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Intake of Vitamins A, C, and E and Postmenopausal Breast Cancer

The Iowa Women's Health Study

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The association between dietary antioxidant vitamin intake and the risk of breast cancer was examined in a prospective study of 34,387 postmenopausal women in Iowa. Intakes of vitamins A, C, and E and of retinol and carotenoids were assessed in 1986 by mailed semiquantitative food frequency questionnaire. Through December 31, 1992, 879 incident breast cancer cases occurred in this cohort. There was little suggestion that breast cancer risk was associated with differences in intake of these vitamins. For example, from the lowest to highest total vitamin A intake categorized by quintiles, the age-adjusted relative risks of breast cancer were 1.0, 0.95, 1.17, 1.20, and 0.90 (p trend = 0.92). Similarly unremarkable relative risk patterns were seen for the intakes of vitamins C and E and of retinol and carotenoids. These findings were not altered after adjustment for breast cancer risk factors or in analyses confined to women who reported no supplemental vitamin intake. Exclusion of cases that occurred in the first 2 years of follow-up, under the assumption that women may have increased intake of these vitamins in response to preclinical symptoms of breast cancer, did not suggest an inverse association of these vitamins with the risk of breast cancer. Women who reported consuming at least 500 mg/day of supplemental vitamin C had a relative risk of breast cancer of 0.79 compared with women who did not take supplemental vitamin C, and women who reported consuming more than 10,000 IU/day of vitamin A had a corresponding relative risk of 0.73. However, these relative risks were not statistically significant. These results provide little evidence that intake of these vitamins is associated with breast cancer risk. *Am J Epidemiol* 1996;144:165–74.

ascorbic acid; carotene; prospective studies; vitamin A; vitamin E

It has been suggested that the striking geographic differences in breast cancer incidence and mortality are attributable to environmental factors, particularly diet (1). Considerable research has emphasized the role of dietary fat, although the findings in this area have been inconclusive (2). Relatively less attention has been focused on other dietary factors such as vitamins A, C, and E, although it has been suggested that these vitamins may help prevent the development of various cancers, including breast cancer (3–6). One principal mechanism by which vitamins C and E and the provitamin A carotenoids are thought to influence the pathogenesis of cancer is through their role as antioxidants (3–5, 7). Preformed vitamin A, which occurs in the diet as retinol, also is thought to influence carcinogenesis by its role in cellular differentiation (7), while vitamin C is important in collagen synthesis and therefore in maintenance of the extracellular matrix (7).

The majority of evidence from analytic epidemiology studies of antioxidant vitamins and breast cancer risk comes from case-control studies (2, 6, 8–13). A combined analysis of several such studies indicated support for an inverse association with vitamin C intake (8). There have been at least four previous cohort studies that have examined the role of these vitamins in the prevention of breast cancer. In three of these studies (14–16), a modest inverse association was seen for vitamin A intake, although this was statistically significant in only one of these studies (15). In the fourth, no association was seen between breast cancer risk and dietary antioxidant vitamin intake (17). Given the continued interest in identification of possible dietary factors in the etiology of breast cancer, we examined the association of these vitamins with the risk of breast cancer in the Iowa Women's Health Study.

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Abbreviation: CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

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MATERIALS AND METHODS

Descriptions of the study design and dietary assessment of the Iowa Women's Health Study have been published in detail elsewhere (18–20). In brief, a 16-page questionnaire was mailed in January 1986 to 99,826 women with a valid Iowa driver's license who were between the ages of 55 and 69 years; a total of 41,836 women responded and form the cohort under study.

The questionnaire included information of relevance to breast cancer risk, including family history of breast cancer, pregnancy history, reproductive factors, physical activity, and anthropometry. It also included a semiquantitative food frequency questionnaire with 127 food items and other supplementary questions related to nutrient intake. A section on the intake of vitamin supplements included questions on the use of multivitamins as well as on the use of supplements containing only vitamins A, C, or E, along with ranges of doses consumed per day. Because there are numerous multivitamin preparations, respondents were asked the brand name of the multivitamin and the frequency of intake. These multivitamin brands were coded individually for estimation of intake of vitamins from supplements. Additional questions allowing specification of the type of breakfast cereal consumed, some of which may be fortified with these vitamins, and the type of cooking oil used, which may vary in vitamin E content, were also asked, with answers contributing to estimates of intake. This questionnaire was similar to that used in the 1984 dietary assessment in the Nurses' Health Study (21); however, no information on duration of use was obtained.

