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Dietary and Supplemental Vitamin C Intake and Risk of Breast Cancer: Results from the Nurses' Health Studies

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ABSTRACT

Background: Some previous studies suggested that high supplemental vitamin C intake may be associated with an increased risk of breast cancer, although evidence is inconsistent.

Objectives: Our objective was to study the association between vitamin C intake and breast cancer risks using regularly updated assessments of intake over a long follow-up.

Methods: We prospectively followed 88,041 women aged 33 to 60 years from the Nurses' Health Study (1980–2014) and 93,372 women aged 26 to 45 years from the Nurses' Health Study II (1991–2013). A total of 11,258 incident invasive breast cancers among 181,413 women were diagnosed. Data on vitamin C intake were collected every 2–4 years via a validated FFQ and specific questions on dietary supplement use. Multivariate HRs and 95% CIs for incident invasive breast cancer were estimated with Cox models.

Results: During follow-up, 82% of participants ever used supplements containing vitamin C, including multivitamins. Cumulative total vitamin C intake (HR for quintiles 5 compared with 1 = 0.97; 95% CI: 0.91–1.03; $P_{trend} = 0.81$), dietary vitamin C intake (HR for quintiles 5 compared with 1 = 0.98; 95% CI: 0.92–1.04; $P_{trend} = 0.57$), and supplemental vitamin C intake (HR for quintiles 5 compared with 1 in users = 1.02; 95% CI: 0.94–1.09; $P_{trend} = 0.77$) were not associated with breast cancer risks. Results were unchanged when different exposure latencies were considered. The results did not differ by menopausal status, postmenopausal hormone therapy use, or BMI. No differences were observed by estrogen receptor status of the tumor.

Conclusions: Our results do not support any important association between total, dietary, or supplemental vitamin C intake and breast cancer risks. *J Nutr* 2022;152:835–843.

Keywords: vitamin C, dietary supplements, nutrition, breast cancer, prospective study

Introduction

Vitamin C, as an antioxidant, is expected to protect cells against oxidative DNA damage, and thereby reduce carcinogenesis. However, most trials have reported no effect of vitamin C supplementation on various biomarkers of oxidative DNA damage (1, 2). In vitro and animal studies have suggested both potential beneficial and detrimental effects of vitamin C on carcinogenesis, but the interpretation of these studies is limited by technical considerations, such as the stability of vitamin C under typical incubation conditions and endogenous production of vitamin C in most animal models (1). Concerning breast cancer specifically, 2 studies reported that oral vitamin C supplementation decreased the incidence of breast tumors induced by estrogen in rats (3, 4). In vitro studies of very high vitamin C concentrations that could not be reached with oral supplementation showed that vitamin C had prooxidant effects on some breast cancer cell lines (5–7) but not on normal mammary cells (5, 6, 8). More recently, 1 in vitro study reported that at physiological concentrations, vitamin C induced apoptosis in breast cancer cell lines (9).

In the Women's Antioxidant Cardiovascular Study, a randomized, double-blind, clinical trial of vitamin C, vitamin E, and beta-carotene among 7627 females at high risk of cardiovascular disease, supplementation of 500 mg/day of

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Abbreviations used: AHEI, alternate healthy eating index; ER, estrogen receptor; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; PR, progesterone receptor.

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vitamin C over 9 years was not associated with breast cancer risk, but the influence of larger doses was not investigated (10).

Most prospective cohort studies did not report any association between dietary vitamin C intake and breast cancer risks (11–17). Three cohort studies suggested that high vitamin C intake from dietary supplements (11, 15) or vitamin C supplementation in women with high dietary vitamin C intake (18) could be associated with a higher risk of breast cancer, but others did not (12, 13). In other cohort studies, the highest category of total vitamin C intake at baseline was not associated with breast cancer risk (14, 16, 17). A potential association between high supplemental vitamin C intake and breast cancer risk may have been missed or biased because of methodological issues, such as a single baseline assessment of dietary supplement use in most previous studies (11–13, 15–17), a very low cutoff or unknown level of supplemental vitamin C intake (12, 13, 16, 18) or comparing women with high supplemental vitamin C intake to women with low dietary vitamin C intake for risk estimates (14, 16, 17). The use of multivitamins or individual supplements containing vitamin C is common. Thus, it is important to clarify whether high supplemental vitamin C intake could expose women to an increased risk of breast cancer.

In an earlier study using data from the Nurses' Health Study (NHS) collected between 1980 and 1994, total vitamin C intake ≥710 mg/d was not associated with breast cancer risk compared with lower levels of intake (14). Here, our objectives were: *1*) to prospectively study the association between total vitamin C intake and breast cancer risks in the NHS and Nurses' Health Study II (NHSII) over a longer follow-up period; and *2*) to specifically examine the association between dietary and supplemental vitamin C intake and breast cancer risks using regularly updated quantitative data on dietary and supplemental vitamin C intake.

Methods

Study population

The NHS is a prospective cohort study of 121,700 female registered nurses living across the United States aged 30–55 years at enrollment in 1976. The NHSII is a prospective cohort study of 116,429 female registered nurses from the United States aged 25–42 years at enrollment in 1989. Information about their lifestyle factors and medical history have been collected through self-administered questionnaires every 2 years. The cumulative follow-up in both cohorts is greater than 90%.

Among the 103,268 women from the NHS and 100,835 women from the NHSII who answered the questionnaire used as the baseline in this analysis (1980 for the NHS and 1991 for the NHSII), we excluded participants diagnosed with a cancer other than nonmelanoma skin cancer prior to baseline ($n = 4161$ for the NHS and 1322 for the NHSII), no or extreme dietary data at baseline ($n = 10{,}361$ for the NHS and 5517 for the NHSII) and those who did not answer any additional questionnaire after the baseline questionnaire ($n = 695$ for the NHS and 624 for the NHSII). Thus, data from 88,041 women in the NHS and 93,372 women in the NHSII were available for analysis.

Voluntary return of the questionnaires was considered to imply informed consent. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Identification of breast cancer cases

Breast cancer cases were initially self-reported on questionnaires or identified through death records and then confirmed by physician review of medical records. Information on the hormone receptor status and invasiveness of the tumor was retrieved from clinical pathology reports. In this study, the main outcome was incident invasive breast cancer ($n = 11{,}258$). Since validation studies found that 99% of self-reported breast cancer cases were accurate (99% confirmed with medical review) (19), self-reported cases with no medical record ($n = 924$) were included.

