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Indices of Diet Quality and Risk of Lung Cancer in the Women's Health Initiative Observational Study

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ABSTRACT

Background: Prospective evidence on associations between diet quality indices and lung cancer risk is limited, particularly among older women.

Objectives: We investigated associations between 4 diet quality indices [Healthy Eating Index-2015 (HEI-2015), Alternate Healthy Eating Index 2010 (AHEI-2010), alternate Mediterranean Diet (aMED), and Dietary Approaches to Stop Hypertension (DASH)] and lung cancer incidence and mortality in the Women's Health Initiative Observational Study.

Methods: Postmenopausal women aged 50–79 y at baseline (1993–1998) self reported their diet intake and information on relevant covariates. We used Cox proportional hazards regression models to estimate HRs and 95% CIs after controlling for age, smoking, and other relevant covariates.

Results: During ~17 y of follow-up among 86,090 participants, 1491 lung cancer cases and 1393 lung cancer deaths were documented. Dietary indices were not associated with overall lung cancer incidence but were protective against squamous cell carcinoma (12.8% of total lung cancer) cases (HEI-2015: HR: 0.85; 95% CI: 0.76, 0.96; AHEI-2010: HR: 0.87; 95% CI: 0.78, 0.98; aMED: HR: 0.90; 95% CI: 0.81, 0.99; DASH: HR: 0.87; 95% CI: 0.77, 0.98). Among the indices, only HEI-2015 showed an inverse trend (P-trend = 0.02) with overall lung cancer mortality. Smoking status or participant age at baseline did not modify the association between dietary indices and lung cancer incidence or mortality.

Conclusions: After comprehensive control of smoking exposure, we found that diet quality was not associated with overall lung cancer among postmenopausal women. However, a high-quality diet was inversely related to incident lung cancer of the squamous cell subtype. Future studies in populations with diverse age, smoking history, and dietary intake may further elucidate the relation between diet quality indices and lung cancer, especially by histological subtype. *J Nutr* 2021;151:1618–1627.

Keywords: dietary patterns, diet quality indices, lung cancer risk, prospective cohort study, postmenopausal women, diet and cancer, lung cancer in women

Introduction

Among both men and women in the United States, lung cancer is the second most common cause of cancer incidence and the leading cause of cancer mortality (1). While tobacco smoking is the single most important cause of lung cancer, not all lung cancer cases are attributed to tobacco exposure. About 17,000–26,000 estimated deaths annually due to lung cancer occur in never smokers (2), only some of which are due to exposure to secondhand smoke (3). Along with addressing the burden of tobacco smoking, it is important to identify and address other risk factors, such as diet, which may be associated with development of lung cancer.

The Third Expert Report by the World Cancer Research Fund/American Institute for Cancer Research summarized the available evidence on the role of diet in lung cancer risk and concluded that there is limited suggestive evidence that higher consumption of fruits and vegetables (among current and former smokers) as well as foods containing carotenoids, β carotene, retinol, vitamin C (among current smokers), and isoflavones (among never smokers) lower lung cancer risk. The report also found that there is limited suggestive evidence

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that red meat, processed meat, and alcoholic drinks might increase lung cancer risk (4). Dietary patterns rather than single foods/nutrients better capture the complexity of broader dietary intake and reflect the cumulative effect of an individual's regular diet as a factor in health or disease (5). Dietary patterns also account for interactions between individual dietary components and therefore may reveal associations that might not have been evident by studying single foods/nutrients (6, 7).

Previous retrospective (8–12) and limited prospective (13–16) studies on the association of dietary patterns and lung cancer concluded that healthier diet patterns (e.g., higher consumption of fruits, vegetables, and fiber) were associated with lower lung cancer risk while diet patterns based on higher consumption of red/processed meat and saturated fat were associated with higher lung cancer risk (8–12, 14, 15, 17). However, most of these studies based their conclusions on diet patterns generated using data reduction techniques (8–12, 14, 15, 17) and hence limited the reproducibility of their findings and their comparability across studies conducted in different populations (7). Alternatively, indices of diet quality generated a priori and based on nutrition guidelines or specific dietary patterns (e.g., the Mediterranean diet) overcome the above limitations.

Recent studies that used dietary indices to measure diet exposure reported that a high-quality diet was protective against lung cancer (13, 16) and that these associations may vary by smoking status (13). On the other hand, a proinflammatory dietary index was reported to be associated with increased risk of lung cancer among smokers (18–20). Other dietary exposure studies examining differences in these associations among histological subtypes of lung cancer (8, 9, 15, 21), which included only a few among women (22, 23), reported very inconsistent findings.

In a recently reported study using data from the Women's Health Initiative Observational Study (WHI OS), the investigators observed that a higher score in the Healthy Eating Index-2010 (HEI-2010), alternate Mediterranean Diet (aMED), and Dietary Approaches to Stop Hypertension (DASH) indices, but not in the Alternate Healthy Eating Index-2010 (AHEI-2010), was associated with lower total cancer mortality (24). Building off this previous work and with a focus on lung cancer, we hypothesized that higher diet quality, as represented by higher scores on (or adherence to) HEI-2015, AHEI-2010, aMED, or DASH diet patterns, would be associated with lower lung cancer incidence and mortality among postmenopausal women in the WHI OS. We further examined whether these associations differed by self-reported never, former, and current smoking status as well as among histological subtypes of lung cancer.

