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

Maya Schulpen¹ and Piet A. van den Brandt¹²

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-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 (Ptrend = 0.04). For bladder cancer risk, no association was observed with aMEDr [HRper 2-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.
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 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

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subcohort</td>
<td>Prostate cancer cases</td>
<td>Bladder cancer cases</td>
<td>Subcohort</td>
</tr>
<tr>
<td></td>
<td>N = 2,057</td>
<td>N = 2,397</td>
<td>N = 1,294</td>
<td>N = 813</td>
</tr>
<tr>
<td>aMEDr</td>
<td>3.9 (16)</td>
<td>4.1 (16)</td>
<td>4.0 (16)</td>
<td>3.9 (16)</td>
</tr>
<tr>
<td>mMEDr</td>
<td>4.0 (15)</td>
<td>4.1 (15)</td>
<td>4.0 (15)</td>
<td>4.0 (15)</td>
</tr>
<tr>
<td>Age (years)a</td>
<td>61 (7)</td>
<td>62 (7)</td>
<td>62 (7)</td>
<td>62 (7)</td>
</tr>
<tr>
<td>Current cigarette smokers (%)</td>
<td>35.1</td>
<td>30.1</td>
<td>30.8</td>
<td>41.1</td>
</tr>
<tr>
<td>Cigarette smoking frequency (cig/day)b</td>
<td>15 (10)</td>
<td>15 (10)</td>
<td>15 (10)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Cigarette smoking duration (years)b</td>
<td>36 (17)</td>
<td>34 (19)</td>
<td>34 (18)</td>
<td>39 (16)</td>
</tr>
<tr>
<td>Higher vocational education or university (%)</td>
<td>19.3</td>
<td>24.4</td>
<td>20.9</td>
<td>20.1</td>
</tr>
<tr>
<td>Alcohol consumption (g/day)a</td>
<td>9.7 (20.9)</td>
<td>10.3 (21.3)</td>
<td>10.5 (20.3)</td>
<td>12.1 (21.7)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.9 (26.9)</td>
<td>24.9 (25.2)</td>
<td>25.0 (2.5)</td>
<td>25.1 (2.6)</td>
</tr>
<tr>
<td>Daily energy intake (kcal)</td>
<td>216 (501)</td>
<td>216 (485)</td>
<td>216 (492)</td>
<td>215 (475)</td>
</tr>
<tr>
<td>Non-occupational physical activity (min/day)a</td>
<td>62.1 (671)</td>
<td>66.4 (621)</td>
<td>63.5 (67.5)</td>
<td>63.5 (67.1)</td>
</tr>
<tr>
<td>Family history of prostate cancer (%)</td>
<td>2.4</td>
<td>3.6</td>
<td>3.4</td>
<td>NA</td>
</tr>
<tr>
<td>Family history of bladder cancer (%)</td>
<td>0.7</td>
<td>NA</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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.

aMedian (IQR) values are reported.
bMedian (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 prostate cancer, 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 per 2-point increment (95% CI)] 1.09 (1.01–1.17); Table 2], although this positive association was mainly present in nonadvanced cases.
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-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 mMED 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-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 mMEDr 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 present between MD adherence and risks of total 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 mMEDr 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.

**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).
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 remained undiagnosed and untreated (45). The prevalence of undiagnosed prostate cancer in elderly men is high, in 47.3% of cases, whereas 37.5% were estimated to not have caused any harm if they had been undiagnosed prostate cancer in elderly men is high, in 47.3% of cases, whereas 37.5% were estimated to not have caused any harm if they had been.

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.
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 (36). Furthermore, the positive association between MD adherence and nonadvanced prostate cancer risk was strongest among subjects with a normal BMI, but not among overweight or obese subjects. An inverse association has been suggested between MD adherence and nonadvanced prostate cancer (no, yes).

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

<table>
<thead>
<tr>
<th></th>
<th>All Cases</th>
<th>Prostate cancer</th>
<th>Nonadvanced</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HR (95% CI)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Overall</td>
<td>3.868</td>
<td>1.09 (1.01–1.17)</td>
<td>2.329</td>
<td>1.12 (1.04–1.22)</td>
</tr>
<tr>
<td>Alcohol consumption&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 g/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0–15.0 g/day</td>
<td>1.09 (1.01–1.17)</td>
<td>1.11 (0.91–1.35)</td>
<td>291</td>
<td>1.19 (0.89–1.60)</td>
</tr>
<tr>
<td>≥15.0 g/day</td>
<td>1.06 (0.95–1.20)</td>
<td>1.02 (0.90–1.16)</td>
<td>903</td>
<td>1.07 (0.93–1.22)</td>
</tr>
<tr>
<td>Body mass index&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥18.5–25.0 kg/m²</td>
<td>1.08 (0.97–1.20)</td>
<td>1.08 (0.97–1.20)</td>
<td>1.256</td>
<td>1.12 (1.00–1.25)</td>
</tr>
<tr>
<td>≥25.0 kg/m²</td>
<td>1.07 (0.98–1.23)</td>
<td>1.07 (0.98–1.23)</td>
<td>1.067</td>
<td>1.14 (1.01–1.29)</td>
</tr>
<tr>
<td>Highest level of education&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school or lower vocational</td>
<td>1.572</td>
<td>1.03 (0.92–1.17)</td>
<td>929</td>
<td>1.07 (0.93–1.22)</td>
</tr>
<tr>
<td>Secondary school or medium vocational</td>
<td>1.405</td>
<td>1.06 (0.95–1.20)</td>
<td>827</td>
<td>1.12 (0.98–1.27)</td>
</tr>
<tr>
<td>Higher vocational or university</td>
<td>0.891</td>
<td>1.24 (1.04–1.47)</td>
<td>573</td>
<td>1.26 (1.04–1.52)</td>
</tr>
<tr>
<td>Family history of prostate cancer&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3.731</td>
<td>1.10 (1.02–1.18)</td>
<td>2.244</td>
<td>1.14 (1.05–1.24)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.37</td>
<td>0.85 (0.53–1.38)</td>
<td>85</td>
<td>0.84 (0.50–1.41)</td>
</tr>
<tr>
<td>Follow-up period&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1986–1994</td>
<td>2.983</td>
<td>1.09 (1.01–1.19)</td>
<td>1.874</td>
<td>1.13 (1.04–1.24)</td>
</tr>
<tr>
<td>1995–2006</td>
<td>2.983</td>
<td>1.09 (1.01–1.19)</td>
<td>1.874</td>
<td>1.13 (1.04–1.24)</td>
</tr>
</tbody>
</table>

