Mediterranean diet adherence and risk of postmenopausal breast cancer

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Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis

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The Mediterranean Diet (MD) has been associated with reduced mortality and risk of cardiovascular diseases, but there is only limited evidence on cancer. We investigated the relationship between adherence to MD and risk of postmenopausal breast cancer (and estrogen/progesterone receptor subtypes, ER/PR). In the Netherlands Cohort Study, 62,573 women aged 55–69 years provided information on dietary and lifestyle habits in 1986. Follow-up for cancer incidence until 2007 (20.3 years) consisted of record linkages with the Netherlands Cancer Registry and the Dutch Pathology Registry PALGA. Adherence to MD was estimated through the alternate Mediterranean Diet Score excluding alcohol. Multivariate case–cohort analyses were based on 2,321 incident breast cancer cases and 1,665 subcohort members with complete data on diet and potential confounders. We also conducted meta-analyses of our results with those of other published cohort studies. We found a statistically significant inverse association between MD adherence and risk of ER negative (ER−) breast cancer, with a hazard ratio of 0.60 (95% Confidence Interval, 0.39–0.93) for high versus low MD adherence ($p_{trend} = 0.032$). MD adherence showed only non-significant weak inverse associations with ER positive (ER+) or total breast cancer risk. In meta-analyses, summary HRs for high versus low MD adherence were 0.94 for total postmenopausal breast cancer, 0.98 for ER+, 0.73 for ER− and 0.77 for ER − PR− breast cancer. Our findings support an inverse association between MD adherence and, particularly, receptor negative breast cancer. This may have important implications for prevention because of the poorer prognosis of these breast cancer subtypes.

Key words: breast cancer, Mediterranean diet, cohort study

Abbreviations: AIC: Akaike Information Criterium; AICR: American Institute for Cancer Research; aMED: alternate Mediterranean Diet Score; aMEDr: alternate Mediterranean Diet Score excluding alcohol; BMI: body mass index; EPIC: European Prospective Investigation into Cancer; ER+PR+: estrogen receptor positive and progesterone receptor positive; ER−PR−: estrogen receptor negative and progesterone receptor negative; HR: hazard ratio; HRT: hormone replacement therapy; MD: Mediterranean Diet; mMED: modified Mediterranean Diet Score; mMEDr: modified Mediterranean Diet Score excluding alcohol; NHS: Nurses' Health Study; NLCS: Netherlands Cohort Study; SD: standard deviation; WCRF: World Cancer Research Fund; 95% CI: 95% confidence interval.

Additional Supporting Information may be found in the online version of this article.

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Introduction

Breast cancer is the most commonly diagnosed cancer in Western countries, and prevention is of paramount importance to reduce the burden of this disease. Thus far, very few modifiable (lifestyle) risk factors, such as overweight and alcohol consumption, have been identified. Intake of individual dietary factors has been extensively studied in relation to breast cancer risk, but only for alcohol there is convincing evidence for an increased risk.[1] Because individuals do not consume isolated foods or nutrients, studying dietary patterns in relation to breast cancer seems more fruitful, thereby acknowledging interactions between individual components as well as existing collinearity between components. Dietary patterns might also yield more actionable information on dietary change needed for prevention.

In contrast with dietary patterns that are *a posteriori* derived from factor or cluster analyses of a dataset, the Mediterranean diet (MD) score is a dietary quality index, *a priori* constructed on the basis of dietary recommendations.[2] The traditional MD is characterized by a high intake of plant proteins, whole grains, fish and monounsaturated fat, moderate alcohol intake and low intake of refined grains, red meat and sweets.[3,4] MD adherence is associated with decreased risk of mortality and cardiovascular diseases; however, for cancer risk, results are still rather limited. A recent meta-analysis[5] reported a lower incidence of overall breast cancer for women adhering to the highest category of MD-scores in case–control studies, but not in cohort studies. It is important to

What's new?

When it comes to diet and breast cancer risk, dietary patterns may be of greater importance than individual foods or nutrients. It remains uncertain, however, whether specific dietary patterns impact breast cancer risk. The Mediterranean Diet (MD), which is linked to reduced cardiovascular disease risk, is of particular interest. Here, MD adherence was investigated for potential associations with risk of postmenopausal breast cancer. Analyses of data on 62,573 women ages 55–69 enrolled in the Netherlands Cohort Study show that increased MD adherence is associated with reduced risk of estrogen receptor-negative breast cancer. A meta-analysis of cohort studies confirmed the finding.

distinguish between pre- and postmenopausal breast cancer, as well as hormone receptor subtypes, because of differences in etiology. The meta-analysis suggested that evidence for an inverse association with MD was more convincing for postmenopausal breast cancer. Furthermore, differences were noted between different estrogen/progesterone receptor (ER/PR) subtypes of breast cancer in the associations with MD, but this observation was based on very few cohort studies. Recent evidence from a randomized controlled trial on primary prevention of cardiovascular diseases indicated a strong protective effect of MD on the risk of postmenopausal breast cancer in Spain.[6]

We investigated the association between adherence to MD and postmenopausal breast cancer risk, overall and stratified by hormone receptor status, in the Netherlands Cohort Study (NLCS). Based on earlier findings,[7] we hypothesized that MD-adherence would show a stronger inverse association with ER− breast cancer than ER+ breast cancer, which may have important implications for prevention because of the poorer prognosis of ER− breast cancer. Because alcohol is a risk factor for breast cancer,[8] we excluded it from the MD-score that normally includes moderate alcohol consumption, and tested the effect of this exclusion. We also conducted meta-analyses on MD-adherence and breast cancer risk by subtype.

Material and Methods

Study design and cancer follow-up

The NLCS started in September 1986 and the female part included 62,573 women aged 55–69 years.[9] At baseline, participants completed a mailed, self-administered questionnaire on cancer risk factors. The NLCS study was approved by institutional review boards from Maastricht University and the Netherlands Organization for Applied Scientific Research. All cohort members consented to participation by completing the questionnaire. For data processing and analysis the case–cohort method was used.[10] Accumulated person-years in the cohort were estimated from a subcohort ($n = 2{,}589$ women), randomly sampled from the cohort immediately after baseline. These subcohort members were actively followed up biennially for vital status information. The follow-up of the subcohort was 100% complete at 20.3 years of follow-up.

Follow-up for cancer incidence was established by annual record linkage with the Netherlands Cancer Registry and PALGA, the nationwide Dutch Pathology Registry.[11] Completeness of follow-up through record linkage with cancer registries and PALGA was estimated to be >95%.[12] After 20.3 years of follow-up (September 17, 1986 until January 1, 2007), a total of 3,354 incident breast cancer cases were detected among women. Cases and subcohort members were excluded if they reported a history of cancer (except skin cancer) at baseline and if their dietary data were incomplete or inconsistent. Figure S1 (Supplementary data) shows the selection and exclusion steps that resulted in the number of cases and female subcohort members that were included in the analysis. There were 1,665 subcohort members and 2,321 breast cancer cases available for analysis.

