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Original Article

Associations of intakes of magnesium and calcium and survival among women with breast cancer: results from Western New York Exposures and Breast Cancer (WEB) Study

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Abstract: Magnesium (Mg) and calcium (Ca) antagonizes each other in (re) absorption, cell cycle regulation, inflammation, and many other physiologic activities. However, few studies have investigated the association between magnesium and calcium intakes and breast cancer survival, and the interaction between calcium and magnesium intake. In a cohort of 1,170 women with primary, incident, and histologically confirmed breast cancer from Western New York State, we examined the relationship between intakes of these two minerals and survival. Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Mean follow-up time was 87.4 months after breast cancer diagnosis; there were 170 deaths identified. After adjustment for known prognostic factors, and intakes of energy, total vitamin D and total calcium, higher dietary intake of magnesium was inversely associated with risk of all-cause mortality (HR = 0.50, 95% CI, 0.28-0.90 for highest *vs.* lowest tertile; *p* trend = 0.02). Likewise, a marginal association was found for total Magnesium intake from foods and supplements combined (HR = 0.58, 95% CI, 0.31-1.08; *p* trend = 0.09). The inverse association of higher total magnesium intake with all-cause mortality was primarily presented among postmenopausal women and was stronger among women who had a high Ca:Mg intake ratio (>2.59). There were no clear associations for prognosis with intake of calcium. We found that magnesium intake alone may improve overall survival following breast cancer, and the association may be stronger among those with high Ca:Mg intake ratio.

Keywords: Magnesium, calcium, breast cancer survival, epidemiology

Introduction

Breast cancer survival has been improved greatly due to improvements in treatment and early diagnosis with a 5-year relative survival rate of 89% for US women, resulting in approximately 2.9 million US women living with a history of breast cancer in 2012 [1]. Although many prognostic factors of breast cancer, including tumor characteristics, have been established, our understanding of modifiable lifestyle factors, such as dietary factors in relation to breast cancer survival after cancer diagnosis is still evolving.

Magnesium (Mg), the second most abundant intracellular cation in the body, plays essential roles in more than 300 biological reactions, including cell proliferation, inflammation, energy production, and nucleic acid metabolism [2-4]. Food sources rich in Mg include green vegetables, whole seeds, unrefined whole grains, beans, peas, and nuts, while refined foods are poor sources of Mg [2]. Although not entirely consistent, some studies have linked low intakes of Mg to risk of metabolic syndrome [5], type 2 diabetes [6, 7], coronary heart disease [8, 9], as well as the risk of colorectal cancer [10, 11] and adenoma [12]. Based on the 2007-

2008 National Health and Nutritional Examination Survey (NHANES), it was estimated that around 70% of US adults has dietary Mg intake below Recommended Dietary Allowance (RDA) [13-15].

As the most abundant divalent cation in the body, calcium (Ca) plays a key role in a variety of cellular activities including cell proliferation, differentiation and apoptosis [16]. Ca can directly or indirectly compete with Mg for (re) absorption in intestine and kidney [17, 18]. Ionized magnesium (Mg^{2+}) and calcium (Ca^{2+}) also antagonize to each other in many physiological activities [18]. Studies have shown the importance of the balance between Mg and Ca in relation to physiological functions of these micronutrients. Rats fed with a low Mg and an adequate Ca (thus, a high Ca:Mg) diet exhibited an increase in Ca absorption, retention, or balance [19-21]. In humans, a high Ca and low or insufficient Mg diet showed to interfere with both Mg and Ca absorption in postmenopausal women, resulting increased Ca retention and depressed absorption of Mg [2, 22].

Few studies have evaluated intake of micronutrients including Mg and Ca in relation to breast cancer survival and results have been inconsistent [23-26]. Moreover, results from randomized trials showed little evidence of a protective effect of calcium and vitamin D supplementation on breast cancer risk or total cancer death [27, 28]. However, none of these previous breast cancer studies considered the potential antagonism between Mg and Ca. Previous studies conducted in US populations with high Ca:Mg intake ratio found that the associations between Ca and/or Mg and risk of colorectal neoplasia were modified by the Ca:Mg intake ratio [12, 29]. Further, a recent study conducted in a Chinese population with low intake ratio of Ca:Mg observed modifying effects of the Ca:Mg intake ratio on the association between Ca and Mg intakes and total mortality and cardiovascular disease mortality [30]. In the US, the ratio of Ca:Mg intake has substantially increased over the past 30 years, particularly for older women [13]. Therefore, in this study, we investigated the relationship between magnesium and calcium intakes and survival following diagnosis of breast cancer, and tested for possible effect modification by the Ca:Mg intake ratio using data from a cohort of breast cancer patients recruited into the Western New York Exposures and Breast Cancer (WEB) Study.

