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Prevalence and predictors of antioxidant supplement use during breast cancer treatment: The Long Island Breast Cancer Study Project

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Abstract

Background—Although many patients take antioxidant dietary supplements during breast cancer treatment, the benefits of such supplementation are unproven. We analyzed the prevalence of and factors associated with antioxidant supplement use during breast cancer treatment among women who participated in the Long Island Breast Cancer Study Project.

Methods—In 2002–2004, women with breast cancer (BC) who had participated in the 1996–1997 case-control study were invited to participate in a follow-up interview. We defined antioxidant supplement use as any self-reported intake of supplemental vitamin C, vitamin E, beta-carotene, or selenium, in individual supplements or multivitamins.

Results—Follow-up interview participants were younger, more predominantly white, and of higher socioeconomic status, than women who did not respond. Among 764 participants who completed the follow-up interview, 663 (86.8%) reported receiving adjuvant treatment for their BC. Of these 663 women, 401 (60.5%) reported using antioxidants during adjuvant treatment: 120/310 (38.7%) during chemotherapy, 196/464 (42.2%) during radiation, and 286/462 (61.9%) during tamoxifen therapy. Of the 401 antioxidant users, 278 (69.3%) used high doses (doses higher than those contained in a Centrum multivitamin). Factors associated with high antioxidant supplement use during treatment were higher fruit and vegetable intake at diagnosis (RR 1.71,

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95% CI 1.13–2.59), tamoxifen use (RR 3.66, 95% CI 2.32–5.78), ever using herbal products (RR 3.49, 95% CI 2.26–5.38), and ever engaging in mind-body practices (RR 1.72, 95% CI 1.13–2.64).

Conclusions—Given the common use of antioxidant supplements during BC treatment, often at high doses and in conjunction with other complementary therapies, future research should address the effects of antioxidant supplementation on BC outcomes.

Keywords

antioxidants; dietary supplements; breast cancer; chemotherapy; radiation therapy; hormonal therapy

INTRODUCTION

An estimated 45–87% of breast cancer patients use antioxidant supplements after diagnosis 1⁻9. However, the characteristics of women who use antioxidants specifically during treatment for breast cancer have not been described.

Many breast cancer patients take antioxidant supplements because they believe antioxidants will protect them from the side effects of breast cancer treatment, help prevent breast cancer recurrence, and improve their overall health 7. However, the actual consequences of using antioxidant supplements during cancer treatment are poorly understood and controversial 10⁻18. In the past few decades, the idea that antioxidant supplementation could protect normal tissue from the adverse effects of cancer treatments has become widespread 19.

Radiation therapy and some chemotherapeutic agents induce apoptosis by generating reactive oxygen species, which damage tumor cell DNA and disrupt mitochondrial membranes 20⁻22. Many medical and radiation oncologists believe that antioxidant supplements interfere with this process and that use during treatment may reduce therapeutic efficacy 14. However, the effects of taking antioxidant supplements during cancer therapy on cancer recurrence or mortality and the characteristics of antioxidant users have not been well studied 18, 23.

We determined the prevalence and predictors of the antioxidant supplement use, taken as multivitamins and single vitamin supplements, during breast cancer treatment among women with breast cancer who participated in the population-based Long Island Breast Cancer Study Project (LIBCSP). To our knowledge, ours is the first detailed study of antioxidant use during treatment in a cohort study setting.

PARTICIPANTS & METHODS

Participants

The LIBCSP began as a federally mandated, population-based case-control study to investigate whether breast cancer risk was associated with environmental exposures among women in Nassau and Suffolk counties in New York State 24. A subsequent follow-up study was conducted among cases to determine whether environmental exposures are associated with mortality. The LIBCSP case-control study cases (n=1,508) were women diagnosed with a first primary *in-situ* or invasive breast cancer between August 1, 1996 and July 31, 1997. Cases were identified by rapid ascertainment methods, through daily or weekly contact with local pathology departments of hospitals known to diagnose and treat residents of Nassau and Suffolk counties with newly diagnosed breast cancer, including some hospitals in New York City. Once a case was identified, her physician was contacted to

verify the diagnosis and to obtain permission to contact the patient. Among eligible cases, the response rate for the parent case-control study was 82.1%.