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Abbreviations used: AARP, American Association of Retired Persons; AHEI-2010, Alternate Healthy Eating Index-2010; AHEI-2010, Alternate Healthy Eating Index 2010; aMED, alternate Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; HEI-2015, Healthy Eating Index-2015; MET, metabolic equivalent; NDSR, Nutrition Data Systems for Research; RFS, Recommended Food Score; WHI OS, Women's Health Initiative Observational Study.

Materials and Methods

We utilized prospective epidemiological data from the WHI OS cohort. Previous publications described the design and recruitment of the WHI study population in detail (25, 26). Briefly, postmenopausal women aged 50–79 y were recruited from 40 clinical centers across 24 US states and the District of Columbia between 1993 and 1998 either into WHI clinical trials (n = 68,132) or the WHI OS (n = 93,676). The main study activities were closed out in 2004–2005, and consenting participants were followed in 2 extension studies conducted in 2005–2010 and 2010–2020. Follow-up study outcome data until 30 September 2016 were available for the present analysis.

Of the 93,676 women enrolled in the WHI OS at baseline, we excluded participants with incomplete dietary data (n = 96), improbable energy intake (<600 kcal/d or > 5000 kcal/d, n = 3571), diagnosed lung cancer at baseline (n = 211), missing information on baseline smoking (n = 3305), and those with no follow-up information after baseline (n = 403). Following these exclusions, the final analytic sample was 86,090 women. Since this study utilized only deidentified data provided by WHI, it met the criteria for exemption by the University at Buffalo Institutional Review Board.

Assessment of diet

Diet quality indices were generated using participant dietary exposures assessed at the WHI OS baseline using a self-administered FFQ consisting of 122 composite and single-food line items asking portion size and frequency of intake, 19 adjustment questions related to the type of fat intake, and 4 summary questions about the usual intakes of fruits and vegetables and added fats for comparison with data obtained from line item questions (24). The FFQ was adapted from the Health Habits and Lifestyle Questionnaire (27) and has demonstrated validity and reliability in the WHI population (28). The FFQ was analyzed using the Nutrition Data Systems for Research (NDSR) (version 2005) developed by the Nutrition Coordinating Center, University of Minnesota (29, 30). NDSR was linked to the MyPyramid Equivalents Database, version 2.0 (USDA) (31) to derive dietary units of MyPyramid equivalents, which convert foods consumed to standardized dietary components of interest (24). The MyPyramid equivalents and nutrients were used to develop individual components of 4 commonly used dietary indices: HEI-2015 (updated from HEI-2010), AHEI-2010, aMED, and DASH. The development and basis of creating these indices were previously described in detail (13, 24, 32). Briefly, HEI-2015, which was developed by the USDA and National Cancer Institute, conforms to the updated 2015 US Dietary Guidelines for Americans (32–34). HEI-2015 has 13 components worth 5–10 points each. The "empty calories" component worth 20 points from HEI-2010 was replaced by "added sugars" and "saturated fats" components worth 10 points each. In addition, legumes contributed to both vegetable components ("total vegetables" and "greens and beans") and both protein food components ("total protein foods" and "seafood and plant proteins"). AHEI-2010 is based on current specific evidence on diet and health and incorporates data on foods and nutrients predictive of chronic disease risk (35). aMED and DASH reflect adherence to the Mediterranean (36) and DASH (37) diets, respectively. The participant's diet quality was calculated by aggregating the scores contributed by individual components of

TABLE 1 Optimal (highest) scoring criteria for components of 4 dietary indices using standardized cup and ounce equivalents from the MyPyramid Equivalents Database in the WHI OS[1]

Index component	HEI-2015[2]	AHEI-2010[3]	aMED[4]	DASH[5]
Added sugars	≤6.5% of energy			
Alcohol		0.5–1.5 drinks/d	5–15 g/d	
Fish	Seafood and plant proteins (includes legumes): ≥0.8 oz eq/1000 kcal		>median	
Fruit	Total fruit: ≥0.8 cup eq/1,000 kcal; whole fruit: ≥0.4 cup eq/1000 kcal	≥2 cup eq/d	>median	Highest quintile
Fats/fatty acids	Fatty acids: ≥2.5 ratio of fatty acids (PUFAs + MUFAs)/SFAs; saturated fats: ≤8% of energy	Trans fats: ≤0.5; %EPA + DHA: 250 mg/d; PUFAs: ≥10%	Ratio of MUFA to SFA: >median	
Low-fat dairy	≥1.3 cup eq/1000 kcal			Highest quintile
Nuts, seeds, and legumes		≥1 oz eq/d	Legumes: >median; nuts and seeds: >median	Highest quintile
Red and processed meats		0 oz eq/d	<median	Lowest quintile
Refined grains	≥1.8 oz eq/1000 kcal			
Sodium	≤1.1 g/1000 kcal	Lowest decile		Lowest quintile
Sugar sweetened beverages[6]		0 cup eq/d		Lowest quintile
Total protein foods	≥2.5 oz eq/1,000 kcal			
Vegetables (excluding potatoes)	Total vegetables (includes potatoes and legumes): ≥1.1 cup eq/1000 kcal; greens and beans (includes legumes): ≥0.2 cup eq/1000 kcal	≥2.5 cup eq/d	>median	Highest quintile
Whole grains	≥1.5 oz eq/1000 kcal	5 oz eq/d	>median	Highest quintile

