Research Article

Cancer Epidemiology, Biomarkers & Prevention

Vitamin Supplement Use During Breast Cancer Treatment and Survival: A Prospective Cohort Study

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Abstract

Background: Antioxidants may protect normal cells from the oxidative damage that occurs during radiotherapy and certain chemotherapy regimens; however, the same mechanism could protect tumor cells and potentially reduce effectiveness of cancer treatments. We evaluated the association of vitamin supplement use in the first 6 months after breast cancer diagnosis and during cancer treatment with total mortality and recurrence.

Methods: We conducted a population-based prospective cohort study of 4,877 women aged 20 to 75 years diagnosed with invasive breast cancer in Shanghai, China, between March 2002 and April 2006. Women were interviewed approximately 6 months after diagnosis and followed up by in-person interviews and record linkage with the vital statistics registry.

Results: During a mean follow-up of 4.1 years, 444 deaths and 532 recurrences occurred. Vitamin use shortly after breast cancer diagnosis was associated with reduced mortality and recurrence risk, adjusted for multiple lifestyle factors, sociodemographics, and known clinical prognostic factors. Women who used antioxidants (vitamin E, vitamin C, multivitamins) had 18% reduced mortality risk (HR = 0.82, 95% CI: 0.65–1.02) and 22% reduced recurrence risk (HR = 0.78, 95% CI: 0.63–0.95). The inverse association was found regardless of whether vitamin use was concurrent or nonconcurrent with chemotherapy, but was present only among patients who did not receive radiotherapy.

Conclusions: Vitamin supplement use in the first 6 months after breast cancer diagnosis may be associated with reduced risk of mortality and recurrence.

Impact: Our results do not support the current recommendation that breast cancer patients should avoid use of vitamin supplements. *Cancer Epidemiol Biomarkers Prev; 20(2); 262–71. ©2010 AACR.*

Introduction

Radiotherapy and certain chemotherapy agents act through various oxidative stress mechanisms to produce free radicals that damage tumor cells (1). Oxidative stress during cancer therapy also harms healthy tissue. Antioxidant supplements may help protect normal cells from oxidative damage and reduce the short- and long-term harmful effects of cancer treatment (1–5). On the other hand, concern has been raised that antioxidant supplements may also protect tumor cells during radiotherapy and chemotherapy, thereby compromising treatment efficacy (1, 5–10). This has resulted in controversy over guidelines for the use of vitamin supplements during cancer treatment (1, 3, 11–13).

Although many investigators and clinicians recommend that vitamin supplements, in particular antioxidants in high doses, should not be used by patients during cancer treatment (1, 11–13), the use of vitamin supplements is common among breast cancer patients (4, 14–17). To our knowledge, no large, prospective cohort study or clinical trial has been conducted to evaluate the influence of vitamin supplement use during breast cancer treatment on long-term outcomes among breast cancer patients. Using data from a prospective cohort study of approximately 5,000 breast cancer survivors, we evaluated the associations of total mortality and breast cancer recurrence with vitamin supplement use following cancer diagnosis and concurrent with cancer treatment.

Materials and Methods

Study cohort

The Shanghai Breast Cancer Survival Study (SBCSS) is a population-based, prospective cohort study of Chinese women diagnosed with breast cancer. Study

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methods have been previously described (18). Briefly, women newly diagnosed with invasive breast cancer and aged 20 to 75 years were identified from the Shanghai Cancer Registry within approximately 6 months of diagnosis between March 2002 and April 2006. Eligibility criteria included the following: (i) first diagnosis of primary breast cancer; (ii) permanent resident of Shanghai; and (iii) alive at study recruitment. Of the 6,299 eligible cases, 5,042 participated (80.0%) and provided written informed consent. Reasons for nonparticipation included refusal, absent during study enrollment, could not be contacted, and other miscellaneous reasons. For the present study, we excluded women with stage 0 tumors ($n = 156$) and women who did not have surgery ($n = 9$), leaving a final sample of 4,877 women for the analyses.

Data collection

In-person interviews were conducted by trained interviewers, all retired medical professionals, on average 6.5 months (range: 3–11) after diagnosis to obtain information on reproductive history, medical history, selected dietary and other lifestyle factors, complementary and alternative medicine use, sociodemographics, and quality of life. Anthropometric measurements were taken using a standard protocol. Medical records were reviewed for 98.1% of participants to obtain and verify clinical data, including cancer diagnosis, treatment history, and tumor characteristics [e.g., estrogen receptor (ER) and progesterone receptor (PR) status and tumor stage]. The agreement rates between self-reported and medical chart information ranged from 94% to 98%. In-person follow-up surveys have been conducted at 18 months (4,572 completed among survivors), 36 months (4,149 completed among survivors), and 60 months (ongoing follow-up with 2,228 interviews completed to date). The in-person follow-up rate for the 36-month interview was 88.2%. Information on survival status was also obtained by annual linkage to the Shanghai Vital Statistics Registry database. Procedures followed were in accordance with the ethical standards of the involved institutions, and Human Subjects Institutional Review Board approval was obtained from all participating institutions.

