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Vitamins, Carotenoids, Dietary Fiber, and the Risk of Gastric Carcinoma

Results from a Prospective Study after 6.3 Years of Follow-Up

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BACKGROUND. Numerous components of fruit and vegetables are considered to decrease the risk of gastric carcinoma. In the current prospective study, the authors examined the association between the intake of vitamins, carotenoids, and dietary fiber and vitamin supplement use and the incidence rate of gastric carcinoma.

METHODS. The Netherlands Cohort Study began in 1986 with 120,852 men and women ages 55–69 years. Data regarding diet and other covariates were collected by means of a self-administered questionnaire. After 6.3 years of follow-up, data regarding 282 incident cases of gastric carcinoma and 3123 subcohort members were available for case-cohort analyses.

RESULTS. In analyses adjusted for age, gender, smoking history, education, stomach disorders, and family history of gastric carcinoma, an inverse association with vitamin C intake (relative risk [RR] for highest vs. lowest intake category, 0.7; 95% confidence interval [95% CI], 0.5–1.0) was observed, with a borderline significant trend across three intake categories ($P = 0.06$). After the exclusion of cases diagnosed in the first and second follow-up years, the RR was 0.9 (95% CI, 0.6–1.2; P trend = 0.44). Intake of retinol and β-carotene were associated positively with gastric carcinoma risk with highest versus lowest quintile RRs of 1.6 (95% CI, 1.0–2.5; P trend = 0.02) and 1.6 (95% CI, 1.0–2.6; P trend = 0.13), respectively, after the exclusion of first-year and second-year cases. Intake of folate, vitamin E, α-carotene, lutein plus zeaxanthin, β-cryptoxanthin, lycopene, and dietary fiber was not associated with gastric carcinoma. Patients who used vitamin A-containing supplements had a lower risk of gastric carcinoma than nonusers (RR = 0.4; 95% CI, 0.2–0.9).

CONCLUSIONS. No clear inverse associations were found between the intake of vitamins, carotenoids, and dietary fiber and the risk of gastric carcinoma after adjustment for confounding variables and the exclusion of first-year and second-year cases. ***Cancer* 2000;88:737–48.** *© 2000 American Cancer Society.*

KEYWORDS: gastric neoplasms, vitamins, carotenoids, dietary fiber, vitamin supplements, cohort study.

Case-control studies have shown a rather consistent inverse association between fruit and vegetable consumption and the risk of gastric carcinoma.[1–3] The results of prospective studies, however, are more variable.[4–12] Numerous components of fruit and vegetables, e.g., vitamins C and E, carotenoids, dietary fiber, flavonoids, phenols, and hydrolysis products of glucosinolates, may be responsible for the protective effect against gastric carcinoma. The mechanisms of action

by which these components may act include antioxidant effects (vitamins C, E, carotenoids, and flavonoids), inhibition of nitrosamine formation (vitamins C and E), and dilution or binding of carcinogens (fiber).[13–15]

With regard to the risk of gastric carcinoma, dietary intake of vitamins C and E, β-carotene, and retinol (or vitamin A) have been studied most extensively in case–control studies. For vitamin C and β-carotene, a consistent inverse association was found, but none was found for vitamin E.[16] Retinol is found only in foods derived from animal sources but is studied in relation to the risk of gastric carcinoma because of its vitamin A activity. Retinol is supposed to reduce risk because it is involved in the regulation of cell differentiation.[1] However, the intake of retinol was not associated clearly with the risk gastric carcinoma.[16] Furthermore, two prospective studies[6,11] and two randomized nutrition intervention trials[17,18] have been conducted on the dietary intake of vitamins C and E, β-carotene, and retinol, all with conflicting results.

The association between other components of fruit and vegetables (e.g., folate, dietary fiber, and carotenoids)[19–22] and the use of vitamin-containing supplements[11,21] and the risk of gastric carcinoma have been investigated only in a few studies.

In the Netherlands Cohort Study on diet and cancer (NLCS), we studied the association between the intake of vitamins C and E, folate, retinol and dietary fiber, and the use of vitamin-containing supplements and the risk of gastric carcinoma after 6.3 years of follow-up. Furthermore, with the use of a recently developed carotenoid food composition table,[23] analyses were performed with α-carotene, β-carotene, lutein plus zeaxanthin, β-cryptoxanthin, and lycopene.

MATERIALS AND METHODS

The Netherlands Cohort Study

The NLCS is a prospective cohort study that began in September 1986 among the general population. The study design has been described previously.[24] Briefly, the cohort included 62,573 women and 58,279 men ages 55–69 years at the beginning of the study. At baseline, the cohort members completed a mailed, self-administered questionnaire on dietary habits and other risk factors for cancer. For data analysis, the case-cohort approach was used in which cases were derived from the entire cohort, whereas the person-years at risk of the entire cohort were estimated from a random sample of 3500 subjects (subcohort).[25] This subcohort (1688 men and 1812 women) was sampled from the cohort after the baseline measurement and was followed for vital status over 6.3 years. No subcohort members were lost to follow-up.

Follow-up to determine the incidence rate of cancer was established by record linkage with cancer registries and a pathology register.[26] The current analyses were restricted to cancer incidence in the first 6.3 years of follow-up from September 1986 until December 1992. After excluding subjects who reported prevalent gastric carcinoma at baseline, patients with in situ gastric carcinoma, and those with gastric carcinoma other than carcinoma or without microscopically confirmed gastric carcinoma, there were 310 (242 men and 68 women) incident gastric carcinoma cases remaining. In the subcohort, 1630 men and 1716 women remained on the study after excluding prevalent cancer cases other than skin carcinoma.

