

Multivitamin supplement use and risk of invasive breast cancer

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Abstract

Objective: Multivitamin supplements are used by nearly half of middle-aged women in the USA. Despite this high prevalence of multivitamin use, little is known about the effects of multivitamins on health outcomes, including cancer risk. 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 2968 incident breast cancer cases (aged 20–69 years), diagnosed between 2004 and 2007, and 2982 control women from Wisconsin, USA. All participants completed a structured telephone interview which ascertained supplement use prior to diagnosis, demographics and risk factor information. Odds ratios and 95% confidence intervals were calculated using multivariable logistic regression.

Results: Compared with never users of multivitamins, the OR for breast cancer was 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 for trend = 0.25) nor frequency (>7 times/week: OR = 1.00, 95% CI 0.77, 1.28, P for trend = 0.97) was related to risk in current users. Stratification by menopausal status, family history of breast cancer, age, alcohol, tumour staging and postmenopausal hormone use did not significantly modify the association between multivitamin use and breast cancer.

Conclusions: The current study found no association between multivitamin supplement use and breast cancer risk in women.

Keywords
Multivitamin
Supplement
Breast cancer
Case–control

All types of dietary supplements are becoming increasingly common in the USA 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 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 USA has been fortifying food with specific micronutrients, starting in 1924 with iodized salt. Since then the USA has 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 USA 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 Level (UL)⁽⁶⁾.

The use of dietary supplements may adversely impact health due to excessive intake of certain micronutrients⁽⁷⁾. At the same time, dietary supplements have been associated with meeting the Recommended Daily Allowances (RDA) and Adequate Intakes (AI) for certain micronutrients in the US population⁽⁷⁾. Therefore, the role that supplementation for these micronutrients plays in promoting health and preventing disease is unclear⁽⁶⁾. 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 status⁽⁸⁾. 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 high⁽⁹⁾. Therefore, the role and optimal intake of folate for cancer prevention remain uncertain⁽¹⁰⁾.

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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), while 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 USA and the potential carcinogenic role of excessive micronutrient intake, it is important to evaluate the role of multivitamins in cancer risk. In the present 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, the 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, aged 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 4021 eligible cases, eighty-four (2.1%) were deceased, 198 (4.9%) could not be located and 747 (18.6%) refused to participate. A total of 2992 were interviewed (74% response rate). Data for four interviewed cases were considered unreliable by the interviewers. After removing twenty (0.7%) cases for missing values of multivitamin use, 2968 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 4500 eligible women, but were not able to interview all women due to inability to locate 327 (7.3%), refusal of 1152 (25.6%) or death of sixteen (0.4%). A total of 3005 were interviewed, and overall response rate was 67%. Data for one interviewed control were considered unreliable by the interviewer and twenty-two (0.7%) controls were removed from analysis for missing values of

multivitamin supplement use, leaving 2982 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 participants' questions, and obtained oral consent for study participation prior to the interview. Case subjects and controls then completed a structured 30 min 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 date. 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 3 months. 'Former' use was defined as taking multivitamin supplements for 3 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 3 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 and 95% confidence intervals 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), BMI (<18.5 , 18.5 – 24.9 , 25.0 – 29.9 , ≥ 30.0 kg/m²), 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 years), parity (0, 1–2, ≥ 3), age at first birth (<20 , 20 – 30 , >30 years), 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 data were analysed using the SAS statistical software package version 9.1 (SAS Institute, Cary, NC, USA).

Results

Use of multivitamin supplements was common among women in the present study; approximately 50% of cases and controls were current users of multivitamins and 8–9% 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 OR was 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 with 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* for trend = 0.25). In addition, frequency of use was not associated with intake; women who took multivitamins >7 times/week had an OR of 1.00 (95% CI 0.77, 1.28) compared with never users of multivitamins (*P* for trend = 0.97).