Postdiagnosis vitamin use

For women who responded "yes" to ever taking vitamins at least once a week for 1 month or more after diagnosis at the 6-month interview, specific information was collected for the time period from diagnosis to the interview for multivitamins; cod-liver oil; vitamins A, C, D, and E; B vitamins (data on individual types of B vitamins were not collected); and other nonspecified vitamins. Vitamin use was also assessed at the 36-month and ongoing 60-month follow-up surveys. For this report, we were interested in vitamin use during cancer treatments; hence, we used only data from the 6-month interview, which were collected for the time period when most women received their cancer treatments.

Categorical variables were created to examine postdiagnosis use of any type of vitamin supplement, multivitamins, vitamin E, vitamin C, and use of any antioxidants (including multivitamins, vitamins C, and vitamin E). For each type of vitamin, variables were created for any use and for duration of use ($\leq$3 months and > 3 months, 3 months is approximately half the time between diagnosis and the baseline interview). Women were also classified according to the timing of vitamin use in relation to cancer treatment. Information regarding the specific brand, composition, and dosage of vitamin supplements was not available.

Statistical analysis

Differences in clinical characteristics, lifestyle factors, and sociodemographics by postdiagnosis vitamin supplement use were assessed with the chi-square test. Given the known health benefits of vitamin supplement use in the general population and concern that the use of antioxidant supplements during cancer treatment may reduce the effectiveness of cancer therapies, we chose both total mortality and recurrence as the main outcomes for our analysis. We also conducted analyses with breast cancer–specific mortality as the outcome. Survival time was calculated as the time from breast cancer diagnosis to event, with censoring at non–breast cancer deaths for breast cancer–specific mortality, the last date of in-person contact, or May 31, 2008 (5 months before the most recent linkage to the vital statistics registry, whichever was the latest date).

Adjusted HRs and their corresponding 95% CIs were derived from Cox proportional hazards regression models, using age as the time scale (19). Entry time was defined as age at diagnosis, and exit time was defined as age at event or censoring. The reference group for all analyses was never use of any vitamin supplement after diagnosis.

Potential confounders included known clinical predictors of survival (ER/PR status, TNM stage, chemotherapy, radiotherapy, tamoxifen use) and baseline sociodemographic and lifestyle factors associated with both vitamin use and survival [education, income, body mass index (BMI)], regular tea drinker, regular exercise participation calculated using standard metabolic equivalents (METs; ref. 20) in MET-hours per week, cruciferous vegetable intake, soy protein intake] with statistical definitions shown in Table 1. To address the potential for residual confounding due to inadequate adjustment for categorized confounders, we created a propensity score (21), which combined these potential confounders into a summary variable (and also included smoking and alcohol intake), using logistic regression with vitamin use as the dependent variable and potential confounders as the independent variables (21). We evaluated the associations of vitamin use with mortality and recurrence, adjusting for the propensity score, and results were similar to those generated from analyses with adjustment for individual confounders. Therefore, only the results from the latter are presented.

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Table 1. Clinical characteristics, sociodemographics, and postdiagnosis lifestyle factors by vitamin use at the 6-month interview after breast cancer diagnosis, SBCSS ($N = 4,877$)

