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Multivitamin supplement use and risk of invasive breast cancer

Johanna M. Meulepas[1,2], **Polly A. Newcomb**[2,3], **Andrea N. Burnett-Hartman**[2,4], **John M. Hampton**[3,5], and **Amy Trentham-Dietz**[3,5]

[1] Wageningen University, Department of Agrotechnology and Food Sciences, Division of Human Nutrition and Epidemiology, Wageningen, the Netherlands [2] Fred Hutchinson Cancer Research Center, Cancer Prevention Program, 1100 Fairview Avenue North, Seattle, WA 98109, USA [3] University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, 610 Walnut Street, Madison, WI 53726, USA [4] University of Washington, Department of Epidemiology, School of Public Health and Community Medicine, 1959 NE Pacific St., Seattle, WA 98195, USA [5] Department of Population Health Sciences, University of Wisconsin-Madison, 610 Walnut Street, Madison, WI 53726, USA

Abstract

Background—Multivitamin supplements are used by nearly half of middle aged women in the United States. Despite this high prevalence of multivitamin use, little is known about the effects of multivitamins on health outcomes, including cancer risk.

Objective—Our main objective was to determine the association between multivitamin use and the risk of breast cancer in women.

Design—We conducted a population-based case-control study among 2,968 incident breast cancer cases (ages 20–69 years) diagnosed between 2004–2007, and 2,982 control women from Wisconsin, U.S.A. All participants completed a structured telephone interview which ascertained supplement use prior to diagnosis, demographics, and risk factor information. Odds ratios (ORs) and 95% confidence intervals were calculated using multivariable logistic regression.

Results—Compared to never users of multivitamins, the ORs for breast cancer were 1.02 (95%CI: 0.87–1.19) for current users and 0.99 (95%CI: 0.74–1.33) for former users. Further, neither duration of use (for ≥ 10 years, OR= 1.13, 95%CI: 0.93–1.38, p*trend*: 0.25) nor frequency (>7 times/week, OR= 1.00, 95%CI: 0.77–1.28, p*trend*: 0.97) was related to risk in current users. Stratification by menopausal status, family history of breast cancer, age, alcohol, tumour staging and post-menopausal hormone use did not significantly modify the association between multivitamin use and breast cancer.

Conclusion—This study found no association between multivitamin supplement use and breast cancer risk in women.

Keywords

multivitamin; supplement; breast cancer; case-control

Correspondence to Polly A Newcomb, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, M4-B402, Seattle, WA 98109, USA, pnewcomb@fhcrc.org.

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Introduction

All types of dietary supplements are becoming increasingly common in the United States, and the prevalence of use is highest in adult women, with 38% reporting multivitamin use[1,2]. This increasing trend in the use of dietary supplements may have an impact on health in the population[3]. Commonly, individuals use multivitamin supplements for a general health promotion or to make an existing disease less severe.

However, assessing the role of dietary supplements on the intake of vitamins and minerals is complicated by the fact that the U.S. has been fortifying food with specific micronutrients, starting in 1924 with iodized salt. Since then the U.S. added vitamin D in milk, B-vitamins in flour and bread, and folate in cereal grain-based foods for public health reasons[4]. The level and variety of food fortification in the United States has increased over time[4,5] and in combination with dietary supplements, might lead to a daily intake of certain nutrients above the Upper Tolerable Intake Levels[6].

The use of dietary supplements may adversely impact health due to excessive intake of certain micronutrients7. At the same time, dietary supplements have been associated with meeting Recommended Daily Allowances (RDA) and Adequate Intakes (AIs) for certain micronutrients in the U.S. population7. Therefore, the role that supplementation for these micronutrients play in promoting health and preventing disease is unclear6. Such intake may be particularly relevant in carcinogenesis. For example, many multivitamin supplements include folate (or folic acid). Additional folate may provide protection early in carcinogenesis, especially in individuals with a low folate status8. On the other hand, folate may promote carcinogenesis if precancerous lesions or malignant cells are already present in an individual or if folate intake is particularly high9. Therefore, the role and optimal intake of folate for cancer prevention remains uncertain10.

Several observational studies have specifically assessed the influence of multivitamin use on breast cancer risk and showed contradictory results. Some studies report a 19–33% increased risk of breast cancer associated with multivitamin use[11,12], and others show a reduced risk of 20–43% [13–15] or find no association[16–19].

