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ORIGINAL ARTICLE

Case Control Study

Effect of dietary vitamin C on gastric cancer risk in the Korean population

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Abstract

AIM: To investigate the effects of dietary vitamin C and foods containing vitamin C on gastric cancer risk.

METHODS: Our study included 830 control subjects and 415 patients. Data regarding demographics, medical history, and lifestyle, including dietary and nutrient intake, were collected using reliable self-administered questionnaires. Dietary intake information was collected from the participants using a food frequency questionnaire that has been previously reported as reliable and valid. A rapid urease test and a histological evaluation were used to determine the presence of *Helicobacter pylori* (*H. pylori*) infection. Twenty-three vitamin C-contributing foods were selected, representing over 80% of the cumulative vitamin C contribution.

RESULTS: In analyses adjusted for first-degree family history of gastric cancer, education level, job, household income, smoking status, and regular exercise, an inverse association between vitamin C intake and gastric cancer risk was observed for the highest (⩾ 120.67 mg/d) *vs* the lowest (< 80.14 mg/d) intake category [OR (95%CI): 0.64 (0.46-0.88)], with a significant trend across the three intake categories (*P* = 0.007). No protective effect of vitamin C was detected after stratification by gender. No effect of vitamin C intake on the gastric cancer incidence was found in either men or women infected with *H. pylori*. Vitamin C-contributing foods, including cabbage [0.45 (0.32-0.63), 0.50 (0.34-0.75), 0.45 (0.25-0.81)], strawberries [0.56 (0.40-0.78), 0.49 (0.32-0.74), 0.52 (0.29-0.93)], and bananas [0.40 (0.29-0.57), 0.41 (0.27-0.62), 0.34 (0.19-0.63)], were protective factors against the risk of gastric cancer based on the results of the overall adjusted analyses and the results for men and women, respectively.

CONCLUSION: A protective effect of vitamin C and vitamin C-contributing foods against gastric cancer was observed. Further studies using larger sample sizes are required to replicate our results.

Key words: Vitamin C; Vitamin C-contributing foods; *Helicobacter pylori*; Gastric cancer; Korean population

Core tip: An increased intake of vitamin C and vitamin C-contributing foods, including vegetables and fruits, may protect individuals against the risk of gastric cancer. However, we have no sufficient evidence to support the hypothesis that vitamin C has protective effect against gastric cancer in individuals infected with *Helicobacter pylori*.

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INTRODUCTION

Although the incidence and mortality rates of gastric cancer have decreased worldwide, stomach cancer remains the fifth most common cancer and the third leading cause of cancer death in both sexes worldwide[1]. Being the most common cancer among men in Korea, gastric cancer had 41.3 and 7.8 per 100000 persons in the estimated age-standardized incidence and mortality rates in 2015, respectively[2].

Dietary habits and nutrient intake play important roles in the prevention and etiology of gastric cancer[3]. According to the World Cancer Research Fund and the American Institute for Cancer Research report, increased consumption of non-starchy vegetables and fruits may decrease the risk of gastric cancer, whereas salt and salted foods may be the risk factors of gastric cancer. Additionally, a number of other foods may associate with gastric cancer. However, no specific constituent of these foods has yet been identified to explain these reported associations[3]. Being one of the most common antioxidants found in fruits and vegetables, vitamin C may have a chemopreventive effect[4]. Vitamin C protects cells from oxidative DNA damage, thereby blocking carcinogenesis[5]. Additionally, the protective effect of vitamin C is supported by many observational studies and meta-analyses[6-15]. However, some observational studies did not successfully demonstrate a significant association between vitamin C intake and gastric cancer[16-18]. To date, the association between vitamin C intake and gastric cancer risk has been inconsistent.

Helicobacter pylori (H. pylori) is classified as a cause of stomach cancer in a monograph from the International Agency for Research on Cancer (IARC)[19,20]. Epidemiological studies in humans have linked vitamin C deficiency to more severe *H. pylori*-associated gastritis and a higher risk of gastric cancer[21,22]. Furthermore, reduced vitamin C levels in the gastric juice and plasma in *H. pylori*-infected patients returned to normal levels after *H. pylori* eradication[7,22-24]. Therefore, *H. pylori*-induced gastric cancer may be prevented by an appropriate diet.