Exposure assessment

The 11-page baseline questionnaire measured dietary intake, detailed smoking habits, anthropometry, physical activity and other risk factors related to cancer.[9] Habitual consumption of food and beverages during the year preceding baseline was assessed using a 150-item semi-quantitative food-frequency questionnaire, which was validated against a 9-day diet record.[13] Nutrient intakes were calculated using the computerized Dutch food composition table.[14] Non-occupational physical activity was calculated by adding the minutes spent per day on cycling or walking, shopping, walking the dog, gardening and sports or exercise as reported previously.[15]

Mediterranean diet score

Conformity with the MD was assessed using the alternate Mediterranean Diet Score (aMED),[16,17] which is an adapted version of the traditional Mediterranean Diet Score created by Trichopoulou *et al.*[18,19] The aMED contains 9 dietary components that are typical of the Mediterranean diet. To control for energy intake, the intake of each component was first adjusted to a daily intake of 2,000 kcal.[16,17,19] For each of the presumed beneficial food items (vegetables (without potatoes), legumes, fruits, nuts, whole grains, fish and the ratio of monounsaturated to saturated fatty acid intake (MUFA:SFA)), one point was given when the intake was at least the sex-specific median intake, and zero otherwise. For red and processed meat, 1 point was given (and 0 otherwise) when the intake was below the sex-specific median intake. In the full aMED, 1 additional point is normally given when alcohol intake is between 5 and 25 g/day, and 0 otherwise.[17]

However, since alcohol is a risk factor for breast cancer,[8] we excluded alcohol from the score in the present analysis. The reduced 9-point sum score (aMEDr) ranged from zero to eight points (minimal to maximal conformity). Mediterranean diet adherence was also assessed using the modified MD score by Trichopoulou *et al.*,[20] abbreviated as mMED. Apart from alcohol, this score differs from aMED as follows: fruits and nuts are combined in one component; dairy is considered as component; cereals are considered as component instead of whole grains, total meat is used instead of red and processed meat, and for fatty acids the ratio of (MUFA + PUFA):SFA is used.

Statistical analysis

The reduced scores (aMEDr and mMEDr) were categorized in three categories: 0–3, 4–5 and 6–8 points. The distribution of the subcohort members by aMEDr-score, mMEDr-score and various characteristics was examined by cross-tabulations and summary statistics.

The relationship between Mediterranean diet adherence and breast cancer risk was evaluated using Cox proportional hazards models. It was verified that the proportional hazards assumption was not violated using scaled Schoenfeld residuals[21] and -ln(-ln) survival plots. Standard errors were estimated using the robust Hubert–White sandwich estimator to account for additional variance introduced by the subcohort sampling.[22] We conducted age- and multivariable-adjusted survival analyses in which aMEDr and mMEDr were tested on categorical and continuous scales. In the multivariable analyses, hazard ratios (HRs) were corrected for potential confounding by age at baseline (55–59, 60–64, 65–69 years), cigarette smoking (status (never, former, current), frequency (number of cigarettes per day; continuous, centered), duration (number of years; continuous, centered)), body height (continuous, cm), BMI (<18.5, 18.5–<25, 25–<30, ≥30 kg/m^2), non-occupational physical activity (≤30, >30–60, >60–90, >90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational and higher vocational or university), family history of breast cancer in mother or sisters (no, yes), history of benign breast disease (no, yes), 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 (<45, 45–49, 50–54, ≥55 years), oral contraceptive use (never, ever), postmenopausal hormone replacement therapy (never, ever), energy intake (continuous, kcal/day) and, depending on the analysis, alcohol intake (0, 0.1–<5, 5–<15, 15–<30, ≥30 g/day).

Tests for trends were assessed by fitting ordinal exposure variables as continuous terms.

The Akaike Information Criterium (AIC)[23] was used to compare performance of models with aMEDr and mMEDr scores. We also analyzed associations with the full aMED and mMED-scores (including alcohol) to compare these with models using aMEDr and mMEDr, using the AIC. Besides overall postmenopausal breast cancer, we conducted these analyses for subtypes defined by hormone receptor status: ER+, ER−, PR+, PR−, ER + PR+ and ER − PR−. Differences in associations with MD-scores between breast cancer subtypes were tested using a heterogeneity test,[24] in which the standard error for the observed difference in rate ratios was estimated using a bootstrapping method developed for the case–cohort design.[25] To evaluate potential residual confounding by breast cancer risk factors, and effect modification, analyses of MD-scores and breast cancer were also conducted within strata of age at baseline, smoking status, alcohol intake, BMI and physical activity and family history of breast cancer. Interactions with these factors were tested using Wald tests and cross-product terms. In sensitivity analyses, we repeated analyses after excluding cancers (and person-years) occurring in the first 2 years of follow-up, and we also split the follow-up period in 3 periods.

Population attributable fractions were calculated[26] to estimate the potentially avoidable proportion of cancer if all participants would shift towards the highest MD-score category. As a more realistic scenario, preventable proportions were also calculated to estimate the preventable proportion of cancer if all participants in the lowest 2 categories of MD-scores would shift their pattern 1 category upward.[27,28] The STATA-command "punafcc" was used to calculate the population attributable fractions and 95% CIs.[29]

To investigate possible dominance of certain components of the MD-scores,[30] we ran analyses in which all components were entered as dichotomous variables simultaneously in Cox regression models. We then subtracted alternately one component at a time from the original 9-point sum score (thus reducing it to an 8-point score), and estimated HRs per 2-point increment in the reduced score (corrected by 8/9 before exponentiating them to preserve comparability), as in Trichopoulou *et al.*[30]

The MD-scores are relative measures, using cohort-specific medians as cut-offs. We compared the MD-score findings with a score that uses absolute cut-offs, based on the dietary part of the cancer prevention recommendations issued by World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).[1] We operationalized their dietary recommendations by using the same absolute cut-offs per recommendation (sometimes subrecommendations) as in EPIC,[31,32] using scores of 1 if the recommendation was met, 0.5 if half met, and 0 if not met. This concerned intake of energy-dense foods (≤125, >125–<175, ≥175 kcal/100 g per day) and sugary drinks (0, ≤250, >250 g/day); vegetables and fruit (≥400, 200–<400, <200 g/day), and dietary fiber (≥25, 12.5–<25, <12.5 g/day); red and processed meat (red& processed meat <500 g/week and processed meat <3 g/day; red& processed meat <500 g/wk and processed meat 3–<50 g/day; red& processed meat ≥500 g/wk and processed meat ≥50 g/day); and alcohol (<10, 10–20, >20 g/day). We additionally operationalized the WCRF/AICR-recommendation on salt intake by categorizing the calculated[33] total salt intake (from food and salt added during cooking or consumption) into <6, 6–<9, 9+ g/day with scores 1,

