Vitamin A, retinol, and carotenoids and the risk of gastric cancer: a prospective cohort study[1–3]

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ABSTRACT

Background: Vitamin A may influence gastric carcinogenesis through its essential role in controlling cell proliferation and differentiation. However, epidemiologic studies of vitamin A, retinol (preformed vitamin A), and provitamin A carotenoids in relation to the risk of gastric cancer have documented inconsistent results.

Objective: The objective of the study was to examine the associations between intakes of vitamin A, retinol, and specific carotenoids and the risk of gastric cancer in a prospective population-based cohort study of Swedish adults.

Design: The study cohort consisted of 82 002 Swedish adults aged 45–83 y who had completed a food-frequency questionnaire in 1997. The participants were followed through June 2005.

Results: During a mean 7.2-y follow-up, 139 incident cases of gastric cancer were diagnosed. High intakes of vitamin A and retinol from foods only (dietary intake) and from foods and supplements combined (total intake) and of dietary α-carotene and β-carotene were associated with a lower risk of gastric cancer. The multivariate relative risks for the highest versus lowest quartiles of intake were 0.53 (95% CI: 0.32, 0.89; *P* for trend = 0.02) for total vitamin A, 0.56 (95% CI: 0.33, 0.95; *P* for trend = 0.05) for total retinol, 0.50 (95% CI: 0.30, 0.83; *P* for trend = 0.03) for α-carotene, and 0.55 (95% CI: 0.32, 0.94; *P* for trend = 0.07) for β-carotene. No significant associations were found for β-cryptoxanthin, lutein and zeaxanthin, or lycopene intake.

Conclusion: High intakes of vitamin A, retinol, and provitamin A carotenoids may reduce the risk of gastric cancer. *Am J Clin Nutr* 2007;85:497–503.

KEY WORDS Carotenoids, gastric cancer, prospective cohort studies, retinol, vitamin A

INTRODUCTION

Worldwide, gastric cancer is the fourth most common malignancy and the second leading cause of death due to cancer (1). Although infection with the bacterium *Helicobacter pylori* has been recognized as a major risk factor for noncardia gastric cancer, it probably accounts for less than half the cases in Western populations (2). Dietary factors are also thought to have an important role in the development of gastric cancer (3), but the specific dietary components involved remain unclear.

Vitamin A is a generic term referring to both preformed vitamin A (retinol and its esters) and some of the carotenoids (4). Retinol is present only in foods of animal origin, such as liver, kidney, dairy products, and egg, whereas fruit and vegetables are major sources of provitamin A carotenoids [largely α-carotene, β-carotene, and β-cryptoxanthin (4)]. Retinol and its metabolites (retinoids) have essential roles in the regulation of cell proliferation and differentiation, and they also modulate immune responses (4). Retinoic acid (RA), the primary active metabolite of vitamin A, exerts most of its function via interaction with RA receptors and retinoid X receptors, both of which are expressed in human gastric epithelium (5). Tatsuta et al (6) showed that RA suppressed gastric carcinogenesis in rats. Furthermore, a multicenter randomized controlled trial found that vitamin A had a healing effect on gastric ulcers (7), and gastric ulcer disease has been associated with a greater risk of gastric cancer (8, 9). Besides their ability to be converted into vitamin A, carotenoids have antioxidant properties and may reduce gastric cancer risk by neutralizing DNA-damaging free radicals generated by various factors, including chronic *H. pylori* infection (10, 11). One study in animals showed that β-carotene reduced the occurrence of chemically induced gastric cancer (12).

Most (13–25) but not all (26–31) case-control studies have reported a significant inverse association between dietary intake of vitamin A, β-carotene, or both and gastric cancer risk. However, findings from prospective studies of dietary intakes (32–34) or blood concentrations (34–41) of retinol, β-carotene, or total carotene in relation to gastric cancer risk have been inconsistent. Prospective data on total vitamin A intake are lacking. Moreover, relatively few case-control (20, 24, 28, 29, 31) and prospective (33, 34, 38–40) studies have provided results on any association of specific carotenoids besides β-carotene with gastric cancer.

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Given the paucity of prospective data on vitamin A and specific carotenoids other than β-carotene in relation to risk of gastric cancer—and the lack of consistency of the data that do exist—we investigated these relations in a prospective population-based study of Swedish women and men. We also examined whether the associations were modified by smoking and alcohol consumption.

