Post-diagnosis supplement use and breast cancer prognosis in the After Breast Cancer Pooling Project

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Abstract

Purpose—Vitamin supplement use after breast cancer diagnosis is common, but little is known about long-term effects on recurrence and survival. We examined post-diagnosis supplement use and risk of death or recurrence in the After Breast Cancer Pooling Project, a consortium of 4 cohorts of 12,019 breast cancer survivors from the United States and China.

Methods—Post-treatment supplement use (Vitamins A, B, C, D, E, and multivitamins) was assessed one to five years post-diagnosis. Associations with risk of recurrence, breast cancerspecific mortality, or total mortality were analyzed in Cox proportional hazards models separately by cohort. Individual cohort results were combined using random effects metaanalysis. Interactions with smoking, treatment, and hormonal status were examined.

Results—In multivariate models, vitamin E was associated with a decreased risk of recurrence (RR: 0.88; 95% CI: 0.79–0.99) and vitamin C with decreased risk of death (RR: 0.81; 95% CI: 0.72–0.92) However, when supplements were mutually adjusted, all associations were attenuated. There were no statistically significant associations with breast cancer mortality. Use of anti-oxidant supplements (multivitamins, vitamin C or E) was not associated with recurrence, but was associated with a 16% decreased risk of death (95% CI: 0.72–0.99). Additionally, vitamin D was associated with decreased risk of recurrence among ER positive, but not ER negative tumors (p-interaction=0.01).

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Conclusion—In this large consortium of breast cancer survivors, post-treatment use of vitamin supplements was not associated with increased risk of recurrence or death. Post-treatment use of anti-oxidant supplements were associated with improved survival, but the associations with individual supplement were difficult to determine. Stratification by ER status and considering antioxidants as a group may be more clinically relevant when evaluating associations with cancer risk and mortality.

Keywords

breast cancer; vitamins; survival; mortality

Introduction

Use of vitamin supplements after breast cancer diagnosis is common; 45–80% of patients use some form of supplement [1]. However, the potential risks and benefits of these supplements remain unclear. The anti-oxidant effects of some supplements may protect normal tissue during treatment [2]; however there is concern that these same effects may also protect tumor tissue from the effects of treatment [2]. Additionally, the effects of non-anti-oxidant supplements have not been studied in-depth. Therefore, the role of vitamin supplements on risk of recurrence or death among breast cancer survivors remains to be resolved.

Although some studies have investigated specific supplements in relation to breast cancer outcomes [3–9], most have focused on anti-oxidants and had limited power to simultaneously control for use of multiple supplements. Therefore, we investigated the associations of antioxidants and other commonly used vitamin supplements on risk of breast cancer recurrence, breast cancer-specific mortality, and total mortality in the After Breast Cancer Pooling Project (ABCPP).

Methods

The After Breast Cancer Pooling Project

The ABCPP is a consortium of four prospective studies of 18,333 Stage I-IV breast cancer survivors. Details on the consortium have been published previously [10]. Briefly, two cohorts specifically recruited breast cancer patients: the Shanghai Breast Cancer Survival Study (SBCSS) [11] and the Life after Cancer Epidemiology (LACE) Study [12]. The third, the Women's Healthy Eating and Living (WHEL) Study, was a randomized dietary intervention trial among breast cancer patients [13]. The fourth study included breast cancer patients from the Nurses' Health Study (NHS), a large prospective study of female nurses [14].

Each cohort collected data on tumor characteristics, cancer treatment, reproductive factors, family history of breast cancer, quality of life, medical history, anthropometry, smoking history, alcohol intake, supplement use, physical activity, and diet. These data have been harmonized into a common dataset. Investigators of each individual cohort received IRB approval from their respective institutions to participate in this collaboration.