[1]AHEI, Alternate Healthy Eating Index; aMED, Alternate Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; eq, equivalent; HEI, Healthy Eating Index; WHI OS, Women's Health Initiative Observational Study.
[2]From Krebs-Smith et. al., 2018 (32). HEI-2015 has 13 components worth 5–10 points each with a maximum total score of 100.
[3]From Chiuve et. al., 2012 (35). AHEI-2010 has 11 components worth 10 points each with a maximum total score of 110.
[4]From Fung et. al., 2009 (36). aMED has 9 components worth 1 point each with a maximum score of 9.
[5]From Fung et. al., 2008 (37). DASH has 8 components worth 1–5 points each with total score ranging from 8–40.
[6]Includes soft drinks, Kool-Aid (Kraft Foods, Inc., Northfield, Illinois), orange juice and other fruit juices for AHEI-2010 and soft drinks and Kool-Aid for DASH.

the 4 indices, as presented in **Table 1** [updated table adopted from George et. al., 2014 (24)].

Ascertainment of lung cancer outcomes

We utilized information on lung cancer incidence and mortality, determined during follow-up from baseline enrollment until September 30, 2016. Participants in the WHI OS completed an annual health update that included reporting of cancers, including any diagnosis of lung cancer (26). Medical records were obtained and reviewed by trained study physician adjudicators to confirm lung cancer cases, according to the guidelines from Surveillance Epidemiology and End Results (SEER) (38). Using pathology reports when available, lung cancer cases were histologically classified according to the *International Classification of Disease for Oncology*, second edition, the SEER Program, and the American Joint Committee on Cancer Staging Handbook (39). Cases were classified into small cell and non–small cell lung carcinoma, including adenocarcinoma, squamous cell, large cell, neuroendocrine, carcinoid, and other subtypes. All stages (except in situ carcinoma) and grades were included in our sample. Lung cancer deaths were recorded after reviewing death certificates. Periodic searches of the National Death Index augmented mortality ascertainment (38, 40).

Assessment of covariates

Based on review of previous studies on the relation between diet and lung cancer, we considered relevant covariates from information reported by participants at baseline, including demographics, lifestyle factors, personal and family medical history, and medication use. Trained study staff measured participants' weight and height, which were used to calculate BMI (in kg/m^2). We defined relevant covariates for the present analysis as follows: age (years), race/ethnicity (white, black, Hispanic, or other), education (high school or less, some college, or college graduate or higher), marital status (married/living in a marriage-like relation, yes/no), BMI, and recreational physical activity [calculated as total metabolic equivalent (MET) h/wk].

Self-reported smoking status at baseline was used to categorize participants as never, former, or current smokers. We further quantified participants' active smoking exposure by combining pack years of smoking and smoking status at baseline into a single covariate (never smokers, former smokers with <10 pack y, former smokers with 10–24.9 pack y, former smokers with ≥25 pack y, current smokers with <10 pack y, current smokers with 10–24.9 pack y, and current smokers with ≥25 pack y). When testing the associations among former smokers, we further accounted for time since quitting regular smoking (<5, 5–9, 10–19, 20–29, 30–39, and ≥40 y). Years of secondhand smoke exposure were assessed during childhood (not exposed, <10 and 10–18 y), adult years living with a smoker (not exposed, <5, 5–9, 10–19, 20–29, 30–39, and ≥40 y), and finally, adult years working with a smoker (not exposed, <5, 5–9, 10–19, 20–29, and ≥30 y). Alcohol drinking was assessed as grams of standardized alcohol consumed per day. Energy intake was calculated as kilocalories per day.

Statistical analysis

Participants were followed from their date of baseline assessment until diagnosis of lung cancer or death due to lung cancer, loss to follow-up, or end of study period, whichever occurred

first. Participants who were alive, not diagnosed with lung cancer, and did not consent to participate in the WHI Extension Studies were censored at the end of main study activities. If periodic searches of the National Death Index indicated lung cancer as a cause of death for any of these participants, we included them in the analysis as a lung cancer death.

Distributions of participant characteristics were assessed according to quintiles of dietary indices as well as according to lung cancer incidence (case or not) and lung cancer mortality (decedent or not). Distributions of continuous variables were assessed using means and SDs, and the differences were analyzed using *t*-tests or ANOVA. Distributions of categorical variables were assessed by frequencies, and differences were analyzed using chi-square tests.

Time-to-event analysis was used to test study hypotheses on dietary pattern and lung cancer risks. We used Cox proportional hazards regression models with survival time as the underlying time metric. Survival time (person-years) was computed for each participant from the date of baseline examination until diagnosis of lung cancer or death due to lung cancer, loss to follow-up, or end of the study period. Two multivariable regression models were used to estimate HRs ± 95% CIs separately for each lung cancer outcome. Model 1 represented the most parsimonious model, which was adjusted for the most influential covariates that when added singly to the unadjusted regression model made the greatest change in the HR estimate (age and active smoking). Model 2 was adjusted for race/ethnicity, education, and the secondhand smoke exposure variables BMI, physical activity, and energy intake in addition to age and active smoking. We tested and confirmed the proportional hazards assumption using product terms of dietary indices and follow-up time in separate models. We used quintiles of the index scores to test the association between diet indices and lung cancer with the lowest quintile as the reference. Linear trend was assessed by examining the association of continuous diet index scores with lung cancer.

