-Diet scores in relation to PCa incidence outcomes (advanced and lethal disease). In a case-only survival analysis, we examined postdiagnostic Med-Diet and risk of lethal (metastases or PCa death) and fatal PCa as well as overall mortality among men diagnosed with nonmetastatic disease.

Results and limitations—Between 1986 and 2010, 6220 PCa cases were confirmed. The Med-Diet was not associated with risk of advanced or lethal PCa. In the case-only analysis, there was no association between the Med-Diet after diagnosis and risk of lethal or fatal PCa. However, there was a 22% lower risk of overall mortality (hazard ratio: 0.78; 95% confidence interval, 0.67–0.90; $p_{trend} = 0.0007$) among men with greater adherence to the Med-Diet after PCa diagnosis. We found similar associations for the alternative score.

Conclusions—A higher Med-Diet score was not associated with risk of advanced PCa or disease progression. Greater adherence to the Med-Diet after diagnosis of nonmetastatic PCa was associated with lower overall mortality.

Keywords

Prostate cancer; Risk; Mortality; Mediterranean diet; Epidemiology

1. Introduction

The traditional Mediterranean diet (Med-Diet) consists of abundant plant foods (fruits, vegetables, legumes, nuts, breads, and other largely unrefined cereals); olive oil as the main fat; moderately high fish; moderate alcohol, mainly wine; low consumption of milk and dairy products, mainly from yogurt and cheeses; and low consumption of poultry, red meat, and eggs [1]. In cohort studies, Med-Diet adherence has been associated with lower risk of cancer [2,3] at various sites [4–6], coronary heart disease [7–9], and other health outcomes. Variations of the Med-Diet used in intervention trials reduced cardiovascular disease [10] and cancer incidence [11].

Countries following the traditional Med-Diet, particularly southern European countries, have lower prostate cancer (PCa) incidence and mortality compared with other European regions [12,13]. Specific Med-Diet components including specific vegetables, tomato sauce, fish, and vegetable fat are associated with lower risk of PCa mortality [14–16] or progression [17]. Although cohort data on healthy dietary patterns determined by factor analyses [18, 19] and the alternative Med-Diet pattern [20] in healthy men have reported null associations with incidence of advanced or fatal PCa, the effect of the Med-Diet pattern after diagnosis on PCa outcomes is unknown.

We examined the association between the Med-Diet and the risk of incident advanced PCa as well as the relation between postdiagnostic adherence to the Med-Diet pattern and the risk of progression to lethal PCa and all-cause mortality. We hypothesized that the Med-Diet pattern after PCa diagnosis would be associated with a lower risk of progression to lethal PCa and overall mortality.

2. Patients and methods

2.1. Study population

The Health Professionals Follow-up Study (HPFS) is a prospective cohort study initiated in 1986 among 51 529 US male health professionals aged 40–75 yr. At baseline, participants reported medical diagnoses, medications, height, weight, ethnicity, and lifestyle factors (eg, smoking, physical activity, supplement use) and completed a validated semiquantitative food-frequency questionnaire (FFQ) [21]. These data are updated every 2 yr, and diet information is updated every 4 yr. The average questionnaire response rate is 96%. We excluded men reporting implausible energy intake (<800 or >4200 kcal/d) or missing ≥70 food items on the baseline FFQ and men diagnosed with cancer (except nonmelanoma skin cancer) before baseline, leaving 47 867 men for follow-up of PCa incidence until January 2010. For the case-only postdiagnosis survival analyses, we excluded men with advanced cancer at diagnosis (clinical T stage T3b or higher; $n = 288$) and those missing clinical stage ($n = 936$). We also excluded men without any postdiagnosis diet data, leaving 4538 men for follow-up of lethal outcomes through January 2010.

2.2. Assessment of diet and Mediterranean diet scores

The FFQ assessed consumption of approximately 130 food items and supplements. A commonly used portion size was specified, and participants indicated frequency of consumption, from never or less than one serving per month to six or more servings per day. In a validation study, the mean Pearson correlation coefficient for all foods comparing the FFQ and diet records was 0.63, and 73% of the food items had correlation coefficients ≥0.50 [21].

Food items were sorted into nine categories (Table 1) of the traditional Med-Diet [1] and an alternative Med-diet score [5]. For the traditional Med-Diet score, each participant received 1 point each for being below the median in dairy and meat intake; 1 point for alcohol intake between 10 and 50 g/d; and 1 point each for being above the median intake of vegetables, legumes, fruits and nuts, grains, fish, and the ratio of polyunsaturated to saturated lipids (total score range: 0–9). Monounsaturated fat, used in the traditional Med-Diet score [1], was not used in the lipid ratio because the main dietary contributor of monounsaturated fat in our cohort was beef. The traditional Med-Diet score was evaluated continuously and categorically (0–3, 4–5, and 6–9 points indicating low, moderate, and high adherence, respectively). The alternative score ranged from 0 to 9 and was evaluated in quintiles for consistency with previous analyses [5,22].

