Adherence to the Mediterranean Diet and Overall Cancer Incidence: The Netherlands Cohort Study

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ARTICLE INFORMATION

Article history:
Submitted 10 January 2020
Accepted 24 July 2020

Keywords:
Mediterranean diet
Cancer
Cohort study
Epidemiology
Prevention

https://doi.org/10.1016/j.jand.2020.07.025

ABSTRACT

Background Mediterranean diet adherence has been associated with reduced risks of various cancer types. However, prospective findings for overall cancer risk are inconclusive.

Objective The aim of this study was to examine sex-specific relations of Mediterranean diet adherence with overall cancer risk.

Design This analysis was conducted as part of the prospective Netherlands Cohort Study. Baseline data on diet and other cancer risk factors were collected using a self-administered questionnaire. Participants were followed up for cancer incidence for 20.3 years through record linkages with the Netherlands Cancer Registry and the Dutch Pathology Registry. The alternate Mediterranean diet score without alcohol was the principal measure of Mediterranean diet adherence.

Participants/setting The study population consisted of 120,852 inhabitants of the Netherlands, who were aged 55 to 69 years in September 1986.

Main outcome measure The primary outcome was overall cancer incidence.

Statistical analyses performed Cox regression analyses (case-cohort design) were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of Mediterranean diet adherence with incidence of cancer (subgroups). In total, 12,184 male and 7,071 female subjects with cancer had complete data on potential confounders and were eligible for inclusion in the Cox models.

Results Middle compared with low Mediterranean diet adherence (alternate Mediterranean diet score without alcohol) was significantly associated with a reduced overall cancer risk in women (HR [95% CI]: 0.85 [0.75-0.97]). Decreased HR estimates for the highest Mediterranean diet adherence category and per 2-point increase in score were also observed, but did not reach statistical significance in multivariable-adjusted analyses. In men, there was no evidence of an association for overall cancer risk ($HR_{\text{per 2-point increment}}$ [95% CI]: 1.02 [0.95-1.10]). Results for cancer subgroups, defined by relations with tobacco smoking, obesity, and alcohol consumption, were largely similar to the overall findings. Model fits diminished when alcohol was included in the Mediterranean diet score.

Conclusions Mediterranean diet adherence was not associated with overall cancer risk in male participants of the prospective Netherlands Cohort Study. HR estimates in women pointed in the inverse direction, but lost statistical significance after full adjustment for confounding in most cases.
J Acad Nutr Diet. 2021;121(2):242-252.

CANCER POSES A LARGE SOCIAL AND ECONOMIC burden to the world's population with an estimated 18.1 million incident cases and 9.6 million deaths in 2018.[1] Additionally, cancer was the leading cause of premature mortality in Northern America and the majority of Europe in 2015.[1] The cancer incidence and mortality are increasing rapidly as a result of the expanding and aging world population along with changes in the prevalence and distribution of the major cancer risk factors.[1] Lanting et al estimated that just under 10% of the cancer diagnoses in the Netherlands in 2010 could be attributed to a less than optimal diet.[2]

The traditional Mediterranean diet of the early 1960s is characterized by a high consumption of plant foods (ie, vegetables, legumes, fruits, nuts, and whole grains). Meat and dairy products are consumed in low to moderate amounts, which in combination with the abundant use of olive oil leads to the high ratio of monounsaturated to saturated fatty acids that is characteristic of the Mediterranean diet. Alcohol, particularly wine, is consumed in moderate amounts in the traditional Mediterranean diet.[3,4]

Mediterranean diet adherence has been associated with reduced risks of multiple, but not all, types of cancer.[5-8] Therefore, it would be useful to have an impression of the relation between Mediterranean diet adherence and overall cancer risk as well. Currently, the available prospective evidence for the potential relation between *a priori* defined Mediterranean diet adherence and overall cancer risk is inconclusive.[9-13] Higher Mediterranean diet adherence was associated with a reduced overall cancer risk in some studies,[9,10,13] but not in others.[11,12] Furthermore, the potential inverse relation might be stronger in women compared with men.[9] However, only 3 prospective studies have reported sex-specific associations thus far.[9,10,13]

The aim of the present study was to evaluate the association between *a priori* defined Mediterranean diet adherence and overall cancer risk in men and women participating in the prospective Netherlands Cohort Study (NLCS). It was hypothesized that Mediterranean diet adherence is inversely related to overall cancer risk in both sexes. In addition to overall cancer risk, associations of Mediterranean diet adherence with risk of cancer subgroups defined as cancers known to be related to tobacco smoking, obesity, and alcohol consumption were investigated. As a final aim, performances of models including Mediterranean diet scores with and without alcohol were compared.

RESEARCH SNAPSHOT

Research Question: Is Mediterranean diet adherence associated with overall cancer risk in men and women?

Key Findings: In this analysis of the prospective Netherlands Cohort Study, middle compared with low Mediterranean diet adherence was significantly associated with a reduced overall cancer risk in women. Decreased hazard ratio estimates for the highest Mediterranean diet adherence category and per 2-point increase in score were also observed, but lost statistical significance after full adjustment for confounding. In men, there was no evidence of an association between Mediterranean diet adherence and overall cancer risk.

