Multivitamin Use and Breast Cancer Outcomes in Women with Early-Stage Breast Cancer: The Life After Cancer Epidemiology (LACE) Study

Marilyn L. Kwan, PhD[1], **Heather Greenlee, ND, PhD**[2,3], **Valerie S. Lee, MHS**[1], **Adrienne Castillo, MS, RD**[1], **Erica P. Gunderson, PhD**[1], **Laurel A. Habel, PhD**[1], **Lawrence H. Kushi, ScD**[1], **Carol Sweeney, MS, PhD**[4], **Emily K. Tam, BA**[1], and **Bette J. Caan, DrPH**[1]

[1]Division of Research, Kaiser Permanente, Oakland, CA

[2]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY

[3]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY

[4]Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, UT

Abstract

Little is known about the relation of multivitamin use to breast cancer outcomes. 2,236 women diagnosed from 1997 to 2000 with early-stage breast cancer (Stage I ≥1 cm, II, or IIIA) were enrolled about two years post-diagnosis, primarily from the Kaiser Permanente Northern California Cancer Registry (83%). Multivitamin use pre-diagnosis and post-diagnosis was assessed via mailed questionnaire. Outcomes were ascertained yearly by self-report and verified by medical record review. Delayed-entry Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), adjusting for sociodemographic, tumor, and lifestyle factors. Overall, 54% and 72% of the cohort reported using multivitamins pre- and post-diagnosis, respectively. A total of 380 recurrences, 212 breast cancer deaths, and 396 total deaths were confirmed. Compared to never use, multivitamin use after diagnosis was not associated with any outcome (recurrence HR = 0.92; 95% CI: 0.71, 1.20; total mortality HR = 0.92; 95% CI: 0.71, 1.19). Compared to never use, persistent use of multivitamins from pre- to post-diagnosis was associated with a non-significant decreased risk of recurrence (HR = 0.76; 95% CI: 0.54, 1.06) and total mortality (HR = 0.79; 95% CI: 0.56, 1.12). The protective associations were limited to women who had been treated by radiation only (p for trend = 0.048 and 0.083 for recurrence and total mortality, respectively) and both radiation and chemotherapy (p for trend = 0.015 and 0.095 for recurrence and total mortality, respectively). In stratified analyses, women who consistently used multivitamins before and after diagnosis and ate more fruits/vegetables (p for trend = 0.008) and were more physically active (p for trend = 0.034) had better overall survival. Multivitamin use along with practice of other health-promoting behaviors may be beneficial in improving breast cancer outcomes in select groups of survivors.

Keywords

multivitamins; dietary supplements; vitamins; breast cancer; prognosis; recurrence; all-cause mortality; survival

Corresponding Author: Marilyn L. Kwan, PhD, 2000 Broadway, Oakland, CA 94612, 510-891-3521 (phone), 510-891-3761 (fax), Marilyn.L.Kwan@kp.org.

Performance Site: Division of Research, Kaiser Permanente Oakland, CA

Introduction

In the United States, over 2.5 million women are living with breast cancer [1]. Many of these women question if lifestyle changes can improve their prognosis, including whether taking vitamin supplements can reduce adverse side effects from treatment, decrease risk of recurrence, and improve survival [2].

Multivitamin and mineral supplements are the most commonly-used dietary supplements in the United States. Approximately 57% of adult women reported taking a dietary supplement in the past month, and 38% reported regular use of a multivitamin-multimineral [3, 4]. Female gender, older age, higher education, non-Hispanic White race/ethnicity, any physical activity, and normal weight were associated with greater use of multivitamin-multiminerals.

Compared to healthy populations, cancer patients appear to be more frequent users of multivitamins and vitamin/mineral supplements [2, 4]. In previous studies of women with breast cancer undergoing treatment and up to nine years post-diagnosis, any vitamin or mineral use ranged from 67–87%, and multivitamin use specifically 57–62% [2]. To date, only one prospective cohort study of over 4,800 Chinese breast cancer survivors has examined the association between multivitamin use and breast cancer prognosis [5]. This study reported decreased risks of recurrence and total mortality with any multivitamin use within the first six months post-diagnosis.

In the Life After Cancer Epidemiology (LACE) Study, a prospective study of 2,236 early-stage breast cancer survivors, we describe pre-diagnosis and post-diagnosis multivitamin use in the cohort, and investigate the association between multivitamin use and breast cancer recurrence and survival. We also examine associations by important healthy lifestyle factors (smoking, non-sedentary physical activity, fruit and vegetable intake) and adjuvant therapy received (radiation therapy, chemotherapy, hormonal therapy).

Methods

Study Population

The LACE cohort consists of 2,264 women diagnosed with invasive breast cancer between 1997 and 2000 and recruited primarily from the Kaiser Permanente Northern California (KPNC) Cancer Registry (83%) and the Utah Cancer Registry (12%) from 2000–2002. Further details are provided elsewhere [6].

Eligibility criteria included age 18–79 years old at diagnosis; a diagnosis of early-stage, primary breast cancer (Stage I ≥1 cm, Stage II, or Stage IIIA); enrollment within 39 months post-diagnosis; completion of breast cancer treatment (except for adjuvant hormonal therapy); no recurrence; and no history of other cancers in the five years before enrollment.

Between January 2000 and April 2002, 5,656 women who initially met the eligibility criteria were contacted. Of these, 2,614 (46%) agreed to participate, and an additional 350 were excluded after medical record review did not confirm eligibility. The remaining 2,264 women constitute the LACE cohort. The study was approved by the institutional review boards of KPNC and the University of Utah.