SUBJECTS AND METHODS

Study population

The Swedish Mammography Cohort and the Cohort of Swedish Men provided data for these analyses. The Swedish Mammography Cohort was established between 1987 and 1990, when all women born between 1914 and 1948 and residing in central Sweden (Västmanland and Uppsala counties) received a mailed questionnaire on diet, weight, height, and education. In the autumn of 1997, all living participants received a new questionnaire that was expanded to include ≈350 items on diet and other lifestyle factors (including smoking), dietary supplement use, and medical history; 39 227 women answered the questionnaire. The Cohort of Swedish Men was initiated in the autumn of 1997, when all men born between 1918 and 1952 and residing in central Sweden (Västmanland and Örebro counties) received a mailed questionnaire that was identical (except for some sex-specific questions) to the 1997 Swedish Mammography Cohort questionnaire; 48 850 men returned a completed questionnaire.

For these analyses, we used information from respondents to the 1997 questionnaire. We excluded participants with implausible values for total energy intake (ie, 3 SDs from the $\log_e$-transformed mean energy intake in women and men), those with an erroneous or missing National Registration Number, and those who had a diagnosis of cancer (other than nonmelanoma skin cancer) before January 1998. These exclusions left 82 002 participants (36 664 women and 45 338 men) for the analyses.

The subjects' completion of the self-administered questionnaire was considered to convey informed consent. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Dietary assessment

Dietary information was collected through a self-administered 96-item food-frequency questionnaire that assessed each participant's usual dietary intakes during the previous year. On the food-frequency questionnaire, participants were asked to report their usual frequency of consumption of each food item, according to 8 possible responses that ranged from "never" to "≥3 times/d." Intakes of nutrients were calculated by multiplying the frequency of consumption of each food by the nutrient content of age- and sex-specific portion sizes. Values for the amounts of nutrients in the foods were derived from the Swedish food composition database (42). Vitamin A intake was assessed as preformed vitamin A (retinol from animal sources and fortified foods including margarines and dairy products) and provitamin A carotenoids. The questionnaire sought information on the use of dietary supplements, including multivitamins. The participants were asked to indicate whether supplements were used regularly, occasionally, or never, and, if they were used, how many tablets per week were taken. Total vitamin A and retinol intakes were estimated by combining dietary and supplemental intake, assuming that each multivitamin contained 900 μg retinol.

The food-frequency questionnaire has been validated among 248 men in the study area (43). Spearman correlation coefficients between estimates from the dietary questionnaire and the mean of fourteen 24-h recall interviews were 0.4 for retinol from foods only and 0.6 for retinol from foods and supplements combined; the correlation coefficient for β-carotene intake from foods was 0.5 (43).

Case ascertainment and follow-up

Incident cases of gastric cancer (International Classification of Diseases, 9th Revision code 151) were ascertained through computerized record linkage of the study population to the national and regional Swedish cancer registries, both of which provide ≈100% case ascertainment in Sweden (44, 45). Information on dates of death and migration was obtained by linkages to the Swedish Death Registry and the Swedish Population Registry, both of which are maintained by Statistics Sweden.

Statistical analysis

Person-years of follow-up for each participant were calculated from 1 January 1998 to the date of gastric cancer diagnosis, death, migration, or 30 June 2005, whichever came first. All nutrient intakes were adjusted for total energy intake by using the residual method (46). Nutrients were analyzed both as categorical (quartiles) and continuous variables. We used Cox proportional hazards models (47) to compute hazard ratios to estimate relative risks (RRs) and 95% CIs. Separate analyses for women and men showed similar patterns of association. Therefore, we present results for women and men combined, with control for sex as a stratum variable in the Cox model to allow for different baseline hazard rates. All models were further stratified by age (in mo) at baseline. In multivariate analyses, in addition to age and sex, we adjusted for education, smoking status and pack-years of smoking (the number of cigarette packs smoked per day multiplied by number of years of smoking), self-reported diabetes, and total energy intake. We also considered adjustment for body mass index, physical activity, aspirin use, multivitamin supplement use, and intakes of vitamin C, vitamin E, folate, dietary fiber, alcohol, coffee, tea, red meat, processed meat, fish, and chicken; however, because these variables were not confounders in these analyses, they were not included in the final models. We tested the proportional hazards assumption for each nutrient intake variable in relation to gastric cancer risk by using the likelihood ratio test to compare nested models with and without product interaction terms for nutrient intake and follow-up time. No evidence was found of violation of the proportional hazards assumption for any of the exposures.

