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# Vitamin C and survival among women with breast cancer: A Meta-analysis

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**KEYWORDS**
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**Abstract** ***Background:*** The association between dietary vitamin C intake and breast cancer survival is inconsistent and few studies have specifically examined vitamin C supplement use among women with breast cancer. The purpose of this study was to summarise results from prospective studies on the association between vitamin C supplement use and dietary vitamin C intake and breast cancer-specific mortality and total mortality.

***Methods:*** Studies were identified using the PubMed database through February 6, 2014 and by examining the references of retrieved articles. Prospective studies were included if they reported relative risks (RR) with 95% confidence intervals (95% CIs) for at least two categories or as a continuous exposure. Random-effects models were used to combine study-specific results.

***Results:*** The ten identified studies examined vitamin C supplement use ($n = 6$) and dietary vitamin C intake ($n = 7$) and included 17,696 breast cancer cases, 2791 total deaths, and 1558 breast cancer-specific deaths. The summary RR (95% CI) for post-diagnosis vitamin C supplement use was 0.81 (95% CI 0.72–0.91) for total mortality and 0.85 (95% CI 0.74–0.99) for breast cancer-specific mortality. The summary RR for a 100 mg per day increase in dietary vitamin C intake was 0.73 (95% CI 0.59–0.89) for total mortality and 0.78 (95% CI 0.64–0.94) for breast cancer-specific mortality.

***Conclusion:*** Results from this meta-analysis suggest that post-diagnosis vitamin C supplement use may be associated with a reduced risk of mortality. Dietary vitamin C intake was also statistically significantly associated with a reduced risk of total mortality and breast cancer-specific mortality.



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## 1. Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide [1] and in the United States (US) alone there are approximately 2.9 million breast cancer survivors [2]. Multivitamin and supplement use is common among cancer patients with a prevalence reported to range from 75% to 87% among breast cancer survivors [3]. Vitamin C is one of the most commonly consumed supplements [4], however, the safety and benefits of oral vitamin C supplement use among cancer survivors has not been established [5,6], and few studies have specifically examined vitamin C supplement use among women with breast cancer [7–11]. The association between dietary vitamin C intake and breast cancer survival is inconsistent, with some studies reporting a reduced risk of mortality with increasing intake [6,7,9,12–16], and others reporting no association [17–21]. The purpose of this study was to summarise results from prospective studies on the association between vitamin C supplement use and dietary vitamin C intake and breast cancer survival.

## 2. Materials and methods

### 2.1. Search strategy and study selection

We conducted a literature search through February 6, 2014 using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) without restrictions on language. The following search terms were used: 'vitamin C' or 'vitamin C supplements' or 'supplements' and 'breast cancer' or 'breast cancer mortality' or 'breast cancer survival.' In addition, we reviewed the reference lists from retrieved articles to identify additional studies.

To be included in the meta-analysis the following criteria had to be met: (1) the exposure studied was dietary vitamin C or vitamin C supplement use, (2) the outcome of interest was breast cancer-specific mortality or total mortality among women with breast cancer and (3) reported relative risks (RR) with 95% confidence intervals (95% CIs). One study reported a combined outcome of breast cancer recurrence and survival and was included in our meta-analysis [7]. In addition, the After Breast Cancer Pooling Project (ABCPP), a consortium of four prospective studies, presented a summary estimate for all four studies so we obtained study-specific RR (95% CI) from the authors for data that was not previously available [11].

### 2.2. Data extraction

The following data were extracted from each study: the first author's last name, publication year, name of study/studies, country, number of breast cancer cases and number of deaths (total and/or breast cancer-specific), timing (pre- or post-diagnosis) and type of diet and supplement assessment, measure and range of exposure, covariates adjusted for in analyses and RR and corresponding 95% CI for each exposure category. When multiple RRs were presented we extracted the ones that represented the greatest degree of control for potential confounders. If data were duplicated in more than one study we included the study with the most recent data available.

