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# **Dietary acid load, past smoking intensity, and breast cancer survival**

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**Kew words:** dietary acid load; smoking status; pack-years; breast cancer survival; mortality;

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**A list of abbreviations:** WHEL: Women's Healthy Eating and Living ; PRAL: potential renal acid load; NEAP: net endogenous acid production; METS: metabolic equivalent/week; ER: estrogen receptor positive; PR: progesterone receptor positive; BMI, body mass index; HR: hazard ratio; ACS: American Cancer Society

## **Novelty and impacts**

Cancer survivors, especially those who are past smokers, have reduced capacities to adjust their acid-base balance and are more susceptible to an acid-producing diet. This large prospective cohort of breast cancer survivors demonstrated that an acid-producing diet was positively associated with total mortality and breast cancer-specific mortality. An acid-producing diet and past smoking intensity had joint impacts on breast cancer prognosis.

These data highlight the importance of adding dietary acid load to dietary guidelines for breast cancer survivors and providing specific guidelines for past smokers.

## **ABSTRACT**

Current dietary guidelines for breast cancer survivors do not include dietary acid load and are not specific for past smokers. Past smokers are more susceptible to dietary acid load-induced adverse outcomes; however, prospective studies examining the independent association of dietary acid load and joint associations of dietary acid load and past smoking intensity with breast cancer prognosis are scant. We studied 2950 early stage breast cancer survivors who enrolled in the Women's Healthy Eating and Living study and provided dietary information through 24-hour recalls at baseline and during follow-up. We assessed dietary acid load using two common dietary acid load scores: potential renal acid load (PRAL) and net endogenous acid production (NEAP). We assessed past smoking intensity by pack-years of smoking. After an average of 7.3 years of follow-up, there were 295 total deaths, 249 breast cancer-specific deaths, and 490 cases of recurrent breast cancer. Increased dietary acid load was positively associated with total mortality and breast cancer-specific mortality; p-values for point estimates (comparing extreme quartiles) and p-values for trends were significant for NEAP and marginally significant for PRAL. Pack-years of smoking significantly modified the association between dietary acid load and

breast cancer recurrence. Furthermore, dietary acid load and pack-years of smoking had a joint impact on total mortality, breast cancer-specific mortality, and breast cancer recurrence. Our study provides valuable evidence for adding dietary acid load to dietary guidelines for breast cancer survivors and developing specific guidelines for past smokers.

## **Introduction**

Past smokers with a high intensity of past smoking history have a greater than 50% higher risk of death than never smokers among breast cancer survivors<sup>1,2</sup>. Among breast cancer survivors, past smokers accounted for up to 35%–40%, whereas current smokers only accounted for 4%–6%<sup>2-4</sup>. However, current dietary guidelines for cancer survivors are not specifically tailored to past smokers. Quitting smoking can avoid further damage but does not remove past damages by smoking; thus, past smokers may be more susceptible to an unhealthy diet than never smokers. A cross-sectional study from our group has demonstrated that acid-producing diet initiated higher levels of inflammation in breast cancer survivors who were past smokers than never smokers<sup>5</sup>; inflammation is a risk factor for cancer development and total mortality<sup>6-8</sup>. Our study prompted us to analyze an available a prospective cohort of breast cancer survivors to determine

whether acid-producing diets are associated with breast cancer survival and whether past smoking intensity can modify this association.

Western diets, consisting of lower fruit and vegetable intake and higher meat consumption, are considered to be acid-producing diets<sup>9</sup>. Acid-producing diets have been found to be associated with cardiovascular-specific mortality<sup>10,11</sup> among healthy cancer-free populations in cohort studies. An acid-producing diet, if not appropriately adjusted in humans, can lead to metabolic acidosis, which can promote cancer metastasis<sup>12</sup>. However, prospective cohort studies examining the associations of acid-producing diets with mortality among cancer survivors are limited. Furthermore, whether past smoking intensity can further modify the impact of an acid-producing diet on breast cancer prognosis has not been studied.

We will leverage a large cohort of breast cancer survivors, the Women's Healthy Eating and Living (WHEL) study, to conduct the current study. The range of dietary acid load is wider in this cohort than that of the typical American diet<sup>5</sup>, which enabled us to better evaluate the dose-response relationship. Pack-years of smoking was also assessed in this cohort. This study aims to determine whether dietary acid load is a risk factor of total mortality, breast cancer-specific mortality, and breast cancer recurrence among early stage breast cancer survivors who were never smokers and past smokers at enrollment. We will also determine whether past smoking intensity, measured by pack-years of smoking, can modify this association or have a joint impact with dietary acid. We hypothesized that

dietary acid load would be positively associated with poor breast cancer survival and that past smoking intensity can modify or have a joint impact with dietary acid load on these outcomes.