MATERIALS AND METHODS

Study Population and Cancer Follow-Up

The prospective NLCS was initiated in September 1986.[14-17] In total, 58,279 men and 62,573 women, aged 55 to 69 years, completed the baseline questionnaire on cancer risk factors, including diet. A case-cohort approach was used to process and analyze the data efficiently.[14,17,18] In the case-cohort design, accumulated person-time at risk in the whole cohort is estimated based on a randomly sampled subcohort. Cases are identified in the entire cohort. The NLCS subcohort (n = 5000) was randomly selected immediately after baseline and biennially followed up for vital status. Subcohort members contributed to the number of person-years at risk from baseline until December 31, 2006, or censoring (cancer diagnosis, death, emigration, or loss to follow-up). The NLCS was approved by institutional review boards from Maastricht University and the Netherlands Organization for Applied Scientific Research. Study participants consented to participation by filling out the baseline questionnaire.

Incident cancer cases in the total NLCS cohort were identified through annual record linkage with the Netherlands Cancer Registry and the nationwide Dutch Pathology Registry.[15] During 20.3 years of follow-up, 25,848 participants were diagnosed with a microscopically confirmed, first primary cancer (excluding basal cell carcinoma of the skin). In the total NLCS cohort, 4.5% of the participants reported prevalent cancer at baseline (other than skin cancer) and were excluded. Additional exclusion of participants with incomplete or inconsistent data regarding diet, alcohol, or Mediterranean diet adherence left 22,228 cancer cases (men: 13,657, women: 8571) and 4084 subcohort members (men: 2057, women: 2027), who were eligible for inclusion in the present analysis (Figure). Besides overall cancer incidence, incidence of cancers known to be related to tobacco smoking, obesity, and alcohol consumption were considered as secondary end points. The subgroup of smoking-related cancers comprised cancers of the oral cavity (including lip) and pharynx, esophagus, stomach, colorectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, trachea, lung, uterine cervix, ovary, kidney, ureter, and urinary bladder as well as myeloid leukemia.[10,13,19,20] Obesity-related cancers were defined as cancers of the esophagus (adenocarcinoma), stomach (cardia), colorectum, liver, gallbladder, pancreas, breast, corpus uteri, ovary, kidney, and thyroid, and multiple myeloma.[13,20,21] Finally, alcohol-related cancers included cancers of the oral cavity (including lip) and pharynx, esophagus (squamous cell carcinoma), colorectum, liver, larynx, and breast.[10,19,20] Results for the cancer subgroups were compared with results obtained combining all other cancers (ie, cancers not classified as being related to tobacco smoking, obesity, or alcohol consumption, respectively).

Exposure Assessment

The NLCS baseline questionnaire included a 150-item, semiquantitative food frequency questionnaire (FFQ) focusing on the study participant's dietary habits over the past 12 months. This FFQ performed adequately as judged by comparison with 9-day diet records.[16] Spearman correlation coefficients for intakes of food groups ranged from 0.38 for vegetables to 0.89 for alcoholic beverages with a median of 0.60. Moreover, the average test-retest correlation of the FFQ was 0.66 for all nutrients.[22] Intakes of most nutrients were found to be relatively stable for over at least 5 years. After 5 years, correlations between baseline and repeated

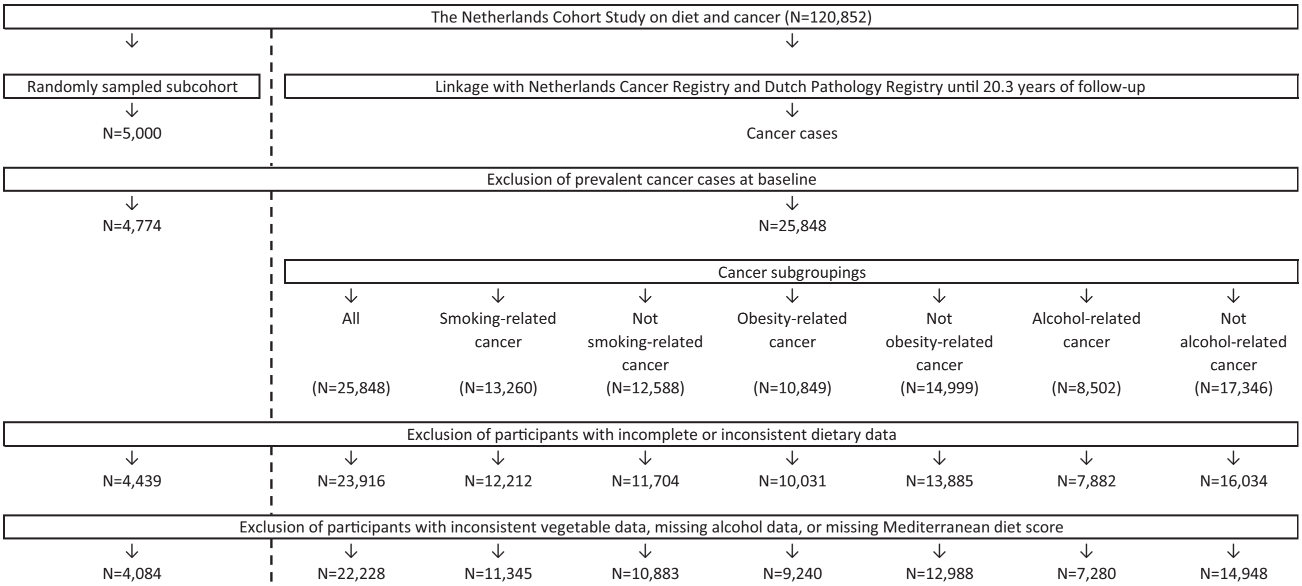

Figure. Flow diagram of the number of participants of the Netherlands Cohort Study, who are eligible for inclusion in the analyses concerning overall cancer (case-cohort design)

measurements had declined on average only 0.07.[22] Mean daily nutrient intakes were calculated from the FFQ data utilizing the Dutch food composition table of the year 1986.[23]