The Dietary Questionnaire

The dietary section of the questionnaire was a 150-item semiquantitative food frequency questionnaire concentrating on habitual consumption of food and beverages during the year preceding the beginning of the study. The questionnaire was validated against a 9-day diet record.[27] In this study, variables of principal interest were vitamins C and E, folate, retinol, carotenoids, dietary fiber, and the use of vitamin-containing supplements. The mean daily intake of vitamins C and E, retinol, and dietary fiber were calculated using the computerized Dutch Food Composition Table.[28] For folate, most information was derived from the McCance and Widderson food composition table.[29]

For calculating the intake of specific carotenoids, an additional food composition table has been constructed recently.[23] With this carotenoid table, we were able to evaluate six of the most important types of carotenoids: α-carotene, β-carotene, lutein, zeaxanthin, β-cryptoxanthin, and lycopene. Briefly, foods that are the main sources of carotenoids (e.g., vegetables) were sampled and analyzed for α-carotene, β-carotene, lutein, zeaxanthin, and lycopene. Some other foods, such as margarines, also were analyzed to check data supplied by manufacturers. For all other foods, data were derived from recent studies based on similar methods of analysis. In the carotenoid food composition table, lutein and zeaxanthin were combined, because most literature sources had not distinguished these two carotenoids. Most vegetables, however, contain primarily lutein and only minor amounts of zeaxanthin.

In the Dutch Food Composition Table dietary fiber is a collective noun for lignin, cellulose, hemicellulose, and pectins (in this study, fiber was regarded

collectively as total dietary fiber). Dietary fiber also can be regarded as nonstarch polysaccharides (NSP). Data from the NSP content of foods were used to calculate the intake of soluble, insoluble, and total NSPs in this study. The NSP content of foods was calculated using the Englyst method.[30] Lignin is not a component of NSPs.

Information on dietary supplement use was collected at baseline using an open-ended question with space for adding four different supplements. Subjects were asked whether they used vitamin tablets, drops, or other preparations during the 5-year period before baseline. We did not have information on the vitamin content of the supplements or how often a supplement was used.

Other factors relevant to the association between vitamins, dietary fiber, and the use of vitamin-containing supplements and the risk of gastric carcinoma included age, gender, level of education (low, medium, and high),[31] gastric disorders (yes or no), family history of gastric carcinoma (yes or no), smoking history (never, exsmoker, and current smoker), pack years of smoking, coffee and alcohol consumption (grams per day), and energy intake (kjoules per day). In this study, gastric disorders were defined as the presence of any gastric disease in the past that required medical attention (e.g., peptic ulcer, gastritis).

Data Analysis

Subjects with incomplete or inconsistent dietary data were excluded,[27] leaving 282 patients (219 men and 63 women) with gastric carcinoma and 3123 subcohort members (1525 men and 1598 women) for the analyses. Subjects were classified by quintile of intake of the vitamins, carotenoids, and dietary fiber or were classified by their use of vitamin-containing supplements (yes or no), depending on the distribution in the subcohort. For vitamin C, quintiles 2 and 3 and quintiles 4 and 5 were combined, because the validation study demonstrated that these quintiles could not be distinguished.[27]

All analyses were conducted for men and women together. Because of potential influence of prediagnostic symptoms of gastric carcinoma on food consumption, all analyses also were conducted after excluding patients who were diagnosed in the first and second years of follow-up.[4,32]

The mean daily intake of vitamins, carotenoids, dietary fiber, or, in the case of vitamin supplements, the number and percentage were presented for all cases, with the exception of those patients who were diagnosed in the first or second years of follow-up and subcohort members. Pearson correlation coefficients were calculated for vitamins, carotenoids, and dietary fiber and for energy intake in the subcohort.

Data were analyzed using the case-cohort approach.[25] Age-adjusted and gender-adjusted rate ratios (RRs) for gastric carcinoma and their 95% confidence intervals (95% CI) were computed for all variables using the GLIM statistical package (Numerical Algorithms Group, Oxford, United Kingdom).[33] Exponentially distributed survival times were assumed in the follow-up period. Specific macros were developed to account for the additional variance introduced by using the subcohort instead of using the entire cohort.[34] Tests for trend in the RRs were based on likelihood ratio tests. The basic multivariate model included age, gender, level of education, gastric disorders, family history of gastric carcinoma, and smoking history. Energy intake, nitrite intake, and sodium intake were not included in multivariate analyses, because these variables were not associated with the risk of gastric carcinoma in our study.[35] This was supported by the fact that additional inclusion of energy, nitrite, or sodium intake levels in the model did not change the risk estimates. Coffee, alcohol consumption, and pack years of smoking were associated positively with the risk of gastric carcinoma risk; however, adding these variables to the multivariate model did not essentially change the results. More elaborate models were build to identify the unique contribution of specific vitamins or carotenoids to the risk of gastric carcinoma. Furthermore, we studied the interaction between vitamins C and E (both antioxidant vitamins) and between vitamin C and folate (both compounds in vegetables) by calculating multivariate RRs for combinations of vitamin C intake (three categories) and vitamin E or folate intake (tertiles).