The reliability and validity of the food frequency questionnaire have been reported elsewhere (22). For the total intake of vitamins A, E, and C, correlations between the food frequency estimate of intake and estimates from the average of five 24-hour dietary recalls were 0.56, 0.55, and 0.76, respectively. For intake excluding supplements, the correlations for vitamins A, E, and C were 0.14, 0.79, and 0.53, respectively.

For the analyses presented here, women were excluded at baseline if they were not postmenopausal (n = 569), had a mastectomy or partial breast removal (n = 1,870), or had any cancer other than skin cancer at baseline (n = 2,293). Women were also excluded if 30 or more items on the food questionnaire were left blank, or if their responses resulted in extreme energy intake values (<600 or ≥5,000 kcal/day) (n = 2,717). These exclusions left a total of 34,387 women eligible for follow-up.

Women were followed through annual linkage with the State Health Registry of Iowa, which includes a cancer registry that is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Women were also followed through questionnaires mailed in 1988, 1990, and 1992 and through linkage of nonrespondents' identifiers with the National Death Index. For the 1992 follow-up, questionnaires were mailed to 39,789 cohort members after excluding the 2,047 women who were known to have died. A total of 33,017 women returned questionnaires, for a response rate of 83 percent. Through December 31, 1992, corresponding to approximately 7 years of follow-up, 879 cases of breast cancer (*International Classification of Diseases for Oncology* code 174) occurred among the women eligible for follow-up.

The length of follow-up was calculated for each individual in the study as the number of days since completion of the baseline questionnaire until the date of breast cancer diagnosis or, for women without breast cancer, December 31, 1992. Since cancer incidence could be detected only for women who resided in Iowa (breast cancer listed as a cause of death was not included among cases unless otherwise detected by the Iowa SEER program), responses from the follow-up questionnaire and information about deaths were used to calculate different termination dates, as follows: 1) the date of death, for deaths in Iowa; 2) the date moved out of Iowa, if the date was known; 3) the midpoint between the last contact in Iowa and first known date out of Iowa or end of follow-up period, if known to have moved from Iowa but the date of the move was not known; 4) the midpoint between the date of last contact in Iowa and date of death, for non-Iowa deaths.

The association of intake of the vitamins of interest with breast cancer was examined primarily by calculating relative risks from proportional hazards regression analysis. Vitamin intake was categorized by quintiles, and the risk of breast cancer in each category of intake was compared with that in the lowest intake category. The correlation between vitamin intake and total energy intake was not very high (the Spearman correlations of intakes of total vitamin A, vitamin E, and vitamin C with total energy intake were 0.38, 0.32, and 0.23, respectively), and total energy intake was not associated with breast cancer risk (20). However, the effect of including total energy intake as a covariate was examined as it may act as an adjustment factor for potential over- and underreporting of food intake (23). Other covariates that were entered into models were those that were significant predictors of breast cancer risk or accepted breast cancer risk factors. These included age, age at menarche, age at menopause, age at first live birth, parity, family history of breast cancer among first degree relatives, body mass index at baseline and at age 18, waist/hip ratio, educational attainment, and alcohol intake. For all relative risks, 95 percent confidence intervals were calculated.

RESULTS

Table 1 presents associations of several breast cancer risk factors with total intake of vitamins A, E, and C. Most reproductive risk factors were not associated with the level of vitamin intake in this cohort, suggesting that any observed effects of these vitamins on breast cancer risk are unlikely to be confounded by these factors. In general, women with higher vitamin intake tended to have lower waist/hip ratios and were more likely to have graduated from college and to be physically active.

Table 2 presents the age-adjusted relative risks of breast cancer according to the total intake of vitamin A, retinol, carotenoids, and vitamins C and E categorized by quintiles. There was no suggestion of an appreciable association of any of these factors with breast cancer risk. Further adjustment for energy intake or for other variables that may have been potential confounders or breast cancer risk factors did not result in any appreciable alteration of the relative risk estimates (results also presented in table 2).

As is well known, the intake of these vitamins could come from both food sources and supplements. The association of breast cancer risk with vitamin intake from food sources alone is presented in table 3. In order to eliminate any possible effect of supplemental intake on these associations, we limited these analyses to women who did not take supplements containing the relevant vitamin of interest. As with the analyses for total intake, there was no association of any of these dietary factors with breast cancer risk in these analyses. The results after adjustment for energy intake and other potential confounders, also presented in table 3, did not show any indication of an association of these vitamins with breast cancer risk.

