Adherence to the Mediterranean Diet and Risks of Prostate and Bladder Cancer in the Netherlands Cohort Study

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Adherence to the Mediterranean Diet and Risks of Prostate and Bladder Cancer in the Netherlands Cohort Study

Maya Schulpen[1] and Piet A. van den Brandt[1,2]

Abstract

Background: Prostate cancer and urinary bladder cancer are frequently occurring cancers with few risk factors identified. We examined the relation of Mediterranean diet (MD) adherence with risks of prostate and bladder cancer in the Netherlands Cohort Study (NLCS).

Methods: Data were available for 58,279 men and 62,573 women, who completed a baseline questionnaire on diet and other cancer risk factors. Multiple MD scores, including the alternate Mediterranean diet score without alcohol (aMEDr), were calculated to assess MD adherence. After 20.3 years of follow-up, 3,868 prostate cancer cases (advanced: 1,256) and 1,884 bladder cancer cases could be included in multivariable Cox proportional hazards analyses.

Results: aMEDr was not associated with advanced prostate cancer risk [hazard ratio $(HR)_{per\ 2\text{-}point\ increment}$ (95% confidence interval, 95% CI) = 1.06 (0.96–1.17)]. In contrast, higher aMEDr values were associated with a significantly increased risk of nonadvanced prostate cancer (P_{trend} = 0.04). For bladder cancer risk, no association was observed with aMEDr [$HR_{per\ 2\text{-}point\ increment}$ (95% CI) = 1.00 (0.92–1.09)]. Absolute scores based on the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) dietary recommendations were not associated with prostate or bladder cancer risk.

Conclusions: MD adherence, measured by aMEDr or other MD scores, was not associated with decreased risks of advanced prostate cancer and bladder cancer in the NLCS. Higher levels of care-seeking behavior, screening attendance, and prostate cancer awareness in higher educated men with healthier lifestyles could potentially explain the positive associations observed for nonadvanced prostate cancer risk.

Impact: MD adherence does not seem to reduce the risk of (advanced) prostate cancer or bladder cancer.

Introduction

Worldwide, cancers of the prostate and urinary bladder were estimated to be the second and tenth most commonly diagnosed cancer types in 2018 (1). Together, these cancer types were responsible for over half a million deaths in this year (1). So far, only advancing age, African-American race, family history of prostate cancer, and genetic predisposition have been identified as established risk factors for prostate cancer (2, 3). Tobacco smoking is the most important risk factor for bladder cancer (4). Other bladder cancer risk factors include *Schistosoma haematobium* infection, environmental and occupational exposure to chemicals, and exposure to arsenic in drinking water (5). The high incidences, slow disease development and progression (prostate cancer), and high recurrence rates (bladder cancer), make prostate and bladder cancer suitable targets for preventive approaches (6–8).

The traditional Mediterranean dietary pattern (MD) is mainly based on plant foods. Intakes of vegetables, legumes, fruits, nuts, whole grains, fish, and monounsaturated fatty acids (MUFA, from olive oil) are high in the MD, whereas animal foods (e.g., meats and dairy products) are consumed in limited amounts. Typically, alcohol is consumed in moderation and usually in the form of wine during meals (9–11).

Prostate cancer is a disease with a heterogeneous nature. Advanced and more aggressive prostate tumors may etiologically differ from early, screening-detected forms that otherwise might never have become clinically relevant (2). Risk factors for prostate cancer subtypes (defined by grade, stage, or survival) may differ as they may exert their effect via different biological pathways (12). Therefore, effects of potential risk factors on advanced prostate cancer risk are of primary interest. Up until now, two prospective cohort studies from the United States have evaluated the relation of *a priori* defined MD adherence with advanced prostate cancer risk and did not observe an association (13, 14). In contrast to the results for advanced prostate cancer, the prospective evidence suggests that MD adherence might be associated with a reduced risk of (invasive) bladder cancer/urothelial cell carcinoma (UCC; refs. 15, 16). However, the inverse associations were not statistically significant.

In this analysis of the Netherlands Cohort Study (NLCS), we examined associations between *a priori* defined MD adherence and risks of prostate and urinary bladder cancer. Associations were compared for subtypes of the investigated cancer sites

[1]Department of Epidemiology, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands. [2]Department of Epidemiology, CAPHRI- School for Public Health and Primary Care, Maastricht University Medical Centre, Maastricht, the Netherlands.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Maya Schulpen, Maastricht University, P.O. Box 616, 6200 MD Maastricht, the Netherlands. Phone: 31-43-3882391; E-mail: maya.schulpen@maastrichtuniversity.nl

Cancer Epidemiol Biomarkers Prev 2019;28:1480–8

doi: 10.1158/1055-9965.EPI-19-0224

classified by stage at diagnosis (prostate cancer) or malignancy grade (bladder cancer). In addition, the effect of exclusion of alcohol from the MD scores was evaluated and performances of the relative MD scores were compared with those of absolute scores based on the dietary recommendations to prevent cancer issued by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).

Materials and Methods

Study population and cancer follow-up

The prospective NLCS includes 58,279 men and 62,573 women, ages 55 to 69 years (17–20). Study participants consented to participate by completing a self-administered baseline questionnaire on diet and other cancer risk factors in September 1986. A case-cohort approach was applied to process and analyze the data efficiently (17, 20, 21). A subcohort ($N = 5{,}000$) was randomly drawn just after baseline to estimate accumulated person-years at risk, whereas cases originated from the entire cohort. Subcohort members were followed-up biennially for vital status. The NLCS was approved by the institutional review boards from Maastricht University and the Netherlands Organization for Applied Scientific Research, and was conducted in accordance with the Declaration of Helsinki.

Incident cancer cases were detected annually for 20.3 years of follow-up (baseline until 31 December 2006) through record linkage with the Netherlands Cancer Registry and the nationwide Dutch Pathology Registry (PALGA; ref. 18). In total, 3,978 prostate cancer cases (ICD-O-3 code C61), 2,049 bladder cancer cases (ICD-O-3 code C67), and 4,084 subcohort members (men: 2,057, women: 2,027) were eligible for inclusion in the present analyses (Supplementary Figs. S1 and S2). Prostate cancer cases were classified as nonadvanced ($N = 2{,}397$, stages T1/T2, N0, and M0) or advanced ($N = 1{,}294$, stages T3/T4 or N+ or M1) at diagnosis, whereas bladder cancer cases were categorized in noninvasive ($N = 1{,}053$, malignancy grade 2) and invasive ($N = 996$, malignancy grade 3) subtypes. All included cases were microscopically confirmed. Furthermore, eligible cases and subcohort members did not have prevalent cancer at baseline (except skin cancer), and had complete and consistent data available on diet, alcohol, and MD adherence.

