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Antioxidant Supplement Use After Breast Cancer Diagnosis and Mortality in the LACE Cohort

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Abstract

Background—There is concern that antioxidant supplement use during chemotherapy and radiation therapy may decrease treatment effects, yet effects on recurrence and survival are largely unknown.

Methods—We prospectively examined the associations between antioxidant use after breast cancer (BC) diagnosis and BC outcomes in 2,264 women in the Life After Cancer Epidemiology (LACE) cohort. The cohort includes women diagnosed with early stage primary BC 1997–2000 who enrolled, on average, two years post-diagnosis. Baseline data were collected on antioxidant supplement use since diagnosis and other factors. BC recurrence and mortality were ascertained, and hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using delayed entry Cox proportional hazards models. All tests of statistical significance were two-sided.

Results—Antioxidant supplement use after diagnosis was reported by 81% of women. Among antioxidant users, frequent use of vitamin C and vitamin E was associated with decreased risk of BC recurrence (HR: 0.73, 95% CI: 0.55–0.97; HR: 0.71, 95% CI: 0.54–0.94, respectively); vitamin E use was associated with decreased risk of all cause mortality (HR: 0.76, 95% CI: 0.58–1.00). Conversely, frequent use of combination carotenoids was associated with increased risk of death from BC (HR: 2.07; 95% CI: 1.21–3.56) and all cause mortality (HR: 1.75; 95% CI: 1.13–2.71).

Conclusion—Frequent use of vitamin C and vitamin E in the period following BC diagnosis was associated with decreased likelihood of recurrence, while frequent use of combination carotenoids was associated with increased mortality. Effects of antioxidant supplement use after diagnosis likely differ by type of antioxidant.

Keywords

Antioxidants; dietary supplements; breast cancer; mortality; epidemiology

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INTRODUCTION

Antioxidant supplement use after breast cancer diagnosis is common,[1] but long-term effects are poorly understood.[2] Concerns have been raised about antioxidant supplementation during cancer treatment possibly protecting tumor cells from the pro-oxidant effects of chemotherapy and radiation,[3] yet there are limited data on recurrence and survival outcomes in women with breast cancer. Previous studies have important limitations including lack of details on antioxidant dose and frequency of use, retrospective data collection, poorly matched control groups, small sample sizes, and limited duration of follow-up.[4–8] A recent report from a well-designed prospective breast cancer cohort study suggests no harm of supplementation with multivitamins, vitamin C and vitamin E in the period following diagnosis, and possible benefit of supplementation on improving recurrence and survival rates.[9]

We used data from the Life After Cancer Epidemiology (LACE) Study, a prospective cohort study of women with early-stage breast cancer, to examine the association between antioxidant use in the two year period following diagnosis and breast cancer outcomes, including all cause mortality, death from breast cancer, and recurrence. Our working hypothesis was that different forms of antioxidant supplements would have differing effects on outcomes.

METHODS

Study Participants

The LACE cohort (n=2,264) consists of women primarily recruited from the Kaiser Permanente Northern California (KPNC) (83%) and the Utah (12%) cancer registries who were diagnosed with early-stage primary breast cancer between 1997 and 2000. Women enrolled between 2000 and 2002, approximately one to three years after breast cancer diagnosis (average: 1.9 years; range: 0.9 years to 3.2 years). Eligibility criteria included diagnosis of early stage-primary breast cancer (Stage 1 ≥1 cm, Stage II, or Stage IIIA); age 18 to 79 years at diagnosis; completion of breast cancer treatment, including surgery, chemotherapy, and radiation therapy (use of hormonal therapy was permitted); no evidence of recurrent disease; and no history of other cancers in the five years prior to enrollment. LACE recruitment and data collection methods have been described elsewhere.[10] The study was approved by the institutional review boards of KPNC and the University of Utah.

Data Collection

At enrollment, a mailed self-administered questionnaire collected detailed data on demographics, medical history, medication use, reproductive history, family history of breast cancer, anthropometric measures (height, weight, waist circumference), weight history, diet, dietary supplement use, physical activity, quality of life, and depressive symptoms.

Detailed questionnaire data were collected on use of antioxidant supplements. Specific questions asked about use of multivitamins with and without minerals, supplements containing combinations of multiple carotenoids (beta-carotene, lycopene, lutein, etc.), as well as the following individual supplements: beta-carotene, lycopene, vitamin C, vitamin E, selenium, and zinc. For each supplement, questions asked about any use since diagnosis (yes/no), use in the five years prior to diagnosis (yes/no), and frequency of use in the period between breast cancer diagnosis and study enrollment (days/week: <1, 1–2, 3–5, 6–7).

Clinical data were obtained using KPNC electronic databases or medical chart review. Data included tumor size, number of positive lymph nodes, tumor hormone receptor status, and

treatments received, including surgery, chemotherapy, radiation therapy, and hormonal therapy. Tumor stage was determined based on the American Joint Committee on Cancer (AJCC) (4th edition) criteria.

