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Healthy dietary patterns and risk of breast cancer by molecular subtype

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Abstract

Purpose—We examined associations between dietary quality indices and breast cancer risk by molecular subtype among 100,643 women in the prospective Nurses' Health Study (NHS) cohort, followed from 1984 to 2006.

Methods—Dietary quality scores for the Alternative Healthy Eating Index (AHEI), alternate Mediterranean diet (aMED), and Dietary Approaches to Stop Hypertension (DASH) dietary patterns were calculated from semi-quantitative food frequency questionnaires collected every 2–4 years. Breast cancer molecular subtypes were defined according to estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), cytokeratin 5/6 (CK5/6) and epidermal growth factor receptor (EGFR) status from immunostained tumor microarrays in combination with histologic grade. Cox proportional hazards models, adjusted for age and breast cancer risk factors, were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Competing risk analyses were used to assess heterogeneity by subtype.

Results—We did not observe any significant associations between the AHEI or aMED dietary patterns and risk of breast cancer by molecular subtype. However, a significant reduced risk of HER2-type breast cancer was observed among women in 5th vs. 1st quintile of the DASH dietary pattern (n=134 cases, Q5 vs. Q1 HR (95%CI) =0.44(0.25–0.77)), and the inverse trend across quintiles was significant (p-trend=0.02). We did not observe any heterogeneity in associations

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The analysis presented here complies with current laws of the country in which they were performed

between AHEI ($p_{\text{het}}=0.25$), aMED ($p_{\text{het}}=0.71$) and DASH ($p_{\text{het}}=0.12$) dietary patterns and breast cancer by subtype.

Conclusions—Adherence to the AHEI, aMED, and DASH dietary patterns was not strongly associated with breast cancer molecular subtypes.

Keywords

Breast cancer; diet; patterns; molecular subtypes

Breast cancer is the most common form of female cancer representing 25% of all cancers among women worldwide, although rates vary by region [1]. Dietary factors have long been considered a potential explanation for the considerable geographic variation in breast cancer rates. Prior prospective studies of dietary influences on breast cancer risk have largely centered on investigations of single nutrients or food groups and, apart from consistent positive associations between alcohol and breast cancer [2], most have been inconclusive [3-6]. Overall dietary quality may be more important in breast cancer etiology than approaches focused on effects of nutrients in isolation, given the potential synergistic effects between individual nutrients and foods [7]. While several prospective [8-16] and case-control [17-24] studies have considered exploratory dietary patterns and breast cancer risk, fewer studies have examined associations of established dietary patterns, such as the Alternative Health Eating Index (AHEI) [25, 26], the alternate Mediterranean diet (aMED) [25-27] and the Dietary Approaches to Stop Hypertension (DASH), which reflect overall dietary quality based on recommended dietary guidelines. Findings from studies of Mediterranean-style dietary patterns and breast cancer risk have been inconsistent [25-31], and to our knowledge, no prior studies have examined DASH dietary pattern and breast cancer risk. In the largest prior prospective study of established dietary patterns and breast cancer risk in the Nurses' Health Study (NHS) cohort ($n=71,058$), the AHEI and aMED dietary patterns were not associated with overall breast cancer risk although both patterns were inversely associated with ER negative tumors (AHEI, Q5 vs. Q1 HR (95%CI), 0.78 (0.59-1.04), $p\text{-trend}=0.01$; aMED, Q5 vs. Q1 HR (95%CI), 0.79 (0.60-1.03), $p\text{-trend}=0.03$), suggesting potential heterogeneity by tumor subtype [25].

Molecular subtypes of breast cancer have been recently described, and may be more important for clinical outcomes and understanding differing etiologies within breast cancer than using single tumor markers [32-36]. To our knowledge, no prior studies have examined associations of healthy dietary patterns with breast cancer classified by molecular subtype. This approach expands upon our prior findings of inverse associations between dietary patterns and ER- breast cancer [25], and may provide important insight into underlying mechanisms for the associations of diet and breast cancer. Thus, we prospectively examined associations of the AHEI, aMED, and DASH dietary quality scores and risk of breast cancer according to molecular subtype within the NHS, a large prospective cohort study with repeated measures of dietary intake over follow-up and detailed information on molecular features of breast tumors.

Methods

Study Population

The NHS prospective cohort was initiated in 1976 when 121,700 female registered nurses ages 30-55 years responded to a baseline questionnaire. Women have been followed biennially since baseline to update risk factor information and ascertain new disease diagnoses, with over 90% follow-up in each cycle. This analysis was approved by the institutional review board of the Brigham and Women's Hospital.