Materials and methods

Study population

Detailed study methods have been published previously [31, 32]. In brief, the population-based WEB Study included 1,170 women aged 35-79 years with incident, primary, histologically confirmed breast cancer. Cases were interviewed within one year of diagnosis; most (64%) were interviewed within 3-6 months following the diagnosis. All participants provided informed consent, and the study protocol was approved by the Institutional Review Boards of the University at Buffalo and all participating institutions.

Extensive interviewer-administrated and self-administered questionnaires were completed by participants, including queries regarding demographic factors, medical history, menstrual and reproductive history, tobacco and alcohol use, physical activity, and other breast cancer risk factors. Dietary daily intake in the year 12-24 months prior to diagnosis was assessed using a modified version of the Health Habits and History food frequency questionnaire (FFQ) [33], described in detail elsewhere [31]. Briefly, dietary nutrient intakes were calculated from the FFQ using the DietSys (version 3.7) nutrient analysis software and US Department of Agriculture food composition tables. Supplement doses and intakes of magnesium, calcium and vitamin D from multivitamins and other types of supplements were obtained from the response to a dietary supplement questionnaire and summed with report of dietary intake to calculate total intakes. BMI was calculated as body weight in kilograms divided by the square of height in meters (weight (kg)/height $(m)^2$).

Vital status through the end of 2006 was determined through matching of participant records with National Death Index data. Survival time was calculated as the time from cancer diagnosis to the study endpoints, censoring at the date of December 31, 2006 or date of death. All-cause mortality was defined as any death, and underlying causes of death were broadly classified as breast cancer, other cancer, cardiovascular diseases, and all others.

Table 1. Descriptive characteristics of breast cancer cases by vital status, WEB Study

	Alives as of December 2006 (n = 1000)	Died as of December 2006 (n = 170)
Mean (SD)		
Age at diagnosis (years)	57.0 (10.9)	59.7 (12.3)**
BMI (kg/m^2)	28.3 (6.2)	29.5 (6.7)*
Daily dietary intake		
Energy (Kcal)	1516.6 (589.4)	1622.8 (734.0)*
Fiber (g)	12.1 (5.7)	12.0 (5.3)
Statured fat (g)	22.5 (12.1)	25.0 (16.4)
Folate (μg)	287.6 (165.1)	285.0 (142.1)
Vitamin E (mg)	9.6 (6.8)	9.5 (5.5)
Calcium (mg)	768.6 (388.0)	797.9 (420.8)
Magnesium (mg)	241.7 (92.3)	241.2 (93.5)
Daily intake		
Total vitamin D (IU)	395.1 (248.5)	387.5 (251.9)
Total Calcium (mg)	1174.7 (786.2)	1138.9 (838.8)
Total Magnesium (mg)	296.5 (123.9)	294.6 (121.4)
Number (%)		
Race		
Caucasian	928 (92.8)	149 (87.6)*
Other	72 (7.2)	21 (12.4)
Education (years)		
<12	76 (7.6)	21 (12.4)**
12	369 (36.9)	76 (44.7)
>12	555 (55.5)	73 (42.9)
Menopausal status		
Premenopausal	281 (28.1)	45 (26.5)
Postmenopausal	719 (71.9)	125 (73.5)
TNM		
0	136 (13.6)	10 (5.9)**
I	440 (44.0)	46 (27.1)
II_a	187 (18.7)	25 (14.7)
II_b	74 (7.4)	30 (17.6)
III-IV	31 (3.1)	30 (17.6)
Unknown	132 (13.2)	29 (17.1)
Radiotherapy		
Received or planned	656 (67.8)	93 (59.2)*
No	312 (32.2)	64 (40.8)
Chemotherapy		
Yes	348 (35.7)	92 (55.4)**
No	627 (64.3)	74 (44.6)
Tamoxifen therapy		
Ever	565 (59.2)	74 (48.1)**
No	390 (40.8)	80 (51.9)
ER status		
Positive	664 (66.4)	88 (51.8)**
Negative	245 (24.5)	70 (41.2)