In addition to dietary intake, the self-administered baseline questionnaire measured detailed smoking habits, anthropometry, physical activity, educational level, reproductive factors, and other risk factors related to cancer.[14] Body mass index (BMI) was calculated (weight in kilograms / [height in square meters]) from the self-reported height and weight data. To calculate the level of nonoccupational physical activity, the minutes spent per day on cycling or walking, shopping, walking the dog, gardening, and sports or exercise were added, as described previously.[24]

Mediterranean Diet Adherence

The relative level of Mediterranean diet adherence was determined using the alternate Mediterranean diet score (aMED),[25,26] which is a variation of the original traditional Mediterranean diet score.[27,28] aMED is composed of 9 dietary components (scored by 0 or 1 point each), which are typical of the Mediterranean diet.[25,26] Participants obtain 1 point for mean daily intakes at or above the sex-specific median of vegetables (excluding potatoes), legumes, fruits, nuts, whole grains, and fish. Reverse scoring is applied to the intake of red and processed meats. Finally, scores of 1 point are assigned to a moderate alcohol consumption of 5 to 25 g per day and a high (≥sex-specific median) ratio of monounsaturated to saturated fatty acids. Thus, a maximum score of 9 points can be obtained, reflecting the highest level of Mediterranean diet adherence.[25,26] Food intakes were adjusted to daily energy intakes of 2500 (men) and 2000 (women) kcal to control for differences in energy intake.[26,27]

Furthermore, a reduced variant from the original aMED was created that did not contain the alcohol component (aMEDr),[6,29] because alcohol consumption has been associated with an increased risk of multiple cancer types even at moderate levels.[19,30,31] aMEDr was considered to be the primary measure of Mediterranean diet adherence.

Statistical Analyses

Sex-specific hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the relation between Mediterranean diet adherence and overall cancer incidence were estimated by Cox proportional hazards modelling using duration of follow-up as time scale. Standard errors of the HRs were estimated using the robust Huber-White sandwich estimator, which accounts for the additional variance associated with sampling from the total cohort.[32] The validity of the proportional hazards assumption was evaluated by scaled Schoenfeld residuals tests.[33] Because of the large number of cases, these tests may easily yield significant results. Therefore, -ln(-ln) survival plots were visually inspected, and it was concluded that the proportional hazards assumption was met for the exposure variables.

Age- and multivariable-adjusted effect estimates were obtained for the Mediterranean diet scores, which were modeled as categorical (low [≤3], middle [4-5], or high [≥6])[26] and continuous (per 2-point increment) terms. The multivariable-adjusted HRs were corrected for potential confounding by age at baseline, cigarette smoking (status, frequency, and duration), BMI, height, alcohol consumption (except for models containing the original aMED including alcohol), total daily energy intake, highest level of education, nonoccupational physical activity, and family history of cancer. Effect estimates obtained among women were additionally adjusted for reproductive factors (age at menarche, parity, age at first birth, age at menopause, oral contraceptive use, and use of postmenopausal hormone replacement therapy). All potential confounders were predefined and selected from the literature. For each adherence category, sex-specific median Mediterranean diet score values were determined in the subcohort. Next, these values were fitted as continuous terms in the Cox regression models to test for linear trends. Akaike's Information Criterion (AIC) was used to evaluate whether inclusion of alcohol in the Mediterranean diet score affected the model performance.[34] Besides overall cancer incidence, sex-

Table 1. Sex-specific baseline characteristics of subcohort members and cancer cases in the Netherlands Cohort Study[a]

Characteristic	Men: Subcohort (n = 2057)	Men: Cancer cases (n = 13,657)	Women: Subcohort (n = 2027)	Women: Cancer cases (n = 8571)
	←median (IQR[b])→			
Age (y)	61 (7)	62 (7)	61 (7)	61 (7)
	←%→			
Current cigarette smokers	35.1	40.3	21.3	23.1
Higher vocational education or university	19.3	19.6	9.5	9.1
	←mean (SD[c])→			
Body mass index[d]	24.9 (2.6)	25.0 (2.6)	25.0 (3.5)	25.2 (3.6)
	←median (IQR)→			
Height (cm)	176 (9)	176 (9)	165 (8)	166 (8)
Nonoccupational physical activity (min/d)	62.1 (67.1)	64.3 (65.7)	54.3 (52.9)	51.4 (53.6)
	←%→			
Family history of cancer	45.1	48.2	47.3	51.5
	←median (IQR)→			
Age at menarche (y)			13 (3)	13 (3)
Age at menopause (y)			50 (6)	50 (6)
	←%→			
Nulliparous			18.5	19.1
	←% of parous→			
Age at first birth ≥30 y			22.5	23.3
	←%→			
Ever use of oral contraceptives			25.4	24.5
Ever use of hormone replacement therapy			13.4	13.3
	←mean (SD)→			
aMEDr[e]	3.9 (1.6)	3.9 (1.6)	4.0 (1.6)	3.9 (1.6)
aMED[f]	4.3 (1.7)	4.3 (1.7)	4.3 (1.7)	4.2 (1.7)
Food intake[g] (g/d)	←median (IQR)→			
Vegetables	207.3 (123.9)	205.3 (116.4)	219.2 (121.1)	218.2 (122.1)
Legumes	6.5 (15.9)	6.6 (16.0)	4.7 (12.2)	4.7 (11.8)
Fruits	157.0 (157.2)	154.4 (162.2)	209.4 (176.5)	210.5 (178.1)
Nuts	3.3 (11.0)	3.2 (10.4)	1.7 (6.1)	1.5 (5.7)
Whole grains	0.0 (9.7)	0.0 (9.4)	0.0 (13.1)	0.0 (11.8)
Fish	11.5 (22.8)	11.7 (21.7)	8.7 (21.9)	8.6 (21.2)
Red and processed meat	125.1 (62.8)	124.7 (65.8)	106.4 (61.2)	106.1 (63.0)
MUFA:SFA ratio[h]	0.98 (0.24)	0.98 (0.23)	0.94 (0.21)	0.93 (0.22)
Alcohol	9.7 (20.9)	11.4 (22.0)	1.6 (7.8)	1.5 (8.6)

