Antioxidant supplementation and breast cancer prognosis in postmenopausal women undergoing chemotherapy and radiation therapy

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ABSTRACT

Background: There is a paucity of information on the prevalence of dietary supplement use in breast cancer survivors. Only a few studies have examined the impact of dietary supplements, particularly antioxidants, on breast cancer prognosis and the results are inconclusive.

Objective: We examined pre- and postdiagnosis use of supplements in postmenopausal breast cancer survivors in Germany and investigated associations between postdiagnosis use of antioxidants and other supplements, and prognosis (total and breast cancer mortality, and recurrence-free survival) both overall and in women who received chemotherapy and radiation therapy.

Design: Data from 2223 postmenopausal women diagnosed with nonmetastatic breast cancer from the population-based Mamma Carcinoma Risk Factor Investigation (MARIE) study were used. Women were interviewed at recruitment in 2002–2005 and again in 2009 and followed-up until 30 June 2015. Multivariate Cox regression analysis was used to estimate HRs and corresponding 95% CIs.

Results: Pre- and postdiagnosis supplement use was reported by 36% and 45% of the women, respectively. There were 240 deaths (134 from breast cancer) and 200 breast cancer recurrences after a median follow-up time of 6.0 y after the 2009 re-interview. After adjusting for relevant confounders, concurrent antioxidant use with chemotherapy or radiation therapy among 1940 women was associated with increased risk of total mortality (HR: 1.64; 95% CI: 1.01, 2.66) and worsened recurrence-free survival (HR: 1.84; 95% CI: 1.26, 2.68). Overall postdiagnosis supplement use was not associated with breast cancer prognosis.

Conclusions: Antioxidant use during chemotherapy or radiation therapy was associated with worsened breast cancer prognosis in postmenopausal women. There was no overall association between postdiagnosis supplement use and breast cancer prognosis. Results from our study align with the current recommendation to possibly avoid the use of antioxidants during chemotherapy or radiation therapy. *Am J Clin Nutr* 2019;109:69–78.

Keywords: antioxidants, dietary supplements, chemotherapy, radiation therapy, breast cancer survival, breast cancer prognosis, postmenopausal

Introduction

Breast cancer is the most common cancer in women worldwide, and the second most common cancer overall (1). Compared with healthy populations (2) and with other cancer patients (3), breast cancer survivors are more likely to be attracted to and use complementary and alternative medicines. The most frequently used complementary and alternative medicine in breast cancer survivors is dietary supplements (including herbal and alternative remedies) (4, 5). The prevalence of supplement use in the German general population aged 14–80 y is 28% (6). We hypothesize that the prevalence of supplement use among breast cancer survivors in Germany could be even higher, because previous studies suggest that increasing age (6), being female (7), and having a cancer diagnosis, especially one in the breast (3, 8), could all increase likelihood of supplement use.

Epidemiologic evidence suggests that lifestyle factors, including fruit and vegetable intake, can influence the risk and prognosis of some types of cancer, including breast (9, 10). Observational studies have suggested that antioxidants, such as vitamins C, E, and selenium, found in fruits and vegetables,

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can be protective against overall and cancer-specific mortality (11, 12). Dietary potassium and magnesium have been found to be beneficial for bone mineral density maintenance (13). Whether supplements, which contain supraphysiologic doses of single or simplex combinations of nutrients compared with normal food, have similar benefits as dietary nutrients on breast cancer prognosis still remains unclear. Existing studies are heterogeneous in terms of population size, participant age, types of supplements studied, and dose, timing, and duration of the supplement examined. A predominant number of studies have investigated the relation between postdiagnosis antioxidant use and breast cancer prognosis, with inconsistent results depending on the type of supplement assessed. For example, postdiagnosis vitamin C supplementation was associated with improved breast cancer survival in one meta-analysis of 5 patient cohort studies (14), whereas postdiagnosis combination carotenoid use was associated with a worsened breast cancer survival rate in a US patient cohort study (15).

There are concerns that supplements, mainly antioxidants, could potentially counteract the effects of chemotherapy or radiation therapy (16–18). Evidence from experimental and human clinical studies is limited, both of which caution against antioxidant use during conventional cancer therapies (16–18).

In order to better understand the prevalence of supplement use, particularly antioxidants, among postmenopausal breast cancer survivors, and the impact of antioxidants and other supplements while undergoing chemotherapy and radiation therapy on breast cancer prognosis, we investigated postdiagnosis supplement use and timing of use in association with prognosis in postmenopausal breast cancer patients enrolled in a German cohort study. This study adds to the current sparse literature concerning supplement use in postmenopausal breast cancer survivors and its associations with prognosis in Europe, where these studies are seldom conducted and where prevalence of supplement use is relatively low compared with that in the United States (5, 15).

Methods

Study population

Data from the Mamma Carcinoma Risk Factor Investigation (MARIE) study were used. The study protocol has been published elsewhere (19). In brief, 3813 participants were initially enrolled in the MARIE study between August 2002 and September 2005 in 2 regions of Germany: the Rhine-Neckar-Karlsruhe and Hamburg. Participants were breast cancer patients, aged 50–74 y and identified through participating clinics and the Hamburg cancer registry. Participants had a histologically confirmed first primary invasive (stage I, II, III, IV) or in situ breast tumor diagnosis before study enrollment, and the women were then followed up until 30 June 2015. Interviews were conducted by trained interviewers with the use of standard questionnaires at recruitment (baseline), in 2009 (first follow-up), and in 2015 (second follow-up). For this analysis, exposure information (supplement use, lifestyle, demographic, clinical, and other participant characteristics) was ascertained at recruitment and first follow-up interviews.