RESULTS

The mean baseline intake levels of vitamins, carotenoids, and dietary fiber in all patients with gastric carcinoma, in the case-group without patients who were diagnosed in the first or second follow-up years, and in the group of subcohort members are presented in Table 1. All patients and the restricted case-group had a slightly higher intake of retinol and vitamin E than subcohort members. The two case groups had a lower intake of vitamin C and lycopene than the subcohort members. For folate and lutein plus zeaxanthin, there were no differences in intake levels between all cases and subcohort members; the intake of the restricted case group was higher than that of subcohort members. Intake levels of α-carotene, β-carotene, and β-cryptoxanthin in the two case groups were comparable to the levels in the subcohort members. Intakes of the four fiber variables were similar in the

TABLE 1
Vitamin, Carotenoids, and Dietary Fiber Intake and Vitamin Supplement Use in all Stomach Carcinoma Cases, in Case Groups with First-Year and Second-Year Cases Excluded, and Subcohort Members: Netherlands Cohort Study 1986–1992

	Vitamin, carotenoids, and dietary fiber intake (mean ± SD)		
	Cases (mean ± SD)		
Nutrient variable	All (n = 282)	First and second year cases excluded (n = 208)	Subcohort (n = 3123)
Vitamins (mg/day)			
Retinol	0.60 ± 0.32	0.61 ± 0.31	0.54 ± 0.31
Vitamin C	96.59 ± 43.85	98.94 ± 44.02	103.42 ± 43.03
Vitamin E	13.53 ± 6.35	13.88 ± 6.53	13.36 ± 6.24
Folate	289.76 ± 74.14	295.54 ± 73.04	289.71 ± 77.33
Carotenoids (mg/day)			
Alpha-carotene	0.66 ± 0.48	0.68 ± 0.48	0.70 ± 0.58
Beta-carotene	2.92 ± 1.43	3.01 ± 1.42	2.97 ± 1.58
Lutein and zeaxanthin	2.54 ± 1.18	2.64 ± 1.21	2.52 ± 1.11
Beta-cryptoxanthin	0.16 ± 0.17	0.16 ± 0.16	0.18 ± 0.17
Lycopene	1.09 ± 1.65	1.01 ± 0.97	1.19 ± 1.74
Dietary fiber (g/day)			
Total dietary fiber	26.98 ± 7.48	27.34 ± 7.26	27.03 ± 8.20
Total nonstarch polysaccharides	19.09 ± 5.69	19.35 ± 5.56	19.06 ± 5.90
Soluble nonstarch polysaccharides	8.40 ± 2.49	8.52 ± 2.43	8.34 ± 2.50
Insoluble nonstarch polysaccharides	10.72 ± 3.40	10.86 ± 3.35	10.74 ± 3.57
Vitamin supplement in use: no. (%)			
Vitamin A-containing supplement	8 (2.8)	5 (2.4)	226 (7.2)
Vitamin C-containing supplement	19 (6.7)	16 (7.7)	325 (10.4)
Vitamin E-containing supplement	11 (3.9)	8 (3.8)	204 (6.5)

SD: standard deviation.

two case groups and the subcohort members. A higher percentage of subcohort members used vitamin-containing supplements (vitamin A, C, or E) compared with the two case groups. There were minor differences in the percentage of vitamin users between the two case groups.

Pearson correlation coefficients (r) were high between vitamin C intake and β-cryptoxanthin intake (r = 0.77), between folate and either vitamin C (r = 0.65), β-carotene (r = 0.60), or lutein plus zeaxanthin (r = 0.66) and between α-carotene and β-carotene (r = 0.93) and β-carotene and lutein plus zeaxanthin (r = 0.68). Highly correlated with energy intake were folate (r = 0.58), vitamin E (r = 0.53), total dietary fiber (r = 0.58), and total NSP (r = 0.57) (data not shown).

In the subcohort, mean intake of vitamins, carotenoids, and dietary fiber was compared across categories of potential confounders (data not shown). With increasing age (three age categories: 55–59 years, 60–64 years, and 65-69 years), the intake of retinol, folate, vitamin E, α-carotene, β-carotene, lutein plus zeaxanthin, and all fiber variables was decreased; the intake of vitamin C and β-cryptoxanthin was increased. Men had a higher intake of retinol, vitamin E, folate, lutein plus zeaxanthin, and dietary fiber and a lower intake of vitamin C, β-cryptoxanthin, and lycopene compared with women. There was no difference in the intake of α-carotene and β-carotene between men and women. Subjects with gastric disorders had a lower intake of vitamins, carotenoids (except lycopene), and dietary fiber compared with subjects without stomach disorders. The intake of vitamins and carotenoids was lower in subjects with a positive family history of gastric carcinoma, but the intake of dietary fiber did not differ between subjects with and without a positive family history. A positive association was found between the three levels of education (low, medium, and high) and the intake of vitamins and lycopene. The intake of β-carotene and dietary fiber did not differ between the levels of education. For the other variables, no clear pattern was shown. Smokers had a higher intake of retinol and lutein plus zeaxanthin but a lower intake of vitamins C and E, folate, and the other carotenoids compared with ex-smokers and never smokers. There was no difference

in dietary fiber intake between never smokers, ex-smokers, and smokers.

A higher percentage of vitamin-containing supplement users were women, had a higher level of education, had no history of gastric carcinoma in the family, and were never smokers. Those who used supplement consumed less coffee and more fruit and vitamins (vitamin C, folate, retinol, α-carotine, β-carotene, β-cryptoxanthin, and lycopene) in this study (data not shown).