Data Collection

Baseline data were collected on average 1.91 years (range: 0.93–3.24) post-diagnosis through mailed questionnaires. Information was gathered on demographics, medical history, medication use, reproductive history, family history of cancer, weight history, dietary supplement use, diet, physical activity, quality of life, depressive symptoms, and functional

limitations. Diet was assessed using the Fred Hutchinson Cancer Research Center Food Frequency Questionnaire [7]. Physical activity was ascertained (MET-hours/week) with a questionnaire adapted from the Arizona Activity Frequency Questionnaire [8].

Details on pre- and post-diagnosis use of dietary supplements were collected at baseline, including multivitamins with minerals (MVM), multivitamins without minerals (MVNM), vitamin C, vitamin E, multiple carotenoids, beta carotene, lycopene, selenium, and zinc. Examples of MVM given were One-A-Day®, Theragran, Centrum®, while for MVNM were B-complex or "stress" Formula, Antioxidant Formula. Women reported ever or never use ≥3 times/week for a year or more during the five years before their breast cancer diagnosis, and ever or never and frequency (less than 1 day/week, 1–2 days/week, 3–5 days/week, 6–7 days/week) since their breast cancer diagnosis. Use during cancer treatment (chemotherapy, radiation therapy, hormonal therapy) was not explicitly asked.

Clinical information was obtained through KPNC electronic data sources (KP women) and/ or medical chart review (all women), including tumor size, positive lymph nodes, hormone receptor status, surgery, and treatment. Tumor stage was calculated according to the *American Joint Committee on Cancer (AJCC)* (5th edition).

Recurrences were ascertained by a semi-annual or annual (after April 2005) mailed health status questionnaire asking participants to report any events occurring in the preceding six or 12 months, respectively. Non-respondents were called to complete the questionnaire by telephone. Medical records were reviewed to verify reported outcomes. Participant deaths were determined through KPNC electronic data sources (KP women), a family member responding to a mailed questionnaire (all women), or a phone call (all women). Copies of death certificates were obtained to verify primary and underlying causes of death based on ICD-9 codes.

Three outcomes were considered: new breast cancer event (hereafter referred to as recurrence), death from breast cancer, and all-cause/total mortality. Recurrence includes a local/regional cancer recurrence, distant recurrence/metastasis, and contralateral primary breast cancer. Death from breast cancer includes death attributable to breast cancer as a primary or underlying cause on the death certificate, and all-cause mortality includes death from any cause including breast cancer. A physician collaborator was consulted in the event a cause of death was unclear.

The final analytic sample size was 2,236 after an additional 28 women were excluded due to missing dietary supplement data.

Statistical Analysis

To examine the independent effects of MVM and MVNM use, women who reported taking both MVM and MVNM pre-diagnosis or post-diagnosis were excluded from the analyses on multivitamin type (n=181 pre-diagnosis, n=279 post-diagnosis). For frequency of post-diagnosis use, never users were those who reported no use of any multivitamin; occasional users were those who reported a frequency of ≥1 day/week up to 3–5 days/week; and frequent users were those who reported a frequency of 6–7 days/week. To characterize combined pre- and post-diagnosis use, never users were classified as those reporting no use of any multivitamin pre- or post-diagnosis; former users as those reporting pre-diagnosis use of ≥3 times/week for a year or more and no post-diagnosis use; new users as those reporting no pre-diagnosis use and post-diagnosis use of ≥3 times/week for a year or more; and persistent users as those reporting pre-diagnosis use of ≥3 times/week for a year or more and post-diagnosis use of ≥3 times/week. Of note, persistent use does not specifically include an evaluation of use during treatment.

Comparisons of pre- and post-diagnosis multivitamin use (never vs. ever) by cohort characteristics were evaluated using Pearson chi-square and Kruskal-Wallis tests. Survival analysis was conducted using time from cancer diagnosis as the time scale and delayed entry so that for each subject, follow-up began at study entry (i.e., baseline questionnaire). Follow-up ended at date of first confirmed cancer recurrence or death, depending on the analysis. Individuals who had no event were censored at date of last contact. Hazard ratios (HR) and 95% confidence intervals (CI) representing the association between a defined event and multivitamin use were computed using Cox proportional hazards models [9, 10]. Linear tests for trend were estimated by modeling categorical variables of exposure on an ordinal scale.

Covariates considered for inclusion in the multivariate models are presented in Table 1. Based on *a priori* covariates from review of the literature or at least 10% change in the effect estimate of multivitamin use when each covariate was added individually to the Cox model [11], age at diagnosis, race/ethnicity, education, tumor characteristics (stage, hormone receptor status, nodal status), treatment (chemotherapy, radiation therapy), pre-diagnosis BMI, other antioxidant supplement use, smoking, non-sedentary physical activity, and fruit and vegetable consumption were retained in the final models.

Stratified analyses of multivitamin use by smoking (never vs. ever); MET-hours/week of non-sedentary physical activity (top vs. bottom quartile); servings per day of fruits and vegetables (top vs. bottom quartile); and treatment (none, chemotherapy only, radiation therapy only, and hormonal therapy) were conducted by generating stratum-specific estimates. Separate overall models were run with interaction terms (multivitamin use x stratification variable), and likelihood ratio tests were used to determine statistical significance.