The study was approved by the ethics committees of the University of Heidelberg, University of Hamburg, and the Medical Board of the State of Rhineland-Palatinate, and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

For the present analysis, we included women who completed both baseline and first follow-up interviews ($n = 2542$). Of these, patients were excluded if they were recruited as a control at baseline ($n = 1$), premenopausal ($n = 148$), had metastases at diagnosis ($n = 22$), previous tumors other than breast cancer ($n = 145$), or missing supplement information ($n = 3$), leaving 2223 women for analyses investigating associations between postdiagnosis supplement use, and overall and breast cancer mortality, and breast cancer recurrence (**Figure 1**).

Dietary supplement assessment

Prediagnosis dietary supplement use.

Prediagnosis supplement use was determined from information collected at the recruitment interview. Use of vitamin or mineral supplements was defined as regular use (≥3 times/wk) of vitamin or mineral supplements for ≥1 y before the recruitment interview. Use of herbal preparations for >3 mo prediagnosis was defined as use of herbal preparations before breast cancer diagnosis and was determined as described previously (20). Taken together then, prediagnosis supplement use was any use of a vitamin or mineral supplement or ever use of herbal preparations prediagnosis according to the aforementioned definitions.

Postdiagnosis dietary supplement use.

Postdiagnosis supplement use was determined from information collected at the follow-up interview in 2009. The question was, "Do (Have) you regularly (at least 3 times per week for at least one year) take(n), herbal preparations, vitamin(s), mineral(s) or similar compounds after your breast cancer diagnosis?" For each supplement reported, additional details were asked: supplement name, the year supplement use started, duration of use (specified to the number of months), dosage and frequency of use, whether supplement use was ongoing, whether the supplement was used prediagnosis, and reason for supplement use. A postdiagnosis supplement user was a woman who had any supplement use after breast cancer diagnosis. A current user was a woman who used supplement postdiagnosis within the 6 mo before the first follow-up interview. A nonuser was a woman who had not used any supplement postdiagnosis. A consistent user was a woman who had used a supplement both pre- and postdiagnosis according to the aforementioned definitions for pre- and postdiagnosis use.

Information relating to chemotherapy and radiation therapy received and corresponding start and end dates was collected retrospectively from medical records. A woman who used antioxidants postdiagnosis for ≥1 mo while simultaneously undergoing chemotherapy and/or radiation therapy was considered a concurrent user. A nonconcurrent user was a woman who used antioxidants postdiagnosis and also underwent chemo- and/or radiation therapy but the overlap between the 2 was <1 mo.

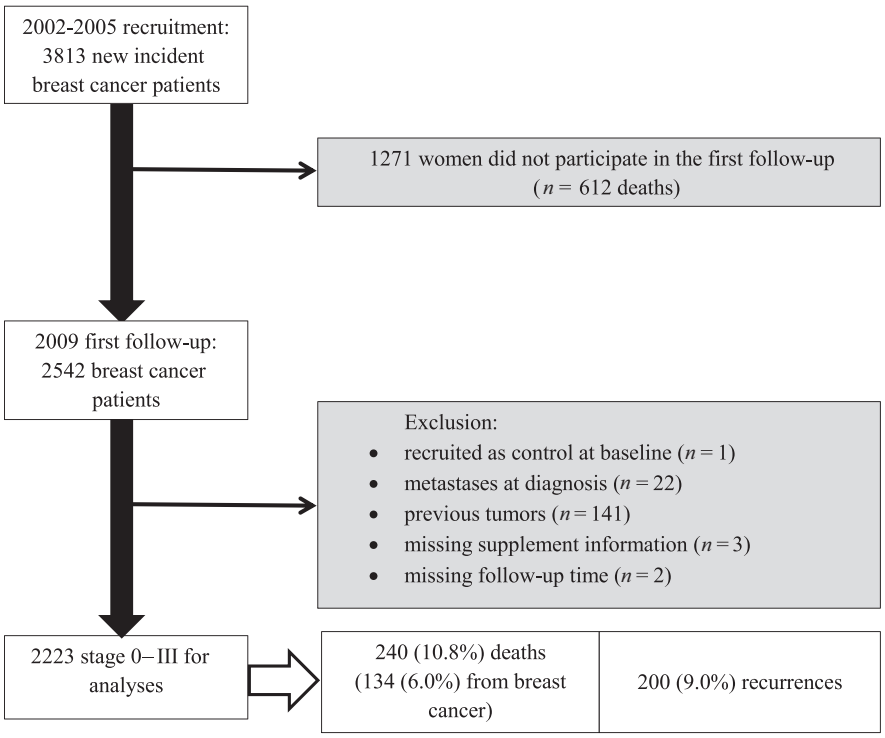

FIGURE 1 Flow diagram of exclusion and inclusion criteria for participants of the Mamma Carcinoma Risk Factor Investigation study for analyses relating postdiagnosis supplement use and overall mortality, breast cancer mortality, and recurrence-free survival.