(*continued on next page*)

specific associations of aMEDr were also estimated with incidence of smoking-, obesity-, and alcohol-related cancers as well as cancers not classified as being related to these factors. Statistical significance of differences in HRs obtained for cancers related vs not related to tobacco smoking, obesity, or alcohol consumption was assessed using a competing risks procedure as previously described.[35] Standard errors for the observed differences in HRs were estimated using a bootstrapping method developed for the case-cohort design.[36]

Table 1. Sex-specific baseline characteristics of subcohort members and cancer cases in the Netherlands Cohort Study[a] (*continued*)

Characteristic	Men		Women	
	Subcohort (n = 2057)	Cancer cases (n = 13,657)	Subcohort (n = 2027)	Cancer cases (n = 8571)
	←mean (SD)→			
Daily energy intake (kcal)	2162 (501)	2165 (494)	1687 (392)	1682 (386)

[a]The % missing values in the total eligible population was <5% for all variables included in this table, with the exception of age at menopause in women (6.4%).
[b]IQR = interquartile range.
[c]SD = standard deviation.
[d]Calculated as kilograms per square meter.
[e]aMEDr = alternate Mediterranean diet score without the alcohol component.
[f]aMED = alternate Mediterranean diet score.
[g]The presented food intakes (with the exception of alcohol) were adjusted to daily energy intakes of 2000 kcal in women and 2500 kcal in men.
[h]MUFA:SFA ratio = ratio of monounsaturated to saturated fatty acids.

Furthermore, sex-specific associations between aMEDr and overall cancer risk were estimated within strata of cigarette smoking status, alcohol consumption, BMI, educational level, and family history of cancer. To assess the statistical significance of potential differences across strata, Wald tests were performed on interaction terms between aMEDr and the stratifying covariates. Finally, the main analyses were repeated excluding the first 2 years of follow-up to check for potential reversed causation, since the presence of preclinical cancer at baseline could have influenced dietary habits. Analyses were performed using Stata software (version 15; 2017, StataCorp, College Station, TX). Statistical significance was indicated by a 2-sided P value < .05.

RESULTS

Table 1 summarizes baseline characteristics of male and female subcohort members and subjects with cancer. The mean (standard deviation) values of aMEDr were 3.9 (1.6) and 4.0 (1.6) in male and female subcohort members, respectively. Largely comparable aMEDr values were observed in subjects with cancer. Furthermore, daily intakes of the aMEDr components did not notably differ between subcohort members and subjects with cancer, regardless of sex. Subjects of both sexes with cancer were more likely to smoke and more often reported a family history of cancer compared with subcohort members. Moreover, male subjects with cancer had a higher level of alcohol consumption than subcohort members. Concerning reproductive factors, female subjects with cancer were older at the birth of their first child and were less often users of oral contraceptives than subcohort members.

Age- and multivariable-adjusted HRs and 95% CIs for associations of Mediterranean diet adherence with overall cancer risk are shown in Table 2, for men and women separately. Of the eligible study population, 3499 subcohort members (men: 1834, women: 1665) and 19,255 subjects with cancer (men: 12,184, women: 7071) had complete data on all potential confounders and could be included in the Cox regression analyses.

Mediterranean diet adherence was not associated with overall cancer risk in men in age- and multivariable-adjusted analyses (Table 2). Multivariable-adjusted HRs (95% CIs) for aMEDr were 0.99 (0.84-1.17) comparing the highest with the lowest adherence category and 1.02 (0.95-1.10) per 2-point increase in score, respectively. Although aMEDr was not significantly associated with any of the cancer subgroups in men (Table 3), HRs were statistically significantly different for cancers related vs not related to tobacco smoking, obesity, and alcohol consumption ($P_{heterogeneity}$ aMEDr categories: <.001 [smoking], .008 [obesity], and .047 [alcohol]) (data not shown).

In women, aMEDr was significantly associated with a reduced overall cancer risk in age-adjusted analyses ($HR_{high\ vs\ low}$ [95% CI]: 0.84 [0.72-0.99], $HR_{per\ 2\text{-}point\ increment}$ [95% CI]: 0.91 [0.85-0.98]) (Table 2). After additional adjustment for other potential confounding factors, a statistically significantly reduced overall cancer risk persisted when comparing the middle with the lowest aMEDr category, with an HR (95% CI) of 0.85 (0.75-0.97). The other inverse associations slightly attenuated and lost statistical significance ($HR_{high\ vs\ low}$ [95% CI]: 0.90 [0.76-1.06], $HR_{per\ 2\text{-}point\ increment}$ [95% CI]: 0.93 [0.86-1.01]). Multivariable-adjusted associations of aMEDr with subgroups of cancers related/not related to tobacco smoking, obesity, and alcohol consumption were comparable to those obtained for overall cancer risk in women (Table 3). Furthermore, heterogeneity tests confirmed similarity of associations for cancers related vs not related to these lifestyle factors ($P_{heterogeneity}$ aMEDr categories: .442 [smoking], .188 [obesity], and .309 [alcohol]) (data not shown).