For the LIBCSP Follow-Up, conducted between 2002 and 2004, interviewers attempted to conduct telephone interviews with all cases who previously agreed to be re-contacted (n=1,414, 93.8%) 24, and 1,098 (77.7%) completed a full or short-form interview in person or by proxy. The study reported here is based on the 784 (55.4%) subjects who personally completed the full follow-up interview.

Written signed informed consent was obtained from all participants prior to the beginning of the in-person baseline interview. The study protocol was approved by all institution review boards of the collaborating institutions.

Data collection

Baseline case-control questionnaire—The baseline questionnaire was administered to participants in their homes shortly (mean = 96 days) after their diagnosis of a first primary breast cancer. The questionnaire asked about known and suspected risk factors for breast cancer (http://epi.grants.cancer.gov/LIBCSP/projects/Questionnaire.html). A 101-item, modified Block food frequency questionnaire was self-administered. Baseline questionnaire variables used in the analyses presented here include age at diagnosis, race/ethnicity, education, annual household income, marital status, body mass index (BMI), family history of breast cancer, menopausal status at diagnosis, mammogram history, oral contraceptive use, hormone replacement therapy use, lifetime physical activity, smoking history, previous alcohol use, and fruit and vegetable intake.

Follow-up questionnaire among cases—The follow-up questionnaire asked about breast cancer recurrence risk factors including demographics, health behaviors, medical history, first course of treatment received, and other clinical variables. The questionnaire included detailed questions about complementary and alternative medicine (CAM) therapy use during three separate periods: before, during, and after breast cancer diagnosis and treatment. CAM modalities assessed included multivitamins, single vitamins, minerals, herbal products, other over-the-counter health products, mind-body activities (e.g., spirituality, support groups, meditation), special treatments (e.g., biofeedback, colon cleansing, hydrotherapy), alternative cancer clinics, special diets (e.g., vegan, macrobiotic, low-fat), and visits with CAM practitioners. The analyses presented here focus on antioxidant supplement use during treatment. Analyses of other CAM use will be presented in a separate paper.

Study participants who reported ever using multivitamins were asked whether they used them during specific phases of their treatment, including surgery, chemotherapy, radiation therapy, and tamoxifen therapy. In addition, participants were asked how many tablets were consumed per week since diagnosis. The questionnaire asked about specific types of multivitamins: multivitamins with minerals, multivitamins without minerals, antioxidant combination type with vitamins A, C, and E; stress-tabs type, women's formula type, multivitamins with herbs, and other multivitamins. For the purpose of analysis, we assumed that each multivitamin pill contained the doses of specific micronutrients found in the commonly used Centrum® multivitamin circa 2002 (60 mg vitamin C, 30 IU vitamin E, 20 mcg selenium, 5,000 IU beta-carotene) 25. To estimate daily doses consumed during treatment of vitamin C, vitamin E, selenium and beta-carotene from multivitamins, we multiplied the Centrum® dose of each individual micronutrient by the number of multivitamin tablets a participant reported taking per week and dividing by seven.

Data were collected in a similar fashion on the use of individual antioxidant supplements during breast cancer treatment, including vitamin C, vitamin E, selenium, and beta-carotene. For each individual supplement, data were collected on dose per tablet and number of tablets taken per week since diagnosis and were used to estimate daily doses consumed during treatment.

Fewer than 4% of participants were missing data on individual antioxidant supplement use (beta-carotene, 1.3%; vitamin C, 2.5%; vitamin E; 3.5%, selenium, 2.4%). Participants who reported taking one of these supplements but provided no information on dose were assumed to have taken the lowest dose. We conducted sensitivity analyses to determine if assuming the median or the highest dose would make any appreciable differences in our results; it did not.

To estimate individual intake of each antioxidant during treatment (vitamin C, vitamin E, selenium and beta-carotene), we added the daily dose values for the multivitamins and the individual supplements. Then, intake of each supplement was categorized as none, low or high. High doses were defined as >60 mg vitamin C, >30 IU vitamin E, >20 mcg selenium, and >5,000 IU beta-carotene; these cutpoints were based on the doses in a typical Centrum® multivitamin circa 2002. Between 1997 and 2004, the Food and Nutrition Board of the Institute of Medicine revised its nutrient intake recommendations, now termed Dietary Reference Intakes (DRIs) 26, 27. Current DRIs are: 90 mg vitamin C, 22 IU natural vitamin E (33 IU synthetic vitamin E), and 55 mcg selenium 28. There is no DRI for beta-carotene.