Outcome assessment

Vital status was retrieved through central population registry databases of the study regions up until the end of June 2015, followed by requests for death certificates from local health offices. Cause of death was coded according to the 10th revision of the International Classification of Diseases (ICD-10-GM). For outcome information (recurrences, second cancers pertaining to the primary breast cancer, metastatic events, and vital status), medical records were checked or treating physicians were contacted to identify recurrences or second cancers, and to verify such information collected at the follow-up interviews. Primary study outcomes were overall mortality and breast cancer mortality, and the secondary study outcome was recurrence-free survival. The event of interest in breast cancer mortality analyses was death attributed to breast cancer (coded as ICD-10 C50), and deaths from other causes were censored at date of occurrence. Events of interest in recurrence-free survival analyses were ipsilateral, local/regional invasive breast cancer recurrence, distant recurrence and metastases occurring after the primary diagnosis, and death (21). Thus, recurrence-free survival is equivalent to the inverse of risk of having any of the mentioned events of interest. Participants without events of interest were censored at date of last contact or 30 June 2015, whichever came first.

Statistical analysis

Differences in demographic, lifestyle, clinical, and tumor characteristics between postdiagnosis supplement users and nonusers were compared via 2-sample *t* test for continuous variables, and logistic regression for categoric variables.

Delayed-entry Cox proportional hazard models, based on time since the first follow-up interview in 2009 until event of interest/censoring, were used to estimate HRs and corresponding 95% CIs for the associations between postdiagnosis supplement use and overall and breast cancer mortality (primary outcomes) and recurrence-free survival (secondary outcome). The main exposures of interest included postdiagnosis use (no postdiagnosis use, postdiagnosis use, current use) of any type of supplement; specific supplements, such as magnesium and calcium; and supplement group, such as antioxidants, in which there was adequate statistical power to conduct analyses. Only a few women reported postdiagnosis use of multivitamins, vitamins A, C, and E, zinc, and selenium, and therefore they were collectively evaluated together as antioxidants in all our analyses.

The proportional hazards assumptions were examined by visualizing the effect of a potential time-dependent covariate on the risk of an outcome throughout the follow-up time, with the use of a weighted least-squares line fitted to the residual plot as proposed by Grambsch and Therneau (22).

All analyses evaluating associations between postdiagnosis supplement use and the outcomes of interest were stratified by study center. Potential covariates were determined a priori, and 2 models were constructed. The first model (model 1) was adjusted for age at diagnosis and breast cancer prognostic factors (23, 24), including tumor grade (neoadjuvant chemotherapy-treated carcinoma, in situ, low, moderate, high), tumor size (neoadjuvant chemotherapy-treated carcinoma, in situ, ≤2 cm, 2–5 cm, >5 cm, growth into chest wall/skin), and number of positive lymph

nodes (neoadjuvant chemotherapy-treated carcinoma, in situ, 0, 1–3, 4–9, ≥10). The second model (model 2) was further adjusted for lifestyle factors, including BMI at the first follow-up, smoking status at the first follow-up, physical activity at the first follow-up, alcohol intake at the first follow-up, and education; prediagnosis supplement use (ever use, never use); menopausal hormone therapy; and clinical characteristics, including tumor hormone receptor status (i.e., estrogen receptor/progesterone receptor), mode of tumor detection, chemotherapy received, radiation therapy received, hormone therapy received (i.e., tamoxifen/aromatase inhibitors), and comorbidities (diabetes and cardiovascular disease, separately). Exclusion of 2 additional covariates (tumor epidermal growth factor receptor 2 status and type of surgery) was determined empirically by manual backward selection, where effect estimates did not change by ≥10%. A category called missing was created for a variable when ≥5% of the variable was missing. Categories of all variables can be seen in **Table 1**.

To address the potential interference of properties of antioxidants with conventional cancer therapies such as chemotherapy and radiation therapy, analyses evaluating the associations between postdiagnosis antioxidant supplement use and breast cancer prognosis were conducted within women who received cancer therapy (chemo- and/or radiation therapy) ($n = 1940$), women who underwent chemotherapy ($n = 1018$), and women who underwent radiation therapy ($n = 1776$). The HRs for overall mortality, breast cancer mortality, and recurrence-free survival with concurrent and nonconcurrent use were calculated; the group of women who received cancer therapy (chemo- or radiation therapy) but reported no postdiagnosis antioxidant use served as reference.

Possible effect modification of the associations of postdiagnosis supplement use with overall mortality, breast cancer mortality, and recurrence-free survival by chemotherapy, radiation therapy, menopausal hormone therapy use, smoking status, and prediagnosis supplement use was examined by including the interaction term of the main exposure and the potential modifier into the models (25). Because there were only a few current smokers at the first follow-up, they were grouped together with former smokers as smokers in order to achieve adequate power for the subsequent stratified analysis. As a sensitivity analysis, all analyses were repeated for all 3 outcomes for women diagnosed with an invasive breast tumor (excluding women with in situ tumors). Also as a sensitivity analysis, all analyses were repeated for all 3 outcomes excluding women who developed a recurrence (ipsilateral, local/regional, distant, and metastatic recurrence or a second tumor) by the first follow-up interview.

All tests of statistical significance were 2-sided and the significance level was set to 0.05. Analyses were conducted with the use of the SAS statistical software package (version 9.4).