Table 1. Baseline characteristics (mean (SD), or percentage) according to category of Mediterranean diet adherence (excluding alcohol) in subcohort women (in those with complete data on aMEDr and mMEDr), the Netherlands Cohort Study

	aMEDr[1]			mMEDr[2]		
Characteristic	0–3 pts	4–5 pts	6–8 pts	0–3 pts	4–5 pts	6–8 pts
Number of subjects	769	901	357	730	981	316
Age (years)	61.7 (4.4)	61.3 (4.2)	60.8 (4.0)	61.7 (4.3)	61.3 (4.2)	61.1 (4.2)
Height (cm)	165.0 (6.4)	165.6 (6.0)	165.4 (5.8)	165.5 (6.2)	165.1 (6.1)	165.4 (6.1)
BMI (kg/m^2)	25.1 (3.6)	25.1 (3.6)	24.7 (3.1)	24.9 (3.6)	25.1 (3.5)	24.9 (3.5)
Physical activity (min/day)	62.0 (55.1)	63.8 (45.8)	72.6 (52.6)	59.7 (48.1)	66.5 (50.0)	70.3 (57.0)
Age at menarche (year)	13.7 (1.8)	13.7 (1.7)	13.5 (1.7)	13.7 (1.7)	13.6 (1.8)	13.6 (1.8)
Age at menopause (year)	48.6 (4.5)	48.7 (4.4)	49 (4.5)	48.6 (4.4)	48.9 (4.5)	48.7 (4.5)
Alcohol intake (g/day)	5.1 (9.1)	6.3 (9.7)	6.5 (9.5)	6.2 (9.4)	5.9 (9.7)	5.4 (9.0)
Energy intake (kcal/day)	1,696 (392)	1,676 (391)	1,698 (397)	1,709 (384)	1,682 (398)	1,654 (392)
Nulliparous (%)	20.2	19.2	13.9	21.3	17.3	16.6
Age at first birth $\geq$ 30 years (% of parous)	22.7	22.3	22.6	22.2	22.3	23.8
Ever used OC (%)	23.2	23.9	33.5	24.7	25.2	27.3
Ever used HRT (%)	12.6	14.0	13.7	14.2	12.8	13.4
Family history breast ca (%)	10.0	8.3	7.3	8.5	9.0	8.9
History benign breast disease (%)	7.2	8.7	7.6	7.7	7.2	10.4
Current cigarette smoker (%)	26.1	19.8	14.6	25.1	20.1	16.1
University or higher vocational education (%)	6.9	10.7	12.1	9.3	8.8	12.3
Alcohol in range 5–25 g/day (%)	22.1	28.3	31.7	28.6	25.4	25.3

[1]aMEDr: alternate Mediterranean Diet Score excluding alcohol.
[2]mMEDr: modified Mediterranean Diet Score excluding alcohol.

0.5 and 0, respectively (based on Dutch dietary guidelines 2015[34]). The resulting sum score (ranging from 0 to 5) was used in survival analyses; an additional sum score without alcohol was also made. The AIC was used to compare the fit of models with these sum scores to models with MD-scores.

Meta-analyses

Using PubMed with search terms Mediterranean diet, and breast cancer/neoplasm/tumor, or mammary carcinoma/tumors, cohort studies of the association between MD-adherence (*a priori* defined) and breast cancer were identified up to August 2016. Six articles on breast cancer (ER/PR subtypes) were identified.[7,35–39] Because Buckland *et al.*[37] presented EPIC-wide results, the results from specific EPIC countries[35,39] were not included in the meta-analysis to avoid overlap. In addition to EPIC-results, the publication by Pot *et al.*[39] also included results of Cade *et al.*[36] Data on total postmenopausal breast cancer and subtypes of the remaining four cohorts (Nurses' Health Study (NHS), UK Women's Cohort Study (UKWCS), European Prospective Investigation into Cancer (EPIC), Women's Lifestyle and Health (WLH)) were combined with NLCS-data in the meta-analysis. HRs for the contrast between highest versus lowest category of MD-adherence from each study were pooled using random-effects models. In these analyses, the HR estimate for each study was weighted by the inverse of the variance of the log HR to calculate the summary HR and its 95% confidence interval (CI). Heterogeneity between studies was estimated using the Cochran's Q test and I^2 (the proportion of variation in HRs attributable to heterogeneity[40]). Publication bias was assessed by the Begg test.[41] Analyses were performed using Stata version 12; presented *p*-values are two-sided, with $p < 0.05$ considered as statistically significant.

Results

The mean (SD) score of aMEDr among subcohort members was 4.0 (1.6), and for mMEDr 4.0 (1.5). Table 1 summarizes several baseline characteristics according to adherence to aMEDr and mMEDr. Conformity with the Mediterranean diet was lower in older women, in nulliparous women, current smokers, in those with a positive family history of breast cancer (for aMEDr), and was higher in physically active women, higher educated women and ever oral contraceptive user. Alcohol intake was somewhat higher in those scoring higher on aMEDr, but this was reversed for mMEDr. Women with a high score on mMEDr more often reported a history of benign breast disease.

Table 2 shows results of the age-adjusted and multivariable-adjusted analyses of the associations of MD-scores with total breast cancer risk. While the aMEDr-score was significantly inversely associated with breast cancer risk in age-adjusted analyses, in multivariable-adjusted continuous analyses, the HR per 2-point increment was 0.92 (95% CI, 0.84, 1.01). In

Table 2. Hazard ratio of breast cancer, according to adherence to aMED and mMED, without and with alcohol, in multivariable-adjusted[1] analyses, the Netherlands Cohort Study

	MD-score without alcohol in score (aMEDr and mMEDr)					MD-score with alcohol in score (aMED and mMED)[2]				
	0–3 pts	4–5 pts	6–8 pts	*p* Trend	Cont, per 2 pts	0–3 pts	4–5 pts	6–9 pts	*p* Trend	Cont, per 2 pts
aMED										
No. of cases	928	987	406			789	996	536		
Person-years in subcohort	10,438	13,016	5,478			9,163	12,599	7,170		
Age-adjusted HR	1	0.85	0.83	0.023	0.91	1	0.92	0.87	0.094	0.94
(95% CI)		(0.74–0.98)	(0.69–1.00)		(0.84–0.99)		(0.79–1.06)	(0.73–1.03)		(0.87–1.01)
Multivariable-adjusted HR	1	0.82	0.87	0.066	0.92	1	0.88	0.88	0.142	0.94
(95% CI)		(0.70–0.96)	(0.72–1.06)		(0.84–1.01)		(0.75–1.03)	(0.73–1.06)		(0.87–1.03)
AIC			33,363					33,384		
mMED										
No. of cases	877	1074	370			731	1077	513		
Person-years in subcohort	9,871	14,224	4,837			8,198	14,242	6,491		
Age-adjusted HR	1	0.85	0.86	0.056	0.94	1	0.85	0.89	0.143	0.96
(95% CI)		(0.74–0.98)	(0.71–1.05)		(0.86–1.03)		(0.73–0.98)	(0.74–1.06)		(0.88–1.04)
Multivariable-adjusted HR	1	0.84	0.85	0.052	0.92	1	0.83	0.88	0.135	0.94
(95% CI)		(0.72–0.98)	(0.69–1.05)		(0.84–1.01)		(0.71–0.97)	(0.73–1.07)		(0.86–1.03)
AIC			33,366					33,377		