Tests for linear trends across increasing quartiles of nutrient intake were performed by assigning the median value for each quartile and treating this variable as continuous with the use of a Wald chi-square statistic. Stratified analyses were conducted according to smoking status (never, past, or current) and alcohol intake [below (<5 g/d) or above (≥5 g/d) median]. To test the statistical significance of interactions on a multiplicative scale, a cross-product term of the nutrient intake value (on a continuous scale) and smoking status or alcohol intake were included in the multivariate model. In additional analyses, we excluded the first 2 y of follow-up to remove early cases in whom the relation between nutrient intake and gastric cancer may have been biased

TABLE 1
Age-standardized baseline characteristics of participants in the highest (Q4) and lowest (Q1) quartiles of energy-adjusted intakes of dietary and total vitamin A and retinol at baseline in 1997[1]

	Vitamin A				Retinol			
	Diet only		Total[2]		Diet only		Total[2]	
Characteristic	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
Women (n = 36 664)								
Age (y)	61.1 ± 9.9[3]	62.5 ± 9.1	61.3 ± 9.8	62.5 ± 9.2	60.8 ± 9.3	62.0 ± 9.1	61.4 ± 9.5	62.1 ± 9.3
Postsecondary education (%)	18.5	17.5	17.0	20.0	23.6	16.6	20.4	19.5
History of diabetes (%)	3.0	5.2	3.3	4.9	3.5	4.7	3.9	4.2
Current smoker (%)	24.3	24.7	25.0	23.9	19.1	26.7	20.4	25.7
Multivitamin supplement use (%)[4]	32.2	34.8	2.7	55.1	39.2	33.4	1.1	58.9
Total energy intake (kcal/d)	1678	1702	1663 ± 550	1718 ± 526	1715 ± 547	1722 ± 485	1699 ± 545	1710 ± 502
Alcohol intake (g/d)	4.5 ± 5.8	3.9 ± 4.6	4.4 ± 5.5	4.0 ± 4.6	4.7 ± 5.8	4.1 ± 4.7	4.5 ± 5.5	4.2 ± 4.8
Men (n = 45 338)								
Age (y)	59.5 ± 10.0	58.9 ± 9.8	59.5 ± 9.9	59.4 ± 9.8	59.5 ± 9.9	59.3 ± 9.7	59.6 ± 9.9	59.3 ± 9.9
Postsecondary education (%)	15.3	17.3	14.3	19.7	18.3	15.6	16.5	18.3
History of diabetes (%)	5.1	8.7	5.0	8.1	5.4	7.4	5.3	6.9
Current smoker (%)	25.4	25.2	25.8	24.2	22.4	26.9	23.2	25.4
Multivitamin supplement use (%)[4]	18.5	20.6	2.7	45.5	21.7	19.0	0.7	46.0
Total energy intake (kcal/d)	2604 ± 849	2503 ± 772	2610 ± 852	2543 ± 795	2587 ± 866	2533 ± 865	2595 ± 853	2542 ± 772
Alcohol intake (g/d)	11.1 ± 9.4	9.7 ± 8.4	10.9 ± 9.3	10.0 ± 8.6	11.8 ± 9.7	10.1 ± 8.5	11.4 ± 9.5	10.1 ± 8.6

[1] Trends across quartiles of dietary and total vitamin A and retinol intakes were significant ($P < 0.05$) except energy intake across quartiles of dietary vitamin A intake in women ($P = 0.59$) and alcohol intake across quartiles of total retinol intake in women ($P = 0.38$). The energy × sex and alcohol intake × sex interactions were significant for dietary vitamin A intake and total retinol intake, respectively (both: $P < 0.05$).

[2] Total intake from foods and supplements combined.

[3] $\bar{x} \pm$ SD (all such values).

[4] Regular or occasional use.

because of preclinical symptoms of disease. All statistical analyses were performed with SAS software (version 9.1; SAS Institute Inc, Cary, NC). All P values are 2-sided; $P < 0.05$ was considered significant.