### 2.3. Statistical analysis

Four different exposure/outcome combinations were examined: (1) post-diagnosis supplement vitamin C supplement intake and total mortality (five studies), and (2) post-diagnosis supplement vitamin C supplement intake and breast cancer-specific mortality (six studies), 3) dietary vitamin C intake and total mortality (five studies) and (4) dietary vitamin C intake and breast cancer-specific mortality (three studies). RRs and their corresponding standard errors (derived from CIs) were transformed to their natural logarithms to normalise the distribution. Study-specific RR values were combined using a random-effects model [22]. When data were available, we performed a dose–response meta-analysis using the method proposed by Greenland and Longnecker [23] and Orsini [24]. This method requires the number of deaths and participants, and the RR with its variance estimate for at least three quantitative exposure categories. The median level of consumption per category was assigned to the corresponding RR estimate. When the median consumption per category was not presented, the midpoint between the upper and lower bound was used. If the lowest category was open-ended, the lower boundary was assumed to be zero. Open-ended upper categories were assumed to be the same magnitude as the preceding category. If the amount of vitamin C per category was not specified in the article [18], we estimated the amount using information from another article in the same cohort [25]. When complete data were not available for examining a dose–response meta-analysis we estimated the linear trend for each study using an inverse variance weighting least squares estimate. To examine a potential departure from linearity in the dose–response relationship we created restricted cubic splines (three knots at fixed percentiles) and then assessed potential departure from a simpler linear trend by testing that the coefficient of the second spline was equal to zero [26]. When the necessary data were not available to perform a dose–response meta-analysis the highest vitamin C intake group was compared with the lowest intake group.

Statistical heterogeneity between studies was assessed using the $I^2$-statistics [27]. Publication bias was assessed with Egger's test [28]. All statistical analyses were conducted with Stata (StataCorp, College Station, TX, USA).

## 3. Results

### 3.1. Study characteristics

We identified 15 papers with data from 11 prospective observational studies that were potentially eligible for inclusion into the meta-analysis [7–21]. Two were excluded because they did not report RRs or CIs for vitamin C intake [12,21], three were excluded because they only reported results for total vitamin C intake (food + supplements) [13,16,19], and one had more recent results available within the pooling project [10]. Thus nine papers with data from 10 prospective observational studies were eligible for inclusion [7–9,11,14,15,17,18,20]. The characteristics of included studies are summarised in Table 1 (total mortality) and Table 2 (breast cancer-specific mortality). The studies were published between 1993 and 2013 and included a total of 17,696 breast cancer cases with a range of 149–3818 cases in individual studies. The number of total deaths and breast cancer-specific deaths reported ranged from 26 to 1055 and 58 to 416, respectively. Seven of these studies were conducted in the US [7,8,11,14,17,18,20], one in Sweden [9], one in China [11] and one in Australia [15]. All of the studies, except for two adjusted for body mass index (BMI) ($n = 8$), over half adjusted for clinical characteristics (i.e. tumour stage or grade, number of positive lymph nodes, treatment) ($n = 7$) and energy intake ($n = 6$). Fewer studies adjusted for smoking ($n = 5$) or physical activity ($n = 4$).

### 3.2. Vitamin C supplement intake

Five studies examined post-diagnosis vitamin C supplement intake and total mortality [8,9,11] (13,203 cases and 1576 deaths), six studies examined breast cancer-specific mortality [7–9,11] (13,423 cases and 997 deaths). Post-diagnosis vitamin C supplement use was associated with a statistically significant 19% reduced risk of total mortality compared to no post-diagnosis supplement use (95% CI 0.72–0.91) (Fig. 1). The association was similar when breast cancer-specific mortality was the outcome (summary estimate 0.85, 95% CI 0.74–0.99).(Fig. 1) There was no statistically significant evidence of heterogeneity among studies ($p = 0.72$ for total mortality and $p = 0.69$ for breast cancer-specific mortality) and there was no statistically significant evidence of publication bias ($p = 0.06$ and $p = 0.34$, respectively).