Due to the high intake of supplemental vitamins and minerals in the United States and the potential carcinogenic role of excessive micronutrient intake, it is important to evaluate the role of multivitamins in cancer risk. In the study, we investigated the association between multivitamin supplement use and breast cancer risk by conducting a population-based case-control study among women in Wisconsin, USA.

Subjects and methods

Ethics

The protocols for, and conduct of, this study were approved by the University of Wisconsin Institutional Review Board.

Selection of cases

Cases were identified via the Wisconsin Cancer Reporting System, a state-wide registry that covers all cases of cancer among residents of Wisconsin. This registry uses hospital, physician, and clinic reports to identify cancer cases. All cases must be reported to the registry within 6 months of diagnosis. For these analyses, we restricted cancer cases to women living in Wisconsin, ages 20–69 years, diagnosed with a first invasive breast cancer between 2004 and 2007. Eligible cases had a published telephone number, reported dates of diagnosis and driver's license verified by self-report. Of the 4,021 eligible cases, 84 (2.1%) were deceased, 198 (4.9%)

could not be located and 747 (18.6%) refused to participate. A total of 2,992 were interviewed (74% response rate). Data for four interviewed cases were considered unreliable by the interviewers. After removing 20 (0.7%) cases for missing values of multivitamin use, 2,968 cases were eligible for the analysis.

Selection of controls

Community controls were selected at random (within 5 year age-strata similar to cases) from lists of licensed drivers from the Wisconsin Department of Transportation. Inclusion criteria required a publicly available telephone number and no personal history of breast cancer. We identified 4,500 eligible women, but were not able to interview all women due to inability to locate 327 (7.3%), subject refusal 1,152 (25.6%) or death 16 (0.4%). A total of 3,005 were interviewed, and overall response rate was 67%. Data for one interviewed control was considered unreliable by the interviewer, and 22 (0.7%) controls were removed from analysis for missing values of multivitamin supplement use, leaving 2,982 controls eligible for analysis.

Exposure Assessment

Study participants were sent letters briefly describing the study before they were contacted via telephone by trained interviewers. These interviewers explained the study, answered participant questions, and obtained oral consent for study participation prior to the interview. Case subjects and controls then completed a structured 30-minute telephone interview eliciting information on known or suspected risk factors for breast cancer. Participants were asked if they had ever taken a multivitamin supplement for at least three consecutive months in the year prior to the reference data. Furthermore, participants were asked the year they started and stopped taking supplements, how long they took multivitamins, and how many multivitamins they took each day. Moreover, information about menstrual and reproductive history, menopausal status, family and personal medical history, education, smoking status, physical activity, height, weight, and demographics was collected.

Clinical information about tumour staging and first course of treatment was obtained from the Wisconsin Cancer Reporting System.

Statistical analysis

A reference date for cases was defined as the registry-supplied date of invasive breast cancer diagnosis. Controls were assigned an individual reference date so that their exposure assessment time-frame was similar to that of cases. Only multivitamin use prior to the reference date was included in the analysis.

Participants were classified as never, former, or current multivitamin users. The reference category, non-users, included only individuals who had never taken multivitamin supplements for at least three months. ‘Former’ use was defined as taking multivitamin supplements for three months or more at any time prior to the reference date, but not taking supplements at the time of the reference date; ‘current’ use was defined as taking multivitamin supplements for at least three months at the time of the reference date. Among former users, duration of use was categorized as <5 years and ≥5 years. Among current users, duration of use was <5 years, 5–9 years and ≥ 10 years. The frequency of use (i.e. the number of multivitamins consumed each week) among current users was categorized as ≤ 7 multivitamins/week and > 7 multivitamins/week. A continuous variable, years of use, was also evaluated.

The association between multivitamin supplement use and the risk of breast cancer was determined by calculating odds ratios (OR) and 95% confidence intervals (95%CI) using multiple logistic regression models. The odds ratios were estimated according to categories of multivitamin supplement use and adjusted for reference age. In addition, we performed a

logistic regression that adjusted for potential confounders, including age at reference date (in 5-year categories), education (less than high school, high school graduate, some college, college graduate), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥ 30 kg/m^2), alcohol (none, 1–7, >7 drinks/week), breast biopsy (never, ever), family history of breast cancer in a mother or sister, age at menarche (<12, 12–14, >14 year), parity (0, 1–2, ≥ 3), age at first birth (<20, 20–30, >30 year), menopausal status, age at menopause, and postmenopausal hormone use (among postmenopausal women only). Tests of trend were evaluated by conducting separate logistic regression analyses replacing the categorical variable for duration and frequency of multivitamin use with the ordinal variables for these terms and examining the Wald p-value for the ordinal terms. Since previous reports have demonstrated that age, alcohol, family history of breast cancer, menopausal status, and postmenopausal hormone use are important risk factors for breast cancer[20], effect modification was assessed through stratified analyses and evaluated by adding cross-product interaction terms to the multivariate model. All p-values were two sided and statistical significance was evaluated at 0.05. The statistical data was analyzed using the statistical software program, SAS, version 9.1.