To evaluate the influence that baseline smoking status might have on an association between diet pattern and lung cancer, we tested the associations within the stratum of never, former, and current smokers using multivariate model 2. Associations among former smokers were further adjusted for time since quitting regular smoking. Multiplicative interaction was tested by including a product term of dietary index and smoking status in the regression models. We also explored whether age of participant at enrollment (50–59, 60–69, and 70–79 y), race/ethnicity (non-Hispanic white and other), BMI (<25, 25–29.9, and ≥30), and use of hormone therapy (yes or no) modified the associations between dietary indices and lung cancer outcomes. Additionally, we explored the associations of dietary indices with risks of major histological subtypes of lung cancer after adjusting for covariates in model 2.

Sensitivity analyses

To assess potential reverse causality, where preclinical symptoms of disease may influence the diet pattern of an individual, we reanalyzed our primary associations after excluding lung cancer cases that were diagnosed within the first 3 and 5 y of follow-up. Next, we re-examined the principal associations between diet quality and lung cancer incidence and mortality among those participants who had a stable diet pattern. Using a second set of dietary indices based on dietary exposure information collected during follow-up year 3 of WHI OS (available in $n = 72{,}169$), we categorized participants as having a stable diet if their diet score was not >11% different from their baseline score. This criterion for diet pattern stability was derived by considering the least possible unit difference among the 4 dietary indices (1-point difference in aMED), which was converted to a percentage difference of 11% applied uniformly across all of the dietary indices.

Statistical analyses were conducted using SAS software version 9.4 (SAS Institute). Hypothesis tests were 2 sided and conducted at an α value of 0.05. When conducting interaction analyses, α was set to 0.10.

Results

The 4 dietary indices were moderately and statistically significantly correlated with each other (Pearson $r = 0.55$ to 0.72; $P < 0.01$). The distribution of baseline participant characteristics according to extreme quintiles of dietary indices is presented in Table 2. Those in the highest quintile of dietary index score were more likely to be older, non-Hispanic Whites, college graduates, married, or living as married, had lower BMI, had higher physical activity levels, had lower exposure to active and secondhand smoking, and consumed more alcohol (AHEI and aMED only), compared with the women in the lowest quintile of dietary indices. Participants in the highest quintiles of HEI and AHEI had a lower energy intake while participants in the highest quintiles of aMED and DASH indices had higher energy intake compared with their peers in the lower categories of the respective score. We also presented differences in intake of selected foods that were commonly scored in the dietary indices, including total fruits, vegetables excluding potatoes, whole grains, and red and processed meats. Participants in the highest quintile of the dietary indices had a much higher intakes of total fruits, vegetables (excluding potatoes), and whole grains and lower intakes of red and processed meats compared with the participants in the lowest quintile.

During a median follow-up period of ~17 y (16.8 y for nonfatal lung cancer and 17.3 y for lung cancer deaths), 1491 incident lung cancer cases were diagnosed and 1393 deaths occurred due to lung cancer. **Supplementary Table 1** shows the differences in distribution of participant characteristics according to follow-up status on each lung cancer outcome. Participants diagnosed with incident lung cancer and those who died of lung cancer were less likely to be college graduates and to be married or living in a marriage-like relation. They had lower BMI and higher exposure to active and secondhand smoking, and they consumed more alcohol. Although participants who died of lung cancer had lower physical activity compared with those who died of other causes, there were no significant differences in physical activity among lung cancer cases and noncases. Most (91.8%) cases were of the non–small cell lung cancer subtype. Overall, 37.2% were adenocarcinoma, 12.8% squamous cell carcinoma, and 12.2% carcinoid (not otherwise specified). Our sample did not have in situ carcinoma cases. Among the cases that were graded, 11.2% were well differentiated, 19.6% were moderately differentiated. 19.3% were poorly differentiated, and 4.3% were anaplastic cancer. The majority of the cancers were diagnosed at an advanced "distant metastasis" stage (35.5%), while 25.0% of the cases were "regional metastasis" and 28.7% cases were localized.

Table 3 show results from the 2 multivariable Cox proportional hazards regression models between the dietary indices and lung cancer outcomes. The results described in this section are from regression model 2 unless otherwise stated. Comparing the higher with lowest (reference) quintile

TABLE 2 Distribution of participant characteristics among lowest and highest quintiles of diet quality indices in the WHI OS ($n = 86,090$)[1]