Outcome Ascertainment

Breast cancer recurrence and death outcomes were ascertained through November 2010 by semi-annual or annual (after April 2005 when average follow-up was 5 years) mailed questionnaires that asked participants to report any major health events in the preceding six or 12 months. Non-respondents were contacted by telephone. Reported outcomes were verified by medical record review. Participant deaths were ascertained via KPNC electronic databases and by family members responding to mailed questionnaires and telephone calls. Death certificates were obtained to verify primary and underlying causes of death based on International Classification of Diseases, Ninth Revision (ICD-9) codes. Trained abstractors performed the initial reviews and a physician reviewer was consulted if the cause of death was unclear. For these analyses, breast cancer recurrence was defined as a local/regional cancer recurrence, distant recurrence/metastasis, or development of a contralateral primary breast cancer. Death from breast cancer was defined as death attributable to breast cancer as the primary or underlying cause, based on the death certificate ICD-9 code. All cause mortality was defined as death from any cause, including breast cancer.

Variable Definitions

A three-level exposure variable for use of each antioxidant in the period between diagnosis and study enrollment was created with the following categories: no use; occasional use (<1–5 days/week); and frequent use (6–7 days/week).

A comorbidity score was calculated using a modified approach to the Charlson comorbidity index.[11] Self-reported data that contributed to the score included angina, myocardial infarction, other heart problems, stroke, insulin-dependent diabetes, non-insulin-dependent diabetes, other cancer diagnosis, cirrhosis, peripheral arterial disease, other kidney disease, ulcer, and lupus. Each condition contributed one point to the score with a possible range of 0–12 points.

Statistical Analyses

The primary goal of the analyses was to relate use of antioxidant supplements in the period after breast cancer diagnosis with subsequent recurrence and death. Delayed entry Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between use of individual antioxidant supplements and breast cancer outcomes, with time since diagnosis defined as the timescale. Follow-up began at date of study entry and ended at date of first confirmed breast cancer recurrence or date of death, depending on the specific analysis. Individuals who did not have an event were censored at date of last contact. All tests of statistical significance were two-sided and considered statistically significant at the α-level of 0.05. Initial analyses dichotomized antioxidant use into ever and never use. To address possible biases related to differences between antioxidant users and non-users, subsequent analyses were restricted to women who used at least one form of antioxidant supplements.[12]

Covariates selected a priori for inclusion in the multivariable adjusted models were age at diagnosis (continuous), race/ethnicity (non-Hispanic white, black, Hispanic, Asian/Pacific Islander, other), education (<high school, high school graduate/some college, college graduate), AJCC stage (I, II, IIIA), number of positive lymph nodes (0, 1–3, ≥4), tumor hormone receptor status (estrogen receptor (ER) and/or progesterone receptor (PR)-positive, ER and PR-negative), chemotherapy received (yes, no), radiation therapy received (yes, no),

hormonal therapy received (yes, no), body mass index (BMI) one year prior to diagnosis (<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2), smoking history at enrollment (never, former, current), alcohol consumption at enrollment (grams/day: ≤0.5, >0.5-<6, 6+), physical activity at enrollment (non-sedentary metabolic equivalent (MET)-hours/week, continuous), daily servings of fruit/vegetable intake at enrollment (continuous), and an enrollment comorbidity score. Additional covariates considered for model inclusion were total caloric intake and antioxidant use in the five years prior to diagnosis; these were not retained in the final models because their inclusion did not substantially change the effect estimates. Tests for interaction were performed between treatment received (chemotherapy, radiation therapy, hormonal therapy) and use of specific antioxidant supplements. Subgroup analyses, defined a priori, were performed based on types of treatment received. Stratified analyses were performed to examine whether smoking was an effect modifier of the association between antioxidant supplementation and breast cancer outcomes.

Analyses were conducted using SAS 9.1.3 (Cary, NC).

RESULTS

Participant Characteristics

Among 2,264 women, the average age was 58.3 years (range: 25.5–79.9) and 80.0% were non-Hispanic white. On average, women were enrolled 1.9 years after breast cancer diagnosis, at which time most had completed chemotherapy and/or radiation therapy and had initiated hormonal therapy. The majority (80.3%) of women were diagnosed with stage I or IIA breast cancer and 57.2% received chemotherapy, 63.0% received radiation therapy, and 80.4% received hormonal therapy. Over ten years of study follow-up (mean (standard deviation, SD): 8.3 (2.4) years), 375 of the women had recurrences of breast cancer, and we observed 393 deaths, 214 of which were due to breast cancer.