## **Materials and Methods**

### ***Study Design***

This study leverages an existing prospective cohort, the WHEL study, comprising mainly early stage (stage I, II, or IIIA) breast cancer survivors. Between 1995 and 2000, the WHEL study enrolled 3,088 women within 4 years of diagnosis. The WHEL study was initially a multi-site randomized trial including several sites in the U.S. (i.e., California, Arizona, Texas, and Oregon). The trial was designed to test whether a diet low in fat and rich in vegetables, fruit, and fiber improved breast cancer prognosis. Extensive details regarding inclusion and exclusion criteria can be found in previous publications<sup>13</sup>. The intervention did not significantly change breast cancer prognosis after an average of 7.3 years of follow-up. Therefore, the present study considered and analyzed the study sample as a single cohort while controlling the initial trial assignment. For this analysis, we excluded women who were current smokers at baseline; as a result, the analytical cohort comprised 2950 women.

The Institutional Review Board at the University of California at San Diego approved the original study. All subjects provided written informed consent. The de-identified data were provided by the principal investigator of

the WHEL study. The current study was an ancillary study using the de-identified data from the WHEL study, thus the exempt IRB was approved by the San Diego State University IRB committee (protocol number: Temp-1286).

### ***Dietary Assessment***

At baseline, year 1, and year 4, dietary intakes were assessed by four prescheduled, 24-hour dietary recalls collected by telephone on random days over a 3-week period: two on the weekends and two during weekdays. Dietary assessors used the multi-pass software-driven recall protocol of the Nutritional Data System software (NDS-R, 1994-2006, 91 University of Minnesota, Minneapolis).

In terms of the assessment of dietary acid load, two commonly used scores were used to estimate dietary acid load in epidemiological studies: the potential renal acid load (PRAL) score and the net endogenous acid production (NEAP) score. The PRAL score considers the intestinal absorption rates for contributing nutrient ionic balances for protein, potassium, calcium, and magnesium and the dissociation of phosphate at pH 7.4<sup>14</sup>. Frassetto et al.<sup>15</sup> developed the NEAP score, which uses total protein and potassium intake as the main components involved in acid production. PRAL and NEAP scores were derived from estimations of several nutrient intakes as follows<sup>16</sup>.

$$\text{PRAL(mEq/day)} = (0.49 \times \text{protein [g/day]}) + (0.037 \times \text{phosphorus [mg/day]}) - (0.021 \times \text{potassium [mg/day]}) - (0.026 \times \text{magnesium [mg/day]}) - (0.013 \times \text{calcium [mg/day]})$$

$$\text{NEAP(mEq/day)} = (54.5 \times \text{protein [g/day]} / \text{potassium [mEq/day]}) - 10.2$$

This study used both scores for dietary acid assessment because they reflect slightly different nutritional intakes and biological mechanisms. A negative PRAL value reflects an alkaline-forming potential; a positive value reflects an acid-forming potential<sup>17</sup>. For NEAP, there is large variation in the general population (ranging from 10 to 150 mEq/day), although a typical Western diet has been characterized by a NEAP score of approximately 50 mEq/day<sup>15,18</sup>.

### ***Smoking Assessment***

A brief smoking history questionnaire was administered to participants at baseline. The questionnaire included age of smoking initiation and cessation, duration of smoking, and the number of cigarettes/day. We classified a lifetime history of <100 cigarettes as never smoking. Former smokers reported having quit at this baseline survey. All ever smokers reported their intensity of smoking (cigarettes/day) and the number of years they smoked regularly. Pack-years exposure was determined by multiplying duration of smoking by intensity. One pack-year is equal to smoking one pack per day for one year or two packs per day for half a year.

### ***Assessment of Study Outcome***

The primary outcome of this study is total mortality, breast cancer-specific mortality, and breast cancer recurrence. At the close of the study in June 2006, vital status was known for 96% of the participants. Information on death from participants was ascertained via confirmation interviews, periodic



reviews (including with a family member), and oncologists' reviews of the medical record and/or death certificate. In addition, both the Social Security and the National Death Index were searched using the Social Security number, name, and date of birth. Causes of death were coded using the International Classification of Diseases, 9th Revision (ICD-9) codes. All breast cancer deaths were confirmed by the study's oncologist. Survival was assessed as the time from study entry to death or the most recent available review of the Social Security Death Index (updated until 2009). Follow-up time was censored at the earlier of (a) time of the last documented staff contact date or (b) study completion (June 2006) for participants without an event (median follow-up time was 7.3 years, range was 0.01–11.2 years). Approximately four percent of study participants were lost during follow-up and these were censored at the date of last contact.