Ascertainment of supplement use and covariates

Supplement use—Regular supplement use was assessed through self-report. Because the effects of supplements and use patterns may differ during and after chemotherapy/radiation, we restricted this analysis to regular supplement use (ever vs. never) at least one year postdiagnosis. The supplements included in this analysis were those queried by all four

studies: multivitamins, vitamins A, B, C, D, and E. Details on how supplements were queried in each study have been published previously [3, 5, 6, 15]. In brief, LACE participants reported supplement use (ever vs. never), post-diagnosis duration, and frequency at study enrollment. Supplements queried included beta-carotene, vitamins A, B, C, D, and E, calcium, and multivitamins [3]. NHS participants were queried about current regular use of multivitamins, Vitamins A, C, and E on biennial questionnaires and vitamins D, B, and calcium at least every other questionnaire. For some supplements, women also reported frequency or dose [15]. SBCSS queried women about use of supplements, including vitamins A, B, C, D, E, and multivitamins, at least once a week for one month or more at the 6-month and 36 month post-diagnosis interviews, including duration and dose information [5]. In the WHEL study, participants reported the brand and number of supplements that were taken in the previous 24 hours at baseline as well as at each follow-up visit [6].

Sociodemographic and lifestyle factors—Data assessed at first post-diagnosis survey included race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Asian, Hispanic, Other), menopausal 5 status at diagnosis (premenopausal, postmenopausal, unknown), and smoking history (never, former, current <25 pack-years, current 25+ pack-years). Body mass index (BMI) was categorized as follows: underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) or obese (30.0 kg/m^2). Post-diagnosis exercise participation in metabolic equivalents (MET-hours/week) was determined from semi-quantitative questionnaires.

Clinical characteristics—Data included age at diagnosis (years), AJCC pathologic stage (I, II, III, IV), ER/PR status (ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−), and cancer therapy (none, chemotherapy only, radiation therapy only, hormonal therapy only, or some combination of the three therapy types).

Ascertainment of Breast Cancer Outcomes

The main outcomes were breast cancer recurrence, breast cancer-specific mortality, and all-cause mortality. Recurrence was defined as recurrence/metastasis or development of new primary breast cancer. Each cohort followed participants to ascertain breast cancer outcomes. Detailed methods were previously published for each cohort [10]; in brief, outcomes were ascertained through a combination of self-report, medical record review and linkage to vital statistics registries.

Statistical Analysis

Users of multivitamins were not considered users of single supplements unless they also reported separate use of that supplement. For each supplement, non-users of that supplement were considered the reference group. Women were excluded from the analysis if they had insitu or stage IV metastatic breast cancer (n=1,072), were missing information on any of the supplements (n=3,608), or did not report on their supplement use in the post-treatment period 6 (n=11). Because the other cohorts recruited patients after 1990, 1,623 women from NHS who were diagnosed before 1990 were excluded to improve comparability across cohorts. Thus, 12,019 breast cancer survivors were included in the analysis. As sensitivity analyses, we included intervention group as a covariate for the WHEL study, limited the analysis to the US studies, included those missing supplement use as a separate category, and used as the reference group non-users of any type of supplement or multivitamin.

Delayed-entry Cox proportional hazards regression with time since diagnosis as the time scale was used to estimate study-specific adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The entry date was the date of the questionnaire on which supplement use

was reported. The exit date was the event date (recurrence or death) or last contact (i.e., date of last survey or registry linkage, whichever was most recent). Studies were combined using random-effects meta-analysis [16]. The Q statistic was used to test for heterogeneity across studies [17]. To test for interactions, we created multiplicative interaction terms in the 4 studies pooled due to small numbers in the individual studies. All models were adjusted for age at diagnosis, AJCC stage, menopausal status, chemotherapy, radiotherapy, hormonal therapy, BMI, physical activity, and smoking history. We additionally adjusted each supplement for the other supplements to estimate the association with the supplement of interest independent of other supplements.