Antioxidant Supplement Use

Of the 2,264 women, 1,829 (81%) used one or more antioxidant-containing supplements. The majority of women (70%) used a multivitamin supplement, all of which contain one or more antioxidant vitamins or minerals. Of the multivitamin supplement users, most (69%) also used one or more other supplements containing antioxidants. Aside from multivitamins, other commonly reported antioxidant supplements among the 2,264 women were vitamin C (40%), vitamin E (48%), zinc (10%), selenium (7%), combination carotenoids (7%), beta-carotene alone (6%), and lycopene alone (1%). Compared to women who were not using any antioxidant supplements, women who reported using antioxidant supplements were older, more likely to be non-Hispanic white, had higher education, had lower BMI, were less likely to have smoked, engaged in more physical activity, ate more fruits and vegetables, and had a lower comorbidity score (Table 1).

Antioxidant use and breast cancer outcomes, among all participants

All Cause Mortality—Compared to non-users of vitamin C, frequent users of vitamin C tended towards a lower risk of all cause mortality (HR: 0.78, 95% CI: 0.61–1.00) (Table 2). Compared to non-users of vitamin E, frequent users of vitamin E had significantly lower all cause mortality (HR: 0.75, 95% CI: 0.59–0.96). In contrast, use of combination carotenoids was associated with significantly increased risk of all cause mortality (versus no use, HR: 1.63; 95%: 1.06–2.50). Relatively few women reported using individual carotenoids that were not part of a combination supplement, and although confidence intervals associated with individual carotenoids were wide, the point estimates suggested increased risk of mortality (beta-carotene, HR: 1.18, 95% CI: 0.71–1.97; lycopene, HR: 1.38, 95% CI: 0.41–4.61).

No statistically significant associations were observed between occasional use of antioxidant supplements after diagnosis and any of the breast cancer outcomes (Table 2). Similarly, no statistically significant associations were observed between use of multivitamins, selenium and zinc and any of the breast cancer outcomes (Tables 2).

Death from Breast Cancer—Analyses were repeated to examine the associations between antioxidant supplement use and risk of death from breast cancer. Associations were in the same direction as those for all cause mortality, though the only associations that reached statistical significance were for combination carotenoids (Table 2). Among all 2,264 women, when compared to non-users, frequent users of combination carotenoids had increased risk of death from breast cancer (HR: 1.93, 95% CI: 1.14–3.28).

Breast Cancer Recurrence—Analyses were repeated to examine the associations between antioxidant supplement use and breast cancer recurrence (Table 2). Again, associations were in the same direction as those for all cause mortality. Among all 2,264 participants, frequent use of vitamin C and vitamin E were associated with lower risk of recurrence (versus no vitamin C use, HR: 0.70, 95% CI: 0.54–0.92; versus no vitamin E use, HR: 0.70, 95% CI: 0.54–0.90) and use of combination carotenoids was associated with a suggestive increased risk of recurrence (versus no use, HR: 1.23, 95% CI: 0.76–1.96).

Antioxidant use and breast cancer outcomes, among antioxidant users

In order to control for any possible unmeasured confounding between antioxidant users and non-users, analyses presented in Table 2 were rerun restricted to the 1,829 women who reported using one or more antioxidants after diagnosis (Table 3). Results followed the same directions as those presented in Table 2. Vitamins C and E tended to be associated with decreased mortality and frequent use of combination carotenoids was associated with increased mortality (versus no use, HR: 1.75, 95% CI: 1.13–2.71). Frequent use of combination carotenoids was associated with increased risk of dying from breast cancer (versus no use, HR: 2.07, 95% CI: 1.21–3.56). Frequent use of vitamin C and vitamin E was associated with a lower risk of breast cancer recurrence (versus no vitamin C use, HR: 0.73, 95% CI: 0.55–0.97; versus no vitamin E use, HR: 0.71, 95% CI: 0.54–0.94).

Antioxidant use and breast cancer outcomes by treatment type

To examine whether associations between antioxidant supplement use and breast cancer outcomes varied by type of breast cancer treatment, we repeated the analyses within groups defined by treatments received (chemotherapy, radiation therapy and hormonal therapy) (Table 4). The associations that were observed within each subgroup had similar directions of effects as in the overall analyses.

All Cause Mortality—Among patients who received chemotherapy and radiation therapy, the strength of the association between frequent use of combination carotenoids and all cause mortality was increased relative to the overall analyses (versus no use during chemotherapy, HR: 2.09, 95% CI: 1.21–3.61; versus no use during radiation therapy, HR: 2.14, 95% CI: 1.20–3.82), although confidence intervals were wide. Among women who received hormonal therapy, the strength of the association between the use of combination carotenoids and mortality remained high and was borderline statistically significant (HR: 1.66; 95% CI: 1.00–2.73). Similarly, relative to the overall analyses a stronger protective effect of vitamin E was observed among women who received radiation therapy and hormonal therapy. No interactions were observed between treatment type and use of specific antioxidant supplements in any analyses (data not shown).

Death from Breast Cancer—Relative to the overall analyses, strengthened associations were observed between frequent use of combination carotenoids and death from breast cancer among women who received chemotherapy, radiation therapy and hormonal therapy (versus no use during chemotherapy, HR: 2.54, 95% CI: 1.37–4.70; versus no use during radiation therapy, HR: 2.54, 95% CI: 1.28–5.05; versus no use during hormonal therapy, HR: 2.14, 95% CI: 1.16–3.97).