[1]Multivariable analyses were adjusted for: age at baseline (55–59, 60–64, 65–69 years), cigarette smoking (status (never, former, current), frequency (number of cigarettes per day; continuous, centered), duration (number of years; continuous, centered)), body height (continuous, cm), BMI (<18.5, 18.5–<25, 25–<30, ≥30 kg/m2), non-occupational physical activity (≤30, >30–60, >60–90, >90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), family history of breast cancer in mother or sisters (no, yes), history of benign breast disease (no, yes), 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 (<45, 4,549, 50–54, >55 years), oral contraceptive use (never, ever), postmenopausal HRT (never, ever), energy intake (continuous, kcal/day) and alcohol intake (0, 0.1–<5, 5–<15, 15–30, >30 g/day).
[2]Without additional adjustment for alcohol intake.

multivariable-adjusted categorical analyses, only the medium category showed a significantly decreased risk with a HR of 0.82 (95% CI, 0.70, 0.96), compared to low adherence score, and there was no clear decreasing trend across categories (*p*-trend = 0.066). The AIC of the model using aMEDr was smaller compared to the mMEDr-model, indicating a better fit using aMED-scoring. For comparison, the table also shows analyses when using the full aMED and mMED including alcohol. The AIC-values indicated a worse fit for both aMED and mMED when alcohol was included in the scores (Table 2). Based on this, ensuing analyses were conducted primarily with aMEDr; at several places we also present results for mMEDr for reasons of comparison.

Table 3 shows age- and multivariable-adjusted associations between aMEDr and risk of estrogen and progesterone receptor subtypes of breast cancer. There was a stronger inverse association with aMEDr for ER− breast cancer than for ER+ breast cancer, with HRs when comparing high versus low adherence of 0.60 (95% CI, 0.39, 0.93), *p*-trend = 0.032 for ER−, and 0.87 (95% CI, 0.69, 1.10), *p*-trend = 0.101 for ER+, respectively. The same pattern was seen for PR subtypes, albeit somewhat less strongly inverse in PR− than ER− subtype. Similarly, ER − PR− breast cancer was significantly inversely related to MD-adherence (*p*-trend= 0.047) with a HR per 2-point increment of 0.75 (95% CI, 0.60, 0.94), while the ER + PR+ subtype showed no significant association. Heterogeneity tests across subtypes using bootstrapping were not significant. The analyses in Table 3 were also conducted with mMEDr. When mMEDr was used, the HRs per 2-point increment were 0.95 (95% CI, 0.85–1.07) in ER+ breast cancer, 0.85 (0.71–1.03) for ER− breast cancer, 0.95 (0.83–1.08) in PR+, 0.90 (0.76–1.07) in PR−, 0.94 (0.83–1.08) in ER + PR+ and 0.79 (0.63–0.99) in ER−PR− breast cancer, i.e. all somewhat weaker associated than with aMEDr.

Estimation of the population attributable fractions (PAFs) indicated that 2.3% (95% CI, −13.1%, 15.5%) of total breast

Table 3. Hazard Ratio of breast cancer subtypes, according to adherence to Mediterranean diet (aMEDr) in multivariable-adjusted[1] analyses, the Netherlands Cohort Study

	aMEDr					
	0–3 pts	4–5 pts	6–8 pts	*p* Trend	AIC	Cont, per 2 pts
Total breast cancer						
No. of cases	928	987	406			
Person-years in subcohort	10,438	13,016	5,478			
Age-adjusted HR	1	0.85	0.83	0.023		0.91
(95% CI)		(0.74–0.98)	(0.69–1.00)			(0.84–0.99)
Multivariable-adjusted HR	1	0.82	0.87	0.066	33,363	0.92
(95% CI)		(0.70–0.96)	(0.72–1.06)			(0.84–1.01)
ER+ breast cancer						
No. of cases	460	466	195			
Age-adjusted HR	1	0.82	0.80	0.022		0.89
(95% CI)		(0.69–0.97)	(0.64–1.00)			(0.81–0.99)
Multivariable-adjusted HR	1	0.81	0.87	0.101	16,119	0.91
(95% CI)		(0.68–0.97)	(0.69–1.10)			(0.82–1.02)
ER− breast cancer						
No. of cases	100	116	32			
Age-adjusted HR	1	0.93	0.59	0.024		0.81
(95% CI)		(0.69–1.24)	(0.39–0.91)			(0.69–0.97)
Multivariable-adjusted HR	1	0.92	0.60	0.032	3,623	0.81
(95% CI)		(0.67–1.25)	(0.39–0.93)			(0.67–0.96)
PR+ breast cancer						
No. of cases	276	305	122			
Age-adjusted HR	1	0.89	0.83	0.139		0.93
(95% CI)		(0.73–1.09)	(0.64–1.08)			(0.82–1.04)
Multivariable-adjusted HR	1	0.90	0.90	0.378	10,101	0.94
(95% CI)		(0.73–1.11)	(0.69–1.19)			(0.83–1.07)
PR− breast cancer						
No. of cases	158	157	60			
Age-adjusted HR	1	0.79	0.69	0.017		0.80
(95% CI)		(0.61–1.01)	(0.48–0.96)			(0.69–0.93)
Multivariable-adjusted HR	1	0.76	0.72	0.047	5,422	0.81
(95% CI)		(0.59–1.00)	(0.52–1.05)			(0.69–0.96)
ER+PR+ breast cancer						
No. of cases	270	295	120			
Age-adjusted HR	1	0.88	0.84	0.146		0.93
(95% CI)		(0.72–1.08)	(0.65–1.09)			(0.83–1.04)
Multivariable-adjusted HR	1	0.89	0.91	0.400	9,838	0.95
(95% CI)		(0.71–1.10)	(0.69–1.21)			(0.83–1.08)
ER−PR− breast cancer						
No. of cases	71	75	24			
Age-adjusted HR	1	0.83	0.61	0.042		0.77
(95% CI)		(0.59–1.18)	(0.37–0.99)			(0.63–0.95)
Multivariable-adjusted HR	1	0.79	0.61	0.047	2,483	0.75
(95% CI)		(0.55–1.14)	(0.36–1.01)			(0.60–0.94)

[1]Multivariable analyses were adjusted for: age at baseline (55–59, 60–64, 65–69 years), cigarette smoking (status (never, former, current), frequency (number of cigarettes per day; continuous, centered), duration (number of years; continuous, centered)), body height (continuous, cm), BMI (<18.5, 18.5–<25, 25–<30, ≥30 kg/m2), non-occupational physical activity (≤30, >30–60, >60–90, >90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational and higher vocational or university), family history of breast cancer in mother or sisters (no, yes), history of benign breast disease (no, yes), 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 (<45, 45–49, 50–54, >55 years), oral contraceptive use (never, ever), postmenopausal HRT (never, ever), energy intake (continuous, kcal/day) and alcohol intake (0, 0.1–<5, 5–<15, 15–<30, >30 g/day).