The association between vitamin intake from supplements and the risk of breast cancer is presented in table 4. Since at the time of the baseline dietary assessment there were few supplements containing β-carotene that were available, results are presented for supplemental intake from total vitamin A and not for either retinol (virtually synonymous with total vitamin A intake from supplements) or carotenoids from supplements. Women who consumed doses of vitamin A greater than 10,000 IU/day had a modestly decreased age-adjusted risk of breast cancer compared with those who did not take vitamin A supplements (relative risk = 0.73, 95 percent confidence interval (CI) 0.50–1.05). There was also a nonsignificant inverse association of supplemental vitamin C intake with breast cancer risk. Compared with those who did not take vitamin C supplements, women who took supplemental vitamin C in doses between 500 and 1,000 mg/day had an age-adjusted relative risk of breast cancer of 0.79 (95 percent CI 0.60–1.05), while those whose daily dose was greater than 1,000 mg/day had an age-adjusted relative risk of 0.77 (95 percent CI 0.51–1.16). Adjustment for potential confounders did not substantially alter these suggested associations, although the observed relative risk for 500–1,000 mg of daily intake of vitamin C was weakened somewhat (relative risk = 0.86, 95 percent CI 0.65–1.14).

Under the assumption that women may have increased their intake of these vitamins when they developed preclinical symptoms of breast cancer, thereby resulting in no association, analyses were conducted after excluding the first 2 years of cases (table 5). Generally, there was little suggestion that these vitamins were inversely related to breast cancer risk. Indeed, in analyses focused on food sources, there was a suggestion of increased breast cancer risk with increasing intake of total vitamin A (relative risks from lowest to highest intake = 1.0, 0.87, 1.26, 1.23, and 1.26, p trend = 0.050). This appeared to be attributable principally to the intake from provitamin A carotenoids (corresponding relative risks = 1.0, 1.00, 1.31, 1.14, and 1.41, p trend = 0.044) and not to intake from retinol. As with analyses not excluding the first 2 years of follow-up, intake from supplements of greater than 10,000 IU/day of vitamin A was nonsignificantly associated with a lower risk of breast cancer (relative risk = 0.74, 95 percent CI 0.47–1.18) as was supplemental intake of greater than 1,000 mg/day of vitamin C (relative risk = 0.78, 95 percent CI 0.47–1.30).

DISCUSSION

In recent years, there has been increased attention directed at the association of antioxidant vitamins and retinol with the risk of breast and other cancers. This has been spurred in part by the considerable evidence that intake of vegetables and fruits appears to decrease the risk of various cancers (3–7) and by the concomitant search for biologic explanations for these observations. Because of their antioxidant properties and, hence, their cancer prevention potential, vitamins C and E and the provitamin A carotenoids have been the focus of some attention (3–7). In addition, vitamin A-related compounds may play other roles in the prevention of cancer, including promotion of cellular differentiation (4, 7). Although the evidence relating vegetable and fruit intake to the risk of breast cancer is somewhat limited (4, 6), there has been some suggestion from other epidemiologic studies that dietary an-

TABLE 1. Distribution of various risk factors for breast cancer according to antioxidant vitamin intake categorized by quintiles, among 34,387 postmenopausal Iowa women, 1986

Category of antioxidant vitamin intake	Age (years)*			Age at menarche (years)*			Age at menopause (years)*			Age at first live birth (years)*		
	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E
1 (low)	61.2	61.2	61.4	12.9	12.9	12.9	47.3	47.2	47.4	20.4	20.4	20.5
2	61.5	61.6	61.5	12.9	12.8	12.8	47.7	47.8	47.6	20.8	20.9	20.7
3	61.5	61.7	61.6	12.9	12.8	12.8	47.8	47.9	47.8	20.7	20.8	20.8
4	61.8	61.7	61.7	12.8	12.8	12.8	47.9	47.9	47.8	20.8	20.9	20.8
5 (high)	61.9	61.7	61.7	12.8	12.8	12.8	47.8	47.6	47.8	20.9	20.7	20.8
	Body mass index (kg/m²)*			Body mass index at age 18 (kg/m²)*			Waist/hip ratio*			First degree relative with breast cancer (%)		
	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E
1 (low)	27.1	27.0	27.2	21.7	21.7	21.8	0.843	0.843	0.844	12.3	12.1	12.5
2	27.0	27.1	27.2	21.7	21.7	21.7	0.840	0.838	0.839	11.7	12.4	12.4
3	26.9	27.1	27.2	21.6	21.7	21.6	0.837	0.838	0.837	12.6	12.1	11.9
4	27.0	27.0	26.7	21.6	21.6	21.6	0.835	0.836	0.835	11.9	11.8	11.3
5 (high)	26.9	26.7	26.7	21.6	21.6	21.6	0.832	0.831	0.832	11.8	11.9	12.2
	Current alcohol use (%)			Any live births (%)			Education (% college graduates)			Activity (% high)		
	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E	Vitamin A	Vitamin C	Vitamin E
1 (low)	42.1	42.0	40.5	90.6	90.9	90.5	8.5	8.5	9.7	17.4	16.9	18.7
2	45.5	45.4	44.9	91.5	91.1	90.7	11.3	12.5	12.2	21.5	22.3	22.9
3	46.4	45.9	47.2	91.0	90.6	90.8	12.6	14.1	14.0	24.4	26.2	25.5
4	46.0	45.1	47.0	90.9	91.1	91.0	15.4	14.3	15.0	28.5	28.6	27.9
5 (high)	45.5	47.0	45.9	91.0	91.3	92.0	16.3	14.7	13.3	33.2	31.0	30.0