The RRs of vitamins, carotenoids, supplement use, and dietary fiber are shown in Tables 2–5. The three types of analyses included age-adjusted and gender-adjusted, and multivariate analyses of all patients with gastric carcinoma and multivariate analyses after the exclusion of patients who were diagnosed in the first and second follow-up years. For retinol, no clear association was found with the risk of gastric carcinoma in the age-adjusted and gender-adjusted, and multivariate adjusted analyses. However, after the exclusion of first-year and second-year cases, a positive association was observed (RR highest vs. lowest quintile, 1.6; 95% CI, 1.0–2.5; P trend = 0.02) (Table 2). Vitamin C showed a significant inverse association with risk of gastric carcinoma in the age-adjusted and gender-adjusted analyses, with RRs of 0.6 and 0.7 for the second and third intake categories, respectively (P trend = 0.01). This association became weaker and was of borderline significance in the multivariate analysis (P trend = 0.06). The RRs moved close to 1.0 after the exclusion of first-year and second-year cases: The RRs for increasing intake categories were 1.0, 0.8, and 0.9 (P trend = 0.44) (Table 2). Additional adjustment for other vitamins did not change appreciably the observed associations for retinol and vitamin C (data not shown). No clear associations were found between the intake of vitamin E, folate, α-carotene, lutein and zeaxanthin, and lycopene and the risk of gastric carcinoma in the age-adjusted and gender-adjusted, and multivariate analyses. For folate and α-carotene, RRs became higher than 1.0 after the exclusion of first-year and second-year cases but without an apparent trend (P trend = 0.40 and P trend = 0.48, respectively) (Tables 2 and 3). Also, no association was observed with the intake of β-carotene in the age-adjusted and gender-adjusted analyses and the multivariate analysis. Exclusion of first-year and second-year cases resulted in a nonsignificant, positive association with the risk of gastric carcinoma; the RRs for increasing quintiles were 1.0, 1.5, 1.2, 1.3, and 1.6 (P trend = 0.13) (Table 3). Inclusion of the other vitamins in the models did not alter the RRs (data not shown). The nonsignificant, inverse association between β-cryptoxanthin and gastric carcinoma that was observed in the age-adjusted and gender-adjusted analyses became weaker after multivariate adjustment and disappeared totally after the exclusion of first-year and second-year cases (Table 3).

Those who used vitamins A, C, or E containing supplements had a lower risk of gastric carcinoma compared with nonusers in all types of analyses, but only those who used vitamin A-containing supplements had a significantly decreased RR (Table 4). The additional inclusion of vitamin variables and the use of vitamin C and E containing supplements in the model did not change the RRs substantially for users of vitamin A-containing supplements (data not shown). However, the nonsignificant association between the use of vitamin C or E containing supplements and the risk of gastric carcinoma disappeared completely after additional adjustment for vitamins and use of supplements containing vitamins A and E and vitamins C and A, respectively.

No association was found for total dietary fiber, total NSP, soluble NSP, and insoluble NSP in either the age-adjusted and gender-adjusted, or multivariate analyses or in the analyses that excluded first-year and second-years cases (Table 5). The RRs for combined exposure to vitamins C and E and to vitamin C and folate are presented in Table 6. In each tertile of vitamin E, increasing intake of vitamin C was associated with a lower risk of gastric carcinoma. The pattern was less clear for vitamin E. After the exclusion of first-year and second-year cases, the RRs all were closer to 1.0. For combined exposure of vitamin C and folate, no consistent pattern was observed in any of the analyses.

DISCUSSION

In this study, an inverse association of vitamin C with the risk of gastric carcinoma was found in age-adjusted and gender-adjusted analyses that became less apparent after controlling for several confounders and after the exclusion of patients who were diagnosed in the first and second follow-up years. The intake of retinol and β-carotene were associated positively with the risk of gastric carcinoma. No clear associations were observed for vitamin E, folate, α-carotene, lutein plus zeaxanthin, β-cryptoxanthin, lycopene, or dietary fiber. The use of vitamin A-containing supplements was associated with a reduced risk of gastric carcinoma.

The NLCS was carried out in a large sample of the general population of men and women ages 55–69 years at baseline. After 6.3 years of follow-up, 310 gastric carcinoma cases were detected, substantially greater than any other prospective study that investigated the association between vitamins and the risk of gastric carcinoma.[6,11]

TABLE 2
Age-Adjusted and Gender-Adjusted Rate Ratios, Multivariate Rate Ratios, and 95% Confidence Intervals of Stomach Carcinoma According to Quintiles of Vitamins: Netherlands Cohort Study 1986–1992