The follow-up period for this analysis began in 1984, when dietary quality scores were first calculated from an extensive food frequency questionnaire. We excluded women who were diagnosed with cancer (other than non-melanoma skin) or died before the beginning of follow-up (n=5,253), and women who did not have any dietary quality score information over follow-up (n=15,804), leaving a total population of 100,643 women for analysis. Follow-up continued to 2006, the last year with available tumor tissue data.

Exposure and covariate measurement

Dietary quality scores for the Alternative Healthy Eating Index (AHEI), alternate Mediterranean diet (aMED), and Dietary Approaches to Stop Hypertension (DASH) were calculated from a semi-quantitative food frequency questionnaire first administered in 1984 and updated every 2-4 years. For each food item, women selected from 9 intake frequencies, ranging from never to ≥ 6 servings per day over the prior year. The reproducibility and validity of the FFQ has been demonstrated in a subset of the NHS women, with average correlation of all foods with diet records=0.63 [37, 38].

The AHEI was modified from the Healthy Eating Index developed by the United States Department of Agriculture, and was designed to incorporate foods and nutrients that have been consistently associated with chronic disease risk [39]. AHEI score is based on consumption of 11 components: fruits, vegetables, red and processed meat, trans fat, polyunsaturated fat, long-chain (n-3) fats, whole grains, nuts and legumes, sugar-sweetened beverages and fruit juice, moderate alcohol consumption, and sodium [39]. Because of the consistent associations between alcohol and breast cancer [2], we omitted the alcohol component of the AHEI score for this analysis. Points were assigned on a scale from 0 to 10, with 10 indicating greater adherence to the recommended levels of serving per day; scores were categorized proportionately for intermediate intake of the dietary components. Total AHEI score was calculated as a sum across components and ranged from 12.3 to 96.2 in our study, with higher scores indicating higher adherence to the dietary pattern.

The aMED dietary pattern was based on the Mediterranean diet scale [40, 41] and was modified to reflect dietary patterns that have been consistently associated with reduced risk of chronic disease [42]. For the aMED score, women were assigned 1 point for being above the median number of servings per day for the following components; fruits, vegetables, legumes and soy, nuts, fish and seafood, whole grains and the ratio of monounsaturated to saturated fatty acids (MUFA:SFA). Women were assigned 1 point for red and processed meat below the median intake and 1 point for moderate alcohol intake defined as between 5

and 15 g/day [25]. Total aMED adherence scores were computed from summing points across components, and ranged from 0 to 9.

The DASH dietary pattern is based on food and nutrients emphasized or minimized in the DASH diet [43]. The DASH score was derived by assigning 1 to 5 points based on quintile of intake in servings per day of fruits, vegetables, nuts & legumes, red and processed meats, whole grains, low-fat dairy, and sodium in milligrams [44, 45]. Sweetened beverages were derived from quartiles of usual intake due to less variability in this measure. Scoring was inverse for red and processed meat, sugar-sweetened beverages, and sodium, with more points for lower consumption. Total DASH adherence scores were calculated as the sum of points across all dietary components, with a higher score indicating a higher adherence; scores ranged from 7 to 37 in our study population.

Cumulative average dietary pattern scores for AHEI, aMED, and DASH were calculated as an average of respective dietary pattern score over time for years where dietary information was available. In addition to the cumulative average assessment, we evaluated baseline dietary pattern score in 1984 and current dietary pattern adherence without accounting for prior use. For analysis of most recent dietary pattern score, person-time for missing dietary pattern during a specific questionnaire cycle was excluded; women re-entered the analysis when dietary pattern score information became available.

We evaluated age, age at menarche, age at menopause, menopausal status, menopausal hormone (MH) status and duration of use, oral contraceptive use, parity/age at first birth, breastfeeding, first-degree family history of breast cancer, personal history of benign breast disease, body mass index (BMI) at age 18, weight change since age 18, alcohol consumption, physical activity, and energy intake as potential confounders. Information on height and age at menarche was collected at study baseline in 1976, weight at age 18 was collected in 1980; all other covariates were updated from biennial questionnaires. Missing indicators were created for missing responses for covariates.

Molecular Subtypes of Breast Cancer

The primary outcomes for this analysis were diagnosis of each breast cancer molecular subtype (luminal A, luminal B, HER2-type, basal-like, and unclassified). Breast cancer diagnosis and date of diagnosis were assessed on each follow-up questionnaire and carcinomas in situ were excluded. Medical record reviews were conducted to confirm diagnosis and ascertain information on ER and progesterone receptor (PR) status. Pathology reports were available for 96% of the breast cancer cases in this study with 99.4% confirmation rate.