RESULTS

Of the 82 002 participants included in the analysis, 139 (55 women and 84 men) were diagnosed with gastric cancer during a mean follow-up of 7.2 y (total of 591 556 person-years). The mean ± SD age of the participants at baseline was 61.0 ± 9.5 y (range: 48–83 y). Baseline characteristics of participants according to dietary and total intakes of vitamin A and retinol are presented in **Table 1**. Women and men in the highest quartiles of dietary and total vitamin A intakes were significantly more likely to have a history of diabetes and a postsecondary education than were those in the lowest quartiles of vitamin A. Those in the highest quartiles of dietary and total retinol intakes were significantly more likely to have a history of diabetes and to be current smokers than were those in the lowest retinol quartiles. Whereas the prevalence of multivitamin use did not differ appreciably according to dietary intakes of vitamin A or retinol, those in the highest quartiles of total intakes of these nutrients were, as expected, significantly more likely to use multivitamins than were those in the lowest quartiles of total vitamin A and retinol intakes.

Intakes of dietary and total vitamin A and retinol were significantly and inversely associated with the risk of gastric cancer in both the age- and sex-adjusted analyses and multivariate analyses (**Table 2**). Women and men in the highest quartile of vitamin A and retinol intakes had a risk of gastric cancer ≈40% to 60% lower than did those in the lowest quartile. The associations remained after exclusion of the first 2 y of follow-up. For example, the multivariate RR for the highest versus lowest quartile of dietary vitamin A intake was 0.42 (95% CI: 0.22, 0.79).

The RRs of gastric cancer by quartiles of dietary intake of specific carotenoids are presented in **Table 3**. High intakes of α-carotene and β-carotene were associated with a significantly lower risk of gastric cancer. The multivariate RRs of gastric cancer comparing the highest with the lowest quartiles of intake were 0.50 (95% CI: 0.30, 0.83) for α-carotene and 0.55 (95% CI: 0.32, 0.94) for β-carotene. Excluding the first 2 y of follow-up did not change the results materially; the multivariate RRs comparing extreme quartiles of intake were 0.44 (95% CI: 0.24, 0.79) for α-carotene and 0.47 (95% CI: 0.25, 0.87) for β-carotene. No significant associations were found between β-cryptoxanthin, lutein and zeaxanthin, or lycopene intake and the risk of gastric cancer.

Among the participants in this cohort, liver and carrots were the greatest contributors to vitamin A. We found that consumption of liver and carrots was associated with a significantly lower risk of gastric cancer. Women and men who reported consumption of liver (median, 2 serving/mo) had a multivariate RRs of 0.63 (95% CI: 0.41, 0.96) compared with those who never consumed liver. The multivariate RR of gastric cancer for an increase in carrot consumption of 3 servings/wk (≈1 SD in the study population) was 0.75 (95% CI: 0.58, 0.96).

We converted retinol and β-carotene intakes into retinol equivalents (REs), assuming that 1 μg retinol or 6 μg β-carotene is equivalent to 1 μg RE. The multivariate RRs of gastric cancer for a 1000-μg RE/d increase in intake were 0.72 (95% CI: 0.51, 1.02) for dietary retinol, 0.72 (95% CI: 0.53, 0.99) for total retinol, and 0.57 (95% CI: 0.31, 1.03) for dietary β-carotene.

TABLE 2
Relative risks (RRs) of gastric cancer according to quartiles of intake of vitamin A and retinol[1]

	Quartile of intake				
Nutrient	1 (lowest)	2	3	4 (highest)	*P* for trend[2]
Vitamin A					
Diet only					
Median intake (μg RE/d)	862	1174	1589	2277	
Cases (*n*)	47	33	38	21	
Person-years	147 268	147 995	147 938	148 355	
Age- and sex-adjusted RR	1.0	0.67 (0.42, 1.05)[3]	0.73 (0.47, 1.13)	0.42 (0.24, 0.72)	0.004
Multivariate RR[4]	1.0	0.66 (0.42, 1.04)	0.72 (0.46, 1.12)	0.41 (0.24, 0.71)	0.003
Total[5]					
Median intake (μg RE/d)	890	1260	1745	2474	
Cases (*n*)	48	34	30	27	
Person-years	147 388	147 641	148 139	148 388	
Age- and sex-adjusted RR	1.0	0.66 (0.42, 1.04)	0.59 (0.37, 0.93)	0.54 (0.32, 0.89)	0.02
Multivariate RR[4]	1.0	0.66 (0.42, 1.03)	0.58 (0.37, 0.93)	0.53 (0.32, 0.89)	0.02
Retinol					
Diet only					
Median intake (μg/d)	502	680	950	1614	
Cases (*n*)	34	40	43	22	
Person-years	148 165	148 069	147 251	148 071	
Age- and sex-adjusted RR	1.0	1.11 (0.71, 1.78)	1.09 (0.69, 1.72)	0.63 (0.37, 1.09)	0.05
Multivariate RR[4]	1.0	1.11 (0.70, 1.77)	1.05 (0.66, 1.65)	0.61 (0.35, 1.05)	0.03
Total[5]					
Median intake (μg/d)	527	743	1143	1780	
Cases (*n*)	38	37	42	22	
Person-years	147 886	147 744	147 782	148 144	
Age- and sex-adjusted RR	1.0	0.90 (0.57, 1.42)	1.03 (0.66, 1.61)	0.56 (0.33, 0.95)	0.05
Multivariate RR[4]	1.0	0.88 (0.56, 1.39)	1.01 (0.64, 1.57)	0.56 (0.33, 0.95)	0.05