We performed a case-control study to investigate the effects of dietary vitamin C and vitamin C-contributing foods on gastric cancer risk.

MATERIALS AND METHODS

Study population

This study is an expansion of two previously published case-control studies[25,26]. The control and case groups were obtained from the National Cancer Center Hospital in South Korea between March 2011 and December 2014. Individuals who were histologically confirmed as early gastric cancer patients within the preceding three months at the Center for Gastric Cancer were included in the case group. Early gastric carcinoma is an invasive carcinoma confined to the mucosa and/or submucosa, with or without lymph node metastases, irrespective of the tumor size[27]. Patients in the case group did not have diabetes mellitus, a history of cancer within the past five years, advanced gastric cancer, or severe systemic or mental disease, nor were they women who were pregnant or breastfeeding. We selected the control group from patients undergoing health-screening examinations at the Center for Cancer Prevention and Detection at the same hospital.

In total, 1727 participants were recruited, with 1227 in the control group and 500 in the case group; 1671 individuals provided data through a food frequency questionnaire (FFQ) and a self-administered questionnaire. Participants with a total energy intake of < 500 kcal or ⩾ 4000 kcal (*n* = 15) were excluded

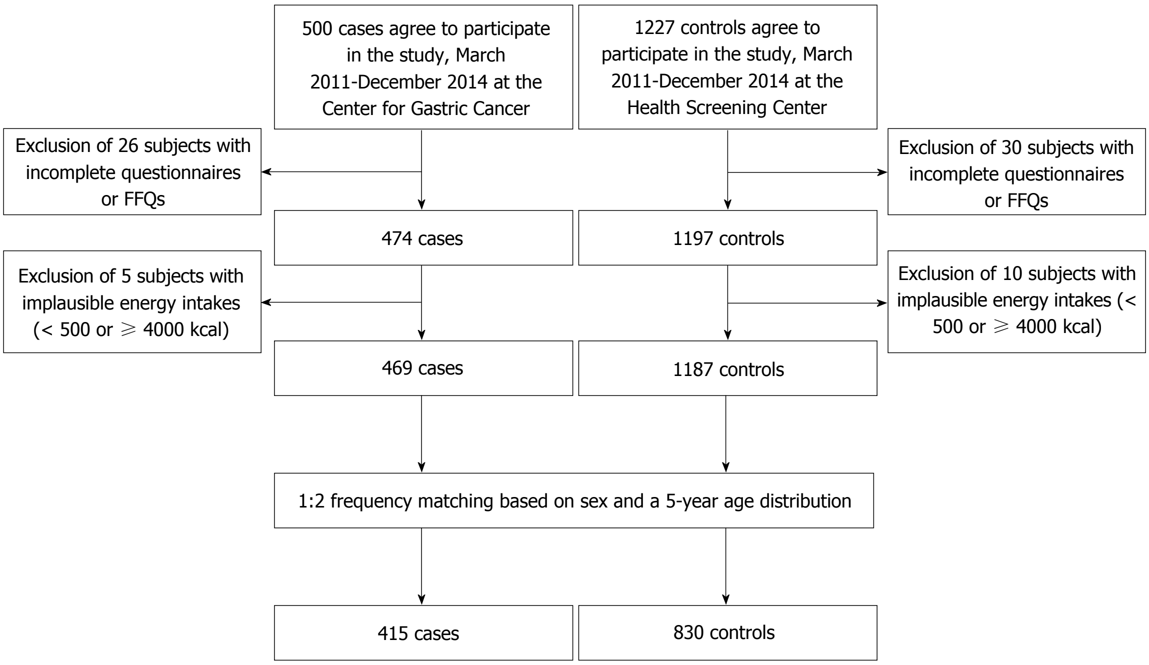

Figure 1 Flow diagram for included participants.

because of the implausibility of the data. Of the 1656 individuals remaining, the control and case subjects were frequency-matched by age (within 5 years) and sex at a ratio of 2:1 (controls:cases). The final analysis consisted of 1245 participants, including 830 controls and 415 cases (men, 810; women, 435; Figure 1). Our study was approved by the Institutional Review Board of the National Cancer Center [IRB Number: NCCNCS-11-438]. We collected written informed consent from all participants.