Exposure assessment

At baseline, participants were asked about their usual dietary intake during the previous year via a validated, 150-item, semi-quantitative food frequency questionnaire (FFQ; refs. 19, 22). Nutrient intakes were derived from the FFQ data utilizing the 1986 Dutch food composition (NEVO) table (23).

Mediterranean diet adherence

The alternate and modified Mediterranean diet scores (aMED and mMED, respectively) were calculated to estimate the relative level of MD adherence (24–26). These scores are adaptations of the traditional Mediterranean diet score (tMED) created by Trichopoulou and colleagues (27, 28) and are each composed of 9 dietary components. For aMED (24, 26), 1 point (and 0 otherwise) is assigned to mean daily intakes at or above the sex-specific median of vegetables (excluding potatoes), legumes, fruits, nuts, whole grains, fish, and the ratio of MUFA to saturated fatty acids (SFA). Inverse scoring is applied to red and processed meats. Finally, 1 point can be obtained for a moderate alcohol consumption, defined as 5 to 25 g/day (24, 26). mMED (25) differs from aMED as follows: fruits and nuts are combined, total intakes of cereal and meat are considered, dairy intake is included (1 point if below sex-specific median), and the ratio of unsaturated fatty acids (MUFA + polyunsaturated fatty acids) to SFA replaces the MUFA:SFA ratio. Furthermore, other cut-offs are used to define moderate alcohol consumption (men: 10–50 g/day, women: 5–25 g/day; ref. 25). Before calculation of the MD scores, food intakes were standardized to daily energy intakes of 2,000 kcal (women) and 2,500 kcal (men; refs. 26, 27). aMED and mMED range from 0 to 9 points (lowest to highest MD adherence). Because alcohol consumption has been associated with increased risks of several types of cancer (29), we also created aMED and mMED variants without alcohol (aMEDr and mMEDr, respectively) ranging from 0 to 8 points.

Statistical analyses

We evaluated relations between MD adherence and risks of prostate and bladder cancer (subtypes) using Cox proportional hazards models with duration of follow-up as time scale to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Person-years at risk in the subcohort were calculated from baseline until prostate or bladder cancer diagnosis, death, emigration, loss to follow-up or end of follow-up, whichever came first. Sampling from the cohort introduces additional variance. Therefore, standard errors were calculated using the Huber–White sandwich estimator (30). The proportional hazards assumption was checked by scaled Schoenfeld residuals tests and visual inspection of –ln(–ln) survival plots (31).

We tested associations of MD adherence with risks of prostate and bladder cancer (subtypes) in age- (and sex-)adjusted and fully adjusted analyses, in which MD scores were modelled both categorically [low: 0–3, middle: 4–5, high: 6–8(9)] and continuously (per 2-point increment; refs. 25, 26). Men and women were combined in the models for bladder cancer, because there was no statistically significant interaction by sex. The fully adjusted models concerning prostate cancer risk were adjusted for the following predefined confounders: age at baseline, body mass index (BMI), alcohol consumption (except for models containing MD scores including alcohol), total daily energy intake, highest level of education, and family history of prostate cancer. For bladder cancer risk, sex and cigarette smoking behavior (status, frequency, and duration) were also listed as predefined confounders. Additionally, these analyses were adjusted for family history of bladder cancer instead of prostate cancer. Other confounders considered, but not included (removal resulted in <10% change in the effect estimate of the MD score), were cigarette smoking status (prostate cancer only), non-occupational physical activity, history of diabetes, height (prostate cancer only), tea consumption, and coffee consumption (bladder cancer only). Sex-specific median MD score values in the subcohort were appointed to each adherence category and fitted continuously in Cox regression models to perform trend tests. A competing risks procedure was applied to test for heterogeneity across the prostate and bladder cancer subtypes (32). Standard errors for the observed differences were estimated using a bootstrapping method specifically designed for the case-cohort approach (33).

Model fits of the various MD scores considered (aMEDr and mMEDr, with and without alcohol) were compared using Akaike's Information Criterion (AIC; ref. 34). Because of the equal

Table 1. Baseline characteristics of subcohort members, and cases of prostate and bladder cancer in the Netherlands Cohort Study

	Men					Women		
		Prostate cancer cases		Bladder cancer cases			Bladder cancer cases	
	Subcohort $N = 2,057$	Nonadvanced $N = 2,397$	Advanced $N = 1,294$	Noninvasive $N = 913$	Invasive $N = 831$	Subcohort $N = 2,027$	Noninvasive $N = 140$	Invasive $N = 165$
aMEDr	3.9 (1.6)	4.1 (1.6)	4.0 (1.6)	3.9 (1.6)	3.8 (1.6)	4.0 (1.6)	3.7 (1.5)	4.0 (1.6)
mMEDr	4.0 (1.5)	4.1 (1.5)	4.0 (1.5)	4.0 (1.5)	3.9 (1.5)	4.0 (1.5)	4.0 (1.3)	4.0 (1.4)
Age (years)[a]	61 (7)	62 (7)	62 (7)	62 (7)	62 (6)	61 (7)	61 (7)	62 (7)
Current cigarette smokers (%)	35.1	30.1	30.8	41.1	45.0	21.3	35.7	28.5
Cigarette smoking frequency (cig/day)[a,b]	15 (10)	15 (10)	15 (10)	15 (10)	20 (15)	10 (13)	12 (15)	12 (14)
Cigarette smoking duration (years)[a,b]	36 (17)	34 (19)	34 (18)	39 (16)	40 (15)	30 (20)	35 (19)	35 (19)
Higher vocational education or university (%)	19.3	24.4	20.9	20.1	19.3	9.5	7.1	8.5
Alcohol consumption (g/day)[a]	9.7 (20.9)	10.3 (21.3)	10.5 (20.1)	12.1 (21.7)	12.6 (23.9)	1.6 (7.8)	2.5 (8.7)	2.1 (11.1)
Daily energy intake (kcal)	2162 (501)	2162 (483)	2164 (492)	2154 (475)	2161 (482)	1687 (392)	1621 (357)	1662 (366)
Body mass index (kg/m^2)	24.9 (2.6)	24.9 (2.5)	25.0 (2.5)	25.1 (2.6)	24.9 (2.5)	25.0 (3.5)	25.1 (3.6)	25.1 (3.8)
Non-occupational physical activity (min/day)[a]	62.1 (67.1)	66.4 (62.1)	64.3 (65.7)	62.5 (64.3)	63.6 (67.1)	54.3 (52.9)	53.6 (60.0)	55.7 (60.0)
Family history of prostate cancer (%)	2.4	3.6	3.4	NA	NA	NA	NA	NA
Family history of bladder cancer (%)	0.7	NA	NA	0.9	1.0	1.4	2.9	1.8

NOTE: The % missing values in the total eligible population was <5% for all variables included in this table, with the exception of cigarette smoking frequency in men. Mean (SD) values are reported unless otherwise specified.