Estrogen receptor (ER) and progesterone receptor (PR) statuses were determined using immunohistochemical staining of tumor tissue (collected for approximately 34% of cases). The procedures for breast cancer tissue collection, tissue microarray construction, and staining and reading for tumor markers have been described in detail elsewhere (20). When tissue microarray results were unavailable, medical record documentation of ER and PR statuses were used instead.

Assessment of vitamin C intake

Dietary vitamin C intake was assessed through a validated semi-quantitative FFQ at baseline and every 4 years thereafter. The validity and reliability of the FFQ has been previously described (21–25). Participants self-reported how often, on average, during the previous year they had consumed a common unit or portion size of foods and beverages. The frequency of consumption of each food and beverage was multiplied by the nutrient content of the portion, as derived from the USDA food composition database and additional information from manufacturers, and then summed to obtain the mean daily dietary vitamin C intake, including fortified foods and beverages, for each participant over the previous year.

At baseline and every 2 years thereafter, participants were asked to report use of supplements containing only vitamin C, including the dose, as well as the brand and type of any multivitamins used. A comprehensive database on multivitamin supplements that provides the dose of vitamin C from each supplement was developed at the Harvard T.H. Chan School of Public Health.

Total vitamin C intake was obtained by summing the estimated vitamin C intakes from diet, vitamin C supplements, and multivitamins. The cumulative average intake for dietary, supplemental, and total vitamin C intakes was assessed at each questionnaire cycle as an average of the vitamin C intake reported since the baseline questionnaire.

Assessment of covariates

Data on menopausal status, parity, postmenopausal hormone use, oral contraceptive use, personal history of benign breast disease, and weight have been collected every 2 years and data on dietary intake, physical activity, and alcohol consumption have been collected every 4 years since baseline. Data on mammography screening have been collected every 2 years since 1990 in the NHS and 1997 in the NHSII. Data on family history of breast cancer have been collected regularly from 1982 in the NHS and 1989 in the NHSII. Data on breastfeeding duration were collected in 1986 in the NHS and every 2 years in the NHSII until 2003. Data on height, BMI at age 18, and age at menarche were collected at baseline.

Statistical analysis

Analyses were conducted in a pooled data set including both NHS and NHSII data. Participants contributed person-time from the date that the baseline questionnaire was returned until the first date of diagnosis of breast or other cancer (except nonmelanoma skin cancer), death, or the end of follow-up (1 June 2014 for the NHS and 1 June 2013 for the NHSII), whichever occurred first.

The associations between vitamin C intake and breast cancer risks were estimated with a Cox proportional hazards models, with age in months as the time scale, to estimate HRs and 95% CIs.

All models were stratified by cohort, age, and calendar time, and updated through follow-up as available. All variables were assessed prospectively. Total, dietary, and supplemental vitamin C cumulative average intakes were assessed at each questionnaire and categorized into quintiles for analyses. Model 1 was unadjusted. Models 2 and 3 were adjusted for the following known risk factors for breast cancer: age at menarche; age at menopause; parity and age at first full-term pregnancy; use of oral contraceptives; use of postmenopausal hormone therapy; personal history of benign breast disease; family history of breast cancer

in first-degree relatives; alcohol consumption; physical activity; BMI at age 18; and weight change since age 18. We additionally adjusted for the modified alternate healthy eating index (AHEI) score without alcohol, as previously described (26), and recent mammography. Dietary and total vitamin C intakes were energy-adjusted using the residual method (27). Model 3 was mutually adjusted for the dietary vitamin C intake and supplemental vitamin C intake. Missing values for covariates were imputed to the value of the previous questionnaire if answered or else to the median or modal category if the percentage of missing values was <5%. If the percentage of missing values was higher, missing values were assigned to a separate category for that covariate.

The median value for each quintile of vitamin C intake was used as a continuous variable to test for trends in HRs across quintiles. We investigated potential interactions between total, dietary, or supplemental vitamin C intakes and menopausal status (premenopausal, postmenopausal), BMI (<25 or ≥25 kg/m^2), or use of postmenopausal hormone therapy in postmenopausal women (never, ever) by including a cross-product interaction term in the multivariable model and performing a likelihood ratio test.

We examined the associations between vitamin C intake and breast cancer risks at different latencies by considering breast cancer cases 0–4, 4–8, 8–12, 12–16, 16–20, and 20–24 years after the vitamin C intake assessment.

We investigated whether the associations differed according to the ER status (ER+ compared with ER−) and ER/PR status (ER+/PR+ compared with ER−/PR− compared with ER+/PR−) of the tumor by performing competing risks models and Wald chi-square tests for heterogeneity.

All statistical tests were 2-sided, and significance was set at the 0.05 level. We performed all analyses with the use of SAS software (version 9.3; SAS Institute).

Results

Characteristics of the study population

During follow-up, 11,258 incident invasive breast cancer cases were diagnosed (7,947 in the NHS and 3,311 in the NHSII) among 181,413 women. At baseline, the mean dietary vitamin C intake was 127 mg/day in the NHS and 129 mg/day in the NHSII, which is above the RDA of 75 mg/day for females.

When considering the dietary vitamin C intake at baseline (foods only), the main contributors were fruit juices, which are generally fortified with vitamin C (27% in the NHS and 28% in the NHSII); vegetables (30% in the NHS and 35% in the NHSII); and whole fruits (26% in the NHS and 21% in the NHSII). Contributions from fruit juices remained stable in the NHS but decreased over time in the NHSII, from 28% in 1991 to 17% in 2011.

The frequency of use of supplements containing vitamin C increased from 39% to 61% between 1980 and 2012 in the NHS and from 45% to 60% between 1991 and 2011 in the NHSII. At baseline, 51% (NHS) and 46% (NHSII) of users had vitamin C supplemental intake from multivitamins only, 16% (both the NHS and NHSII) from supplements with only vitamin C, and 33% (NHS) and 38% (NHSII) from both multivitamins and supplements with only vitamin C. Their mean supplemental vitamin C intakes were 422 mg/day in the NHS and 262 mg/day in the NHSII. Most users had a supplemental vitamin C intake ≥400 mg/d at some point during follow-up (65% in the NHS and 56% in the NHSII), while 39% (NHS) and 35% (NHSII) of users had supplemental intake ≥750 mg/d at some point.

Baseline characteristics associated with higher supplemental vitamin C intakes, compared with nonusers or users of low doses, were similar in the NHS and NHSII (Table 1). Participants with higher supplemental vitamin C intakes were more frequently postmenopausal, users of postmenopausal hormone therapy, and nulliparous. They had higher AHEI scores and were more frequently physically active. Supplemental vitamin C users of any dose were more frequently users of multivitamins and other types of supplements compared with nonusers. These characteristics remained similar over follow-up.