[1] Cox proportional hazards models were used to estimate RRs. RE, retinol equivalents.
[2] Two-sided *P* value for test of trend was calculated with the Wald statistic by using median values for each quartile of intake.
[3] 95% CI in parentheses (all such values).
[4] Multivariate model adjusted for age (in mo), sex, education (less than high school, high school graduate, or more than high school), diabetes (yes or no), smoking status and pack-years of smoking (never, past <20 pack-years, past ≥20 pack-years, current <20 pack-years, or current ≥20 pack-years), and total energy intake (continuous).
[5] Total intake from foods and supplements combined.

We examined whether the association between nutrient intake and gastric cancer was modified by smoking status and alcohol consumption. Significant interactions were found between smoking status and intakes of dietary vitamin A ($P = 0.01$), total vitamin A ($P = 0.01$), and α-carotene ($P = 0.01$). The multivariate RRs of gastric cancer for a 1600-μg RE/d increase in total vitamin A intake (approximately the difference between the median intake in the highest and lowest quartiles) were 0.29 (95% CI: 0.12, 0.67) in never smokers, 0.45 (95% CI: 0.17, 1.18) in former smokers, and 1.02 (95% CI: 0.53, 1.97) in current smokers. Likewise, the multivariate RRs for a 1700-μg/d increase in α-carotene intake (the difference between the median intake in the highest and lowest quartiles) were 0.50 (95% CI: 0.27, 0.93) in never smokers, 0.39 (95% CI: 0.15, 0.97) in former smokers, and 1.18 (95% CI: 0.68, 2.04) in current smokers. The associations between vitamin A, retinol, or carotenoid intake and the risk of gastric cancer did not differ significantly across strata of alcohol consumption (*P* for interaction > 0.2 for all).

DISCUSSION

In this prospective cohort study of Swedish adults, intakes of vitamin A, retinol, and the provitamin A carotenoids α-carotene and β-carotene were inversely associated with the risk of gastric cancer. Those with the highest intake of these nutrients had a risk of gastric cancer ≈40% to 60% lower than did those in the lowest quartile of intake. Carotenoids with no provitamin A activity (ie, lutein and zeaxanthin and lycopene) and β-cryptoxanthin showed no significant association with gastric cancer risk.

The major strengths of this study include its population-based and prospective design, the completeness of follow-up, and information on multiple potential confounders. The prospective design precluded recall bias, and the completeness of follow-up reduces the likelihood that our results reflect bias due to differential follow-up. Moreover, because our results persisted after exclusion of cases diagnosed during the first 2 y of follow-up, it is unlikely that the observed associations are biased by dietary changes related to preclinical symptoms of disease.

This study also has several limitations. First, because dietary intake was assessed with a self-administered food-frequency questionnaire, some misclassification of nutrient intake is inevitable, and that misclassification would tend to underestimate the magnitude of associations. Second, because data on *H. pylori* infection were not available in our study, we could not evaluate whether the associations between nutrient intake and gastric cancer risk varied by *H. pylori* infection status. The prevalence of *H.*

TABLE 3
Relative risks (RRs) of gastric cancer according to quartiles of dietary intake of specific carotenoids[1]