Information on tumor size, histological grade, cancer stage (as measured by tumor-node-metastasis (TNM) stage), and cancer treatment was abstracted from medical records by trained research nurses using a standardized protocol. Estrogen receptor (ER)/progesterone receptor (PR) status was determined in tumor blocks by immunohistochemical analysis, described in detail elsewhere [32]. For patients for whom tumor blocks were unavailable or for whom hormone receptor status was unable to be determined (e.g., insufficient tumor tissue), status of those tumor features was obtained from hospital chart review. There were good agreements between our assessment and medical record assessment of ER/PR status [34].

Statistical analysis

The Cox proportional hazards regression model was utilized to examine the associations between intakes of Mg and Ca and the risk of all-cause and breast cancer-specific mortality. Dietary and total Mg and Ca intake were categorized into tertiles on the basis of intakes of the study population, using the lowest category as the reference. Tests for dose-response relationship over the categories of intake were estimated by fitting the models with exposure variables included as continuous variables. We considered as potential confounders in multivariable modeling known and suspected prognostic factors of breast cancer including age at diagnosis, race, education, BMI, regular physical activity, menopausal status, stage of breast cancer at diagnosis, ER status, cancer treatment (radiotherapy, chemotherapy, and hormonal therapy), as well as intakes of total energy and total vitamin D. PR status was highly correlated with ER status, we examined results with adjustment for both ER and PR; results were similar to those with adjustment for ER alone. Potential confounding effects from other dietary factors and prognostic factors of breast cancer, including HER2 status, *TP53* mutation status, alcohol drinking status, intakes of saturated fat, fiber, vita-

Unknown	91 (9.1)	12 (7.0)
PR status		
Positive	580 (58.0)	76 (44.7)**
Negative	311 (31.1)	81 (47.7)
Unknown	109 (10.9)	13 (7.6)

Data are shown as Means ± SD (all such continuous variables). TNM: tumor-node-metastasis; ER: estrogen receptor; PR: progesterone receptor. * $P<0.05$; **: $P\leq0.01$.

min E, folate, retinol equivalent, and zinc were also examined and no appreciable confounding was observed. BMI was classified into three categories: <25.0, 25.0-29.9, and ≥30.0, categories of normal, overweight, and obese, respectively.

Ca and Mg were further mutually adjusted to each other to assess the independent association of Mg and Ca, respectively. Further, we examined whether the Ca:Mg intake ratio modified the associations of Mg and Ca intake with mortality following breast cancer diagnosis. Our study population reported a very high Ca:Mg intake ratio. According to physiological range of the ratio and previous reports on the ratio in the US population [12, 29], the lowest quartile of the Ca:Mg intake ratio in our population was used as the cut-off point for stratifying high or low Ca:Mg intake in the analyses. However, we also examined associations stratified by the lowest tertile and the median of Ca:Mg intake based on the distribution in our population, similar results were obtained. Additional analyses stratified on menopausal status and ER status were conducted. Possible interactions between Mg, or Ca intake and other covariates of interest, including the Ca:Mg intake ratio, menopausal and ER status, were examined in the Cox regression model by evaluation of a multiplicative term. All statistical tests were based on two-sided probability. Statistical analyses were conducting using SAS, Version 9.3 (SAS Institute, Cary, NC).

Results

During the study period, 170 of the 1,170 patients died. Of those deaths, 100 were from breast cancer. Mean follow-up time was 87.4 months (standard deviation (SD): 20.8, range: 9.0-125.0 months). **Table 1** summarizes selected patient characteristics at time of questionnaire completion. Compared to women alive through 2006, those who died were slightly older and less likely to be Caucasian, less educated, had a higher BMI, higher total energy intake, higher TNM stage, less likely to have had radiotherapy, more likely to have had chemo treatment for the breast cancer, and to have a tumor that was ER^- or PR^-.

Associations of intakes of Mg and Ca with the risk of all-cause mortality are presented in **Table 2**. After adjustment for age at diagnosis, other known prognostic factors, and intakes of energy, total vitamin D and total Ca, patients with highest tertile of dietary Mg intake had significantly lower risk of all-cause mortality than those in the lowest tertile (HR = 0.50, 95% confidence interval (CI), 0.28-0.90; *p* trend = 0.02). When examining total intake of Mg, the inverse association was slightly attenuated (HR = 0.58, 95% CI, 0.31-1.08; *p* trend = 0.09). Neither dietary nor total intake of Ca was associated with risk of death from any cause.

