Multivitamin use and breast cancer incidence in a prospective cohort of Swedish women

Susanna C Larsson, Agneta Åkesson, Leif Bergkvist, and Alicja Wolk

ABSTRACT

Background: Many women use multivitamins in the belief that these supplements will prevent chronic diseases such as cancer and cardiovascular disease. However, whether the use of multivitamins affects the risk of breast cancer is unclear.

Objective: We prospectively examined the association between multivitamin use and the incidence of invasive breast cancer in the Swedish Mammography Cohort.

Design: In 1997, 35,329 cancer-free women completed a self-administered questionnaire that solicited information on multivitamin use as well as other breast cancer risk factors. Relative risks (RRs) and 95% CIs were calculated by using Cox proportional hazard models and adjusted for breast cancer risk factors.

Results: During a mean follow-up of 9.5 y, 974 women were diagnosed with incident breast cancer. Multivitamin use was associated with a statistically significant increased risk of breast cancer. The multivariable RR of women who reported the use of multivitamins was 1.19 (95% CI: 1.04, 1.37). The association did not differ significantly by hormone receptor status of the breast tumor.

Conclusions: These results suggest that multivitamin use is associated with an increased risk of breast cancer. This observed association is of concern and merits further investigation. Am J Clin Nutr 2010;91:1268–72.

INTRODUCTION

There is a widespread use of multivitamin supplements in North America and Europe. Many people believe that these supplements will reduce the risk of chronic diseases such as cancer and cardiovascular disease. About 40% of US women reported using multivitamins in 1999–2000 (1). Thus, the potential health benefits or adverse effects associated with multivitamin use are of great public health importance. Of concern, a recent study (2) showed that the use of multivitamin-multimineral supplements was associated with higher breast density, which is directly related to breast cancer risk.

Epidemiologic studies (3–8) of the association between multivitamin use and breast cancer risk yielded inconsistent results. In the Nurses’ Health Study, the use of multivitamins was associated with a lower risk of breast cancer among women with high-alcohol consumption (6). In contrast, 2 other US cohort studies showed an increased risk of breast cancer associated with multivitamin use in the whole cohort (4) and in premenopausal women (5). Other US cohort studies (3, 7, 8) showed no association between multivitamin use and breast cancer risk.

We used data from a population-based cohort study of Swedish women to investigate the relation between multivitamin use and the risk of breast cancer overall and by the estrogen receptor (ER) and progesterone receptor (PR) status of the breast tumors.

SUBJECTS AND METHODS

Study cohort

Data used in the current study were obtained from participants of the Swedish Mammography Cohort. Details of this population-based cohort study were reported previously (9). In brief, the cohort was established between 1987 and 1990 when all women born between 1914 and 1948 and living in central Sweden (Västmanland and Uppsala counties) received a mailed questionnaire on diet and other risk factors for breast cancer. In the late autumn of 1997, all participants who were still alive and residing in the study area received a new questionnaire that was expanded to include ~350 items concerning diet and other lifestyle factors as well as dietary supplement use; 39,227 women (70%) completed the second questionnaire.

For the current analyses, we used data from the 1997 questionnaire because information on supplement use was not obtained at baseline. We excluded women with an erroneous or a missing National Registration Number, women who did not provide information on supplement use, and women with a history of cancer other than nonmelanoma skin cancer, leaving 35,329 women aged 49–83 y for analysis. The study was approved by the Ethical Review Board at the Uppsala University Hospital (Uppsala, Sweden) and Karolinska Institutet (Stockholm, Sweden).

1 From the Division of Nutritional Epidemiology, The National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (SCL, AA, and AW), and the Department of Surgery and Centre for Clinical Research, Central Hospital, Västerås, Sweden (LB).
2 Supported by research grants from the Swedish Cancer Foundation and the Swedish Research Council for Infrastructure.
3 Address correspondence to SC Larsson, Division of Nutritional Epidemiology, National Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-17177 Stockholm, Sweden. E-mail: susanna.larsson@ki.se.