### ***Other Assessments***

Demographic characteristics and health status, including a series of comorbid conditions (e.g., diabetes, cardiovascular diseases, digestive conditions, arthritis, osteoporosis, and medications such as diabetic, cardiovascular, and digestive medications), were self-reported.

Variables abstracted from patient records included initial cancer diagnosis and treatment. Specific variables abstracted included tumor stage, size, hormone receptor status, and use of radiation, chemotherapy, and/or post treatment anti-estrogens use. Physical activity levels were assessed using an adapted validated questionnaire from the Women's Health Initiative <sup>19</sup>.

Physical activity was converted into metabolic equivalent tasks (METs), as previous studies did<sup>20</sup>.

### ***Statistical Analyses***

Differences in sociodemographic and clinical characteristics across breast cancer prognosis (total mortality, breast cancer-specific mortality, and breast cancer recurrence) or across baseline dietary acid load were evaluated using a *t*-test or ANOVA for continuous variables and  $\chi^2$  test for categorical variables.

We used Cox proportional hazard models to assess the association of dietary acid load with total mortality, breast cancer-specific mortality, and breast cancer recurrence. We treated death from other cause as a competing risk when we examined the association between dietary acid load and breast cancer-specific mortality. Time was calculated from the study entry to the time when participants died, were diagnosed with the incidence of recurrent breast cancer, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. As previously introduced, dietary acid load was characterized by PRAL and NEAP scores. Repeated measures of PRAL and NEAP at year 0, year 1, and year 4 were analyzed as time-varying covariates. PRAL and NEAP scores were classified into quartiles using the average intakes at years 0, 1, and 4 to set up the cut-point for each quartile. We classified baseline pack-years of smoking into three categories (i.e., 0, 0-15, and 15+). We controlled the following covariates

based on a priori assumption: age at diagnosis, race/ethnicity, education level, intervention group, menopausal status at baseline, total calorie intake, alcohol intake, smoking status, pack-years, physical activity, body mass index (BMI), education level, tumor stage, tumor size, estrogen and progesterone receptor status, type of anti-estrogen therapy, radiotherapy, chemotherapy, study site, and baseline medical comorbidities. Among these covariates, time-varying covariates included BMI, physical activity, smoking status, total calorie intake, alcohol intake, and types of anti-estrogen therapy.

We further evaluated both joint impacts of dietary acid load and past smoking intensity on outcomes and effect modification by past smoking intensity. To evaluate joint impacts, dietary acid load was categorized by tertile to improve the stability of point estimates. Women with the lowest tertile of dietary acid load and pack-years of smoking = 0 were treated as the reference group. To evaluate the effect modification by smoking intensity, we conducted stratified analyses by two pack-years of smoking strata (= 0 and > 0). To assess whether a significant interaction occurred between dietary acid load and pack-years of smoking, we used the Wald P-value for the interaction term in a model that also included the main effects.

The proportional hazards assumption was examined and satisfied in all Cox proportional hazard regression models by testing the significance of the product terms for our variable of interest and log time. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

## **Results**

### ***Baseline Characteristics by Disease Outcomes in the Whole Cohort***

After a median 7.3 years of follow-up, 295 deaths and 249 breast cancer-specific deaths as well as 490 breast cancer recurrences were reported in the cohort (Table 1). Compared to living group, women who died from all causes tended to have lower proportions of normal weight, above-college education, pack-years of smoking = 0, and positive estrogen receptor (ER) or progesterone receptor (PR) status; they also tended to have higher proportions of women on chemotherapy and higher clinical stage (stage II and stage IIIa). The death group also tended to have lower levels of physical activities. Compared to the living group, women who died of breast cancer tended to have similar patterns to that of the all-cause mortality group except for the tamoxifen users, who tended to have a lower percentage than women who died of breast cancer. Compared to the non-recurrent group, the breast cancer recurrent group tended to have lower proportions of women who had an above-college education, were in menopause, had a positive ER or PR status, and were on tamoxifen; they also tended to have higher proportions of women on chemotherapy and higher clinical stage (stage II and stage IIIa). P-values were <0.05 for these comparisons.

### ***Baseline Characteristics by Dietary Acid Load in the Whole Cohort***

As shown in Table 2, compared to women with a low dietary acid load, women with a higher dietary acid load were younger and had a lower

proportion of White women, postmenopausal women, positive ER or PR status women, and tamoxifen users; they included higher proportions of obese and overweight women and were likely to have less education and engage in less physical activity. P-values were <0.01 for these comparisons.