For breast cancer-specific mortality, there was a suggestion of an inverse association for higher Mg intake; however, point estimates were weaker than those for all-cause mortality and results were not statistically significant (**Table 3**). On the other hand, higher intake of dietary or total Ca tended to be associated with increased risk of breast cancer-specific mortality. However, none of the associations were statistically significant, possibly due to smaller sample size for breast cancer-specific deaths. Similar association patterns for all-cause mortality and breast cancer specific mortality were observed when analyses were limited to those who did not take Ca and Mg supplements (data not shown).

We further conducted stratified analyses of total Mg and Ca intake by the ratio of Ca:Mg intake (data not shown). Among those with a high ratio of Ca:Mg intake (>2.59), compared to those with the lowest tertile intake, patients who consumed total Mg at the highest tertile had reduced risk of all-cause mortality (HR = 0.36, 95% CI, 0.17-0.77; *p* trend = 0.01). Among those with a low Ca:Mg intake ratio (≤ 2.59), the corresponding HR (95% CI) was 1.45 (0.31-6.89). Although the association pattern indicated an interaction, we did not observe a statistically significant interaction between Ca:Mg intake ratio and intake of total Mg in relation to all-cause mortality (*p* for interaction = 0.28). No

Table 2. All-cause mortality after diagnosis of breast cancer, by intakes of calcium and magnesium

	Deaths/ cohort	HR (95% CI)[a]	HR (95% CI)[b]
Dietary calcium intake (g/d)			
<558.27	59/417	1.0	1.0
558.27-858.12	54/376	1.11 (0.72-1.73)	1.14 (0.73-1.77)
≥858.13	57/376	0.77 (0.45-1.32)	0.84 (0.49-1.45)
P trend		0.43	0.55
Dietary magnesium intake (g/d)			
<193.64	66/417	1.0	1.0
193.64-268.14	52/376	0.77 (0.50-1.20)	0.77 (0.49-1.20)
≥268.15	52/376	0.51 (0.29-0.91)	0.50 (0.28-0.90)
P trend		0.02	0.02
Total calcium intake (g/d)			
<766.55	67/417	1.0	1.0
766.55-1338.07	56/377	0.73 (0.46-1.14)	0.76 (0.48-1.20)
≥1338.07	47/376	0.68 (0.40-1.14)	0.75 (0.44-1.29)
P trend		0.15	0.31
Total magnesium intake (g/d)			
<234.22	63/417	1.0	1.0
234.22-332.29	60/378	0.88 (0.56-1.38)	0.87 (0.55-1.38)
≥332.29	47/375	0.59 (0.32-1.08)	0.58 (0.31-1.08)
P trend		0.09	0.09

a: Adjusted for age at diagnosis (continuous variable), race (white, others), education (<12 yrs, 12 yrs, >12 yrs), BMI (<25, 25-29, ≥30), physical activity (<3, 3-6, >6 hours/ week), menopausal status, TNM (0, I, IIa, IIb, III-IV, unknown), radiotherapy (yes, no), chemotherapy (yes, no), tamoxifen therapy (yes, no), ER status (positive, negative, unknown), intakes of total energy and total vitamin D. b: The model was extra mutually adjusted for calcium and magnesium intakes.

significant association or interaction was found for total Ca intake in different groups of Ca:Mg intake. In the stratified analyses by menopausal status, we found the inverse association between intake of Mg and risk of all-cause mortality primarily limited to postmenopausal women (HR = 0.50, 95% CI, 0.23-1.08 for the highest *vs* the lowest tertile of intake, *p* for interaction <0.01) (data not shown). Total intake of Ca was not significantly associated with all-cause mortality in both pre- and postmenopausal women. The association between intakes of Mg and risk of all-cause mortality did not differ by ER^+ and ER^- status (data not shown). Again, no significant association or interaction was found for total Ca intake in either ER^+ or ER^- tumors.