The breast cancer tissue collection and tissue microarray (TMA) construction has been detailed in prior publications [46, 47]. Briefly, archived formalin-fixed paraffin-embedded breast cancer tissue blocks were obtained for approximately 70% of incident primary breast cancer cases from 1976-2006. Women with tissue specimens were very similar with respect to breast cancer risk factors and tumor characteristics compared to the women without tissue specimens available [46]. TMAs were constructed in the Dana Farber Harvard Cancer Center Tissue Microarray Core Facility, Boston, MA from 4,308 breast cancers, using three

0.6mm cores from each breast cancer. Immunohistochemical staining was performed for ER, PR, human epidermal growth factor receptor 2 (HER2), cytokeratin 5/6 (CK5/6), and epidermal growth factor receptor (EGFR) on 5- μ m paraffin sections of the TMA block, using previously described immunostaining methods [46, 48]. Each marker was assessed in a single staining run on a Dako Autostainer (Dako Corporation, Carpinteria, CA), including positive and negative controls in each run.

Each core on the immunostained TMA slides was evaluated manually for ER, PR, HER2, CK5/6 and EGFR expression. Cases with any nuclear staining for ER or PR in any of the three tissue cores were considered positive; all ER or PR-negative cases had complete absence of tumor cell staining in all tissue cores for that case. HER2 protein overexpression was defined as greater than 10% of cells showing moderate (2+) or strong (3+) membrane staining in any of the tissue cores. Based on prior scoring criteria [36,49,50], cases were considered basal CK-positive or EGFR-positive if any cytoplasmic or membranous staining was detected in tumor cores. Markers were selected based on evidence for their utility in the classification of molecular phenotypes [33,34, 36, 49-54].

Breast cancer molecular subtypes were defined according to ER, PR, HER2, CK5/6 and EGFR status from immunostained TMAs in combination with histologic grade. Luminal A cases were defined as ER-positive and/or PR-positive and HER2-negative and grade 1 or 2; luminal B cases were either ER-positive and/or PR-positive and HER2-positive or ER-positive, PR-positive and HER2-negative with grade 3; HER2-type cases were ER-negative, PR-negative and HER2-positive; basal-like cases were negative for ER and PR, and HER2 and positive for CK 5/6 and/or EGFR; unclassified tumors lacked expression of all five markers.

Statistical Analyses

Multivariable Cox proportional hazards models with age in months and calendar year as the underlying time metric were used to estimate hazard ratios (HR) and 95% confidence intervals for the association between dietary pattern score and the risk of each breast cancer molecular subtype. Women contributed person-time from the return date of the baseline questionnaire in 1984 until the first diagnosis of any type of cancer (except non-melanoma skin cancer), death, or the end of follow-up (June 1, 2006). Multivariate models were adjusted for energy intake, physical activity in MET-hours/week, parity and age at first birth, age at menarche, duration of oral contraceptive use, family history of breast cancer, benign breast disease diagnosis, menopausal hormone use, BMI at age 18 years, and weight change since age 18, based on prior knowledge. We adjusted for alcohol consumption in the analyses of AHEI without the alcohol component and for the DASH score, but not for the aMED pattern, as alcohol is a component of this index. We evaluated interaction terms between exposure and time period in our model to assess the proportionality assumptions of the Cox models.

We used Cox proportional hazards competing risk analysis, with data duplication methods to assess heterogeneity by subtype [55]. In these models, the estimates for dietary pattern score variables and covariates with reported heterogeneity by subtype were allowed to vary between breast cancer subtypes, while estimates for other covariates were constrained to a

single effect estimate. We compared these models to a model that held all associations constant between the subtypes using a likelihood ratio test to evaluate differences across subtype.