Results

Table 1 gives selected characteristics of pre- and post-diagnosis multivitamin users in the cohort (pre-diagnosis n=1,121; 54%; post-diagnosis n=1,595; 72%) and never users. Compared to never users, women who took multivitamins, either pre-diagnosis or post-diagnosis, were more educated and more often white. They had lower BMI one year before diagnosis, were more physically active, were more likely to consume greater amounts of fruits and vegetables at entry into the cohort, and took individual antioxidants at baseline. Pre-diagnosis users were more likely to be older and menopausal while post-diagnosis users were more likely to be non-smokers. Women who used multivitamins persistently ≥3 times/week from pre- to post-diagnosis (n=992; 52%) had a similar profile to pre-diagnosis users (not shown). Only 51 women (2%) took multivitamins before diagnosis and discontinued after diagnosis, and they were excluded from analyses of combined pre- and post-diagnosis use.

A total of 380 breast cancer recurrences (of which 66% were distant metastases and 56% eventually died from breast cancer) and 396 deaths were ascertained through January 31, 2011. Among the 396 deaths, 212 (54%) were attributable to breast cancer (of which 83% had any documented recurrence). Mean follow-up times from cohort entry (~1.91 years post-diagnosis) until recurrence or death were 4.07 years (range: 0.27–10.28) and 5.56 years (range: 0.33–10.74), respectively. Overall, cohort members were followed a mean of 8.33 years (range: 0–10.97), and 101 (4.5%) were lost-to-follow-up.

The primary associations between multivitamin use and breast cancer outcomes are given in Table 2. While all the HRs were below 1.00, any multivitamin use after diagnosis was not associated with breast cancer recurrence (HR = 0.92; 95% CI: 0.71, 1.20), breast cancer

death (HR = 0.87; 95% CI: 0.60, 1.24), or total mortality (HR = 0.92; 95% CI: 0.71, 1.19). Furthermore, no significant associations were observed by type of multivitamin or frequency of multivitamin use. Similar to post-diagnosis use, any multivitamin use five years before diagnosis was not associated with recurrence (HR = 0.87; 95% CI: 0.67, 1.14), breast cancer death (HR = 0.75; 95% CI: 0.52, 1.09), or total mortality (HR = 0.87; 95% CI: 0.66, 1.15).

New use (only post-diagnosis ≥3 times/week) was not associated with any breast cancer outcome. Yet persistent use (both pre-diagnosis and post-diagnosis ≥3 times/week), compared to never use, was associated with a non-significant reduction in risk of recurrence (HR = 0.76; 95% CI: 0.54, 1.06), breast cancer mortality (HR = 0.70; 95% CI: 0.44, 1.11), and total mortality (HR = 0.79; 95% CI: 0.56, 1.12) (Table 2). The tests for linear trend were not significant.

Stratified analyses of multivitamin use by select lifestyle factors are given in Table 3. Overall, multivitamin use was most beneficial for risk of total mortality in the subgroups that were representative of a "healthier lifestyle," defined by top quartiles of fruit/vegetable intake and non-sedentary physical activity and never smoking. Persistent multivitamin use among women who were in the top quartile of fruit and vegetable intake (at least 5.5 servings/day) was associated with a significant reduced risk of total mortality (HR = 0.28; 95% CI: 0.11, 0.72) compared to women who were in the bottom quartile (at most 2.4 servings/day) (HR = 0.82; 95% CI: 0.43, 1.58). Similarly, persistent multivitamin use among women who were in the top quartile of non-sedentary physical activity (at least 66.9 MET-hours/week or 16 hours/week) was associated with a reduced risk of total mortality (HR = 0.39; 95% CI: 0.16, 0.95) compared to women who were in the bottom quartile (at most 30.0 MET-hours/week) (HR = 0.73; 95% CI: 0.40, 1.32). For both diet and physical activity, inverse linear trends of new and persistent use were apparent (p ≤ 0.05). Persistent multivitamin use was associated with a significant reduced risk of recurrence among never smokers but not among ever smokers (never smokers HR = 0.61; 95% CI: 0.37, 0.99; ever smokers HR = 1.00; 95% CI: 0.62, 1.61), and a linear trend of new and persistent use was observed (p = 0.042). No other differences by subgroup were found for recurrence. Results for breast cancer death were similar to those of recurrence, yet were somewhat attenuated due to the smaller number of events. No multiplicative interactions were observed of lifestyle factors and history of multivitamin use across all outcomes.

Stratified analyses of multivitamin use by adjuvant therapy are given in Table 4. Among women who had radiation therapy only, persistent multivitamin use was associated with decreased risks of recurrence (HR = 0.49; 95% CI: 0.23, 1.01), breast cancer death (HR = 0.25; 95% CI: 0.09, 0.68), and total mortality (HR = 0.54; 95% CI: 0.26, 1.10). Inverse linear trends of new and persistent use and decreasing risk were apparent across all endpoints among women who had radiation therapy only (p for trends ≥ 0.05 except for total mortality which was 0.083). Persistent multivitamin use was also associated with decreased risks of recurrence (HR = 0.52; 95% CI: 0.31, 0.86), breast cancer death (HR = 0.56; 95% CI: 0.28, 1.15), and total mortality (HR = 0.59; 95% CI: 0.32, 1.07) among women who had both radiation therapy and chemotherapy, and linear trends were apparent for recurrence (p for trend = 0.015) and total mortality (p for trend = 0.095). No such protective associations were observed among the women who had chemotherapy only and the women who had no treatment. Significant multiplicative interactions were observed for recurrence and total mortality (p for interaction = 0.03 for both outcomes). Similar to the radiation therapy only group, persistent multivitamin use among women who had hormonal therapy was associated with decreased, yet non-significant, risks of recurrence (HR = 0.72; 95% CI: 0.50, 1.05), breast cancer death (HR = 0.61; 95% CI: 0.37, 1.02), and total mortality (HR = 0.76; 95% CI: 0.52, 1.11). Both recurrence and breast cancer death had significant inverse linear trends

with history of multivitamin use. No multiplicative interactions of hormonal treatment and history of multivitamin use were observed.