Results

After applying exclusion criteria, 2223 women were eligible for analyses examining postdiagnosis supplement use and breast cancer prognosis (Figure 1). Median age at breast cancer diagnosis was 62 y. Postdiagnosis supplement use was ascertained at the first follow-up interview, conducted a median of 5.8 y after breast cancer diagnosis (min–max 3.8–8.6 y). By 30 June 2015, which was a median of 6.0 y (min–max 0.5–6.2 y) after the first follow-up interview and a median of 11.6 y after diagnosis (min–max 4.5–14.5 y), 200 women (9%) developed a breast cancer recurrence ($n = 171$ of these occurred between the initial breast cancer diagnosis and the first follow-up interview), and 240 women (11%) died, 134 (6%) of them from breast cancer.

Eight hundred and seven women (36%) reported prediagnosis supplement use, 989 women (45%) reported postdiagnosis supplement use (i.e., was a user), and 878 women (40%) were currently using supplements at the first follow-up (current user). Changes in supplement use behavior pre- and postdiagnosis were observed for a substantial proportion of the population (37%): 506 women (23%) started using supplements only after being diagnosed with breast cancer, and 324 (15%) stopped using supplements after being diagnosed with breast cancer. The most frequently used supplements were antioxidants (21% postdiagnosis users) followed by magnesium (18%) and calcium (17%). In order to ensure adequate statistical power for our survival analyses, use of different antioxidants was combined into 1 antioxidant variable. In total, 457 women used antioxidants. The relative proportions of antioxidants used were: selenium (40.5%), multivitamins (36.3%), zinc (30.4%), vitamin C (16.2%), vitamin E (16.2%), and vitamin A (3.1%).

Compared with nonusers, users were more likely to use supplements prediagnosis and use menopausal hormone therapy at diagnosis. Users were better educated, had lower BMI, and were more likely to have their tumors detected by routine investigation compared with nonusers. In addition, a higher proportion of users also had cardiovascular disease (Table 1).

There was no violation of the proportional hazard assumption upon visual examination of potential time-dependent covariates on the risk of overall mortality, breast cancer mortality, and recurrence-free survival. Postdiagnosis use of any supplement was not associated with overall mortality, breast cancer mortality, nor recurrence-free survival. After multiple covariate adjustment, there was a tendency for increased risk of breast cancer mortality with postdiagnosis use (HR: 1.64; 95% CI: 1.07, 2.50) and current use (HR: 1.59; 95% CI: 1.00, 2.55) of antioxidants (within the 6 mo before the first follow-up interview) compared with no use of antioxidants postdiagnosis (**Table 2**).

There were 398 women (20%) who received one or both of chemotherapy and radiation therapy and were also postdiagnosis antioxidant users—167 of these women (9% of those who received chemotherapy and/or radiation therapy) were concurrent users. Compared with women who did not use antioxidants postdiagnosis, concurrent users had a significantly higher risk of overall mortality (HR: 1.64; 95% CI: 1.01, 2.66) and worsened recurrence-free survival (HR: 1.84; 95% CI: 1.26, 2.68). There was also a tendency for increased breast cancer mortality in concurrent users of antioxidants compared with women who did not use antioxidants (HR: 1.80; 95% CI: 0.97, 3.35). In contrast, nonconcurrent use was not associated with breast cancer prognosis (**Table 3**).

Twenty-two percent of women who received chemotherapy used antioxidants postdiagnosis ($n = 221$), and 7% of these women ($n = 70$) used antioxidants postdiagnosis while on a chemotherapy regimen (concurrent users). Twenty-one percent of women who received radiation therapy ($n = 365$) used antioxidants postdiagnosis, and 9% of these women ($n = 156$) used antioxidants postdiagnosis while on a radiation therapy reg-

TABLE 1 Characteristics of 2223 breast cancer patients overall and according to postdiagnosis dietary supplement use[1]