	Prevalence		Vitamin use[a] after breast cancer diagnosis				
			Yes ($n = 1,776$)		No ($n = 3,101$)		P[b]
	n	%	*n*	%	*n*	%	
Age at diagnosis							0.49
<40	236	4.8	85	4.8	151	4.9	
40–49	1,940	39.8	692	39.0	1,248	40.3	
50–59	1,445	29.6	519	29.2	926	29.9	
≥60	1,256	25.8	480	27.0	776	25.0	
Education							<0.001
None	188	3.9	39	2.2	149	4.8	
Elementary	385	7.9	117	6.6	268	8.6	
Middle or high school	3,537	72.5	1,241	69.9	2,296	74.0	
College and above	767	15.7	379	21.3	388	12.5	
Income[c]							<0.001
<700	1,376	28.2	446	25.1	930	30.0	
700–999	1,441	29.6	482	27.1	959	30.9	
1,000–1,999	1,482	30.4	576	32.4	906	29.2	
≥2,000	578	11.9	272	15.3	306	9.9	
ER/PR status							0.66
Unknown	91	1.9	29	1.6	62	2.0	
ER^+/PR^+	2,439	50.0	888	50.0	1,551	50.0	
ER^+/PR^-	635	13.0	220	12.4	415	13.4	
ER^-/PR^+	362	7.4	132	7.4	230	7.4	
ER^-/PR^-	1,350	27.7	507	28.6	843	27.2	
TNM stage							0.42
Missing	223	4.6	82	4.6	141	4.6	
I	1,680	34.5	630	35.5	1,050	33.9	
IIA/IIB	2,482	50.9	894	50.3	1,588	51.2	
III–IV	492	10.1	170	9.6	322	10.4	
Chemotherapy							0.63
No	380	7.8	134	7.6	246	7.9	
Yes	4,497	92.2	1,642	92.5	2,855	92.1	
Radiotherapy							0.11
No	3,280	67.3	1,169	65.8	2,111	68.1	
Yes	1,597	32.8	607	34.2	990	31.9	
Tamoxifen use							0.06
No	2,354	48.3	825	46.5	1,529	49.3	
Yes	2,523	51.7	951	53.6	1,572	50.7	
BMI, kg/m^2							0.05
<25	3,156	64.7	1,176	66.2	1,980	63.9	
25–29	1,447	29.7	518	29.2	929	30.0	
≥30	274	5.6	82	4.6	192	6.2	
Number of pregnancies							0.14
0	197	4.0	83	4.7	114	3.7	
1	959	19.7	351	19.8	608	19.6	
2	1,614	33.1	559	31.5	1,055	34.0	
≥3	2,107	43.2	783	44.1	1,324	42.7	
Regular smoker							0.004
No	4,749	97.4	1,745	98.3	3,004	96.9	

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Table 1. Clinical characteristics, sociodemographics, and postdiagnosis lifestyle factors by vitamin use at the 6-month interview after breast cancer diagnosis, SBCSS ($N = 4,877$) (Cont'd)

	Prevalence		Vitamin use[a] after breast cancer diagnosis				
			Yes ($n = 1,776$)		No ($n = 3,101$)		P[b]
	n	%	*n*	%	*n*	%	
Yes	128	2.6	31	1.8	97	3.1	
Regular alcohol drinker							0.53
No	4,727	96.9	1,725	97.1	3,002	96.8	
Yes	150	3.1	51	2.9	99	3.2	
Regular tea drinker							0.002
No	3,720	76.3	1,311	73.8	2,409	77.7	
Yes	1,157	23.7	465	26.2	692	22.3	
Regular exerciser							<0.001
No	576	32.4	576	32.4	1,155	37.3	
<5.1 MET-h/wk	356	20.1	356	20.1	631	20.4	
5.1 to 12.6 MET-h/wk	404	22.8	404	22.8	643	20.7	
≥12.7 MET-h/wk	440	24.8	440	24.8	672	21.7	
Family history of breast cancer							0.58
No	4,606	94.4	1,673	94.2	2,933	94.6	
Yes	271	5.6	103	5.8	168	5.4	
Cruciferous vegetable intake, g/d							0.003
<39.96	1,220	25.0	408	23.0	812	26.2	
39.96 to <63.72	1,217	25.0	421	23.7	796	25.7	
63.72 to <96.70	1,222	25.1	460	25.9	762	24.6	
≥96.70	1,218	25.0	487	27.4	731	23.6	
Meat intake, g/d							0.11
<136.4	1,220	25.0	413	23.3	807	26.0	
136.4 to <200.0	1,182	24.2	433	24.4	749	24.2	
200.0 to <278.70	1,255	25.7	459	25.8	796	25.7	
≥278.70	1,220	25.0	471	26.5	749	24.2	
Soy protein intake, g/d							<0.001
<5.31	1,218	25.0	383	21.6	835	26.9	
5.31 to <9.49	1,221	25.0	438	24.7	783	25.3	
9.49 to <15.33	1,217	25.0	449	25.3	768	24.8	
≥15.33	1,221	25.0	506	28.5	715	23.1	

[a]Vitamin use includes multivitamins; cod-liver oil; vitamins A, C, D, and E; B vitamins; and other unknown vitamin supplements.
[b]*P* value from chi-square test for general association of vitamin use with baseline participant characteristics.
[c]Yuan reminibi per person per month. U.S. $1= 6.79 Chinese Yuan on August 17, 2010.

Radiotherapy, ER/PR status, TNM stage, and tamoxifen were examined as potential modifiers of the associations of vitamin use and breast cancer outcomes. Multiplicative interactions were tested for using −2 log likelihood ratio test statistics, which compared models with and without the interaction terms. All analyses were carried out using SAS version 9.2. Tests of statistical significance were based on 2-sided probability and values of $P < 0.05$ were considered statistically significant. Results for breast cancer–specific mortality were very similar to those for total mortality; hence, breast cancer–specific mortality results were included only as supplemental information (see Supplementary Tables S1–S3).