Vitamin C intake and invasive breast cancer risk

We did not observe any association between cumulative average total (Table 2), dietary (Table 3), or supplemental (Table 3) vitamin C intakes and breast cancer risks in unadjusted or adjusted models. Ever using supplemental vitamin C at doses ≥750 mg/d and duration of use of supplements containing only vitamin C were not associated with the breast cancer risk compared with never using any supplements containing vitamin C (Table 4).

The association between the cumulative average dietary vitamin C intake and the breast cancer risk remained null when restricting the analysis to those who never used dietary supplements containing vitamin C (HR for quintile 5 compared with 1 = 0.99; 95% CI: 0.88–1.11; P_{trend} = 0.65). The association between the cumulative average supplemental vitamin C intake and the breast cancer risk remained null when stratifying by quintiles of cumulative average dietary vitamin C intake (data not shown).

Results for the cumulative average vitamin C intake did not differ according to the ER status of the tumor ($P_{heterogeneity}$ = 0.54 for total vitamin C intake, 0.45 for dietary intake, and 0.16 for supplemental intake; Table 2) or ER/PR status of the tumor ($P_{heterogeneity}$ = 0.43 for total vitamin C intake, 0.51 for dietary intake, and 0.35 for supplemental vitamin C intake).

We did not observe any interaction between the cumulative average vitamin C intake and menopausal status ($P_{interaction}$ = 0.44 for total intake, 0.47 for dietary intake and 0.98 for supplemental intake), BMI ($P_{interaction}$ = 0.18 for total intake, 0.91 for dietary intake, and 0.64 for supplemental intake), or postmenopausal hormone therapy use ($P_{interaction}$ values = 0.55 for total intake, 0.59 for dietary intake, and 0.58 for supplemental intake) on the breast cancer risk. There was an interaction between family history of breast cancer in first-degree relatives and total vitamin C intake [$P_{interaction}$ = 0.03; HR for quintiles 5 compared with 1 = 0.89 in those with history (95% CI: 0.77–1.03; P_{trend} = 0.07) and 0.99 in those without history (95% CI: 0.92–1.05; P_{trend} = 0.58)] but not dietary intake ($P_{interaction}$ = 0.10) or supplemental intake ($P_{interaction}$ = 0.09) of vitamin C.

The associations between total, dietary, or supplemental vitamin C intakes and breast cancer risks remained null when vitamin C intake was simply updated rather than when the cumulative average intake was included and when considering events 0–4, 4–8, 8–12, 12–16, 16–20, 20–24, and 24–28 years after assessing the vitamin C intake (Table 5).

Discussion

In the NHS and NHSII, we did not observe any overall association between total or supplemental vitamin C intakes and breast cancer risks during up to 32 years of follow-up.

Most cohort studies did not report any association between dietary vitamin C intake and breast cancer risk (11–17). One study reported that a high dietary vitamin C intake was

TABLE 1 Age and age-standardized characteristics of participants according to their supplemental vitamin C intake at baseline in the NHS (1980; $n = 88,041$) and NHSII (1991; $n = 93,372$)[1]

	NHS				NHSII			
Characteristics	Nonusers	Quintile 1	Quintile 3	Quintile 5	Nonusers	Quintile 1	Quintile 3	Quintile 5
n	53,473	4668	6482	7077	51,125	8455	8420	8621
Age, years	46.0 ± 7.1	44.9 ± 7.1	46.9 ± 7.3	47.2 ± 7.1	36.8 ± 4.6	36.0 ± 4.6	35.2 ± 4.6	37.6 ± 4.5
Dietary factors and physical activity								
Dietary vitamin C intake, mg/d	124 ± 70	127 ± 67	133 ± 71	136 ± 73	121 ± 68	130 ± 68	141 ± 75	143 ± 80
Supplemental vitamin C intake in users, mg/d	NA	36 ± 12	201 ± 60	1303 ± 1083	NA	36 ± 10	107 ± 21	845 ± 368
Use of single vitamin C supplements, %	NA	6.9	54.9	86.4	NA	7.1	42.4	93.5
Use of multivitamins, %	1.9	96.0	73.6	78.1	8.4	94.5	74.8	81.3
Total energy intake without alcohol, kcal/d	1555 ± 499	1609 ± 496	1593 ± 506	1568 ± 506	1758 ± 541	1826 ± 551	1875 ± 554	1794 ± 561
Alcohol intake, g/d	6.2 ± 10.4	6.8 ± 10.7	6.5 ± 10.8	6.8 ± 11.0	3.1 ± 6.0	3.2 ± 6.2	2.7 ± 5.3	3.7 ± 6.7
AHEI score (in 1984 for NHS)	41.7 ± 9.8	42.5 ± 10.1	44.0 ± 10.3	46.8 ± 11.4	42.9 ± 10.2	43.8 ± 10.1	44.3 ± 10.3	47.8 ± 11.1
Physical activity level (in 1986 for NHS), MET-h/wk	12.0 + 17.0	13.4 + 17.7	13.7 + 19.7	14.3 + 22.7	19.3 ± 25.3	20.7 ± 27.2	20.8 ± 27.2	26.9 ± 34.0
Reproductive factors								
Menopausal status, %								
Premenopausal	60.9	60.3	58.8	58.0	92.1	93.4	92.8	92.2
Postmenopausal	32.9	33.7	35.1	34.8	7.7	6.4	6.8	7.6
Unknown	6.2	6.0	6.2	7.2	0.2	0.2	0.5	0.2
Age at menopause, y	47.0 ± 5.8	47.5 ± 6.3	47.2 ± 5.5	46.7 ± 5.9	38.9 ± 4.3	39.5 ± 4.1	38.6 ± 5.1	38.5 ± 4.2
Postmenopausal hormone therapy use, %								
Never	82.6	80.5	78.4	75.5	96.1	96.7	96.4	95.5
Current	7.0	8.7	10.6	11.5	3.0	2.5	2.8	3.7
Past	10.4	10.8	11.0	13.1	0.9	0.8	0.8	0.8
Age at menarche <12 years, %	23.1	22.4	23.0	23.7	24.9	23.1	23.7	23.8
Parity, %								
Nulliparous	5.6	4.6	6.5	7.4	24.4	23.2	21.0	39.5
1 child	7.0	6.7	7.4	8.5	16.3	17.2	18.9	16.9
2 + children	87.4	88.7	86.1	84.0	59.3	59.5	60.0	43.7
Age at first birth, years	25.1 ± 3.3	25.2 ± 3.2	25.2 ± 3.4	25.1 ± 3.4	25.5 ± 4.0	26.0 ± 4.1	26.7 ± 4.5	26.0 ± 4.3
Duration of breastfeeding, months	3.2 ± 2.5	3.4 ± 2.5	3.4 ± 2.6	3.4 ± 2.6	0.3 ± 0.4	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.4
Ever use of oral contraceptive, %	48.3	48.9	50.2	50.8	88.1	89.3	93.5	88.7
Medical factors								
Personal history of benign breast disease, %	23.2	25.3	27.4	27.8	9.5	9.5	9.1	9.9
Family history of breast cancer, %	6.1	6.1	6.1	6.6	5.8	5.9	6.2	6.5
Anthropometric factors								
Height, cm	164 ± 8.2	164 ± 7.6	164 ± 9.2	164 ± 8.2	165 ± 6.6	165 ± 6.5	165 ± 6.7	165 ± 6.7
BMI, kg/m^2	24.6 ± 4.6	24.0 ± 4.1	24.0 ± 4.1	24.1 ± 4.5	24.8 ± 5.4	24.2 ± 4.8	24.8 ± 5.0	23.9 ± 4.9
BMI at age 18, kg/m^2	21.4 ± 3.0	21.1 ± 2.8	21.2 ± 2.9	21.4 ± 3.1	21.3 ± 3.4	21.1 ± 3.0	21.2 ± 3.2	21.2 ± 3.3
Weight change since age 18, kg	6.7 ± 9.9	6.1 ± 8.9	6.1 ± 9.3	5.9 ± 9.6	9.6 ± 11.7	8.8 ± 10.5	10.0 ± 11.0	7.6 ± 11.2