	Postdiagnosis dietary supplement use			
	Total $n = 2223$	Nonusers (%) $n = 1234$ (55.5)	Users (%) $n = 989$ (44.5)	P
Age at diagnosis, y	62.0 (58.0–66.0)[2]	62.0 (58.0–66.0)	62.0 (58.0–66.0)	0.42
BMI at first follow-up, kg/m^2	25.3 (22.9–28.3)	25.5 (23.2–28.6)	25.0 (22.7–28.0)	<0.001
Smoking status, *n* (%)				0.45
Never smoker	1196 (53.8)	659 (53.4)	537 (54.3)	
Former smoker	819 (36.8)	451 (36.5)	368 (37.2)	
Current smoker	208 (9.4)	124 (10.0)	84 (8.5)	
Alcohol intake, *n* (%)				0.10
0–0.5 g/d	1024 (46.1)	589 (47.7)	435 (44.0)	
0.5–6.0 g/d	670 (30.1)	370 (30.0)	300 (30.3)	
6.0–12.0 g/d	198 (8.9)	107 (8.7)	91 (9.2)	
>12.0 g/d	324 (14.6)	161 (13.0)	163 (16.5)	
Missing	7 (0.3)	7 (0.6)	0 (0.0)	
Education, *n* (%)				<0.001
Less than high/middle school	1244 (56.0)	740 (60.0)	504 (51.0)	
High/middle school graduate	629 (28.3)	330 (26.7)	299 (30.2)	
College or university graduate	350 (15.7)	164 (13.3)	186 (18.8)	
Total physical activity, MET h/wk	40.0 (24.0–66.5)	40.0 (23.4–65.0)	40.0 (24.0–70.0)	0.16
Menopausal hormone use, *n* (%)				0.03
No current use at diagnosis	1133 (51.0)	655 (53.1)	478 (48.3)	
Current use at diagnosis	1076 (48.4)	571 (46.3)	505 (51.1)	
Missing	14 (0.6)	8 (0.6)	6 (0.6)	
Prediagnosis supplement use, *n* (%)				<0.001
No use	1416 (63.7)	910 (73.7)	506 (51.2)	
Use	807 (36.3)	324 (26.3)	483 (48.8)	
Tumor type, *n* (%)				0.77
Not invasive	129 (5.8)	70 (5.7)	59 (6.0)	
Invasive	2094 (94.2)	1164 (94.3)	930 (94.0)	
Tumor grade, *n* (%)				0.64
Low	435 (19.6)	238 (19.3)	197 (19.9)	
Moderate	1095 (49.3)	600 (48.6)	495 (50.1)	
High	484 (21.8)	275 (22.3)	209 (21.1)	
Neoadjuvant chemotherapy-treated carcinoma	71 (3.2)	45 (3.6)	26 (2.6)	
In situ	129 (5.8)	70 (5.7)	59 (6.0)	
Missing	9 (0.4)	6 (0.5)	3 (0.3)	
Tumor size, *n* (%)				0.47
≤2 cm	1252 (56.3)	676 (54.8)	576 (58.2)	
2–5 cm	686 (30.9)	393 (31.8)	293 (29.6)	
>5 cm	53 (2.4)	32 (2.6)	21 (2.1)	
Growth into chest wall/skin	29 (1.3)	15 (1.2)	14 (1.4)	
Neoadjuvant chemotherapy-treated carcinoma	71 (3.2)	45 (3.6)	26 (2.6)	
In situ	129 (5.8)	70 (5.7)	59 (6.0)	
Missing	3 (0.1)	3 (0.2)	0 (0.0)	
Number of positive lymph nodes, *n* (%)				0.55
0	1435 (64.6)	795 (64.4)	640 (64.7)	
1–3	438 (19.7)	234 (19.0)	204 (20.6)	
4–9	105 (4.7)	62 (5.0)	43 (4.3)	
≥10	45 (2.0)	28 (2.3)	17 (1.7)	
Neoadjuvant chemotherapy-treated carcinoma	71 (3.2)	45 (3.6)	26 (2.6)	
In situ	129 (5.8)	70 (5.7)	59 (6.0)	
Hormone receptor status, *n* (%)				0.73
ER- and PR-positive	1349 (60.7)	746 (60.5)	603 (61.0)	
ER- or PR-positive	373 (16.8)	209 (16.9)	164 (16.6)	
ER- and PR-negative	301 (13.5)	164 (13.3)	137 (13.9)	
Neoadjuvant chemotherapy-treated carcinoma	71 (3.2)	45 (3.6)	26 (2.6)	
In situ	129 (5.8)	70 (5.7)	59 (6.0)	
Her2 status, *n* (%)				0.44
Her2 positive	343 (15.4)	196 (15.9)	147 (14.9)	
Her2 negative	1532 (68.9)	837 (67.8)	695 (70.3)	
Neoadjuvant chemotherapy-treated carcinoma	71 (3.2)	45 (3.6)	26 (2.6)	
In situ	129 (5.8)	70 (5.7)	59 (6.0)	
Missing	148 (6.7)	86 (7.0)	62 (6.3)	

(*Continued*)

TABLE 1 (*Continued*)

	Postdiagnosis dietary supplement use			
	Total $n = 2223$	Nonusers (%) $n = 1234$ (55.5)	Users (%) $n = 989$ (44.5)	P
Type of surgery, *n* (%)				0.72
Mastectomy	581 (26.1)	319 (25.9)	262 (26.5)	
Breast-conserving therapy	1639 (73.7)	914 (74.1)	725 (73.3)	
Missing	3 (0.1)	1 (0.1)	2 (0.2)	
Mode of tumor detection, *n* (%)				0.005
Self-detected by palpation/secretion/pain	1108 (49.8)	648 (52.5)	460 (46.5)	
Routine examination, mammography, ultrasound	1109 (49.9)	583 (47.2)	526 (53.2)	
Missing	6 (0.3)	3 (0.2)	3 (0.3)	
Chemotherapy, *n* (%)	1018 (45.8)	574 (46.5)	444 (44.9)	0.46
Radiation therapy, *n* (%)	1776 (79.9)	1000 (81.0)	776 (78.5)	0.18
Hormone therapy, *n* (%)	1794 (80.7)	992 (80.4)	802 (81.1)	0.96
Diabetes, *n* (%)	197 (8.9)	119 (9.6)	78 (7.9)	0.15
Cardiovascular disease, *n* (%)	1066 (48.0)	558 (45.2)	508 (51.4)	0.003

[1]Differences in patient characteristics between users and nonusers tested by 2-sample *t* test for continuous variables and logistic regression for categoric variables ($P < 0.05$ for statistical significance). ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MET, metabolic equivalent; PR, progesterone receptor.