Table 4. Hazard ratios of breast cancer associated with two point increment in aMEDr, after alternate subtraction of each aMEDr-component, in multivariable-adjusted[1] analyses, the Netherlands Cohort Study

	Total breast cancer (2,321 cases)			ER+ (1,121 cases)			ER− (248 cases)		
aMEDr variant	HR	(95% CI)	HR reduction (%)[2]	HR	(95% CI)	HR reduction (%)[2]	HR	(95% CI)	HR reduction (%)[2]
aMEDr	0.919	(0.840–1.006)		0.912	(0.817–1.018)		0.806	(0.673–0.964)	
Excluding vegetables	0.938	(0.857–1.027)	23.8	0.930	(0.832–1.039)	20.8	0.809	(0.671–0.977)	2.1
Excluding legumes	0.904	(0.825–0.989)	−20.6	0.900	(0.805–1.007)	−14.0	0.817	(0.679–0.982)	6.2
Excluding fruits	0.938	(0.86–1.023)	23.8	0.925	(0.833–1.027)	15.0	0.849	(0.716–1.007)	24.3
Excluding nuts	0.928	(0.851–1.013)	11.1	0.921	(0.830–1.023)	11.1	0.869	(0.733–1.031)	35.0
Excluding whole grains	0.945	(0.863–1.034)	32.3	0.948	(0.851–1.056)	42.0	0.801	(0.663–0.967)	−2.9
Excluding red & processed meat	0.913	(0.837–0.996)	−7.9	0.908	(0.818–1.009)	−4.3	0.794	(0.667–0.945)	−7.0
Excluding fish	0.925	(0.845–1.012)	6.9	0.930	(0.835–1.036)	20.8	0.824	(0.687–0.987)	10.3
Excluding MUFA:SFA ratio	0.930	(0.855–1.011)	13.2	0.917	(0.828–1.014)	5.3	0.830	(0.704–0.977)	13.6

[1]Multivariable analyses were adjusted for: age at baseline (55–59, 60–64, 65–69 years), cigarette smoking (status (never, former, current), frequency (number of cigarettes per day; continuous, centered), duration (number of years; continuous, centered)), body height (continuous, cm), BMI (<18.5, 18.5–<25, 25–<30, ≥30 kg/mh2), non-occupational physical activity (≤30, >30–60, >60–90, >90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational and higher vocational or university), family history of breast cancer in mother or sisters (no, yes), history of benign breast disease (no, yes), 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 (<45, 45–49, 50–54, >55 years), oral contraceptive use (never, ever), postmenopausal HRT (never, ever), energy intake (continuous, kcal/day) and alcohol intake (0, 0.1–<5, 5–<15, 15–<30, >30 g/day), and the subtracted aMEDr-component (dichotomized by median intake).
[2]Compared to aMEDr.

cancer could be avoided if all participants would shift towards the highest aMEDr category. The estimated PAF for ER+ breast cancer was 2.3% (95% CI, −16.4%, 18.0%), and 32.4% (95% CI, 4.1%, 52.3%) for ER− breast cancer. If participants would shift their pattern 1 category upward, the estimated preventable proportions were 4.8% for total breast cancer, 5.2% for ER+, and 20.0% for ER− breast cancer.

Table S1 shows the hazard ratio of breast cancer associated with each of the components of aMEDr, dichotomized at the median intakes, when they were simultaneously entered in the model. Nut intake was significantly inversely associated with ER− breast cancer; other components were mostly weakly inversely associated with breast cancer (subtypes), but not statistically significant. Table 4 shows the HR of breast cancer associated with a 2-point increment in aMEDr, and how this HR changed after alternate removal of each of its eight components; the percentage reduction in the size of the HR is also presented. For example, when vegetables were excluded from the score, the HR of 0.938 indicated the apparent beneficial effect was reduced by 23.8%, compared to HR = 0.919 for the full score. These analyses are presented for total breast cancer and ER subtypes. Table 4 shows that whole grain intake contributed most to the inverse association for total and ER+ breast cancer, but for ER− breast cancer nut intake seemed most dominant. For total breast cancer, the second and third most dominant components were vegetables and fruit, for ER+ these were vegetables and fish, and for ER− breast cancer fruit and the MUFA/SFA-ratio. Excluding red and processed meat, and legumes showed opposite effects on HRs for breast cancer, i.e. somewhat stronger HRs.

In Figure 1, associations between a 2-point increment in aMEDr and breast cancer are presented, in subgroups of potential effect modifiers: age at baseline, smoking status, alcohol intake, BMI and physical activity and family history of breast cancer. Inverse associations were seen in most subgroups, and there was no significant interaction. Similarly, associations were essentially similar when the follow-up period was split in 0–2 years, 2–10 and 10–20 years (Fig. 1). The corresponding interaction analyses for the ER subtypes of breast cancer are also presented in Figure 1. Only for ER− breast cancer, statistically significant interactions were seen with age at baseline and alcohol intake. While aMEDr showed a stronger inverse association with ER− breast cancer in women drinking 15+ g/day alcohol, the inverse association was also more apparent in younger women.