Results

Characteristics of the ABCPP participants are shown in Table 1 and by cohort in Supplemental Table 1. 60.6% of participants reported supplement use 1–5 years post-diagnosis; of these, 27.5% reported use of a multivitamin only. Supplement users were more likely to be white and meet physical activity recommendations. In contrast, supplement non-users were more likely to have received chemotherapy and be non-smokers, but this is likely due to the fact that the 50% of the non-users were from SBCSS, where chemotherapy is much more common than in the US cohorts, and smoking much less. Of the women who died during the study period (N=1,298), 65% died due to their breast cancer.

Use of vitamin E was associated with decreased risk of recurrence (HR: 0.88; 95% CI: 0.79-0.99) and suggestively associated with decreased risk of breast cancer-specific death (HR: 0.86; 95% CI: 0.69–1.07) and death due to any cause (HR: 0.85; 95% CI: 0.71–1.03; Table 2). Additionally, vitamin C use was associated with a decreased risk of death due to any cause (HR: 0.81; 95% CI: 0.72–0.92) and suggestively associated with decreased risk of recurrence (HR: 0.90; 95% CI: 0.80–1.01) and breast cancer-specific death (HR: 0.87; 95% CI: 0.75–1.01). However, after adjusting for use of other supplements, the associations were attenuated. Since vitamins C and E have anti-oxidant properties, we examined use of anti-oxidant supplements (vitamins C, E, or multivitamins) in relation to risk of recurrence, breast cancer-specific mortality or total mortality. Use of any anti-oxidant supplement was not associated with recurrence, but was associated with a 16% decreased risk of death due to any cause (95% CI: 0.72–0.99) in models adjusting for use of other supplements. Women who reported use of all 3 anti-oxidantcontaining supplements had a 21% decreased risk of death due to any cause (95% CI: 0.66- 0.95). Women who used 2 types of anti-oxidants had similar, but non-significant associations (HR: 0.75; 95% CI: 0.54–1.05). Results were similar, but not statistically significant, for breast cancer-specific mortality.

Analyses limited to the US cohorts yielded results similar to the main analysis; however power was limited and none of the associations were statistically significant (Supplemental Table 2). Results were also similar when women who used none of the supplements were considered the reference group, rather than non-users of the single supplement of interest (Supplemental Table 3). Adjusting for intervention group in the WHEL study did not affect results (data not shown). Vitamin D use was associated with decreased risk of recurrence among ER+ (HR: 0.64; 95% CI: 0.47–0.87) but not ER- tumors (HR: 1.25; 95% CI: 0.78–1.98; p-interaction=0.01; Table 3). When stratified by joint ER/PR status, vitamin D use was only associated with a decreased risk of recurrence among ER+/PR+ and ER+/PR– tumors, but not ER-/PR+ or ER−/PR− tumors (pinteraction= 0.002). However, this low p-value was partially driven by an HR of 4.5 in the ER−/PR+ tumors (N=9 vitamin D users). Because the ER/PR interaction looked very similar to the ER interaction described above and there were few subjects in the ER−/PR+ subgroup, we elected to show only the ER stratification results. A similar pattern was observed for risk of breast cancer-specific mortality and total mortality, but the p-interaction was not statistically significant (0.07). We observed no

interactions between supplements or by chemotherapy, radiation therapy, smoking, or menopausal status (data not shown).

Discussion

In over 12,000 breast cancer survivors from 4 cohort studies, we observed no increased risk of breast cancer recurrence, breast cancer-specific mortality, or total mortality associated with use of supplements. Vitamin E use was associated with decreased recurrence risk and vitamin C use was associated with decreased risk of death due to any cause; however, these associations did not retain statistical significance when supplements were mutually adjusted. These findings demonstrate the difficulty of understanding the independent contribution of specific supplements when use of multiple supplements is common. In contrast, we observed a 15% risk reduction for use of any anti-oxidant supplement, with stronger effects among women who used more than one type of anti-oxidant, suggesting that grouping supplements with similar physiologic effects may better capture the underlying biology. Additionally, we found that, among ER+ tumors, vitamin D was associated with decreased risk of recurrence, suggesting that the effects of certain supplements may differ by tumor subtype.