	Intake in quintiles/category					
Vitamins	1 (low)[a]	2	3	4	5 (high)	Test for trend *P* value
Retinol						
Median intake (mg/day)	0.26	0.38	0.48	0.61	0.86	—
Cases/person years	50/3807	32/3812	63/3807	56/3820	81/3769	—
RR[b]	1.0	0.6	1.0	0.8	1.1	—
95% CI	—	0.4–0.9	0.7–1.5	0.6–1.2	0.8–1.7	0.13
Cases/person years	50/3763	32/3780	63/3788	55/3814	81/3741	—
Multivariate RR[c]	1.0	0.6	1.0	0.8	1.2	—
95% CI	—	0.4–0.9	0.7–1.5	0.5–1.2	0.8–1.7	0.12
Cases/person years[d]	30/2534	27/2519	47/2543	39/2569	64/2480	—
Multivariate RR	1.0	0.8	1.3	0.9	1.6	—
95% CI	—	0.5–1.4	0.8–2.0	0.6–1.5	1.0–2.5	0.02
Vitamin C						
Median intake (mg/day)	55.00	86.65	134.80	—	—	—
Cases/person years	84/3771	101/7600	97/7644	—	—	—
RR[b]	1.0	0.6	0.7	—	—	—
95% CI	—	0.5–0.9	0.5–0.9	—	—	0.01
Cases/person years	83/3737	101/7537	97/7613	—	—	—
Multivariate RR[c]	1.0	0.7	0.7	—	—	—
95% CI	—	0.5–1.0	0.5–1.0	—	—	0.06
Cases/person years[d]	56/2506	75/5049	76/5090	—	—	—
Multivariate RR	1.0	0.8	0.9	—	—	—
95% CI	—	0.5–1.1	0.6–1.2	—	—	0.44
Vitamin E						
Median intake (mg/day)	6.59	9.26	12.26	15.82	21.70	—
Cases/person years	54/3765	46/3842	62/3807	62/3818	58/3783	—
RR[b]	1.0	0.8	1.0	1.0	0.8	—
95% CI	—	0.5–1.2	0.7–1.5	0.7–1.4	0.5–1.2	0.46
Cases/person years	53/3724	46/3817	62/3789	62/3812	58/3745	—
Multivariate RR[c]	1.0	0.8	1.1	1.0	0.8	—
95% CI	—	0.5–1.2	0.7–1.6	0.7–1.5	0.5–1.2	0.62
Cases/person years[d]	38/2481	29/2552	46/2539	50/2565	44/2508	—
Multivariate RR	1.0	0.7	1.1	1.1	0.9	—
95% CI	—	0.4–1.2	0.7–1.7	0.7–1.7	0.6–1.4	0.83
Folate						
Median intake (mg/day)	201.96	245.93	282.06	321.34	384.16	
Cases/person years	53/3762	56/3840	59/3662	54/3749	60/3803	
RR[b]	1.0	0.9	0.9	0.9	0.9	
95% CI	—	0.6–1.4	0.6–1.4	0.6–1.3	0.6–1.3	0.39
Cases/person years	53/3715	55/3827	59/3830	54/3718	60/3797	—
Multivariate RR[c]	1.0	1.0	1.0	0.9	1.0	—
95% CI	—	0.7–1.5	0.7–1.5	0.6–1.4	0.6–1.4	0.71
Cases/person years[d]	32/2485	41/2570	45/2564	40/2486	49/2539	—
Multivariate RR	1.0	1.2	1.3	1.1	1.3	—
95% CI	—	0.8–1.9	0.8–2.1	0.9–1.8	0.8–2.1	0.40

RR: rate ratio; CI: confidence interval.

[a] Reference category.

[b] Adjusted for age and gender.

[c] Adjusted for age, gender, smoking status, education, stomach disorders, and family history of stomach carcinoma.

[d] Analyses with first-year and second-year cases excluded and adjusted for age, gender, smoking status, education, stomach disorders, and family history of stomach carcinoma.

Biased recall of diet was unlikely in this study, because the dietary intake data were collected before gastric carcinoma was diagnosed. Selection bias also was unlikely because of the high completeness of follow-up of the patients and subcohort members.[36] In the multivariate analyses, we controlled for all measured risk factors of gastric carcinoma. However, unmeasured or unknown factors may have caused residual confounding. We had no information about the prevalence of *Helicobacter pylori* infection among the

TABLE 3
Age-Adjusted and Gender-Adjusted Rate Ratios, Multivariate Rate Ratios, and 95% Confidence Intervals of Stomach Carcinoma According to Quintiles of Carotenoids: Netherlands Cohort Study 1986–1992

	Intake in quintiles					Test for trend
Carotenoids	1 (low)[a]	2	3	4	5 (high)	*P* value
Alpha-carotene						
Median intake (mg/day)	0.19	0.38	0.57	0.82	1.32	—
Cases/person years	61/3769	55/3824	58/3808	51/3802	57/3813	—
RR[b]	1.0	0.9	0.9	0.8	1.0	—
95% CI	—	0.6–1.3	0.7–1.4	0.6–1.2	0.7–1.4	0.79
Cases/person years	61/3709	55/3792	57/3789	51/3796	57/3800	—
Multivariate RR[c]	1.0	0.9	1.0	0.9	1.0	—
95% CI	—	0.6–1.3	0.7–1.4	0.6–1.3	0.7–1.5	1.00
Cases/person years[d]	39/2465	41/2546	44/2545	40/2545	43/2545	—
Multivariate RR	1.0	1.0	1.1	1.0	1.2	—
95% CI	—	0.6–1.6	0.7–1.8	0.7–1.6	0.8–1.9	0.45
Beta-carotene						
Median intake (mg/day)	1.43	2.11	2.66	3.36	4.77	—
Cases/person years	54/3775	63/3818	52/3813	52/3785	61/3824	—
RR[b]	1.0	1.1	0.9	0.9	1.2	—
95% CI	—	0.8–1.6	0.6–1.9	0.6–1.4	0.8–1.7	0.83
Cases/person years	54/3722	63/3805	51/3782	52/3766	61/3812	—
Multivariate RR[c]	1.0	1.2	1.0	1.0	1.2	—
95% CI	—	0.8–1.7	0.6–1.5	0.6–1.5	0.8–1.8	0.61
Cases/person years[d]	32/2484	49/2547	37/2542	41/2522	48/2550	—
Multivariate RR	1.0	1.5	1.2	1.3	1.6	—
95% CI	—	1.0–2.4	0.7–1.9	0.7–2.1	1.0–2.6	0.13
Lutein and zeaxanthin						
Median intake (mg/day)	1.35	1.87	2.34	2.83	3.81	—
Cases/person years	68/3794	47/3787	53/3817	47/3802	67/3816	—
RR[b]	1.0	0.7	0.7	0.7	1.0	—
95% CI	—	0.5–1.0	0.5–1.1	0.5–1.0	0.7–1.4	0.86
Cases/person years	68/3766	46/3768	53/3785	47/3770	67/3797	—
Multivariate RR[c]	1.0	0.7	0.8	0.7	1.0	—
95% C	—	0.5–1.1	0.5–1.2	0.5–1.0	0.7–1.5	0.94
Cases/person years[d]	43/2513	34/2520	41/2550	36/2530	53/2532	—
Multivariate RR	1.0	0.8	0.9	0.8	1.3	—
95% CI	—	0.5–1.3	0.6–1.5	0.5–1.3	0.8–2.0	0.25
Beta-cryptoxanthin						
Median intake (mg/day)	0.02	0.06	0.13	0.25	0.39	—
Cases/person years	82/3783	54/3823	52/3791	42/3806	52/3812	—
RR[b]	1.0	0.7	0.7	0.6	0.8	—
95% CI	—	0.5–1.0	0.5–1.1	0.4–0.9	0.6–1.2	0.14
Cases/person years	81/3752	54/3798	52/3775	42/3775	52/3787	—
Multivariate RR[c]	1.0	0.8	0.8	0.7	0.9	—
95% CI	—	0.6–1.2	0.6–1.2	0.5–1.0	0.6–1.4	0.36
Cases/person years[d]	54/2500	42/2553	38/2532	36/2527	37/2533	—
Multivariate RR	1.0	1.0	0.9	0.9	1.0	—
95% CI	—	0.6–1.5	0.6–1.4	0.6–1.4	0.6–1.5	0.77
Lycopene						
Median intake (mg/day)	0.15	0.48	0.81	1.21	2.20	—
Cases/person years	70/3790	49/3834	55/3789	55/3810	53/3792	—
RR[b]	1.0	0.7	0.9	1.0	0.9	—
95% CI	—	0.5–1.1	0.6–1.3	0.7–1.4	0.6–1.3	0.87
Cases/person years	70/3765	48/3821	55/3776	55/3769	53/3755	—
Multivariate RR[c]	1.0	0.7	0.9	1.1	1.0	—
95% CI	—	0.5–1.1	0.6–1.4	0.7–1.5	0.7–1.5	0.50
Cases/person years[d]	50/2525	30/2567	42/2532	45/2521	40/2500	—
Multivariate RR	1.0	0.6	1.0	1.2	1.1	—
95% CI	—	0.4–1.0	0.6–1.5	0.8–1.9	0.7–1.7	0.16