Breast Cancer Recurrence—Among women who received radiation and/or hormonal therapy, slightly strengthened associations were observed relative to overall analyses between frequent use of vitamins C and E and decreased risk of recurrence (versus no use during radiation therapy: vitamin C, HR: 0.60, 95% CI: 0.42–0.86; vitamin E, HR: 0.70, 95% CI: 0.49–0.98; versus no use during hormonal therapy: vitamin C, HR: 0.72, 95% CI: 0.52–0.99; vitamin E, HR: 0.70, 95% CI: 0.51–0.96). Among women who received chemotherapy, there was a trend towards increased recurrence among frequent users of multiple carotenoids (versus no use: HR: 1.66, 95% CI: 0.96–2.88).

Effect of Smoking

We repeated the analyses in subgroups defined by smoking status (ever/never). The associations in ever smokers and never smokers were similar to the overall analyses (data not shown).

DISCUSSION

In a prospective cohort study of antioxidant supplement use after breast cancer diagnosis, we report several findings. First, a large proportion of recent breast cancer survivors consumed antioxidant-containing multivitamins and individual supplements in the early (on average two years) post-diagnosis period, which encompasses breast cancer treatment. Second, in the ten years after breast cancer diagnosis, women who frequently used combination carotenoids after diagnosis had an approximately two-fold higher risk of all cause mortality as compared with non-users. This association was found even after adjustment for clinical and behavioral prognostic risk factors and conventional cancer therapies that may have been potential confounders. Third, frequent users of vitamin C and vitamin E supplements after diagnosis tended to have more favorable outcomes, including decreased risk of breast cancer recurrence and mortality.

In these analyses, we observed that frequent use of combination carotenoids in the period following diagnosis was associated with an increased risk of death from breast cancer and all causes, but not breast cancer recurrence. The mechanism through which combination carotenoids may cause death is unclear, and at least three scenarios are possible. It is possible that carotenoids may protect cancer cells against oxidative damage during treatment, and therefore decrease the effects of treatment, resulting in increased breast cancer progression.[3,13–16] It is also possible that the increased risk of death is not related to use of carotenoid supplements during treatment, but that carotenoid supplementation in general places a woman at increased risk of breast cancer progression. In the randomized trials for lung cancer prevention, beta-carotene appeared to promote existing tumors rather than initiate tumors, as was evidenced by the rapid increase in lung cancer among the group receiving beta-carotene. After beta-carotene cessation in the Alpha-Tocopherol, Beta-Carotene Prevention (ATBC) Study, there was a compensatory decrease in incidence such that after ten years of follow-up, there was no overall increase in incidence among the beta-carotene group[17]. Finally, carotenoid supplementation may place women at increased risk of non-breast cancer death. The Beta-Carotene and Retinol Efficacy Trial (CARET), a trial of beta-carotene plus retinyl palmitate among individuals at high lung cancer risk, reported that

six years after the study was closed due to harm, women who received the intervention continued to be at increased risk of death from cardiovascular disease (44%), lung cancer (33%), and all causes (37%).[18] Though the mechanism by which carotenoid supplementation may increase mortality is not clear, our results suggest that there may be cause for concern with carotenoid supplementation in the period after a breast cancer diagnosis and during treatment.

We also observed that frequent use of vitamins C and E after diagnosis was associated with reduced risk of all cause mortality, death from breast cancer, and breast cancer recurrence. Our findings are similar to those recently reported from the Shanghai Breast Cancer Survival Study (SBCSS).[9] Nechuta et al examined the associations between use of antioxidants in the six months following breast cancer diagnosis and found that women who used any form of antioxidants (vitamin E, vitamin C, multivitamins) had a 22% reduced risk of recurrence and an 18% reduced risk of death. In previous analyses within the LACE cohort, we reported that continuous use of multivitamins with minerals before and after breast cancer diagnosis was associated with a 20% decreased risk of recurrence, 32% decreased risk of breast cancer death, and 22% decreased risk of all cause death.[19] The protective mechanisms by which vitamins C and E could reduce breast cancer recurrence and mortality may be through oxidative stress pathways related to cancer and cardiovascular disease, but precise mechanisms are unclear.