We created a composite antioxidant index to summarize total intake of supplemental beta-carotene, vitamin C, vitamin E, and selenium during treatment. We computed a categorical variable with a range of 0–8 points based on scoring intake of each antioxidant as never = 0, low = 1, or high = 2. The antioxidant index itself was divided into three categories: none (score of 0), low (score of 1–4), and high (score of 5–8).

Medical records—Signed medical record release forms were obtained from case women at the baseline and follow-up interviews. Medical records were obtained from in-patient and out-patient facilities involved in the diagnosis, treatment, and follow-up of breast cancer cases. Medical records were abstracted at baseline and follow-up to ascertain tumor characteristics and first course of treatment for the primary breast cancer diagnosis. For the 598 women for whom we had complete medical record data on the first course of treatment, the agreement between self-reported breast cancer treatment and treatment recorded on the medical record was high for chemotherapy (Kappa=0.96), radiation therapy (Kappa=0.97), and hormonal therapy (Kappa=0.92) 29. Therefore, the analyses presented here use treatment information collected via self-report during the follow-up interview.

Statistical Analyses

Chi-squared tests and t-tests were used to evaluate the statistical significance of the associations of the demographic, health behavior, clinical, and CAM use variables with antioxidant supplement use during treatment.

Multivariable logistic and polytomous regression analyses were performed to identify independent predictors of antioxidant use, categorized as either none/any or none/low dose/high dose. Model building procedures were performed in the following three basic steps. Step 1 identified candidate predictors as those that were statistically significant ($P<0.10$) in unadjusted analyses 30 as well as any *a priori* confounders. Step 2 involved fitting a full model including all variables identified in Step 1,where variables were retained in the model if the corresponding p-value was less than 0.05. Finally, in Step 3, variables rejected in the first step were added back to the model, one at a time, for reassessment and were kept in the

final model if the corresponding p-value was less than 0.05. Tests of significance were based on the likelihood ratio test statistic. Analyses were performed using Stata 9.2 (College Station, TX).

RESULTS

Respondents

A total of 784 subjects personally completed the full telephone interview. They were younger, more educated, more likely to be white, and had higher household income than women who did not respond to the follow-up questionnaire (Table 1). Of the 784, 764 provided data on antioxidant supplement use (Table 2). Their mean age at the time of diagnosis with a first primary breast cancer was 56.3 years (±11.4), and 94.0% were non-Hispanic whites. Over 60% of the women had at least some college education. A total of 555 respondents (72.6% of 764) used multivitamin or single antioxidant supplements before diagnosis, and the number of users increased to 650 (85.1% of 764) after diagnosis. All 764 women had surgical treatment for their breast cancer, and 663 of them (86.8%) also received adjuvant treatment: 310 (40.6%) chemotherapy, 464 (60.7%) radiation therapy, and 462 (60.5%) tamoxifen. Of the 663 women who received adjuvant treatment, 560 (84.5%) reported using antioxidants after their breast cancer diagnosis, and 401 (60.5%) specifically reported using antioxidants during their treatment. Women who had adjuvant treatment did not differ from those who did not with respect to antioxidant use after diagnosis (data not shown).

Factors associated with antioxidant use during specific treatments

Of the 310 women who had chemotherapy, 120 (38.7%) used antioxidants during chemotherapy. Antioxidant use during chemotherapy was positively associated with ever having used herbal products and high fruit and vegetable intake prior to diagnosis (Table 3). Of the 464 women who had radiation therapy, 196 (42.2%) used antioxidants during radiation therapy. Antioxidant use during radiation therapy was positively associated with ever having used herbal products and having *in-situ* (as opposed to invasive) disease (Table 3). Of the 462 women who had tamoxifen treatment for their breast cancer, 286 (61.9%) used antioxidants during that treatment. Antioxidant use during tamoxifen therapy was positively associated with ever having used herbal products, lower BMI (<25 kg/m^2), moderate lifetime alcohol intake, and family history of breast cancer.