### 3.3. Dietary vitamin C intake

Five studies examined the association between dietary vitamin C intake and total mortality [9,14,17,18,20] (6521 cases and 1642 deaths) and three studies examined breast cancer-specific mortality (4241 cases and 627 deaths) [7,9,15]. Three of the five studies examining total mortality and all of the studies examining breast cancer-specific mortality utilised pre-diagnosis diet. We observed that an increase in vitamin C intake of 100 mg/day was associated with a reduction in total mortality (summary estimate = 0.73, 95% CI 0.59–0.89) (Fig. 2). Among the three studies [9,14,18] that had data in categories, we calculated that high versus low dietary vitamin C intake was associated with a statistically significant 20% reduced risk of total mortality (95% CI 0.69–0.92). Dietary vitamin C intake was also significantly associated with reduced risk of breast cancer-specific mortality (summary estimate = 0.78, 95% CI 0.64–0.94 for an increase of 100 mg/day). Comparing high versus low dietary vitamin C intake there was a 23% reduced risk of breast cancer-specific mortality (95% CI 0.61–0.98). We flexibly modelled the dose–response relationships using restricted cubic splines and found no significant departure from linearity ($p_{\text{non-linearity}} = 0.16$ for total mortality and $p_{\text{non-linearity}} = 0.08$ for breast cancer-specific mortality). There was no significant heterogeneity among studies ($p = 0.08$ for total mortality and $p = 0.24$ for breast cancer-specific mortality) and there was no evidence of publication bias ($p = 0.33$ and $p = 0.73$, respectively).

## 4. Discussion

In this meta-analysis, dietary vitamin C intake and post-diagnosis oral vitamin C supplement use were statistically significantly associated with a reduced risk of total mortality and breast cancer-specific mortality.

There are several mechanisms through which intake of vitamin C may influence mortality among women with breast cancer. Vitamin C exhibits antioxidant actions including the neutralisation of free radicals which may impact cancer progression [29,30]. At higher doses it may also act as a pro-oxidant as *in vitro* experiments have demonstrated cytotoxicity to cancer cells without similar effects on normal cells [31,32].

Conversely, evidence from some laboratory studies and randomised trials suggests that use of antioxidant supplements, including vitamin C, during chemotherapy and radiation therapy may actually protect tumour cells from treatment agents and decrease the efficacy of treatment [33–35]. Recently, Subramani et al. reported that pre-treatment of MCF-7 breast cancer cells with vitamin C protected these cells from Tamoxifen treatment [35]. However, few studies, observational or clinical trials, have specifically examined post-diagnosis vitamin C supplement use and survival among breast cancer patients before, during or after treatment [7–11,36].

Results from our meta-analysis indicate that post-diagnosis vitamin C supplement use among breast cancer patients is associated with a reduction in total mortality and breast cancer-specific mortality. Vitamin C supplement use can occur at physiological (low dose) or pharmacological (high dose) levels. Two of the studies included in the meta-analysis have published estimates of post-diagnosis supplement dosages. Nechuta et al.

Table 1
Summary of previous observational studies of vitamin C intake and total mortality following breast cancer diagnosis.