### ***Dietary Acid Load, Past Smoking Intensity, and Risk of Total Mortality for Breast Cancer-specific Mortality and Breast Cancer Recurrence***

As shown in Table 3, the positive associations of dietary acid load with total mortality and breast cancer-specific mortality were statistically significant for NEAP and marginally significant for PRAL; however, no significant association was found between dietary acid load and breast cancer recurrence. The hazard ratios (HR) comparing the highest to the lowest quartiles of NEAP were 1.54 (95% confidence interval [CI] 1.04-2.29) for total mortality and 1.52 (95%CI 1.01-2.32) for breast cancer-specific mortality; p-values for trends were <0.05 for both outcomes. The corresponding HRs for PRAL were similar but marginally significant. Pack-years of smoking was positively and statistically significantly associated with the three outcomes.

### ***Joint Impact of Dietary Acid Load and Past Smoking Intensity on Breast Cancer Prognosis***

We found statistically significant joint associations of dietary acid load and past smoking intensity with total mortality, breast cancer-specific mortality, and breast cancer recurrence (see Table 4). Both dietary acid load

scores and smoking intensity appeared to be positively associated with total mortality. Compared to women in the lowest tertile of dietary acid load and pack-year category (pack-year of smoking = 0), women in the highest tertile of dietary acid load and pack-year category (pack-years of smoking > 15) had the greatest increased risk of total mortality (HR=2.86, 95%CI 1.73-4.74 for PRAL; HR=3.23, 95%CI 1.99-5.26 for NEAP). P-values for trend were <0.0001 for both PRAL and NEAP. We also observed that the positive associations between dietary acid load and total mortality were stronger in the highest category of pack-years of smoking (>15) than the lower two categories of pack-years of smoking (0 and 0-15). Similar patterns were observed for breast cancer-specific mortality and recurrence, although the magnitude was attenuated for recurrence.

### ***Stratified Associations of Dietary Acid Load with Disease Outcomes by Past Smoking Intensity***

We observed stronger positive associations of dietary acid load with total mortality, breast cancer-specific mortality, and breast cancer recurrence in strata with pack-years of smoking > 0 than strata with pack-years of smoking = 0. The positive associations tended to be stronger for NEAP (p-values for interactions were 0.1 for total mortality, 0.03 for breast cancer-specific mortality, and 0.01 for breast cancer recurrence).

### **Discussion**

In these comprehensive analyses of a cohort of breast cancer survivors, increased dietary acid load was positively associated with

increased total mortality and breast cancer-specific mortality. The positive associations were stronger among women with higher past smoking intensity. We also found an increased risk of breast cancer recurrence among women with pack-years of smoking >0.

Our study is the first to highlight the importance of the independent and joint impacts of dietary acid load and past smoking intensity on breast cancer prognosis among early stage breast cancer survivors. Previous prospective studies have demonstrated that the dietary acid load or higher metabolic acid load (measured by lower serum bicarbonate and overnight fasting urine pH) had a positive or U-shaped relationship with total mortality or cardiovascular mortality but not with cancer-associated mortality<sup>10,21,22</sup>. These studies followed apparently healthy individuals without cancer at baseline<sup>10,21,22</sup>; thus, whether dietary acid load is associated with total and cancer-specific mortality among cancer survivors cannot be concluded from these studies. Dietary acid load has been shown to increase the risk of hypertension, diabetes, chronic kidney diseases, and hip fractures in cohort studies<sup>23-27</sup>; all of these are risk factors for total mortality<sup>28-30</sup>. Furthermore, animal studies have shown that metabolic acidosis can lead to increased cancer development and metastasis<sup>12</sup>. The following discussion helps explain some of the mechanisms.

Adaptation to acidosis, in conjunction with oncogenic mutations, endows cancer cells with increased fitness for survival<sup>31</sup>. An acidic microenvironment suppresses antitumor immune responses<sup>32,33</sup> and facilitates treatment

resistance<sup>34</sup>. Cancer or cancer treatment itself can damage our bodily systems (electrolytes, respiratory system, kidneys or bone) that need to adjust the acid-base balance<sup>35</sup>. Smoking can further damage these acid-base regulating systems<sup>36-39</sup> and can promote acidosis<sup>40,41</sup> in patients with or without cancer. All of these factors help explain the mechanism associated with dietary acid load on total mortality, breast cancer-specific mortality, and recurrence in breast cancer survivors as well as the accelerated risk for past smokers.

This study has several strengths. It is the first large prospective cohort study investigating the independent and joint associations of dietary acid load and past smoking intensity with breast cancer prognosis among breast cancer survivors. Four 24-hour recalls during each visit (baseline, year 1, and year 4) were the unique advantages of this cohort but were rarely conducted in other cohorts. Such advantages enable us to assess dietary acid load more accurately and examine its longitudinal relationships with prognosis outcomes. As this study was originally a trial of high-vegetable, high-fruit, and low-fat intake interventions, we observed a wider range of dietary acid load than other cohorts. This study assessed pack-years of smoking, which can better evaluate past smoking intensity than smoking status. The large sample size provided us with sufficient power to adjust for multiple covariates. However, this cohort's follow-up time was relatively short and comprised predominantly of White women, which will not allow us to examine long-term impacts or generalize our results to other ethnic groups.