Data collection

The participants were asked to complete a self-administered questionnaire that included demographic, lifestyle, and medical history information. Dietary intake information was collected from the participants using the FFQ, which has been previously reported as a reliable and valid questionnaire[28]. The FFQ contains nine food consumption frequency categories (never or rarely, once a month, 2 or 3 times a month, once or twice a week, 3 or 4 times a week, 5 or 6 times a week, once a day, twice a day, and 3 times a day) and three portion size categories (small, medium, and large) for specific food items consumed within the past 12 mo. We used CAN-Pro 4.0 (Computer Aided Nutritional Analysis Program, The Korean Nutrition Society, Seoul, Korea) to calculate the average daily nutrient intake for each participant, and we summed the amounts of vitamin C obtained from various food groups to compute the vitamin C intake (mg/d). A rapid urease test and histological evaluation were used to assess *H. pylori* infection.

Statistical analysis

We used *t* tests and χ^2 tests for continuous and categorical variables, respectively, to compare the characteristics of the control and case groups. We conducted a contribution analysis to select vitamin C-contributing foods, which were ranked by the percentage of the total vitamin C intake that they provide for the population as a whole. A total of 23 vitamin C-contributing foods were selected, representing over 80% of the cumulative contribution. To compare the difference in dietary vitamin C intake and vitamin C-contributing foods, consumption was adjusted for total energy intake using the linear residual regression method[29]. The intake levels of vitamin C and vitamin C-contributing foods were categorized into tertiles according to the distribution of the control group. The lowest tertile group was used as the reference group. The median values of each tertile category of the dietary vitamin C intake and vitamin C-contributing foods were used as a continuous variable to test for trends.

The association between dietary factors and gastric cancer risk was assessed using an analysis with logistic regression models adjusted for potential confounding variables, and the odds ratios (OR) and their 95% confidence intervals (CIs) were calculated. Multivariate models were adjusted for first-degree family history of gastric cancers (yes, no), education level (middle school or less, high school, and college or more), job (managers and professionals, clerical, sales and service, production workers and laborers, and not in the labor force), monthly household income (< 2000000 KRW, 2000000-4000000 KRW, ≥ 4000000 KRW), smoking status (nonsmoker, ex-smoker, and current smoker), regular exercise (yes, no), and *H. pylori* infection (positive, negative). SAS 9.3 software (SAS Institute., Cary, NC, United States) was used to perform the calculations, and a two-sided *P* value less