[1]Vitamin C intake was adjusted for total energy intake using the residual method. Data are shown as percentage or mean ± SD. Abbreviations: AHEI, alternate healthy eating index; MET, metabolic equivalent of task; NA, not applicable; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.

TABLE 2 HRs of invasive breast cancer associated with cumulative average total vitamin C intake in the NHS (1980–2014; $n = 88{,}041$) and NHSII (1991–2013; $n = 93{,}372$)[1]

	Median, mg/d	All tumors			ER+ tumors		ER− tumors		$P_{\text{heterogeneity ER status}}$[4]
		No. of cases/person-years	HR (95% CI)[2]	HR (95% CI)[3]	No. of cases/person-years	HR (95% CI)[3]	No. of cases/person-years	HR (95% CI)[3]	
NHS									
Quintile 1	105	1452/480,533	1 (ref)	1 (ref)	956/480,533	1 (ref)	249/480,533	1 (ref)	
Quintile 2	167	1593/499,223	1.03 (0.95–1.10)	0.98 (0.91–1.05)	1116/499,223	1.01 (0.93–1.10)	262/499,223	0.96 (0.81–1.15)	
Quintile 3	237	1621/499,331	1.04 (0.97–1.11)	0.98 (0.91–1.05)	1136/499,331	1.00 (0.92–1.09)	251/499,331	0.91 (0.76–1.09)	
Quintile 4	371	1660/498,641	1.06 (0.99–1.14)	0.98 (0.91–1.05)	1171/498,641	1.00 (0.92–1.09)	265/498,641	0.94 (0.79–1.13)	
Quintile 5	723	1621/474,478	1.07 (1.00–1.15)	0.99 (0.92–1.06)	1097/474,478	0.98 (0.89–1.07)	263/474,478	0.98 (0.82–1.17)	
—	—	—	$P_{\text{trend}} = 0.06$	$P_{\text{trend}} = 0.97$	—	$P_{\text{trend}} = 0.46$	—	$P_{\text{trend}} = 0.92$	0.68
NHSII									
Quintile 1	88	663/383,385	1 (ref)	1 (ref)	436/383,385	1 (ref)	110/383,385	1 (ref)	
Quintile 2	139	653/394,836	0.96 (0.86–1.07)	0.92 (0.83–1.03)	426/394,836	0.90 (0.79–1.03)	104/394,836	0.88 (0.67–1.16)	
Quintile 3	197	642/393,514	0.95 (0.85–1.05)	0.90 (0.81–1.00)	421/393,514	0.87 (0.76–1.00)	107/393,514	0.92 (0.70–1.20)	
Quintile 4	305	659/391,260	0.97 (0.87–1.09)	0.92 (0.82–1.02)	454/391,260	0.93 (0.81–1.06)	110/391,260	0.96 (0.73–1.26)	
Quintile 5	625	694/380,880	0.99 (0.89–1.11)	0.92 (0.83–1.03)	461/380,880	0.90 (0.78–1.03)	114/380,880	0.99 (0.75–1.30)	
—	—	—	$P_{\text{trend}} = 0.71$	$P_{\text{trend}} = 0.47$	—	$P_{\text{trend}} = 0.42$	—	$P_{\text{trend}} = 0.73$	0.51
Pooled									
Quintile 1	105	2115/863,919	1 (ref)	1 (ref)	1392/863,919	1 (ref)	359/863,919	1 (ref)	
Quintile 2	167	2246/894,059	0.99 (0.94–1.06)	0.95 (0.90–1.01)	1542/894,059	0.97 (0.90–1.04)	366/894,059	0.95 (0.82–1.10)	
Quintile 3	237	2263/892,845	1.01 (0.95–1.07)	0.95 (0.90–1.01)	1557/892,845	0.96 (0.89–1.03)	358/892,845	0.93 (0.80–1.07)	
Quintile 4	371	2319/889,901	1.03 (0.97–1.09)	0.96 (0.90–1.02)	1625/889,901	0.98 (0.91–1.05)	375/889,901	0.93 (0.80–1.08)	
Quintile 5	723	2315/855,358	1.05 (0.99–1.11)	0.97 (0.91–1.03)	1558/855,358	0.95 (0.88–1.02)	377/855,358	0.99 (0.85–1.15)	
—	—	—	$P_{\text{trend}} = 0.05$	$P_{\text{trend}} = 0.81$	—	$P_{\text{trend}} = 0.37$	—	$P_{\text{trend}} = 0.82$	0.54

[1] Vitamin C intake was adjusted for total energy intake using the residual method. Numbers do not add up to total numbers of cases and person-years because of missing values. Abbreviations: AHEI, alternate healthy eating index; ER, estrogen receptor; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.