Discussion

In this prospective cohort study of early-stage breast cancer survivors, we found that use of multivitamins in the two years after breast cancer diagnosis was not associated with breast cancer recurrence and survival after adjusting for sociodemographic, clinical, and lifestyle factors. Persistent use starting pre-diagnosis and into the two years post-diagnosis was possibly associated with a reduction in breast cancer-related outcomes and overall death. For those women who were in the top quartile of the cohort of adhering to a healthy lifestyle represented by diet (consuming at least 5.5 servings of fruits and vegetables per day) and physical activity (engaging in non-sedentary activity of at least 16 hours/week), persistent multivitamin use was associated with a 60–70% reduction in risk of dying from any cause. No associations were observed among women who were leading less healthy lifestyles. Furthermore, among women who only had radiation therapy and no chemotherapy as part of their adjuvant treatment, multivitamin use was associated with a consistent reduction in risk of recurrence, breast cancer death, and overall death. These results add to the evidence that multivitamin use after a breast cancer diagnosis may be safe, and suggest that consistent use of multivitamins may be beneficial to subgroups of breast cancer survivors (i.e., those who already follow a healthy lifestyle, and those who were treated by radiotherapy).

Many laboratory studies have reported beneficial effects of vitamins and minerals on mechanisms of cancer risk and progression, including angiogenesis, immunity, cell differentiation, proliferation, and apoptosis [12, 13]. Despite the fairly rich literature on the effects of vitamins and supplements on cancer prevention in humans [14–25], few studies exist on the association of vitamins and supplements with cancer outcomes [4, 26–29]. Current studies on breast cancer outcome have focused on antioxidants, yet most suffer from serious sample size and study design issues [30] with mixed results [31, 32]. The largest and most rigorous study to date is a prospective study of 4,877 breast cancer survivors in Shanghai, China that reported antioxidant use (vitamin C, vitamin E, and/or multivitamins) during the first six months post-diagnosis was associated with decreased risk of recurrence (HR = 0.78; 95% CI: 0.63, 0.95) and overall mortality (HR = 0.82; 95% CI: 0.65, 1.02) [5]. Similar to our study results, multivitamin use was associated with a non-significant decreased risk for recurrence (HR = 0.74; 95% CI: 0.53, 1.03) and overall mortality (HR = 0.82; 95% CI: 0.57, 1.17). In another LACE analysis addressing only post-diagnosis use of individual antioxidant supplements, frequent use of vitamin C (HR = 0.73; 95% CI: 0.55, 0.97) and vitamin E (HR = 0.71; 95% CI: 0.54, 0.94) was associated with reduced risks of breast cancer recurrence, and vitamin E (HR = 0.76; 95% CI: 0.58, 1.00) was associated with reduced risk of overall mortality, after adjustment for multivitamin use (H. Greenlee manuscript under review).

The evidence on use of antioxidant supplements, including multivitamins, for people with cancer is controversial. Two randomized clinical trials have demonstrated that concurrent administration of antioxidants with radiation therapy or chemotherapy reduces treatment-related side effects [30, 33]. However, one trial also demonstrated reduced survival among smokers who took antioxidants during radiation for head and neck cancer [34, 35]. Use of antioxidants during cancer treatment may possibly interact with radiation therapy and chemotherapy regimens [2, 33] by either protecting against treatment-related toxicities [36–38] or counteracting treatments acting through production of reactive oxygen species and induction of apoptosis [39, 40]. Their effects on adjuvant hormonal therapy are unknown [30].

We found that among women who received radiation therapy only, long-term multivitamin use from five years pre-diagnosis to about two years post-diagnosis was associated with improved outcomes compared to no use, while no associations were observed for women who had no radiation therapy. Contrary results were reported in the Shanghai breast cancer survivor study where an inverse association of any antioxidant use (vitamin C, vitamin E, and/or multivitamins) was only observed among patients who did not receive radiation therapy [5]. The authors hypothesized that the lack of a protective association among women who used antioxidants and received radiation therapy might be due to insufficient dosages of supplementation; indeed, in the Shanghai cohort, only 36% of women took a supplement after diagnosis compared to 71% in our LACE cohort. In addition, we are the first to report possible improved prognosis associated with persistent multivitamin use among women who had hormonal therapy. Further studies are warranted with larger sample sizes and wide-ranging exposures of vitamin supplementation to elucidate the association of multivitamin users and breast cancer outcomes by receipt of adjuvant therapy, especially radiotherapy.