For both sexes, largely comparable HRs and 95% CIs for overall cancer risk were obtained when alcohol was included in the Mediterranean diet score. However, AIC values were higher for models in which Mediterranean diet adherence was assessed using the Mediterranean diet score variant including alcohol (aMED), indicating a worse fit. The respective AIC values for the categorical Mediterranean diet score variants (without vs with alcohol) were 172,977 vs 173,025 in men and 101,366 vs 101,402 in women (data not shown). Associations between aMEDr and overall cancer risk within strata of potential effect modifying factors are presented in Table 4. The relation of aMEDr with overall cancer risk in men became more positive with increasing level of education ($P_{interaction}$ = .049), reaching statistical significance in the highest category. Although aMEDr did not significantly interact with educational level in women, a similar pattern was observed. Associations did not significantly differ across strata of cigarette smoking status, alcohol consumption, BMI,

Table 2. Associations of aMED[a] (including and excluding alcohol) with overall cancer risk for men and women in the Netherlands Cohort Study

	aMED				
	0-3	4-5	6-8[b]	P_{trend}	Continuous, per 2 points
Men					
Excluding alcohol (aMEDr)[c]					
$PY_{subcohort}$[d]/cases	11,189/5068	11,773/5243	4416/1873		27,378/12,184
HR[e] age (95% CI)[fg]	1.00	0.99 (0.88-1.12)	0.92 (0.78-1.07)	.294	0.98 (0.92-1.05)
HR multivariable-adjusted (95% CI)[h]	1.00	1.00 (0.88-1.13)	0.99 (0.84-1.17)	.948	1.02 (0.95-1.10)
Including alcohol (aMED)					
$PY_{subcohort}$/cases	8690/4014	12,191/5292	6,497/2,878		27,378/12,184
HR multivariable-adjusted (95% CI)[hi]	1.00	0.96 (0.85-1.10)	1.02 (0.88-1.19)	.996	1.02 (0.95-1.09)
Women					
Excluding alcohol (aMEDr)					
$PY_{subcohort}$/cases	10,191/2843	12,537/3003	5328/1225		28,056/7071
HR age (95% CI)[g]	1.00	0.87 (0.77-0.98)	0.84 (0.72-0.99)	.030	0.91 (0.85-0.98)
HR multivariable-adjusted (95% CI)[hj]	1.00	0.85 (0.75-0.97)	0.90 (0.76-1.06)	.188	0.93 (0.86-1.01)
Including alcohol (aMED)					
$PY_{subcohort}$/cases	8,939/2461	12,149/3024	6969/1586		28,056/7071
HR multivariable-adjusted (95% CI)[hij]	1.00	0.91 (0.79-1.04)	0.88 (0.75-1.03)	.139	0.94 (0.87-1.01)

[a]aMED = alternate Mediterranean diet score.
[b]The highest score category of the original aMED including alcohol was defined as 6-9 points.
[c]aMEDr = alternate Mediterranean diet score without the alcohol component.
[d]$PY_{subcohort}$ = person-years in the subcohort.
[e]HR = hazard ratio.
[f]CI = confidence interval.
[g]Adjusted for age at baseline (years).
[h]Adjusted for age at baseline (years), cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (<18.5, ≥18.5 to <25.0, ≥25.0 to <30.0, ≥30.0), height (cm), alcohol consumption (0, >0 to <5, ≥5 to <15, ≥15 to <30, ≥30 g/d), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), nonoccupational physical activity (≤30, >30 to ≤60, >60 to ≤90, >90 min/d), and family history of cancer (no, yes).
[i]Not adjusted for alcohol consumption.
[j]Analyses conducted among women were additionally adjusted for age at menarche (≤12, 13-14, 15-16, ≥17 years), parity (nulliparous, 1-2, ≥3 children), age at first birth (<25, ≥25 years), age at menopause (≤44, 45-49, 50-54, ≥55 years), oral contraceptive use (never, ever), and use of postmenopausal hormone replacement therapy (never, ever).

and family history of cancer in both men and women. Excluding the first 2 years of follow-up did not essentially change the associations (data not shown).

DISCUSSION

In this NLCS analysis, sex-specific associations of *a priori* defined Mediterranean diet adherence with risks of overall cancer and cancer subgroups defined by relations with 3 major cancer risk factors (tobacco smoking, obesity, and alcohol consumption) were investigated. In women, middle compared with low aMEDr values were significantly associated with a reduced risk of overall cancer and the majority of the cancer subgroups investigated. Other associations in women were not statistically significant after full adjustment for confounding, but all estimates were below 1. No association was observed between aMEDr and risk of overall cancer or any of the cancer subgroups in men. Inclusion of alcohol in the Mediterranean diet score diminished the model performance.

Even though the association of Mediterranean diet adherence with overall cancer risk is comprised of a combination of potentially diverging associations with individual cancer (sub)types, overall cancer risk is an interesting end point for epidemiological studies. It provides insight in the overall possible benefits of Mediterranean diet adherence and the potential of the Mediterranean diet as a dietary strategy for cancer prevention. Findings of previously conducted prospective studies evaluating the relation between *a priori* defined Mediterranean diet adherence and overall cancer risk have been inconclusive and were rarely specified by sex.