There are important limitations to consider when interpreting these results. First, data on antioxidant supplement use in the period after diagnosis and during treatment was collected at the point of study enrollment, which was on average 1.9 years after diagnosis. Recall bias may have affected our findings. Data on specific dates of treatment and specific dates of antioxidant use are not available and it is possible that patients may have completed their breast cancer treatment prior to initiating antioxidant supplement use, which could have induced misclassification on. Second, we lacked information on specific doses, formulations and duration of use. Therefore, we have limited ability to comment on the dose threshold for benefit or harm of supplementation with specific antioxidants. We used frequency of use as our metric of exposure intensity. We observed the strongest effects among those whom we defined as frequent users; this category identified women who were daily users and therefore most likely had the highest cumulative exposure. We also lacked specific information on the various formulations of combination carotenoids and do not know which carotenoids conferred the most risk. Third, as this is an observational study, we have limited ability to establish a causal relationship. The tendency for breast cancer survivors to be more health conscious is well established,[20,21] and the healthy user bias may explain the findings related to vitamins C and E. At the same time, this renders our observation of increased mortality with combination carotenoid use even more striking as this cannot be explained by the healthy user bias. Finally, we are unable to draw conclusions about agents that were not frequently used (beta-carotene, lycopene, selenium, zinc) as we lacked sufficient power to detect differences between groups.

In summary, we examined the association between use of various antioxidant supplements in the period between breast cancer diagnosis and enrollment (average 1.9 years) into a prospective study of early-stage breast cancer survivors on breast cancer outcomes. We hypothesized that outcomes would differ by type of antioxidant supplement and found that outcomes did in fact differ. We observed protective associations between use of vitamin C and vitamin E and breast cancer recurrence and death from all causes, which could be true associations or could be caused by healthy user bias. However, we found that use of combination carotenoids was associated with increased risk of death from breast cancer and death from all causes, which cannot be explained by healthy user bias. To our knowledge, this is the first report from a prospective study suggesting possible harm of using a specific

type of antioxidant supplement after a breast cancer diagnosis. Our findings should be considered hypothesis-generating and need to be replicated in other study settings.

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There is concern that antioxidant supplement use during chemotherapy and radiation therapy may decrease treatment effects, yet effects on recurrence and survival are largely unknown. Data from a prospective cohort study of women with early stage breast cancer suggest that long-term effects of antioxidant supplement use after diagnosis likely differ by type of antioxidant.

Table 1

Baseline Demographics, Tumor and Lifestyle Characteristics of LACE Cohort Participants, by Use of Any Antioxidants Since Diagnosis (n=2,264)

	Antioxidant Use Since Diagnosis[a]			
	No Use (n=425)	Occasional Use[b] (n=335)	Frequent Use[c] (n=1,494)	*P* value[d]
Age at diagnosis, No. (%)				
≤50 yrs	128 (30.1)	115 (34.3)	305 (20.4)	<0.001
>50 yrs	297 (69.9)	220 (65.7)	1189 (79.6)	
Race/ethnicity, No. (%)				
Non-Hispanic white	306 (72.7)	251 (74.9)	1243 (83.3)	<0.001
Black	24 (5.7)	21 (6.3)	66 (4.4)	
Hispanic	40 (9.5)	25 (7.5)	74 (5)	
Asian/Pacific Islander	41 (9.7)	24 (7.2)	64 (4.3)	
Other	10 (2.4)	14 (4.2)	45 (3)	
Education, No. (%)				
Less than high school	32 (7.6)	19 (5.7)	72 (4.8)	0.001
High school graduate/some college	275 (65.3)	197 (59.2)	856 (57.4)	
College graduate	114 (27.1)	117 (35.1)	563 (37.8)	
Stage, No. (%)				
I	210 (49.4)	146 (43.6)	693 (46.4)	0.75
IIA	136 (32.0)	121 (36.1)	504 (33.8)	
IIB	67 (15.8)	55 (16.4)	252 (16.9)	
IIIA	12 (2.8)	13 (3.9)	44 (2.9)	
Number positive nodes, No. (%)				
0	272 (64.6)	207 (62.2)	938 (63.2)	0.96
1–3	106 (25.2)	91 (27.3)	396 (26.7)	
≥4	43 (10.2)	35 (10.5)	151 (10.2)	
ER/PR status, No. (%)				
ER+ and/or PR+	360 (86.1)	268 (81)	1253 (84.7)	0.14
ER− and PR−	58 (13.9)	63 (19)	227 (15.3)	
Treatment, No. (%)				
Chemotherapy	238 (56)	208 (62.1)	843 (56.6)	0.15
Radiation	261 (61.4)	227 (67.8)	931 (62.3)	0.13
Hormone therapy	338 (80.1)	256 (77.6)	1220 (81.8)	0.19
BMI one year before diagnosis (kg/m^2), No. (%)				
<25	171 (41)	136 (41.5)	716 (48.3)	0.01
25 - <29	124 (29.7)	107 (32.6)	433 (29.2)	
≥30	122 (29.3)	85 (25.9)	334 (22.5)	
Smoking status, No. (%)				
Never	204 (48.3)	201 (60)	785 (52.6)	0.001
Former	171 (40.5)	109 (32.5)	607 (40.7)	
Current	47 (11.1)	25 (7.5)	100 (6.7)	