[2] Unadjusted. Stratified by age and period.

[3] Adjusted for menopausal status and age at menopause (premenopausal; postmenopausal and <45 years at menopause; postmenopausal and 45–49 years at menopause; postmenopausal and 50–52 years at menopause; postmenopausal and ≥53 years at menopause; missing; time-dependent), age at menarche (<12, 12 to <13, 13 to <14, 14 to <15, ≥15 years), parity and age at first birth (nulliparous; 1 child and <25 years at first birth; 1 child and ≥25 years at first birth; ≥2 children and <25 years at first birth; ≥2 children and ≥25 years at first birth; missing; time-dependent), use of oral contraceptive (ever, never; time-dependent), personal history of biopsy-confirmed benign breast disease (yes, no; time-dependent), family history of breast cancer (yes, no; time-dependent), cumulative average alcohol intake (nonusers and quartiles of intakes; time-dependent), BMI at age 18 (<19, 19 to <21, 21 to <23, 23 to <27, ≥27 kg/m2, missing), weight change since age 18 by menopausal status (lost ≥2 kg and premenopausal; lost <2 kg or gained ≤2 kg and premenopausal; gained >2 to 5 kg and premenopausal; gained >5 to 10 kg and premenopausal; gained >10 to 20 kg and premenopausal; gained >20 to 25 kg and premenopausal; gained ≥25 kg and premenopausal; lost ≥2 kg and postmenopausal; lost <2 kg or gained ≤2 kg and postmenopausal; gained >2 to 5 kg and postmenopausal; gained >5 to 10 kg and postmenopausal; gained >10 to 20 kg and postmenopausal; gained >20 to 25 kg and postmenopausal; gained ≥25 kg and postmenopausal; missing; time-dependent), physical activity (quintiles and missing category; time-dependent), recent mammography (yes, no, missing; time-dependent), postmenopausal hormone use (never, past, current, missing; time-dependent), duration of use of postmenopausal hormone therapy with estrogen alone (continuous in months; time-dependent), duration of use of estrogen and progestin postmenopausal hormone therapy (continuous in months), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, ≥1.75 meters), total duration of lactation (<12, ≥12 months), and AHEI score without alcohol (quintiles and missing category; time-dependent). Stratified by age and period and additionally stratified by cohort in pooled analyses.

[4] The median value for each quintile of vitamin C cumulative average intake was used as a continuous variable to test for heterogeneity across ER+ and ER- breast tumors.

TABLE 3 HRs of invasive breast cancer associated with cumulative average dietary and supplemental vitamin C intake in the NHS (1980–2014; $n = 88{,}041$) and NHSII (1991–2013; $n = 93{,}372$)[1]

	Dietary vitamin C intake				Supplemental vitamin C intake			
	Median, mg/d	No. of cases/person-years	HR (95% CI)[2]	HR (95% CI)[3]	Median, mg/d	No. of cases/person-years	HR (95% CI)[2]	HR (95% CI)[3]
NHS								
Quintile 1	76	1505/478,025	1 (ref)	1 (ref)	23	1118/325,936	1 (ref)	1 (ref)
Quintile 2	110	1600/501,631	1.00 (0.93–1.07)	0.96 (0.90–1.04)	60	1060/323,735	0.97 (0.89–1.05)	0.97 (0.89–1.06)
Quintile 3	137	1617/502,616	0.99 (0.92–1.06)	0.94 (0.88–1.01)	139	1139/325,885	1.01 (0.93–1.09)	0.98 (0.90–1.07)
Quintile 4	167	1689/501,743	1.02 (0.95–1.10)	0.98 (0.91–1.05)	298	1194/324,466	1.06 (0.97–1.15)	1.03 (0.95–1.12)
Quintile 5	218	1536/468,192	1.00 (0.93–1.07)	0.97 (0.90–1.04)	652	1033/300,888	0.99 (0.91–1.07)	0.97 (0.89–1.05)
—	—	—	$P_{trend} = 0.83$	$P_{trend} = 0.62$	—	—	$P_{trend} = 0.73$	$P_{trend} = 0.74$
NHSII								
Quintile 1	63	641/384,334	1 (ref)	1 (ref)	21	439/268,518	1 (ref)	1 (ref)
Quintile 2	92	708/396,290	1.07 (0.96–1.19)	1.04 (0.94–1.16)	46	441/256,218	1.09 (0.96–1.25)	1.11 (0.97–1.27)
Quintile 3	117	641/394,030	0.96 (0.86–1.07)	0.93 (0.83–1.04)	98	461/260,297	1.11 (0.97–1.26)	1.11 (0.97–1.26)
Quintile 4	147	668/393,090	1.00 (0.89–1.11)	0.96 (0.86–1.07)	231	472/261,119	1.06 (0.93–1.21)	1.05 (0.92–1.19)
Quintile 5	200	653/376,131	1.03 (0.92–1.15)	1.00 (0.89–1.12)	558	501/247,581	1.14 (1.01–1.30)	1.13 (0.99–1.29)
—	—	—	$P_{trend} = 0.88$	$P_{trend} = 0.76$	—	—	$P_{trend} = 0.12$	$P_{trend} = 0.22$
Pooled								
Quintile 1	76	2146/862,359	1 (ref)	1 (ref)	21	1557/594,455	1 (ref)	1 (ref)
Quintile 2	110	2308/897,921	1.02 (0.96–1.08)	0.99 (0.93–1.05)	51	1501/579,953	1.00 (0.93–1.08)	1.01 (0.94–1.09)
Quintile 3	137	2258/896,645	0.98 (0.92–1.04)	0.94 (0.88–1.00)	118	1600/586,182	1.04 (0.97–1.11)	1.02 (0.95–1.09)
Quintile 4	167	2357/894,833	1.02 (0.96–1.08)	0.97 (0.92–1.03)	265	1666/585,584	1.06 (0.99–1.13)	1.04 (0.97–1.11)
Quintile 5	218	2189/844,322	1.01 (0.95–1.07)	0.98 (0.92–1.04)	601	1534/548,469	1.03 (0.96–1.11)	1.02 (0.94–1.09)
—	—	—	$P_{trend} = 0.80$	$P_{trend} = 0.57$	—	—	$P_{trend} = 0.29$	$P_{trend} = 0.77$