	HEI-2015		AHEI-2010		aMED		DASH	
Study characteristics	Q1 ($n = 17,218$)	Q5 ($n = 17,218$)	Q1 ($n = 17,218$)	Q5 ($n = 17,217$)	Q1 ($n = 16,911$)	Q5 ($n = 22,181$)	Q1 ($n = 18,446$)	Q5 ($n = 19,122$)
Index score	59 (24, 64)	86 (83, 100)	38 (12, 43)	67 (62, 94)	2 (0, 2)	6 (6, 9)	18 (8, 20)	31 (29, 39)
Age, y	62.4 (7.4)	64.8 (7.2)[2]	63.1 (7.4)	63.7 (7.2)[2]	63.6 (7.5)	63.7 (7.2)[2]	62.4 (7.3)	64.3 (7.3)
Race/ethnicity, % N-H white	78.9	89.2[2]	79.5	88.9[2]	80.5	87.7[2]	74.8	90.9
Education, % college graduate or more	29.6	52.7[2]	27.6	57.6[2]	32.2	52.0[2]	27.9	56.3
Marital status, % married or living as married	58.0	63.7[2]	59.2	64.6[2]	56.4	67.6[2]	60.8	61.3
BMI	29.0 (6.7)	25.9 (5.2)[2]	29.1 (6.5)	25.6 (4.9)[2]	27.6 (6.0)	26.9 (5.7)[2]	28.9 (6.5)	25.8 (5.2)
Physical activity, MET h/wk	8.7 (11.8)	18.1 (15.4)[2]	8.8 (11.4)	19.1 (15.9)[2]	10.9 (12.9)	16.1 (14.8)[2]	8.5 (11.2)	19.0 (16.0)
Smoking, pack y	12.8 (21.6)	8.1 (16.1)[2]	10.8 (20.4)	10.0 (17.7)[2]	10.9 (19.8)	9.0 (17.2)[2]	11.9 (20.8)	8.4 (16.7)
Secondhand smoking exposure during childhood, % 10–18 y	57.9	50.4[2]	55.4	53.3[2]	55.5	52.7[2]	56.6	51.5
Secondhand smoking exposure, adults at home, % ≥10 y	58.8	47.1[2]	57.3	47.3[2]	55.0	48.8[2]	58.4	46.2
Secondhand smoking exposure, adults at work, % ≥10 y	47	34.9[2]	45.0	35.5[2]	43.0	36.7[2]	45.8	34.5
Alcohol, g/d	4.7 (11.6)	5.1 (8.9)[2]	3.6 (12.1)	7.4 (8.9)[2]	4.4 (10.9)	6.6 (10.6)[2]	5.0 (11.5)	5.1 (9.6)
Energy intake, calories	1790 (744)	1444 (465)[2]	1677 (665)	1546 (523)[2]	1170 (434)	1959 (616)[2]	1580 (638)	1625 (535)
Optimal intake of selected foods								
Total fruits, cup equivalents	1.0 (0.8)	2.2 (1.0)	1.2 (0.8)	2.1 (1.0)	1.0 (0.7)	2.3 (0.9)	0.9 (0.6)	2.5 (0.9)
Vegetables, excluding potatoes, cup equivalents	0.9 (0.5)	1.7 (0.7)	0.9 (0.5)	1.8 (0.7)	0.8 (0.4)	1.8 (0.7)	0.9 (0.5)	1.8 (0.7)
Whole grains, ounce equivalents	0.7 (0.7)	1.8 (1.1)	0.9 (0.8)	1.6 (1.2)	0.7 (0.6)	1.8 (1.1)	0.7 (0.7)	1.8 (1.1)
Red and processed meat, ounce equivalents	2.5 (1.9)	1.1 (0.9)	2.6 (1.8)	1.1 (0.9)	2.0 (1.4)	1.5 (1.4)	2.5 (1.7)	1.0 (0.9)

[1] Values for study characteristics are presented as mean (SD) or median (minimum, maximum) unless otherwise indicated. Differences in distribution of characteristics among the quintiles of the 4 diet quality indices were tested for statistical significance using chi-square test for categorical variables and ANOVA for continuous variables. AHEI, Alternate Healthy Eating Index; aMED, Alternate Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension; HEI, Healthy Eating Index; N-H, non-Hispanic; MET, metabolic equivalent; Q1, first or lowest quintile; Q5, fifth or highest quintile; WHI OS, Women's Health Initiative Observational Study.

[2] Statistically significant differences between Q1 and Q5.

TABLE 3 Association between diet quality indices and lung cancer incidence and mortality in overall WHI OS cohort[1]

Dietary index	Participants ($n = 86,090$)	Cases ($n = 1491$)	aHR (95% CI)[1] model 1[2]	aHR (95% CI)[1] model 2[3]	Deaths ($n = 1393$)	aHR (95% CI)[1] model 1[2]	aHR (95% CI)[1] model 2[3]
HEI-2015							
Q1	17,218	345	1.00	1.00	358	1.00	1.00
Q2	17,218	320	1.06 (0.91, 1.23)	1.12 (0.95, 1.31)	287	0.94 (0.80, 1.09)	0.94 (0.80, 1.09)
Q3	17,218	290	1.00 (0.85–1.17)	1.03 (0.87, 1.21)	272	0.97 (0.82, 1.14)	0.97 (0.82, 1.10)
Q4	17,218	264	0.95 (0.81–1.12)	0.97 (0.82, 1.16)	237	0.89 (0.75, 1.05)	0.87 (0.73, 1.04)
Q5	17,218	272	0.98 (0.83–1.16)	1.04 (0.87,1.25)	239	0.90 (0.76, 1.07)	0.86 (0.72, 1.04)
P-trend			0.36	0.81		0.04	0.02
AHEI-2010							
Q1	17,218	316	1.00	1.00	305	1.00	1.00
Q2	17,218	284	0.92 (0.78, 1.08)	0.92 (0.78, 1.08)	291	1.01 (0.86, 1.18)	0.97 (0.82, 1.14)
Q3	17,218	300	0.98 (0.83, 1.14)	0.99 (0.84, 1.17)	269	0.95 (0.81, 1.12)	0.96 (0.81, 1.14)
Q4	17,219	276	0.90 (0.76, 1.05)	0.93 (0.79, 1.11)	264	0.95 (0.80, 1.12)	0.93 (0.78, 1.10)
Q5	17,217	315	0.98 (0.84, 1.15)	1.04 (0.88, 1.24)	264	0.92 (0.78, 1.09)	0.91 (0.76, 1.10)
P-trend			0.91	0.26		0.35	0.51
aMED							
Q1	16,911	323	1.00	1.00	307	1.00	1.00
Q2	14,688	279	0.93 (0.79, 1.08)	0.96 (0.82, 1.13)	269	0.89 (0.76, 1.05)	0.88 (0.75, 1.04)
Q3	16,656	293	1.01 (0.87, 1.18)	1.03 (0.87, 1.21)	278	0.98 (0.84, 1.15)	0.98 (0.83, 1.15)
Q4	15,654	242	0.89 (0.75, 1.04)	0.94 (0.79, 1.12)	223	0.85 (0.72, 1.01)	0.88 (0.73, 1.05)
Q5	22,181	354	0.90 (0.77, 1.05)	0.96 (0.81, 1.13)	316	0.89 (0.75, 1.04)	0.93 (0.78, 1.11)
P-trend			0.14	0.50		0.07	0.27
DASH							
Q1	18,446	340	1.00	1.00	346	1.00	1.00
Q2	16,922	325	1.08 (0.93, 1.26)	1.03 (0.97, 1.32)	312	1.06 (0.91, 1.24)	1.11 (0.95, 1.30)
Q3	13,129	215	0.95 (0.80, 1.13)	0.97 (0.81, 1.17)	203	0.94 (0.79, 1.12)	0.96 (0.80, 1.16)
Q4	18,471	306	1.01 (0.86, 1.18)	1.03 (0.87, 1.21)	269	0.94 (0.80, 1.11)	0.95 (0.80, 1.13)
Q5	19,122	305	1.01 (0.86, 1.19)	1.09 (0.92, 1.30)	263	0.94 (0.79, 1.11)	0.97 (0.81, 1.16)
P-trend			0.98	0.42		0.27	0.44