RR: rate ratio; CI: confidence interval.

[a] Reference category.

[b] Adjusted for age and gender.

[c] Adjusted for age, gender, smoking status, education, stomach disorders, and family history of stomach carcinoma.

[d] Analyses with first-year and second-year cases excluded and adjusted for age, gender, smoking status, education, stomach disorders, and family history of stomach carcinoma.

TABLE 4
Age-Adjusted and Gender-Adjusted Rate Ratios, Multivariate Rate Ratios, and 95% Confidence Intervals of Stomach Carcinoma According to Users and Nonusers of Vitamin Supplements: Netherlands Cohort Study 1986–1992

Use of vitamin supplements	Nonusers[a]	Users
Supplement with vitamin A		
Cases/person years	274/17,636	8/1380
RR[b]	1.0	0.4
95% CI	—	0.2–0.9
Cases/person years	273/17,520	8/1367
Multivariate RR[c]	1.0	0.5
95% CI	—	0.2–1.0
Cases/person years[d]	202/11,720	5/925
Multivariate RR	1.0	0.4
95% CI	—	0.2–0.9
Supplement with vitamin C		
Cases/person years	263/17,043	19/1972
RR[b]	1.0	0.7
95% CI	—	0.4–1.1
Cases/person years	262/16,940	19/1947
Multivariate RR[c]	1.0	0.8
95% CI	—	0.5–1.2
Cases/person years[d]	191/11,339	16/1306
Multivariate RR	1.0	0.9
95% CI	—	0.5–1.5
Supplement with vitamin E		
Cases/person years	271/17,772	11/1243
RR[b]	1.0	0.7
95% CI	—	0.4–1.2
Cases/person years	270/17,669	11/1218
Multivariate RR[c]	1.0	0.7
95% CI	—	0.4–1.4
Cases/person years[d]	199/11,828	8/817
Multivariate RR	1.0	0.7
95% CI	—	0.4–1.5

RR: rate ratio; CI: confidence interval.
[a] Reference category.
[b] Adjusted for age and gender.
[c] Adjusted for age, gender, smoking status, education, stomach disorders, and family history of stomach carcinoma.
[d] Analyses with first-year and second-year cases excluded and adjusted for age, gender, smoking status, education, stomach disorders, and family history of stomach carcinoma.

cohort members. Infection with *Helicobacter pylori* is regarded as an important risk factor for gastric carcinoma.[37] In the healthy Dutch population ages 50–70 years, the prevalence of infection was estimated to be 50% in 1990.[38]

Another fact that may have influenced the results is the nondifferential misclassification of exposure, which may have resulted in underestimation of the strength of the association. When information about food consumption is converted into nutrient intake, this conversion adds further inaccuracy to the data due to variability in the nutrient density of foods, e.g., seasonal influences and methods of preparation or food consumption (raw or cooked). However, the results of the validation study show that the questionnaire was able to rank subjects adequately according to their intake of nutrients. The crude Pearson correlation coefficients and the energy-adjusted and gender-adjusted Pearson correlation coefficients (in parentheses) between the dietary record and the questionnaire for vitamins A and C and dietary fiber intake were r = 0.52 (r = 0.48), r = 0.58 (r = 0.55), and r = 0.74 (r = 0.74), respectively.[27] Nevertheless, the reference instrument (9-day diet record) used in the validation study may be subject to error; therefore, the possibility of measurement error cannot be excluded.

Furthermore, patients with preclinical symptoms of gastric carcinoma may have changed their dietary habits 1–2 years before the diagnosis of gastric carcinoma. We found in an earlier analysis that patients who were diagnosed in the first or second years of follow-up had a significantly lower consumption of vegetables[4] and, consequently, a lower intake of certain vitamins, carotenoids, and dietary fiber. Therefore, all analyses also were conducted with the exclusion of patients who were diagnosed in the first or second follow-up years, resulting overall in different RRs compared with the RRs from the analyses in which all cases were included.