[2]Median; IQR in parentheses (all such values).

imen (concurrent users). In women who received chemotherapy, concurrent use of antioxidants was associated with a significantly worsened recurrence-free survival (HR: 2.24; 95% CI: 1.39, 3.63) and nonsignificantly increased total mortality and breast cancer mortality (HR: 1.80; 95% CI: 0.96, 3.40 and HR: 1.99; 95% CI: 0.94, 4.20, respectively) compared with no use of antioxidants. There was no association between nonconcurrent use with chemotherapy and prognosis. Among women who received radiation therapy, concurrent use was associated with significantly increased overall mortality (HR: 1.70; 95% CI: 1.01, 2.83) and significantly decreased recurrence-free survival (HR: 1.63; 95% CI: 1.07, 2.48). Both nonconcurrent use and concurrent use of antioxidants in women who underwent radiation therapy were associated with an increased risk of breast cancer mortality (HR: 1.76; 95% CI: 1.04, 3.00 and HR: 1.73; 95% CI: 0.87, 3.44, respectively); however, the association was significant only for nonconcurrent use (Table 3). There were no women who underwent chemotherapy and radiation therapy simultaneously.

There was no effect measure modification by smoking status, chemotherapy, radiation therapy, menopausal hormone use, prediagnosis supplement use, or tumor invasiveness in the relations between postdiagnosis supplement use and breast cancer prognosis. In addition, sensitivity analyses showed no change in risk estimates for all 3 outcomes when women with in situ tumors and women with recurrences before first follow-up were excluded.

Discussion

In the analysis of 2223 postmenopausal breast cancer survivors in the MARIE study, we found that whereas postdiagnosis use of any supplements was not associated with overall mortality, breast cancer mortality, or recurrence-free survival, concurrent antioxidant use during conventional cancer therapy (chemotherapy or radiation therapy) increased risks significantly for overall mortality and breast cancer recurrence. In women who received radiotherapy, nonconcurrent antioxidant use was associated with increased risk of breast cancer mortality.

In this patient series, postdiagnosis supplement use (45%) was higher than prediagnosis supplement use (36%) and similar to that reported by breast cancer patients in Europe (5), but lower than reported use in studies from the United States (~80%) (15, 26). As we hypothesized, prevalence of prediagnosis supplement use among breast-cancer survivors in our study was higher than in the general female population in Germany (31%) (6), which could in part be attributed to our older study population, because older persons tend to use supplements more frequently (6, 27). In line with other studies, postdiagnosis supplement use was more prevalent among women who were better educated, and diagnosed with routine examination or imaging (5, 26).

Antioxidants, magnesium, and calcium were the most widely used postdiagnosis supplements in our study, which is in agreement with another study conducted among older persons in southern Germany (27). Magnesium and calcium are essential to skeleton and muscle function (28, 29), thus it seems reasonable that postmenopausal women would use these supplements to maintain bone health (28, 30). Overall, we found that postdiagnosis calcium and/or magnesium use was not associated with prognosis. Conversely, dietary (not supplemental) calcium and magnesium have previously been shown to improve survival in breast cancer patients in Taiwan (31) and western New York in the United States (32). The study carried out in Taiwan was an ecologic study, in which concentrations of calcium and magnesium in drinking water in relation to breast cancer mortality were examined (31). The study carried out in western New York in the United States looked at both dietary and total intakes of calcium and magnesium, and found only dietary magnesium intake but not total magnesium intake to be associated with better survival (32). The difference between our results and the results from these studies could stem from supplement compared with dietary intake and from timing and frequency of exposure.

TABLE 2 Associations of postdiagnosis dietary supplement use with total mortality, breast cancer mortality, and recurrence-free survival for the whole cohort ($n = 2223$)[1]

		Total mortality					Breast cancer mortality					Recurrence-free survival				
			HR (95% CI)					HR (95% CI)					HR (95% CI)			
Postdiagnosis dietary supplement use	*n*	Events, *n*	Model 1[2]	*P*	Model 2[3]	*P*	Events, *n*	Model 1[2]	*P*	Model 2[3]	*P*	Events, *n*	Model 1[2]	*P*	Model 2[3]	*P*
Any type																
No use	1234	136	1.00		1.00		77	1.00		1.00		210	1.00		1.00	
Use	989	104	0.96 (0.74, 1.24)	0.76	1.13 (0.86, 1.50)	0.38	57	0.97 (0.68, 1.37)	0.85	1.11 (0.76, 1.63)	0.58	164	1.00 (0.81, 1.23)	0.97	1.10 (0.88, 1.38)	0.41
Current use	878	88	0.91 (0.69, 1.19)	0.49	1.11 (0.83, 1.49)	0.49	46	0.88 (0.61, 1.28)	0.51	1.04 (0.70, 1.55)	0.84	141	0.97 (0.78, 1.20)	0.77	1.09 (0.86, 1.38)	0.46
Magnesium																
No use	1818	197	1.00		1.00		113	1.00		1.00		313	1.00		1.00	
Use	405	43	1.02 (0.73, 1.42)	0.91	1.11 (0.78, 1.57)	0.56	21	0.97 (0.60, 1.55)	0.89	1.09 (0.67, 1.78)	0.73	61	0.93 (0.70, 1.23)	0.62	0.99 (0.74, 1.33)	0.95
Current use	376	38	0.97 (0.68, 1.38)	0.87	1.08 (0.75, 1.56)	0.67	20	1.00 (0.62, 1.62)	0.99	1.15 (0.69, 1.89)	0.60	54	0.89 (0.66, 1.19)	0.44	0.96 (0.71, 1.30)	0.80
Calcium																
No use	1853	206	1.00		1.00		117	1.00		1.00		320	1.00		1.00	
Use	369	33	0.79 (0.54, 1.14)	0.79	0.90 (0.61, 1.33)	0.61	17	0.74 (0.44, 1.24)	0.25	0.84 (0.49, 1.45)	0.54	53	0.87 (0.65, 1.16)	0.33	0.92 (0.67, 1.25)	0.92
Current use	355	31	0.76 (0.52, 1.12)	0.17	0.90 (0.61, 1.34)	0.61	16	0.72 (0.42, 1.22)	0.22	0.86 (0.50, 1.48)	0.59	50	0.85 (0.63, 1.15)	0.30	0.92 (0.67, 1.26)	0.59
Magnesium or calcium																
No use	1609	178	1.00		1.00		103	1.00		1.00		280	1.00		1.00	
Use	614	62	0.92 (0.69, 1.24)	0.59	1.02 (0.75, 1.39)	0.90	31	0.86 (0.57, 1.29)	0.45	0.93 (0.60, 1.42)	0.73	94	0.92 (0.73, 1.17)	0.49	0.97 (0.75, 1.24)	0.79
Current use	582	56	0.88 (0.65, 1.19)	0.40	1.01 (0.73, 1.38)	0.97	29	0.86 (0.56, 1.29)	0.45	0.96 (0.62, 1.48)	0.84	86	0.89 (0.70, 1.14)	0.37	0.96 (0.74, 1.24)	0.73
Antioxidant[4]																
No use	1765	188	1.00		1.00		98	1.00		1.00		286	1.00		1.00	
Use	457	51	1.02 (0.75, 1.39)	0.91	1.20 (0.86, 1.68)	0.29	36	1.34 (0.91, 1.97)	0.14	1.64 (1.07, 2.50)	0.02	87	1.14 (0.89, 1.45)	0.31	1.26 (0.97, 1.64)	0.09
Current use	367	39	0.97 (0.69, 1.37)	0.86	1.17 (0.80, 1.70)	0.42	27	1.27 (0.83, 1.96)	0.27	1.59 (1.00, 2.55)	0.05	67	1.12 (0.85, 1.47)	0.41	1.27 (0.95, 1.70)	0.11