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Assessment of supplement use

The 1997 questionnaire asked about the use of dietary supplements, including multivitamins with and without minerals and some specific vitamin and mineral supplements. The question about supplement use was as follows: “Do you use vitamin-, mineral-, or other supplements?” Those who answered yes were asked to indicate how many tablets they took per week and for how many years they had been using each supplement, including multivitamins with minerals, multivitamins without minerals, vitamin C, vitamin E, vitamin B-6, calcium, and fish oil. For other less commonly used supplements the question was as follows: “Which of the following supplements do you usually use?” Because few participants reported using multivitamins without minerals (1.6%), we combined multivitamins with and without minerals in the analyses. Multivitamin use was classified into 2 categories: none use in 1997 and any use in 1997 defined as ≥1 tablet/wk or ≥1 y of use. Blank multivitamin questions were interpreted as none use. Because participants were not asked about multivitamin brand names, information on nutrient composition of multivitamins was not available. However, the number of multivitamin brands on the Swedish market is limited. Multivitamins in Sweden generally contain doses of vitamins and minerals close to the recommended daily allowances of vitamin A (0.9 mg), vitamin C (60 mg), vitamin D (5 µg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (2.1 mg), vitamin B-12 (3 µg), and folic acid (300–400 µg). The minerals usually included are iron (10 mg), zinc (12 mg), copper (2 mg), chromium (50 µg), selenium (40 µg), and iodine (150 µg). The questionnaire used in this study was validated among Swedish men (10). In the validation study among Swedish men, the sensitivity and specificity of self-reported use of multivitamins were estimated to be 69% and 98%, respectively (10).

Case ascertainment and follow-up

Histologically confirmed incident cases of invasive breast cancer diagnosed through 31 December 2007 were ascertained by linkage of the study cohort with the national and regional Swedish Cancer registers. The completeness of cancer follow-up was estimated to be almost 100% (11). Information on ER and PR status of the breast tumors was obtained by linkage with the clinical database (Quality Register) at the Regional Oncology Centre in Uppsala, which was based on the patients’ original medical records. ER status and PR status were evaluated by using an immunohistochemical method. Cases were considered as receptor-positive when the percentage of positive cells was ≥10%, and receptor-negative when the percentage of positive cells was <10%. Information on dates of death was obtained from the Swedish Death Registry.

Statistical analyses

Each participant contributed follow-up time from 1 January 1998 to the date of breast cancer diagnosis, death, or 31 December 2007, whichever came first. We used Cox proportional hazard models with age as the underlying time metric to estimate relative risks (RRs) with 95% CIs. Entry time was defined as a subject’s age in months at the start of follow-up, and exit time was defined as a subject’s age in months at cancer diagnosis or censoring. The covariates chosen for inclusion in the multivariable model were based on previously identified risk factors for breast cancer. Multivariable models were adjusted for age, education (primary school, high school, and university), family history of breast cancer (no or yes), history of benign breast disease (no or yes), parity (nulliparous, 1–2 or ≥3 births), age at first birth (nulliparous or <26, 26–30, or ≥31 y), age at menarche (≤12, 13, or ≥14 y), age at menopause (<51 or ≥51 y), oral contraceptive use (never or ever), postmenopausal hormone use (never and <3, 3–5, or ≥6 y; or users with missing data on duration), body mass index (in kg/m²) (<18.5, 18.5–24.9, 25–29.9, or ≥30), total physical activity (in quartiles of metabolic equivalent hours per day), smoking status (never, past, or current), calcium supplement use (no or yes), and alcohol intake (nondrinkers or <3.4, 3.4–9.9, or ≥10.0 g alcohol/d).

We conducted stratified analyses to examine whether the association between multivitamin use and breast cancer was modified by the use of postmenopausal hormones (never, quit <5 or ≥5 y ago, or current), smoking status (never, past, or current), and alcohol intake (0–4, 5–9, or ≥10 g alcohol/d). To test the statistical significance of interactions on a multiplicative scale, we used the log-likelihood ratio test and compared the models with or without interaction terms. All statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC). All P values were 2-sided.

RESULTS

Among participants of this cohort study, 25.5% reported the use of multivitamins. Most women were taking multivitamins with minerals (23.4%). Only a few participants used multivitamins without minerals (1.6%); 0.5% of participants reported the use of multivitamins with and without minerals. Compared with women who did not use multivitamins, multivitamin users were more likely to have a postsecondary education, have a history of benign breast disease, be nulliparous, and to have used oral contraceptives and postmenopausal hormones, but they were less likely to smoke (Table 1). Multivitamin users were also more likely to use specific vitamin or mineral supplements and were, on average, leaner than nonusers.

During a mean follow-up of 9.5 y (334,117 person-y), 974 incident cases of breast cancer were diagnosed among 35,329 women. Information on ER and PR status was available for 894 cases (91.8%). Among them, 539 cases (60.3%) were ER-positive/PR-positive (ER+/PR+), 240 (26.8%) were ER+/PR-negative (ER+/PR−), 106 (11.9%) were ER-negative/PR-positive (ER−/PR+), and 9 (1.0%) were ER−/PR+. ER−/PR+ tumors were not analyzed separately because of the small number of cases.