	Antioxidant Use Since Diagnosis[a]			
	No Use (n=425)	Occasional Use[b] (n=335)	Frequent Use[c] (n=1,494)	*P* value[d]
Alcohol consumption (g/day), No. (%)				
≤0.5	167 (51.5)	141 (51.3)	626 (48.7)	0.78
0.5–6.0	80 (24.7)	70 (25.5)	323 (25.1)	
6.0+	77 (23.8)	64 (23.3)	336 (26.1)	
Antioxidant use 5 years before diagnosis				
Multivitamins, No. (%)	31 (8.8)	163 (52.2)	929 (65.6)	<.0001
Vitamin C, No. (%)	14 (4.1)	87 (33)	521 (44.8)	<.0001
Vitamin E, No. (%)	12 (3.5)	71 (27.5)	572 (45.4)	<.0001
Comorbidity score, mean (SD)	0.11 (0.38)	0.06 (0.27)	0.07 (0.31)	0.09
Non-sedentary MET-hrs/wk, mean (SD)	45.5 (29.5)	51.91 (31.09)	53.42 (32.51)	<.001
Daily fruit/vegetable servings, mean (SD)	3.6 (2.2)	3.9 (2.11)	4.36 (2.41)	<.001

Abbreviations: ER/PR, estrogen receptor/progesterone receptor; BMI, body mass index; MET, metabolic equivalents.

[a] Use of antioxidants since diagnosis is defined as the use of any of the following in the period between diagnosis and study enrollment: multivitamins, combination carotenoids, vitamin C, vitamin E, beta-carotene, lycopene, selenium and zinc.

[b] Occasional use is defined as using antioxidant supplements 1–5 days per week in the period between diagnosis and study enrollment.

[c] Frequent use is defined as using antioxidant supplements 6–7 days per week in the period between diagnosis and study enrollment.

Table 2

Associations between antioxidant use since diagnosis and breast cancer recurrence, death from breast cancer, and death from all causes, among all participants (n=2,264)

		Death from All Causes				Death from Breast Cancer				Breast Cancer Recurrence			
	n	# Events	HR (95% CI)[a]	*P* value	*P* for trend	# Events	HR (95% CI)[a]	*P* value	*P* for trend	# Events	HR (95% CI)[a]	*P* value	*P* for trend
Multivitamins					0.18				0.21				0.13
No use	520	99	1 (Ref)			51	1 (Ref)			94	1 (Ref)		
Occasional use	256	37	0.83 (0.56–1.22)	0.35		22	0.75 (0.45–1.25)	0.27		48	0.91 (0.64–1.3)	0.61	
Frequent use	1051	180	0.84 (0.65–1.08)	0.16		95	0.79 (0.56–1.12)	0.18		171	0.82 (0.63–1.06)	0.13	
Vitamin C alone					0.05				0.25				<.01
No use	1072	198	1 (Ref)			103	1 (Ref)			203	1 (Ref)		
Occasional use	192	25	0.78 (0.51–1.18)	0.24		16	0.84 (0.49–1.43)	0.52		30	0.78 (0.53–1.14)	0.2	
Frequent use	540	89	0.78 (0.61–1.01)	0.06		48	0.82 (0.58–1.16)	0.26		79	0.71 (0.54–0.92)	0.01	
Vitamin E alone					0.02				0.34				<.01
No use	918	174	1 (Ref)			88	1 (Ref)			175	1 (Ref)		
Occasional use	161	27	0.88 (0.58–1.32)	0.53		18	1.08 (0.64–1.81)	0.78		35	1.08 (0.75–1.57)	0.67	
Frequent use	713	113	0.75 (0.59–0.96)	0.02		62	0.85 (0.61–1.18)	0.33		102	0.7 (0.54–0.9)	<0.01	
Combination carotenoids					0.04				0.03				0.52
No use	1698	284	1 (Ref)			147	1 (Ref)			286	1 (Ref)		
Occasional use	33	6	0.95 (0.41–2.19)	0.91		3	0.77 (0.24–2.48)	0.66		6	0.79 (0.34–1.8)	0.57	
Frequent use	89	24	1.63 (1.06–2.5)	0.03		16	1.93 (1.14–3.28)	0.02		19	1.23 (0.76–1.96)	0.40	
Beta-carotene alone					0.41				0.34				0.90
No use	1726	295	1 (Ref)			157	1 (Ref)			297	1 (Ref)		
Occasional use	21	4	1.65 (0.61–4.46)	0.33		2	1.56 (0.38–6.4)	0.54		5	1.7 (0.7–4.15)	0.25	
Frequent use	71	16	1.18 (0.71–1.97)	0.52		10	1.33 (0.69–2.55)	0.39		12	0.89 (0.5–1.6)	0.70	
Lycopene alone					0.46				0.15				
No use	1804	312	1 (Ref)			165	1 (Ref)			309	1 (Ref)		1804
Occasional use	4	1	2.82 (0.39–20.67)	0.31		1	4.84 (0.64–36.4)	0.13		1	2.09 (0.29–15.22)	0.47	4
Frequent use	10	3	1.38 (0.41–4.61)	0.60		3	2.09 (0.59–7.43)	0.25		3	1.17 (0.35–3.89)	0.80	10
Selenium alone					0.65				0.87				0.75
No use	1687	298	1 (Ref)			156	1 (Ref)			291	1 (Ref)		