[a]Median (IQR) values are reported.

[b]Median (IQR) values for frequency and duration of smoking were based on former and current smokers.

or better performance of aMEDr compared with mMEDr in both the current and previous NLCS analyses (35–37), the Results section of this article mainly focuses on associations with aMEDr and subgroup analyses were only performed using this score. We preferred the aMED variant without alcohol (aMEDr), because alcohol consumption is a risk factor for several types of cancer (29).

Potential effect modification by sex (bladder cancer only), cigarette smoking status (bladder cancer only), alcohol consumption, BMI, educational level, and family history of prostate/bladder cancer was explored by testing the statistical significance of interaction terms between these factors and aMEDr. In addition, HRs were estimated for strata of the potential effect modifying factors. For prostate cancer risk, we estimated associations with the MD scores within time periods before (1986–1994) and after (1995–2006) the introduction of PSA testing in clinical practice in the Netherlands. Furthermore, the effect of excluding the first 2 years of follow-up was evaluated.

Because of the use of cohort-specific cut-offs, the MD scores used measure relative levels of MD adherence. Therefore, we also evaluated associations of prostate and bladder cancer (subtypes) with an absolute score based on the dietary part of the 2007 cancer prevention recommendations published by the WCRF/AICR (38). The WCRF/AICR score used in this study includes the recommendations concerning intakes of foods and drinks that promote weight gain, plant foods, red and processed meats, alcohol, and salt. When possible, recommendations were operationalized as in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (39, 40). For a detailed description of the scoring method and the absolute cut-offs used we refer to a previous NLCS article (35). The resulting sum score ranged from 0 to 5 points (lowest to highest adherence). In addition, we created a variant of the WCRF/AICR score without the alcohol recommendation that ranged from 0 to 4 points. Fully adjusted HRs and 95% CIs were estimated per SD increase in WCRF/AICR score. For comparison, we also estimated HRs and 95% CIs per SD-increment for the aMED variables (with and without alcohol). Finally, AIC was used to compare model fits of the WCRF/AICR score and aMED variables. All analyses were performed using Stata version 15. Two-sided P values <0.05 were considered statistically significant.

Results

Baseline characteristics of NLCS of subcohort and cases of prostate and bladder cancer

Table 1 compares baseline characteristics of subcohort members with those of prostate and bladder cancer cases. The mean level of MD adherence was similar for cases and subcohort members, except for the slightly lower mean aMEDr value in female noninvasive bladder cancer cases. Compared with subcohort members, prostate cancer cases were less often current smokers, higher educated (particularly nonadvanced prostate cancer), more physically active (particularly nonadvanced prostate cancer), and more likely to have a family history of prostate cancer. When comparing nonadvanced with advanced cases at diagnosis, nonadvanced cases more frequently had a high level of education and were slightly more active. Bladder cancer cases were more often current smokers, consumed higher amounts of alcohol, and reported more commonly a family history of bladder cancer than subcohort members. Patterns were mostly comparable for noninvasive and invasive bladder cancer cases.

Mediterranean diet adherence and risks of prostate and bladder cancer

Fully adjusted associations of MD adherence with prostate and bladder cancer incidence are presented in Tables 2 and 3, respectively. For age- (and sex-)adjusted associations we refer to Supplementary Tables S1 (prostate) and S2 (bladder). The number of subjects included in the Cox models is slightly smaller than the number of eligible participants due to missing values in covariates.

Prostate cancer. Higher MD adherence, measured by aMEDr, was associated with an increased risk of prostate cancer [$HR_{\text{per 2-point increment}}$ (95% CI): 1.09 (1.01–1.17); Table 2], although this positive association was mainly present in nonadvanced cases.

Table 2. Fully adjusted associations of aMED and mMED (including and excluding alcohol) with prostate cancer risk in the Netherlands Cohort Study

		Prostate cancer								
		All			Nonadvanced			Advanced		
	$PY_{subcohort}$	Cases	HR (95% CI)[a]	AIC	Cases	HR (95% CI)[a]	AIC	Cases	HR (95% CI)[a]	AIC
aMEDr										
0–3	12,637	1,473	1.00		854	1.00		497	1.00	
4–5	13,363	1,713	1.09 (0.96–1.24)		1,048	1.14 (0.99–1.31)		545	1.03 (0.88–1.21)	
6–8	4,817	682	1.14 (0.96–1.36)	55,789	427	1.22 (1.01–1.48)	33,513	214	1.08 (0.87–1.35)	18,198
P_{trend}			0.139			0.037			0.483	
Continuous, per 2 pts	30,816	3,868	1.09 (1.01–1.17)	55,780	2,329	1.12 (1.04–1.22)	33,505	1,256	1.06 (0.96–1.17)	18,195
aMED[b]										
0–3	9,833	1,156	1.00		666	1.00		392	1.00	
4–5	13,722	1,661	1.03 (0.89–1.18)		1,008	1.07 (0.92–1.25)		528	0.97 (0.81–1.15)	
6–9	7,261	1,051	1.19 (1.02–1.40)	55,778	655	1.28 (1.08–1.53)	33,505	336	1.14 (0.93–1.39)	18,192
P_{trend}			0.065			0.012			0.376	
Continuous, per 2 pts	30,816	3,868	1.09 (1.01–1.17)	55,777	2,329	1.12 (1.04–1.21)	33,503	1,256	1.07 (0.98–1.17)	18,192
mMEDr										
0–3	11,536	1,329	1.00		790	1.00		437	1.00	
4–5	14,176	1,857	1.10 (0.97–1.26)		1,111	1.11 (0.96–1.28)		614	1.12 (0.95–1.32)	
6–8	5,104	682	1.10 (0.92–1.31)	55,790	428	1.17 (0.97–1.41)	33,519	205	1.01 (0.81–1.26)	18,196
P_{trend}			0.285			0.111			0.889	
Continuous, per 2 pts	30,816	3,868	1.07 (0.99–1.16)	55,787	2,329	1.11 (1.02–1.21)	33,511	1,256	1.02 (0.92–1.13)	18,197
mMED[b]										
0–3	8,128	955	1.00		571	1.00		310	1.00	
4–5	14,828	1,817	1.00 (0.87–1.16)		1,069	0.99 (0.84–1.16)		612	1.05 (0.87–1.26)	
6–9	7,860	1,096	1.12 (0.95–1.32)	55,788	689	1.18 (0.99–1.41)	33,512	334	1.07 (0.87–1.31)	18,197
P_{trend}			0.122			0.034			0.577	
Continuous, per 2 pts	30,816	3,868	1.07 (1.00–1.16)	55,784	2,329	1.11 (1.02–1.20)	33,509	1,256	1.04 (0.95–1.14)	18,195

Abbreviation: $PY_{subcohort}$, person-years in the subcohort.
[a]Adjusted for age at baseline (years), body mass index (kg/m^2), alcohol consumption (g/day), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and family history of prostate cancer (no, yes).
[b]Not adjusted for alcohol consumption.