To enable comparison of HR-estimates using aMED-scores with models using the WCRF/AICR-score for dietary recommendations, the scores were assessed as continuous variables with 1 SD as increment. This was done for the scores including and excluding alcohol. For comparability, models for aMED-scores were rerun with the same participants as in the WCRF/AICR-score models because the inclusion of salt data introduced some additional missing values. The results in Table 5 show that the model performance was

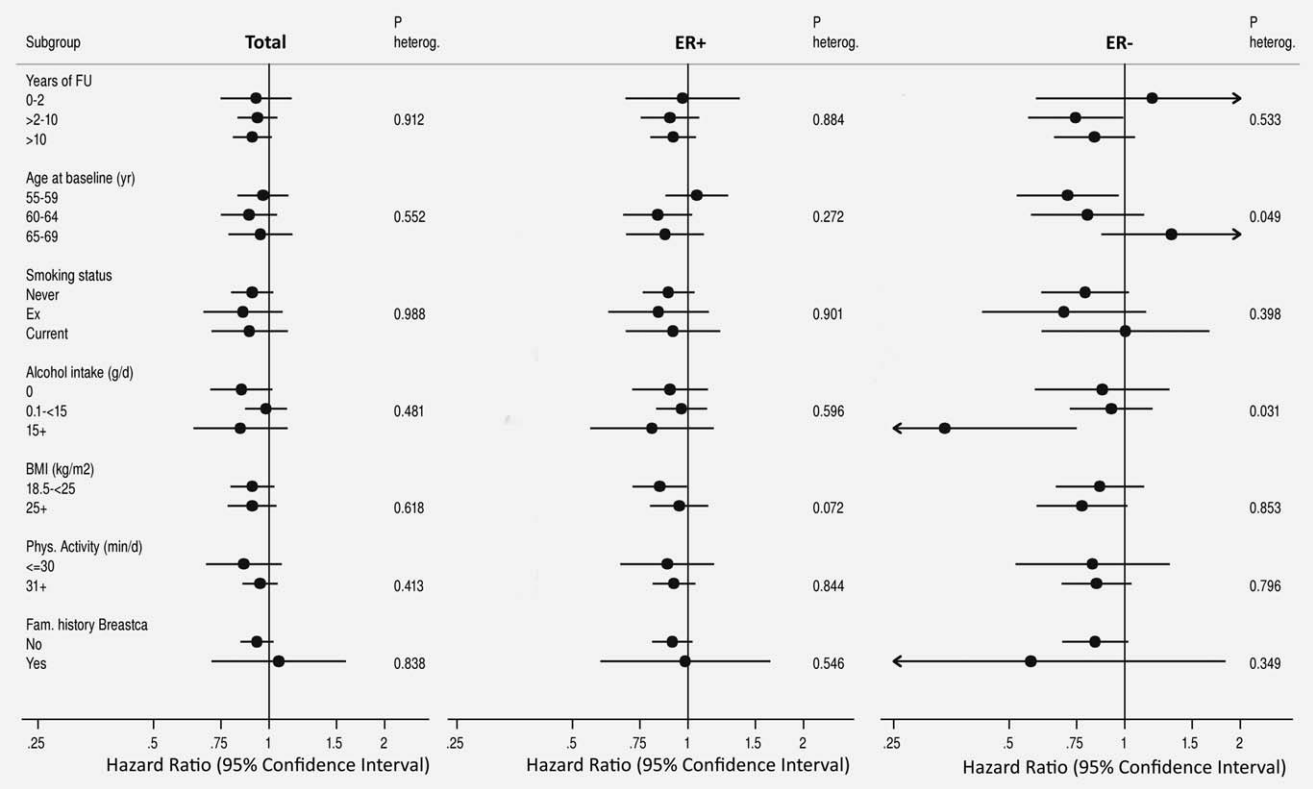

Figure 1. Hazard ratios of breast cancer associated with a 2-point increment in aMEDr, in subgroups. Multivariable analyses were adjusted for: age at baseline (55–59, 60–64, 65–69 years), cigarette smoking (status (never, former, current), frequency (number of cigarettes per day; continuous, centered), duration (number of years; continuous, centered)), body height (continuous, cm), BMI (<18.5, 18.5–<25, 25–<30, ≥30 kg/m2), non-occupational physical activity (≤30, >30–60, >60–90, >90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational and higher vocational or university), family history of breast cancer in mother or sisters (no, yes), history of benign breast disease (no, yes), 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 (<45, 45–49, 50–54, >55 years), oral contraceptive use (never, ever), postmenopausal HRT (never, ever), energy intake (continuous, kcal/day) and alcohol intake (0, 0.1–<5, 5–<15, 15–<30, >30 g/day).

better (as judged by lower AIC) when using the aMED-scores (excluding or including alcohol), compared to the dietary WCRF/AICR-scores, for total breast cancer and the ER subtypes. The analyses in Table 5 were also conducted with mMED. For comparison, when mMED (including alcohol) was used, the HR per 1-SD increment was 0.96 (95% CI, 0.90–1.03). When mMEDr was used, the HRs per 1-SD increment were 0.95 (95% CI, 0.88–1.02) in total breast cancer, 0.95 (0.88–1.04) in ER+, and 0.89 (0.77–1.02) in ER− breast cancer, i.e. all somewhat weaker associated than with aMEDr.

Meta-analyses

The forest plots and summary estimates for highest versus lowest MD-adherence category are presented in Figure 2, for total postmenopausal breast cancer and subtypes, when at least 2 studies were available. For total breast cancer, the summary HR (95% CI) was 0.94 (0.88, 1.01), with no evidence of between-study heterogeneity ($p = 0.330$). While there was no evidence for an association with ER+ breast cancer, the common HRs (95% CI) for ER− and ER − PR− breast cancer (each based on 2 cohorts) were 0.73 (0.57, 0.93) and 0.77 (0.63, 0.94), respectively, with no evidence of between-study heterogeneity. As a further sensitivity analysis, Figure S2 (Supplementary data) shows results of a meta-analysis of studies on total postmenopausal breast cancer, that included or excluded alcohol from the MD-score, respectively. When alcohol was excluded, the summary HR (95% CI) was 0.92 (0.87, 0.98), while there was no association when alcohol was included.

Discussion

In our large prospective study, we found a statistically significant inverse association between adherence to Mediterranean Diet and risk of estrogen receptor negative postmenopausal breast cancer, with a HR of 0.60 for high versus low adherence to MD. There were no significant inverse associations with ER+ or total breast cancer risk. The model fit was better when alcohol was excluded from the aMED-score, and the aMED performed better than the mMed in our cohort. We found no association between breast cancer and adherence to WCRF/AICR-dietary recommendations. In meta-analyses, summary HRs for high versus low MD-adherence were 0.94 for total postmenopausal breast cancer, 0.98 for ER+, 0.73 for ER− and 0.77 for ER − PR− breast cancer.