		Death from All Causes				Death from Breast Cancer				Breast Cancer Recurrence			
	n	**# Events**	**HR (95% CI)[a]**	***P* value**	***P* for trend**	**# Events**	**HR (95% CI)[a]**	***P* value**	***P* for trend**	**# Events**	**HR (95% CI)[a]**	***P* value**	***P* for trend**
Occasional use	34	7	1.72 (0.8–3.7)	0.16		4	1.33 (0.48–3.67)	0.58		7	1.16 (0.54–2.48)	0.70	
Frequent use	91	13	0.80 (0.45–1.41)	0.43		9	0.9 (0.45–1.79)	0.76		16	0.89 (0.53–1.49)	0.66	
Zinc alone					0.29				0.49				0.26
No use	1642	289	1 (Ref)			153	1 (Ref)			287	1 (Ref)		
Occasional use	51	10	1.11 (0.58–2.12)	0.74		4	0.83 (0.31–2.27)	0.72		7	0.72 (0.34–1.54)	0.40	
Frequent use	113	18	0.75 (0.46–1.21)	0.24		11	0.82 (0.44–1.53)	0.54		18	0.79 (0.49–1.28)	0.34	

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Multivariable hazard ratio models were conducted separately for each type of antioxidant supplement and were adjusted for the following potential confounders: age at diagnosis, race/ethnicity, education, breast cancer stage at diagnosis, number positive lymph nodes, tumor hormone receptor status, chemotherapy received, radiation therapy received, hormonal therapy received, BMI one year prior to diagnosis, smoking history at enrollment, alcohol consumption at enrollment, physical activity at enrollment, daily servings of fruits and vegetables at enrollment, and comorbidity score at enrollment.

Table 3

Associations between antioxidant use since diagnosis and death from all causes, death from breast cancer, and breast cancer recurrence, among all antioxidant users (n=1,829)

		Death from All Causes				Death from Breast Cancer				Breast Cancer Recurrence			
	n	# Events	HR (95% CI)[a]	*P* value	*P* for trend	# Events	HR (95% CI)[a]	*P* value	*P* for trend	# Events	HR (95% CI)[a]	*P* value	*P* for trend
Multivitamins					0.95				0.50				0.43
No use	199	33	1 (Ref)			19	1 (Ref)			33	1 (Ref)		
Occasional use	256	36	0.95 (0.59–1.55)	0.84		22	0.78 (0.41–1.47)	0.44		47	1.04 (0.66–1.64)	0.88	
Frequent use	1051	176	0.98 (0.67–1.42)	0.90		94	0.81 (0.49–1.33)	0.40		168	0.90 (0.62–1.31)	0.58	
Vitamin C alone					0.15				0.44				0.02
No use	752	130	1 (Ref)			70	1 (Ref)			139	1 (Ref)		
Occasional use	192	25	0.80 (0.52–1.23)	0.31		16	0.88 (0.51–1.52)	0.63		29	0.78 (0.52–1.16)	0.22	
Frequent use	540	87	0.82 (0.62–1.08)	0.17		48	0.87 (0.60–1.26)	0.45		79	0.73 (0.55–0.97)	0.03	
Vitamin E alone					0.05				0.60				0.02
No use	598	107	1 (Ref)			55	1 (Ref)			112	1 (Ref)		
Occasional use	161	27	0.86 (0.56–1.33)	0.50		18	1.13 (0.65–1.95)	0.67		35	1.12 (0.76–1.65)	0.56	
Frequent use	713	110	0.76 (0.58–1.00)	0.05		62	0.91 (0.63–1.32)	0.61			0.71 (0.54–0.94)	0.02	
Combination carotenoids					0.01				0.02				0.32
No use	1376	213	1 (Ref)			114	1 (Ref)			221	1 (Ref)		
Occasional use	33	6	1.04 (0.45–2.42)	0.93		3	0.77 (0.24–2.52)	0.67		6	0.84 (0.36–1.94)	0.68	
Frequent use	89	24	1.75 (1.13–2.71)	0.01		16	2.07 (1.21–3.56)	0.01		19	1.33 (0.83–2.15)	0.24	
Beta-carotene alone					0.42				0.24				0.91
No use	1404	226	1 (Ref)			124	1 (Ref)			232	1 (Ref)		
Occasional use	21	4	1.80 (0.66–4.91)	0.25		2	1.70 (0.42–6.98)	0.12		5	1.87 (0.76–4.58)	0.17	
Frequent use	71	15	1.18 (0.69–2.00)	0.55		10	1.44 (0.74–2.78)	0.24		12	0.95 (0.53–1.71)	0.86	
Lycopene alone					0.41				0.14				0.59
No use	1483	242	1 (Ref)			132	1 (Ref)			245	1 (Ref)		
Occasional use	4	1	3.24 (0.44–24.02)	0.25		1	5.03 (0.66–38.31)	0.49		1	2.13 (0.29–15.68)	0.46	
Frequent use	10	3	1.44 (0.43–4.87)	0.56		3	2.16 (0.60–7.77)	0.69		3	1.25 (0.37–4.22)	0.72	
Selenium alone					0.73				0.81				0.87
No use	1365	228	1 (Ref)			124	1 (Ref)			227	1 (Ref)		