Most women (60.6%) in this study used at least one supplement, and, of these, 59.6% used multiple supplements. Thus, use of any supplement is correlated with use of other supplements and determining the independent effects of each supplement is difficult. To address this methodologic issue, we examined two reference groups: 1) non-users of the supplement of interest, and 2) non-users of any supplement included in this analysis. These two reference groups enabled us to test two somewhat different hypotheses: 1) users of a specific supplement have different risks than non-users of that supplement, and 2) users of a specific supplement have different risks than women who do not take any supplements. Since results of these two analyses were similar, we used analysis 1 in our main tables and provided results from analysis 2 in supplemental tables. Additionally, use of western vitamin supplements is rare in China and reasons for use may differ in China vs. the US. If we had pooled the four ABCPP cohorts, most of the non-users would have been from the SBCSS. We were concerned that a pooled analysis might be biased if the predictors of use vs. non-use of supplements differed by study and were related to breast cancer outcomes. In particular, one potentially important variable, socio-economic status, was not available in the pooled dataset. Therefore, we chose to use meta-analysis to combine studies due to concerns about unmeasured confounding by study.

Four previous prospective cohorts have examined supplements and breast cancer prognosis [3–7]; three are ABCPP contributing cohorts. The LACE study found that frequent use of vitamins C and E was associated with decreased recurrence risk, but that carotenoids were associated with increased risk of death [3]. However, the total number of events was low (n=316 deaths due to any cause). The SBCSS also found reduced risk of recurrence for anti-oxidant use (multivitamin, vitamin C or vitamin E), but use of western vitamin supplements was infrequent and that analysis combined supplement use during and after treatment [5]. In the current study, to avoid potential differences in the effects of supplement use during and post-treatment, we focused on supplement use more than one year post-diagnosis. The WHEL study examined supplement use in combination with food sources of vitamins and found no association with allcause mortality [6]. The Iowa Women's Health Study examined folate from diet and supplements and found no association with all-cause mortality [7]. We do not have detailed information on dietary sources of nutrients in the ABCPP and therefore could not address whether total intake of specific nutrients is associated with breast cancer outcomes.

The association between supplements and breast cancer survival has also been assessed in two case-control studies. In 220 breast cancer cases from the Boston area, use of anti-oxidant supplements (β-carotene, vitamins C or E, or selenium) was associated with a non-significant decreased risk of recurrence [8]. However, the number of cases was small, 21% used proxy respondents and the questionnaire was sent 10 years after the initial recruitment into the study, raising a concern about the validity of the exposure assessment. A second study examined prediagnostic B-vitamin use among 1,479 breast cancer cases from the Long Island Breast Cancer Study Project [9] and found decreased risk of all-cause and breast cancer-specific mortality among users of vitamins B_1 and B_3. However, use of vitamin supplements was assessed at baseline to reflect use in the year prior to breast cancer diagnosis; thus post-diagnosis vitamin use was not included in this study. The ABCPP does not have detailed information on specific types of B vitamins, so we could not attempt to replicate these findings.

Several clinical trials in cancer survivors have found increased risk of death among smokers randomized to receive anti-oxidant supplements [18–20]. Although these trials were not conducted among breast cancer patients, there is concern that anti-oxidants may be harmful in breast cancer survivors, particularly those who smoke. In our study, we observed no interaction with smoking. One limitation of our analysis is that we intentionally restricted our analysis to the post-treatment period to remove the potential for different effects of supplement use during and after treatment. Thus, we cannot rule out the possibility that anti-oxidant supplements may have different effects during active breast cancer treatment vs. post-treatment.