Taking multivitamins might be part of an overall health-promoting lifestyle for general health maintenance or to improve nutritional status; thus, attention to healthy lifestyles, rather than the supplements, could be related to better prognosis. Furthermore, women who take multivitamins regularly after a breast cancer diagnosis are more likely to be adherent to their cancer treatment regimen, as well as clinical follow-up of their breast cancer. While we cannot completely rule out such confounding, we did account for sociodemographics, BMI, smoking, fruit and vegetable consumption, physical activity, and other antioxidant use in our multivariate models. To explore the role of multivitamins as part of a healthy lifestyle construct, we examined multivitamin use in subgroups of women categorized by indicators of a healthy compared to an unhealthy lifestyle represented by smoking, fruit and vegetable consumption, and physical activity. Interestingly, women who were strong adherers of a healthy lifestyle attained further benefit from taking multivitamins, specifically lowering their risk of dying from any cause. We also saw that among the non-healthy lifestyle followers, multivitamin use did not appear to influence prognosis, thus suggesting that other lifestyle factors play a larger role in influencing breast cancer outcomes. Of note, previous LACE analyses found that consuming a more healthful diet of fruits and vegetables, whole grains, and poultry [41], and engaging in at least moderate physical activity, were each associated with decreased overall mortality but not breast cancer-related outcomes [41, 42].

The LACE Study is one of the larger prospective studies of breast cancer survivors to examine multivitamin use overall, and by lifestyle factors and adjuvant therapy, in relation to breast cancer outcomes, yet several limitations should be considered. Our analyses relied on self-report of multivitamin use relative to breast cancer diagnosis, thus over-reporting is a possibility. However, multivitamin use in our cohort (54% pre-diagnosis, 72% post-diagnosis) was comparable to studies of US healthy study populations [3, 43] and breast cancer survivors [2, 30, 44, 45]. Furthermore, post-diagnosis use appears fairly consistent through extended follow-up of the cohort; 82% of women who reported use at baseline (about two years post-diagnosis) also cited use at six years of follow-up (about eight years post-diagnosis). We did not specifically ask women about multivitamin use during treatment, and therefore, we cannot draw any conclusions about the safety or benefit of multivitamin use during radiation, chemotherapy, and hormonal therapy. Finally, one could hypothesize that the beneficial effects of multivitamins on breast cancer prognosis and survival might be driven by the antioxidant ingredients contained in the multivitamin. In post-hoc analyses examining multivitamin use by concurrent use of any individual antioxidant, we found that being a concurrent user was possibly associated with improved outcomes, yet none of the associations were statistically significant (Table 5).

In conclusion, taking multivitamins in the two years after a breast cancer diagnosis was not associated with any adverse outcomes, and was associated with improved outcomes among women who were already following a healthy lifestyle as a cancer survivor [46, 47]. Multivitamin use among those who received radiation therapy was also not associated with any detrimental outcomes, and may be associated with improved prognosis. Considering the few studies to date addressing outcomes associated with multivitamin use after a breast cancer diagnosis, our results are intriguing and warrant confirmation in other large prospective and intervention studies of breast cancer survivors.

Acknowledgments

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Table 1

Characteristics of LACE Study participants (n=2,236), by pre-diagnosis and post-diagnosis multivitamin use

	Five Years Pre-Diagnosis			Two Years Post-Diagnosis		
	Never Use (n=969)	Ever Use [a] (n=1,121)	p value [b]	Never Use (n=637)	Ever Use [a] (n=1,595)	p value [b]
Age at Diagnosis, mean (sd) years [c]	56.64 (11.20)	59.38 (10.59)	<0.0001	58.41 (11.66)	58.20 (10.70)	0.59
BMI 1 Year Pre-diagnosis, mean (sd) kg/m² [c]	27.11 (5.77)	26.64 (5.82)	0.017	27.33 (6.06)	26.71 (5.78)	0.026
Non-sedentary Physical Activity at Baseline, mean (sd) MET-hours/wk [c]	50.47 (32.52)	52.62 (30.86)	0.029	49.63 (32.70)	52.65 (31.65)	0.0068
Fruit and Vegetable Consumption, mean (sd) servings/day [c]	4.02 (2.39)	4.29 (2.32)	0.0043	3.82 (2.23)	4.29 (2.38)	<0.0001
	n	%		n	%	
Race			0.0021			<0.0001
White	737	76.14		475	74.57	
	932	83.21		1,307	82.05	
Black	56	5.79		34	5.34	
	50	4.46		77	4.83	
Hispanic	75	7.75		51	8.01	
	59	5.27		90	5.65	
Asian/Pacific Islander	66	6.82		57	8.95	
	49	4.38		70	4.39	
Other	34	3.51		20	3.14	
	30	2.68		49	3.08	
Education			0.023			<0.0001
Less than high school	66	6.82		48	7.55	
	52	4.65		76	4.77	
High school graduate/some college	581	60.02		403	63.36	
	646	57.78		912	57.29	
College graduate	321	33.16		185	29.09	
	420	37.57		604	37.94	
Menopausal Status at Diagnosis			<0.0001			0.14
Premenopausal	279	33.29		161	28.65	
	205	21.16		348	25.42	
Postmenopausal	559	66.71		401	71.35	
	764	78.84		1,021	74.58	
Smoking Status at Baseline			0.16			0.031
Never	520	53.72		319	50.08	
	586	52.32		861	54.05	
Former	366	37.81		255	40.03	
	459	40.98		623	39.11	
Current	82	8.47		63	9.89	
	75	6.70		109	6.84	
Treatment			0.039			0.31
None	156	16.10		121	19.00	
	208	18.57		269	16.88	
Chemotherapy only	202	20.85		123	19.31	
	207	18.48		309	19.39	
Radiation therapy only	217	22.39		168	26.37	
	293	26.16		391	24.53	