| Author (year) | Study ($n$ = breast cancer cases) | Primary event type(s) ($n$) | Diet and supplement assessment | Exposure categorisation (highest versus lowest category) | Results (Hazard Ratio [95% confidence interval (CI)])[a] | Adjustment |
|---|---|---|---|---|---|---|
| *Supplements only* | | | | | | |
| Harris (2013) | Swedish Mammography Cohort, Sweden ($n = 717$) | Total deaths ($n = 228$) | Post-diagnosis intake assessed via 96-item food frequency questionnaire (FFQ) | Any vitamin C supplement use versus no use | 0.81 (0.53–1.26) | Age at diagnosis, energy intake, education, marital status, menopausal status at diagnosis, body mass index (BMI), alcohol intake, year of diagnosis, disease stage, grade, treatment |
| Poole (2013) | After Breast Cancer Pooling Project | | | Regular vitamin C supplement use (ever versus never) at least 1-year post-diagnosis | | Adjusted for age at diagnosis, physical activity, stage, treatment, BMI, menopausal status and smoking |
| | Nurses' Health Study, United States of America (USA) ($n = 3324$) | Total deaths ($n = 369$) | Post-diagnosis supplement intake on biennial questionnaires | | 0.84 (0.66–1.05) | |
| | Shanghai Breast Cancer Survival Study, China ($n = 3818$) | Total deaths ($n = 139$) | Post-diagnosis supplement intake assessed via in-person interview at 6-month and 36-month post-diagnosis interviews | | 0.52 (0.27–1.00) | |
| | Women's Healthy Eating and Living Study, USA ($n = 3080$) | Total deaths ($n = 447$) | Post-diagnosis intake of supplements taken in the previous 24 h assessed at baseline and follow-up visits | | 0.84 (0.69–1.02) | |
| Greenlee (2012) | Life After Cancer Epidemiology Study, USA ($n = 2264$) | Total deaths ($n = 393$) | Post-diagnosis intake via questionnaire | Three categories Frequent vitamin C supplement use (6–7 days/week) versus no use | 0.78 (0.61–1.01); $p_{trend} = 0.06$ | Age at diagnosis, race/ethnicity, education, BMI, smoking, physical activity, fruit/vegetable intake, comorbidity score, stage, # of positive lymph nodes, tumour hormone receptor status, treatment |
| *Dietary vitamin C intake (foods only)* | | | | | | |
| Harris (2013) | Swedish Mammography Cohort, Sweden ($n = 3405$) | Total deaths ($n = 1055$) | Pre-diagnosis intake assessed via 67-item FFQ | Quartiles $\geqslant$92.5 versus $<$42.9 mg/d | 0.84 (0.71–1.00); $p_{trend} = 0.08$ | Age at diagnosis, energy intake, education, marital status, menopausal status at diagnosis, BMI, alcohol intake, year of diagnosis, disease stage, grade, treatment |
| McEligot (2006) | Orange County (CA), USA ($n = 516$) | Total deaths ($n = 96$) | Pre-diagnosis intake assessed via 100-item FFQ | Tertiles $\geqslant$135.32 versus $<$80.08 mg/d | 0.45 (0.25–0.78); $p_{trend} = 0.004$ | Age at diagnosis, energy intake, BMI, parity, hormone replacement therapy (HRT) use, oral contraceptive (OC) use, alcohol intake, multivitamin use |
| Holmes (1999) | Nurses' Health Study, USA ($n = 1982$) | Total deaths ($n = 378$) | Post-diagnosis intake via FFQ | Quintiles 5th versus 1st quintile | 0.80 (0.58–1.10); $p_{trend} = 0.54$ | Age, energy intake, diet interval, year of diagnosis, BMI, menopausal status, postmenopausal hormone (PMH) use, smoking, age at first birth/parity, # of metastatic lymph nodes, tumour size |

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|---|---|---|---|---|---|---|
| Saxe (1999) | University of Michigan, USA ($n = 149$) | Total deaths ($n = 26$) | Pre-diagnosis intake via FFQ | Per 100 mg/d increase in vitamin C | 0.92 (0.57–1.47) | Energy intake |
| Hebert (1998) | Memorial Sloan-Kettering Cancer Center, USA ($n = 469$) | Total deaths ($n = 87$) | Pre- and post-diagnosis intake via 34-item FFQ | Per 100 mg/d increase in vitamin C | RR = 0.48, $p = 0.14$ | Age at diagnosis, energy intake, BMI, menopausal status, alcohol intake, stage |

[a] Results presented for highest versus lowest category unless otherwise stated.

reported that approximately 85% of women with dosage information in the Shanghai Breast Cancer Survival Study (SBCSS) used 400 mg or less per day [10] while in the Swedish Mammography Cohort (SMC) the most frequent dose was estimated to be 1000 mg [9]. No information was available on post-diagnosis supplement dosages in the Fatty Acid Stores Tumour Characteristics and Breast Cancer (FASTCAB) study; however, pre-diagnosis supplement intake of 500 or more mg/day was reported in only 17% of participants [7]. These doses are much lower than the doses reported in previous studies of vitamin C supplement use and cancer outcomes [34,36] and different levels of intake may influence the safety and efficacy in cancer patients [34]. In addition, whether or not the supplements are consumed during chemotherapy or radiation therapy may also influence their effects. In the After Breast Cancer Pooling Project, from which this meta-analysis included estimates from the Nurses' Health Study (NHS), SBCSS and Women's Healthy Eating and Living (WHEL) Study, supplement use at least one year post diagnosis was examined which restricted the analysis of these studies to the post-treatment period [11]. In a previously published study from the SBCSS, any antioxidant use (defined as use of vitamin C, vitamin E and/or multivitamins) was examined by cancer treatment type, however data by treatment were not presented individually for vitamin C. Among women receiving chemotherapy there was a borderline statistically significant inverse association between any antioxidant use and total mortality (0.81; 0.62–1.05, $p_{trend} = 0.11$). In contrast, there was no association between any antioxidant use and total mortality among those who used any antioxidant while receiving radiotherapy (0.92; 0.63–1.33, $p_{trend} = 0.66$), but a significant association among those who did not receive any radiotherapy (0.65; 0.47–0.92, $p_{trend} = 0.01$) [10]. The Life After Cancer Epidemiology (LACE) Study examined vitamin C use during the early post-diagnosis period which included the time of breast cancer treatment. In the LACE study, the suggestion of an inverse association observed between vitamin C and total and breast cancer-specific mortality had a similar direction of effect when the association was stratified by treatment received (chemotherapy and radiation therapy) [8]. Based on these limited results, there does not appear to be a clear detrimental effect of vitamin C (or vitamin C, vitamin E and/or multivitamins), when taken during chemotherapy or radiation treatment at the levels observed in these cohorts.