Antioxidant supplement dose used during treatment

Of the 401 women who used antioxidants during therapy, 342 (51.6%) used multivitamins, 199 (30.0%) used individual vitamin C, 215 (32.4%) used individual vitamin E, 54 (8.1%) used individual selenium, and 14 (2.1%) used individual beta-carotene (data not shown). Of the 401, 278 (69.3%) used high doses of antioxidant supplements. Of the 376 women using any form of vitamin C (from multivitamins or individual supplements), 211 (56.1%) used >60 mg per day (Table 4). Of the 392 women using any form of vitamin E, 224 (57.1%) used >30 IU per day. Of the 352 using any form of selenium, 88 (25.0%) used >20 mcg per day. Of the 345 women using any form of beta-carotene, 54 (15.7%) used >5,000 IU per day.

Antioxidant index—Of the 663 women who received any adjuvant therapy treatment, 232 (35.0%) scored high on the antioxidant index, which is a proxy for simultaneous high-dose use of multiple antioxidant supplements. In the polytomous model for predicting level of antioxidant use during treatment, the strongest predictor of using low dose antioxidants during treatment was tamoxifen use (Table 5). The strongest predictors of using high

antioxidant use during treatment were high fruit and vegetable intake prior to diagnosis, tamoxifen use, ever using herbal products, and ever using mind-body activities.

DISCUSSION

Among women with breast cancer who participated in the LIBCSP Follow-Up Study, 38.7% reported antioxidant supplement use during chemotherapy, 42.2% during radiation therapy, and 61.9% during tamoxifen therapy. Over half of the study participants who used antioxidants during treatment consumed doses that exceeded the DRI.

The majority of participants in our study were well-educated, non-Hispanic white, postmenopausal women with high household incomes who engaged in other health-oriented behaviors prior to diagnosis (e.g., regular physical activity, high fruit and vegetable intake, not smoking). Our results are generalizable to similar populations. Almost all participants reported prior use of one or more forms of CAM. Most women who reported antioxidant supplement use during treatment, especially those women who used high doses, also engaged in other health-oriented behaviors. Women who used high dose antioxidant supplements during treatment were much more likely to have ever used herbal products and to receive tamoxifen therapy than women who did not use antioxidant supplements.

Antioxidant supplement use appears to have been more prevalent among the Long Island breast cancer patients in our sample than among respondents to the 2000 National Health Interview Survey. In that sample 51% of women, including 62% of non-Hispanic white women, reported using vitamins or minerals anytime in the past year 31. However, in a literature review of women with a history of breast cancer, 67% to 87% reported using vitamins and minerals 9; those figures are similar to our observations.

We found a strong association between antioxidant supplement use and tamoxifen use. This association may reflect tamoxifen users' strategies to manage vasomotor symptoms associated with this therapy (e.g., taking vitamin E supplements to help with hot flashes 32). We did not ask women about their motives for dietary supplement use during treatment, but previous studies have shown that women may take supplements to counteract toxicities due to breast cancer treatment 7.

To our knowledge, this study is the first to report on antioxidant use during specific phases of breast cancer treatment. A recent review found eight papers reporting on vitamin/mineral supplement use among breast cancer survivors 9, but only one focused on the 12 months post-resection 33. A report from the Nurses Health Study showed that 20% of breast cancer survivors used high-dose vitamins during the two years prior to the assessment (mean 3.2 years post-diagnosis) 6. Among Canadian breast cancer patients (mean 2.4 years post-diagnosis), 51.0% reported ever using vitamins and minerals other than those in a multivitamin; to treat symptoms associated with breast cancer, 13.2% used vitamin E, 12.3% used vitamin C, and 6.0% used beta-carotene 8. Neither study reported on use during specific breast cancer treatments.

Another strength of the study is our cumulative antioxidant index and categorization of study participants as high-dose, low-dose, or non-users of multiple forms of antioxidants. We developed this approach to exposure measurement because antioxidants are rarely taken alone and may have cumulative physiological effects. Although our categorization of antioxidant use as low-dose or high-dose was based on detailed questionnaire data, it is at best an approximation of actual intake. We were conservative in calculating the specific doses of antioxidants consumed in multivitamins; hence we may have underestimated some actual doses.

The main limitation of the study is its relatively low response rate, especially compared to the high response rate of the original LIBCSP case-control study. However, we have complete first-hand follow-up questionnaire data on 764 of the 1,414 (55.4%) women who agreed to be re-contacted for the follow-up study, including the CAM questionnaire. Our response bias analyses (data not shown) showed that women who completed the full questionnaire were of higher socioeconomic status than those who did not. Because such women are also more likely than others to use CAM 34, our study participants may have been heavier users of antioxidants than breast cancer patients in the general population.