	Five Years Pre-Diagnosis			Two Years Post-Diagnosis		
	Never Use (n=969)	Ever Use[a] (n=1,121)	p value[b]	Never Use (n=637)	Ever Use[a] (n=1,595)	p value[b]
Both	394 / 40.66	412 / 36.79		225 / 35.32	625 / 39.21	
Adjuvant Hormonal Therapy			0.48			0.92
No	191 / 19.83	208 / 18.62		122 / 19.27	303 / 19.08	
Yes (77% tamoxifen)	772 / 80.17	909 / 81.38		511 / 80.73	1,285 / 80.92	
Stage			0.90			0.075
I ≥1 cm	443 / 45.72	523 / 46.65		318 / 50.00	722 / 45.27	
IIA	333 / 34.37	378 / 33.72		198 / 31.13	554 / 34.73	
IIB	165 / 17.03	183 / 16.32		107 / 16.82	264 / 16.55	
IIIA	28 / 2.89	37 / 3.30		13 / 2.04	55 / 3.45	
Hormone Receptor Status			0.71			0.45
ER−, PR−	147 / 15.31	178 / 16.06		88 / 14.01	255 / 16.15	
ER−, PR+	21 / 2.19	17 / 1.53		14 / 2.23	26 / 1.65	
ER+, PR−	140 / 14.58	160 / 14.44		95 / 15.13	219 / 13.87	
ER+, PR+	652 / 67.92	753 / 67.96		431 / 68.63	1,079 / 68.33	
Positive Lymph Nodes			0.90			0.23
0	603 / 62.62	706 / 63.38		416 / 65.82	988 / 62.33	
1–3	260 / 27.00	291 / 26.12		160 / 25.32	426 / 26.88	
≥4	100 / 10.38	117 / 10.50		56 / 8.86	171 / 10.79	
Other Antioxidant Use[d]			<0.0001			<0.0001
No	815 / 85.16	405 / 36.99		428 / 67.19	470 / 30.24	
Yes	142 / 14.84	690 / 63.01		209 / 32.81	1,084 / 69.76	
Type of Multivitamin Use			---			---
Multivitamin with Minerals	not applicable	839 / 74.84		not applicable	1,181 / 74.04	
Multivitamin without Minerals	not applicable	101 / 9.01		not applicable	135 / 8.46	
Combination[e]	not applicable	181 / 16.15		not applicable	279 / 17.49	

[a] Pre-diagnosis ever use is ≥3 times/week for a year or more during the five years before diagnosis; post-diagnosis ever use is any use since breast cancer diagnosis (mean = 1.91 years)

[b] Pearson chi-square test, unless otherwise specified

[c] Kruskal-Wallis test

[d] vitamin C, vitamin E, carotenoid combinations, beta carotene, lycopene, selenium, zinc

[e] used both multivitamin with minerals and multivitamin without minerals

Table 2

Pre-diagnosis and post-diagnosis multivitamin use and breast cancer recurrence and survival in the LACE Study (n=2,236)

Two Years Post-Diagnosis Use

	n	Recurrence [a]				Breast Cancer Death [a]				Total Mortality [a]			
		events	HR	95% CI	p value	Events	HR	Lower CI	p value	events	HR	95% CI	p value
Any MV [b]													
No	637	92	Ref	---	---	49	Ref	---	---	96	Ref	---	---
Yes	1595	220	0.92	0.71, 1.20	0.56	118	0.87	0.60, 1.24	0.43	215	0.92	0.71, 1.19	0.51
Type of MV													
None	637	92	Ref	---	---	49	Ref	---	---	96	Ref	---	---
MV without Minerals	135	22	0.83	0.49, 1.42	0.50	12	0.82	0.39, 1.73	0.60	19	0.87	0.50, 1.51	0.61
MV with Minerals	1181	151	0.89	0.67, 1.17	0.39	80	0.87	0.60, 1.27	0.48	151	0.93	0.71, 1.22	0.60
Frequency of Any MV Use [b,c]													
Never	637	92	Ref	---	---	49	Ref	---	---	96	Ref	---	---
Occasional	321	47	1.02	0.70, 1.47	0.94	21	0.82	0.47, 1.40	0.46	35	0.89	0.59, 1.33	0.56
Frequent	1250	168	0.90	0.69, 1.19	0.48	94	0.88	0.61, 1.28	0.50	175	0.92	0.70, 1.20	0.52
			p for trend = 0.44				p for trend = 0.56				p for trend = 0.55		

Combined Pre- and Post-Diagnosis Use [d]

	n	Recurrence [a]				Breast Cancer Death [a]				Total Mortality [a]			
		events	HR	95% CI	p value	Events	HR	Lower CI	p value	events	HR	95% CI	p value
Never Use	446	69	Ref	---	---	38	Ref	---	---	66	Ref	---	---
New Use	456	65	0.86	0.61, 1.22	0.40	37	0.99	0.62, 1.58	0.95	57	0.96	0.66, 1.39	0.83
Persistent Use	993	127	0.76	0.54, 1.06	0.11	70	0.70	0.44, 1.11	0.13	138	0.79	0.56, 1.12	0.19
			p for trend = 0.11				p for trend = 0.12				p for trend = 0.18		

[a]
adjusted for age at diagnosis, race/ethnicity, education, positive nodes, stage, hormone receptor status, treatment, pre-diagnosis BMI, other antioxidant use, smoking, non-sedentary physical activity, and fruit and vegetable consumption

[b]
includes combination users (i.e., those who used MV with minerals and MV without minerals)

[c]
Never = none, Occasional = <1 day/week; 1–2 days/week; 3–5 days/week; Frequent = 6–7 days/week

[d]Never Use includes never taking any multivitamin before and after diagnosis; New Use includes taking any multivitamin after diagnosis but not before diagnosis for at least 3 times per week for a year or more; Persistent Use includes taking any multivitamin before diagnosis for at least 3 times/week for a year or more and after diagnosis for at least 3 times/week.