Dietary pattern scores were categorized into quintiles for analyses, using the same cut points for all follow-up cycles based on cumulative average measure distribution. We used the Wald test to examine the linear trend across quartiles of dietary pattern score, using the median of each intake category as a continuous variable. Stratified models were examined to assess heterogeneity by age (<50/ 50 years) and BMI (<25/ 25 kg/m²). Tests for interaction were conducted using the likelihood ratio test, comparing models with and without the cross-product interaction terms. Additionally, we evaluated associations between AHEI score including the alcohol component, unadjusted for alcohol, and breast cancer subtype. Given prior findings of an inverse association between fruits and vegetable intake and ER negative breast tumors [56], we also examined associations between fruit and vegetable intake and breast cancer molecular subtype. All statistical tests were two-sided and were considered statistically significant at p-value<0.05. All analyses were conducted using SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

Over nearly 2 million years of follow-up, 2,372 incident breast cancer cases that could be classified by molecular subtype were diagnosed among 100,643 women in this study. The majority of tumors were classified as luminal A (n=1,394, 59%), followed by luminal B (n=569, 24%), basal-like (n=208, 9%), Her2 type (n=134, 6%) and unclassified (n=67, 3%) tumors. At baseline in 1984, women in the highest vs. lowest quintile of the AHEI, DASH and aMED dietary scores were slightly older, had gained less weight since age 18 years, were more physically active, less likely to be premenopausal, more likely to be nulliparous, have history of oral contraceptive and menopausal hormone use, have history of benign breast disease, and have a family history of breast cancer. Further, parous women with higher dietary quality scores were more likely to have breastfed. Total energy intake in kilocalories per day were higher among women in the highest vs. lowest quintile of the DASH and aMED patterns, but lower among women with higher AHEI adherence (Table 1).

Results from the simple model were generally similar to the adjusted models, and no single risk factor appeared to be accounting for the differences. The AHEI dietary pattern was not significantly associated with breast cancer molecular subtypes, and we did not observe any heterogeneity in associations of AHEI score across subtypes (p-het=0.25) (Table 2). No clear associations were observed for the aMED dietary pattern and breast cancer risk by molecular subtype (p-het=0.71) (Table 3). We did not observe any heterogeneity in associations of the DASH dietary pattern and breast cancer risk by molecular subtype (p-het=0.12). However, we observed a significant inverse association for the DASH dietary patterns and risk of Her2-type breast cancer (p-trend=0.02). Compared to women in Q1 of the DASH score, the adjusted HRs (95%CI) were 0.52 (0.31, 0.89) for Q2, 0.37 (0.21, 0.66) for Q3, 0.72 (0.45, 1.18) for Q4, and 0.44 (0.25, 0.77) for Q5 (Table 4).

Results were similar in models stratified by BMI and age, although limited by sample size for certain subtypes. While inverse associations of AHEI and risk of Luminal A tumors were more suggestive among women with BMI ≥ 25 kg/m² (Q5 vs. Q1 HR (95%CI), 0.82 (0.63-1.05), p-value for trend=0.06) compared to those with BMI <25 kg/m² (Q5 vs. Q1 HR (95%CI), 0.93 (0.72-1.20), p-value for trend=0.59) the interaction was not significant (p=0.50) (data not shown). In models of AHEI dietary score including the alcohol component, we did not observe any significant trends in risk of breast cancer molecular subtype, although women in Q5 vs. Q1 had a significant reduced risk of Luminal B tumors (HR: 0.75, 95%CI: 0.57, 0.99, p-value for trend=0.10). Finally, we did not observe any significant associations between vegetable consumption with risk of any of the breast cancer subtypes. However, we did observe an inverse association of fruit consumption with risk of Her2-type breast cancer (Q5 vs. Q1 HR (95%CI), 0.46 (0.24-0.85), p-value for trend=0.02, but not for the other subtypes, and heterogeneity across subtypes was not significant (p=0.47) (Supplemental Table 1). In models evaluating the contribution of individual components of the dietary pattern scores, the inverse association of DASH dietary pattern and Her2-type breast cancer was no longer significant after adjusting for the fruit component of the score (p-trend=0.57).

Discussion

In this large, prospective study, we did not observe any clear associations between the AHEI, aMED, or DASH dietary quality scores and risk of breast cancer molecular subtypes, although a significant inverse trend between the DASH score and Her2-type breast cancer was observed. Further, we did not observe any heterogeneity in associations of dietary patterns and breast cancer molecular subtypes.

While the present study is the first, to our knowledge, to examine associations of the AHEI, aMED and DASH dietary quality scores and molecular subtypes of breast cancer, our findings are generally consistent with previous studies of these dietary patterns and overall breast cancer risk [25-27]. In the largest prior prospective study of established dietary patterns and breast cancer, in the NHS cohort, AHEI and aMED patterns were not associated with overall breast cancer risk, although higher AHEI scores were associated with lower risk of estrogen-receptor negative breast cancer [25], suggesting potential heterogeneity by tumor subtype. However, we did not observe any significant associations between the AHEI and aMED indices and the ER negative molecular subtypes (basal-like, HER2-type, or unclassified tumors) in this study; although a significant inverse trend for the DASH dietary pattern and HER2-type breast cancer was observed. Suggestive inverse associations between the AHEI score and luminal A tumors observed in this study, particularly among overweight or obese women compared to those with a BMI <25 kg/m², could be potentially explained by dietary-induced alterations in sex hormone concentrations, as a prior cross-sectional study of 578 women in NHS observed inverse associations between AHEI adherence and postmenopausal estradiol concentrations, particularly among overweight and obese women [57]. However, given the lack of significant trend observed for AHEI, these results should be interpreted with caution.