The follow-up survey was conducted at least five years after participants were diagnosed with a first primary breast cancer. The passage of time may have led to poor recall of supplement use before diagnosis and during treatment. Despite possible misclassification, our analyses identified strong predictors of supplement use that are consistent with those reported by other investigators 3, 35, 36.

Data on the actual effects of antioxidant supplements during breast cancer treatment are limited 37. Some studies of antioxidant supplement use during treatment of other cancer sites have suggested harm 18. In a randomized clinical trial of patients undergoing radiation therapy for head and neck cancers, α-tocopherol supplementation (400 IU/day for 3 years, beginning at the initiation of radiation therapy) was associated with a decrease in both adverse side effects during treatment 38 and overall survival at 8 years 39. However, patients with head and neck cancer may differ from breast cancer patients in behaviors, such as tobacco use, that may be relevant to the effects of antioxidants. The effects of antioxidant supplementation during treatment may also depend on the doses and types of supplements, intake of fruits and vegetables, tumor site and stage, type of treatment, and genetic polymorphisms in endogenous antioxidant enzymes.

Areas in which further research is needed include the physiological interactions between antioxidants and radiation therapy, chemotherapy, and hormonal therapy; whether there is a dose threshold above which an antioxidant exerts benefit or harm; and the long-term effect of antioxidants on breast cancer recurrence and survival. Prospective observational studies and clinical trials need to elucidate whether antioxidants affect treatment toxicities, treatment efficacy, and recurrence and survival. Our data suggest that many women diagnosed with breast cancer who use antioxidant supplements are also engaging in other behaviors that may affect their risk of recurrence, and these behaviors should be accounted for in studies of antioxidant supplements during treatment. Results of these studies will shed light on whether or not patients can use antioxidant supplements to enhance the effects of conventional treatment or alleviate its side effects without adversely affecting their prospects for survival.

In summary, we observed that a majority of breast cancer patients in Long Island, many of whom were of high socioeconomic status, used antioxidants during treatment. We believe that oncologists should discuss supplement use and dosing with their patients. More specifically, oncologists can inform patients that antioxidant supplements may dampen the effects of chemotherapy and radiation therapy but that clear evidence of benefit or harm is not yet available 9, 18, 37.

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Table 1

Demographic and breast cancer-related characteristics at diagnosis of subject responders and non-responders

		Subject responders (n=764)		Non-responders (n=724)		P-value*
		n	%	n	%	
Demographic characteristics						
Age at diagnosis	<45 years	136	17.8%	80	11.0%	**<0.001**
	45 – 54 years	231	30.2%	162	22.4%	
	55 – 64 years	204	26.7%	160	22.1%	
	65+ years	193	25.3%	322	44.5%	
Race/ethnicity	Non-Hispanic white	718	94.0%	626	86.5%	**<0.001**
	Hispanic white	20	2.6%	27	3.7%	
	Black/African-American	15	2.0%	54	7.5%	
	Other	11	1.4%	14	1.9%	
Education	High school or less	301	39.4%	409	56.5%	**<0.001**
	Some college	195	25.5%	160	22.1%	
	College graduate	111	14.5%	78	10.8%	
	Post college	157	20.5%	71	9.8%	
Annual household income	<$25,000	76	9.9%	182	25.1%	**<0.001**
	$25,000 – $49,999	186	24.3%	177	24.4%	
	$50,000 – $89,999	230	30.1%	150	20.7%	
	$90,000+	182	23.8%	95	13.1%	
Breast cancer-related characteristics						
Mammogram	Never	21	2.7%	56	7.7%	**<0.001**
	≥ 5 yrs ago	11	1.4%	28	3.9%	
	Within past 5 yrs	721	94.4%	623	86.0%	
Stage at diagnosis	In situ	137	17.9%	95	13.1%	**0.01**
	Invasive	627	82.1%	629	86.9%	

*P-values are based on chi-squared tests and do not include subjects with missing data.