Our results are similar to recent estimates from the After Breast Cancer Pooling Project [11]. The ABCPP includes breast cancer patients from the SBCSS, the LACE Study, the NHS and the WHEL Study. We obtained study-specific RR (95% CI) from the ABCPP for the SBCSS, the NHS and the WHEL Study [11], but not for the LACE study; however, previously published results from the LACE Study were instead

Table 2
Summary of previous observational studies of vitamin C intake and breast cancer-specific mortality following breast cancer diagnosis.

| Author (year) | Study ($n$ = breast cancer cases) | Primary event type(s) ($n$) | Diet and supplement assessment | Exposure categorisation (highest versus lowest category) | Results (Hazard Ratio [95% confidence interval (CI)])[a] | Adjustment |
|---|---|---|---|---|---|---|
| *Supplements only* | | | | | | |
| Harris (2013) | Swedish Mammography Cohort, Sweden ($n = 717$) | Breast cancer deaths ($n = 66$) | Post-diagnosis intake assessed via 96-item food frequency questionnaire (FFQ) | Any vitamin C supplement use versus no use | 1.06 (0.52–2.17) | Age at diagnosis, energy intake, education, marital status, menopausal status at diagnosis, body mass index (BMI), alcohol intake, year of diagnosis, disease stage, grade, treatment |
| Poole (2013) | After Breast Cancer Pooling Project | | | Regular vitamin C supplement use (ever versus never) at least 1-year post-diagnosis | | Adjusted for age at diagnosis, physical activity, stage, treatment, BMI, menopausal status and smoking |
| | Nurses' Health Study, United States of America (USA) ($n = 3324$) | Breast cancer deaths ($n = 190$) | Post-diagnosis supplement intake on biennial questionnaires | | 0.96 (0.70–1.31) | |
| | Shanghai Breast Cancer Survival Study, China ($n = 3818$) | Breast cancer deaths ($n = 118$) | Post-diagnosis supplement intake assessed via in-person interview at 6-month and 36-month post-diagnosis interviews | | 0.56 (0.28–1.11) | |
| | Women's Healthy Eating and Living Study, USA ($n = 3080$) | Breast cancer deaths ($n = 351$) | Post-diagnosis intake of supplements taken in the previous 24 h assessed at baseline and follow-up visits | | 0.86 (0.69–1.07) | |
| Greenlee (2012) | Life After Cancer Epidemiology Study, USA ($n = 2264$) | Breast cancer deaths ($n = 214$) | Post-diagnosis intake via questionnaire | Three categories Frequent vitamin C supplement use (6–7 days/week) versus no use | 0.82 (0.58–1.16); $p_{trend} = 0.26$ | Age at diagnosis, race/ethnicity, education, BMI, smoking, physical activity, fruit/vegetable intake, comorbidity score, stage, # of positive lymph nodes, tumour hormone receptor status, treatment |
| Fleischauer (2003) | Fatty Acid Tumour Stores Characteristics and Breast Cancer case-control study, USA ($\underline{n} = 385$ with pre-diagnosis data; 220 with post-diagnosis data) | Breast cancer recurrence and survival (combined outcome) ($n = 99$ pre-diagnosis data; $n = 58$ post-diagnosis data) | Post-diagnosis intake via questionnaire | Post-diagnosis: Ever versus never supplement use | 0.64 (0.32–1.27) | Age at diagnosis, age at menopause, smoking, physical activity, dietary intake of vitamin E, hormone replacement therapy (HRT) use, stage, treatment |
| | | | Pre-diagnosis intake via 124-item FFQ | Pre-diagnosis: >500 mg/d versus none | 1.60 (0.72–2.13) | |
| *Dietary vitamin C intake (foods only)* | | | | | | |
| Harris (2013) | Swedish Mammography Cohort, Sweden ($n = 3405$) | Breast cancer deaths ($n = 416$) | Pre-diagnosis intake assessed via 67-item FFQ | Quartiles $\geqslant$92.5 versus <42.9 mg/d | 0.75 (0.57–0.99); $p_{trend} = 0.03$ | Age at diagnosis, energy intake, education, marital status, menopausal status at diagnosis, BMI, alcohol intake, year of diagnosis, disease stage, grade, treatment |