* Average values in each category.

TABLE 2. Relative risks (RRs) and 95% confidence intervals of breast cancer according to total intake of vitamins A, C, and E categorized by quintiles, among 34,387 postmenopausal Iowa women, 1986–1992

	No. of cases					Intake (IU/day)				
	Vitamin A	Retinol	Carot-enoids	Vitamin C	Vitamin E	Vitamin A	Retinol	Carotenoids	Vitamin C†	Vitamin E
Category of intake										
1 (low)	167	180	182	176	168	<7,254	<1,233	<4,426	<112	<5.66
2	159	179	148	180	184	7,254–10,733	1,233–2,983	4,426–6,106	112–161	5.67–7.79
3	196	160	186	161	185	10,734–14,582	2,984–4,858	6,107–8,901	162–227	7.80–12.18
4	203	181	191	206	178	14,583–20,342	4,859–7,491	8,902–13,469	228–391	12.19–35.65
5 (high)	154	179	172	156	164	≥20,343	≥7,492	≥13,470	≥392	≥35.66

	Age-adjusted RR				
	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake					
1 (low)	1.0	1.0	1.0	1.0	1.0
2	0.95 (0.76–1.17)‡	0.98 (0.79–1.20)	0.81 (0.65–1.01)	1.01 (0.82–1.24)	1.09 (0.88–1.34)
3	1.17 (0.95–1.43)	0.88 (0.71–1.09)	1.01 (0.82–1.24)	0.90 (0.73–1.11)	1.09 (0.89–1.35)
4	1.20 (0.98–1.47)	0.99 (0.81–1.22)	1.04 (0.85–1.28)	1.15 (0.94–1.41)	1.05 (0.85–1.29)
5 (high)	0.90 (0.72–1.12)	0.98 (0.79–1.20)	0.92 (0.75–1.14)	0.88 (0.71–1.09)	0.97 (0.78–1.21)
p (trend)	0.92	0.90	0.71	0.61	0.68

	Age- and energy-adjusted RR				
	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake					
1 (low)	1.0	1.0	1.0	1.0	1.0
2	0.94 (0.75–1.17)	0.96 (0.78–1.19)	0.81 (0.65–1.00)	1.00 (0.81–1.24)	1.08 (0.87–1.34)
3	1.15 (0.93–1.42)	0.87 (0.70–1.08)	1.00 (0.81–1.23)	0.89 (0.72–1.11)	1.08 (0.86–1.36)
4	1.18 (0.95–1.46)	0.98 (0.79–1.21)	1.03 (0.83–1.27)	1.14 (0.93–1.40)	1.03 (0.82–1.30)
5 (high)	0.88 (0.70–1.11)	0.96 (0.78–1.19)	0.90 (0.72–1.13)	0.87 (0.70–1.08)	0.96 (0.77–1.21)
p (trend)	0.91	0.80	0.88	0.55	0.63

	Multivariate-adjusted RR*				
	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake					
1 (low)	1.0	1.0	1.0	1.0	1.0
2	0.99 (0.78–1.25)	0.98 (0.79–1.23)	0.80 (0.63–1.00)	1.02 (0.82–1.27)	1.12 (0.89–1.51)
3	1.21 (0.97–1.52)	0.89 (0.71–1.12)	1.00 (0.80–1.24)	0.88 (0.70–1.12)	1.18 (0.92–1.51)
4	1.25 (1.00–1.57)	1.04 (0.83–1.30)	1.02 (0.81–1.27)	1.09 (0.87–1.36)	1.07 (0.84–1.36)
5 (high)	0.88 (0.68–1.14)	1.01 (0.81–1.26)	0.88 (0.70–1.12)	0.88 (0.70–1.11)	1.05 (0.83–1.33)
p (trend)	0.96	0.79	0.98	0.46	0.85

* Relative risks and 95% confidence intervals adjusted for age, energy intake, age at menarche, age at menopause, age at first live birth, parity, body mass index at time of baseline questionnaire, body mass index at age 18, family history of breast cancer, history of benign breast disease, alcohol intake, and educational attainment.