Discussion

In this study of 1,170 patients with primary breast cancer, high intake of dietary and total Mg was independently associated with reduced risk of all-cause mortality. Moreover, we found that the inverse association of higher total Mg intake with all-cause mortality was primarily presented among postmenopausal women, and among women with a high ratio of Ca:Mg intake (>2.59), while the statistically significant interaction was only observed for menopausal status. On the other hand, dietary and total Ca intake was not significantly associated with all-cause mortality. There were no associations between Mg and Ca intakes and breast cancer-specific mortality in our study.

The association between dietary or total Mg intake and breast cancer prognosis has only been investigated in a few studies with inconsistent results. McEligot et al. [23] reported inverse associations between dietary Mg intake and risk of dying from any cause among postmenopausal breast cancer cases. A follow-up study of breast cancer patients from the Nurse's Health Study found a marginal association of dietary Mg intake with reduced risk of mortality [24]. However, results from the Women's Healthy Eating and Living (WHEL) Study showed no association between post-diagnostic total Mg intake and all-cause mortality among breast cancer survivors [25]. Possible explanations for the inconsistency in these previous studies include that Ca intake was not adjusted, and the potential modifying effect by Ca:Mg intake ratio and menopausal status was not considered.

It is possible that the beneficial effect of high Mg intake on all-cause mortality could be due to a beneficial effect of Mg on cardiovascular disease prognosis [8, 9]. However, it is unlikely

Table 3. Association between intakes of Ca and Mg and risk of breast cancer-specific mortality

	Deaths/ cohort	HR (95% CI)[a]	HR (95% CI)[b]
Dietary calcium intake (g/d)			
<558.27	28/417	1.0	1.0
558.27-858.12	32/376	1.49 (0.81-2.76)	1.56 (0.84-2.90)
≥858.13	40/376	1.13 (0.55-2.31)	1.31 (0.63-2.76)
P trend		0.77	0.48
Dietary magnesium intake (g/d)			
<193.64	33/417	1.0	1.0
193.64-268.14	32/376	1.08 (0.59-1.98)	1.02 (0.56-1.86)
≥268.15	35/376	0.76 (0.36-1.62)	0.70 (0.33-1.49)
P trend		0.46	0.35
Total calcium intake (g/d)			
<766.55	32/417	1.0	1.0
766.55-1338.07	36/377	1.00 (0.54-1.84)	1.11 (0.59-2.06)
≥1338.07	32/376	1.09 (0.54-2.17)	1.31 (0.64-2.68)
P trend		0.81	0.46
Total magnesium intake (g/d)			
<234.22	33/417	1.0	1.0
234.22-332.29	37/378	1.14 (0.62-2.07)	1.05 (0.57-1.93)
≥332.29	30/375	0.81 (0.37-1.79)	0.74 (0.33-1.64)
P trend		0.63	0.46

a: Adjusted for age at diagnosis (continuous variable), race (white, others), education (<12 yrs, 12 yrs, >12 yrs), BMI (<25, 25-29, ≥30), physical activity (<3, 3-6, >6 hours/ week), menopausal status, alcohol drinking (yes, no), TNM (0, I, IIa, IIb, III-IV, unknown), radiotherapy (yes, no), chemotherapy (yes, no), tamoxifen therapy (yes, no), ER status (positive, negative, unknown), intakes of total energy and total vitamin D. b: The model was extra mutually adjusted for calcium and magnesium intakes.

that this is the sole explanation because we also found non-significant inverse association between Mg intake and breast cancer-specific mortality. Mg may protect against breast cancer progression through its important role in maintaining genomic stability, regulation of cell differentiation, proliferation and apoptosis, and prevention of angiogenesis [3, 35]. Mg deficiency may affect the process of carcinogenesis by multiple pathways, including affecting oxidative stress and inducing immune-inflammatory response in the body [4, 35, 36]. *In vivo* studies have shown that mice with Lewis lung carcinoma and received Mg-deficient diet showed to have 60% inhibition of primary tumor growth, and had an increased metastatic potential compared to Mg-sufficient mice [37]. However, the effect of Mg may also be through its antagonistic effects against Ca in many physiologic processes [18, 36]. Recent human studies have shown that the imbalance between Ca and Mg intake may affect pathogenesis of cancers in the gut as well as cardiovascular disease mortality. In a study conducted in the US population, Dai et al. [12] reported that inverse associations between total intake of Mg or Ca and risk of colorectal adenoma were more significant among those with low Ca:Mg ratio (<2.78). In a subsequent study from a large-scale clinical trial, Ca supplementation reduced the risk of adenoma recurrence only among those with Ca:Mg ratio <2.62 [29]. In a very recent analyses of one prospective cohort study from Shanghai, a modification effect of Ca:Mg intake ratio was observed; total Mg intake was inversely associated with risk of total cancer mortality among women with a high Ca:Mg ratio (>1.7) [30]. Additionally, animal studies showed that mice with breast cancer who received balanced oral supplements of Mg and Ca in their drinking water (concentration of 2 mg/cc for Mg and 0.36 mg/cc for Ca) had significantly longer survival and had tolerance to larger tumor than those receiving Mg alone, Ca alone, or controls [38]. In our study, we found a stronger inverse association with total Mg intake among breast cancer cases with a high Ca:Mg intake (>2.59), although the interaction was not statistically significant. Studies with a larger sample size, particularly for those with a low Ca:Mg intake ratio, are warranted to replicate our findings and to further assess the modification effect of Ca:Mg intake ratio on the associations of Mg and Ca intake with breast cancer survival.