| | | | | | | |
|---|---|---|---|---|---|---|
| Fleischauer (2003) | Fatty Acid Tumour Stores Characteristics and Breast Cancer case-control study, USA ($n = 385$) | Breast cancer recurrence and survival (combined outcome) ($n = 99$) | Pre-diagnosis intake via 124-item FFQ | Three categories >180 versus <121.5 mg/d | 1.21 (0.48–3.04) | Age at diagnosis, age at menopause, smoking, physical activity, dietary intake of vitamin E, HRT use, stage, treatment |
| Rohan (1993) | Adelaide metropolitan area, Australia ($n = 451$) | Breast cancer deaths ($n = 112$) | Pre-diagnosis intake via FFQ | Quintiles ⩾234 versus ⩽71 mg/d | 0.74 (0.42–1.30); $p_{trend} = 0.14$ | Energy intake, BMI, age at menarche |

[a] Results presented for highest versus lowest category unless otherwise stated.

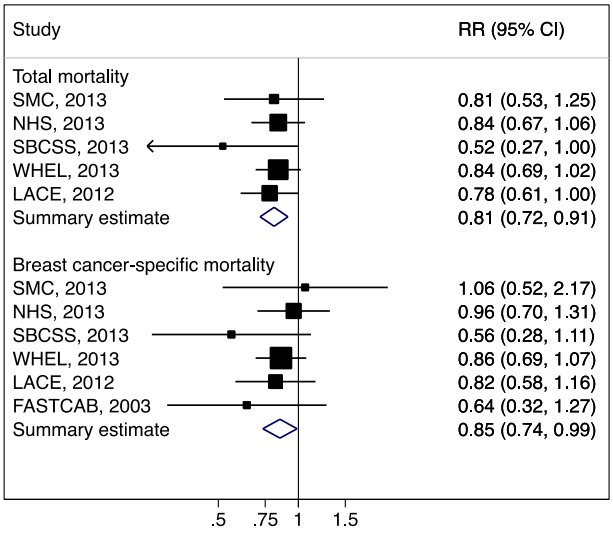


Fig. 1. Relative risk estimates of mortality following breast cancer diagnosis associated with a post-diagnosis vitamin C supplement use, stratified by total and breast cancer-specific mortality. Squares indicate study-specific relative risks (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% confidence intervals (CIs) and diamond indicates the summary relative risk estimate with its 95% CI. Study abbreviations: Swedish Mammography Cohort (SMC), Nurses' Health Study (NHS), Shanghai Breast Cancer Survival Study (SBCSS), Women's Healthy Eating and Living Study (WHEL), Life After Cancer Epidemiology cohort (LACE), Fatty Acid Stores Tumour Characteristics and Breast Cancer study (FASTCAB).