Current dietary guidelines, such as the American Cancer Society's (ACS) dietary guidelines for breast cancer survivors, do not include dietary acid load and specific dietary guidelines for former smokers<sup>42,43</sup>. The independent and joint impacts of dietary acid load and past smoking intensity on breast cancer prognosis are important messages for clinicians and dietitians. Precision care and individualized nutrition for breast cancer survivors are important emerging trends. Our results provide valuable evidence for modifying current ACS dietary guidelines and offer specific guidelines for past smokers with different past smoking intensities.

**Disclosure of Potential Conflicts of Interest:** No potential conflicts of interest were disclosed.

**Author Contributions:** T.W. designed and developed the research plan and conducted the main analyses. F.-C.H. and S.W. help create the statistical program. T.W. wrote the manuscript.

F.-C.H. provided comments and edits for the manuscript. J.P.P. was the P.I. of the WHEL study and collected the dietary, covariate and outcome data. T.W. had primary responsibility for the final content. All authors have read and approved the final manuscript.

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**Table 1. Baseline characteristics of breast cancer survivors by breast cancer recurrence, total mortality and breast cancer specific mortality (n = 2950)**

	Total mortality			Breast cancer specific mortality			Breast cancer recurrence		
	No (2655)	Yes (n=295)	P-value	No (n=2655)	Yes (n=249)	P-value	No (n =2460)	Yes (n =490)	P-value
<b>PRAL (mEq/day)<sup>a</sup></b>	-3.97 (-14.11 to 4.42)	-2.93 (-13.12 to 5.17)	0.3	-3.97 (-14.10 to 4.42)	-2.52 (-12.59 to 5.85)	0.2	-4.10 (-14.15 to 4.42)	-2.84 (-13.14 to 5.17)	0.1
<b>NEAL (mEq/day)</b>	39.78 (32.25 to 48.22)	40.79 (33.12 to 48.89)	0.3	39.80 (32.21 to 48.22)	41.03 (33.50 to 48.68)	0.3	39.65 (32.08 to 48.22)	40.87 (33.36 to 48.68)	0.2
<b>Basic</b>									
Age at diagnosis (years)	50.0 (45.0-57.0)	51.0 (44.0-59.0)	0.3	50.0 (45.0-57.0)	50.0 (43.0-57.0)	0.2	50.0 (45.0-57.0)	49.0 (42.0-56.0)	0.3
White (%)	85.4	82.4	0.2	85.4	83.1	0.3	85.4	85.5	0.7
Body mass index									
Normal weight (%)	44.0	37.3	0.006	44.0	39.0	0.03	43.5	42.7	0.2
Overweight and obese (%)	56.0	63.7		56.0	61.0		56.4	57.3	
Education, at or above college (%)	56.3	46.8	0.002	56.3	46.4	0.0003	56.3	50.4	0.04
Postmenopausal women (%)	79.2	79.7	0.3	79.2	76.7	0.3	80.2	74.5	0.001
Smoking status									
Past smoker (%)	43.2	48.1	0.1	43.2	47.3	0.2	43.4	43.8	0.9
Never smoker (%)	56.8	51.9		56.8	52.7		56.6	56.2	
Pack-year status									
Pack-years =0 (%)	56.3	50.8	<0.0001	56.3	51.4	<0.0001	55.7	55.7	0.11
Pack-years >0 to 15 (%)	27.8	21.7		27.8	22.5		27.7	24.9	
Pack-years >15 (%)	14.5	23.4		14.5	21.3		15.1	16.5	
Alcohol abstainer (%)	31.2	35.9	0.1	31.2	35.9	0.1	31.3	33.5	0.5
Physical activity (MET/week)	600 (180-1300)	450 (105-930)	0.001	600 (180-1300)	435 (100-975)	0.003	600 (180-1295)	525 (120-1110)	0.09
Intervention group (%)	49.8	50.2	0.9	49.9	48.6	0.7	49.6	50.1	0.9
Chemotherapy (%)	68.8	80.3	0.0002	68.8	86.8	<0.0001	67.9	80.6	<0.0001
Radiation (%)	61.8	61.4	0.8	61.8	61.9	0.8	61.6	62.5	0.8
Hormone receptor status									
ER+/PR+ (%)	62.9	50.9	0.0002	62.9	47.8	<0.0001	62.9	55.3	0.01
ER-/PR- (%)	21.3	29.8		21.3	32.5		19.1	24.5	
Cancer stage at diagnosis (%)									
I	40.4	20.0	<0.0001	40.4	14.5	<0.0001	41.9	20.2	<0.0001
II	55.5	67.1		55.5	71.1		54.1	69.6	
IIIa	4.2	12.9		4.2	14.5		4.0	10.2	
Tamoxifen use (%)	66.8	61.0	0.1	66.8	57.4	0.009	67.6	59.4	0.001