In the current study, we observed a stronger inverse association between total Mg intake and overall mortality in postmenopausal than in premenopausal women. Several previous

studies have reported how sexual hormones such as estrogen and progesterone levels modulate Mg homeostasis in women. In cycling young women, there was a cyclic alteration in the ionized Ca:Mg ratio [39]. Serum ionized Mg level was significant decrease at the time of ovulation; ionized and total Mg levels were lowest when the progesterone level peaked [39, 40]. This may be due to the inhibitory effect of estrogen on parathyroid hormone (PTH)-induced bone resorption [41]. In postmenopausal women, however, loss of estrogen led to increased bone breakdown; serum ionized Ca level was higher than in the young women at any stage of their menstrual cycle. Further, the postmenopausal decreased estrogen and increased progesterone levels in the blood can induce Mg loss through urine, resulting in increased serum ionized Ca:Mg ratio in postmenopausal women, especially in those with low Mg intake [40-42]. However, another possible explanation is that the small sample size of premenopausal women in our study limited our ability to estimate the effect of Mg intake.

Results on Ca intake in relation to breast cancer survival have not been entirely consistent in previous studies [23-26]. However, intake of Mg was not adjusted as a confounding factor in these previous studies. Recent results from Women Health's Initiative Ca-Vitamin D Supplement Trial [27], or a meta-analysis of ten randomized trials [28] also showed little association of calcium and vitamin D supplement with total cancer death. In the current study, our results with additional adjustment of Mg intake are consistent with previous null association between Ca intake and all-cause mortality or breast cancer-specific mortality. However, we cannot eliminate the limitation of sample size in our study. Thus, further studies with large sample size are needed to confirm our findings.

Our study had a few limitations. Although cases were interviewed shortly after their diagnosis in our study, some eligible cases might have died before they could be enrolled in the study. However, this unlikely significantly biased the results because the 1- and 5-year overall breast cancer survival is 99.6% and 90.9% in our study. It is possible that recall bias in reporting FFQ and dietary supplement intake occurred. However, it is unlikely that such recall bias would be differential by the vital status. We were unable to estimate the contents of Mg and Ca in the drinking water, which may have led to non-differential misclassification of Mg and Ca intakes, and biased associations toward the null. In addition, information on changes of diet and supplement intake after cancer treatment was not available for our study subjects; we were unable to evaluate the relationship between post-diagnostic Mg and Ca intakes and breast cancer mortality. Finally, sample size was smaller in stratified analysis by Ca:Mg intake ratio, particularly those with a low ratio, thus limited our ability to examine the associations, and to generalize our results toward populations with a low Ca:Mg intake ratio before further large studies are conducted. Our study's strengths include the population-based patient cohort, the prospectively collected detailed information on usual diet and supplement intakes, cancer characteristics and treatments, and relatively long follow-up period.

In current study, we observed an independent inverse association between dietary and total Mg intake and all-cause mortality in breast cancer patients. Our preliminary findings indicate that risk reduction in mortality may be stronger among tumors with high Ca:Mg intake ratio. Further large studies are needed to confirm our findings and to better understanding the potential modifying effects of the Ca:Mg intake ratio on associations between Mg and Ca intake and breast cancer survival.

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Disclosure of conflict of interest

None.

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