[1] Active smoking was adjusted as never smokers, former smoker <10 pack y, former smoker 10 to <24.9 pack y, former smoker ≥25 pack y, current smoker <10 pack y, current smoker 10 to <24.9 pack y, and current smoker ≥25 pack y. AHEI, Alternate Healthy Eating Index; aHR, adjusted hazard risk; aMED, Alternate Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension; HEI, Healthy Eating Index; Q1, first or lowest quintile; Q5, fifth or highest quintile; WHI OS, Women's Health Initiative Observational Study.

[2] Model 1 ($n = 86,090$) adjusted for age (years) and active smoking.

[3] Model 2 ($n = 80,866$): adjusted for age (years), race, education, BMI (kg/m^2), physical activity (MET hours/week), active smoking, years of exposure to secondhand smoke during childhood and as an adult (living and working), and energy intake. Estimates in model 2 are based on a shorter analytic sample due to missing values in the additional covariates.

of the diet quality indices, there was a suggestive inverse pattern (but not statistically significant) of association with lung cancer incidence for HEI-2015 and aMED. However, none of the associations of dietary indices with lung cancer incidence was statistically significant. Among the associations of dietary indices with lung cancer mortality, we also observed a statistically significant linear trend in the inverse associations between HEI-2015 quintiles and lung cancer mortality in both model 1 (*P*-trend = 0.04) and model 2 (*P*-trend = 0.02). Other dietary indices were not associated with lung cancer mortality. When the associations were tested among never smokers, former smokers, and current smokers (**Supplementary Tables 2** and **3**) using multivariable model 2, the third (HR: 0.60; 95% CI: 0.40, 0.91) and fourth (HR: 0.59; 95% CI: 0.39, 0.93), but not the fifth, quintiles of AHEI-2010 were inversely associated with lung cancer incidence among never smokers. This inverse association in never smokers was not seen with lung cancer mortality. The other dietary indices were not associated with either lung cancer incidence or mortality when stratified on smoking status. Additionally, age (50–59, 60–69 and 70–79 y), race/ethnicity (non-Hispanic White and other), BMI (<25, 25–29.9 and ≥30) and use of hormone therapy (yes/no) did not modify the associations between diet quality indices and lung cancer (results not shown).

We also examined the associations between dietary indices and nonfatal and fatal major histological subtypes of lung cancer (**Table 4**). For this analysis, because of the lower sample sizes among these subgroups, we modeled the dietary indices as continuous variables defining the exposure as a 1-SD increment, adjusted for covariates in model 2. All 4 dietary patterns (HEI-2015: HR: 0.85; 95% CI: 0.76, 0.96; AHEI-2010: HR: 0.87; 95% CI: 0.78, 0.98; aMED: HR: 0.90; 95% CI: 0.81, 0.99; and DASH: HR: 0.87; 95% CI: 0.77 0.97) showed statistically significant inverse associations with incidence of squamous cell carcinoma. Associations of the dietary indices with other histological subtypes were not statistically significant. The associations of the 4 dietary indices with deaths due to individual histological subtypes of lung cancer were not statistically significant. Additionally, dietary indices were not associated with subtypes of lung cancer grade or stage (**Supplementary Table 4**).