Table 5. Hazard ratios of breast cancer associated with 1-SD increment in WCRF-diet score compared to aMED, including or excluding alcohol, in multivariable-adjusted[1] analyses, the Netherlands Cohort Study

Score	HR	(95% CI)	AIC
Scores including alcohol			
Breast ca total (2,289 cases)			
WCRFdietalc[2,3]	1.01	(0.93–1.08)	32,853
aMED[2]	0.95	(0.89–1.02)	32,848
Scores excluding alcohol			
Breast ca total (2,289 cases)			
WCRFdiet[4]	1.02	(0.94–1.09)	32,844
aMEDr	0.94	(0.87–1.01)	32,837
Breast ca ER+ (1,108 cases)			
WCRFdiet[4]	0.99	(0.90–1.08)	15,826
aMEDr	0.92	(0.85–1.01)	15,820
Breast ca ER− (244 cases)			
WCRFdiet[4]	1.00	(0.86–1.16)	3,532
aMEDr	0.84	(0.73–0.97)	3,525

[1]Multivariable analyses were adjusted for: age at baseline (55–59, 60–64, 65–69 years), cigarette smoking (status (never, former, current), frequency (number of cigarettes per day; continuous, centered), duration (number of years; continuous, centered)), body height (continuous, cm), BMI (<18.5, 18.5–<25, 25–<30, ≥30 kg/m2), non-occupational physical activity (≤30, >30–60, >60–90, >90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational and higher vocational or university), family history of breast cancer in mother or sisters (no, yes), history of benign breast disease (no, yes), 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 (<45, 45–49, 50–54, >55 years), oral contraceptive use (never, ever), postmenopausal HRT (never, ever), energy intake (continuous, kcal/day) and alcohol intake (0, 0.1–<5, 5–<15, 15–<30, >30 g/day).
[2]Model excluding alcohol as covariate.
[3]WCRF/AICR dietary recommendations including alcohol.
[4]WCRF/AICR dietary recommendations excluding alcohol.

When alcohol was excluded from MD-scores, the summary HR (95% CI) was 0.92 (0.87, 0.98) for total breast cancer, while there was no association when alcohol was included.

Several cohort studies have investigated the association between *a priori* defined MD-pattern and overall breast cancer risk, or subtypes. In the NHS-cohort, no association was found with total or ER+ postmenopausal breast cancer risk,[7] but for ER− breast cancer, the HR comparing highest to lowest quintiles of aMED (including alcohol) was 0.79 (p-trend= 0.03). In EPIC overall, high versus low rMED-score (variant of mMED) (excluding alcohol) was related to reduced postmenopausal breast cancer risk (HR = 0.93), especially with ER−/PR− tumors (HR = 0.80), and not with premenopausal breast cancer.[37] Thus, our findings are in accordance with these cohorts. In a Swedish cohort study, high versus low mMED-score (including alcohol) was non-significantly inversely associated with postmenopausal breast cancer (HR = 0.59), but not in continuous analyses.[38] Apart from overall EPIC-results, there are also some country-specific reports. MD-adherence was inversely associated with overall postmenopausal breast cancer in EPIC-Greece (HR = 0.78 per 2-point increment).[35] A UK Cohort consortium which included EPIC-Oxford and EPIC-Norfolk reported no association between MD-adherence and breast cancer,[39] but no information was available on ER/PR− status. In EPIC-France, an inverse association was found between *a posteriori* defined "healthy/Mediterranean" diet and postmenopausal breast cancer, particularly ER+/PR− tumors, but not in ER− tumors.[42]

Our meta-analysis of cohort studies did not show a significantly inverse association between overall postmenopausal breast cancer and high versus low MD-adherence, although the HR-estimate of 0.94 was marginally significant, with no obvious heterogeneity. However, in contrast to ER+, our meta-analysis showed inverse associations with ER− or ER − PR− breast cancer subtypes, with significant HRs of 0.73 and 0.77, respectively. Although still based on few cohort studies, these subtype findings may be of particular importance because identification of preventive factors for ER− breast cancers may help to reduce the burden of breast cancer since these tumors respond less well to treatment and have lower 5-year survival rates than ER+ tumors. As has been suggested before,[7,37] any potential influence of dietary factors may be difficult to detect in ER+ tumors given the strong influence of hormonal factors. In ER− tumors, other risk factors, including diet, may exert a relatively larger influence and be more easily detectable.[7]

Interestingly, a recent secondary analysis of a RCT on primary prevention of cardiovascular diseases (PREDIMED) indicated a strong protective effect of Mediterranean diet versus low-fat diet on the risk of postmenopausal breast cancer in Spain, with a HR of 0.43 (95% CI, 0.21–0.88). The effect was stronger in those randomized to the MD supplemented with extra-virgin olive oil than with nuts, but in both MD-intervention groups the effect was significant.[6] Nevertheless, because the trial had only 35 incident breast cancer cases as outcome, this needs to be confirmed in larger trials, preferably also with analyses per receptor subtype.

Consistent with evidence on alcohol and breast cancer,[8] our model fit was also worse when moderate alcohol was included in the scores. This was also confirmed in our meta-analysis of MD-scores excluding and including alcohol. In our study, the performance of models with aMED-scores was better than with mMED-scores. This may possibly be due to the fact that the cereal group in mMED aggregates refined and whole grain cereals, while aMED uses whole grain cereals; both cereal types may have distinct effects on breast cancer risk.[37,43] In our analysis with aMED-components, whole grain intake contributed most to the inverse association for total and ER+ breast cancer, whereas nut intake seemed most dominant for associations with ER− breast cancer. Such an analysis of dominant components has only been done before with total mortality using mMED,[30] which makes it difficult to compare to our results. We did not specifically use a MD score that included olive oil as component.