Table 2

Demographic, clinical, and lifestyle characteristics of study participants, by antioxidant supplement use during adjuvant treatment (n=764)

	No adjuvant treatment (n=101)		Antioxidant supplement use during chemotherapy, radiation therapy, or hormonal therapy (n=663)						P-value
			No use (n=262)		Low use (n=169)		High use (n=232)		
	n	%	n	%	n	%	n	%	
Demographic Characteristics									
Age at diagnosis									
<45 years	25	24.8%	49	18.7%	22	13.0%	40	17.2%	0.026
45 – 54 years	32	31.7%	75	28.6%	43	25.4%	81	34.9%	
55 – 64 years	26	25.7%	60	22.9%	56	33.1%	62	26.7%	
65+ years	18	17.8%	78	29.8%	48	28.4%	49	21.1%	
Race/ethnicity									
Non-Hispanic white	98	97.0%	246	93.9%	161	95.3%	213	91.8%	0.233
Hispanic white	2	2.0%	8	3.1%	3	1.8%	7	3.0%	
Black/African-American	1	1.0%	6	2.3%	4	2.4%	4	1.7%	
Other	0	0.0%	2	0.8%	1	0.6%	8	3.4%	
Education									
≤ High school graduate	27	26.7%	117	44.7%	81	47.9%	76	32.8%	0.001
Some college	25	24.8%	66	25.2%	43	25.4%	61	26.3%	
College graduate	18	17.8%	40	15.3%	19	11.2%	34	14.7%	
Post college	31	30.7%	39	14.9%	26	15.4%	61	26.3%	
Annual household income at diagnosis									
< $25,000	10	9.9%	33	12.6%	16	9.5%	20	8.6%	0.003
$25,000 – $49,999	15	14.9%	86	32.8%	64	37.9%	69	29.7%	
$50,000 – $89,999	45	44.6%	79	30.2%	61	36.1%	81	34.9%	
$90,000+	31	30.7%	64	24.4%	28	16.6%	62	26.7%	
Clinical Characteristics									
Stage									
In situ	72	71.3%	24	9.2%	18	10.7%	23	9.9%	<0.001

	No adjuvant treatment (n=101)		Antioxidant supplement use during chemotherapy, radiation therapy, or hormonal therapy (n=663)						P-value
			No use (n=262)		Low use (n=169)		High use (n=232)		
	n	%	n	%	n	%	n	%	
Invasive	29	28.7%	238	90.8%	151	89.3%	209	90.1%	
Hormone Receptor Status									
ER−/PR−	6	5.9%	48	18.3%	24	14.2%	21	9.1%	0.156
ER−/PR+	1	1.0%	11	4.2%	5	3.0%	10	4.3%	
ER+/PR−	5	5.0%	16	6.1%	17	10.1%	19	8.2%	
ER+/PR+	14	13.9%	106	40.5%	65	38.5%	107	46.1%	
Treatments Received									
Chemotherapy	n/a		119	45.4%	81	47.9%	110	47.4%	<0.001
Radiation therapy	n/a		181	69.1%	118	69.8%	165	71.1%	<0.001
Hormonal therapy	n/a		152	58.0%	125	74.0%	185	79.7%	<0.001
BMI at diagnosis									
<25 kg/m^2	64	63.4%	109	41.6%	75	44.4%	127	54.7%	0.001
25 – <30 kg/m^2	26	25.7%	91	34.7%	53	31.4%	71	30.6%	
30+ kg/m^2	11	10.9%	62	23.7%	41	24.3%	34	14.7%	
Family history of breast cancer									
No	76	75.2%	208	79.4%	121	71.6%	190	81.9%	0.082
Yes	20	19.8%	45	17.2%	45	26.6%	41	17.7%	
Menopausal status at diagnosis									
Premenopausal	45	44.6%	86	32.8%	50	29.6%	98	42.2%	0.011
Menopausal	55	54.5%	166	63.4%	117	69.2%	127	54.7%	
Health Behavior Characteristics Prior to Diagnosis									
Mammogram									
Never had mammogram	0	0.0%	8	3.1%	8	4.7%	5	2.2%	0.325
Had mammogram, > 5 yrs	2	2.0%	2	0.8%	3	1.8%	4	1.7%	
Had mammogram, ≤ 5 yrs	99	98.0%	246	93.9%	157	92.9%	219	94.4%	
Oral contraceptive use									
Never	48	47.5%	137	52.3%	86	50.9%	105	45.3%	0.390