2.3. Ascertainment of prostate cancer

After participants report a PCa diagnosis, we obtain medical records to confirm the diagnosis and record clinical T stage, grade (Gleason score), prostate-specific antigen (PSA) at diagnosis, metastasis, and treatments. Starting in 2000, participants with confirmed PCa and their physicians completed biennial questionnaires to update information regarding treatments, disease progression, and metastases. Deaths were identified from family reports and National Death Index searches; we ascertained >98% of deaths [23]. Causes of death were adjudicated by study physicians who reviewed medical records and death certificates.

2.3.1. Prostate cancer incidence outcome definitions—We categorized PCa incidence as total (excluding T1a cancers, discovered incidentally during treatment for benign prostatic hypertrophy), advanced, lethal, fatal, low grade (Gleason score 2–6), and high grade (Gleason score >7). Advanced cancers were stage T3b, T4, N1, or M1 at diagnosis or lymph node metastases, distant metastases, or PCa death during follow-up. Lethal cancers were those that metastasized to distant organs at diagnosis or over follow-up or that caused PCa death.

2.3.2. Case-only survival outcome definitions—We examined postdiagnostic Med-Diet adherence in relation to risk of lethal PCa, PCa-specific mortality, and overall mortality among men initially diagnosed with localized or regional PCa (clinical stage T1–T3a).

2.4. Statistical analysis

All analyses were performed using SAS v.9.3 (SAS Institute, Inc, Cary, NC, USA), and results with a two-sided p value <0.05 were considered statistically significant.

2.4.1. Prostate cancer incidence analysis—We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of prediagnostic traditional and alternative Med-Diet scores with risk of incident PCa. Participants contributed person-time from the return of the baseline questionnaire until diagnosis, death, or end of follow-up (January 31, 2010), whichever occurred first. The time scale was calendar time in 2-yr intervals.

We calculated cumulative average dietary intakes from 1986 until diagnosis, death, or end of follow-up [24]. For example, the average of 1986, 1990, and 1994 FFQs was applied to person-time contributed between 1994 and 1998. Our age-adjusted model included age (months), time period (2-yr intervals), and total calories (kilocalories per day; quartiles). In the primary multivariate model, we also adjusted for body mass index (BMI; <25, 25–29.9, and ≥30 kg/m^2), vigorous physical activity (<1 h/wk, 1 h/wk to <3 h/wk, and ≥3 h/wk), smoking status (current, former, never), and PSA screening history (yes, no, or unknown). Additional adjustment for race, height, diabetes, family history of PCa, multivitamin use, or specific supplements did not affect the estimates, and these variables were omitted. Tomato sauce is considered an important component of the Med-Diet [25] and reduced PCa risk in this cohort [26]. In multivariate models, tomato sauce did not affect the main estimates and was left out of the models. We considered adjustment for whole milk and total dairy when evaluating the alternative score [27], and this did not affect the main estimates. Because

olive oil is not directly assessed as a component in the score, we assessed olive oil intake (olive oil added to food, bread, or used in salad dressing) separately. The diet scores and covariates were updated in each questionnaire cycle. We also evaluated diet at baseline to assess whether distant past adherence was related to PCa risk. Linear trends across categories were evaluated using the median of each category as a continuous variable [28]. We assessed interactions by southern European ancestry (participant selected "Southern European/Mediterranean" ancestry at enrollment), age (<70 yr vs ≥70 yr), and by BMI (<25 kg/m^2 vs ≥25 kg/m^2). We entered the cross-products of the diet score with those variables in multivariate models and used Wald tests.

2.4.2. Case-only survival analysis—We used Cox proportional hazards regression to examine postdiagnostic Med-Diet and risk of lethal and fatal PCa and overall mortality. Person-time was calculated from diagnosis to diagnosis of metastases (for lethal disease), death, or end of follow-up (January 31, 2010), whichever occurred first. We calculated cumulative average postdiagnostic dietary intakes from the most recent FFQ preceding diagnosis until the end of follow-up. The FFQ preceding diagnosis was used to classify the participants' diets from diagnosis until the next FFQ. Our age-adjusted model included age at diagnosis (years), time period (2-yr intervals), energy (kilocalories per day; quartiles), and time from diagnosis to the FFQ (years; continuous). In the primary multivariate model, we also adjusted for primary treatment (radical prostatectomy, radiation, hormonal therapy, active surveillance, other), Gleason score (<7, 7, >7), clinical T stage (T1, T2, T3), BMI, smoking, and vigorous physical activity. For all-cause mortality, additional adjustment for parental history of myocardial infarction before age 60 yr, high blood pressure, diabetes, and elevated cholesterol—all defined as yes or no—did not affect the estimates, and these variables were omitted. As a sensitivity analysis, we adjusted for prediagnostic Med-Diet scores using the 1986 FFQ. We examined whether the association between postdiagnostic Med-Diet intake and lethal PCa was modified by southern European ancestry, age at diagnosis (<70 yr vs ≥70 yr), Gleason score (<7 vs ≥7), or BMI (<25 kg/m^2 vs ≥25 kg/m^2).