We observed an increased risk of breast cancer associated with multivitamin use (Table 2). In a multivariable model adjusted for breast cancer risk factors, women who reported the use of multivitamins had a significant 19% higher risk of breast cancer than nonusers. The association persisted when we excluded breast cancer cases diagnosed within the first 2 y of follow-up (RR = 1.20; 95% CI: 1.02, 1.40) and after further adjustment for intakes of total energy, fruits, and vegetables (RR = 1.19; 95% CI: 1.03, 1.37). Multivitamin use was positively associated with risk of all subtypes of breast cancer defined by ER and PR status of the tumor, but only the association with ER+/PR+ tumors was
in analyses by frequency and duration of multivitamin use, women who took ≥7 tablets/wk had a 19% increase in breast cancer risk, and women who had used multivitamins ≥3 y had a 22% increased risk of breast cancer, compared with nonusers (Table 2).

Multivitamin use was significantly positively associated with breast cancer risk among women who consumed <5 g alcohol/d (RR = 1.30; 95% CI: 1.09, 1.55; n = 24,041) but not among women who consumed 5–9 g alcohol/d (RR = 1.11; 95% CI: 0.83, 1.48; n = 7568) or among women who consumed ≥10 g alcohol/d (RR = 0.97; 95% CI: 0.66, 1.43; n = 3720). A test for interaction between alcohol intake and multivitamin use in relation to breast cancer risk was not significant ($P = 0.26$). The association between multivitamin use and the risk of breast cancer was not modified by postmenopausal hormone use (Table 3; $P$ for interaction = 0.59) or smoking status ($P$ for interaction = 0.29).

The use of specific vitamin supplements was not associated with the risk of breast cancer. The multivariable RRs comparing users of supplements with nonusers of supplements were 1.06 (95% CI: 0.90, 1.26) for vitamin C ($n = 164$ cases among users), 0.94 (95% CI: 0.72, 1.23) for vitamin E ($n = 61$ cases among users), 1.10 (95% CI: 0.85, 1.42) for vitamin B-6 ($n = 66$ cases among users), and 0.99 (95% CI: 0.55, 1.81) for folic acid ($n = 11$ cases among users). Women who reported the use of calcium supplements had a 26% decreased risk of total breast cancer compared with nonusers of calcium supplements ($RR = 0.74; 95\% \text{ CI: } 0.56, 0.97$). The use of zinc or magnesium supplements was not associated with total breast cancer risk (data not shown). Results for specific vitamin and mineral supplements were similar when we restricted the analysis to nonusers of multivitamins except for zinc supplement use, which was positively associated with a breast cancer risk, although the association did not reach significance (users compared with nonusers of zinc supplements: $RR = 1.55; 95\% \text{ CI: } 0.95, 2.51$).

**DISCUSSION**

In this prospective cohort of Swedish women, we observed a 19% increased risk of breast cancer associated with multivitamin use after adjustment for other breast cancer risk factors. The association between multivitamin use and breast cancer did not vary appreciably by hormone receptor status of the breast tumor.

Our findings are consistent with those of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort, in which an 18% increased risk of breast cancer was observed among users of multivitamins ($RR = 1.18; 95\% \text{ CI: } 0.95, 1.48$) who were followed up from 1993 to May 2003 (4). In the study, the observed positive association between multivitamin use and breast cancer was explained by the supplemental folic acid in multivitamins (≥400 μg folic acid/d compared with 0 μg folic acid/d: $RR = 1.19; 95\% \text{ CI: } 1.01, 1.41$). In the Women’s Health Study (5), with follow-up from 1992 to 1995 through March 2004, there was no overall association between multivitamin use and breast cancer risk; however, the past and current uses of multivitamins were associated with a nonsignificant 31% and 36% increased risk of breast cancer, respectively, among premenopausal women. The Nurses’ Health Study (6) showed an inverse association between multivitamin use and breast cancer risk among women who consumed >10 g alcohol/d. Three other US cohort studies, with follow-up from 1993 to 1998 through March 2005 (7), from 2000 to 2002 through 2006 (3), and from 1992 through August 1997 (8) observed no overall association between multivitamin use and breast cancer. In a French randomized trial (12) of the health effects of antioxidants, a combination of vitamins C and E, β-carotene, selenium, and zinc did not affect the risk of breast cancer.