[1]Vitamin C intake was adjusted for total energy intake using the residual method. Numbers do not add up to total numbers of cases and person-years because of missing values. Abbreviations: AHEI, alternate healthy eating index; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.
[2]Unadjusted. Stratified by age and period.
[3]Adjusted for menopausal status and age at menopause (premenopausal; postmenopausal and <45 years at menopause; postmenopausal and 45–49 years at menopause; postmenopausal and 50–52 years at menopause; postmenopausal and ≥53 years at menopause; missing; time-dependent), age at menarche (<12, 12 to <13, 13 to <14, 14 to <15, ≥15 years), parity and age at first birth (nulliparous; 1 child and <25 years at first birth; 1 child and ≥25 years at first birth; ≥2 children and <25 years at first birth; ≥2 children and ≥25 years at first birth; missing; time-dependent), use of oral contraceptive (ever, never; time-dependent), personal history of biopsy-confirmed benign breast disease (yes, no; time-dependent), family history of breast cancer (yes, no; time-dependent), cumulative average alcohol intake (nonusers and quartiles of intakes; time-dependent), BMI at age 18 (<19, 19 to <21, 21 to <23, 23 to <27, ≥27 kg/m2, missing), weight change since age 18 by menopausal status (lost ≥2 kg and premenopausal; lost <2 kg or gained ≤2 kg and premenopausal; gained >2 to 5 kg and premenopausal; gained >5 to 10 kg and premenopausal; gained >10 to 20 kg and premenopausal; gained >20 to 25 kg and premenopausal; gained ≥25 kg and premenopausal; lost ≥2 kg and postmenopausal; lost <2 kg or gained ≤2 kg and postmenopausal; gained >2 to 5 kg and postmenopausal; gained >5 to 10 kg and postmenopausal; gained >10 to 20 kg and postmenopausal; gained >20 to 25 kg and postmenopausal; gained ≥25 kg and postmenopausal; missing; time-dependent), physical activity (quintiles and missing category; time-dependent), recent mammography (yes, no, missing; time-dependent), postmenopausal hormone use (never, past, current, missing; time-dependent), duration of use of postmenopausal hormone therapy with estrogen alone (continuous in months; time-dependent), duration of use of estrogen and progestin postmenopausal hormone therapy (continuous in months), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, ≥1.75 meters), total duration of lactation (<12, ≥12 months), AHEI score without alcohol (quintiles and missing category; time-dependent), and mutually adjusted for dietary vitamin C intake (quintiles and missing category; time-dependent) or use of supplements containing vitamin C (never, current, past, missing; time-dependent). Stratified by age and period and additionally stratified by cohort in pooled analyses.

associated with a decreased risk of breast cancer in participants who never used dietary supplements containing vitamin C only (18). In our study, the dietary vitamin C intake was not associated with the breast cancer risk when restricting the analyses to those who never used supplements containing vitamin C. In a previous study in the NHS and NHSII, high compared with low consumption of fruits and vegetables rich in vitamin C, but not fruit juices, was associated with a decreased risk of breast cancer (28). It is possible that the observed association was due to components of the fruits and vegetables other than vitamin C, given our null findings regarding the vitamin C intake specifically.

Three previous prospective studies suggested a potential increased risk of breast cancer associated with high supplemental vitamin C intake. In 2 North American cohort studies, supplemental vitamin C intake ≥711 mg/day (15) or ≥250 mg/day (11) at baseline was associated with an increased risk of breast cancer compared to nonuse. Two other studies comparing a low supplemental vitamin C intake (>50 mg/day) with nonuse (12) or comparing use and nonuse of supplemental vitamin C (13) at baseline did not observe any association with the breast cancer risk. In the Women's Antioxidant Cardiovascular Study, a randomized, double-blind, clinical trial of vitamin C, vitamin E, and beta-carotene among 7627 females at high risk of cardiovascular disease, supplementation of 500 mg/day of vitamin C for 9 years was not associated with the overall breast cancer risk but was associated with an increased breast cancer risk in women with a BMI < 25 kg/m^2 (10). In the E3N (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale) French cohort, ever using supplements containing vitamin C was associated with an increased risk of breast cancer compared to never using supplements among women with the highest level of dietary vitamin C intake only (18). Our results remained null when we stratified by dietary vitamin C intake or BMI in the current study.

In 1 study that reported an increased risk of breast cancer associated with high supplemental vitamin C intake, a total vitamin C intake at baseline ≥686 mg/day compared with <97 mg/day was associated with an 18% increased risk

TABLE 4 HRs of invasive breast cancer associated with the use of dietary supplements containing vitamin C in the NHS (1980–2014; $n = 88{,}041$) and NHSII (1991–2013; $n = 93{,}372$)[1]

Pooled	No. of cases/person-years	HR (95% CI)[2]	HR (95% CI)[3]	HR (95% CI)[4]
Ever supplemental vitamin C intake ≥750 mg/day				
Never use	3103/1,412,452	1 (ref)	1 (ref)	1 (ref)
Ever use ≥750 mg/d	2888/976,073	1.06 (1.00–1.11)	0.96 (0.90–1.01)	0.96 (0.90–1.01)
Ever use <750 mg/d	5267/2,007,555	1.04 (0.99–1.09)	0.97 (0.93–1.02)	0.97 (0.92–1.02)
Duration of use of single vitamin C supplements				
Never use of any supplement with vitamin C	3103/1,412,452	1 (ref)	1 (ref)	1 (ref)
Current use, <5 years	628/270,176	1.05 (0.96–1.14)	0.96 (0.88–1.04)	0.95 (0.87–1.04)
Current use, 5–9 years	602/224,035	1.05 (0.96–1.14)	0.94 (0.86–1.03)	0.94 (0.86–1.03)
Current use, ≥10 years	1329/395,256	1.11 (1.04–1.19)	0.97 (0.91–1.04)	0.97 (0.91–1.04)
Past use, <5 years	1098/364,227	1.12 (1.04–1.20)	1.00 (0.93–1.07)	0.99 (0.92–1.07)
Past use, 5–9 years	525/170,352	1.08 (0.98–1.18)	0.95 (0.87–1.05)	0.95 (0.86–1.05)
Past use, ≥10 years	517/161,107	1.06 (0.96–1.17)	0.93 (0.84–1.02)	0.93 (0.84–1.02)
Ever use of multivitamins containing vitamin C	2912/1,217,158	0.99 (0.94–1.04)	0.97 (0.92–1.02)	0.97 (0.92–1.02)