		Death from All Causes				Death from Breast Cancer				Breast Cancer Recurrence			
	n	# Events	HR (95% CI)[a]	*P* value	*P* for trend	# Events	HR (95% CI)[a]	*P* value	*P* for trend	# Events	HR (95% CI)[a]	*P* value	*P* for trend
Occasional use	34	7	1.78 (0.82–3.85)	0.14		4	1.43 (0.52–3.97)	0.72		7	1.23 (0.57–2.65)	0.59	
Frequent use	91	13	0.82 (0.46–1.45)	0.50		9	0.87 (0.43–1.74)	0.64		16	0.92 (0.55–1.55)	0.76	
Zinc alone					0.50				0.59				0.34
No use	1322	219	1 (Ref)			121	1 (Ref)			223	1 (Ref)		
Occasional use	51	10	1.25 (0.65–2.41)	0.50		4	0.83 (0.30–2.29)	0.72		7	0.73 (0.34–1.57)	0.42	
Frequent use	113	18	0.80 (0.50–1.31)	0.38		11	0.86 (0.46–1.61)	0.64		18	0.82 (0.51–1.34)	0.44	

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Multivariable hazard ratio models were conducted separately for each type of antioxidant supplement and were adjusted for the following potential confounders: age at diagnosis, race/ethnicity, education, breast cancer stage at diagnosis, number positive lymph nodes, tumor hormone receptor status, chemotherapy received, radiation therapy received, hormonal therapy received, BMI one year prior to diagnosis, smoking history at enrollment, alcohol consumption at enrollment, physical activity at enrollment, daily servings of fruits and vegetables at enrollment, and comorbidity score at enrollment.

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Table 4

Associations between antioxidant use since diagnosis and death from all causes, death from breast cancer, and breast cancer recurrence, among all antioxidant users who received treatment

		Death from All Causes			Death from Breast Cancer			Breast Cancer Recurrence		
	n	# Events	HR (95% CI)[a], Frequent use vs. no use	*P* value	# Events	HR (95% CI)[a], Frequent use vs. no use	*P* value	# Events	HR (95% CI)[b], Frequent use vs. no use	*P* value
Women who received chemotherapy (n=1,051)										
Vitamin C alone	289	289	0.73 (0.49–1.08)	0.12	30	0.74 (0.47–1.18)	0.21	51	0.74 (0.52–1.05)	0.09
Vitamin E alone	378	378	0.85 (0.58–1.25)	0.42	40	0.86 (0.55–1.34)	0.50	65	0.79 (0.56–1.12)	0.18
Carotenoids	51	51	2.09 (1.21–3.61)	0.01	13	2.54 (1.37–4.70)	<0.01	15	1.66 (0.96–2.88)	0.07
Women who received radiation therapy (n=1,158)										
Vitamin C alone	334	45	0.69 (0.47–1.00)	0.05	28	0.68 (0.42–1.09)	0.11	45	0.60 (0.42–0.86)	0.01
Vitamin E alone	442	59	0.69 (0.48–0.99)	0.04	40	0.86 (0.55–1.36)	0.53	63	0.70 (0.49–0.98)	0.04
Carotenoids	50	14	2.14 (1.20–3.82)	0.01	10	2.54 (1.28–5.05)	0.01	11	1.37 (0.73–2.57)	0.32
Women who received hormonal therapy (n=1,476)										
Vitamin C alone	435	71	0.83 (0.61–1.13)	0.23	38	0.94 (0.61–1.43)	0.76	60	0.72 (0.52–0.99)	0.04
Vitamin E alone	597	88	0.68 (0.50–0.92)	0.01	48	0.84 (0.55–1.29)	0.42	81	0.70 (0.51–0.96)	0.03
Carotenoids	70	18	1.66 (1.00–2.73)	0.05	12	2.14 (1.16–3.97)	0.02	14	1.31 (0.75–2.27)	0.35

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Multivariable hazard ratio models were conducted separately for each type of antioxidant supplement and were adjusted for the following potential confounders: age at diagnosis, race/ethnicity, education, breast cancer stage at diagnosis, number positive lymph nodes, tumor hormone receptor status, BMI one year prior to diagnosis, smoking history at enrollment, alcohol consumption at enrollment, physical activity at enrollment, daily servings of fruits and vegetables at enrollment, and comorbidity score at enrollment. Within each treatment group, we also controlled for other treatments received (chemotherapy, radiation therapy, hormonal therapy).