Studies of circulating vitamin D levels suggest that higher vitamin D may improve prognosis for several cancer types [21–26], although not always consistently [27–29]. However, studies of vitamin D supplements in cancer patients are limited [30]. We found no overall association with use of vitamin D supplements, but vitamin D was associated with a 46% decreased risk of breast cancer recurrence among women with ER+ tumors. However, vitamin D from supplements contributes a relatively small amount to the total available vitamin D, compared to sunlight exposure. Two recent studies of breast cancer patients suggested that circulating vitamin D levels were higher in ER+ patients compared with ER-patients [31, 32]. No information on prognosis, however, was available from these two studies. In addition, vitamin D has been associated with body mass index [27, 33], suggesting that the role of vitamin D in breast cancer survivors may also differ by adiposity. We found no interaction between vitamin D and BMI in the current study (data not shown). Further, circulating vitamin D levels have been shown to differ between Caucasians and east Asians [34]; therefore, racial differences in total vitamin D should also be accounted for in studies of the role of vitamin D in breast cancer survivors. In the current study, vitamin D supplement use was low in the SBCSS and the USbased studies were more than 85% Caucasian; our ability to address potential racial differences was limited. However, when we performed analyses restricted to the US cohorts, we observed very similar results, suggesting that racial differences did not play an important role in the current study. Additional studies, particularly with measurement of circulating vitamin D, incorporating ER status would help to confirm our observed ER-vitamin D interaction and shed light on the biologic pathways through which vitamin D supplementation may impact ER+, but not ER−, tumors.

One limitation of this study is the lack of detailed dose and duration information across studies. For example, not all studies collected dose information and those that did did not do so in a consistent manner: in the NHS, dose was not collected in for all supplements on all questionnaires and was collected in wide categories and in various units. In the SBCSS, both the dose and its units were collected for each supplement by write-in; thus units were not

consistent within the study. In the WHEL study, total supplemental intake was calculated by summing over the ingredients in multivitamins and single supplements, whereas NHS and SBCSS only had dose of single supplements. Dose was not collected in the LACE study. In addition, not all studies collected the same supplements; hence, we could not investigate supplements such as beta-carotene or specific types of B-vitamins. Nevertheless, this is the largest study of post-diagnosis supplement use and breast cancer outcomes to date. Due to the large sample size, we could control for use of multiple supplements simultaneously, obtaining an estimate of the effects of each specific supplement. Further, we could account for important prognostic variables, including stage and treatment, as well as important potential confounders of the associations between supplements and breast cancer outcomes, including body size, smoking, and physical activity.

In summary, post-treatment supplement use was not associated with increased risk of breast cancer recurrence or all-cause mortality. Importantly, grouping supplements by their biologic effects may be a better way of measuring associations with breast cancer prognosis. Additionally, it is crucial to consider the concomitant use of other supplements when evaluating effects of specific supplements. Future studies should take dose and duration into account and specifically evaluate the associations with supplement use during active treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Age-standardized characteristics of the pooled cohorts by supplement use

	No supplements (n=4,741)	Multivitamin only (n=1,999)	Any other single supplement (n=5,279)
Mean (SD)			
Age at diagnosis[a]	54.8 (10.8)	57.5 (11.2)	58.0 (10.0)
Years between diagnosis and study entry[a]	2.7(0.7)	2.3(0.7)	2.2(0.7)
Percentages			
Stage			
I	44	46	48
II	43	43	40
III	13	11	12
Treatment			
Received Chemotherapy	75	65	60
Received Radiation	44	56	56
Received Hormonal Therapy	60	69	71
ER status[b]			
Positive	70	75	76
Negative	28	23	21
PR status[b]			
Positive	61	63	65
Negative	36	33	31
Race			
Non-Hispanic White	37	71	77
Non-Hispanic Black	2	3	2
Asian	58	21	16
Hispanic	2	3	3
Other race	1	2	3
BMI			
<25	51	47	48
25–29.9	32	32	32
30+	17	21	19
Physical Activity >10 met hrs/wk	30	41	48
Smoking status			
Never smoker	75	60	56
Past smoker	20	34	38
Current smoker	5	6	5

[a]Value is not age adjusted

[b]3% were missing information on ER status; 3% were missing information on PR status. Missingness did not differ by supplement use.