Results

Use of multivitamin supplements was common among women in this study; approximately 50% of cases and controls were current users of multivitamins, and 8–9% were former multivitamin users.

Cases had an earlier age of menarche and fewer pregnancies than controls (Table 1). Furthermore, cases tended to have higher education, higher levels of alcohol intake, a previous breast biopsy, a family history of breast cancer, a later age at first birth and a later age at menopause.

In the multivariable adjusted models, multivitamin use was not associated with the risk of breast cancer (Table 2). The adjusted ORs were 0.99 (95%CI: 0.74–1.33) for former use and 1.02 (95%CI: 0.87–1.19) for current use of multivitamin supplements. Furthermore, no significant association with breast cancer risk was observed for duration of multivitamin use, regardless of whether women were current or former users. These data suggested that current users who took multivitamins for at least 10 years had a modest increased risk compared to never users (OR: 1.13, 95% CI: 0.93–1.38), but this was not statistically significant and did not reflect a dose-response (p*trend* = 0.25). In addition, frequency of use was not associated with intake; women who took multivitamins more than 7 times per week, had an OR of 1.00 (95% CI: 0.77–1.28, p*trend* = 0.97) compared to never users of multivitamins.

The association between breast cancer and multivitamin use stratified by menopausal status is presented in Table 3. Among premenopausal women, the adjusted ORs were 0.87 (95% CI: 0.62–1.23) for former users and 0.87 (95% CI: 0.70–1.08) for current users. Among postmenopausal women, the ORs were 0.99 (95% CI: 0.74–1.33) for former users and 1.03 (95% CI: 0.88–1.20) for current users. There was not a significant interaction between multivitamin use and postmenopausal hormone use (p=0.82). In addition, neither age, alcohol use, family history of breast cancer, nor tumour stage significantly modified the association between multivitamin use and breast cancer (p interaction >0.05) (*data not shown*).

Discussion

Our findings indicate that there is no association between use of multivitamin supplements and breast cancer risk in this population. Neither current users who used multivitamins for long durations, nor those who took more than one multivitamin a day, had a significantly different risk of breast cancer than those who never took multivitamins. Moreover, neither menopausal

status, family history of breast cancer, postmenopausal hormone use, tumour stage, alcohol use, nor age modified the association between multivitamin use and breast cancer risk.

Several previous studies examined the relationship between multivitamin supplement use and the risk of breast cancer. Two case-control studies found no association[18,19]. One of these studies by Moorman, et al was a population-based case-control study in North Carolina similar to our study except that it had a higher proportion of African American Participants[19]. The other was a population-based case-control study in Shanghai[18]. Furthermore, the Nurses' Health study,[16] a prospective cohort study, reported null results for multivitamin supplements and breast cancer risk. The researchers classified participants as never, former and current multivitamin users and presented duration for current users as we did in our study.

Two observational studies demonstrated inverse associations between breast cancer risk and multivitamins. The Women's Health Study15 observed a non-significant inverse association between the risk of estrogen receptor negative breast cancer and past multivitamin use (OR: 0.60, 95%CI: 0.42–1.06). In our study, tumor hormone receptor status was not available. Furthermore, the Nurses' Health Study II[14] presented an inverse association (RR=0.57, 95% CI: 0.33–0.98), but the cases were restricted to 67 women diagnosed with atypical hyperplasia.

A case-control study in Denmark reported an increased risk of breast cancer associated with multivitamin use (OR: 1.33, 95%CI: 1.09–1.62)[11]. This case-control study included information on all dietary factors. Furthermore, the study was conducted in a European population where the composition of the multivitamins and the level of food fortification may differ compared to those in the United States. Moreover, this study population had a lower percentage of multivitamin users (26%) compared to our study population which might have attenuated our results. For example, if only a very low folate status increases the risk of breast cancer, then strong associations can be detected only in study populations that include a sufficient number of subjects in the low-folate range10.

The participants of our study had a higher percentage (50%) of having ever used multivitamins compared with the general population (38%)[2]. However, our study population was predominantly white women and had an older age distribution than the general population. Compared to a different survey where the authors stratified for race and age, 47% of white adults used multivitamin supplements21. Therefore, our results may not be generalizable to populations with higher proportions of minorities.