Results

After an average of 4.1 years of follow-up (range: 0.5–6.2 years), 4,433 women were alive and 444 died (389 from breast cancer, 55 from other causes). A total of 4,325 women remained disease free during follow-up, and 532 had a breast cancer recurrence. Approximately 36.4% of breast cancer survivors ever used any type of vitamin supplement after diagnosis. Vitamin C was the

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most common (17.5%), followed by B vitamins (16.3%), vitamin E (7.6%), vitamin A (1.7%), and vitamin D (0.4%); about 11% used multivitamins.

Women who reported vitamin use tended to have higher education, income, daily intake of cruciferous vegetables and soy protein, and were more likely to have a lower BMI as well as to report not smoking, drinking tea, and exercising regularly (Table 1). Vitamin use did not vary significantly by age at diagnosis, joint ER and PR tumor status, TNM stage, chemotherapy, radiotherapy, tamoxifen use, number of pregnancies, family history of breast cancer, alcohol intake, or meat intake (Table 1).

As shown in Table 2, in general, postdiagnosis vitamin use within the first 6 months of cancer diagnosis [including any vitamins, multivitamins, vitamin E alone, vitamin C alone, and any antioxidants (multivitamins, vitamin C, and/or vitamin E)] was associated with reduced risk of total mortality and breast cancer recurrence, although not all HRs reached statistical significance. HRs were adjusted for multiple lifestyle factors (e.g., physical activity in MET-hours per week, soy protein intake), education, income, and clinical characteristics. Age-adjusted results were similar to the fully adjusted results (data not shown). The largest reduction in risk was seen for women who used vitamin C or E for a longer duration after diagnosis, estimated by use longer than approximately half the time period between diagnosis and the baseline interview. Specifically, women who

Table 2. Postdiagnosis vitamin supplement use in association with total mortality and breast cancer recurrence, SBCSS ($N = 4,877$)

		Total mortality			Breast cancer recurrence		
Vitamin use	**Cohort**	**No. of events**	**HR[a] (95% CI)**	***P***	**No. of events**	**HR[a] (95% CI)**	***P***
Never postdiagnosis	3,101	297	1.00 (referent)		357	1.00 (referent)	
Any type							
Postdiagnosis use	1,776	147	0.88 (0.72–1.08)	0.23	175	0.84 (0.70–1.01)	0.06
Duration of use							
≤3 mo	547	56	1.09 (0.81–1.45)	0.57	60	0.90 (0.69–1.19)	0.48
>3 mo	1,229	91	0.79 (0.62–1.00)	0.05	115	0.81 (0.65–1.00)	0.05
Multivitamins							
Postdiagnosis use	535	36	0.82 (0.57–1.17)	0.27	41	0.74 (0.53–1.03)	0.08
Duration of use							
≤3 mo	225	18	1.01 (0.63–1.64)	0.96	16	0.70 (0.42–1.17)	0.17
>3 mo	310	18	0.69 (0.42–1.11)	0.12	25	0.77 (0.51–1.16)	0.21
Vitamin E[b]							
Postdiagnosis use	297	22	0.71 (0.46–1.11)	0.13	25	0.65 (0.43–0.97)	0.04
Duration of use							
≤3 mo	128	13	0.97 (0.55–1.70)	0.90	13	0.74 (0.42–1.29)	0.29
>3 mo	169	9	0.52 (0.27–1.01)	0.05	12	0.57 (0.32–1.01)	0.05
Vitamin C[b]							
Postdiagnosis use	746	61	0.81 (0.61–1.07)	0.13	78	0.81 (0.63–1.03)	0.09
Duration of use							
≤3 mo	339	38	1.08 (0.77–1.52)	0.66	46	1.00 (0.74–1.37)	0.98
>3 mo	407	23	0.56 (0.37–0.87)	0.009	32	0.62 (0.43–0.90)	0.01
Any antioxidant[c]							
Postdiagnosis use	1,380	107	0.82 (0.65–1.02)	0.08	129	0.78 (0.63–0.95)	0.02
Duration of use							
≤3 mo	537	60	1.13 (0.85–1.50)	0.40	63	0.92 (0.70–1.21)	0.56
>3 mo	843	47	0.60 (0.44–0.82)	0.001	66	0.67 (0.51–0.88)	0.004

[a]HRs are adjusted for ER/PR status, TNM stage, chemotherapy, radiotherapy, tamoxifen use, education, income, BMI, regular tea consumption, regular exercise participation (MET-hours per week), daily cruciferous vegetable intake, daily soy protein intake, and other vitamin variables in the table. Adjusted HRs and their corresponding 95% CIs were derived from Cox proportional hazards regression models, using age as the time scale.

[b]Excludes women who took a multivitamin ($n = 535$).