† Intake (mg/day).

‡ Numbers in parentheses, 95% confidence interval.

tioxidants or retinol may be inversely related to breast cancer risk (4, 6, 8–12, 14–16). The results presented here, however, provide no evidence of an association of breast cancer risk with the total intake of vitamin A, C, or E, of provitamin A carotenoids, or of retinol and only weak support for an inverse association with the intake of supplemental vitamin A or C.

These observations are in contrast to the results of several case-control studies that have examined the association of these vitamins with breast cancer risk (4, 7, 8–13). In their combined analysis of breast cancer risk in nine case-control studies, Howe et al. (8) reported inverse associations for dietary intakes of vitamin C, total vitamin A, and β-carotene; the relative risk for the highest versus the lowest intake category was 0.69 for vitamin C and 0.85 for β-carotene. Support for such inverse associations also comes from more recent case-control studies not in-

TABLE 3. Relative risks (RRs) and 95% confidence intervals of breast cancer according to intake of vitamins A, C, and E categorized by quintiles, among postmenopausal Iowa women who did not supplement intake from these vitamins, 1986–1992

	No. of cases					Intake (IU/day)				
	Vitamin A†	Retinol†	Carot-enoids†	Vitamin C‡	Vitamin E§	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake										
1 (low)	114	125	117	96	111	<6,189	<914	<4,349	<87	<4.89
2	100	123	98	102	100	6,189–8,773	914–1,666	4,349–5,967	87–120	4.90–6.23
3	122	111	126	97	119	8,774–11,976	1,667–3,217	5,968–8,485	121–152	6.24–7.60
4	135	113	125	102	123	11,977–16,775	3,218–4,568	8,486–13,047	153–197	7.61–9.64
5 (high)	128	127	133	110	117	≥16,776	≥4,569	≥13,048	≥198	≥9.65

	Age-adjusted RR				
	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake					
1 (low)	1.0	1.0	1.0	1.0	1.0
2	0.87 (0.67–1.14)‖	0.97 (0.75–1.24)	0.83 (0.64–1.09)	1.04 (0.79–1.38)	0.88 (0.67–1.16)
3	1.06 (0.82–1.37)	0.87 (0.67–1.12)	1.06 (0.82–1.36)	0.98 (0.74–1.31)	1.07 (0.82–1.38)
4	1.17 (0.91–1.50)	0.89 (0.69–1.15)	1.05 (0.82–1.35)	1.03 (0.78–1.37)	1.09 (0.85–1.41)
5 (high)	1.09 (0.85–1.40)	0.99 (0.77–1.27)	1.10 (0.86–1.42)	1.12 (0.85–1.47)	1.04 (0.80–1.34)
p (trend)	0.11	0.72	0.13	0.49	0.34

	Age- and energy-adjusted RR				
	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake					
1 (low)	1.0	1.0	1.0	1.0	1.0
2	0.87 (0.67–1.15)	0.95 (0.74–1.23)	0.83 (0.64–1.09)	1.04 (0.79–1.38)	0.91 (0.69–1.20)
3	1.06 (0.82–1.38)	0.84 (0.64–1.10)	1.06 (0.82–1.37)	0.98 (0.74–1.31)	1.12 (0.85–1.48)
4	1.18 (0.91–1.53)	0.87 (0.67–1.13)	1.06 (0.81–1.37)	1.03 (0.77–1.38)	1.17 (0.87–1.58)
5 (high)	1.10 (0.83–1.45)	0.96 (0.73–1.25)	1.11 (0.85–1.45)	1.11 (0.82–1.50)	1.15 (0.81–1.64)
p (trend)	0.13	0.56	0.16	0.56	0.19

	Multivariate-adjusted RR*				
	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake					
1 (low)	1.0	1.0	1.0	1.0	1.0
2	0.88 (0.66–1.18)	1.02 (0.78–1.33)	0.86 (0.64–1.15)	1.02 (0.76–1.37)	0.89 (0.66–1.20)
3	1.15 (0.87–1.52)	0.84 (0.63–1.12)	1.11 (0.84–1.46)	0.95 (0.70–1.29)	1.09 (0.81–1.47)
4	1.21 (0.92–1.61)	0.92 (0.70–1.22)	1.10 (0.81–1.43)	0.96 (0.70–1.31)	1.20 (0.87–1.65)
5 (high)	1.15 (0.85–1.56)	1.04 (0.78–1.39)	1.17 (0.87–1.56)	1.06 (0.77–1.47)	1.08 (0.74–1.58)
p (trend)	0.08	0.95	0.12	0.88	0.32

* Relative risks and 95% confidence intervals adjusted for age, energy intake, age at menarche, age at menopause, age at first live birth, parity, body mass index at time of baseline questionnaire, body mass index at age 18, family history of breast cancer, history of benign breast disease, alcohol intake, and educational attainment.