Findings from several large studies, including a pooled analysis [58], suggest inverse associations of total fruits and vegetables with estrogen receptor negative (ER-) but not ER+ breast cancer [3, 56, 59].

Further, in pooled analyses of dietary carotenoids, which may act as antioxidants and are evident in the yellow-red pigments in fruits and vegetables, inverse associations were much stronger in, or limited to, ER- breast cancer [60, 61]. Thus, an overall healthy diet may not be as important as specific food components (i.e. fruits and vegetables) for risk reduction of ER- breast cancer subtypes. In this study, we observed a significant reduction in risk of Her2-type breast cancer in relation to total fruit consumption, though no significant associations for vegetable intake. Future pooled studies with greater power may be necessary to examine which of the ER negative molecular subtypes may be most strongly inversely associated with fruit and vegetable consumption.

The lack of clear associations between the aMED, DASH, and AHEI dietary scores and breast cancer subtypes is also consistent with prior findings from several prospective studies of a healthy “prudent” diet and breast cancer risk [8, 9, 13]. However, inverse associations have been observed in some specific subgroups, including premenopausal smokers [8], and ER-negative tumors [9].

Strengths of this study include the prospective study design, the large number of breast cancer cases, and detailed tissue information to assess molecular subtypes. Further, we incorporated comprehensive and updated information on dietary factors and covariate information. Potential limitations of this study include misclassification of dietary information, which we do not expect to be associated with breast cancer risk, and may potentially lead to attenuation of associations. However, the indices for diet quality examined in this study have been linked with risk of other chronic diseases including cancer [39, 62–64], cardiovascular disease [39, 62, 65], and type 2 diabetes mellitus [39, 63], so it is possible to detect associations using self-reported dietary information. We did not have detailed data on these dietary patterns during childhood, and thus, we could be missing a critical period of exposure to protect DNA damage. Indeed, several recent studies have highlighted the potential impact of adolescent diet on a woman's future breast cancer risk [66–68]. Thus, future studies of overall dietary patterns in adolescence and breast cancer subtypes are warranted. Finally, due to the rare nature of the ER negative subtypes, our study may not have been well powered to detect associations and we had limited power to assess associations within strata of age, BMI, physical activity and other factors, which could influence associations between diet and breast cancer risk. Thus, future pooled studies may be necessary to examine the associations of diet and breast cancer molecular subtypes within subgroups of interest.

In summary, we did not observe consistent associations between the AHEI, aMED and DASH dietary patterns and breast cancer risk by molecular subtypes. However, given substantial evidence of benefits of certain food components, like fruits and vegetables with ER negative breast cancer, future studies of diet and breast cancer risk according to molecular subtype are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Age and age-standardized characteristics of 76,493 women in the Nurses' Health Study in 1984 in highest and lowest quintile of dietary pattern score