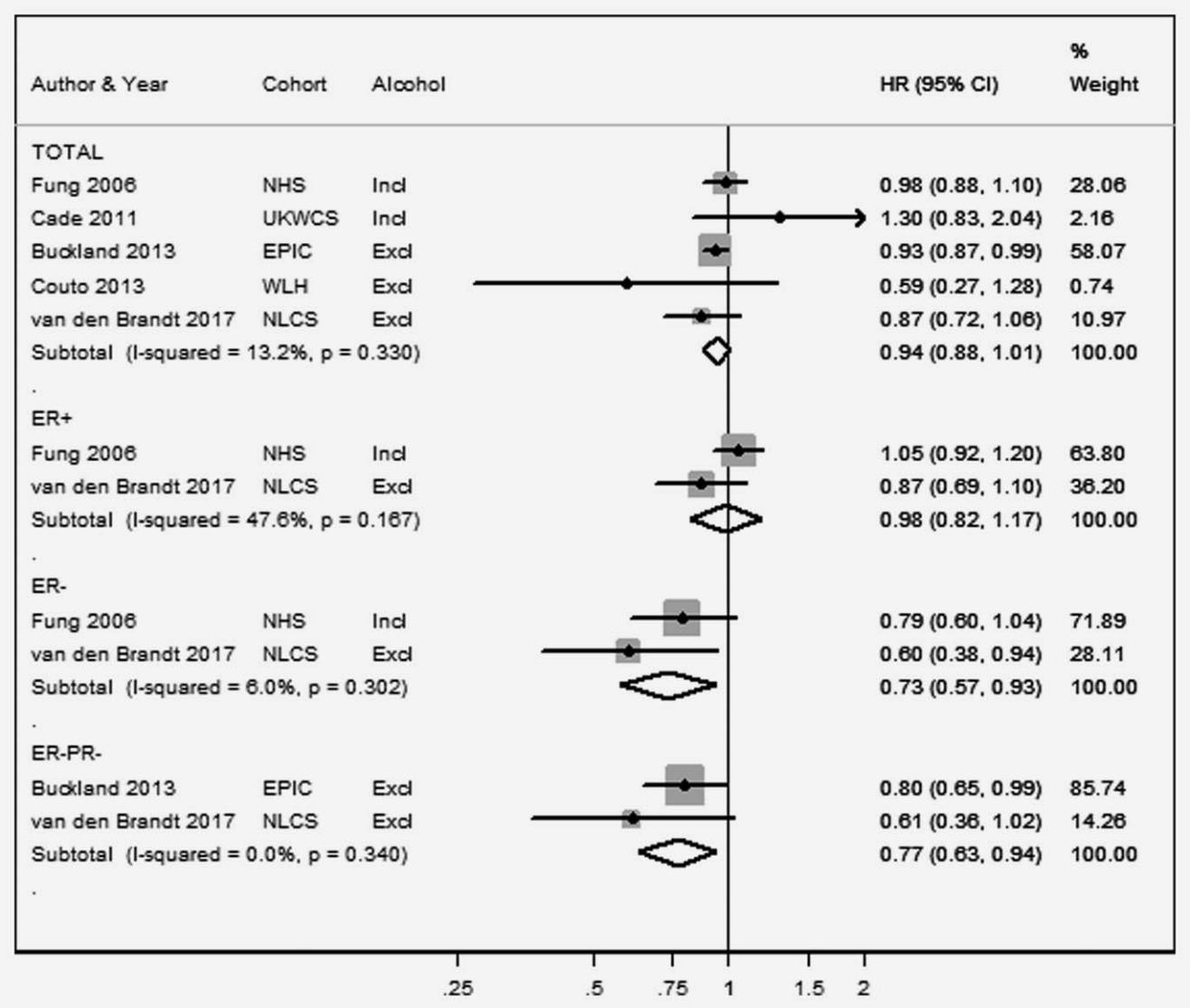

Figure 2. Forest plots of postmenopausal breast cancer hazard ratios (HRs) and 95% confidence intervals (CIs) comparing highest versus lowest category of adherence to MD, from random-effects meta-analyses. Separate plots are presented for total postmenopausal breast cancer and subtypes. Studies are referred to by first author, year of publication, and cohort abbreviation (EPIC, European Prospective Investigation into Cancer; NHS, Nurses' Health Study; NLCS, Netherlands Cohort Study; UKWCS, UK Women's Cohort Study; WLH, Women's Lifestyle and Health). In addition, it is indicated whether or not alcohol was included in the MD score. Studies are weighted according to the inverse of the variance of the log hazard ratio estimate. The HRs are represented by the squares (the size is proportional to the weights used in the meta-analysis) and confidence intervals are represented by the error bars. Diamonds represent the summary HR estimates and 95% confidence interval per endpoint.

Olive oil was infrequently used in the NLCS population in 1986, as in many non-Mediterranean countries. Therefore, the mMED was developed[20] in which fatty acid intake is assessed by calculating the ratio of unsaturated (the sum of monounsaturated and polyunsaturated fatty acids) to saturated fatty acids, to allow for the low consumption of olive oil-derived monounsaturated fatty acids in non-Mediterranean countries.

The potential beneficial effects of the MD on cancer risk have been attributed to high amounts of fiber, antioxidants including polyphenols, and vitamins, and may be mediated through several biological mechanisms such as chronic inflammation and oxidative stress,[44] and associated DNA oxidative damage,[45] and through body weight regulation.[46] The evidence of the cancer protective effect of the MD-pattern is generally stronger than the evidence from individual foods, food groups, or nutrients and cancer risk.[1] Some possible explanations of this could be that interactions and synergisms exist between the components; individual components could have also health effects that are undetectable alone but when integrated with other foods or nutrients in a dietary index, the health benefits become more pronounced.[19] In addition, dietary indexes can overcome the issues of collinearity or confounding between components in the score, and dietary pattern indexes evaluate only the extremes of

cumulative exposure, limiting the background noise of individual components.[47]

According to a recent review,[48] six cohort studies[31,49–53] investigated the association between adherence to WCRF/AICR-cancer prevention guidelines and breast cancer incidence. These guidelines contain a dietary part (including alcohol) and nondietary part (body fatness, physical activity, breastfeeding). Most, but not all[52] studies found a lower breast cancer risk for high versus low adherence to these guidelines. We compared the performance of the dietary part of these guidelines with MD-adherence (± alcohol), and found that models with the MD-score performed better in our population. We found no association between breast cancer and adherence to WCRF/AICR-dietary recommendations. This might seem in contrast with inverse associations in the earlier cohort studies, but these primarily investigated dietary and nondietary recommendations combined (i.e., including overweight and physical activity (and lactation)). It might be that these nondietary factors were dominating the inverse associations reported earlier. For example, Nomura *et al.*[51] found no effect of dietary recommendations beyond BMI and alcohol, but such dominance was not reported by Catsburg *et al.*[53] When comparing our results with those of Romaguera *et al.*,[31] whose operationalization of the dietary guidelines we followed (except salt), they reported a HR of 0.95 per 1-point increment in their 7-component score. However, their score also included nondietary recommendations; further research on this is needed. A recent pooled analysis of seven cohort studies also showed no significant association between WCRF/AICR dietary recommendations and breast cancer risk.[54]

The prospective design and high completeness of follow-up of the NLCS make information bias and selection bias unlikely. A potential weakness is the moderate proportion of breast cancer cases for whom ER/PR status was known. Breast cancer cases with known and unknown receptor status did not differ importantly according to baseline and tumor characteristics, making selection bias of the cases unlikely (data not shown). Although many possible confounders were taken into account, the possibility of confounding by unmeasured factors remains. The validation study of the food frequency questionnaire has shown that it performs relatively well,[13] but measurement error may still have attenuated associations. The lack of possibilities to update dietary intake or other lifestyle data during follow-up may have resulted in some attenuated associations too.

In conclusion, our cohort study showed, in accordance with major cohort studies as the NHS and EPIC, that MD-adherence showed moderately strong inverse associations with risk of ER− (40% reduction), and ER − PR− (39% reduction) breast cancers, and weak inverse associations with ER+ and total postmenopausal breast cancer. Assuming causality, we estimated that 32.4% of ER− breast cancer, and 2.3% of total and ER+ breast cancer could be avoided if the population would shift intake towards the highest MD-category.

Acknowledgements

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Conflict of Interest

There are no competing financial interests in relation to this work.

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