Women with breast cancer may be more likely to begin using multivitamin supplements after diagnosis. To limit this potential bias, participants were asked about the use of multivitamin supplements in the year prior to the reference date.

The constituents of a multivitamin tablet vary by brand and may be equal to or exceed the Recommended Daily Allowance (RDA) for a particular nutrient[22]. Therefore, the supplement in conjunction with nutrients from food intake could exceed the Upper Tolerable Limit for important nutrients. On average, one multivitamin tablet is a major source of folate and vitamin B_6, and has levels of these vitamins that are equivalent to, or greater than, the daily RDA for adults in the United States[23]. In addition, the biological effects of a nutrient are heavily dependent on its absorption, transport, function and metabolism, all of which can be affected by the presence of other nutrients[12]. Thus, the evaluations of dietary supplements are complex.

Some limitations should be considered in interpreting our results. Information about total energy intake was not available in our study. Therefore, we could not adjust for possible confounding effect of total calorie intake. However, we did adjust for BMI, which is a strong risk factor for breast cancer and associated with total calorie intake[20]. Also, we did not collect the exact supplement composition in this study, and other studies have found that estimating

the exact intake of each micronutrient from dietary supplements was important to evaluating outcome in epidemiological studies[24]. We did however obtain information about the frequency and duration of multivitamin use for an examination of possible dose-effects. Furthermore, the goal of this study was not to examine individual components of multivitamins, but rather to evaluate an extremely common risk factor, multivitamin intake, in relation to breast cancer risk.

Finally, selection bias, recall bias and confounding may have influenced the results of our study. Selection bias may be present because of restriction criteria (drivers' licenses and telephone numbers) for eligible women. This may lead to the inclusion of women who tend to be better educated that the general population and be partially responsible for the higher percentage of supplement users in our study population, because supplement use is positively associated with education[1]. In general, women report the use of medications, including supplements, with a high degree of validity so that recall bias is probably limited25. Also, confounding was unlikely to have introduced substantial bias because we were able to adjust for multiple potential confounders. Furthermore, we did not recruit cases on the date of their diagnosis, and therefore, bias could be introduced into our study if multivitamin use is associated with aggressive breast cancers that are rapidly fatal. This is less of a concern with breast cancer than it is with other types of cancer, because greater than 90% of breast cancer cases survive at least five years. Even so, we attempted to limit this possible bias by enrolling cases as soon as possible after diagnosis. The majority of cases were enrolled within two years of diagnosis.

This study has several strengths. This population-based study included a large sample size and good response rates. We were able to evaluate both the frequency and duration of multivitamin supplements by making use of a standardized instrument.

In conclusion, this study did not find an association between multivitamin use and breast cancer risk. While dietary factors may be an important determinant of cancer risk[26], the role of vitamin supplementation on breast cancer risk is still unclear. Understanding the risks and benefits of dietary supplements is especially important in the U.S. and other western countries, where dietary supplement use is high and the food supply is already fortified with vitamins. Future studies evaluating the relationship between specific micronutrients and breast cancer risk should attempt to characterize the composition of dietary supplements along with the intake of specific nutrients from diet.

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Table 1

Baseline characteristics among breast cancer cases and controls, 2002–2007

	Cases		Controls	
Characteristics	**No**	**%***	**No**	**%***
Age (y)				
20–40	184	6.2	167	5.6
40–49	787	26.5	743	24.9
50–59	1075	36.2	1080	36.2
60–69	922	31.1	992	33.3
Education				
less than high school	79	3.0	108	4.0
high school graduate	1130	42.7	1125	41.7
some college	782	29.5	880	32.6
college graduate	639	24.1	566	21.0
BMI (kg/m^2)				
<18.5	41	1.4	36	1.2
18.5–24.9	1224	41.8	1184	30.0
25.0–29.9	870	29.7	882	40.3
≥30	759	25.9	797	27.1
Alcohol consumption				
0 drinks/week	577	19.4	641	21.5
1–7 drinks/week	2109	71.1	2068	69.4
>7 drinks/week	277	9.3	264	8.9
Breast biopsy				
never	2120	71.4	2331	78.2
ever	805	27.1	605	20.3
Positive family history of breast cancer				
no	2314	78.0	2489	83.5
yes	591	19.9	427	14.3
Age at menarche (y)				
<12	609	21.1	530	18.3
12–14	1927	66.8	1980	68.3
>14	343	11.9	384	13.3
Parity				
nulliparous	425	14.3	370	12.4
1–2	1440	48.5	1317	44.2
3 or more	1088	36.7	1289	43.2
Age at first birth (y)†				
<20	431	14.5	509	17.1
20–30	1687	56.8	1800	60.4
>30	387	13.0	285	9.6
Menopausal status				