Table 1

	Dietary Pattern score in 1984							
	AHEI		aMED		DASH			
	Q1	Q5	Q1	Q5	Q1	Q5		
Age in years (mean, SD)	52.1 (6.5)	55.2 (6.2)	52.5 (6.5)	54.8 (6.4)	51.6 (6.2)	55.7 (6.3)		
BMI at age 18 years in kg/m ² (mean, SD)	21.1 (3.0)	21.8 (3.1)	21.3 (3.0)	21.4 (2.9)	21.1 (3.0)	21.6 (2.9)		
BMI in kg/m ² (mean, SD)	25.3 (5.1)	24.5 (4.3)	25.1 (4.9)	24.7 (4.4)	25.2 (5.1)	24.5 (4.2)		
Weight change since age 18 years in kilograms (mean, SD)	11.2 (11.7)	7.4 (10.5)	10.3 (11.5)	8.8 (10.5)	10.9 (11.8)	7.7 (10.4)		
Height in inches (mean, SD)	64.5 (2.4)	64.5 (2.4)	64.5 (2.4)	64.7 (2.4)	64.4 (2.4)	64.7 (2.4)		
Physical Activity in MET-hrs/week (mean, SD)	9.9 (15.4)	19.9 (27.1)	10.7 (17.6)	18.9 (24.9)	9.4 (15.5)	21.0 (29.3)		
Energy intake in kcal/day (mean, sd)	1,937 (489)	1,579 (508)	1,544 (471)	2,006 (533)	1,755 (528)	1,804 (494)		
Alcohol intake in g/day (mean, sd)	5.3 (10.3)	4.7 (8.3)	5.0 (10.5)	5.1 (7.9)	5.7 (11.0)	4.3 (7.7)		
Age at menarche (mean, SD)	12.5 (1.7)	12.3 (1.8)	12.5 (1.7)	12.4 (1.7)	12.5 (1.8)	12.3 (1.7)		
Age at Menopause ^a (mean, SD)	47.3 (5.9)	47.3 (5.2)	47.3 (5.7)	47.4 (5.2)	47.1 (6.2)	47.3 (5.1)		
Premenopausal (%)	57.7%	56.6%	57.8%	56.7%	57.5%	56.5%		
Nulliparous (%)	4.7%	7.4%	5.4%	5.8%	5.1%	6.8%		
Age at first birth ^a (mean, sd)	25.0 (3.3)	25.0 (3.3)	24.9 (3.2)	25.0 (3.2)	24.9 (3.3)	25.0 (3.2)		
Ever breastfed ^b (%)	57.6%	63.3%	55.4%	67.1%	53.5%	67.3%		
Past OC use (%)	52.2%	53.0%	51.8%	53.3%	51.2%	52.0%		
History of benign breast disease (%)	29.1%	34.1%	28.7%	33.0%	28.4%	33.9%		
Family history of breast cancer (%)	7.4%	8.0%	7.7%	7.8%	7.3%	7.7%		
Ever PMH use (%)	17.6%	20.8%	17.8%	20.6%	17.2%	20.8%		

^a Among women with natural menopause or bilateral oophorectomy

^b Among parous women only

Cumulative Average AHEI Score (not including alcohol component) and Risk of Breast Cancer by Molecular Subtype

Table 2

	Q1	Q2	Q3	Q4	Q5	p for trend	P-het
<i>Range</i>	(12.3-37.0)	(37.1-42.5)	(42.6-47.6)	(47.7-53.8)	(53.9-96.2)		0.25
Luminal A (n=1,363)							
# cases/person-years	289/348,263	271/347,901	267/347,396	265/347,343	271/347,236		
Age-adjusted HR (95% CI)	1.00 (ref)	0.93 (0.79, 1.10)	0.91 (0.77, 1.08)	0.88 (0.74, 1.04)	0.89 (0.75, 1.05)	0.14	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.92 (0.78, 1.09)	0.90 (0.76, 1.07)	0.86 (0.72, 1.02)	0.88 (0.73, 1.05)	0.11	
Luminal B (n=563)							
# cases/person-years	104/348,443	116/348,022	109/347,529	119/347,476	115/347,392		
Age-adjusted HR (95% CI)	1.00 (ref)	0.99 (0.75, 1.29)	0.92 (0.70, 1.21)	0.92 (0.70, 1.20)	0.90 (0.69, 1.19)	0.39	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.98 (0.75, 1.28)	0.92 (0.69, 1.21)	0.91 (0.69, 1.20)	0.92 (0.69, 1.21)	0.46	
Her2 type (n=133)							
# cases/person-years	29/348,521	30/348,106	32/347,617	23/347,554	19/347,472		
Age-adjusted HR (95% CI)	1.00 (ref)	0.97 (0.57, 1.63)	1.04 (0.62, 1.74)	0.74 (0.42, 1.30)	0.58 (0.32, 1.06)	0.05	
Multivariate HR ^a (95% CI)	1.00 (ref)	1.02 (0.60, 1.73)	1.11 (0.66, 1.88)	0.81 (0.46, 1.44)	0.66 (0.36, 1.23)	0.14	
Basal-like (n=206)							
# cases/person-years	47/348,500	35/348,100	39/347,608	40/347,536	45/347,446		
Age-adjusted HR (95% CI)	1.00 (ref)	0.80 (0.52, 1.25)	0.92 (0.59, 1.41)	0.91 (0.59, 1.40)	1.05 (0.69, 1.61)	0.67	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.78 (0.50, 1.22)	0.90 (0.58, 1.40)	0.88 (0.56, 1.37)	1.00 (0.65, 1.56)	0.83	
Unclassified (n=65)							
# cases/person-years	17/348,530	7/348,130	12/347,633	14/347,565	15/347,481		
Age-adjusted HR (95% CI)	1.00 (ref)	0.48 (0.20, 1.17)	0.92 (0.43, 1.94)	1.12 (0.54, 2.32)	1.22 (0.59, 2.51)	0.27	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.46 (0.19, 1.13)	0.96 (0.44, 2.09)	1.20 (0.57, 2.54)	1.37 (0.63, 2.97)	0.16	