<sup>a</sup>HRs were estimated per two-point increment in aMEDr.
<sup>b</sup>Adjusted for age at baseline (years), body mass index (kg/m²), alcohol consumption (g/day), 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).
<sup>c</sup>Not adjusted for alcohol consumption.
<sup>d</sup>Values for interaction were obtained by testing the statistical significance of interaction terms between aMEDr and the stratifying covariates in fully adjusted models.
<sup>e</sup>Not adjusted for body mass index.
<sup>f</sup>Not adjusted for highest level of education.
<sup>g</sup>Not adjusted for family history of prostate cancer.

Overall 3,868

- Cases HR (95% CI): 3.868
  - 1.09 (1.01–1.17)

Not adjusted for family history of prostate cancer.

Not adjusted for highest level of education.

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 cases 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. Nevertheless, largely similar results were obtained when we used absolute scores based on the WCRF/AICR dietary recommendations.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>All Cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1,884</td>
<td>1.00 (0.92–1.09)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>593</td>
<td>1.01 (0.92–1.11)</td>
</tr>
<tr>
<td>Women</td>
<td>291</td>
<td>0.94 (0.79–1.10)</td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>912</td>
<td>1.01 (0.92–1.12)</td>
</tr>
</tbody>
</table>

*All HRs were estimated per two-point increment in aMEDr.

1Adjusted 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/m²), 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).

2Not adjusted for sex.

3P-values for interaction were obtained by testing the statistical significance of interaction terms between aMEDr and the stratifying covariates in fully adjusted models.

4Not adjusted for cigarette smoking status.

5Not adjusted for alcohol consumption.

6Not adjusted for body mass index.

7Not adjusted for highest level of education.

8The 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.

9Not adjusted for family history of bladder cancer.

<table>
<thead>
<tr>
<th>Group</th>
<th>All Cases</th>
<th>Noninvasive Cases</th>
<th>Noninvasive Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1,884</td>
<td>1.00 (0.92–1.09)</td>
<td>972</td>
</tr>
</tbody>
</table>

1Adjusted 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/m²), 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).

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3P-values for interaction were obtained by testing the statistical significance of interaction terms between aMEDr and the stratifying covariates in fully adjusted models.

4Not adjusted for cigarette smoking status.

5Not adjusted for alcohol consumption.

6Not adjusted for body mass index.

7Not adjusted for highest level of education.

8The 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.

9Not adjusted for family history of bladder cancer.
Table 6. Fully adjusted associations of the absolute WCRF/AICR score and aMED (per 5D-increment) with risks of prostate and bladder cancer in the Netherlands Cohort Study

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Prostate cancer</th>
<th>Bladder cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR(95% CI)**</td>
<td>Nonadvanced Advanced</td>
<td>Noninvasive Invasive</td>
</tr>
<tr>
<td>PYsubcohort/Casesa</td>
<td>30.049/3,763</td>
<td>30.049/2,272 30.049/1,212</td>
<td>61.976/1,836 61.976/945 61.976/891</td>
</tr>
<tr>
<td>Excluding alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCRF/AICR scoree</td>
<td>1.03 (0.97–1.09)</td>
<td>1.05 (0.97–1.13)</td>
<td>0.98 (0.92–1.05)</td>
</tr>
<tr>
<td>aMEDr</td>
<td>1.07 (1.01–1.13)</td>
<td>1.05 (0.98–1.14)</td>
<td>0.99 (0.95–1.06)</td>
</tr>
<tr>
<td>Including alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCRF/AICR scoref</td>
<td>1.04 (0.97–1.10)</td>
<td>1.04 (0.97–1.13)</td>
<td>0.95 (0.98–1.02)</td>
</tr>
<tr>
<td>aMEDf</td>
<td>1.07 (1.01–1.14)</td>
<td>1.07 (0.99–1.15)</td>
<td>0.99 (0.93–1.06)</td>
</tr>
</tbody>
</table>

Abbreviation: PYsubcohort, person-years in the subcohort.

aAdjusted for age at baseline (years), body mass index (kg/m²), 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).

bAdjusted 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/m²), 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).

cAdjusted 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/m²), 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).

dScore based on WCRF/AICR dietary recommendations to prevent cancer.

References