Some previous prospective studies (3, 5, 6) but not all (7, 8) observed an inverse association between multivitamin use and the risk of breast cancer among women who consumed ≥10 or ≥15 g alcohol/d but no association among women with lower alcohol consumption. In the American Cancer Society Cancer Prevention Study II Nutrition Cohort (8), the long-term use of multivitamins was significantly positively associated with breast cancer risk among women who consumed ≥15 g alcohol/d. In contrast, in the current study, multivitamin use was significantly positively associated with breast cancer risk only among women who consumed <5 g alcohol/d.
The possibility that multivitamin use may increase the risk of breast cancer is biologically plausible. A recent study (2) showed that the current use of multivitamins and minerals in premenopausal women was associated with a significant 5.3% higher mean mammographic breast density (after adjustment for potential confounders), which is strongly and positively related to breast cancer risk. Folic acid in supplements could possibly increase the risk of breast cancer. High doses of folic acid from supplements or fortified foods are of concern because synthetic folic acid is more bioavailable than folate from natural food sources and, hence, potentially more potent in promoting cancer growth (13). Findings from animal studies (14, 15) showed that folic-acid deficiency reduced chemically induced mammary growth (13). Findings from animal studies (14, 15) showed that folic-acid deficiency reduced chemically induced mammary cancer. Moreover, in a trial (16) of folic-acid supplementation during pregnancy, women who were randomly assigned 5 mg folic acid/d had a 2-fold higher risk of mortality from breast cancer (n = 31 cases) (RR = 2.02; 95% CI: 0.88, 4.72) compared with women in the placebo group. In another randomized trial (17), combined folic acid, vitamin B-6, and vitamin B-12 treatment had no significant effect on the breast cancer incidence among women during the folic-acid fortification era. Furthermore, in the VITamins And Lifestyle (VITAL) cohort study (3) of predominantly supplement users who were followed up from 2000 to 2002 through 2006, high intakes of total folate averaged over 10 y were associated with a decrease in breast cancer risk. High intakes of total folate were not associated with breast cancer risk in a large cohort of premenopausal US women (18).

In the current study, we showed no association with folic-acid supplement use, but we had very limited statistical power to assess this association (only 1% of participants reported the use of a folic-acid supplement).

If folic acid is responsible for the observed association between multivitamin use and a risk of breast cancer, the association may not be seen in the US population because breakfast cereals and grain products have been fortified with folic acid since 1998 in the United States. Of note, those studies that did not observe any association with multivitamins (3, 7, 8) or combined folic-acid, vitamin B-6, and vitamin B-12 supplementation (17) were conducted during the folic-acid fortification era. The exposure of folic acid from foods in those populations may have limited the opportunity to detect an association between multivitamins and breast cancer risk. There is no mandatory folic-acid fortification in Sweden.

In the current cohort study, calcium supplement use was inversely associated with breast cancer risk, suggesting that calcium is unlikely to be responsible for the observed positive association between multivitamin use and the risk of breast cancer. Some of the calcium supplements sold on the Swedish market contain small doses (5–10 µg) of vitamin D. Hence, we cannot exclude the possibility that the inclusion of vitamin D in calcium supplements explains the observed inverse association between calcium supplement use and breast cancer. Because the

### Table 2

<table>
<thead>
<tr>
<th>Multivitamin use</th>
<th>No. of cases</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable RR (95% CI)</th>
<th>No. of cases</th>
<th>Multivariable RR (95% CI)</th>
<th>No. of cases</th>
<th>Multivariable RR (95% CI)</th>
<th>No. of cases</th>
<th>Multivariable RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>681</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>374</td>
<td>1.00 (reference)</td>
<td>168</td>
<td>1.00 (reference)</td>
<td>74</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>293</td>
<td>1.25 (1.09, 1.44)</td>
<td>1.19 (1.04, 1.37)</td>
<td>165</td>
<td>1.25 (1.04, 1.51)</td>
<td>72</td>
<td>1.12 (0.84, 1.48)</td>
<td>32</td>
<td>1.28 (0.84, 1.96)</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 tablets/wk</td>
<td>71</td>
<td>1.33 (1.04, 1.69)</td>
<td>1.28 (1.00, 1.63)</td>
<td>37</td>
<td>1.23 (0.89, 1.73)</td>
<td>21</td>
<td>1.43 (0.91, 2.26)</td>
<td>6</td>
<td>1.08 (0.47, 2.49)</td>
</tr>
<tr>
<td>≥7 tablets/wk</td>
<td>215</td>
<td>1.25 (1.07, 1.46)</td>
<td>1.19 (1.02, 1.39)</td>
<td>125</td>
<td>1.29 (1.05, 1.59)</td>
<td>51</td>
<td>1.08 (0.78, 1.48)</td>
<td>23</td>
<td>1.25 (0.78, 2.01)</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 y</td>
<td>35</td>
<td>0.98 (0.70, 1.38)</td>
<td>0.96 (0.68, 1.34)</td>
<td>22</td>
<td>1.12 (0.73, 1.72)</td>
<td>4</td>
<td>0.42 (0.15, 1.12)</td>
<td>4</td>
<td>1.09 (0.40, 2.99)</td>
</tr>
<tr>
<td>≥3 y</td>
<td>139</td>
<td>1.30 (1.08, 1.56)</td>
<td>1.22 (1.01, 1.47)</td>
<td>71</td>
<td>1.16 (0.90, 1.50)</td>
<td>40</td>
<td>1.30 (0.91, 1.85)</td>
<td>17</td>
<td>1.53 (0.89, 2.62)</td>
</tr>
</tbody>
</table>