[c]Includes women who used vitamin C, vitamin E, and/or multivitamins.

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used vitamin C for more than 3 months had a 44% decrease in risk of mortality (adjusted HR: 0.56; 95% CI: 0.37–0.87) and a 38% decrease in risk of recurrence (adjusted HR: 0.62; 95% CI: 0.43–0.90). Similarly, users of vitamin E for more than 3 months had a reduced risk of mortality (adjusted HR: 0.52; 95% CI: 0.27–1.01) and recurrence (adjusted HR: 0.57; 95% CI: 0.32–1.01), although point estimates were of marginal statistical significance (Table 2).

Associations of mortality and recurrence with vitamin use concurrent with chemotherapy and nonconcurrent with chemotherapy (vitamin use before or after chemotherapy) are shown in Table 3. This analysis was limited to women who received chemotherapy (n = 4,497), which comprised about 92% of study participants. We found that vitamin use concurrent or nonconcurrent with chemotherapy was associated with reduced risk of both mortality and recurrence, although the point estimates were not statistically significant, partially due to the reduced sample sizes for these analyses.

We evaluated the associations of mortality and recurrence with vitamin use by radiotherapy status (Table 4). Vitamin use was not associated with breast cancer outcomes among radiotherapy users (n = 1,597). In contrast, among women who did not receive radiotherapy (n = 3,280), vitamin use was associated with decreased risk for both mortality and recurrence, with the strongest association seen for the use of any antioxidant (adjusted HR for mortality: 0.65; 95% CI: 0.47–0.92; adjusted HR for recurrence: 0.63; 95% CI: 0.46–0.86). However, P values for multiplicative interactions were not statistically significant (Table 4). Women who received radiotherapy tended to be younger at diagnosis, have higher education, higher TNM stage at diagnosis, higher total meat intake, lower soy protein intake, were more likely to have received chemotherapy or drink tea, and were less likely to use tamoxifen or exercise regularly compared with women who did not receive radiotherapy (data not shown). Radiotherapy was associated with increased risk of mortality (adjusted HR: 1.40; 95% CI: 1.13–1.73) and breast cancer recurrence (adjusted HR: 1.39; 95% CI: 1.14–1.68). These associations were not significantly modified by other clinical characteristics or lifestyle factors (data not shown).

We also examined the joint associations for radiotherapy and vitamin use with breast cancer outcomes. In comparison to women who did not receive radiotherapy or take vitamin supplements during the first 6 months after diagnosis, women who took antioxidant vitamins and did not receive radiotherapy were at reduced risk of mortality (adjusted HR: 0.67; 95% CI: 0.48–0.94) and recurrence (adjusted HR: 0.66; 95% CI: 0.49–0.89); women who did not take antioxidant vitamins and received radiotherapy were at nonsignificantly increased risk of mortality (adjusted HR: 1.26; 95% CI: 0.92–1.72) and recurrence (adjusted HR: 1.26; 95% CI: 1.00–1.57); and women jointly exposed to radiotherapy and antioxidant vitamins had nonsignificantly increased risk of mortality (adjusted HR: 1.27; 95% CI: 0.99–1.64) and recurrence (adjusted HR: 1.17; 95% CI: 0.88–1.54). Similar results were found for analyses for any type of vitamin use (data not shown).

In stratified analyses, the associations of vitamin use with risk of mortality and recurrence varied little by TNM

Table 3. Postdiagnosis vitamin supplement use in association with total mortality and breast cancer recurrence among women who received chemotherapy, SBCSS (N = 4,497)

		Total mortality			Breast cancer recurrence		
Vitamin use	**Cohort**	**No. of events**	**HR[a] (95% CI)**	***P***	**No. of events**	**HR[a] (95% CI)**	***P***
Never postdiagnosis	2,855	270	1.00 (referent)		331	1.00 (referent)	
Postdiagnosis use							
Any type	1,642	135	0.89 (0.72–1.09)	0.26	170	0.87 (0.72–1.06)	0.17
Any antioxidant[b]	1,267	97	0.82 (0.64–1.04)	0.09	125	0.81 (0.66–1.00)	0.05
Used during chemotherapy							
Any type	1,339	112	0.91 (0.72–1.14)	0.40	146	0.93 (0.76–1.13)	0.44
Any antioxidant[b]	998	74	0.81 (0.62–1.05)	0.11	101	0.84 (0.67–1.06)	0.13
Did not use during chemotherapy							
Any type	303	23	0.79 (0.52–1.22)	0.29	24	0.66 (0.43–1.00)	0.05
Any antioxidant[b]	269	23	0.85 (0.55–1.31)	0.46	24	0.71 (0.47–1.08)	0.11

[a]HRs are adjusted for ER/PR status, TNM stage, radiotherapy, tamoxifen use, education, income, BMI, regular tea consumption, regular exercise participation (MET-hours per week), daily cruciferous vegetable intake, daily soy protein intake, and other vitamin variables in the table. Adjusted HRs and their corresponding 95% CIs were derived from Cox proportional hazards regression models, using age as the time scale.