† Cohort (n = 22,776); breast cancer cases (n = 599).

‡ Cohort (n = 18,910); breast cancer cases (n = 507).

§ Cohort (n = 21,782); breast cancer cases (n = 570).

‖ Numbers in parentheses, 95% confidence interval.

cluded in the analyses of Howe et al. For example, Holmberg et al. (9), in a recent Swedish study, reported inverse associations with β-carotene, retinol, and vitamin E. Similar findings were reported by Graham et al. (10) in a study in western New York, with inverse associations with breast cancer risk noted for carotenoids, vitamin C, and vitamin E. Landa et al. (11) observed inverse associations between dietary vitamin C intake and breast cancer risk in a case-control study in Spain. In a study in Moscow, Zaridze et al. (12) reported inverse associations of vitamin C and β-carotene intake with breast cancer risk.

Although findings specific to individual vitamins differ from study to study, the overall impression from case-control studies is that these vitamins or some

TABLE 4. Relative risks (RRs) and 95% confidence intervals of breast cancer according to supplemental intake of vitamins A, C, and E, among 34,387 postmenopausal Iowa women, 1986–1992

	No. of cases				No. of subjects				No. of person-years			
	Vitamin A	Retinol	Vitamin C	Vitamin E	Vitamin A	Retinol	Vitamin C	Vitamin E	Vitamin A	Retinol	Vitamin C	Vitamin E
Category of intake												
1 (low)	599	600	507	570	22,776	22,825	18,910	21,782	149,659	149,984	124,373	143,117
2	161	175	217	129	7,138	7,404	8,720	5,161	46,850	48,559	57,268	33,950
3	90	81	76	71	2,957	3,032	2,974	2,979	19,321	19,838	19,357	19,536
4	29	23	55	28	1,516	1,126	2,593	1,064	9,893	7,341	17,013	6,942
5 (high)			24	81			1,190	3,401			7,711	22,176

	Intake (IU/day)				Age-adjusted RR			
	Vitamin A	Retinol	Vitamin C†	Vitamin E	Vitamin A	Retinol	Vitamin C	Vitamin E
Category of intake								
1 (low)	0	0	0	0	1.0	1.0	1.0	1.0
2	<5,000	<5,000	<200	<25	0.86 (0.72–1.02)‡	0.90 (0.76–1.06)	0.92 (0.79–1.08)	0.95 (0.78–1.15)
3	5,000–10,000	5,000–10,000	200–500	25–100	1.15 (0.92–1.44)	1.01 (0.80–1.27)	0.95 (0.75–1.22)	0.92 (0.72–1.17)
4	>10,000	>10,000	501–1,000	100–250	0.73 (0.50–1.05)	0.78 (0.51–1.18)	0.79 (0.60–1.04)	1.00 (0.69–1.46)
5 (high)			>1,000	>250			0.77 (0.51–1.16)	0.91 (0.72–1.15)
p (trend)					0.40	0.38	0.13	0.67

	Multivariate-adjusted RR*			
	Vitamin A	Retinol	Vitamin C	Vitamin E
Category of intake				
1 (low)	1.0	1.0	1.0	1.0
2	0.88 (0.74–1.06)	0.92 (0.78–1.10)	0.91 (0.77–1.08)	0.97 (0.79–1.18)
3	1.17 (0.93–1.48)	1.02 (0.80–1.30)	0.94 (0.73–1.21)	0.94 (0.72–1.21)
4	0.71 (0.47–1.06)	0.77 (0.49–1.21)	0.86 (0.65–1.14)	1.06 (0.72–1.57)
5 (high)			0.77 (0.50–1.17)	0.96 (0.76–1.23)
p (trend)	0.35	0.38	0.20	0.97

* Relative risks and 95% confidence intervals adjusted for age, age at menarche, age at menopause, age at first live birth, parity, body mass index at time of baseline questionnaire, body mass index at age 18, family history of breast cancer, history of benign breast disease, alcohol intake, and educational attainment. Further adjustment for energy intake did not alter these results.