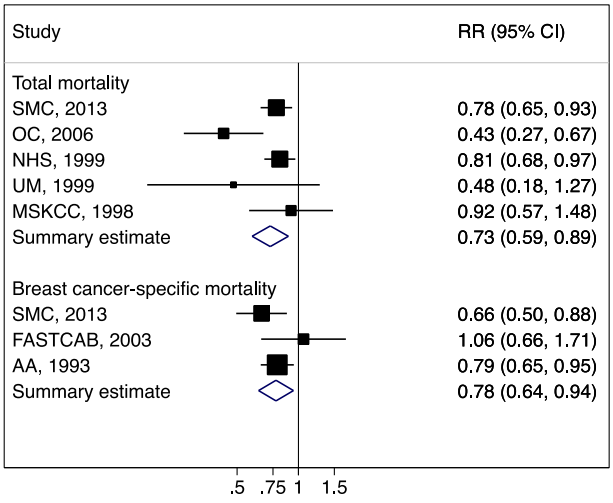


Fig. 2. Relative risk estimates of mortality following breast cancer diagnosis associated with a 100 mg per day increase in dietary vitamin C intake, stratified by total and breast cancer-specific mortality. Squares indicate study-specific relative risks (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates the summary relative risk estimate with its 95% CI. Study abbreviations: Swedish Mammography Cohort (SMC), Cohort of breast cancer cases diagnosed in Orange County, California (OC), Nurses' Health Study (NHS), Breast cancer patients from the Medical Centre, University of Michigan (UM), Breast cancer patients from Memorial Sloan-Kettering Cancer Center (MSKCC), Fatty Acid Stores Tumour Characteristics and Breast Cancer study (FASTCAB), Breast cancer patients from a case-control study in Adelaide metropolitan area, Australia (AA).

included in our meta-analysis [8]. The ABCPP calculated the associations between post-treatment vitamin C supplement use and breast cancer-specific and total mortality using Cox proportional hazards models separately by cohort and then combined individual cohort results using random effects meta-analysis. Poole et al. reported that regular vitamin C supplement use (ever versus never) was significantly associated with a decreased risk of total mortality (0.81; 0.72–0.92) and showed the suggestion of an association with breast cancer-specific mortality (0.87; 0.75–1.01) [11]. These results are consistent with our estimates for total and breast cancer-specific mortality (0.81; 0.72–0.91 and 0.85; 0.74–0.99, respectively). However, when the ABCPP results were mutually adjusted for other supplements the associations were attenuated (0.87; 0.76–1.01 for total mortality and 0.94; 0.79–1.12 for breast cancer-specific mortality) [11]. A limitation of our study was the inability to control for the use of other supplements.

This meta-analysis of observational studies has limitations. First, we cannot control for confounders that were not adjusted for in the individual studies. All but a few studies adjusted for BMI while over half adjusted for total energy intake and clinical characteristics, however there remains the possibility of residual or unmeasured confounding. There is also the possibility that women who take vitamin C supplements may be more health conscious than those who do not consume supplements leading to healthy user bias and this cannot be directly addressed in our meta-analysis. However, in the LACE Study, intake of supplements containing multiple carotenoids was associated with increased risk of mortality while vitamin C and E supplements were associated with a reduced risk of breast cancer recurrence, making health user bias an unlikely explanation for the results [8]. Some misclassification of vitamin C intake is also likely. Dietary intake was assessed with a self-reported food frequency questionnaire (FFQ) in most studies and supplement intake was assessed with questionnaires or in-person interviews. However, it was assessed before the outcome of interest (mortality) and thus is most likely non-differential. In addition, dietary intake was assessed both pre- and post-diagnosis. Finally, publication bias is also a possibility as we included only published studies. However, we found no evidence of publication bias.

To our knowledge this is the first meta-analysis to combine the limited number of published studies available on vitamin C supplement intake and dietary vitamin C intake and survival following breast cancer diagnosis. By combining these studies we had increased statistical power and could detect weaker associations than in the individual studies.

In conclusion, results from this meta-analysis suggest that post-diagnosis vitamin C supplement intake did not have a negative impact on breast cancer survival and may be associated with a reduced risk of mortality. Dietary vitamin C intake was also associated with a reduced risk of total mortality and breast cancer-specific mortality. More studies of post-diagnosis supplement use, including vitamin C, are warranted to further our understanding of how their intake during chemotherapy or radiation therapy may influence breast cancer outcomes.

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The funding source had no role in the study design, collection, analysis, and interpretation of data, in the writing of the manuscript or in the decision to submit the manuscript for publication.

## Conflict of interest statement

None declared.