1 ER+, estrogen receptor positive; PR+, progesterone receptor positive; ER−, estrogen receptor negative; PR−, progesterone receptor negative. RR and 95% CIs were estimated by using Cox proportional hazard models.

2 The number of cases does not add up to the total number of cases because of missing data on the frequency or duration of multivitamin use.

3 Adjusted for age, education, family history of breast cancer, history of benign breast disease, parity, age at first birth, age at menarche, age at menopause, oral contraceptive use, postmenopausal hormone use, BMI, physical activity, smoking, calcium supplement use, and alcohol intake.

4 Person-years of follow-up were 248,564 among nonusers of multivitamins and 85,553 among multivitamin users.

### Table 3

<table>
<thead>
<tr>
<th>Multivitamin use</th>
<th>Never</th>
<th>Quit &gt;5 y ago</th>
<th>Quit ≤5 y ago</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.00</td>
<td>0.86 (0.53, 1.38)</td>
<td>1.34 (0.75, 2.40)</td>
<td>1.87 (1.55, 2.25)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.20</td>
<td>1.25 (0.67, 2.36)</td>
<td>—</td>
<td>2.12 (1.69, 2.66)</td>
</tr>
</tbody>
</table>

1 Relative risks and 95% CIs were estimated by using Cox proportional hazards models and were adjusted for age, education, family history of breast cancer, history of benign breast disease, parity, age at first birth, age at menarche, age at menopause, oral contraceptive use, BMI, physical activity, smoking, calcium supplement use, and alcohol intake.

2 The number in brackets indicates the number of cases. The number of cases does not add up to the total number of cases because of incomplete information on postmenopausal hormone use.
use of supplements of vitamins C, E, or B-6 was not associated with breast cancer risk in this study, these nutrients are probably not responsible for the observed association with multivitamin use.

Other constituents of multivitamins with minerals that may be associated with cancer risk include iron and zinc. Experimental studies showed that a diet low in iron (19) or zinc (20) can suppress carcinogen-induced mammary cancer in rats. In a case-control study (21) nested in a cohort of women with benign breast disease, iron and zinc concentrations in benign breast tissue were positively associated with breast cancer risk. Results from other prospective studies (22–24) of dietary intake or toenail concentrations of iron or zinc in relation to the risk of breast cancer have been inconsistent. In the current study, there was a non-significant 55% increase in breast cancer risk associated with zinc supplement use among nonusers of multivitamins. Information on iron supplement use was not available.

Strengths of this study include its prospective and population-based design, information on the hormone-receptor status of the breast tumor, and the nearly complete follow-up of study participants by linkage with various population-based Swedish registers. A limitation of this study is that dietary supplement use was assessed by using a self-administered questionnaire. A misclassification of exposure will inevitably lead to some attenuation of RR estimates. Because information on multivitamin brand names was not available, we were not able to identify the components of multivitamins that could be linked to the observed increase in breast cancer incidence. Another limitation is the observational design. Thus, although we adjusted for known breast cancer risk factors, we cannot rule out the possibility that our findings may be due to residual confounding.

In conclusion, results from this prospective study suggest that the use of multivitamins may increase the risk of breast cancer. Because multivitamins consist of a combination of several vitamins and minerals, we were unable to identify the individual nutrient or nutrients responsible for the observed association. Findings from this study are of concern and merit further research.

The authors’ responsibilities were as follows—SCL: statistical analyses and manuscript writing; SCL and AW: study concept and design; AW: data collection; and SCL, AA, LB, and AW: interpretation of results and critical revision of the manuscript. None of the authors reported a personal or financial conflict of interest.

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