^aMultivariate model adjusted for BMI at age 18 (continuous), weight change since age 18 in kgs (continuous), physical activity in MET hours/week (<3, 3-9, 9-18, 18-27, 27+), energy intake in kilocalories/day (continuous), parity/age at first birth (nulliparous, 1-2 children <25 years, 1-2 children 25-29 years, 3+ children <25 years, 3+ children 25-29 years, 3+ children 30+ years), menopausal hormone use (premenopausal, postmenopausal never/past/current/unknown), alcohol intake (Nondrinker, 0.1-5g/day, 5-10 g/day, 10-20g/day, 20+ g/day), oral contraceptive use (never/ever), age at menarche (<12, 12, 13, 14, 15+ years), age at menopause (continuous), family history of breast cancer (yes/no), and benign breast disease diagnosis (yes/no).

Table 3
Cumulative Average aMED Score and Risk of Breast Cancer by Molecular Subtype

	Q1	Q2	Q3	Q4	Q5	p for trend	P-het
<i>Range</i>	(0-2.6)	(2.7-3.5)	(3.6-4.4)	(4.5-5.4)	(5.5-9.0)		
Luminal A (n=1,363)							0.71
# cases/person-years	249/351,960	274/355,124	253/330,356	292/356,141	326/377,754		
Age-adjusted HR (95% CI)	1.00 (ref)	1.09 (0.92, 1.30)	1.07 (0.90, 1.28)	1.11 (0.94, 1.32)	1.15 (0.97, 1.36)	0.13	
Multivariate HR ^a (95% CI)	1.00 (ref)	1.07 (0.89, 1.27)	1.03 (0.86, 1.23)	1.06 (0.89, 1.27)	1.09 (0.91, 1.30)	0.44	
Luminal B (n=563)							
# cases/person-years	95/352,096	117/355,275	101/330,492	133/356,280	125/377,931		
Age-adjusted HR (95% CI)	1.00 (ref)	1.11 (0.85, 1.46)	0.99 (0.75, 1.32)	1.24 (0.95, 1.62)	1.08 (0.82, 1.42)	0.52	
Multivariate HR ^a (95% CI)	1.00 (ref)	1.09 (0.83, 1.43)	0.94 (0.70, 1.26)	1.18 (0.89, 1.56)	1.02 (0.76, 1.37)	0.87	
Her2 type (n=133)							
# cases/person-years	31/352,171	27/355,366	25/330,561	22/356,378	29/378,015		
Age-adjusted HR (95% CI)	1.00 (ref)	0.78 (0.46, 1.31)	0.83 (0.48, 1.43)	0.62 (0.36, 1.09)	0.79 (0.47, 1.32)	0.30	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.77 (0.45, 1.30)	0.81 (0.47, 1.40)	0.60 (0.33, 1.07)	0.74 (0.42, 1.29)	0.24	
Basal-like (n=206)							
# cases/person-years	42/352,154	44/355,348	44/330,537	37/356,369	41/378,003		
Age-adjusted HR (95% CI)	1.00 (ref)	1.10 (0.72, 1.69)	1.26 (0.82, 1.93)	0.95 (0.61, 1.48)	0.93 (0.60, 1.45)	0.65	
Multivariate HR ^a (95% CI)	1.00 (ref)	1.05 (0.68, 1.62)	1.15 (0.74, 1.78)	0.84 (0.53, 1.33)	0.78 (0.49, 1.26)	0.24	
Unclassified (n=65)							
# cases/person-years	16/352,183	10/355,380	14/330,573	9/356,392	18/378,032		
Age-adjusted HR (95% CI)	1.00 (ref)	0.68 (0.30, 1.50)	1.14 (0.55, 2.37)	0.63 (0.28, 1.44)	1.10 (0.56, 2.18)	0.74	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.62 (0.28, 1.40)	1.01 (0.48, 2.14)	0.57 (0.24, 1.34)	0.89 (0.41, 1.89)	0.86	

^aMultivariate model adjusted for BMI at age 18 (continuous), weight change since age 18 in kgs (continuous), physical activity in MET hours/week (<3, 3-<9, 9-<18, 18-<27, 27+), energy intake in kilocalories/day (continuous), parity/age at first birth (nulliparous, 1-2 children <25 years, 1-2 children 25-29 years, 3+ children <25 years, 3+ children 25-29 years, 3+ children 30+ years), menopausal hormone use (premenopausal, postmenopausal never/past/current/unknown), oral contraceptive use (never/ever), age at menarche (<12, 12, 13, 14, 15+ years), age at menopause (continuous), family history of breast cancer (yes/no), and benign breast disease diagnosis (yes/no).