Sensitivity analysis evaluating the potential influence of lung cancer occurring early in the follow-up interval produced results that were similar to the primary findings following exclusion

TABLE 4 Association of histological subtypes of lung cancer with a 1-SD increment in dietary indices in the WHI OS[1]

Tumor histology	*n*	HEI-2015[2]	AHEI-2010[2]	aMED[2]	DASH[2]
Lung cancer incidence ($n = 1483$)					
Small cell lung cancer	121	0.99 (0.86, 1.14)	0.92 (0.80, 1.06)	0.96 (0.84, 1.11)	0.90 (0.78, 1.04)
Non–small cell lung cancer	1362	0.98 (0.94, 1.02)	0.99 (0.95, 1.03)	0.98 (0.94, 1.02)	1.00 (0.96, 1.04)
Adenocarcinoma	552	0.98 (0.92, 1.05)	1.05 (0.98, 1.12)	1.01 (0.95, 1.08)	1.05 (0.98, 1.12)
Squamous cell	190	0.85 (0.76, 0.96)[3]	0.87 (0.78, 0.98)[3]	0.90 (0.81, 0.99)[3]	0.87 (0.77, 0.98)[3]
Large cell/neuroendocrine	54	1.21 (0.98, 1.49)	1.03 (0.84, 1.27)	1.15 (0.94, 1.42)	0.94 (0.77, 1.15)
Carcinoma NOS	181	0.97 (0.86, 1.09)	0.94 (0.84, 1.05)	0.93 (0.83, 1.04)	0.94 (0.84, 1.06)
Other	385	1.00 (0.93, 1.08)	0.99 (0.91, 1.07)	0.96 (0.89, 1.03)	1.02 (0.95, 1.10)
Lung cancer mortality ($n = 844$)					
Small cell lung cancer	101	1.03 (0.89, 1.20)	0.93 (0.80, 1.09)	0.95 (0.82, 1.11)	0.93 (0.80, 1.08)
Non–small cell lung cancer	743	0.99 (0.93, 1.04)	1.00 (0.94, 1.05)	1.01 (0.95, 1.06)	1.00 (0.95, 1.06)
Adenocarcinoma	305	0.99 (0.90, 1.08)	1.04 (0.95, 1.14)	1.03 (0.94, 1.12)	1.05 (0.96, 1.14)
Squamous cell	111	0.87 (0.74, 1.02)	0.91 (0.78, 1.06)	0.93 (0.80, 1.08)	0.89 (0.77, 1.04)
Large cell/neuroendocrine	34	1.29 (0.99, 1.68)	1.05 (0.81, 1.36)	1.21 (0.93, 1.57)	0.94 (0.73, 1.21)
Carcinoma NOS	130	1.01 (0.88, 1.15)	0.98 (0.85, 1.12)	0.97 (0.85,1.11)	0.98 (0.86, 1.12)
Other	163	0.99 (0.88, 1.12)	0.98 (0.87, 1.10)	1.00 (0.89, 1.13)	1.02 (0.91, 1.14)

[1]Values are number of subjects or aHRs (95% CIs). 1-SD units for the dietary indices were HEI-2015,10.74; AHEI-2010, 11.19; aMED, 1.79; DASH, 4.87. AHEI, Alternate Healthy Eating Index; aHR, adjusted HR; aMED, Alternate Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension; HEI, Healthy Eating Index; NOS, not otherwise specified; WHI OS, Women's Health Initiative Observational Study.
[2]Adjusted for age (years), active smoking (never smokers, former smoker <10 pack y , former smoker 10–<24.9 pack y, former smoker ≥25 pack y, current smoker <10 pack y, current smoker 10–<24.9 pack y and current smoker ≥25 pack y), y of exposure to secondhand smoke during childhood and as an adult (living and working) race, education, body mass index, physical activity (MET h/wk), and energy intake.
[3]aHR (95% CIs) values are statistcally significant.

of incident lung cancer outcomes that occurred during the first 3 and 5 y of follow-up (**Supplementary Table 5**). When we restricted analyses to participants who had a stable dietary pattern between the study baseline and follow-up year 3, the associations between dietary indices and lung cancer outcomes also were similar to the primary findings (**Supplementary Table 6**).

Discussion

In the current prospective study among postmenopausal women, quintiles of dietary indices of HEI-2015, AHEI-2010, aMED, and DASH were not associated with overall lung cancer incidence or mortality. HEI-2015 showed a significant inverse linear trend with lung cancer mortality, while the other indices did not have similar associations with lung cancer mortality. We utilized the 4 dietary indices because even though they were similar in having some individual components, their scoring pattern varied considerably. For example, fruits contain carotenoids and quercetin among several other micronutrients that may protect against lung cancer owing to their antitumorigenic and antiproliferative properties (41, 42). HEI-2015 scores total fruits and whole fruits as separate components while the other indices scored them as a single component. Similarly, whole grains containing the potent antioxidant selenium, which may lower lung cancer risk (43), is scored differently in the 4 dietary indices. While dietary indices were not associated with lung cancer overall, they were inversely related to incidence of squamous cell carcinoma. None of the other histological subtypes of lung cancer were associated with diet quality.

As mentioned previously, current epidemiological evidence between dietary patterns and lung cancer is mostly from case-control studies (8–12). Additionally, some of the studies were done in specific population subgroups associated with lower or higher risk of lung cancer [e.g., never smokers (10) or heavy smokers (15)]. Their results may have been limited by residual confounding from active tobacco smoking exposure. None of these previous studies addressed exposure to secondhand smoke. Our study results may not be directly comparable to these findings from earlier studies due to differences in study populations and development of dietary patterns (data-driven compared with a priori approaches). However, we were able to address some of the limitations by utilizing extensive information available in the WHI OS to control for relevant covariates including both active and passive smoking, which enhances the internal validity of the present results.