3. Results

3.1. Prostate cancer incidence

During 24 yr of follow-up, 6220 PCa cases were confirmed among 47 867 men. The median follow-up from baseline to PCa event or January 2010 was 23.3 yr. At baseline, 37% of men had low adherence to the traditional Med-Diet (score 0–3), 34% had moderate adherence (score 4–5), and 29% had high adherence (score 6–9). Among men without PCa, 30% had high adherence in 1994 and 33% had high adherence in 2006. At baseline, men of southern European ancestry composed 26% of those with high adherence compared with 22% of those with low adherence. Median levels of the specific Med-diet components in 1986 and 2006 (cumulatively updated since 1986), respectively, were (1) vegetables, 2.9 and 3.2 servings per day; (2) fruit, 2.8 and 2.8 servings per day; (3) legumes, 0.4 and 0.4 serving per day; (4) cereal, 2.1 and 2.7 servings per day; (5) fish and seafood, 0.3 and 0.3 serving per day; (6) ratio of polyunsaturated to saturated lipids, 0.5 and 0.6; (7) alcohol, 5.6 and 6.9 g/d (categories, not median used in score); (8) red and processed meat products, 0.9 and 0.9 serving per day; and (9) dairy products, 1.8 and 1.9 servings per day. Compared with men

with low adherence to the Med-Diet, men with high adherence were slightly older, smoked less, had lower BMI, consumed fewer calories, did more vigorous physical activity, took more multivitamins and other supplements, and ate more tomato products (Table 2). Those with southern European ancestry consumed more olive oil and tomatoes (1.6 vs 1.0 olive oil servings per week and 4.4 vs 4.1 servings per week for southern European and nonsouthern Europeans, respectively).

We observed no statistically significant associations between the traditional Med-Diet score and incident PCa outcomes in multivariate models (Table 3; all $p_{trend} > 0.05$). Comparing men with a Med-Diet score of 6–9 versus 0–3, the HRs were 0.95 (95% CI, 0.81–1.11) for advanced PCa and 0.95 (95% CI, 0.79–1.13) for lethal PCa. Results for the alternative score were similar (Supplemental Table 1). Higher olive oil intake was not associated with PCa risk (data not shown). Baseline Med-Diet scores also were not significantly associated with PCa incidence outcomes: The HRs for a Med-Diet score of 6–9 versus 0–3 were 0.88 (95% CI, 0.72–1.07; $p_{trend} = 0.26$) for fatal disease and 0.87 (95% CI, 0.79–0.95; $p_{trend} = 0.002$) for Gleason 2–6 cancer and 1.08 (95% CI, 0.96–1.21; $p_{trend} = 0.18$) for Gleason ≥7 cancer. In secondary analyses using cumulative average dietary intakes, we observed no interactions by BMI, age, or southern European ancestry ($p_{int} > 0.05$; data not shown).

3.2. Case-only survival analysis

Of the 4538 men with nonmetastatic PCa at diagnosis, we documented 1181 deaths, 263 (22.3%) due to PCa. Other causes of death included cardiovascular disease (29.0%), other cancer (19.4%), nervous system diseases (8.0%), and respiratory disease (6.9%). The median duration of follow-up from diagnosis until lethal or fatal PCa event or January 2010 was 8.9 yr for lethal PCa and 9.1 yr for fatal outcomes. Of the 4538 men, 30% had high adherence to the traditional Med-Diet at the first postdiagnostic dietary assessment. These men had healthier characteristics (smoked less, more exercise, lower BMI) compared with those with worse adherence. We found no relationship of postdiagnostic Med-Diet with lethal outcomes. The HRs comparing men with a traditional Med-Diet score of 6–9 versus 0–3 after diagnosis were 0.98 (95% CI, 0.75–1.29) for lethal disease and 1.01 (95% CI, 0.75–1.38) for fatal disease (Table 5). Similarly, we found no relationships with the alternative score and these outcomes (Supplemental Table 2).

In contrast, we observed a 22% reduced risk of overall mortality (HR: 0.78; 95% CI, 0.67–0.90; $p_{trend} = 0.0007$) for men with a traditional Med-Diet score of 6–9 versus 0–3 after diagnosis and similar results for the alternative score (Table 5 and Supplemental Table 2). Further adjustment for prediagnosis Med-Diet score did not alter the findings. A 2-point increase in the traditional Med-Diet score after diagnosis was associated with 10% lower risk of overall mortality (HR: 0.90; 95% CI: 0.85–0.96). Furthermore, men who consumed five or more servings per week of olive oil after diagnosis had a 31% lower risk of overall mortality (HR: 0.69; 95% CI, 0.55–0.88) compared with men who consumed no olive oil. The association remained significant after adjustment for the traditional Med-Diet score. We observed no interactions by BMI, age, or Gleason score ($p_{int} > 0.05$).