	No adjuvant treatment (n=101)		Antioxidant supplement use during chemotherapy, radiation therapy, or hormonal therapy (n=663)						P-value
			No use (n=262)		Low use (n=169)		High use (n=232)		
	n	%	n	%	n	%	n	%	
Ever	53	52.5%	123	46.9%	83	49.1%	127	54.7%	
Hormone replacement therapy use									
Never	59	58.4%	189	72.1%	113	66.9%	150	64.7%	0.070
Ever	42	41.6%	73	27.9%	56	33.1%	82	35.3%	
Physical activity (from menarche to diagnosis)									
0 hours /wk	25	24.8%	74	28.2%	48	28.4%	38	16.4%	0.091
0 – 0.69 hours/wk	21	20.8%	59	22.5%	39	23.1%	53	22.8%	
0.70 – 2.6 hours/wk	23	22.8%	55	21.0%	42	24.9%	64	27.6%	
2.7+ hours/wk	24	23.8%	64	24.4%	30	17.8%	63	27.2%	
Smoking history									
Never	45	44.6%	111	42.4%	73	43.2%	108	46.6%	0.196
Current (within 12 months)	15	14.9%	62	23.7%	32	18.9%	33	14.2%	
Past/former	41	40.6%	89	34.0%	64	37.9%	91	39.2%	
Alcohol use									
Never	33	32.7%	90	34.4%	58	34.3%	77	33.2%	0.985
Ever	68	67.3%	172	65.6%	111	65.7%	155	66.8%	
Fruit and vegetable intake									
0–34 servings per week	65	64.4%	181	69.1%	103	60.9%	126	54.3%	0.011
35+ servings per week	34	33.7%	80	30.5%	64	37.9%	103	44.4%	
CAM Use (ever)									
Any CAM	101	100.0%	252	96.2%	169	100.0%	232	100.0%	Not estimable
Multivitamins	91	90.1%	190	72.5%	152	89.9%	229	98.7%	<0.001
Single vitamins	88	87.1%	182	69.5%	137	81.1%	229	98.7%	<0.001
Herbal supplements	48	47.5%	82	31.3%	56	33.1%	144	62.1%	<0.001
Other over-the-counter healthcare products	40	39.6%	71	27.1%	48	28.4%	90	38.8%	0.010
Mind-body activities	54	53.5%	112	42.7%	76	45.0%	147	63.4%	<0.001

	No adjuvant treatment (n=101)		Antioxidant supplement use during chemotherapy, radiation therapy, or hormonal therapy (n=663)						P-value
			No use (n=262)		Low use (n=169)		High use (n=232)		
	n	%	n	%	n	%	n	%	
Special treatments	6	5.9%	6	2.3%	1	0.6%	11	4.7%	0.032
Alternative cancer clinics	0	0.0%	0	0.0%	0	0.0%	0	0.0%	Not estimable
Special diets	39	38.6%	82	31.3%	42	24.9%	97	41.8%	0.002
CAM practitioners	45	44.6%	76	29.0%	47	27.8%	93	40.1%	0.002

Table 3

Adjusted analyses of antioxidant supplement use during chemotherapy, radiation therapy, and tamoxifen therapy

	Antioxidant use during chemotherapy n=309			Antioxidant use during radiation therapy n=464			Antioxidant use during tamoxifen therapy n=452		
	OR	**(95% CI)**	**P-value**	**OR**	**(95% CI)**	**P-value**	**OR**	**(95% CI)**	**P-value**
Age at diagnosis (per year)	1.02	(0.99, 1.04)	*0.22*	1.01	(0.99, 1.02)	*0.54*	0.99	(0.97, 1.01)	*0.49*
Race (vs. non-Hispanic white)			*0.53*			*0.67*			*0.23*
Hispanic white	0.46	(0.08, 2.58)		0.57	(0.17, 1.96)		0.75	(0.20, 2.80)	
Black/African-American	0.86	(0.19, 3.91)		0.89	(0.24, 3.30)		3.69	(0.41, 32.88)	
Other	2.94	(0.45, 19.42)		1.76	(0.45, 6.92)		4.35	(0.50, 37.45)	
Education (vs. high school graduate or less)			*0.66*			*0.43*			*0.10*
Some college	0.81	(0.43, 1.53)		1.46	(0.91, 2.34)		1.29	(0.77, 2.17)	
College grad	0.63	(0.29, 1.39)		1.16	(0.62, 2.16)		0.56	(0.29, 1.09)	
Post graduate	0.73	(0.37, 1.43)		1.34	(0.78, 2.30)		1.24	(0.68, 2.24)	
BMI (vs. <25 kg/m^2)									0.03
25 – <30 kg/m^2							0.54	(0.34, 0.87)	
30+ kg/m^2							0.60	(0.34, 1.06)	
Lifetime Alcohol Intake (vs. non-drinkers)									*<0.01*
< 15g/day							0.81	(0.52, 1.27)	
15–30 g/day							2.84	(1.23, 6.56)	
30+ g/day							1.51	(0.52, 4.40)	
Family history of breast cancer (yes vs. no)							1.82	(1.07, 3.09)	0.02
Fruit and vegetable intake (vs. <35 servings/wk)			*0.05*						
35+ servings/wk	1.64	(1.00, 2.69)							
Stage (invasive vs. in situ)				0.51	(0.28, 0.94)	*0.03*			
Herbal products (ever vs. never)	2.71	(1.64, 4.49)	*<0.001*	1.74	(1.17, 2.57)	*0.006*	2.31	(1.49, 3.58)	*<0.001*