The association between breast cancer and multivitamin use stratified by menopausal status is presented in Table 3. Among premenopausal women, the adjusted OR was 0.87 (95% CI 0.62, 1.23) for former users and 0.87 (95% CI 0.70, 1.08) for current users. Among

Table 1 Baseline characteristics among breast cancer cases and controls, Wisconsin, USA, 2002–7

Characteristic	Cases		Controls	
	<i>n</i>	%*	<i>n</i>	%*
Age (years)				
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/m²)				
<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
≥ 30.0	759	25.9	797	27.1
Alcohol consumption (drinks/week)				
None	577	19.4	641	21.5
1–7	2109	71.1	2068	69.4
>7	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 (years)				
<12	609	21.1	530	18.3
12 – 14	1927	66.8	1980	68.3
>14	343	11.9	384	13.3
Parity				
0	425	14.3	370	12.4
1–2	1440	48.5	1317	44.2
≥ 3	1088	36.7	1289	43.2
Age at first birth (years)†				
<20	431	14.5	509	17.1
20 – 30	1687	56.8	1800	60.4
>30	387	13.0	285	9.6
Menopausal status				
Premenopausal	989	33.3	918	30.8
Postmenopausal	1664	56.1	1797	60.3
Age at menopause (years)‡				
<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.

postmenopausal women, the OR was 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 no significant interaction between multivitamin use and postmenopausal hormone use (*P* = 0.82). In addition, age, alcohol use, family history of breast cancer or tumour stage did not significantly modify the association between multivitamin use and breast cancer (*P* for 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

Table 2 Odds ratios and 95 % confidence intervals for the risk of breast cancer according to use of multivitamin supplements among women in Wisconsin, USA, 2002–7

Multivitamin use	Cases/controls	OR*	95 % CI	Multivariable OR†	95 % CI
Status					
Never use	1216/1213	1.00	ref	1.00	ref
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	ref	1.00	ref
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
<i>P</i> 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
<i>P</i> for trend			0.15		0.25
Frequency (no. of times/week)‡					
Never use	1216/1213	1.00	ref	1.00	ref
≤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
<i>P</i> for trend			0.41		0.97

ref, referent category.

*Models were adjusted for reference age.

†Multivariable models were adjusted for reference age, education, BMI, alcohol consumption, 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 and 95 % confidence intervals for the risk of breast cancer according to use of multivitamin supplements among women stratified by menopausal status, Wisconsin, USA, 2002–7

Multivitamin use	Premenopausal			Postmenopausal		
	Cases/controls	Multivariable OR*	95 % CI	Cases/controls	Multivariable OR*	95 % CI
Status						
Never use	417/373	1.00	ref	675/741	1.00	ref
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 (years)						
Never use	417/373	1.00	ref	67/741	1.00	ref
Former use						
<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
<i>P</i> for trend			0.50			0.93
Current use						
<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
<i>P</i> for trend			0.85			0.25
Frequency (no. of times/week)†						
Never use	417/373	1.00	ref	675/741	1.00	ref
≤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
<i>P</i> for trend			0.65			0.97

ref, referent category.

*Multivariable models were adjusted for reference age, education, BMI, alcohol consumption, 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.

this population. Neither current users who used multivitamins for long durations, nor those who took more than one multivitamin per day, had a significantly different risk of breast cancer than those who never took multivitamins. Moreover, menopausal status, family history

of breast cancer, postmenopausal hormone use, tumour stage, alcohol use or age did not modify 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.*⁽¹⁹⁾, 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. 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 Study⁽¹⁵⁾ observed a non-significant inverse association between the risk of oestrogen-receptor-negative breast cancer and past multivitamin use (OR = 0.60, 95% CI 0.42, 1.06). In our study, tumour hormone receptor status was not available. Furthermore, the Nurses' Health Study⁽¹⁴⁾ presented an inverse association (relative risk = 0.57, 95% CI 0.33, 0.98), but the cases were restricted to sixty-seven 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⁾. That 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 from those in the USA. Moreover, the Danish study population had a lower percentage of multivitamin users (26%) compared with 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 range⁽¹⁰⁾.

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 with a different survey where the authors stratified for race and age, 47% of white adults used multivitamin supplements⁽²¹⁾. 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 RDA for a particular nutrient⁽²²⁾. Therefore, the supplement in conjunction with nutrients from food intake could exceed the UL for important nutrients. On average, one multivitamin tablet is a major source of folate and vitamin B₆, and has levels

of these vitamins that are equivalent to, or greater than, the daily RDA for adults in the USA⁽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 the possible confounding effect of total energy intake. However, we did adjust for BMI, which is a strong risk factor for breast cancer and associated with total energy intake⁽²⁰⁾. Also, we did not collect the exact supplement composition in our study, and other studies have found that estimating the exact intake of each micronutrient from dietary supplements is important to evaluating outcomes 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 the present 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 (driver's license and telephone number) for eligible women. This may lead to the inclusion of women who tend to be better educated than 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 limited⁽²⁵⁾. 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 2 years of diagnosis.

The present study has several strengths. It is a population-based study including 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, the present 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 USA 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 the diet.

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