Only two prospective studies have reported previously on the association between vitamin intake and gastric carcinoma. The Iowa Women's Health Study, in contrast with the current findings, reported an inverse association with vitamins C and E, carotenoids, and retinol and gastric carcinoma.[11] A cohort study among Japanese men in Hawaii reported no statistically significant difference between cases and noncases in mean intake of vitamins C and E, retinol, and carotenoids.[6] Limitations of these studies included a poor control for confounders[6] and a small number of gastric carcinoma cases.[11] Furthermore, nutrient intake was based on a limited number of food items,[6] and no results of analyses were reported that excluded first-year and second year cases.

Two randomized nutrition intervention trials on the effects of vitamin/mineral supplementation on the occurrence of gastric carcinoma showed conflicting results. The General Population Trial in Linxian, China, showed that supplements containing β-carotene, vitamin E, and selenium reduced the incidence of gastric carcinoma 16% and the mortality rate with 21% after a 5.25-year intervention,[17] whereas, in the ATBC trial in Finland, more cases of gastric carcinoma were diagnosed among those who received β-carotene or α-tocopherol compared with those who did not after 7.5 years of follow-up.[18] These latter observations may have been due to chance because of the small

TABLE 5
Age-Adjusted and Gender-Adjusted Rate Ratios, Multivariate Rate Ratios, and 95% Confidence Intervals of Stomach Carcinoma According to Quintiles of Dietary Fiber: Netherlands Cohort Study 1986–1992

	Intake in quintiles					Test for trend
Dietary fiber	1 (low)[a]	2	3	4	5 (high)	*P* value
Total dietary fiber						
Median intake (mg/day)	17.80	22.40	26.20	30.30	37.60	—
Cases/person years	52/3807	57/3833	58/3783	60/3798	55/3794	—
RR[b]	1.0	1.0	1.0	1.0	0.8	—
95% CI	—	0.7–1.5	0.7–1.4	0.7–1.4	0.6–1.2	0.27
Cases/person years	52/3760	56/3814	58/3764	60/3766	55/3781	—
Multivariate RR[c]	1.0	1.1	1.0	1.0	0.9	—
95% CI	—	0.7–1.6	0.7–1.5	0.7–1.5	0.6–1.4	0.55
Cases/person years[d]	35/2507	41/2567	40/2505	47/2525	44/2542	—
Multivariate RR	1.0	1.1	1.0	1.2	1.1	—
95% CI	—	0.7–1.8	0.7–1.7	0.8–1.9	0.7–1.7	0.75
Total nonstarch polysaccharides						
Median intake (mg/day)	12.26	15.73	18.45	21.52	26.62	—
Cases/person years	56/3785	54/3797	46/3809	69/3820	57/3805	—
RR[b]	1.0	0.9	0.7	1.1	0.8	—
95% CI	—	0.6–1.3	0.5–1.1	0.7–1.5	0.6–1.2	0.60
Cases/person years	56/3731	53/3784	46/3777	69/3801	57/3792	—
Multivariate RR[a]	1.0	0.9	0.7	1.1	0.9	—
95% CI	—	0.6–1.3	0.5–1.1	0.8–1.6	0.6–1.3	0.97
Cases/person years[d]	38/2493	40/2529	31/2529	51/2546	47/2548	—
Multivariate RR	1.0	1.0	0.7	1.2	1.1	—
95% CI	—	0.6–1.6	0.5–1.2	0.8–1.9	0.7–1.7	0.41
Soluble nonstarch polysaccharides						
Median intake (mg/day)	5.48	6.92	8.03	9.36	11.54	—
Cases/person years	53/3774	47/3810	73/3805	49/3841	60/3785	—
RR[b]	1.0	0.8	1.2	0.8	0.9	—
95% CI	—	0.6–1.2	0.8–1.7	0.5–1.1	0.6–1.3	0.53
Cases/person years	53/3715	46/3791	73/3792	49/3816	60/3772	—
Multivariate RR[c]	1.0	0.8	1.2	0.8	1.0	—
95% CI	—	0.5–1.2	0.8–1.8	0.5–1.2	0.6–1.4	0.81
Cases/person years[d]	35/2476	33/2539	54/2544	36/2552	49/2534	—
Multivariate RR	1.0	0.9	1.3	0.9	1.2	—
95% CI	—	0.5–1.4	0.9–2.1	0.5–1.4	0.7–1.9	0.48
Insoluble nonstarch polysaccharides						
Median intake (mg/day)	6.59	8.70	10.39	12.22	15.33	
Cases/person years	54/3778	59/3821	52/3795	55/3803	62/3818	
RR[b]	1.0	1.1	0.9	0.9	1.0	
95% CI	—	0.7–1.6	0.6–1.3	0.6–1.3	0.7–1.4	0.52
Cases/person years	54/3734	58/3799	52/3764	55/3778	62/3812	
Multivariate RR[c]	1.0	1.1	0.9	1.0	1.1	
95% CI	—	0.7–1.6	0.6–1.4	0.6–1.4	0.7–1.6	0.95
Cases/person years[d]	38/2492	42/2548	36/2509	41/2532	50/2565	
Multivariate RR	1.0	1.1	0.9	1.0	1.2	
95% CI	—	0.7–1.8	0.6–1.5	0.6–1.6	0.8–1.9	0.54

RR: Rate ratio; CI: confidence interval.

[a] Reference category.

[b] Adjusted for age and gender.

[c] Adjusted for age, gender, smoking status, education, stomach disorders, and family history of stomach carcinoma.