Table 4
Cumulative Average DASH Score and Risk of Breast Cancer by Molecular Subtype

	Q1	Q2	Q3	Q4	Q5	p for trend	P-het
<i>Range</i>	(7.0-19.6)	(19.7-22.2)	(22.3-24.6)	(24.7-27.0)	(27.1-38.0)		
Luminal A (n=1,394)							0.12
# cases/person-years	248/352,753	246/355,877	295/351,637	297/353,650	308/354,837		
Age-adjusted HR (95% CI)	1.00 (ref)	0.93 (0.78, 1.11)	1.13 (0.95, 1.34)	1.09 (0.92, 1.29)	1.06 (0.89, 1.26)	0.23	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.90 (0.75, 1.08)	1.08 (0.91, 1.29)	1.04 (0.87, 1.24)	0.99 (0.83, 1.19)	0.63	
Luminal B (n=569)							
# cases/person-years	98/352,891	106/356,004	115/351,792	121/353,800	129/355,009		
Age-adjusted HR (95% CI)	1.00 (ref)	0.95 (0.72, 1.26)	1.02 (0.77, 1.34)	1.06 (0.81, 1.39)	1.10 (0.84, 1.45)	0.34	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.91 (0.69, 1.20)	0.96 (0.73, 1.27)	1.00 (0.76, 1.32)	1.04 (0.78, 1.38)	0.59	
Her2 type (n=139)							
# cases/person-years	41/352,952	22/356,085	17/351,885	33/353,882	21/355,107		
Age-adjusted HR (95% CI)	1.00 (ref)	0.53 (0.31, 0.89)	0.36 (0.20, 0.65)	0.73 (0.45, 1.16)	0.43 (0.25, 0.73)	0.01	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.52 (0.31, 0.89)	0.37 (0.21, 0.66)	0.72 (0.45, 1.18)	0.44 (0.25, 0.77)	0.02	
Basal-like (n=225)							
# cases/person-years	45/352,940	38/356,074	47/351,850	39/353,881	39/355,085		
Age-adjusted HR (95% CI)	1.00 (ref)	0.87 (0.56, 1.35)	1.12 (0.74, 1.69)	0.89 (0.58, 1.39)	0.87 (0.56, 1.36)	0.58	
Multivariate HR ^a (95% CI)	1.00 (ref)	0.86 (0.55, 1.33)	1.04 (0.68, 1.59)	0.83 (0.53, 1.30)	0.77 (0.48, 1.22)	0.26	
Unclassified (n=74)							
# cases/person-years	14/352,970	15/356,097	8/351,891	12/353,905	18/355,116		
Age-adjusted HR (95% CI)	1.00 (ref)	1.13 (0.54, 2.37)	0.60 (0.25, 1.45)	0.92 (0.42, 2.01)	1.36 (0.66, 2.80)	0.55	
Multivariate HR ^a (95% CI)	1.00 (ref)	1.20 (0.57, 2.54)	0.61 (0.25, 1.49)	0.94 (0.42, 2.12)	1.37 (0.64, 2.94)	0.56	

^aMultivariate model adjusted for BMI at age 18 (continuous), weight change since age 18 in kgs (continuous), physical activity in MET hours/week (<3, 3-9, 9-18, 18-27, 27+), energy intake in kilocalories/day (continuous), parity/age at first birth (nulliparous, 1-2 children <25 years, 1-2 children 25-29 years, 3+ children <25 years, 3+ children 25-29 years, 3+ children 30+ years), menopausal hormone use (premenopausal, postmenopausal never/past/current/unknown), alcohol intake (Nondrinker, 0.1-5g/day, 5-10g/day, 10-20g/day, 20+g/day), oral contraceptive use (never/ever), age at menarche (<12, 12, 13, 14, 15+ years), age at menopause (continuous), family history of breast cancer (yes/no), and benign breast disease diagnosis (yes/no).