[1] Numbers do not add up to total numbers of cases and person-years because of missing values. Abbreviations: AHEI, alternate healthy eating index; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.
[2] Unadjusted. Stratified by age and period.
[3] Adjusted for menopausal status and age at menopause (premenopausal; postmenopausal and <45 years at menopause; postmenopausal and 45–49 years at menopause; postmenopausal and 50–52 years at menopause; postmenopausal and ≥53 years at menopause; missing; time-dependent), age at menarche (<12, 12 to <13, 13 to <14, 14 to <15, ≥15 years), parity and age at first birth (nulliparous; 1 child and <25 years at first birth; 1 child and ≥25 years at first birth; ≥2 children and <25 years at first birth; ≥2 children and ≥25 years at first birth; missing; time-dependent), use of oral contraceptive (ever, never; time-dependent), personal history of biopsy-confirmed benign breast disease (yes, no; time-dependent), family history of breast cancer (yes, no; time-dependent), total energy intake without alcohol (quintiles; time-dependent), cumulative average alcohol intake (nonusers and quartiles of intakes; time-dependent), BMI at age 18 (<19, 19 to <21, 21 to <23, 23 to <27, ≥27 kg/m2, missing), weight change since age 18 by menopausal status (lost ≥2 kg and premenopausal; lost <2 kg or gained ≤2 kg and premenopausal; gained >2 to 5 kg and premenopausal; gained >5 to 10 kg and premenopausal; gained >10 to 20 kg and premenopausal; gained >20 to 25 kg and premenopausal; gained ≥25 kg and premenopausal; lost ≥2 kg and postmenopausal; lost <2 kg or gained ≤2 kg and postmenopausal; gained >2 to 5 kg and postmenopausal; gained >5 to 10 kg and postmenopausal; gained >10 to 20 kg and postmenopausal; gained >20 to 25 kg and postmenopausal; gained ≥25 kg and postmenopausal; missing; time-dependent), physical activity (quintiles and missing category; time-dependent), recent mammography (yes, no, missing; time-dependent), postmenopausal hormone use (never, past, current, missing; time-dependent), duration of use of postmenopausal hormone therapy with estrogen alone (continuous in months; time-dependent), duration of use of estrogen and progestin postmenopausal hormone therapy (continuous in months), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, ≥1.75 meters), and total duration of lactation (<12, ≥12 months). Stratified by age and period and additionally stratified by cohort in pooled analyses.
[4] Additionally adjusted for AHEI score without alcohol (quintiles and missing category; time-dependent) and dietary vitamin C intake.

of breast cancer (15). In an earlier study conducted in the NHSII cohort from 1980 to 1994, total vitamin C intakes at similar levels were not associated with breast cancer risks (14). The association with supplemental vitamin C intake was not specifically addressed. Other studies that considered lower levels of total vitamin C intakes at baseline (>203 mg/day compared with ≤98 mg/day or >414 mg/day compared with ≤ 39 mg/day) did not observe any association (16, 17).

The main strength of our study is that we had regularly updated quantitative data on the use of dietary supplements containing vitamin C, which allowed us to better estimate supplemental vitamin C intakes and to conduct latency analyses. Other strengths include the prospective design, large sample of both pre- and postmenopausal women, long follow-up, and information on a large set of potential confounders.

We cannot exclude potential residual confounding, although adjustments for potential confounders and considering different reference categories (never users or users of lower doses) had minor impacts on risk estimates. Our results may not be generalizable to the general US population or other populations. We cannot rule out a potential association in individuals with poorer dietary vitamin C intakes or with very high doses of supplemental vitamin C (≥1000 mg/day).

In conclusion, our results in 2 large cohort studies with repeated quantitative data on dietary and supplemental vitamin C intakes do not support an association between total, dietary, or supplemental vitamin C intakes and breast cancer risks.

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The authors' responsibilities were as follows—CC, WCW, and AHE: designed the research; CC: performed the statistical analysis and drafted the manuscript; WCW: led the data collection on dietary intake and dietary supplement use; MSF, BAR, WCW, and AHE: critically reviewed the manuscript; CC and AHE: had primary responsibility for the final content; and all authors: read and approved the final manuscript.

TABLE 5 HRs of invasive breast cancer associated with dietary and supplemental vitamin C intake in the NHS (1980–2014; $n = 88{,}041$) and NHSII (1991–2013; $n = 93{,}372$)[1]