Southern European ancestry appeared to modify the relationship between the alternative score ($p_{int} = 0.01$) and risk of total mortality. Compared with nonsouthern Europeans in the

lowest quintile of the alternative score, nonsouthern Europeans in the highest quintile had a 32% reduction in risk of overall mortality (HR: 0.68; 95% CI, 0.54–0.84; $p_{trend} < 0.0001$). In contrast, there was no clear association among southern-Europeans (HR for southern Europeans in the fifth quintile vs nonsouthern Europeans in the first quintile: 1.01; 95% CI, 0.75–1.36; $p_{trend} = 0.70$).

4. Discussion

Our results suggest no statistically significant association between the Med-Diet prior to diagnosis and incidence of advanced, lethal, or fatal PCa. These null results confirm prospective cohort studies that found no protective association of healthy dietary patterns with incidence of advanced PCa [18–20]. In the HPFS cohort, for example, the prudent dietary pattern defined by factor analysis showed no association with risk of advanced PCa [18]. Similarly, there was no significant association with the alternative Med-Diet score and the risk of advanced or fatal PCa in the National Institutes of Health–AARP cohort [20].

Our study extends these null observations to postdiagnostic adherence to the Med-Diet and risk of lethal PCa (HR: 0.98; 95% CI, 0.75–1.29). This study does not rule out the potential association of individual foods or nutrients that have modest effects on the overall Med-Diet score and are not weighted in the score [29]. Nuts, for example, were a main source of vegetable fat driving the protective association we recently observed with lethal PCa in the HPFS. The benefit of nuts on lethal PCa would be diluted when examining the Med-Diet pattern as a whole because of their small contribution (4 of 23 items) to the fruits and nuts category [16]. Likewise, greater intake of specific vegetables (eg, tomato sauce, cruciferous) may reduce the risk of development or progression of PCa [17,26,30,31]; however, when analyzed as a group, total fruits and vegetables may not be protective. In addition, many of the individual nutrient and food studies observed significant inverse associations only at the highest intakes [17,31], and the Med-Diet cut-points use the median intake, which would attenuate any protective association. Five or more servings per week of fish (vs less than one), for example, was associated with a significant 48% reduction in risk of PCa-specific mortality in the Physicians' Health Study [32]; the median in our study was 2.1 servings per week, which is likely too low for risk reduction. Consequently, our findings do not preclude the possibility of an inverse association between individual components of the Med-Diet and PCa.

As expected, our results suggest that greater adherence to the Med-Diet after diagnosis and greater olive oil consumption were associated with 22% and 31% reductions, respectively, in overall mortality among men diagnosed with nonmetastatic PCa, independent of diet prior to diagnosis. Large prospective studies and trials reported protective effects of the Med-Diet on overall mortality [10,33] of similar magnitude. In the European Prospective Investigation into Cancer and Nutrition–Spain cohort, high versus low Med-Diet adherence was associated with a 21% reduction in overall mortality [33], mostly due to reduced cardiovascular mortality (HR: 0.66; 95% CI, 0.49–0.89) rather than cancer mortality (HR: 0.92; 95% CI, 0.72–1.12); the recent PREDIMED trial reported an HR of 0.89 (95% CI, 0.71–1.12) for all-cause mortality [10]. The Med-Diet may offer cardiovascular protection by regulating blood pressure and insulin sensitivity and providing resistance to oxidation,

inflammation, and vasoreactivity [7,10]. Although some of these mechanisms are likely important for prostate carcinogenesis, higher levels of individual components composing the Med-Diet, such as nuts and unsaturated oils, may be required to affect PCa risk and progression. Study limitations include the use of self-reported diet, which will have some nondifferential error, and our inability to study change in diet before and after diagnosis because few men changed in extremes of adherence after diagnosis. Study strengths include the prospective, validated, and repeated assessment of diet used to derive the Med-Diet score, long and complete follow-up, and a large number of events.

5. Conclusions

Adherence to the Med-Diet was not associated with risk of advanced or lethal PCa or with PCa-specific mortality. Among men initially diagnosed with nonmetastatic PCa, adherence to the Med-Diet was associated with lower overall mortality. Among those men, the Med-Diet may be beneficial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the participants, Lauren McLaughlin, and other staff of the Health Professionals Follow-up Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. In addition, this study was approved by the Connecticut Department of Public Health (DPH) Human Investigations Committee. Certain data used in this publication were obtained from the DPH. The authors assume full responsibility for analyses and interpretation of these data.

Funding/Support and role of the sponsor: This work was supported by grants from the National Institutes of Health/National Cancer Institute (UM1 CA167552, T32CA009001, R25CA098566, R01CA141298, R01CA133891) and the Prostate Cancer Foundation.