For nonadvanced prostate cancer risk, the HR (95% CI) comparing high to low aMEDr values was 1.22 (1.01–1.48) with a significant test for trend ($P = 0.04$). However, aMEDr was not significantly associated with the risk of advanced prostate cancer [$HR_{per\ 2\text{-}point\ increment}$ (95% CI): 1.06 (0.96–1.17)]. Despite this difference between the prostate cancer subtypes, tests for heterogeneity were not statistically significant. Associations of similar directions were observed when MD adherence was assessed using mMEDr and inclusion of alcohol in the MD scores did not notably change the results. Comparison of model performances showed equal or better (nonadvanced prostate cancer) fits for aMEDr compared with mMEDr (Table 2). In addition, model fits were generally better for scores with alcohol than scores without alcohol.

Associations of aMEDr with risks of nonadvanced and advanced prostate cancer did not significantly differ across strata of potential effect modifiers (Table 4). Nevertheless, increasing aMEDr was associated with a significantly increased risk of both prostate cancer subtypes among men in the highest education category, whereas there was no clear evidence of an association in the other education categories. Results were comparable after exclusion of the first 2 years of follow-up [$HR_{per\ 2\text{-}point\ increment\ in\ aMEDr}$: 1.09 (total), 1.13 (nonadvanced), 1.06 (advanced)]. In addition, the strength of the associations did not significantly differ before (1986–1994) and after (1995–2006) the introduction of PSA testing in clinical practice in the Netherlands (Table 4). However, the positive association between aMEDr and nonadvanced prostate cancer risk was only statistically significant in the late period (1995–2006).

Bladder cancer. MD adherence was not significantly associated with bladder cancer risk, regardless of the MD score used (Table 3). HRs (95% CIs) per 2-point increase in aMEDr were 1.00 (0.92–1.09), 1.01 (0.92–1.12), and 0.99 (0.89–1.09) for total, noninvasive, and invasive bladder cancer, respectively. In contrast to the fully adjusted analyses, inverse trends (not always significant) seemed to be present between MD adherence and risks of total and invasive bladder cancer in age- and sex-adjusted analyses ($P = 0.04$ for mMED and invasive bladder cancer; Supplementary Table S2). Comparable performances were observed for models containing aMEDr and mMEDr (Table 3). Furthermore, MD scores without alcohol fitted equally or better than their equivalents including alcohol.

There was no evidence of effect modification by sex, cigarette smoking status, alcohol consumption, educational level, and family history of bladder cancer (Table 5). Higher aMEDr values seemed to be associated with a nonsignificantly decreased risk of bladder cancer in subjects with a normal BMI, but not in overweight or obese subjects [$P_{interaction} = 0.026$ (total), 0.037 (noninvasive), 0.128 (invasive)]. Associations did not essentially change after exclusion of the first 2 years of follow-up [$HR_{per\ 2\text{-}point\ increment\ in\ aMEDr}$: 1.01 (total), 1.02 (noninvasive), 1.00 (invasive)].

Dietary WCRF/AICR recommendations and risks of prostate and bladder cancer

Because values of aMED indices are population-dependent, we compared these indices to absolute WCRF/AICR scores (Table 6). The WCRF/AICR scores were not significantly associated with prostate and bladder cancer risk, but as with the aMED indices, associations with prostate cancer risk were in the positive direction. For prostate cancer risk, WCRF/AICR scores had worse model fits compared with aMED indices, particularly when considering the nonadvanced subtype (Supplementary Table S3).

Table 3. Fully adjusted associations of aMED and mMED (including and excluding alcohol) with bladder cancer risk in the Netherlands Cohort Study

		Bladder cancer								
		All			Noninvasive			Invasive		
	$PY_{subcohort}$	Cases	HR (95% CI)[a]	AIC	Cases	HR (95% CI)[a]	AIC	Cases	HR (95% CI)[a]	AIC
aMEDr										
0–3	24,302	790	1.00		398	1.00		392	1.00	
4–5	28,005	796	0.95 (0.82–1.09)		418	0.98 (0.83–1.17)		378	0.91 (0.76–1.08)	
6–8	11,055	298	1.00 (0.83–1.21)	28,540	156	1.02 (0.81–1.28)	14,711	142	0.98 (0.77–1.24)	13,840
P_{trend}			0.931			0.898			0.783	
Continuous, per 2 pts	63,362	1,884	1.00 (0.92–1.09)	28,540	972	1.01 (0.92–1.12)	14,709	912	0.99 (0.89–1.09)	13,840
aMED[b]										
0–3	20,107	646	1.00		316	1.00		330	1.00	
4–5	28,038	795	0.90 (0.78–1.05)		422	0.98 (0.81–1.17)		373	0.84 (0.70–1.00)	
6–9	15,217	443	0.99 (0.83–1.18)	28,544	234	1.05 (0.85–1.29)	14,712	209	0.93 (0.75–1.16)	13,840
P_{trend}			0.591			0.850			0.279	
Continuous, per 2 pts	63,362	1,884	1.00 (0.93–1.08)	28,546	972	1.03 (0.94–1.14)	14,710	912	0.97 (0.88–1.07)	13,843
mMEDr										
0–3	22,721	725	1.00		360	1.00		365	1.00	
4–5	30,384	882	0.98 (0.85–1.13)		465	1.04 (0.87–1.23)		417	0.92 (0.77–1.10)	
6–8	10,256	277	0.90 (0.74–1.09)	28,539	147	0.94 (0.74–1.19)	14,710	130	0.85 (0.67–1.09)	13,839
P_{trend}			0.273			0.645			0.182	
Continuous, per 2 pts	63,362	1,884	0.97 (0.89–1.06)	28,539	972	1.00 (0.90–1.11)	14,709	912	0.95 (0.85–1.06)	13,839
mMED[b]										
0–3	17,618	531	1.00		265	1.00		266	1.00	
4–5	30,953	888	0.91 (0.78–1.06)		462	0.95 (0.78–1.14)		426	0.87 (0.72–1.05)	
6–9	14,791	465	0.95 (0.80–1.14)	28,545	245	0.99 (0.80–1.23)	14,712	220	0.91 (0.73–1.13)	13,842
P_{trend}			0.730			0.954			0.533	
Continuous, per 2 pts	63,362	1,884	0.99 (0.91–1.08)	28,546	972	1.03 (0.93–1.13)	14,710	912	0.96 (0.87–1.07)	13,842

Abbreviation: $PY_{subcohort}$, person-years in the subcohort.