Table 2

Associations between post-diagnosis supplement use and risk of recurrence, breast cancer-specific mortality, and total mortality. [a]

Supplement		Recurrence			Breast cancer mortality			Total mortality		
		Event/Total	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)	Event/Total	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)	Event/Total	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)
Multivitamin	No	591/6,406	1.00 (ref.)	1.00 (ref.)	414/6,653	1.00 (ref.)	1.00 (ref.)	617/6,653	1.00 (ref.)	1.00 (ref.)
	Yes	734/5,266	0.93 (0.83–1.05)	0.97 (0.86–1.09)	435/5,266	0.92 (0.79–1.06)	0.95 (0.82–1.11)	681/5,366	0.90 (0.77–1.05)	0.94 (0.83–1.07)
Vitamin A	No	1224/11,087	1.00 (ref.)	1.00 (ref.)	796/11,418	1.00 (ref.)	1.00 (ref.)	1,193/11,418	1.00 (ref.)	1.00 (ref.)
	Yes	101/585	1.07 (0.72–1.60)	1.16 (0.80–1.70)	53/601	0.96 (0.71–1.30)	0.95 (0.68–1.34)	105/601	1.02 (0.82–1.27)	1.06 (0.82–1.36)
Vitamin B	No	1135/10,023	1.00 (ref.)	1.00 (ref.)	728/10,332	1.00 (ref.)	1.00 (ref.)	1,121/10,332	1.00 (ref.)	1.00 (ref.)
	Yes	190/1,649	0.88 (0.75–1.03)	0.94 (0.79–1.11)	121/1,687	0.90 (0.74–1.10)	0.98 (0.80–1.21)	177/1,687	0.87 (0.74–1.02)	0.96 (0.81–1.15)
Vitamin C	No	887/8,455	1.00 (ref.)	1.00 (ref.)	586/8,732	1.00 (ref.)	1.00 (ref.)	913/8,732	1.00 (ref.)	1.00 (ref.)
	Yes	438/3,217	0.90 (0.80–1.01)	0.98 (0.85–1.12)	263/3,287	0.87 (0.75–1.01)	0.94 (0.79–1.12)	385/3,287	0.81 (0.72–0.92)	0.87 (0.76–1.01)
Vitamin D	No	1255/10,919	1.00 (ref.)	1.00 (ref.)	808/11,244	1.00 (ref.)	1.00 (ref.)	1229/11,244	1.00 (ref.)	1.00 (ref.)
	Yes	70/753	0.82 (0.60–1.12)	0.92 (0.62–1.35)	41/775	0.93 (0.67–1.29)	0.97 (0.68–1.38)	69/775	0.86 (0.67–1.11)	0.95 (0.72–1.24)
Vitamin E	No	845/8,190	1.00 (ref.)	1.00 (ref.)	566/8,472	1.00 (ref.)	1.00 (ref.)	844/8,472	1.00 (ref.)	1.00 (ref.)
	Yes	480/3,482	0.88 (0.79–0.99)	0.90 (0.78–1.03)	283/3,547	0.86 (0.69–1.07)	0.89 (0.72–1.10)	454/3,547	0.85 (0.71–1.03)	0.92 (0.79–1.07)
Anti-oxidants[d]	No	402/4867	1.00 (ref.)	1.00 (ref.)	300/5076	1.00 (ref.)	1.00 (ref.)	444/5076	1.00 (ref.)	1.00 (ref.)
	Yes	923/6805	0.94 (0.83–1.06)	0.94 (0.83–1.07)	549/6943	0.86 (0.73–1.02)	0.88 (0.74–1.03)	854/6943	0.84 (0.71–0.99)	0.84 (0.72–0.99)
Number of anti-oxidants	None	402/4867	1.00 (ref.)	1.00 (ref.)	300/5076	1.00 (ref.)	1.00 (ref.)	444/5076	1.00 (ref.)	1.00 (ref.)
	1	424/3173	1.03 (0.90–1.19)	1.03 (0.90–1.19)	254/3244	0.95 (0.79–1.13)	0.95 (0.79–1.14)	394/3244	0.92 (0.79–1.06)	0.91 (0.79–1.06)
	2	269/2104	0.85 (0.66–1.08)	0.84 (0.66–1.07)	158/2141	0.79 (0.59–1.06)	0.79 (0.58–1.08)	254/2141	0.76 (0.55–1.06)	0.75 (0.54–1.05)
	3	230/1528	0.87 (0.73–1.03)	0.88 (0.74–1.05)	137/1558	0.84 (0.67–1.05)	0.85 (0.67–1.07)	206/1558	0.78 (0.65–0.93)	0.79 (0.66–0.95)