<sup>a</sup> Continuous variables are presented as median (inter-quartile range). Abbreviations: PRAL: potential renal acid load; NEAP: net endogenous acid production; METS: metabolic equivalent/week; ER: estrogen receptor positive; PR: progesterone receptor positive.

**Table 2. Baseline characteristics of breast cancer survivors by quartiles of the PRAL score (n = 2950)**

	PRAL score quartiles (mEq/day)				P-value
	Quartile 1 <-13.7 (n = 771)	Quartile 2 -13.7 to <-3.7 (n = 769)	Quartile 3 -3.7 to <4.7 (n = 771)	Quartile 4 ≥4.7 (n = 770)	
<b>NEAL (mEq/day)<sup>a</sup></b>	27.4 (23.9 - 30.7)	36.4 (33.7 - 38.5)	43.7 (41.1 - 46.3)	55.4 (50.9 - 61.3)	<0.001
<b>Basic</b>					
Age at diagnosis (years)	52.0 (47.0 - 58.0)	51.0 (46.0 - 58.0)	50.0 (45.0 - 57.0)	48.0 (42.0 - 55.0)	<0.001
White (%)	89.6	88.7	83.8	78.2	<0.001
Body mass index					
Normal weight (%)	56.6	46.7	37.1	32.8	<0.001
Overweight and obese (%)	43.4	53.3	63.9	67.2	
Education, at or above college (%)	64.8	57.4	52.7	46.3	<0.001
Postmenopausal women (%)	84.5	80.1	80.0	73.2	0.001
Smoking status					
Past smoker (%)	44.6	43.0	44.1	43.1	0.9
Never smoker (%)	55.4	56.9	55.9	56.9	
Pack-year status					
Pack-years =0 (%)	54.8	56.6	55.3	56.3	0.06
Pack-years >0 to 15 (%)	28.0	24.6	27.9	28.3	
Pack-years >15 (%)	15.8	17.7	14.3	13.6	
Alcohol abstainer (%)	32.1	30.5	33.7	30.8	0.3
Physical activity (MET/week)	825 (330-1500)	630 (225-1335)	480 (150-1080)	405 (60-1080)	<0.001
Chemotherapy (%)	63.6	61.4	59.5	62.5	0.3
Radiation (%)	63.6	61.0	59.1	62.2	0.6
Hormone receptor status					
ER+/PR+ (%)	63.2	63.1	62.3	58.1	0.003
ER-/PR- (%)	16.2	18.8	21.7	23.6	
Cancer stage at diagnosis (%)					
I	38.8	36.7	38.7	38.9	0.4
II	55.4	59.6	56.7	55.0	

IIIa	5.7	3.7	4.6	6.2	
Tamoxifen use (%)	72.0	66.9	63.6	62.2	0.001

a Continuous variables are presented as median (inter-quartile range). Abbreviations: PRAL: potential renal acid load; NEAP: net endogenous acid production; METS: metabolic equivalent/week; ER: estrogen receptor positive; PR: progesterone receptor positive.

**Table 3.** Dietary acid load and past smoking intensity in relation to total mortality, breast cancer-specific mortality  
breast cancer  
recurrence

		<b>Total mortality</b>		<b>Breast cancer-specific mortality</b>		<b>Breast cancer recurrence</b>	
		Even	HR (95%CI)	Event	HR (95%CI)	Even	HR (95% CI)
		t				t	
<b>Dietary acid load</b>							
	Range						
<b>PRAL(mEq/day)</b>							
Quartile 1	<-19.50	40	Ref	34	Ref	61	Ref
Quartile 2	-19.50 to <-6.94	77	1.17 (0.81-1.69)	60	1.08 (0.73-1.54)	133	0.98 (0.76-1.27)
Quartile 3	-6.94 to <3.22	89	1.41 (0.97-2.06)	80	1.43 (0.96-2.13)	147	1.07 (0.82-1.39)
Quartile 4	≥3.22	89	1.30 (0.87-1.94)	75	1.27 (0.83-1.94)	149	1.09 (0.83-1.43)
<b>P for trend</b>			0.09		<b>0.09</b>		0.5
<b>NEAP(mEq/day)</b>							
	Range						
Quartile 1	<28.44	35	Ref	29	Ref	61	Ref
Quartile 2	28.44 to <37.25	82	1.27 (0.88-1.84)	66	1.27 (0.87-1.87)	127	1.06 (0.82-1.37)
Quartile 3	37.25 to <46.90	86	1.50 (1.02-2.21)	77	1.46 (0.96-2.21)	152	1.01 (0.77-1.32)
Quartile 4	≥46.90	92	1.54 (1.04-2.29)	77	1.52 (1.01-2.32)	150	1.15 (0.88-1.50)
<b>P for trend</b>			<b>0.03</b>		0.04		0.4
<b>Past smoking intensity</b>							