[b]Includes women who used vitamin C, vitamin E, and/or multivitamins.

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Table 4. Postdiagnosis vitamin supplement use in association with total mortality and breast cancer recurrence by use of radiotherapy, SBCSS ($N = 4,877$)[a]

	Radiotherapy ($n = 1,597$)			No radiotherapy ($n = 3,280$)		
Vitamin use	Events/cohort	HR (95% CI)	*P*	Events/cohort	HR (95% CI)	*P*
			Total mortality			
Never postdiagnosis	128/990	1.00 (referent)		169/2,111	1.00 (referent)	
Postdiagnosis use						
Any type	79/607	1.03 (0.77–1.38)	0.86	68/1,169	0.75 (0.56–1.00)	0.05
Any antioxidant[b]	63/500	1.00 (0.73–1.37)	0.99	44/880	0.65 (0.47–0.92)	0.01
Used during radiotherapy						
Any type	50/418	0.94 (0.67–1.32)	0.72	–		
Any antioxidant[b]	40/333	0.92 (0.63–1.33)	0.66	–		
Did not use during radiotherapy						
Any type	29/189	1.21 (0.80–1.84)	0.36	–		
Any antioxidant[b]	23/167	1.14 (0.72–1.80)	0.51	–		
			Breast cancer recurrence			
Never postdiagnosis	159/990	1.00 (referent)		198/2,111	1.00 (referent)	
Postdiagnosis use						
Any type	96/607	1.02 (0.78–1.33)	0.90	79/1,169	0.72 (0.55–0.94)	0.02
Any antioxidant[b]	78/500	0.99 (0.74–1.31)	0.92	51/880	0.63 (0.46–0.86)	0.003
Used during radiotherapy						
Any type	61/418	0.93 (0.69–1.26)	0.66	–		
Any antioxidant[b]	48/333	0.90 (0.64–1.26)	0.53	–		
Did not use during radiotherapy						
Any type	35/189	1.21 (0.83–1.76)	0.33	–		
Any antioxidant[b]	30/167	1.16 (0.78–1.73)	0.47	–		

[a]HRs are adjusted for ER/PR status, TNM stage, chemotherapy, tamoxifen use, education, income, BMI, regular tea consumption, regular exercise participation (MET-hours per week), daily cruciferous vegetable intake, daily soy protein intake, and use of other types of vitamins (as appropriate). Adjusted HRs and their corresponding 95% CIs were derived from Cox proportional hazards regression models, using age as the time scale. *P* values for multiplicative interactions between radiotherapy and vitamin use were as follows: for use of any type of vitamin, $P = 0.17$ for total mortality and $P = 0.14$ for recurrence; for use of any antioxidant, $P = 0.23$ for total mortality and $P = 0.17$ for recurrence.

[b]Includes women who used vitamin C, vitamin E, and/or multivitamins.

stage or tamoxifen use (Table 5). Some differences were found by ER/PR status, with stronger inverse associations among women with ER/PR-negative tumors than among women with ER/PR-positive tumors, although the *P* values for multiplicative interactions were not statistically significant (data not shown).

Discussion

There is a widespread concern that the use of antioxidant supplements during cancer treatment may protect tumor cells from the oxidative damage induced by cancer therapies, thereby reducing the effectiveness of treatment and increasing risk of mortality (1, 11, 12). The epidemiologic data to support this concern are limited, in particular among breast cancer patients (1, 3). In fact, no large, prospective cohort study to date has reported findings on vitamin supplement use in conjunction with cancer treatment and subsequent mortality and recurrence risk among breast cancer survivors. Given the concern regarding the safety of antioxidant use during cancer treatment, as well as the few previous studies in this area, a randomized controlled trial may not be feasible or appropriate at this time; hence, results from observational studies are particularly warranted. In this first large, prospective cohort study of vitamin use in conjunction with cancer treatment among breast cancer survivors, we found that vitamin supplement use shortly after diagnosis, including antioxidant vitamins C and E, was associated with reduced risk of mortality and recurrence among breast cancer survivors regardless of whether vitamin use was concurrent or not concurrent with chemotherapy. In results stratified by radiotherapy status, the inverse association

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Table 5. Postdiagnosis vitamin supplement use in association with total mortality and breast cancer recurrence by tumor characteristics and tamoxifen use, SBCSS ($N = 4,877$)