	Cases		Controls	
Characteristics	**No**	**%***	**No**	**%***
premenopausal	989	33.3	918	30.8
postmenopausal	1664	56.1	1797	60.3
Age at menopause (y)‡				
<45	207	12.4	317	17.7
45–54	821	49.3	825	46.0
>54	258	15.5	258	14.4

*Due to missing values, some categories do not sum to 100%

†among parous women only

‡among postmenopausal women only

Table 2

Odds Ratios (OR) and 95%confidence intervals (95% CI) for the risk of breast cancer according to use of multivitamin supplements, 2002–2007

				Multivariable	
Multivitamin use	**Cases/Controls**	**OR***	**95% CI**	**OR†**	**95%CI**
Status					
Never use	1216/1213	1.00		1.00	
Former use	247/276	0.88	(0.72–1.06)	0.99	(0.74–1.33)
Current use	1505/1493	1.01	(0.91–1.12)	1.02	(0.87–1.19)
Duration *(years)*					
Never use	1216/1213	1.00		1.00	
Former use					
<5	161/179	0.88	(0.70–1.10)	0.90	(0.62–1.30)
≥5	86/97	0.88	(0.65–1.19)	1.14	(0.73–1.78)
P for trend			0.92		0.89
Current use					
<5	471/462	1.02	(0.87–1.18)	1.09	(0.87–1.35)
5–9	338/399	0.85	(0.72–1.00)	0.82	(0.65–1.03)
≥10	696/632	1.10	(0.97–1.26)	1.13	(0.93–1.38)
P for trend			0.15		0.25
Frequency *(no. of times/week)*‡					
Never use	1216/1213	1.00		1.00	
≤7	1170/1182	0.99	(0.89–1.11)	1.02	(0.87–1.20)
>7	335/311	1.08	(0.90–1.28)	1.00	(0.77–1.28)
P for trend			0.41		0.97

*Models were adjusted for reference age

†Multivariable models were adjusted for reference age, education, body mass index, alcohol, biopsy, family history of breast cancer, age at menarche, parity, age at first birth, menopausal status, postmenopausal hormone use (among postmenopausal women only) and age at menopause (among postmenopausal women only)

‡Analysis among current users and never users

Table 3

Odds Ratios (OR) and 95%confidence intervals (95% CI) for the risk of breast cancer according to use of multivitamin supplements among women stratified by menopausal status, 2002–2007

	Premenopausal			Postmenopausal		
		Multivariable			Multivariable	
Multivitamin use	**Cases/Controls**	**OR***	**95%CI**	**Cases/Controls**	**OR***	**95% CI**
Status						
Never use	417/373	1.00		675/741	1.00	
Former use	103/113	0.87	(0.62–1.23)	116/135	0.99	(0.74–1.33)
Current use	469/432	0.87	(0.70–1.08)	873/921	1.03	(0.88–1.20)
Duration of use						
Never use	417/373	1.00		675/741	1.00	
Former use *(years)*						
<5	73/75	0.93	(0.63–1.39)	69/83	0.90	(0.62–1.30)
≥5	30/38	0.75	(0.42–1.34)	47/52	1.14	(0.73–1.78)
P for trend			0.50			0.93
Current use *(years)*						
<5	146/159	0.75	(0.56–1.01)	270/268	1.09	(0.87–1.35)
5–9	104/106	0.80	(0.56–1.13)	201/259	0.82	(0.65–1.03)
≥10	219/167	1.02	(0.78–1.34)	402/394	1.13	(0.93–1.38)
P for trend			0.85			0.25
Frequency† *(no. of times/week)*						
Never use	417/379	1.00		675/741	1.00	
≤7	356/334	0.87	(0.69–1.10)	690/736	1.02	(0.87–1.20)
>7	113/98	0.93	(0.66–1.30)	183/185	1.00	(0.77–1.28)
P for trend			0.65			0.97

*Multivariable models were adjusted for reference age, education, body mass index, alcohol, biopsy, family history of breast cancer, age at menarche, parity, age at first birth, menopausal status, postmenopausal hormone use (among postmenopausal women only) and age at menopause (among postmenopausal women only)

†Analysis among current users and never users