Table 3

Combined pre-diagnosis and post-diagnosis multivitamin use, recurrence, and survival in the LACE Study, by select lifestyle factors (n=2,236)

Recurrence [a,b]

	n	events	Never Use HR (95% CI)	New Use HR (95% CI)	Persistent Use HR (95% CI)	p for trend	p for interaction
Smoking							0.55
Ever	1051	153	Reference	1.03 (0.61, 1.74)	1.00 (0.62, 1.61)	0.99	
Never	1183	159	Reference	0.83 (0.51, 1.35)	**0.61 (0.37, 0.99)**	**0.042**	
Fruit and Vegetable Consumption (servings/day)							0.98
Bottom quartile (≤2.39)	468	87	Reference	1.01 (0.54, 1.87)	0.72 (0.39, 1.31)	0.28	
Top quartile (≥5.48)	468	74	Reference	0.70 (0.31, 1.59)	0.58 (0.25, 1.36)	0.22	
Non-sedentary Physical Activity (MET-hours/week)							0.92
Bottom quartile (≤29.95)	482	88	Reference	1.06 (0.55, 2.02)	0.81 (0.42, 1.56)	0.52	
Top quartile (≥66.85)	482	84	Reference	0.96 (0.46, 1.99)	0.69 (0.33, 1.46)	0.30	

Breast Cancer Death [a,b]

	n	events	Never Use HR (95% CI)	New Use HR (95% CI)	Persistent Use HR (95% CI)	p for trend	p for interaction
Smoking							0.40
Ever	1051	89	Reference	1.38 (0.71, 2.70)	0.84 (0.44, 1.60)	0.55	
Never	1183	78	Reference	0.84 (0.42, 1.69)	0.62 (0.31, 1.24)	0.17	
Fruit and Vegetable Consumption (servings/day)							0.73
Bottom quartile (≤2.39)	468	51	Reference	1.34 (0.59, 3.06)	0.76 (0.34, 1.70)	0.47	
Top quartile (≥5.48)	468	32	Reference	1.04 (0.28, 3.81)	0.48 (0.11, 2.03)	0.22	
Non-sedentary Physical Activity (MET-hours/week)							0.91
Bottom quartile (≤29.95)	482	53	Reference	0.98 (0.42, 2.31)	0.57 (0.24, 1.39)	0.21	
Top quartile (≥66.85)	482	38	Reference	1.03 (0.36, 2.89)	0.45 (0.15, 1.40)	0.13	

Total Mortality [a,b]

	n	events	Never Use HR (95% CI)	New Use HR (95% CI)	Persistent Use HR (95% CI)	p for trend	p for interaction
Smoking							0.11
Ever	1051	176	Reference	1.02 (0.62, 1.68)	0.71 (0.45, 1.11)	0.12	
Never	1183	135	Reference	0.95 (0.54, 1.67)	0.89 (0.52, 1.53)	0.68	

	n	events	Never Use HR (95% CI)	New Use HR (95% CI)	Persistent Use HR (95% CI)	p for trend	p for interaction
Recurrence [a,b]							
Fruit and Vegetable Consumption (servings/day)							0.24
Bottom quartile (≤2.39)	468	86	Reference	1.10 (0.55, 2.20)	0.82 (0.43, 1.58)	0.54	
Top quartile (≥5.48)	468	62	Reference	0.48 (0.21, 1.07)	**0.28 (0.11, 0.72)**	**0.0078**	
Non-sedentary Physical Activity (MET-hours/week)							0.20
Bottom quartile (≤29.95)	482	111	Reference	1.11 (0.60, 2.06)	0.73 (0.40, 1.32)	0.26	
Top quartile (≥66.85)	482	69	Reference	0.93 (0.42, 2.09)	**0.39 (0.16, 0.95)**	**0.030**	

[a] All stratified models were adjusted for age at diagnosis, race/ethnicity, education, positive nodes, stage, hormone receptor status, treatment, pre-diagnosis BMI, other antioxidant use, smoking (not in smoking analyses), non-sedentary physical activity (not in physical activity analyses), and fruit and vegetable consumption (not in diet analyses).

[b] Never Use includes never taking any multivitamin before and after diagnosis; New Use includes taking any multivitamin after diagnosis but not before diagnosis for at least 3 times per week for a year or more; Persistent Use includes taking any multivitamin before diagnosis for a year or more and after diagnosis for at least 3 times/week for a year or more and after diagnosis for at least 3 times/week.