[a]Adjusted for age at baseline (years), sex (men, women), cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (kg/m^2), alcohol consumption (g/day), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and family history of bladder cancer (no, yes).

[b]Not adjusted for alcohol consumption.

Comparable model performances were observed for bladder cancer risk (Supplementary Table S3).

Discussion

In the large prospective NLCS, *a priori* defined MD adherence (aMEDr) was associated with a significantly increased risk of nonadvanced prostate cancer. In contrast, no association was observed with advanced prostate cancer risk. MD adherence was not associated with risks of total, noninvasive, and invasive bladder cancer. Model fits were equal or better for aMEDr compared with mMEDr. In addition, inclusion of alcohol in the MD scores resulted in generally better model fits for prostate cancer risk, whereas the opposite was observed for bladder cancer risk. Finally, adherence to the dietary WCRF/AICR recommendations was not associated with risks of both prostate and bladder cancer.

Previously conducted cohort studies in the United States and Europe consistently found no association between *a priori* defined MD adherence and prostate cancer risk (13, 14, 41, 42). Similar results were obtained when focusing on advanced cases of prostate cancer specifically (13, 14). Case–control studies showed less consistent results. One study observed a significant inverse association between *a priori* defined MD adherence and prostate cancer risk, whereas no relation was present in another study (43, 44). The vulnerability of the case–control design to several types of bias, including recall and selection biases, could potentially explain this inconsistency. Furthermore, prospective cohort studies may also have some limitations. For example, reliance on a single assessment of dietary intake at baseline may lead to exposure misclassification and attenuated associations. Although exposure misclassification could have contributed to the null findings of the previously conducted cohort studies, some cohorts did have updated dietary information available during follow-up (14, 42).

Results of this study were partially in concordance with results of previous cohort studies. We found higher MD adherence to be significantly associated with an increased risk of nonadvanced prostate cancer, whereas there was no evidence of an association with advanced prostate cancer risk. Prostate cancer is a heterogeneous disease with potentially etiologically different subtypes that may differ in risk factors (2, 12, 45). The subgroup of nonadvanced cancers at diagnosis mainly encompasses relatively nonaggressive forms of prostate cancer that progress slowly and might never have become clinically relevant. Approximately half of the diagnosed prostate cancers were estimated to not have caused any harm if they had remained undiagnosed and untreated (45). The prevalence of undiagnosed prostate cancer in elderly men is high, in 47.3% of US White and European men above the age of 80 years incident prostate cancer was detected at autopsy (45). Because of the often indolent nature of nonadvanced prostate cancers, advanced prostate cancer is the subtype of our primary interest. In this study, MD adherence was not significantly associated with advanced prostate cancer risk.

The significant positive associations that we observed between MD adherence and nonadvanced prostate cancer risk could potentially be explained by differences in care-seeking behavior, screening attendance, and prostate cancer awareness related to education and lifestyle. Male NLCS subcohort members with higher MD adherence overall seemed to have a healthier lifestyle

Table 4. Fully adjusted associations of aMEDr (per two-point increment) with prostate cancer risk for various subgroups in the Netherlands Cohort Study

	Prostate cancer					
	All		Nonadvanced		Advanced	
	Cases	HR (95% CI)[a,b]	Cases	HR (95% CI)[a,b]	Cases	HR (95% CI)[a,b]
Overall	3,868	1.09 (1.01–1.17)	2,329	1.12 (1.04–1.22)	1,256	1.06 (0.96–1.17)
Alcohol consumption[c]						
0 g/day	488	1.11 (0.91–1.35)	291	1.10 (0.89–1.37)	154	1.22 (0.93–1.61)
>0–<15.0 g/day	1,891	1.15 (1.03–1.28)	1,135	1.20 (1.06–1.36)	628	1.08 (0.94–1.24)
≥15.0 g/day	1,489	1.02 (0.90–1.16)	903	1.07 (0.93–1.22)	474	0.99 (0.85–1.15)
$P_{interaction}$[d]		0.484		0.506		0.387
Body mass index[e]						
≥18.5–<25.0 kg/m^2	2,054	1.08 (0.97–1.20)	1,256	1.12 (1.00–1.25)	646	1.07 (0.94–1.22)
≥25.0 kg/m^2	1,804	1.10 (0.98–1.23)	1,067	1.14 (1.01–1.29)	608	1.05 (0.92–1.21)
$P_{interaction}$[d]		0.699		0.623		0.897
Highest level of education[f]						
Primary school or lower vocational	1,572	1.03 (0.92–1.17)	929	1.07 (0.93–1.22)	525	0.97 (0.84–1.13)
Secondary school or medium vocational	1,405	1.06 (0.95–1.20)	827	1.12 (0.98–1.27)	470	1.05 (0.91–1.22)
Higher vocational or university	891	1.24 (1.04–1.47)	573	1.26 (1.04–1.52)	261	1.27 (1.01–1.60)
$P_{interaction}$[d]		0.235		0.362		0.188
Family history of prostate cancer[g]						
No	3,731	1.10 (1.02–1.18)	2,244	1.14 (1.05–1.24)	1,214	1.07 (0.97–1.18)
Yes	137	0.85 (0.53–1.38)	85	0.84 (0.50–1.41)	42	0.85 (0.47–1.54)
$P_{interaction}$[d]		0.191		0.164		0.363
Follow-up period						
1986–1994	985	1.06 (0.96–1.18)	455	1.08 (0.95–1.24)	397	1.09 (0.95–1.25)
1995–2006	2,883	1.09 (1.01–1.19)	1,874	1.13 (1.04–1.24)	859	1.05 (0.94–1.17)
$P_{interaction}$[d]		0.611		0.456		0.440

[a]All HRs were estimated per two-point increment in aMEDr.
[b]Adjusted for age at baseline (years), body mass index (kg/m^2), alcohol consumption (g/day), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and family history of prostate cancer (no, yes).
[c]Not adjusted for alcohol consumption.
[d]*P*-values for interaction were obtained by testing the statistical significance of interaction terms between aMEDr and the stratifying covariates in fully adjusted models.
[e]Not adjusted for body mass index.
[f]Not adjusted for highest level of education.
[g]Not adjusted for family history of prostate cancer.