[d] Analyses with first-year and second-year cases excluded and adjusted for age, gender, smoking status, education, stomach disorders, and family history of stomach carcinoma.

number of cancer cases. In addition, the intervention period was relatively short, and supplementation was given relatively late in life in both trials. In the General Population Trial, it is not clear whether a specific component or a combination of components of the supplement were responsible for the reduction in the incidence gastric carcinoma.

We did not observe an inverse association between vitamin E, folate, α-carotene, lutein plus zeaxanthin, β-cryptoxanthin, and dietary fiber and the risk

TABLE 6
Rate Ratios for Combinations of Vitamin C Intake Categories and Tertiles of Vitamin E Intake and Vitamin C Intake Categories and Tertiles of Folate Intake: Netherlands Cohort Study 1986–1992

	RR for tertiles of vitamin E (no. of cases)			RR for tertiles of folate (no. of cases)		
Vitamin C categories	**1**	**2**	**3**	**1**	**2**	**3**
Analyses with all cases[a]						
1	1.00 (38)[b]	0.83 (27)	0.73 (18)	1.00 (57)[b]	0.96 (21)	0.99 (5)
2	0.54 (27)[c]	0.66 (38)	0.61 (36)[c]	0.50 (23)[c]	0.79 (49)	0.73 (29)
3	0.70 (23)	0.63 (30)	0.62 (44)[c]	0.51 (6)	0.90 (33)	0.68 (58)
Analyses with first and second year cases excluded[a]						
1	1.00 (25)[b]	0.85 (18)	0.80 (13)	1.00 (35)[b]	1.26 (17)	1.37 (4)
2	0.64 (21)	0.72 (27)	0.69 (27)	0.56 (16)	1.11 (41)	0.74 (18)
3	0.75 (16)	0.73 (23)	0.78 (37)	0.41 (3)	0.92 (21)	0.99 (52)

[a] Adjusted for age, sex, smoking status, education, stomach disorders, and family history of stomach carcinoma.
[b] Reference category.
[c] CI excludes one.

of gastric carcinoma. Several case–control studies, however, have found a decrease in the risk of gastric carcinoma associated with vitamin E,[21,39] folate intake,[20,22,40,41] and dietary fiber.[19,21] One case–control study reported protective effects for lutein and lycopene but not for α-carotene.[22]

Only vitamin C was associated with a decreased risk of gastric carcinoma; however, after adjustment for several confounders and exclusion of first-year and second-year cases, this association weakened and became nonsignificant. However, the RRs did not change after adjustment for other vitamins. For vitamin C, several different mechanisms of action were described, such as antioxidant effects, free-radical scavenger effects, and the inhibition of nitrosamine formation.[13,15] Another biologic explanation for an inverse association is a direct action of vitamin C on the growth of *Helicobacter pylori*.[42] However, a mechanism for this anti-*Helicobacter pylori* activity is not known.

For retinol, subjects with the highest intake had a significantly increased risk of gastric carcinoma. This also was found in several case–control studies.[20,43,44] Retinol is derived from animal food sources. It has been suggested that components other than retinol in these foods, such as toxicants in liver, may be responsible for the observed effect.[44,45]

The finding of a positive association between β-carotene and the risk of gastric carcinoma seems to be in line with the finding of the ATBC trial, in which more cases were detected in the β-carotene supplement group. It has been hypothesized that β-carotene may be involved in potentially harmful nutrient interactions and that β-carotene may inhibit the apoptosis of preneoplastic or neoplastic cells, thus enhancing the survival of such cells.[46]

The results of this study indicated that the use of vitamin supplements, particular vitamin A-containing supplements, was associated with a reduced risk of gastric carcinoma. In a Swedish case–control study, the regular use of vitamin supplementation was found to be protective.[21] In the Iowa Women's Health Study, vitamin supplement use also seemed to be associated with a reduced risk of cancer; however, due to the small numbers of patients, no specific or stable risk estimates could be calculated.[11] In the current analysis, the small numbers of patients were a limitation as well; therefore, this result may have been a chance finding. At the beginning of the study in 1986, use of vitamin supplements was not a common habit in the Dutch population. In the Dutch National Food Consumption Survey 1987–1988, the use of vitamin supplements in the group ages 50–65 years was estimated to be about 6%.[47] In addition, the use of supplements was related positively to adherence to alternative diets (e.g., vegetarian diet).[47] Supplements users, in our study, tended to eat more servings of fruit and vegetables and had a higher level of education; in other studies, they were more likely to exercise and follow a low-fat diet pattern, that is, they had a generally more health-oriented life style.[48] This may indicate that this small group of users probably are different in many ways compared with people who do not use vitamin-containing supplements.

There probably is not one specific component in fruit and vegetables that acts on gastric carcinogenesis, but several potentially anticarcinogenic agents may all act together.[15] This may explain why we found

no effect from several specific components in fruit and vegetables and only a slight protective effect against gastric carcinoma from fruit and vegetables.[4] It is also possible that components in fruit and vegetables other than those studied are involved in the development of gastric carcinoma or that factors early in life may be important in its development . The results of migrant studies suggest that this may be the case.[49,50] In the current study, it was found that food habits in our study population (ages 55–69 years) were relatively stable.[51] This may be more of an indicator of food consumption in adult life than in childhood or adolescence.

In this study, there was no indication of a protective effect of vitamin E, folate, α-carotene, lutein plus zeaxanthin, β-cryptoxanthin, lycopene, and dietary fiber intake against gastric carcinoma. A weak inverse association was found between vitamin C and the risk of gastric carcinoma. The positive association between intake of retinol and β-carotene and gastric carcinoma deserves further investigation.

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