A priori defined Mediterranean diet adherence has previously significantly been associated with a reduced overall cancer risk in the total European Prospective Investigation into Cancer and Nutrition (EPIC) cohort as well as the Greek EPIC cohort.[9,10] Comparing the highest with the lowest Mediterranean diet adherence category in the total EPIC cohort, HRs (95% CIs) of 0.93 (0.88-0.99) and 0.93 (0.89-0.96) were observed for men and women,

Table 3. Multivariable-adjusted associations of aMEDr[a] with risks of cancer subgroups for men and women in the Netherlands Cohort Study

	aMEDr in Men[b]					aMEDr in Women[bc]				
	0-3	4-5	6-8	P_{trend}	Continuous[d]	0-3	4-5	6-8	P_{trend}	Continuous[d]
All cancers										
$PY_{subcohort}$[e]	11,189	11,773	4416		27,378	10,191	12,537	5328		28,056
Cases	5068	5243	1873		12,184	2843	3003	1225		7071
HR[f] (95% CI)[g]	1.00	1.00 (0.88-1.13)	0.99 (0.84-1.17)	.948	1.02 (0.95-1.10)	1.00	0.85 (0.75-0.97)	0.90 (0.76-1.06)	.188	0.93 (0.86-1.01)
Smoking related										
Cases	2943	2835	945		6723	1236	1261	516		3013
HR (95% CI)	1.00	0.95 (0.83-1.08)	0.96 (0.80-1.14)	.559	0.99 (0.92-1.07)	1.00	0.85 (0.73-0.98)	0.90 (0.74-1.09)	.245	0.92 (0.84-1.01)
Not smoking related										
Cases	2125	2408	928		5461	1607	1742	709		4058
HR (95% CI)	1.00	1.08 (0.95-1.23)	1.05 (0.88-1.25)	.583	1.06 (0.98-1.14)	1.00	0.86 (0.75-0.99)	0.90 (0.75-1.07)	.221	0.94 (0.87-1.02)
Obesity related										
Cases	1159	1292	490		2941	1933	2085	865		4883
HR (95% CI)	1.00	1.07 (0.93-1.23)	1.06 (0.88-1.28)	.506	1.06 (0.98-1.15)	1.00	0.85 (0.75-0.98)	0.91 (0.77-1.08)	.277	0.94 (0.87-1.02)
Not obesity related										
Cases	3909	3951	1383		9243	910	918	360		2188
HR (95% CI)	1.00	0.98 (0.86-1.11)	0.97 (0.82-1.16)	.740	1.01 (0.94-1.08)	1.00	0.85 (0.73-1.00)	0.87 (0.71-1.07)	.172	0.92 (0.84-1.01)
Alcohol related										
Cases	954	1030	401		2385	1501	1580	675		3756
HR (95% CI)	1.00	1.03 (0.89-1.20)	1.08 (0.89-1.32)	.432	1.03 (0.95-1.13)	1.00	0.83 (0.72-0.96)	0.92 (0.77-1.10)	.322	0.93 (0.86-1.01)
Not alcohol related										
Cases	4114	4213	1472		9799	1342	1423	550		3315
HR (95% CI)	1.00	0.99 (0.87-1.12)	0.97 (0.82-1.15)	.753	1.02 (0.95-1.09)	1.00	0.88 (0.76-1.01)	0.88 (0.73-1.06)	.152	0.93 (0.86-1.01)

[a]aMEDr = alternate Mediterranean diet score without the alcohol component.
[b]Adjusted for age at baseline (years), cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (<18.5, ≥18.5 to <25.0, ≥25.0 to <30.0, ≥30.0), height (cm), alcohol consumption (0, >0 to <5, ≥5 to <15, ≥15 to <30, ≥30 g/d), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), nonoccupational physical activity (≤30, >30 to ≤60, >60 to ≤90, >90 min/d), and family history of cancer (no, yes).
[c]Analyses conducted among women were additionally adjusted for age at menarche (≤12, 13-14, 15-16, ≥17 years), parity (nulliparous, 1-2, ≥3 children), age at first birth (<25, ≥25 years), age at menopause (≤44, 45-49, 50-54, ≥55 years), oral contraceptive use (never, ever), and use of postmenopausal hormone replacement therapy (never, ever).
[d]Continuous hazard ratios were estimated per 2-point increment in aMEDr.
[e]$PY_{subcohort}$ = person-years in the subcohort.
[f]HR = hazard ratio.
[g]CI = confidence interval.

respectively.[10] Although inverse associations were also suggested for both sexes in the Greek EPIC cohort, only effect estimates obtained in women reached statistical significance ($HR_{high\ vs\ low}$ [95% CI]: 0.83 [0.63-1.09] for men and 0.73 [0.56-0.96] for women).[9] In addition to the previously mentioned EPIC studies, weak inverse associations between Mediterranean diet adherence and overall cancer risk were observed in men ($HR_{per\ tertile\ increase}$ [95% CI]: 0.97 [0.94-1.01]) and women ($HR_{per\ tertile\ increase}$ [95% CI]: 0.97 [0.93-1.00]) participating in the Swedish prospective Västerbotten Intervention Programme.[13] In the present analysis of the NLCS cohort, *a priori* defined Mediterranean diet adherence was not associated with overall cancer risk in men. In regard to women, although the multivariable-

Table 4. Sex-specific and multivariable-adjusted associations of aMEDr[a] (per 2-point increment) with overall cancer risk for strata of various risk factors in the Netherlands Cohort Study