judged by lower levels of smoking and alcohol consumption, and higher levels of physical activity, and were higher educated (36). Higher educated men with a more health-conscious lifestyle may be more aware of prostate cancer and more prone to seek care or attend screenings, resulting in a larger number of nonadvanced prostate cancer diagnoses in this group, part of which never would have become clinically relevant and otherwise would have remained undiagnosed. Nonadvanced prostate cancer cases in our study were more physically active and higher educated than advanced cases and subcohort members, implying a healthier lifestyle. Furthermore, the positive association between MD adherence and nonadvanced prostate cancer risk was strongest and only statistically significant in the highest education category, which fits our hypothesis that nonadvanced prostate tumors are more likely to be detected in highly educated men. Finally, results of our stratified analyses by follow-up period showed that the positive association between MD adherence and nonadvanced prostate cancer risk only reached statistical significance in the period after the introduction of PSA testing in clinical practice in the Netherlands (1995–2006).

Similar to our findings for bladder cancer risk, *a priori* defined MD adherence was not significantly associated with total UCC risk in the prospective EPIC and Melbourne Collaborative Cohort Study (MCCS) cohorts (15, 16). Although not statistically significant, HR estimates for risks of total, nonaggressive, and aggressive UCC in EPIC were suggestive of an inverse association with MD adherence (15). In addition, higher MD adherence seemed to be associated with a decreased risk of invasive UCC ($P = 0.06$), but not superficial UCC, in the Australian MCCS (16). HR estimates in our study were much closer to unity. Residual confounding by cigarette smoking, which is the most important bladder cancer risk factor (4), could (partially) explain the nonsignificant inverse associations between MD adherence and (invasive) UCC risk that were observed in the previously conducted prospective studies. The adjustment for cigarette smoking seemed to be less comprehensive in these studies compared with this study and the inverse associations were restricted to (former and) current smokers. Besides, we also observed (non-significant) inverse associations with invasive bladder cancer risk when we only adjusted our models for age and sex. Very recently, a pooled analysis of 13 prospective cohorts showed that MD adherence was associated with a significantly decreased risk of total, non-muscle-invasive, and muscle-invasive bladder cancer (46). However, this study did not sufficiently adjust for smoking behavior. Finally, an Italian hospital-based case-control study found higher MD adherence to be associated with a significantly decreased UCC risk (47).

In this study, BMI significantly modified the association between MD adherence and risks of total and noninvasive bladder cancer, with nonsignificant inverse associations being observed among subjects with a normal BMI, but not among overweight or obese subjects. An inverse association has been suggested between BMI and levels of urinary 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, particularly in smokers (48). Therefore, subjects with a normal BMI potentially benefit most from the high

Table 5. Fully adjusted associations of aMEDr (per two-point increment) with bladder cancer risk for various subgroups in the Netherlands Cohort Study

	Bladder cancer					
	All		Noninvasive		Invasive	
	Cases	HR (95% CI)[a,b]	Cases	HR (95% CI)[a,b]	Cases	HR (95% CI)[a,b]
Overall	1,884	1.00 (0.92–1.09)	972	1.01 (0.92–1.12)	912	0.99 (0.89–1.09)
Sex[c]						
Men	1,593	1.01 (0.92–1.11)	840	1.04 (0.93–1.16)	753	0.98 (0.87–1.10)
Women	291	0.94 (0.79–1.10)	132	0.86 (0.69–1.08)	159	1.00 (0.81–1.25)
$P_{interaction}$[d]		0.472		0.091		0.622
Cigarette smoking status[e]						
Never	271	0.99 (0.82–1.18)	137	0.93 (0.73–1.18)	134	1.05 (0.83–1.33)
Former	855	1.09 (0.97–1.22)	457	1.10 (0.96–1.27)	398	1.07 (0.92–1.24)
Current	758	0.93 (0.80–1.08)	378	0.98 (0.82–1.16)	380	0.89 (0.74–1.07)
$P_{interaction}$[d]		0.206		0.457		0.151
Alcohol consumption[f]						
0 g/day	234	1.00 (0.82–1.22)	111	0.91 (0.69–1.20)	123	1.09 (0.86–1.38)
>0–<15.0 g/day	888	1.01 (0.90–1.13)	475	1.03 (0.89–1.18)	413	0.98 (0.85–1.14)
≥15.0 g/day	762	0.96 (0.84–1.11)	386	1.00 (0.84–1.18)	376	0.93 (0.78–1.11)
$P_{interaction}$[d]		0.988		0.807		0.661
Body mass index[g]						
≥18.5–<25.0 kg/m^2	1,019	0.92 (0.82–1.03)	513	0.91 (0.79–1.05)	506	0.92 (0.80–1.06)
≥25.0 kg/m^2	857	1.10 (0.97–1.24)	455	1.12 (0.97–1.30)	402	1.07 (0.92–1.26)
$P_{interaction}$[d]		0.026		0.037		0.128
Highest level of education[h]						
Primary school or lower vocational	816	0.91 (0.80–1.04)	410	0.94 (0.80–1.11)	406	0.87 (0.74–1.03)
Secondary school or medium vocational	728	1.03 (0.90–1.16)	384	1.01 (0.87–1.18)	344	1.04 (0.89–1.21)
Higher vocational or university	340	1.20 (0.97–1.48)	178	1.20 (0.92–1.57)	162	1.20 (0.92–1.56)
$P_{interaction}$[d]		0.056		0.303		0.055
Family history of bladder cancer[i,j]						
No	1,862	1.01 (0.93–1.09)				
Yes	22	0.34 (0.05–2.34)				
$P_{interaction}$[d]		0.094				

[a]All HRs were estimated per two-point increment in aMEDr.

[b]Adjusted for age at baseline (years), sex (men, women), cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (kg/m^2), alcohol consumption (g/day), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and family history of bladder cancer (no, yes).

[c]Not adjusted for sex.

[d]*P*-values for interaction were obtained by testing the statistical significance of interaction terms between aMEDr and the stratifying covariates in fully adjusted models.

[e]Not adjusted for cigarette smoking status.

[f]Not adjusted for alcohol consumption.

[g]Not adjusted for body mass index.

[h]Not adjusted for highest level of education.

[i]The analyses stratified by family history of bladder cancer were only performed for total bladder cancer risk because of the low number of cases with a positive family history.

[j]Not adjusted for family history of bladder cancer.

antioxidant content (e.g., vitamins and polyphenols) of the MD (49, 50). However, this interaction could also be a chance finding. The interaction with BMI was not detected in the EPIC cohort (15) and requires attention in future research. The association of MD adherence with bladder cancer risk did not significantly differ across strata of other potential effect modifiers including sex and smoking status.