Table 4

Combined pre-diagnosis and post-diagnosis multivitamin use, recurrence, and survival in the LACE Study, by receipt of adjuvant therapy

Recurrence [a,b]

	n	events	Never Use HR (95% CI)	New Use HR (95% CI)	Persistent Use HR (95% CI)	p for trend	p for interaction
Chemotherapy and Radiation Therapy							0.033
None	392	45	Referent	0.74 (0.25, 2.19)	1.64 (0.62, 4.33)	0.27	
Chemotherapy only	434	63	Referent	2.11 (0.84, 5.29)	1.60 (0.67, 3.83)	0.38	
Radiation therapy only	559	68	Referent	0.78 (0.35, 1.73)	0.49 (0.23, 1.01)	**0.048**	
Both	850	136	Referent	**0.58 (0.34, 0.99)**	**0.52 (0.31, 0.86)**	**0.015**	
Hormonal Therapy							0.80
No	427	61	Referent	1.23 (0.56, 2.68)	1.05 (0.44, 2.51)	0.91	
Yes	1798	251	Referent	0.78 (0.52, 1.16)	0.72 (0.50, 1.05)	**0.097**	

Breast Cancer Death [a,b]

	n	events	Never Use HR (95% CI)	New Use HR (95% CI)	Persistent Use HR (95% CI)	p for trend	p for interaction
Chemotherapy and Radiation Therapy							0.24
None	392	21	Referent	0.54 (0.08, 3.54)	3.13 (0.77, 12.74)	0.063	
Chemotherapy only	434	34	Referent	3.17 (0.85, 11.85)	1.10 (0.30, 4.00)	0.95	
Radiation therapy only	559	34	Referent	0.56 (0.19, 1.66)	**0.25 (0.09, 0.68)**	**0.0061**	
Both	850	78	Referent	0.69 (0.33, 1.45)	0.56 (0.28, 1.15)	0.12	
Hormonal Therapy							0.96
No	427	35	Referent	1.93 (0.59, 6.29)	1.86 (0.50, 6.95)	0.36	
Yes	1798	132	Referent	0.87 (0.51, 1.48)	0.61 (0.37, 1.02)	**0.053**	

Total Mortality [a,b]

	n	events	Never Use HR (95% CI)	New Use HR (95% CI)	Persistent Use HR (95% CI)	p for trend	p for interaction
Chemotherapy and Radiation Therapy							0.030
None	392	72	Referent	0.89 (0.37, 2.15)	1.69 (0.77, 3.68)	0.17	
Chemotherapy only	434	50	Referent	1.71 (0.62, 4.76)	0.86 (0.34, 2.21)	0.61	
Radiation therapy only	559	85	Referent	0.86 (0.41, 1.79)	0.54 (0.26, 1.10)	**0.083**	
Both	850	104	Referent	0.66 (0.35, 1.25)	0.59 (0.32, 1.07)	**0.095**	
Hormonal Therapy							0.78

Recurrence [a,b]

	n	events	Never Use HR (95% CI)	New Use HR (95% CI)	Persistent Use HR (95% CI)	p for trend	p for interaction
No	427	56	Referent	1.55 (0.59, 4.10)	1.61 (0.60, 4.29)	0.36	
Yes	1798	255	Referent	0.89 (0.59, 1.34)	0.76 (0.52, 1.11)	0.15	

[a] Adjusted for age at diagnosis, race/ethnicity, education, positive nodes, stage, hormone receptor status, treatment (not in radiation therapy and chemotherapy analyses), pre-diagnosis BMI, other antioxidant use, smoking, non-sedentary physical activity, and fruit and vegetable consumption.

[b] Never Use includes never taking any multivitamin before and after diagnosis; New Use includes taking any multivitamin after diagnosis but not before diagnosis for at least 3 times per week for a year or more; Persistent Use includes taking any multivitamin before diagnosis for at least 3 times/week for a year or more and after diagnosis for at least 3 times/week.

Table 5

Combined pre-diagnosis and post-diagnosis multivitamin use, recurrence, and survival in the LACE Study, by post-diagnosis antioxidant supplement use

	n	events	Never MV Use HR (95% CI)	New MV Use HR (95% CI)	Persistent MV Use HR (95% CI)	p for trend	p for interaction
Recurrence [a,b]							
Overall Antioxidants							
No	899	144	Reference	0.91 (0.56, 1.48)	1.05 (0.69, 1.58)	0.84	0.098
Yes	1296	168	Reference	0.91 (0.50, 1.64)	0.63 (0.37, 1.08)	0.031	
Breast Cancer Death [a,b]							
Overall Antioxidants							
No	899	72	Reference	0.90 (0.45, 1.80)	0.87 (0.48, 1.56)	0.63	0.31
Yes	1296	95	Reference	1.09 (0.50, 2.38)	0.63 (0.30, 1.33)	0.058	
Total Mortality [a,b]							
Overall Antioxidants							
No	899	134	Reference	1.06 (0.63, 1.77)	0.96 (0.62, 1.50)	0.87	0.26
Yes	1296	177	Reference	0.82 (0.46, 1.47)	0.69 (0.41, 1.15)	0.13	

[a] Adjusted for age at diagnosis, race/ethnicity, education, positive nodes, stage, hormone receptor status, treatment, pre-diagnosis BMI, smoking, non-sedentary physical activity, and fruit and vegetable consumption.

[b] Never Use includes never taking any multivitamin before and after diagnosis; New Use includes taking any multivitamin after diagnosis but not before diagnosis for at least 3 times per week for a year or more; Persistent Use includes taking any multivitamin before diagnosis for at least 3 times/week for a year or more and after diagnosis for at least 3 times/week.