	Overall Cancer Risk			
	Men		Women	
	Cases	HR[b] (95% CI)[cde]	Cases	HR (95% CI)[def]
Overall	12,184	1.02 (0.95-1.10)	7071	0.93 (0.86-1.01)
Cigarette smoking status[g]				
Never	1367	0.99 (0.82-1.20)	3970	0.93 (0.85-1.03)
Former	6084	1.05 (0.96-1.15)	1490	0.87 (0.72-1.04)
Current	4733	0.98 (0.85-1.12)	1611	0.97 (0.81-1.18)
$P_{interaction}$[h]		.801		.363
Alcohol consumption[i]				
0 g/d	1488	1.03 (0.86-1.24)	2166	0.91 (0.78-1.05)
>0 to <15.0 g/d	5616	1.07 (0.97-1.19)	3838	0.97 (0.88-1.07)
≥15.0 g/d	5080	0.95 (0.84-1.07)	1067	0.80 (0.63-1.00)
$P_{interaction}$[h]		.344		.532
Body mass index[j]				
≥18.5 to <25.0	6310	0.99 (0.89-1.09)	3699	0.91 (0.82-1.01)
≥25.0	5826	1.07 (0.96-1.19)	3293	0.93 (0.82-1.04)
$P_{interaction}$[h]		.263		.740
Highest level of education[k]				
Primary school or lower vocational	5430	0.96 (0.86-1.08)	3742	0.87 (0.79-0.97)
Secondary school or medium vocational	4319	1.04 (0.93-1.16)	2643	0.96 (0.84-1.10)
Higher vocational or university	2435	1.19 (1.01-1.41)	686	1.19 (0.91-1.57)
$P_{interaction}$[h]		.049		.408
Family history of cancer[l]				
No	6267	1.06 (0.96-1.17)	3375	0.94 (0.84-1.04)
Yes	5917	0.98 (0.89-1.09)	3696	0.94 (0.84-1.04)
$P_{interaction}$[h]		.261		.785

[a]aMEDr = alternate Mediterranean diet score without the alcohol component.
[b]HR = hazard ratio.
[c]CI = confidence interval.
[d]All HRs were estimated per 2-point increment in aMEDr.
[e]Adjusted for age at baseline (years), cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (<18.5, ≥18.5 to <25.0, ≥25.0 to <30.0, ≥30.0), height (cm), alcohol consumption (0, >0 to <5, ≥5 to <15, ≥15 to <30, ≥30 g/d), daily energy intake (kcal), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), nonoccupational physical activity (≤30, >30 to ≤60, >60 to ≤90, >90 min/d), and family history of cancer (no, yes).
[f]Analyses conducted among women were additionally adjusted for age at menarche (≤12, 13-14, 15-16, ≥17 years), parity (nulliparous, 1-2, ≥3 children), age at first birth (<25, ≥25 years), age at menopause (≤44, 45-49, 50-54, ≥55 years), oral contraceptive use (never, ever), and use of postmenopausal hormone replacement therapy (never, ever).
[g]Not adjusted for cigarette smoking status.
[h]*P* values for interaction were obtained by testing the statistical significance of interaction terms between aMEDr and the stratifying covariates in multivariable-adjusted models.
[i]Not adjusted for alcohol consumption.
[j]Not adjusted for body mass index.
[k]Not adjusted for highest level of education.
[l]Not adjusted for family history of cancer.

adjusted associations in female NLCS participants were not statistically significant in most cases, effect estimates were stronger inverse than those observed for women in the total EPIC cohort, which did reach statistical significance possibly due to the larger number of cases.[10] Additional cohort studies in Germany and France have investigated the association between Mediterranean diet adherence and overall cancer risk in men and women together and did not observe an association.[11,12] Besides the prospective cohort evidence, a reduced overall cancer risk (borderline significant, $P = .05$) was indicated in patients with coronary heart disease who followed an α-linolenic acid-rich Mediterranean-type diet as opposed to a control diet close to the step 1 prudent diet of the American Heart Association in the randomized Lyon Diet Heart Study.[37] However, results should be interpreted with caution because they were based on only 24 incident cancer cases.

Differential adjustment for potential confounding factors and residual confounding, particularly by tobacco smoking and female reproductive factors, may have contributed to the varying associations between *a priori* defined Mediterranean diet adherence and overall cancer risk that have been reported thus far. Other potentially contributing factors include differences in the method of Mediterranean diet assessment, the composition of the study population, and the time period and/or geographical region in which the study was conducted. The distribution of the specific cancer types in the overall cancer outcome is likely to vary over time and between countries because of, for example, different distributions of risk factors and the introduction of cancer screening programs. Some specific cancer types are inversely associated with Mediterranean diet adherence, whereas null associations have been observed for others. For example, Mediterranean diet adherence has inversely been associated with risks of postmenopausal breast cancer (particularly of the estrogen receptor negative subtype) and subtypes of esophageal and gastric cancer in previous NLCS analyses.[6,38] However, no association was found with colorectal cancer risk and a positive association with nonadvanced prostate cancer risk.[39,40] Therefore, differences in the relative incidence of specific cancer types could also (partly) be responsible for the inconsistent findings concerning overall cancer risk.