<b>Pack-year category</b>	Range							
1	0	150	Ref	128	Ref	273	Ref	
2	0-15	64	0.96 (0.71-1.28)	56	1.02 (0.75-1.39)	122	0.96 (0.77-1.17)	
3	15+	69	1.71 (1.28-2.31)	53	1.68 (1.23-2.30)	81	1.17 (0.91-1.51)	
P for trend			<0.0001	0.001		0.03		

HRs were derived from Cox proportional hazards regression models adjusted for multiple covariates. Covariates in the Cox model included age at diagnosis, race/ethnicity, education level, intervention group, menopausal status at baseline, total calorie intake, alcohol intake, physical activity, body mass index, number of comorbidities, tumor stage, tumor size, estrogen and progesterone receptor status, tamoxifen use, radiotherapy, and chemotherapy. PRAL and NEAL were not adjust simultaneously. Abbreviations: HR: hazard ratio; PRAL: potential renal acid load; NEAP: net endogenous acid production; WHEL: Women’s Healthy Eating and Living study



<b>Table 4. Joint associations of dietary acid load and past smoking intensity with total mortality, breast cancer-specific mortality, and breast cancer recurrence</b>													
	<b>PRAL (mEq/day)</b>						<b>NEAP (mEq/day)</b>						
	Tertile 1		Tertile 2		Tertile 3		Tertile 1		Tertile 2		Tertile 3		
	<-15.04		-15.04 to <-0.71		≥-0.71		<31.5		31.5 to <43.4		≥43.4		
<b>Total mortality</b>													
	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	
Pack-years =0	32	Ref	60	1.48 (0.98-2.24)	58	1.16 (0.76-1.78)	33	Ref	58	1.39 (0.92-2.08)	59	1.18 (0.76-1.81)	
0<Pack-years ≤15	10	1.13 (0.69-1.85)	24	1.01 (0.58-1.77)	30	1.25 (0.74-2.10)	10	1.05 (0.63-1.74)	25	1.10 (0.65-1.86)	29	1.22 (0.72-2.06)	
Pack-years >15	16	1.26 (0.71-2.21)	24	2.20 (1.33-3.66)	29	2.86 (1.73-4.74)	15	1.35 (0.78-2.35)	23	1.67 (0.97-2.88)	31	3.23 (1.99-5.26)	
P for trend	<0.0001						<0.0001						
<b>Breast cancer-specific mortality</b>													
	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	
Pack-years =0	25	Ref	50	1.39 (0.89-2.20)	53	1.13 (0.71-1.79)	26	Ref	49	1.20 (0.77-1.89)	53	1.08 (0.68-1.72)	
0<Pack-years ≤15	9	1.17 (0.70-1.99)	20	0.92 (0.50-1.70)	27	1.36 (0.78-2.37)	8	1.04 (0.62-1.76)	22	0.99 (0.56-1.75)	26	1.26 (0.72-2.21)	
Pack-years >15	13	1.12 (0.61-2.06)	19	2.08 (1.19-3.63)	21	2.65 (1.54-4.57)	11	1.19 (0.66-2.14)	19	1.48 (0.82-2.68)	23	2.82 (1.67-4.76)	
P for trend	0.006						0.001						
<b>Breast cancer recurrence</b>													
	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)	
Pack-years =0	56	Ref	106	0.90 (0.68-1.23)	111	0.90 (0.67-1.21)	56	Ref	105	0.97 (0.72-1.30)	112	0.94 (0.69-1.27)	
0<Pack-years ≤15	19	0.88 (0.62-1.25)	48	0.88 (0.61-1.28)	55	0.90 (0.62-1.29)	20	0.94 (0.66-1.34)	47	0.80 (0.54-1.17)	55	1.01 (0.70-1.46)	
Pack-years >15	18	0.79 (0.50-1.25)	32	0.97 (0.68-1.52)	31	1.69 (1.10-2.64)	15	0.84 (0.53-1.34)	34	1.03 (0.66-1.59)	32	1.64 (1.09-2.46)	
P for trend	0.01						0.02						