A major strength of the NLCS is its prospective design and the nearly complete follow-up of 20.3 years. The large number of prostate and bladder cancer cases allowed subtype-specific analyses based on tumor stage/invasiveness at diagnosis, extensive adjustment for confounding, and stratified analyses for potential effect modifying factors. Despite the comprehensive adjustment for cigarette smoking habits in the analyses concerning bladder cancer risk, residual confounding by smoking (bladder cancer) or unmeasured factors (prostate and bladder cancer) could still have affected our results. For example, we had no information about PSA testing. Nevertheless, associations of MD adherence with prostate cancer risk did not statistically significantly differ in time periods before and after the introduction of PSA testing in the Netherlands, making a relevant effect on our results unlikely. Moreover, we were not able to adjust the analyses concerning bladder cancer risk for environmental and occupational exposures to chemicals or exposure to arsenic in drinking water. A final strength of our study includes the high quality of the dietary data. The single baseline measurement of the NLCS-FFQ was shown to perform adequately when compared with 9-day dietary records and dietary habits were reproducible for over at least 5 years (19, 22). However, changes in dietary habits and confounding factors after baseline as well as measurement errors may have attenuated associations. The population-dependent assignment of scores is a weakness of the MD scores that we used to assess MD adherence. Therefore, high MD score values may not necessarily represent a truly Mediterranean way of eating, especially in the Netherlands and other non-Mediterranean countries. Nonetheless, largely similar results were obtained when we used absolute scores based on the WCRF/AICR dietary recommendations

Table 6. Fully adjusted associations of the absolute WCRF/AICR score and aMED (per SD-increment) with risks of prostate and bladder cancer in the Netherlands Cohort Study

	Prostate cancer			Bladder cancer		
	All	Nonadvanced	Advanced	All	Noninvasive	Invasive
	HR_{SD} (95% CI)[a,b]	HR_{SD} (95% CI)[a,b]	HR_{SD} (95% CI)[a,b]	HR_{SD} (95% CI)[a,c]	HR_{SD} (95% CI)[a,c]	HR_{SD} (95% CI)[a,c]
$PY_{subcohort}$/cases[d]	30,049/3,763	30,049/2,272	30,049/1,212	61,976/1,836	61,976/945	61,976/891
Excluding alcohol						
WCRF/AICR score[e]	1.03 (0.97–1.09)	1.03 (0.97–1.10)	1.05 (0.97–1.13)	0.98 (0.92–1.05)	0.99 (0.91–1.07)	0.98 (0.90–1.06)
aMEDr	1.07 (1.01–1.13)	1.09 (1.03–1.17)	1.05 (0.98–1.14)	0.99 (0.93–1.06)	1.00 (0.93–1.09)	0.97 (0.90–1.06)
Including alcohol						
WCRF/AICR score[e,f]	1.04 (0.97–1.10)	1.04 (0.98–1.11)	1.04 (0.97–1.13)	0.95 (0.89–1.02)	0.97 (0.90–1.05)	0.94 (0.86–1.02)
aMED[f]	1.07 (1.01–1.14)	1.10 (1.03–1.17)	1.07 (0.99–1.15)	0.99 (0.93–1.06)	1.02 (0.95–1.11)	0.96 (0.89–1.04)

Abbreviation: $PY_{subcohort}$, person-years in the subcohort.

[a]HRs were estimated per SD-increment in the scores.

[b]Adjusted for age at baseline (years), body mass index (kg/m^2), alcohol consumption (g/day), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and family history of prostate cancer (no, yes).

[c]Adjusted for age at baseline (years), sex (men, women), cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (kg/m^2), alcohol consumption (g/day), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and family history of bladder cancer (no, yes).

[d]A lower number of subjects could be included in these analyses as a result of missing values for salt intake.

[e]Score based on WCRF/AICR dietary recommendations to prevent cancer.

[f]Not adjusted for alcohol consumption.

to prevent cancer. In addition, aMED-containing models performed equally well or better than models containing WCRF/AICR scores in our study population.

In conclusion, high adherence to the MD was not associated with decreased risks of advanced prostate cancer as well as total, noninvasive, and invasive bladder cancer in the NLCS. The positive associations that we observed between MD adherence and nonadvanced prostate cancer risk potentially resulted from higher levels of care-seeking behavior, screening attendance, and prostate cancer awareness in higher educated men with healthier lifestyles, causing a larger number of nonadvanced prostate cancer diagnoses in this group. Therefore, we recommend that future studies on dietary factors and prostate cancer risk also report results specifically for advanced prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.A. van den Brandt
Development of methodology: P.A. van den Brandt
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.A. van den Brandt
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Schulpen
Writing, review, and/or revision of the manuscript: M. Schulpen
Study supervision: P.A. van den Brandt

Acknowledgments

This study was funded by the Wereld Kanker Onderzoek Fonds Nederland (WCRF-NL), as part of the World Cancer Research Fund International grant program (Grant No. 2015/1390 to P.A. van den Brandt). We are indebted to the participants of the Netherlands Cohort Study (NLCS) and further wish to thank the Netherlands Cancer Registry and the Dutch Pathology Registry. Additionally, NLCS staff members are acknowledged for their valuable assistance and advice.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 26, 2019; revised May 7, 2019; accepted June 19, 2019; published first June 24, 2019.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. Front Biosci 2006;11:1388–413.
3. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The epidemiology of prostate cancer. Cold Spring Harb Perspect Med 2018;8. doi: 10.1101/cshperspect.a030361.
4. Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of bladder cancer: a systematic review and contemporary update of risk factors in 2018. Eur Urol 2018;74:784–95.
5. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project expert report 2018. Diet, nutrition, physical activity and bladder cancer. 2018. Available from: https://www.wcrf.org/dietandcancer.
6. Crawford ED. Understanding the epidemiology, natural history, and key pathways involved in prostate cancer. Urology 2009;73(5 Suppl):S4–10.
7. Clark PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, Herr HW, et al. Bladder cancer. J Natl Compr Canc Netw 2013;11:446–75.
8. Al-Zalabani AH, Stewart KF, Wesselius A, Schols AM, Zeegers MP. Modifiable risk factors for the prevention of bladder cancer: a systematic review of meta-analyses. Eur J Epidemiol 2016;31:811–51.
9. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr 1995;61(6 Suppl):1402S–6S.
10. Trichopoulou A, Lagiou P. Healthy traditional Mediterranean diet: an expression of culture, history, and lifestyle. Nutr Rev 1997;55(11 Pt 1):383–9.
11. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation 2009;119:1093–100.
12. 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.