		Total mortality			Breast cancer recurrence
Vitamin use	**Cohort**	**No. of Events**	**HR[a] (95% CI)**	**No. of Events**	**HR[a] (95% CI)**
			ER^+/PR^+ ($n = 2,439$)		
Never postdiagnosis	1,551	98	1.00 (referent)	123	1.00 (referent)
Any type postdiagnosis	888	53	0.98 (0.69–1.38)	66	0.95 (0.70–1.29)
Any antioxidant postdiagnosis[b]	683	37	0.91 (0.61–1.34)	49	0.93 (0.66–1.31)
			ER^-/PR^- ($n = 1,350$)		
Never postdiagnosis	843	123	1.00 (referent)	142	1.00 (referent)
Any type postdiagnosis	507	62	0.84 (0.61–1.16)	71	0.78 (0.58–1.05)
Any antioxidant postdiagnosis[b]	394	45	0.77 (0.54–1.11)	51	0.71 (0.51–0.99)
			Stage I or II ($n = 4,162$)		
Never postdiagnosis	2,638	185	1.00 (referent)	231	1.00 (referent)
Any type postdiagnosis	1,524	95	0.86 (0.67–1.10)	116	0.82 (0.65–1.03)
Any antioxidant postdiagnosis[b]	1,180	67	0.79 (0.59–1.05)	83	0.76 (0.59–0.98)
			Stage III or IV ($n = 492$)		
Never postdiagnosis	322	99	1.00 (referent)	113	1.00 (referent)
Any type postdiagnosis	170	48	0.87 (0.60–1.27)	56	0.80 (0.57–1.14)
Any antioxidant postdiagnosis[b]	134	37	0.84 (0.56–1.25)	44	0.75 (0.51–1.09)
			Used tamoxifen ($n = 2,523$)		
Never postdiagnosis	1,572	125	1.00 (referent)	153	1.00 (referent)
Any type postdiagnosis	951	68	0.90 (0.66–1.22)	79	0.77 (0.58–1.02)
Any antioxidant postdiagnosis[b]	730	51	0.89 (0.64–1.25)	61	0.77 (0.57–1.05)
			Did not use tamoxifen ($n = 2,354$)		
Never postdiagnosis	1,529	172	1.00 (referent)	204	1.00 (referent)
Any type postdiagnosis	825	79	0.89 (0.68–1.18)	96	0.89 (0.69–1.15)
Any antioxidant postdiagnosis[b]	650	56	0.78 (0.57–1.06)	68	0.77 (0.58–1.03)

[a]HRs are adjusted for ER/PR status, TNM stage, chemotherapy, radiotherapy, tamoxifen use, education, income, BMI, regular tea consumption, regular exercise participation (MET-hours per week), daily cruciferous vegetable intake, daily soy protein intake, and other type of vitamin use (as appropriate). Adjusted HRs and their corresponding 95% CIs were derived from Cox proportional hazards regression models, using age as the time scale.

[b]Includes women who used vitamin C, vitamin E, and/or multivitamins.

was found only among women who did not receive radiotherapy.

Few studies have directly evaluated whether there is an association of vitamin use after cancer diagnosis and during cancer treatment with mortality and recurrence, in particular among breast cancer patients (1–3, 22). In a recent comprehensive review of studies of antioxidant supplement use during breast cancer treatment and breast cancer patient outcomes (3), only 5 studies were identified that examined vitamin supplement use in association with recurrence and/or mortality. Four of these studies involved fewer than 55 patients (23–26) and were further limited by lack of a concurrent control group (24) or unclear/unreported statistical analyses (23, 25, 26). The largest study, a retrospective cohort study, identified patients from a medical database maintained by the British Columbia Cancer Agency (BCCA; ref. 27). Exposed women ($n = 90$) were seen by an orthomolecular physician who prescribed them a regimen of mega-dose vitamin/mineral supplements. Unexposed women ($n = 180$) were selected from the BCCA database and did not see that orthomolecular physician. After a median follow-up of 68 months, nonsignificantly increased HRs for breast cancer mortality (1.75; 95% CI: 0.83–2.69) and disease-free survival (1.55; 95% CI: 0.94–2.54) were found for women following the regimen of mega-dose vitamin/mineral supplements (27). However, this study was limited because of concerns regarding potential selection bias and lack of data on treatment compliance and over-the-counter vitamin use (27).

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Of note, the main study that has been cited to support concern regarding the safety of antioxidant use during cancer treatment was conducted among head and neck cancer patients. This study was a randomized controlled clinical trial of 540 patients who received 400 IU of α-tocopherol and 30 mg of β-carotene or placebo at the start of radiotherapy and for 3 years thereafter (β-carotene was discontinued after enrollment of 156 patients; ref. 9). After a median of 6.5 years of follow-up, all-cause mortality was increased among participants in the supplement arm as compared with the placebo arm (HR: 1.38; 95% CI: 1.03–1.85; ref. 9). However, in a subsequent report, the increased risk for mortality was found to be limited to patients who smoked during radiation therapy (28). Because smoking rates are low among breast cancer survivors (18, 29), and prognosis and treatment of breast cancer differ substantially from that of head and neck cancer, it is questionable whether the results from this trial can be generalized to breast cancer patients.