References

1. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003; 348:2599–608. [PubMed: 12826634]
2. Benetou V, Trichopoulou A, Orfanos P, et al. Conformity to traditional Mediterranean diet and cancer incidence: the Greek EPIC cohort. Br J Cancer. 2008; 99:191–5. [PubMed: 18594542]
3. Couto E, Boffetta P, Lagiou P, et al. Mediterranean dietary pattern and cancer risk in the EPIC cohort. Br J Cancer. 2011; 104:1493–9. [PubMed: 21468044]
4. Trichopoulou A, Bamia C, Lagiou P, Trichopoulos D. Conformity to traditional Mediterranean diet and breast cancer risk in the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. Am J Clin Nutr. 2010; 92:620–5. [PubMed: 20631204]
5. Fung TT, Hu FB, McCullough ML, Newby PK, Willett WC, Holmes MD. Diet quality is associated with the risk of estrogen receptor-negative breast cancer in postmenopausal women. J Nutr. 2006; 136:466–72. [PubMed: 16424129]
6. Buckland G, Agudo A, Lujan L, et al. Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Am J Clin Nutr. 2010; 91:381–90. [PubMed: 20007304]
7. Buckland G, Gonzalez CA, Agudo A, et al. Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. Am J Epidemiol. 2009; 170:1518–29. [PubMed: 19903723]

8. Mitrou PN, Kipnis V, Thiebaut AC, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. Arch Intern Med. 2007; 167:2461–8. [PubMed: 18071168]
9. Knoops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA. 2004; 292:1433–9. [PubMed: 15383513]
10. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013; 368:1279–90. [PubMed: 23432189]
11. de Lorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N. Mediterranean dietary pattern in a randomized trial: prolonged survival and possible reduced cancer rate. Arch Intern Med. 1998; 158:1181–7. [PubMed: 9625397]
12. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer. 2002; 38:99–166. [PubMed: 11750846]
13. Bray F, Lortet-Tieulent J, Ferlay J, Forman D, Auvinen A. Prostate cancer incidence and mortality trends in 37 European countries: an overview. Eur J Cancer. 2010; 46:3040–52. [PubMed: 21047585]
14. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the Health Professionals Follow-up Study. Int J Cancer. 2007; 121:1571–8. [PubMed: 17450530]
15. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr. 2010; 92:1223–33. [PubMed: 20844069]
16. Richman EL, Kenfield SA, Chavarro JE, et al. Fat intake after diagnosis and risk of lethal prostate cancer and all-cause mortality. JAMA Intern Med. 2013; 173:1318–26. [PubMed: 23752662]
17. Richman EL, Carroll PR, Chan JM. Vegetable and fruit intake after diagnosis and risk of prostate cancer progression. Int J Cancer. 2012; 131:201–10. [PubMed: 21823116]
18. Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. Cancer Epidemiol Biomarkers Prev. 2006; 15:167–71. [PubMed: 16434606]
19. Muller DC, Severi G, Baglietto L, et al. Dietary patterns and prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2009; 18:3126–9. [PubMed: 19861522]
20. Bosire C, Stampfer MJ, Subar AF, et al. Index-based dietary patterns and the risk of prostate cancer in the NIH-AARP Diet and Health Study. Am J Epidemiol. 2013; 177:504–13. [PubMed: 23408548]
21. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc. 1993; 93:790–6. [PubMed: 8320406]
22. Fung TT, Hu FB, Wu K, Chiuve SE, Fuchs CS, Giovannucci E. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets and colorectal cancer. Am J Clin Nutr. 2010; 92:1429–35. [PubMed: 21097651]
23. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. Am J Epidemiol. 1994; 140:1016–9. [PubMed: 7985649]
24. Willett, WC. Nutritional epidemiology. 2. New York, NY: Oxford University Press; 1998.
25. Jenab M, Ferrari P, Mazuir M, et al. Variations in lycopene blood levels and tomato consumption across European countries based on the European Prospective Investigation into Cancer and Nutrition (EPIC) study. J Nutr. 2005; 135:2032S–6S. [PubMed: 16046733]
26. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst. 2002; 94:391–8. [PubMed: 11880478]
27. Pettersson A, Kasperzyk JL, Kenfield SA, et al. Milk and dairy consumption among men with prostate cancer and risk of metastases and prostate cancer death. Cancer Epidemiol Biomarkers Prev. 2012; 21:428–36. [PubMed: 22315365]
28. Rosner, B. Fundamentals of biostatistics. 7. Stamford, CT: Brooks/Cole, Cengage Learning; 2011. Equation 8.28
29. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002; 13:3–9. [PubMed: 11790957]

30. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of cruciferous vegetables and prostate cancer. Cancer Epidemiol Biomarkers Prev. 2003; 12:1403–9. [PubMed: 14693729]

31. Chan JM, Holick CN, Leitzmann MF, et al. Diet after diagnosis and the risk of prostate cancer progression, recurrence, and death (United States). Cancer Causes Control. 2006; 17:199–208. [PubMed: 16425098]

32. Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. Am J Clin Nutr. 2008; 88:1297–303. [PubMed: 18996866]

33. Buckland G, Agudo A, Travier N, et al. Adherence to the Mediterranean diet reduces mortality in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain). Br J Nutr. 2011; 106:1581–91. [PubMed: 21736834]

Take-home message

In a large cohort with long follow-up, higher Mediterranean diet scores were unassociated with incident prostate cancer (PCa), progression, and PCa-specific death. Higher postdiagnostic scores were associated with lower overall mortality, suggesting that this diet improves overall health in men with PCa.