13. Bosire C, Stampfer MJ, Subar AF, Park Y, Kirkpatrick SI, Chiuve SE, 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.
14. Kenfield SA, DuPre N, Richman EL, Stampfer MJ, Chan JM, Giovannucci EL. Mediterranean diet and prostate cancer risk and mortality in the Health Professionals Follow-up Study. Eur Urol 2014;65:887–94.
15. Buckland G, Ros MM, Roswall N, Bueno-de-Mesquita HB, Travier N, Tjonneland A, et al. Adherence to the Mediterranean diet and risk of bladder cancer in the EPIC cohort study. Int J Cancer 2014;134:2504–11.
16. Dugue PA, Hodge AM, Brinkman MT, Bassett JK, Shivappa N, Hebert JR, et al. Association between selected dietary scores and the risk of urothelial cell carcinoma: a prospective cohort study. Int J Cancer 2016;139: 1251–60.
17. van den Brandt PA, Goldbohm RA, van 't Veer P, Volovics A, Hermus RJ, Sturmans F. A large-scale prospective cohort study on diet and cancer in the Netherlands. J Clin Epidemiol 1990;43:285–95.
18. van den Brandt PA, Schouten LJ, Goldbohm RA, Dorant E, Hunen PM. Development of a record linkage protocol for use in the Dutch Cancer Registry for Epidemiological Research. Int J Epidemiol 1990;19: 553–8.
19. Goldbohm RA, van den Brandt PA, Brants HA, van 't Veer P, Al M, Sturmans F, et al. Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. Eur J Clin Nutr 1994;48:253–65.
20. Volovics A, van den Brandt PA. Methods for the analyses of case-cohort studies. Biometrical J 1997;39:195–214.
21. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika 1986;73:1–11.
22. Goldbohm RA, van 't Veer P, van den Brandt PA, van 't Hof MA, Brants HA, Sturmans F, et al. Reproducibility of a food frequency questionnaire and stability of dietary habits determined from five annually repeated measurements. Eur J Clin Nutr 1995;49:420–9.
23. NEVO. Dutch food composition table 1986–1987. The Hague, the Netherlands: Voorlichtingsbureau voor de Voeding; 1986.
24. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2005;82: 163–73.
25. Trichopoulou A, Orfanos P, Norat T, Bueno-de-Mesquita B, Ocke MC, Peeters PH, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. BMJ 2005;330:991.
26. Mitrou PN, Kipnis V, Thiebaut AC, Reedy J, Subar AF, Wirfalt E, 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.
27. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and overall survival in elderly people. BMJ 1995;311:1457–60.
28. 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.
29. World Cancer Research Fund/American Institute for Cancer Research. Diet, nutrition, physical activity and cancer: a global perspective. Continuous update project expert report 2018. 2018. https://www.wcrf.org/dietandcancer.
30. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Am Stat Assoc 1989;84:1074–8.
31. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.
32. de Vogel S, Bongaerts BW, Wouters KA, Kester AD, Schouten LJ, de Goeij AF, et al. Associations of dietary methyl donor intake with MLH1 promoter hypermethylation and related molecular phenotypes in sporadic colorectal cancer. Carcinogenesis 2008;29:1765–73.
33. Wacholder S, Gail MH, Pee D, Brookmeyer R. Alternative variance and efficiency calculations for the case-cohort design. Biometrika 1989;76: 117–23.
34. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974;AC-19:716–23.
35. van den Brandt PA, Schulpen M. Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. Int J Cancer 2017;140:2220–31.
36. Schulpen M, van den Brandt PA. Adherence to the Mediterranean diet and risk of lung cancer in the Netherlands Cohort Study. Br J Nutr 2018;119: 674–84.
37. Schulpen M, Peeters PH, van den Brandt PA. Mediterranean diet adherence and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. Gastric Cancer 2019;22:663–74.
38. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC: American Institute for Cancer Research; 2007.
39. Romaguera D, Vergnaud AC, Peeters PH, van Gils CH, Chan DS, Ferrari P, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 2012;96: 150–63.
40. Vergnaud AC, Romaguera D, Peeters PH, van Gils CH, Chan DS, Romieu I, et al. Adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines and risk of death in Europe: results from the European Prospective Investigation into Nutrition and Cancer cohort study. Am J Clin Nutr 2013;97:1107–20.
41. Ax E, Garmo H, Grundmark B, Bill-Axelson A, Holmberg L, Becker W, et al. Dietary patterns and prostate cancer risk: report from the population based ULSAM cohort study of Swedish men. Nutr Cancer 2014; 66:77–87.
42. Lavalette C, Adjibade M, Srour B, Sellem L, Fiolet T, Hercberg S, et al. Cancer-specific and general nutritional scores and cancer risk: results from the prospective NutriNet-Sante Cohort. Cancer Res 2018;78: 4427–35.
43. Moller E, Galeone C, Andersson TM, Bellocco R, Adami HO, Andren O, et al. Mediterranean Diet Score and prostate cancer risk in a Swedish population-based case-control study. J Nutr Sci 2013;2:e15.
44. Russo GI, Solinas T, Urzi D, Privitera S, Campisi D, Cocci A, et al. Adherence to Mediterranean diet and prostate cancer risk in Sicily: population-based case-control study. Int J Impot Res 2019;31:269–75.
45. Jahn JL, Giovannucci EL, Stampfer MJ. The high prevalence of undiagnosed prostate cancer at autopsy: implications for epidemiology and treatment of prostate cancer in the prostate-specific antigen-era. Int J Cancer 2015;137: 2795–802.
46. Witlox WJA, van Osch FHM, Brinkman M, Jochems S, Goossens ME, Weiderpass E, et al. An inverse association between the Mediterranean diet and bladder cancer risk: a pooled analysis of 13 cohort studies. Eur J Nutr 2019 Feb 8 [Epub ahead of print].
47. Bravi F, Spei ME, Polesel J, Di Maso M, Montella M, Ferraroni M, et al. Mediterranean diet and bladder cancer risk in Italy. Nutrients 2018;10. doi: 10.3390/nu10081061.
48. Mizoue T, Kasai H, Kubo T, Tokunaga S. Leanness, smoking, and enhanced oxidative DNA damage. Cancer Epidemiol Biomarkers Prev 2006;15: 582–5.
49. Brill JB. The Mediterranean diet and your health. Am J Lifestyle Med 2009; 3:44–56.
50. Verberne L, Bach-Faig A, Buckland G, Serra-Majem L. Association between the Mediterranean diet and cancer risk: a review of observational studies. Nutr Cancer 2010;62:860–70.