Table 1 General characteristics of the study subjects

	Total (n = 1245)			Men (n = 810)			Women (n = 435)		
	Case (n = 415)	Control (n = 830)	P value[1]	Case (n = 270)	Control (n = 540)	P value	Case (n = 145)	Control (n = 290)	P value
Age (yr), mean ± SD	53.8 ± 9.3	53.7 ± 9.0	0.892	54.9 ± 8.7	54.8 ± 8.4	0.905	51.7 ± 10.0	51.6 ± 9.8	0.942
Body mass index (kg/m^2)									
< 23	159 (38.3)	314 (37.8)	0.975	91 (33.7)	161 (29.8)	0.509	68 (46.9)	153 (52.8)	0.533
23-25	122 (29.4)	249 (30.0)		78 (28.9)	170 (31.5)		44 (30.3)	79 (27.2)	
≥ 25	133 (32.1)	266 (32.1)		101 (37.4)	209 (38.7)		32 (22.1)	57 (19.7)	
First-degree family history of gastric cancer									
No	332 (80.0)	725 (87.4)	0.001	209 (77.4)	464 (85.9)	0.002	123 (84.8)	261 (90.0)	0.114
Yes	82 (19.8)	103 (12.4)		60 (22.2)	74 (13.7)		22 (15.2)	29 (10.0)	
Marital status									
Married	361 (87.0)	716 (86.3)	0.611	243 (90.0)	478 (88.5)	0.475	118 (81.4)	238 (82.1)	0.975
Other	52 (12.5)	113 (13.6)		26 (9.6)	61 (11.3)		26 (17.9)	52 (17.9)	
Education level									
Less than middle school	142 (34.2)	119 (14.3)	< 0.001	91 (33.7)	71 (13.2)	< 0.001	51 (35.2)	48 (16.6)	< 0.001
High school	174 (41.9)	253 (30.5)		112 (41.5)	140 (25.9)		62 (42.8)	113 (39.0)	
College or higher	97 (23.4)	426 (51.3)		66 (24.4)	301 (55.7)		31 (21.4)	125 (43.1)	
Job									
Managers and professionals	70 (16.9)	156 (18.8)	0.001	59 (21.9)	117 (21.7)	0.010	11 (7.6)	39 (13.5)	0.002
Clerical, sales and service workers	122 (29.4)	266 (32.1)		81 (30.0)	203 (37.6)		41 (28.3)	63 (21.7)	
Production workers, and laborers	104 (25.1)	128 (15.4)		83 (30.7)	111 (20.6)		21 (14.5)	17 (5.9)	
Not in the labor force	117 (28.2)	277 (33.4)		46 (17.0)	106 (19.6)		71 (49.0)	171 (59.0)	
Monthly household income[2]									
< 200	133 (32.1)	149 (18.0)	< 0.001	85 (31.5)	85 (15.7)	< 0.001	48 (33.1)	64 (22.1)	0.016
200-400	148 (35.7)	341 (41.1)		106 (39.3)	232 (43.0)		42 (29.0)	109 (37.6)	
≥ 400	96 (23.1)	273 (32.9)		55 (20.4)	168 (31.1)		41 (28.3)	105 (36.2)	
Alcohol consumption									
Non-drinker	119 (28.7)	236 (28.4)	0.243	44 (16.3)	89 (16.5)	0.282	75 (51.7)	147 (50.7)	0.819
Ex-drinker	41 (9.9)	60 (7.2)		33 (12.2)	47 (8.7)		8 (5.5)	13 (4.5)	
Current drinker	254 (61.2)	534 (64.3)		193 (71.5)	404 (74.8)		61 (42.1)	130 (44.8)	
Smoking status									
Non-smoker	167 (40.2)	384 (46.3)	< 0.001	39 (14.4)	106 (19.6)	< 0.001	128 (88.3)	278 (95.9)	0.021
Ex-smoker	119 (28.7)	284 (34.2)		110 (40.7)	277 (51.3)		9 (6.2)	7 (2.4)	
Current-smoker	128 (30.8)	162 (19.5)		121 (44.8)	157 (29.1)		7 (4.8)	5 (1.7)	
Regular exercise									
No	268 (64.6)	361 (43.5)	< 0.001	161 (59.6)	234 (43.3)	< 0.001	107 (73.8)	127 (43.8)	< 0.001
Yes	147 (35.4)	466 (56.1)		109 (40.4)	303 (56.1)		38 (26.2)	163 (56.2)	
H. pylori infection									
Negative	33 (8.0)	320 (38.6)	< 0.001	18 (6.7)	187 (34.6)	< 0.001	15 (10.3)	133 (45.9)	< 0.001
Positive	382 (92.1)	486 (58.6)		252 (93.3)	333 (61.7)		130 (89.7)	153 (52.8)	

[1]P values were calculated using the t test (for continuous variables) or χ^2 test (for categorical variables); [2]Unit is 10000 won in Korean currency. Values are expressed as the mean ± SD (range) or n (%).

than 0.05 was considered statistically significant.