	Quartile of intake				
Carotenoid	1 (lowest)	2	3	4 (highest)	*P* for trend[2]
α-Carotene					
Median intake (μg/d)	166	458	858	1882	
Cases (*n*)	44	29	39	37	
Person-years	147 495	148 171	147 809	148 081	
Age- and sex-adjusted RR	1.0	0.60 (0.38, 0.97)[3]	0.78 (0.50, 1.22)	0.50 (0.30, 0.82)	0.02
Multivariate RR[4]	1.0	0.61 (0.38, 0.98)	0.80 (0.51, 1.25)	0.50 (0.30, 0.83)	0.03
β-Carotene					
Median intake (μg/d)	1107	1974	3065	5210	
Cases (*n*)	47	27	38	27	
Person-years	146 290	148 466	148 317	148 483	
Age- and sex-adjusted RR	1.0	0.62 (0.38, 0.99)	0.78 (0.50, 1.22)	0.55 (0.33, 0.92)	0.06
Multivariate RR[4]	1.0	0.63 (0.39, 1.02)	0.81 (0.51, 1.27)	0.55 (0.32, 0.94)	0.07
β-Cryptoxanthin					
Median intake (μg/d)	27	121	284	634	
Cases (*n*)	43	24	41	31	
Person-years	144 628	148 163	149 425	149 340	
Age- and sex-adjusted RR	1.0	0.69 (0.42, 1.14)	1.35 (0.87, 2.11)	1.08 (0.66, 1.77)	0.36
Multivariate RR[4]	1.0	0.72 (0.44, 1.20)	1.46 (0.93, 2.29)	1.21 (0.73, 2.01)	0.18
Lutein and zeaxanthin					
Median intake (μg/d)	1034	1607	2218	3417	
Cases (*n*)	46	28	30	35	
Person-years	146 101	148 404	148 667	148 382	
Age- and sex-adjusted RR	1.0	0.65 (0.40, 1.04)	0.68 (0.42, 1.09)	0.72 (0.44, 1.17)	0.28
Multivariate RR[4]	1.0	0.66 (0.41, 1.06)	0.70 (0.43, 1.13)	0.74 (0.45, 1.21)	0.35
Lycopene					
Median intake (μg/d)	739	1502	2257	3541	
Cases (*n*)	47	35	34	23	
Person-years	144 181	148 116	149 186	150 073	
Age- and sex-adjusted RR	1.0	0.94 (0.60, 1.47)	1.09 (0.69, 1.73)	0.87 (0.51, 1.49)	0.76
Multivariate RR[4]	1.0	0.97 (0.62, 1.52)	1.15 (0.72, 1.82)	0.92 (0.53, 1.58)	0.93

[1] Cox proportional hazards models were used to estimate RRs.
[2] Two-sided *P* value for test of trend was calculated with the Wald statistic by using median values for each quartile of intake.
[3] 95% CI in parentheses (all such values).
[4] Multivariate model adjusted for age (in mo), sex, education (less than high school, high school graduate, or more than high school), diabetes (yes or no), smoking status and pack-years of smoking (never, past <20 pack-years, past ≥20 pack-years, current <20 pack-years, or current ≥20 pack-years), and total energy intake (continuous).

pylori infection in Swedish adults is ≈50% to 60% (48). Third, as in any observational study, we cannot exclude the possibility that our results are due to uncontrolled or residual confounding. The possibility that the observed results with respect to total vitamin A and retinol intakes are attributable to other nutrients or nutrient combinations in multivitamins cannot be ruled out. However, we found similar associations for dietary intakes of these nutrients that were not associated with multivitamin use.

Our results for retinol intake are broadly consistent with those from the Iowa Women's Health Study (32) and the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) Study (34), in which an inverse relation between dietary retinol intake and the risk of gastric cancer was observed. The Netherlands Cohort Study found no association between dietary retinol intake and gastric cancer risk but did find a significant reduction in risk associated with the use of supplements containing vitamin A (33). The lack of association with dietary retinol in the Netherlands Cohort Study may be related to the lower intake in that cohort (median intake in highest quintile: 860 μg/d) than in the cohort of the current study (median intake in highest quartile: 1614 μg/d) and in the Iowa Women's Health Study (32) and the ATBC Study (34). The higher retinol intakes in the cohort in the current study and in the Iowa Women's Health Study (32) may be due to fortification of some foods (eg, dairy products) with retinol in Sweden and the United States. In a nutrition intervention trial in Linxian, China, mortality from noncardia gastric cancer was significantly (41%) lower in those who received supplements containing retinol and zinc than in those who received placebo (49).