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## References

[1] World cancer factsheet. Cancer Research UK, London; 2012.
[2] Society AC. Breast cancer overview. http://www.cancer.org/cancer/breastcancer/overviewguide/breast-cancer-overview-key-statistics; 2012 [accessed January 9, 2013].
[3] Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. J Clin Oncol 2008;26(4):665–73.
[4] Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999–2000. Am J Epidemiol 2004;160(4):339–49.
[5] AICR. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2007.
[6] Shekelle P, Hardy M, Coulter I, et al. Effect of the supplemental use of antioxidants vitamin C, vitamin E, and doenzyme Q10 for the prevention and treatment of cancer. Evid Rep Technol Asses (Summ) 2003;75:1–3.
[7] Fleischauer AT, Simonsen N, Arab L. Antioxidant supplements and risk of breast cancer recurrence and breast cancer-related mortality among postmenopausal women. Nutr Cancer 2003;46(1):15–22.
[8] Greenlee H, Kwan ML, Kushi LH, et al. Antioxidant supplement use after breast cancer diagnosis and mortality in the Life After Cancer Epidemiology (LACE) cohort. Cancer 2012;118(8):2048–58.
[9] Harris H, Bergkvist L, Wolk A. Vitamin C intake and breast cancer mortality in a cohort of Swedish women. Br J Cancer 2012;109(1):257–64.
[10] Nechuta S, Lu W, Chen Z, et al. Vitamin supplement use during breast cancer treatment and survival: a prospective cohort study. Cancer Epidemiol Biomarkers Prev 2011;20(2):262–71.
[11] Poole E, Shu X, Caan B, et al. Postdiagnosis supplement use and breast cancer prognosis in the After Breast Cancer Pooling Project. Breast Cancer Res Treat 2013;139(2):529–37.
[12] Ingram D. Diet and subsequent survival in women with breast cancer. Br J Cancer 1994;69(3):592–5.

[13] Jain M, Miller AB, To T. Premorbid diet and the prognosis of women with breast cancer. J Natl Cancer Inst 1994;86(18):1390–7.
[14] McEligot A, Largent J, Ziogas A, Peel D, Anton-Culver H. Dietary fat, fiber, vegetable, and micronutrients are associated with overall survival in postmenopausal women diagnosed with breast cancer. Nutr Cancer 2006;55(2):132–40.
[15] Rohan T, Hiller J, McMichael A. Dietary factors and survival from breast cancer. Nutr Cancer 1993;20(2):167–77.
[16] Jain M, Miller A. Tumor characteristics and survival of breast cancer patients in relation to premorbid diet and body size. Breast Cancer Res Treat 1997;42:43–55.
[17] Hebert JR, Hurley TG, Ma Y. The effect of dietary exposures on recurrence and mortality in early stage breast cancer. Breast Cancer Res Treat 1998;51(1):17–28.
[18] Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. Cancer 1999;86(5):826–35.
[19] Saquib J, Rock CL, Natarajan L, et al. Dietary intake, supplement use, and survival among women diagnosed with early-stage breast cancer. Nutr Cancer 2011;63(3):327–33.
[20] Saxe GA, Rock CL, Wicha MS, Schottenfeld D. Diet and risk for breast cancer recurrence and survival. Breast Cancer Res Treat 1999;53(3):241–53.
[21] Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa women's health study. Cancer 1995;76(2):275–83.
[22] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.
[23] Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135(11):1301–9.
[24] Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata J 2006;6:40–57.
[25] Osganian S, Stampfer M, Rimm E, et al. Vitamin C and risk of coronary heart disease in women. J Am Coll Cardiol 2003;42(2):246–52.
[26] Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175(1):66–73.
[27] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[28] Egger M, Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
[29] Frei B. Reactive oxygen species and antioxidant vitamins: Mechanisms of action. Am J Med 1994;97(3, Suppl. 1):S5–S13.
[30] Willcox JK, Ash SL, Catignani GL. Antioxidants and prevention of chronic disease. Crit Rev Food Sci Nutr 2004;44(4):275–95.
[31] Chen Q, Espey MG, Sun AY, et al. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. Proc Natl Acad Sci U S A 2008;105(32):11105–9.
[32] Ullah M, Khan H, Zubair H, Shamim U, Hadi S. The antioxidant ascorbic acid mobilizes nuclear copper leading to a prooxidant breakage of cellular DNA: implications for chemotherapeutic action against cancer. Cancer Chemother Pharmacol 2011;67(1):103–10.
[33] D'Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J Clin 2005;55(5):319–21.
[34] Lawenda BD, Kelly KM, Ladas EJ, Sagar SM, Vickers A, Blumberg JB. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? J Natl Cancer Inst 2008;100(11):773–83.
[35] Subramani T, Yeap SK, Ho WY, et al. Vitamin C suppresses cell death in MCF-7 human breast cancer cells induced by tamoxifen. J Cell Mol Med 2014;18(2):305–13.
[36] Greenlee H, Hershman D, Jacobson J. Use of antioxidant supplements during breast cancer treatment: a comprehensive review. Breast Cancer Res Treat 2009;115(3):437–52.