[1]Delayed-entry Cox proportional hazard models, based on time since the first follow-up interview in 2009 until event of interest/censoring, were used to estimate HRs and corresponding 95% CIs.

[2]Model 1 adjusted for age at diagnosis, tumor size, nodal status, and tumor grade.

[3]Model 2 adjusted for model 1 covariates and BMI, smoking status, alcohol intake, education, total physical activity, prediagnosis supplement use, menopausal hormone use, tumor hormone receptor status, mode of detection, chemotherapy, radiation therapy, hormone therapy, diabetes, and cardiovascular disease.

[4]Includes vitamin C, vitamin E, vitamin A, selenium, zinc, or multivitamin supplements.

TABLE 3 Associations of concurrent and nonconcurrent postdiagnosis antioxidant use with total mortality, breast cancer mortality, and recurrence-free survival in women who received chemotherapy and/or radiation therapy[1]

		Total mortality					Breast cancer mortality					Recurrence-free survival				
			HR (95% CI)					HR (95% CI)					HR (95% CI)			
Antioxidant use status[2]	*n*	Events, *n*	Model 1[3]	*P*	Model 2[4]	*P*	Events, *n*	Model 1[3]	*P*	Model 2[4]	*P*	Events, *n*	Model 1[3]	*P*	Model 2[4]	*P*
Received chemotherapy and/or radiation therapy	1940															
No use	1542	170	1.00		1.00		94	1.00		1.00		252	1.00		1.00	
Concurrent use	167	24	1.20 (0.78, 1.85)	0.41	1.64 (1.01, 2.66)	0.04	16	1.36 (0.79, 2.33)	0.26	1.80 (0.97, 3.35)	0.06	39	1.40 (1.00, 1.98)	0.05	1.84 (1.26, 2.68)	0.002
Nonconcurrent use	231	23	0.90 (0.58, 1.40)	0.65	1.00 (0.63, 1.60)	0.99	18	1.27 (0.76, 2.12)	0.36	1.34 (0.78, 2.31)	0.30	39	0.94 (0.67, 1.34)	0.74	0.99 (0.68, 1.43)	0.94
Received chemotherapy	1018															
No use	797	116	1.00		1.00		98	1.00		1.00		286	1.00		1.00	
Concurrent use	70	14	1.33 (0.76, 2.34)	0.32	1.80 (0.96, 3.40)	0.07	11	1.53 (0.80, 2.91)	0.20	1.99 (0.94, 4.20)	0.07	25	1.71 (1.12, 2.63)	0.01	2.24 (1.39, 3.63)	0.001
Nonconcurrent use	151	20	0.88 (0.55, 1.42)	0.61	0.96 (0.57, 1.60)	0.86	25	0.94 (0.53, 1.67)	0.83	1.00 (0.54, 1.85)	1.00	62	0.83 (0.56, 1.24)	0.37	0.86 (0.56, 1.31)	0.47
Received radiation therapy	1776															
No use	1411	149	1.00		1.00		81	1.00		1.00		222	1.00		1.00	
Concurrent use	156	21	1.18 (0.74, 1.87)	0.49	1.70 (1.01, 2.83)	0.04	13	1.26 (0.70, 2.27)	0.45	1.73 (0.87, 3.44)	0.12	31	1.24 (0.85, 1.82)	0.27	1.63 (1.07, 2.48)	0.02
Nonconcurrent use	209	25	1.15 (0.75, 1.75)	0.53	1.32 (0.84, 2.07)	0.24	20	1.66 (1.01, 2.72)	0.05	1.76 (1.04, 3.00)	0.04	41	1.18 (0.84, 1.66)	0.34	1.25 (0.87, 1.79)	0.23

[1] Delayed-entry Cox proportional hazard models, based on time since the first follow-up interview in 2009 until event of interest/censoring, were used to estimate HRs and corresponding 95% CIs.