† Intake (mg/day).

‡ Numbers in parentheses, 95% confidence interval.

TABLE 5. Multivariate-adjusted relative risks (RRs)* and 95% confidence intervals of breast cancer according to intake of vitamins A, C, and E and excluding the first 2 years of follow-up, among postmenopausal Iowa women, 1986–1992

	Total intake				
	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake					
1 (low)	1.0	1.0	1.0	1.0	1.0
2	1.04 (0.79–1.37)‖	1.08 (0.83–1.40)	0.86 (0.65–1.13)	1.11 (0.85–1.43)	1.16 (0.89–1.51)
3	1.30 (1.00–1.70)	0.93 (0.71–1.22)	1.16 (0.90–1.51)	0.89 (0.67–1.18)	1.09 (0.82–1.46)
4	1.36 (1.04–1.78)	0.97 (0.74–1.27)	1.10 (0.84–1.43)	1.18 (0.91–1.54)	1.04 (0.78–1.39)
5 (high)	1.02 (0.76–1.37)	1.12 (0.86–1.45)	1.02 (0.77–1.35)	0.95 (0.72–1.26)	1.07 (0.81–1.41)
p (trend)	0.37	0.68	0.39	0.93	0.93

	Intake from food sources†				
	Vitamin A	Retinol	Carotenoids	Vitamin C	Vitamin E
Category of intake					
1 (low)	1.0	1.0	1.0	1.0	1.0
2	0.87 (0.61–1.24)	0.98 (0.71–1.34)	1.00 (0.71–1.42)	0.94 (0.66–1.34)	0.85 (0.60–1.20)
3	1.26 (0.91–1.75)	0.92 (0.66–1.29)	1.31 (0.94–1.83)	0.96 (0.67–1.37)	1.10 (0.78–1.56)
4	1.23 (0.88–1.73)	0.92 (0.66–1.28)	1.14 (0.81–1.61)	0.90 (0.62–1.30)	1.07 (0.74–1.56)
5 (high)	1.26 (0.88–1.80)	0.99 (0.70–1.39)	1.41 (0.99–2.00)	1.01 (0.69–1.48)	0.94 (0.60–1.48)
p (trend)	0.050	0.84	0.044	0.95	0.82

	Intake from supplements‡					
	Vitamin A		Vitamin C		Vitamin E	
	Intake (IU/day)	RR§	Intake (mg/day)	RR	Intake (IU/day)	RR
Category of intake						
1 (low)	0	1.0	0	1.0	0	1.0
2	<5,000	0.92 (0.74–1.13)	<200	0.95 (0.76–1.13)	<25	1.00 (0.79–1.26)
3	5,000–10,000	1.15 (0.88–1.52)	200–500	1.02 (0.76–1.37)	25–100	0.91 (0.67–1.24)
4	>10,000	0.74 (0.47–1.18)	501–1,000	0.96 (0.70–1.32)	101–250	1.01 (0.63–1.63)
5 (high)			>1,000	0.78 (0.47–1.30)	>250	1.02 (0.77–1.34)
p (trend)		0.47		0.40		0.91

* Relative risks and 95% confidence intervals adjusted for age, energy intake, age at menarche, age at menopause, age at first live birth, parity, body mass index at time of baseline questionnaire, body mass index at age 18, family history of breast cancer, history of benign breast disease, alcohol intake, and educational attainment. Excluding the first 2 years of follow-up, the cohort size is 33,515 women, of whom 643 had incident breast cancers through December 31, 1992.

† Among cohort members who did not have supplemental intake of the vitamin of interest.

‡ Intake categories are as provided in the table.

§ Adjusted for all the covariates listed above except for energy intake.

‖ Numbers in parentheses, 95% confidence interval.

correlate of their intake may be associated with decreased risk of breast cancer (2, 6). In one recent review of such studies (2), it was noted that, in all four case-control studies reporting on the association of total vitamin A intake with the risk of breast cancer, an inverse association was seen; this was statistically significant in three of the studies. For the nine case-control studies that reported associations with preformed vitamin A, four suggested positive associations and none reported significant associations. For the 14 studies that examined provitamin A carotenoids, 10 reported odds ratios of 0.8 or less comparing highest with lowest intakes; however, this was statistically significant in only two of the studies. Case-control studies relating breast cancer risk to vitamin E are fewer, but the majority of them—three of five included in the recent review—reported odds ratios of 0.7 or less comparing highest with lowest intake. As noted previously, vitamin C was inversely associated with breast cancer risk in the nine studies included in the pooled analysis of Howe et al. (8).