Table 1
Components of each category included in the Mediterranean diet score

Category	Traditional Med-Diet score	Differences between the alternative[a] and the traditional Med-Diet score
Vegetables	Broccoli, sauerkraut, coleslaw, cooked cabbage, cauliflower, brussels sprouts, raw and cooked carrots, corn, mixed vegetables, alfalfa sprouts, celery, mushrooms, yellow and dark squash, eggplants/zucchini/other squash, yams/sweet potatoes, raw and cooked spinach, kale, romaine and iceberg lettuce, green pepper, garlic, beets, onions, salsa, tomatoes, tomato juice, and tomato sauce; potatoes were excluded	Excludes corn and garlic
Fruits and nuts	Raisins, prunes, prune juice, avocados, bananas, cantaloupe, watermelon, apples, applesauce, apple juice, oranges, orange juice with or without calcium fortification, grapefruit, grapefruit juice, other juices, strawberries, blueberries, peaches, apricots, peanut butter, peanuts, walnuts, and other nuts	Separates fruits and nuts into separate components
Legumes	String beans, peas/lima beans, beans/lentils, tofu, soymilk	–
Cereals	Cooked oatmeal and other cooked breakfast cereal, cold breakfast cereal, English muffin or bagel, white, dark, rye, and whole grain bread, white and brown rice, pasta, other grains, tortillas, bran, oat bran, wheat germ, and light or regular popcorn	Includes only whole grains. English muffin or bagel, white bread, white rice, pasta, tortillas, and non–whole grain cereals are excluded
Fish and seafood	Canned tuna, breaded and dark-meat fish, other fish, and shrimp	Excludes store-bought breaded fish
Fat	Ratio of polyunsaturated fat to saturated fat	Ratio of monounsaturated fat to saturated fat
Alcohol	Beer, light beer, red wine, white wine, liquor	–
Red and processed meat products	Bacon, hot dogs, hamburgers, beef, pork, lamb, salami, bologna and other processed meats, chicken or turkey dogs	–
Dairy products	Skim milk, 2% milk, whole milk, sherbet, ice cream, yogurts, cottage cheese, cream cheese, other cheeses, and butter, cream and sour cream	Dairy component excluded from score

Med-Diet = Mediterranean diet.

[a]The alternative score includes foods similar to the traditional Med-Diet score, unless specified.

Table 2

Age-standardized[a] characteristics of the Health Professionals Follow-Up Study population at baseline in 1986, by adherence to the traditional Mediterranean diet pattern and dietary characteristics by ancestry

	Diet score of 0–3 (low adherence)	Diet score of 4–5 (moderate adherence)	Diet score of 6–9 (good adherence)
Participants, %	36.8	34.0	29.2
Age in 1990, yr, mean	52.6	54.3	55.3
Southern European ancestry, %	22.1	23.7	25.6
History of PSA tests in 1994, among cases diagnosed after 1994, %	54.1	55.7	61.5
Current smoker, %	14.3	9.4	6.4
Past smoker, %	40.2	43.6	46.8
BMI, kg/m^2, mean	25.8	25.6	25.1
Height, cm, mean	70.2	70.1	69.9
Diabetes, %	3.0	3.4	3.1
Family history of prostate cancer, %	5.8	5.4	5.5
Vigorous exercise, h/wk	1.2	1.7	2.3
Current multivitamin use, %	37.6	42.3	46.4
Current vitamin E use, %	14.5	19.0	24.8
Total calories, kcal, mean	2069.9	1971.5	1897.7
Mean dietary intakes			
Vegetables, servings/day	2.2	3.3	4.5
Legumes, servings/day	0.3	0.4	0.6
Fruits, servings/day	1.8	2.5	3.3
Nuts, servings/day	0.4	0.5	0.6
Cereals, servings/day	2.0	2.4	2.7
Whole grains only, servings/day	1.0	1.3	1.7
Fish, servings/day	0.3	0.4	0.6
Meat, servings/day	1.3	0.9	0.5
Dairy, servings/day	2.5	1.9	1.4
Alcohol, grams per day	11.4	11.3	11.4
Olive oil, servings per week[b]	0.8	1.1	1.7
Tomatoes, juice, salsa, servings/week	3.3	4.2	5.2
Tomato sauce, servings/week	0.8	0.9	1.1
Garlic, servings/week	0.6	1.0	1.5
Coffee, servings/day	2.1	1.9	1.7
Ratio of polyunsaturated to saturated fat, g/d	0.4	0.6	0.7
Ratio of monounsaturated to saturated fat, g/d	1.1	1.1	1.2

BMI = body mass index; PSA = prostate-specific antigen.