The Breast Cancer Detection Demonstration Project conducted by the National Cancer Institute and American Cancer Society tested the associations between diet quality [defined using the Recommended Food Score (RFS)] and incidence and mortality of several cancers. This study reported that the highest compared with the lowest quartile of the RFS was inversely associated with lung cancer incidence (RR: 0.62; 95% CI: 0.46–0.84) and mortality (RR: 0.54; 95% CI: 0.38–0.76) (16). The RFS (range: 0–23) incorporated intake of several foods used to generate the indices in the current study, but the calculations performed to achieve the final score differed considerably. The NIH–American Association of Retired Persons (AARP) study population is most comparable to that of the current study. Anic et al. (2016) reported that higher scores on HEI-2010, AHEI-2010, aMED, and DASH indices were associated with a lower risk of incident lung cancer (13). While the published results were from the entire study population, the authors mentioned that the results were similar when they evaluated men and women separately. The distinct difference between this and the current study is the sample size. The NIH-AARP study had more than twice the number of women participants (183,596 compared with 86,090 in the current study) and a similarly higher yield of incident lung cancer cases among women for their analysis (3416 compared with 1491 in the current study). These factors could have prevented the

inverse associations observed in the current study from reaching statistical significance.

The current study did not find associations between dietary indices and lung cancer incidence or mortality among never/former/current smokers. However, other studies reported negative associations between HEI-2015, AHEI-2010, aMED, DASH, and lung cancer cases among former smokers (13) and a positive association between a proinflammatory dietary index and lung cancer among smokers (18–20). Results from a recent pooled analysis showed negative associations between fiber and yogurt intake and lung cancer incidence among overall population as well as among never, former, and current smokers (44). While this study only included specific foods, it may be reflective of a healthier dietary pattern similar to that of participants with high dietary index scores in the current study. While potential mechanisms such as synergism have been suggested (44), further conclusive evidence from studies in diverse populations is necessary to explain the differences in these associations by subgroups of smoking exposure.

Based on findings from the current study, it seems plausible that the potential risk conferred by an individual putative factor in the carcinogenesis of lung cancer could vary by histological subtype. The proportion of major histological subtype of lung cancer diagnosed over the past few decades changed with the change in design and composition of cigarettes (3). However, whether and how they could interact with diet in association with lung cancer is not clear. Studies that examined the associations between dietary components such as alcohol (45) and coffee (46) reported varied associations with different histological subtypes of lung cancer, especially squamous cell and adenocarcinoma. A case-control study in the Czech population that examined the relation between lifestyle factors and lung cancer by histological subtypes reported that among women, intake of fruits (other than apples) and vitamin supplements was inversely associated with squamous cell carcinoma but not adenocarcinoma and small cell carcinoma (47). The NIH-AARP population study reported significant protective associations between high diet quality and both squamous cell as well as adenocarcinoma but not with other histological subtypes of lung cancer (13). It may be plausible that the dietary components in each of the indices might have differences in their interactions and pathways to counteract cancer mechanisms such as inflammation and oxidative damage. For example, while inflammation has been shown to have an important role in pathogenesis of non–small cell lung cancer (48), one of the pathways increasing cyclo-oxygenase-2 expression was found to be more prominent in adenocarcinomas but not in squamous cell carcinomas (49). On the other hand, chance due to multiple hypotheses testing could alternately explain our study findings with the histological subtypes of lung cancer.

Our study has several limitations. The diet quality indices used in the current study were not developed specifically to test associations with lung cancer. However, each of the indices incorporated individual components that were previously reported to be associated with lung cancer. Dietary exposure was assessed using FFQs, which are prone to measurement error. Because the dietary exposure information was collected prior to identification of incident lung cancer events, it is unlikely that such measurement error would result in sufficiently strong exposure misclassification to meaningfully bias measured associations. It is likely that the resulting misclassification of diet pattern would be nondifferential, which in turn would most likely attenuate the study results. Comparability of the primary results with those from sensitivity analyses in which incidence cases occurring in the first 3- and 5-y of follow-up were discarded, enhances confidence that the findings were not primarily a function of information bias. The WHI women also had a very low prevalence of smoking at baseline compared with the national estimates (50), and it is possible we might have observed an interaction with smoking had we had a greater percentage of current smokers in this cohort.

Strengths of our study include *1*) results based on a large nationwide study of postmenopausal women in the community, *2*) the prospective design that avoids some of the methodological issues encountered with case control studies, *3*) ability to examine associations with histological subtypes of lung cancer and *4*) availability of extensive information on relevant covariates, especially smoking, to evaluate the diet–lung cancer associations with rigorous consideration of confounding and potential effect modification. We controlled for smoking exposure comprehensively by adjusting for smoking status and pack-years of smoking, accounting for smoking dose and duration of regular smoking. Additionally, we had the unique opportunity to assess for potential confounding by secondhand smoke exposure, which is an important risk factor for lung cancer (3). Our study contributes to the limited prospective evidence on the association between diet quality/dietary patterns and lung cancer, particularly by utilizing popular diet quality indices allowing for comparison across study populations. Further, a second assessment of dietary exposure information from the FFQ during follow-up year 3 in addition to the baseline data enabled us to test for associations among participants who had a stable diet pattern between the 2 study visits.

In summary, HEI-2015, AHEI-2010, aMED, and DASH indices of diet quality were not consistently associated with overall lung cancer incidence or mortality in a large prospective study of multiethnic postmenopausal women aged 50–79 y at baseline. There was a suggestion of protective associations between each diet score and squamous cell carcinoma incidence, and further research should focus on the mechanisms and differences in associations between dietary patterns/diet quality and histological subtypes of lung cancer. Exploring the association between diet and lung cancer using other diet patterns (e.g., a healthy plant-based pattern or an anti-inflammatory pattern) might further inform the potential role of dietary constituents and intake patterns in lung cancer development and mortality.

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