In addition to the results reported here, only a few prospective studies have examined the association of intake of vitamin A, E, or C with the risk of breast cancer. In one of the earliest such studies, Paganini-Hill et al. (14) reported a nonsignificant inverse association of total vitamin A and β-carotene intake with breast cancer risk among female residents of a California retirement community, with a relative risk estimate of high versus low intake of about 0.8. Hunter et al. (15) observed in the Nurses' Health Study that vitamin A intake, particularly from retinol, was significantly and inversely associated with breast cancer risk; women in the highest fifth of intake had a relative risk of breast cancer of about 0.8 compared with those in the lowest fifth of intake. Vitamins E and C were not associated with breast cancer risk. Rohan et al. (16) observed a similar, though not statistically significant, inverse association of breast cancer risk with vitamin A intake, largely from carotenoids, in the Canadian National Breast Screening Cohort. In the Canadian cohort, a weak inverse association was also observed for vitamin C, but no association was seen for vitamin E. In a cohort of postmenopausal women in western New York, Graham et al. (17) observed a nonsignificant inverse association of vitamin C intake with the risk of breast cancer but no association for either vitamin A or E.

Although we did not observe associations of total intake of vitamin A, C, or E with the risk of breast cancer, there were possible weak inverse associations observed for supplemental vitamin C and vitamin A. Overall, however, analyses that focused on supplemental intake of vitamin C in prospective studies are not consistent with a protective effect of these vitamins. For example, we observed relative risk estimates compared with those of nonusers of slightly less than 0.8 for doses above 500 mg/day (see table 4). In the Nurses' Health Study, there was no suggestion of an association of supplemental vitamin C with breast cancer (15). In the Canadian Breast Screening Study, supplemental vitamin C intake above 250 mg/day was associated with a statistically significant increase in breast cancer risk, with a relative risk estimate of 1.46 compared with that of nonusers (16). Analyses that focused on supplemental intake in the western New York cohort also failed to demonstrate any association of these vitamins with breast cancer risk (17).

The observations for supplemental vitamin A intake have been somewhat more consistent, with possible inverse associations at high intake levels in three cohort studies. In this study, the relative risk of breast cancer for supplemental vitamin A intake above 10,000 IU/day was 0.73 compared with that of nonusers. In the Canadian Breast Screening Study, women with supplemental vitamin A intake above 5,000 IU/day had a relative risk of breast cancer of 0.70 (16), and in the Nurses' Health Study, women with doses above 23,000 IU/day had a relative risk of 0.44 (15). However, in none of these studies were these specific risk estimates statistically significant nor was there evidence of a dose-response relation between the supplemental vitamin A dose level and the risk of breast cancer.

The overall impression from this study is that vitamins A, C, and E are unlikely to be related to breast cancer risk. Indeed, the only statistically significant associations suggest that total vitamin A and carotenoids from foods are associated with an increased risk of breast cancer (table 5). However, failure to detect associations may be a consequence of dietary measurement error, a consideration in most observational epidemiologic studies of diet (23–25). The impact of measurement error may be particularly strong for a dietary factor such as vitamin E, for which the concentration in different foodstuffs is affected directly by processing and handling methods, during both its manufacture and storage and preparation in the home (26). In addition, since much dietary vitamin E comes from oils in processed foods, accurate assessment by dietary methods such as the food frequency questionnaire used in this study may be problematic. Similarly, the vitamin C content of some foods may differ dramatically depending on processing and handling (27). For these reasons, it cannot be ruled out that the general lack of association seen in this study is not a consequence of inaccurate dietary assessment. On the other hand, we have reported previously that vitamin E intake was inversely associated with colon cancer risk in this cohort (28). Although our observations related to colon cancer may have been a chance finding, these results suggest that strong effects of these dietary factors may be detected with the data available in this study.

In summary, biologic mechanisms exist to support the anticancer effects of dietary antioxidant vitamins and retinol, and inverse associations between these or related dietary constituents and breast cancer risk have been observed in several studies. However, with the possible exception of vitamin A as carotenoids or retinol, the overall impression from prospective studies is that intake of vitamins A, C, and E is unlikely to play a substantial role in the prevention of breast cancer. The results presented here do suggest that retinol or vitamin C intake from supplements may be inversely associated with the risk of breast cancer, although the findings from this and other studies are not compelling in this regard. Thus, the observations reported here from the Iowa Women's Health Study provide no evidence to alter the impression that, if these vitamins play a role in breast cancer etiology, their role is likely to be a small one.

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