[a] Referent group is non-users of the supplement of interest.

[b] Adjusted for age at diagnosis, exercise, stage, treatment, BMI, menopausal status, smoking status

[c] Adjusted for same covariates as Model 1 and use of all supplements listed in this table.

[d] Anti-oxidant containing supplements include vitamin C, vitamin E, or multivitamins

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Table 3

Associations between supplement use post-diagnosis and risk of recurrence, stratified by ER status[a]

Supplement		ER− Event/Total	HR	95% CI	ER+ Event/Total	HR	95% CI	p-interaction
Multivitamin	No	149/1685	**1.00**	(ref.)	423/4554	**1.00**	(ref.)	0.19
	Yes	151/1066	**0.75**	(0.59–0.95)	565/4048	**0.99**	(0.87–1.13)	
Vitamin A	No	282/2658	**1.00**	(ref.)	909/8149	**1.00**	(ref.)	0.57
	Yes	18/93	**1.36**	(0.82–2.24)	79/453	**1.12**	(0.88–1.43)	
Vitamin B	No	250/2398	**1.00**	(ref.)	853/7360	**1.00**	(ref.)	0.11
	Yes	50/353	**1.03**	(0.76–1.40)	135/1242	**0.81**	(0.68–0.98)	
Vitamin C	No	201/2071	**1.00**	(ref.)	657/6158	**1.00**	(ref.)	0.91
	Yes	99/680	**0.87**	(0.68–1.11)	331/2444	**0.92**	(0.80–1.05)	
Vitamin D	No	278/2628	**1.00**	(ref.)	944/7999	**1.00**	(ref.)	**0.01**
	Yes	22/123	**1.25**	(0.78–1.98)	44/603	**0.64**	(0.47–0.87)	
Vitamin E	No	199/2109	**1.00**	(ref.)	621/5871	**1.00**	(ref.)	0.70
	Yes	101/642	**0.90**	(0.70–1.15)	367/2731	**0.89**	(0.78–1.02)	
Anti-oxidants[b]	No	102/1357	**1.00**	(ref.)	285/3388	**1.00**	(ref.)	0.94
	Yes	198/1394	**0.87**	(0.67–1.12)	703/5214	**0.95**	(0.82–1.10)	
Number of anti-oxidants	None	102/1357	**1.00**	(ref.)	285/3388	**1.00**	(ref.)	0.89
	1	90/673	**1.00**	(0.75–1.35)	324/2411	**1.03**	(0.88–1.22)	
	2	63/448	**0.78**	(0.56–1.09)	198/1597	**0.84**	(0.69–1.01)	
	3	45/273	**0.73**	(0.51–1.07)	181/1206	**0.93**	(0.77–1.13)	

[a] Adjusted for age at diagnosis, exercise, stage, treatment, BMI, smoking, menopausal status, and cohort

[b] Anti-oxidant containing supplements include vitamin C, vitamin E, or multivitamins