Three prospective studies have reported a significant inverse association of serum or plasma retinol concentrations with the risk of gastric cancer (37, 41) or gastric cardia cancer (38). In a nested case-control study in the Shanghai Cohort Study (39), no overall association was found between serum retinol and the risk of gastric cancer; however, in the group of never smokers who consumed <3 alcoholic drinks/d, those with high serum retinol concentrations had a 53% lower (not significantly lower) risk of gastric cancer than did those with low serum retinol concentrations. Other prospective studies did not observe any significant association with serum retinol concentrations (34–36, 50). Results from the current study on retinol intake are not directly comparable with these results on retinol concentrations because

plasma retinol concentrations tend to be highly regulated, decreasing only when liver retinol stores are almost empty (51). Thus, for persons who are retinol replete, increased retinol intake has little effect on plasma retinol concentrations.

Although case-control studies have almost consistently found a significant (13–19, 21–25) or a nonsignificant (20, 27, 28) inverse association between β-carotene or total carotene intake and the risk of gastric cancer, prospective studies have been less consistent. Of 10 prospective studies of dietary intake or blood concentrations of β-carotene or total carotene in relation to gastric cancer risk (32–41), 5 observed an inverse association (32, 36, 37, 39, 40); in 3 studies, the association was statistically significant (32, 36, 37). Findings from 3 randomized intervention trials involving β-carotene supplements and examining gastric cancer as an endpoint have been inconsistent. In a trial involving ≈30 000 residents from Linxian, China, where the rates of esophageal and gastric cancers are among the highest in the world and diets are marginally deficient in several nutrients, those who received combined supplementation with β-carotene, vitamin E, and selenium had a 16% lower incidence and a 21% lower mortality due to gastric cancer than did those receiving placebo after a 5-y intervention (49). On the other hand, supplementation with β-carotene did not lower the incidence of gastric cancer among Finnish male smokers [ATBC study (52)] or among US male physicians [Physicians' Health Study (53)]. The reasons for the disparate results are unclear. However, the Linxian trial was conducted in a high-risk population for gastric cancer with low plasma β-carotene concentrations at baseline (49), whereas the ATBC (52) and Physicians' Health Study (53) trials were conducted in low-risk populations. In the Physicians' Health Study trial, the number of gastric cancer cases was small (19 in the intervention group and 21 in the placebo group), and therefore the study may have had insufficient statistical power to detect an effect of β-carotene supplementation. In the current study, we found that vitamin A and α-carotene intakes were inversely associated with gastric cancer risk in never and former smokers but not in current smokers. Thus, the null findings from the ATBC trial may be due to the fact that all participants were smokers.

With regard to carotenoids with no provitamin A activity, findings from the current study are in agreement with most previous case-control (20, 24, 28, 29, 31) and prospective (33, 38–40) studies, which did not find a significant association between lutein and zeaxanthin and gastric cancer risk. Furthermore, as in the current study, most case-control (24, 28, 29, 31) and prospective (33, 39–41) studies, although not all (20, 34), found no significant association with lycopene.

In the current study, we found that the inverse associations of vitamin A and α-carotene intakes with the risk of gastric cancer were limited to never and former smokers. Similarly, the Shanghai Cohort Study (39) showed that serum retinol, α-carotene, and β-carotene concentrations were inversely associated with the risk of gastric cancer in nonsmokers who consumed <3 alcoholic drinks/d but were not associated with risk in ever smokers who consumed $\geq$ 3 drinks/d. No significant interaction between smoking and retinol concentrations was found in a prospective study in China (38). The mechanism by which smoking may interact with vitamin A is unclear. Chen et al (54) showed that nicotine, found in cigarette smoke, could abrogate the growth inhibitory effect of RA by down-regulating the expression of RA receptor β, a tumor suppressor.

In conclusion, findings from this prospective study suggest that high intakes of vitamin A, retinol, and the provitamin A carotenoids α-carotene and β-carotene may reduce the risk of gastric cancer. These results support the hypothesis of a possible protective role of vitamin A in gastric carcinogenesis.

SCL and AW were responsible for the study concept and design; AW was responsible for data collection; SCL was responsible for the statistical analyses; SCL, LB, IN, JR, and AW were responsible for the interpretation of results; SCL wrote the draft of the manuscript; SCL, LB, IN, JR, and AW reviewed and revised the manuscript; and all authors reviewed the final manuscript. None of the authors had any personal or financial conflict of interest.

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