ORs displayed are for those variables included in each model.

Table 4

Distribution of no use, low-dose use, and high-dose use for total intake of antioxidant supplements during treatment (n=663)

	Antioxidant supplement use during treatment (n=663)					
	No Use		Low Use		High Use	
	n	%	n	%	n	%
Vitamin C *	287	43.3%	165	24.9%	211	31.8%
Vitamin E †	271	40.9%	168	25.3%	224	33.8%
Selenium ‡	311	46.9%	264	39.8%	88	13.3%
Beta-Carotene §	318	48.0%	291	43.9%	54	8.1%
Antioxidant index	262	39.5%	169	25.5%	232	35.0%

*Vitamin C high-dose use ≥60 mg

†Vitamin E high-dose ≥30 IU

‡Selenium high-dose ≥20 mcg

§Beta-Carotene high-dose ≥5,000 IU

Table 5

Adjusted analyses using polytomous logistic regression for antioxidant use during any treatment (n=642)

		Low-dose antioxidant supplement use n=164*		High-dose antioxidant supplement use n=228*		P-value†
		RR	(95% CI)	RR	(95% CI)	
Age at diagnosis (per year)		1.00	(0.98, 1.02)	1.00	(0.98, 1.02)	*0.85*
Race	Non-Hispanic white	Ref.		Ref.		*0.11*
	Hispanic white	0.71	(0.17, 2.90)	1.04	(0.33, 3.20)	
	Black	1.85	(0.46, 7.48)	1.05	(0.25, 4.49)	
	Other	1.88	(0.11, 31.24)	12.40	(1.36, 112.82)	
Education	High school or less	Ref.		Ref.		*0.62*
	Some college	0.96	(0.58, 1.59)	1.06	(0.63, 1.77)	
	College graduate	0.56	(0.28, 1.10)	0.79	(0.42, 1.46)	
	Post graduate	0.86	(0.47, 1.59)	1.23	(0.70, 2.18)	
Fruit and vegetable	<35 servings/wk	Ref.		Ref.		*0.03*
	35+ servings/wk	1.42	(0.92, 2.19)	1.71	(1.13, 2.59)	
Fam history (br ca)	No	Ref.		Ref.		
	Yes	1.66	(1.02, 2.70)	0.86	(0.51, 1.44)	*0.03*
Tamoxifen	Never	Ref.		Ref.		
	Ever	2.07	(1.32, 3.23)	3.66	(2.32, 5.78)	*<0.0001*
Herbal products	Never	Ref.		Ref.		
	Ever	1.19	(0.75, 1.90)	3.49	(2.26, 5.38)	*<0.0001*
Other OTC products‡	Never	Ref.		Ref.		
	Ever	1.27	(0.80, 2.01)	1.50	(0.97, 2.32)	*0.18*
Mind-body activities	Never	Ref.		Ref.		
	Ever	1.17	(0.76, 1.80)	1.72	(1.13, 2.64)	*0.04*
Special diets	Never	Ref.		Ref.		
	Ever	0.66	(0.41, 1.05)	1.08	(0.71, 1.65)	*0.09*

*Compared to non-users (n=250) of antioxidant supplements during treatment

†P-value based on a likelihood ratio test for significance for each variable in the final adjusted polytomous regression model

‡Over-the-counter products.