The biological activity of antioxidants depends on several factors, including oxidative stress level, interactions with other antioxidants, and the concentration of antioxidants available at the cellular level (1). One explanation for a lack of protection from vitamin use among women who received radiotherapy in our study could be that the dosages of vitamin supplements were not high enough to be beneficial among these women. Further studies with a larger sample size and a wide range of vitamin supplements are needed to confirm the association of vitamin use and breast cancer outcomes among radiotherapy users.

The SBCSS is a large, well-designed, prospective cohort study of breast cancer survivors (30). The potential for selection bias is small due to the population-based design and high response and follow-up rates. Standardized in-person interviews collected information on cancer treatment, lifestyle factors, anthropometrics, and disease history, which improved the exposure assessment and allowed for adjustment for many potential confounders.

Several limitations should be considered. First, we did not have complete information on dosages for vitamin supplements. However, among women with available data who reported taking vitamin C or E (in mg) daily, approximately 85% used 400 mg/d or less of vitamin C and 99% used 400 mg/d or less of vitamin E. These are much lower dosages than those found in mega-dose vitamins, which can be well over 1 g (1, 3). Second, we did not have complete dietary information for participants, which prevented an evaluation of dietary vitamin/antioxidant intake. In the Shanghai Women's Health Study (31), a population-based cohort study of women aged 40 to 70 years residing in Shanghai, where the current study was conducted, dietary intakes of vitamins C and E were very weakly correlated with supplement use of these single vitamins ($r = 0.04$ and $r = 0.08$, respectively). On the other hand, daily intakes of cruciferous vegetables and dietary vitamin C were highly correlated ($r = 0.67$). In our analyses, we adjusted for daily intakes of cruciferous vegetable and soy protein, both of which are major sources of dietary antioxidants for Chinese women in Shanghai. Thus, potential confounding by dietary sources of vitamins should not be a major concern in this study.

Although we adjusted for a wide range of clinical prognostic factors, sociodemographics, and lifestyle factors in multivariable analyses, both as independent covariates and by creating propensity scores, and obtained similar results with both approaches, we cannot exclude the possibility of residual confounding from inadequately measured covariates or unmeasured confounders. For example, one potential concern is that vitamin use is more common in women with higher socioeconomic status, a factor that may also be associated with completing recommended cancer therapy. Although we collected detailed information on chemotherapy treatment regimens and duration of the treatment, we did not obtain information on the prescribed length of treatment. Hence, we are not able evaluate whether women completed the full prescribed courses of chemotherapy. However, in our study population, the weeks of total chemotherapy treatment were very similar for users of vitamins [mean = 17.7; range: 13.1 (25th percentile) to 21.9 (75th percentile)] and for nonusers [mean = 17.4; range: 13.1 (25th percentile) to 21.6 (75th percentile)]. Thus, differences in treatment compliance is an unlikely explanation for our findings.

Another concern is that prediagnosis vitamin use, which could be related to both postdiagnosis vitamin use and breast cancer outcomes, was unavailable for all study participants. We did, however, have information on prediagnosis vitamin use for a subset of participants ($n = 1,442$). The correlation between prediagnosis vitamin use (any type) and use around the time of treatment was 0.18. Results adjusted for prediagnosis vitamin use were similar to overall findings, although not significant because of the smaller sample size. We did not examine vitamin use at 36 months postdiagnosis in relation to breast cancer outcomes, because the focus of this study was to evaluate the association of vitamin use during cancer treatment. In addition, the cohort follow-up time is not yet long enough to evaluate long-term vitamin use in relation to breast cancer outcomes. Continued follow-up of this cohort will allow us to examine this research question in the future. Finally, despite an overall large sample size, the number of women exposed to individual vitamins was small and studies with a larger sample size are warranted.

In conclusion, we found no evidence that vitamin use during the first 6 months following diagnosis had a detrimental effect on breast cancer outcomes. Instead, vitamin use, particularly vitamin C and vitamin E use, may be associated with reduced risk of mortality and recurrence, independent of multiple lifestyle factors, clinical prognostic factors, and sociodemographics. The inverse association was primarily seen among women

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who did not receive radiotherapy. To our knowledge, this is the first large, prospective cohort study to report on vitamin use during cancer treatment in association with recurrence and mortality among breast cancer survivors and future studies of postdiagnosis vitamin use and breast cancer outcomes are needed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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