[2] Includes vitamin C, vitamin E, vitamin A, selenium, zinc, or multivitamin supplements.

[3] Adjusted for age at diagnosis, tumor size, nodal status, and tumor grade.

[4] Adjusted for model 1 covariates and BMI, smoking status, alcohol intake, education, total physical activity, prediagnosis supplement use, menopausal hormone use, tumor hormone receptor status, mode of detection, hormone therapy, diabetes, cardiovascular disease, chemotherapy (in women who received radiation therapy), and radiotherapy (in women who received chemotherapy).

We did not find an association between postdiagnosis antioxidant use and overall mortality, breast cancer mortality, or recurrence-free survival. Antioxidant use in cancer survivors, particularly breast cancer survivors, is very popular (3–5). In this study, 20% of patients regularly used ≥1 type of antioxidant postdiagnosis. Although cancer survivors often use antioxidants hoping to lessen the toxic effects of chemotherapy and radiation therapy (16), whether antioxidant use is beneficial for breast cancer survivors is still unclear (14, 15, 33, 34).

Our findings that concurrent use of antioxidants with conventional cancer therapy (chemotherapy or radiation therapy) increased overall mortality and worsened recurrence-free survival, and to a lesser extent increased breast cancer mortality, are in line with that of a worsened survival associated with concurrent antioxidant use with standard cancer therapy, reported by a historical cohort study in breast cancer survivors (35). Another patient cohort study found no benefit of postdiagnosis antioxidant use during chemotherapy or radiation therapy (36). In that study, Chinese women aged 20–75 y living in Shanghai were followed for a mean of 4.1 y, and postdiagnosis use of a vitamin was defined by use for ≥3 mo. Ethnicity of patients, wider age at diagnosis (including pre- and perimenopausal women), shorter follow-up time, and a shorter duration of use for defining vitamin use could partly explain the divergence between their results and our own. One mechanism by which antioxidants may offset the apoptotic properties of anticancer drugs is by reducing the effects of reactive oxygen species produced by therapeutic agents (37). The findings from these observational cohort studies, in combination with our own, as well as a review of randomized controlled trials investigating effects of chemotherapy and radiation therapy with concurrent antioxidant use on prognosis of different cancers (18), lend support to the case of discouraging use of antioxidants during chemotherapy and radiation therapy (16, 18).

Given that both the use of supplements (38) and the number of breast cancer survivors (39) are increasing, and the current scarce literature on supplement use and breast cancer prognosis, our study contributes several noteworthy findings. There are several strengths to the current study. The relatively long follow-up time and large population-based study sample enabled us to analytically examine associations between supplement use and long-term breast cancer prognosis with enough statistical power. We collected in-depth information on dietary supplement use at 2 different time points, making possible the examination of supplement use patterns, given that supplement use is a modifiable behavior. This information enabled us to later study the influence of consistent supplement use (pre- and postdiagnosis) in relation to breast cancer prognosis. We also had comprehensive clinical information such as tumor size, nodal involvement, metastases, and grade as well as detailed information on timing and duration of cancer therapies. A wide range of demographic and lifestyle factors, ascertained through professional interviews and which could confound and modify our associations of interest, were assessed and carefully accounted for in the analyses. In addition, we restricted our analyses to postmenopausal women, because menopausal status can modify the associations between lifestyle and breast cancer prognosis (39). We had information about timing and duration of supplement use, which allowed us to investigate concurrent antioxidant use and chemo- and/or radiation therapy.

When interpreting our results, there are some caveats to consider. In analyses examining antioxidant use during chemotherapy or radiation therapy, there were few events, specifically deaths from breast cancer, and results warrant replication in larger datasets with more events of interest. Also, unlike studies in the United States (15, 26), antioxidant use (20% of all participants) is uncommon in Germany. In order to achieve statistical power, it was necessary to combine the antioxidants together rather than examine their associations with prognosis individually even though dietary antioxidants encompass a myriad of chemical classes such as carotenoids and polyphenols that are vital for a multitude of biological reactions. We were moreover unable to ascertain frequency and dose of supplements used, so dose-response relations between individual supplements and prognosis could not be studied. Information on postdiagnosis dietary intake of antioxidants, which, alone or in combination with supplemental antioxidants during chemotherapy or radiation therapy, could affect breast cancer prognosis, was also not collected. Postdiagnosis supplement use for the time period after breast cancer diagnosis was collected ∼5 y after diagnosis, so there is potential for recall bias, which could result in both underestimation and overestimation of supplement use. This misclassification is likely to have been nondifferential, and would have resulted in attenuated associations with prognosis (40).

In conclusion, we observed a poorer breast cancer prognosis among postmenopausal breast cancer survivors who used antioxidants concurrently during chemotherapy and/or radiation therapy. Our data do not support an overall association of postdiagnosis supplement use with prognosis in postmenopausal breast cancer survivors. Our results, together with other clinical and experimental evidence, suggest that during breast cancer treatment antioxidants should potentially be used with caution.

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