[a] Age standardized to the age distribution of the study population in 1986.

[b] Includes olive oil added to food, bread, or used in salad dressing and not that used in cooking.

Table 3

Mediterranean diet and risk of prostate cancer among 47 867 men of the Health Professionals Follow-up Study followed from 1986 to 2010

	Traditional Mediterranean diet score[a]				
	Events	**Diet score of 0–3 (low adherence)**	**Diet score of 4–5 (moderate adherence)**	**Diet score of 6–9 (high adherence)**	p_{trend}
Total	6220	2111	2055	2054	
Age-Adj HR (95% CI)[b]		1.00	1.03 (0.97–1.09)	1.01 (0.95–1.07)	0.82
MV-Adj HR (95% CI)[c]		1.00	1.00 (0.94–1.07)	0.95 (0.90–1.02)	0.13
Advanced[d]	1032	356	338	338	
Age-Adj HR (95% CI)[b]		1.00	0.95 (0.82–1.11)	0.96 (0.82–1.11)	0.65
MV-Adj HR (95% CI)[c]		1.00	0.95 (0.82–1.11)	0.95 (0.81–1.11)	0.56
Lethal[e]	783	272	250	261	
Age-Adj HR (95% CI)[b]		1.00	0.90 (0.76–1.07)	0.95 (0.80–1.13)	0.65
MV-Adj HR (95% CI)[c]		1.00	0.90 (0.76–1.08)	0.95 (0.79–1.13)	0.65
Fatal	625	216	198	211	
Age-Adj HR (95% CI)[b]		1.00	0.89 (0.73–1.08)	0.96 (0.79–1.16)	0.83
MV-Adj HR (95% CI)[c]		1.00	0.90 (0.74–1.10)	0.98 (0.80–1.19)	0.98
Gleason score 2–6	3028	1025	986	1017	
Age-Adj HR (95% CI)[b]		1.00	1.06 (0.97–1.16)	1.07 (0.98–1.17)	0.14
MV-Adj HR (95% CI)[c]		1.00	1.01 (0.92–1.10)	0.96 (0.88–1.06)	0.37
Gleason score ≥7	1920	650	613	657	
Age-Adj HR (95% CI)[b]		1.00	1.01 (0.90–1.13)	1.05 (0.94–1.17)	0.29
MV-Adj HR (95% CI)[c]		1.00	0.98 (0.88–1.10)	1.00 (0.89–1.11)	0.94

Adj = adjusted; CI = confidence interval; HR = hazard ratio.

[a] Mediterranean diet scores calculated using cumulative intake of vegetables, fruits and nuts, legumes, cereals, fish and seafood, fat ratio, alcohol, meat products, and dairy products.

[8] Age-adjusted models adjusted for age in months, time period (2-yr intervals), and energy (kilocalories per day, quintiles).

[c] Multivariable models adjusted for age in months, time period (2-yr intervals), energy (kilocalories per day, quintiles), body mass index (<25, 25 to <30, ≥30), vigorous physical activity (<1, 1 to <3, and ≥3 h/wk), and smoking status (never, former, current), and prostate-specific antigen screening history (yes, no, or unknown). Adjustment for race, height, history of diabetes, family history of prostate cancer, and multivitamin use did not change the effect estimates and were left out of the final model.

[d] Advanced disease includes stage T3b-4, N1, M1, or prostate cancer-specific death.

[e] Lethal disease includes metastasis to bone or other organs at diagnosis or over follow-up or prostate cancer-specific death.

Table 4

Age-standardized[a] characteristics by adherence to the Mediterranean diet pattern among 4538 men with nonmetastatic prostate cancer in the Health Professionals Follow-Up Study

	Diet score of 0–3 (low adherence)	Diet score of 4–5 (moderate adherence)	Diet score of 6–9 (high adherence)
Participants, %	33.2	37.0	29.8
Age at diagnosis, yr, mean	69.0	69.4	69.7
Clinical stage, %			
T1	57.2	58.1	61.5
T2	39.3	38.6	35.2
T3 (excluding T3b)	3.5	3.3	3.3
Gleason score, %			
<7	67.0	63.9	64.6
7	24.7	25.8	27.7
>7	8.3	10.3	7.8
Primary treatment, %			
Radical prostatectomy	48.3	49.5	48.2
EBRT or brachytherapy	36.5	36.5	38.6
Hormones	5.8	4.9	4.7
Watchful waiting	7.2	7.1	7.7
Other	2.2	2.1	0.8
PSA at diagnosis among cases diagnosed after 1994, median (25th and 75th percentile)	6.7 (4.9–9.9)	6.5 (4.7–9.4)	6.2 (4.7–9.0)
Southern European ancestry, %	18.2	22.4	24.4
Current smoker, %	6.6	4.4	2.4
Past smoker, %	47.4	49.2	48.9
BMI, kg/m^2, mean	26.2	25.8	25.2
Height, cm, mean	70.1	70.0	70.0
Diabetes, %	7.7	7.3	6.5
Family history of prostate cancer, %	9.5	11.6	10.7
Vigorous exercise, h/wk	1.1	1.4	1.9
Current multivitamin use, %	53.0	57.2	63.0
Current vitamin E use, %	35.8	38.9	45.1
Total calories, kcal, mean	2037.5	1967.0	1916.5
Dietary intakes			
Vegetables, servings/day	2.5	3.4	4.7
Legumes, servings/day	0.3	0.5	0.7
Fruits, servings/day	2.0	2.7	3.4
Nuts, servings/day	0.4	0.5	0.6
Cereals, servings/day	2.9	3.6	3.9
Whole grains only, servings/day	1.7	2.1	2.6
Fish, servings/day	0.2	0.4	0.5