HRs were derived from Cox proportional hazards regression models adjusted for multiple covariates. Covariates in the Cox model included age at diagnosis, race/ethnicity, education level, intervention group, menopausal status at baseline, total calorie intake, alcohol intake, physical activity, body mass index, number of comorbidities, tumor stage, tumor size, estrogen and progesterone receptor status, tamoxifen use, radiotherapy, and chemotherapy. PRAL and NEAL were not adjust simultaneously. Abbreviations: HR: hazard ratio; PRAL: potential renal acid load; NEAP: net endogenous acid production; WHEL: Women’s Healthy Eating and Living study

**in different pack-years of smoking**

strata		Total Mortality		Breast Cancer Mortality		Breast cancer recurrence		
<b>PRAL (mEq/day)</b>								
<b>=0</b>	<b>Pack-Years</b>	Range	Event s	HR (95%CI)	Event s	HR (95%CI)	Event s	HR (95%CI)
	Quartile 1	<-19.50	21	Ref	18	Ref	38	Ref
	Quartile 2	-19.50 to <-6.94	41	1.07 (0.64-1.79)	31	1.04 (0.58-1.85)	75	0.95 (0.67-1.32)
	Quartile 3	-6.94 to <3.22	45	1.35 (0.80-2.29)	40	1.31 (0.71-2.43)	73	0.94 (0.65-1.34)
	Quartile 4	≥3.22	43	1.10 (0.63-1.93)	39	1.13 (0.60-2.10)	87	0.98 (0.68-1.40)
	P for trend			0.6		0.6		0.9
<b>0</b>	<b>Pack-Years &gt;</b>	Range	Event s	HR (95%CI)	Event s	HR (95%CI)	Event s	HR (95%CI)
	Quartile 1	<-19.50	17	Ref	14	Ref	21	Ref
	Quartile 2	-19.50 to <-6.94	33	1.17 (0.69-1.99)	26	1.03 (0.56-1.90)	53	0.98 (0.64-1.50)
	Quartile 3	-6.94 to <3.22	41	1.45 (0.84-2.49)	37	1.54 (0.86-2.75)	71	1.34 (0.89-2.03)
	Quartile 4	≥3.22	42	1.51 (0.84-2.69)	32	1.54 (0.79-3.01)	58	1.28 (0.83-1.99)
	P for trend			0.1		0.6		0.1
	P for interaction			0.4		0.09		0.03
<b>NEAP (mEq/day)</b>								
<b>=0</b>	<b>Pack-Years</b>	Range	Event s	HR (95%CI)	Event s	HR (95%CI)	Event s	HR (95%CI)
	Quartile 1	<28.44	17	Ref	13	Ref	32	Ref
	Quartile 2	28.44 to <37.25	48	1.26 (0.76-2.10)	39	1.26 (0.72-2.23)	78	1.07 (0.76-1.50)
	Quartile 3	37.25 to <46.90	40	1.46 (0.86-2.50)	36	1.39 (0.74-2.61)	79	0.90 (0.62-1.30)
	Quartile 4	≥46.90	45	1.30 (0.75-2.27)	40	1.29 (0.70-2.39)	84	1.05 (0.73-1.50)
	P for trend			0.4		0.6		0.9
	<b>Pack-Years &gt;</b>	Range	Event	HR (95%CI)	Event	HR (95%CI)	Event	HR (95%CI)

0			S		S		S	
	Quartile 1	<28.44	16	Ref	14	Ref	25	Ref
	Quartile 2	28.44 to <37.25	32	1.25 (0.74-2.15)	25	1.20 (0.67-2.13)	47	1.11 (0.72-1.70)
	Quartile 3	37.25 to <46.90	41	1.44 (0.82-2.53)	36	1.38 (0.75-2.56)	68	1.17 (0.76-1.80)
	Quartile 4	≥46.90	44	1.81 (1.04-3.16)	34	1.88 (0.75-2.55)	63	1.45 (0.94-2.40)
	P for trend			0.03		0.04		0.09
	P for interaction			0.1		0.03		0.01

HRs were derived from Cox proportional hazards regression models adjusted for multiple covariates. Covariates in the Cox model included age at diagnosis, race/ethnicity, education level, intervention group, menopausal status at baseline, total calorie intake, alcohol intake, physical activity, body mass index, number of comorbidities, tumor stage, tumor size, estrogen and progesterone receptor status, tamoxifen use, radiotherapy, and chemotherapy. PRAL and NEAL were not adjust simultaneously. Abbreviations: HR: hazard ratio; PRAL: potential renal acid load; NEAP: net endogenous acid production; WHEL: Women’s Healthy Eating and Living study