	Total vitamin C intake		Dietary vitamin C intake		Supplemental vitamin C intake	
	No. of cases	HR (95% CI)[2]	No. of cases	HR (95% CI)[3]	No. of cases	HR (95% CI)[4]
Lag 0–4 years						
Quintile 1	1956	1 (ref)	2005	1 (ref)	926	1 (ref)
Quintile 2	2062	1.01 (0.95–1.07)	1984	0.95 (0.89–1.01)	129	0.97 (0.89–1.05)
Quintile 3	1976	0.94 (0.89–1.01)	2068	0.97 (0.91–1.04)	1024	0.95 (0.86–1.03)
Quintile 4	2010	0.97 (0.91–1.03)	2090	0.97 (0.91–1.03)	1211	1.00 (0.92–1.09)
Quintile 5	2118	0.99 (0.93–1.05)	1975	0.94 (0.89–1.01)	1192	0.99 (0.91–1.08)
—	—	$P_{trend} = 0.89$	—	$P_{trend} = 0.24$	—	$P_{trend} = 0.39$
Lag 4–8 years						
Quintile 1	1706	1 (ref)	1715	1 (ref)	656	1 (ref)
Quintile 2	1706	0.94 (0.88–1.01)	1743	0.96 (0.90–1.03)	1100	1.06 (0.96–1.17)
Quintile 3	1796	0.97 (0.91–1.04)	1745	0.95 (0.89–1.01)	795	0.99 (0.89–1.10)
Quintile 4	1726	0.95 (0.89–1.02)	1808	0.97 (0.90–1.04)	905	1.03 (0.93–1.14)
Quintile 5	1842	0.97 (0.91–1.04)	1765	0.98 (0.91–1.05)	888	1.02 (0.92–1.13)
—	—	$P_{trend} = 0.98$	—	$P_{trend} = 0.71$	—	$P_{trend} = 0.73$
Lag 8–12 years						
Quintile 1	1515	1 (ref)	1546	1 (ref)	605	1 (ref)
Quintile 2	1598	0.99 (0.93–1.07)	1547	0.94 (0.88–1.01)	875	0.99 (0.89–1.10)
Quintile 3	1592	0.98 (0.91–1.05)	1648	0.99 (0.92–1.06)	773	1.06 (0.95–1.17)
Quintile 4	1617	1.01 (0.94–1.08)	1595	0.95 (0.88–1.02)	761	0.96 (0.87–1.07)
Quintile 5	1625	0.98 (0.91–1.06)	1611	0.99 (0.92–1.07)	796	1.06 (0.95–1.17)
—	—	$P_{trend} = 0.60$	—	$P_{trend} = 0.91$	—	$P_{trend} = 0.55$
Lag 12–16 years						
Quintile 1	1272	1 (ref)	1262	1 (ref)	477	1 (ref)
Quintile 2	1241	0.93 (0.79–1.09)	1286	0.97 (0.83–1.14)	689	0.93 (0.74–1.16)
Quintile 3	1306	0.95 (0.81–1.12)	1296	1.01 (0.86–1.19)	530	0.81 (0.63–1.02)
Quintile 4	1250	0.94 (0.80–1.11)	1304	0.97 (0.82–1.14)	614	1.00 (0.80–1.25)
Quintile 5	1288	0.94 (0.79–1.10)	1209	0.83 (0.70–0.99)	567	0.86 (0.69–1.09)
—	—	$P_{trend} = 0.96$	—	$P_{trend} = 0.05$	—	$P_{trend} = 0.85$
Lag 16–20 years						
Quintile 1	964	1 (ref)	973	1 (ref)	333	1 (ref)
Quintile 2	989	0.97 (0.89–1.06)	967	0.93 (0.85–1.02)	469	0.94 (0.81–1.08)
Quintile 3	1015	1.00 (0.91–1.09)	1000	0.97 (0.89–1.07)	418	1.00 (0.86–1.15)
Quintile 4	956	0.97 (0.88–1.06)	1008	0.96 (0.88–1.05)	354	0.83 (0.71–0.96)
Quintile 5	946	0.94 (0.85–1.03)	922	0.92 (0.84–1.01)	397	0.93 (0.80–1.07)
—	—	$P_{trend} = 0.11$	—	$P_{trend} = 0.19$	—	$P_{trend} = 0.49$
Lag 20–24 years[5]						
Quintile 1	549	1 (ref)	573	1 (ref)	158	1 (ref)
Quintile 2	582	1.02 (0.91–1.15)	548	0.90 (0.80–1.01)	271	1.11 (0.91–1.35)
Quintile 3	590	1.04 (0.92–1.17)	571	0.95 (0.85–1.07)	181	0.93 (0.75–1.16)
Quintile 4	543	0.99 (0.87–1.11)	595	0.98 (0.88–1.11)	206	1.03 (0.84–1.27)
Quintile 5	542	1.00 (0.88–1.12)	519	0.90 (0.79–1.01)	236	1.23 (1.01–1.51)
—	—	$P_{trend} = 0.69$	—	$P_{trend} = 0.30$	—	$P_{trend} = 0.20$
Lag 24–28 years[5]						
Quintile 1	387	1 (ref)	359	1 (ref)	126	1 (ref)
Quintile 2	385	0.97 (0.84–1.11)	369	0.97 (0.83–1.12)	179	1.01 (0.81–1.28)
Quintile 3	409	1.04 (0.90–1.20)	377	1.03 (0.89–1.19)	136	0.96 (0.75–1.22)
Quintile 4	353	0.93 (0.80–1.08)	398	1.07 (0.92–1.23)	128	0.87 (0.68–1.11)
Quintile 5	329	0.90 (0.77–1.04)	360	1.03 (0.88–1.19)	145	1.06 (0.83–1.34)
—	—	$P_{trend} = 0.11$	—	$P_{trend} = 0.49$	—	$P_{trend} = 0.93$

[1]Vitamin C intake was adjusted for total energy intake using the residual method. Numbers do not add up to total numbers of cases and person-years because of missing values. Abbreviations: AHEI, alternate healthy eating index; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.

[2]Adjusted for menopausal status and age at menopause (premenopausal; postmenopausal and <45 years at menopause; postmenopausal and 45–49 years at menopause; postmenopausal and 50–52 years at menopause; postmenopausal and ≥53 years at menopause; missing; time-dependent), age at menarche (<12, 12 to <13, 13 to <14, 14 to <15, ≥15 years), parity and age at first birth (nulliparous; 1 child and <25 years at first birth; 1 child and ≥25 years at first birth; ≥2 children and <25 years at first birth; ≥2 children and ≥25 years at first birth; missing; time-dependent), use of oral contraceptive (ever, never; time-dependent), personal history of biopsy-confirmed benign breast disease (yes, no; time-dependent), family history of breast cancer (yes, no; time-dependent), total energy intake without alcohol (quintiles; time-dependent), cumulative average alcohol intake (nonusers and quartiles of intakes; time-dependent), BMI at age 18 (<19, 19 to <21, 21 to <23, 23 to <27, ≥27 kg/m2, missing), weight change since age 18 by menopausal status (lost ≥2 kg and premenopausal; lost <2 kg or gained ≤2 kg and premenopausal; gained >2 to 5 kg and premenopausal; gained >5 to 10 kg and premenopausal; gained >10 to 20 kg and premenopausal; gained >20 to 25 kg and premenopausal; gained ≥25 kg and premenopausal; lost ≥2 kg and postmenopausal; lost <2 kg or gained ≤2 kg and postmenopausal; gained >2 to 5 kg and postmenopausal; gained >5 to 10 kg and postmenopausal; gained >10 to 20 kg and postmenopausal; gained >20 to 25 kg and postmenopausal; gained ≥25 kg and postmenopausal; missing; time-dependent), physical activity (quintiles and missing category; time-dependent), recent mammography (yes, no, missing; time-dependent), postmenopausal hormone use (never, past, current, missing; time-dependent), duration of use of postmenopausal hormone therapy with estrogen alone (continuous in months; time-dependent), duration of use of estrogen and progestin postmenopausal hormone therapy (continuous in months), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, ≥1.75 meters), total duration of lactation (<12, ≥12 months), AHEI score without alcohol (quintiles and missing category; time-dependent). Stratified by age and period and additionally stratified by cohort in pooled analyses.

[3]Additionally adjusted for the use of supplements containing vitamin C (never, current, past, missing; time-dependent).

[4]Additionally adjusted for dietary vitamin C intake (quintiles and missing category; time-dependent).

[5]Analyses conducted in NHS data only (1980–2012, $n = 88{,}041$).

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending. Investigators who wish to use data collected in the Nurses' Health Studies are encouraged to visit http://www.nurseshealthstudy.org/researchers. Access to statistical codes and datasets will be facilitated following the existing data sharing guidelines provided, which can be found on the study website.

Conflict of Interest

None of the authors reported a conflict of interest related to the study.

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