	Diet score of 0–3 (low adherence)	Diet score of 4–5 (moderate adherence)	Diet score of 6–9 (high adherence)
Meat, servings/day	1.2	0.9	0.5
Dairy, servings/day	2.8	2.1	1.5
Alcohol, grams per day	11.3	12.0	12.9
Olive oil, servings/week[b]	1.3	2.0	2.7
Tomatoes, juice, salsa, servings/week	3.0	3.8	4.9
Tomato sauce, servings/week	0.8	0.9	1.2
Garlic, servings/week	0.8	1.1	1.7
Coffee, servings/day	1.7	1.7	1.6
Ratio of polyunsaturated to saturated fat, g/d	0.5	0.6	0.8
Ratio of monounsaturated to saturated fat, g/d	1.1	1.3	1.4

BMI = body mass index; EBRT = external beam radiation therapy; PSA = prostate-specific antigen.

[a] Age-standardized to the age distribution of the study population at prostate cancer diagnosis.

[b] Includes olive oil added to food, bread, or used in salad dressing, and not that used in cooking.

Table 5

Mediterranean diet and prostate-specific and all-cause mortality among 4538 men diagnosed with prostate cancer in the Health Professionals Follow-Up Study, followed from 1986 to 2010

	Traditional Mediterranean diet score[a]				
	Events	**Diet score of 0–3 (low adherence)**	**Diet score of 4–5 (moderate adherence)**	**Diet score of 6–9 (high adherence)**	p_{trend}
Lethal prostate cancer[b]	353	118	127	108	
Age-Adj HR (95% CI)[c]		1.00	1.10 (0.85–1.42)	0.97 (0.75–1.27)	0.74
MV-Adj HR (95% CI)[d]		1.00	1.17 (0.90–1.50)	0.98 (0.75–1.29)	0.76
Fatal prostate cancer	263	91	87	85	
Age-Adj HR (95% CI)[c]		1.00	0.96 (0.72–1.29)	0.97 (0.72–1.30)	0.87
MV-Adj HR (95% CI)[d]		1.00	1.06 (0.79–1.43)	1.01 (0.75–1.38)	0.95
All-cause mortality	1181	455	400	326	
Age-Adj HR (95% CI)[c]		1.00	0.86 (0.75–0.98)	0.69 (0.60–0.80)	<0.0001
MV-Adj HR (95% CI)[d]		1.00	0.92 (0.80–1.05)	0.78 (0.67–0.90)	0.0007

Adj = adjusted; CI = confidence interval; HR = hazard ratio.

[a] Mediterranean diet scores calculated using cumulative intake of vegetables, fruits and nuts, legumes, cereals, fish and seafood, fat ratio, alcohol, meat products, and dairy products.

[b] Lethal disease includes metastasis to bone or other organs at diagnosis or over follow-up or prostate cancer-specific death.

[c] Age-adjusted models adjusted for age at diagnosis, time period (2-yr intervals), time since diagnosis to FFQ (years; continuous), and energy (kilocalories per day, quartiles).

[d] Multivariable models adjusted for age at diagnosis (years), time period (2-yr intervals), time since diagnosis to FFQ (years; continuous), energy (kilocalories per day, quartiles), body mass index (<25, 25 to <30, ≥30), vigorous physical activity (<1, 1 to <3, and ≥3 h/wk), and smoking status (never, former, current), clinical stage, Gleason score, and treatment. Adjustment for race, height, history of (type 1 or 2) diabetes, family history of prostate cancer, multivitamin use did not change the effect estimates for lethal prostate cancer and were left out of the final model. Additional adjustment for parental history of myocardial infarction before age 60 yr, high blood pressure at diagnosis, and elevated cholesterol at diagnosis, all defined as yes or no, did not affect the estimates for all-cause mortality and these variables were omitted. Prediagnostic Mediterranean diet score did not affect estimates and were excluded from this model.

Eur Urol. Author manuscript; available in PMC 2015 May 01.