Results of the present study indicated that the inverse association between Mediterranean diet adherence and overall cancer risk, if present, might be restricted to women. In line with these findings, slightly stronger inverse associations were observed in female participants of EPIC-Greece, though the interaction by sex did not reach statistical significance.[9] Cancers arising in men and women may etiologically differ. The sex-specific levels of sex hormones may influence tumor development and could therefore potentially modulate the association of dietary factors with cancer risk.[41-45] Apart from other factors, sex-related differences may also exist in exposure levels to risk factors and carcinogen metabolism.[41,43-45] Furthermore, the disparate associations of Mediterranean diet adherence with commonly diagnosed sex-specific cancers (ie, postmenopausal breast and prostate cancer) are likely to have contributed to the heterogeneous relations of Mediterranean diet adherence with overall cancer risk for men and women. It should be noted that other studies did not observe clear differences in associations between the sexes,[10,13] stressing the importance of additional research on this topic.

Associations with Mediterranean diet adherence among women in the present study appeared comparable for overall cancer risk and risks of cancer subgroups defined by the presence of a relation with tobacco smoking, obesity, or alcohol consumption. In contrast to the findings for women, significant heterogeneity was observed in all subgroup comparisons in men. However, associations with Mediterranean diet adherence did not reach statistical significance for any of the subgroups in men and the differences did not seem to be relevant. The statistical power in the present study was high, especially for men, which increased the likelihood for small and irrelevant differences to become statistically significant. Additionally, one should realize that the distribution of the individual cancer types differs between the subgroups in men and women, and that in certain subgroups a substantial proportion can be comprised by sex-specific cancers.

Regarding cancers related vs not related to obesity and alcohol consumption, similar results were obtained in previous studies.[10,13] The inverse association with Mediterranean diet adherence was stronger for smoking-related cancers compared with cancers not related to tobacco smoking in the total EPIC cohort,[10] whereas the opposite was observed in the Greek EPIC cohort.[9] Furthermore, associations did not seem to differ in a Swedish cohort.[13] These contrasting findings may have resulted from differences in the classification of cancer types as being related to tobacco smoking or not. For example, although cancers of the colorectum/large bowel were classified as being smoking-related in the studies by Couto et al[10] and Bodén et al,[13] they were considered not being related to smoking in the study by Benetou et al.[9] Moreover, the subgroup of cancers not being related to tobacco smoking constituted all cancers not classified as being related to smoking in one study,[13] whereas the 2 other studies selected specific cancer types.[9,10]

The cancer-preventive effect of the Mediterranean diet seems biologically plausible. The high intake of dietary antioxidants in the Mediterranean diet (eg, polyphenols and vitamins from plant foods and olive oil) and the resulting higher total antioxidant capacity that has been associated with adherence to this dietary pattern may defend the body against the DNA-damaging effects of free radicals and other oxidants.[46-48] Moreover, the anti-inflammatory effects of polyphenols and the favorable fatty acid profile of the Mediterranean diet (high in anti-inflammatory omega-3 polyunsaturated fatty acids) may reduce inflammation.[47,49] Several additional mechanisms have been proposed for the cancer-preventive effect of the Mediterranean diet, which were among others related to body weight regulation[50] and the low consumption of red and processed meats.[31,48]

Important strengths of the NLCS include the large sample size, prospective design, and nearly complete follow-up of 20.3 years, which make information and selection biases unlikely. The statistical power was adequate to perform sex-specific analyses for overall cancer risk as well as risks of cancer subgroups defined by relations with three major cancer risk factors. The possibility of residual confounding was minimized through comprehensive adjustment for cigarette smoking and other potential confounders, including reproductive factors in women.

Limitations of this study include the lack of updated dietary information during follow-up and possible measurement errors in the exposure assessment, which may have attenuated some associations. The use of cohort-specific cutoffs in the assessment of Mediterranean diet adherence may pose a final weakness. Participants with high aMEDr values in the non-Mediterranean study population of the NLCS could potentially be classified in intermediate or low adherence categories in populations with higher intakes of typically Mediterranean foods. As expected, intakes of typically Mediterranean food groups (eg, vegetables, fruits [including nuts], and legumes) were lower in NLCS subcohort members compared with participants of the Greek EPIC cohort, whereas the opposite was observed for the intake of meat.[28] Among men, median daily intakes were 207 and 550 g/d for vegetables, 166 and 363 g/d for fruits (including nuts), 6 and 9 g/d for legumes, and 141 and 121 g/d for meat (all types) in the NLCS subcohort and EPIC-Greece, respectively. The respective intakes among women were 219 and 500 g/d for vegetables, 215 and 356 g/d for fruits, 5 and 7 g/d for legumes, and 124 and 90 g/d for meat.

CONCLUSIONS

Mediterranean diet adherence was not associated with risk of overall cancer or any of the cancer subgroups in male participants of the prospective NLCS. Multivariable-adjusted HR estimates in women pointed in the inverse direction, but were only statistically significant when comparing the middle with the lowest aMEDr category. Associations of Mediterranean diet adherence with subgroups of cancer defined by relations with tobacco smoking, obesity, and alcohol consumption closely resembled the results obtained for overall cancer risk in women.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

FUNDING/SUPPORT

This study was funded by Wereld Kanker Onderzoek Fonds Nederland (WCRF-NL), as part of the World Cancer Research Fund International grant program (grant number 2015/1390 to P. A. van den Brandt). WCRF-NL had no role in the design, analysis, or writing of this article.

ACKNOWLEDGEMENTS

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.

AUTHOR CONTRIBUTIONS

Both authors have made large contributions to the work described in the current paper. M. Schulpen was involved in the formulation of the research questions, design of the research, data analysis, interpretation of the results, and writing of the manuscript. P. A. van den Brandt was involved in the initiation and coordination of the NLCS, the formulation of the research questions, design of the research, collection of the data, coordination of the analyses, interpretation of the results, and critically reviewed the manuscript.