RESULTS

General characteristics

Table 1 shows the distribution of 830 control subjects and 415 patients with gastric cancer according to general characteristics. Gastric cancer patients who had a higher family history of gastric cancer (P = 0.001) and tended to have a lower education level (P < 0.001), lower levels of employment (P < 0.001) and household income (P < 0.001) reported using more tobacco (P < 0.001), performing less regular exercise (P < 0.001), and having a higher proportion of *H. pylori* infection (P < 0.001). Compared with the control group, both men and women in the case group had a lower education level, job, and household income, used more tobacco, performed less regular exercise, and had a higher proportion of *H. pylori* infection. In particular, the men in the case group had a higher percentage of family history of gastric cancer than the men in the control group (P = 0.002).

Vitamin C and vitamin C-contributing food consumption is described in Table 2. Lower vitamin C intake (P < 0.001), increased consumption of potatoes and starches (P = 0.013) and fruits (P < 0.001), and higher energy intake (P < 0.001) were found in the case group. In general, the case group consumed less

Table 2 Comparison of intakes of vitamin C and vitamin C contributing foods[1]

Food (g/d) (mean ± SD)	Total (n = 1245)			Men (n = 810)			Women (n = 435)		
	Case (n = 415)	Control (n = 830)	P value[2]	Case (n = 270)	Control (n = 540)	P value	Case (n = 145)	Control (n = 290)	P value
Energy (Kcal/d)	1924.1 ± 612.9	1713.6 ± 545.5	< 0.001	2038.5 ± 634.8	1760.6 ± 541.5	< 0.001	1711.1 ± 507.0	1626.0 ± 543.1	0.116
Vitamin C (mg/d)	96.1 ± 50.5	108.4 ± 56.1	< 0.001	89.0 ± 45.3	97.1 ± 44.2	0.014	109.3 ± 56.7	129.5 ± 68.5	0.001
Potatoes and starches	39.3 ± 38.1	45.5 ± 45.4	0.013	32.8 ± 34.6	40.3 ± 36.5	0.005	51.5 ± 41.2	55.1 ± 57.4	0.456
Potatoes	32.3 ± 34.0	35.0 ± 35.0	0.209	27.7 ± 32.2	32.7 ± 30.3	0.035	41.0 ± 35.7	39.1 ± 42.1	0.635
Sweet potatoes	24.8 ± 210.0	42.3 ± 234.4	0.183	8.2 ± 41.9	15.1 ± 47.1	0.030	55.6 ± 349.4	92.8 ± 386.8	0.329
Vegetables	327.4 ± 185.0	328.2 ± 166.2	0.947	318.4 ± 177.5	320.5 ± 157.4	0.873	344.3 ± 197.7	342.5 ± 180.8	0.926
Korean cabbage kimchi	99.3 ± 71.0	96.1 ± 69.3	0.450	94.9 ± 66.6	97.3 ± 69.0	0.639	107.4 ± 78.1	93.8 ± 70.0	0.068
Green pepper	7.3 ± 11.0	7.9 ± 10.6	0.347	6.4 ± 6.8	7.5 ± 9.5	0.044	9.0 ± 16.0	8.6 ± 12.5	0.769
Radish	20.3 ± 17.5	21.2 ± 18.3	0.375	20.3 ± 16.8	21.5 ± 17.5	0.348	20.3 ± 18.8	20.8 ± 19.6	0.801
Spinach	9.9 ± 21.6	10.7 ± 22.8	0.572	8.0 ± 18.5	9.1 ± 17.3	0.380	13.6 ± 26.2	13.6 ± 30.4	0.994
Radish kimchi	27.1 ± 80.2	28.5 ± 58.9	0.765	20.7 ± 40.1	26.8 ± 52.3	0.065	39.1 ± 123.6	31.5 ± 69.6	0.491
Cabbage	6.6 ± 13.9	13.4 ± 27.1	< 0.001	4.6 ± 10.3	9.7 ± 20.0	< 0.001	10.3 ± 18.3	20.4 ± 35.8	< 0.001
Chonggak kimchi	15.7 ± 44.9	16.5 ± 33.6	0.769	12.1 ± 23.1	15.6 ± 29.9	0.072	22.4 ± 68.7	18.1 ± 39.4	0.486
Zucchini	18.0 ± 22.1	17.5 ± 20.4	0.711	16.1 ± 20.3	15.4 ± 18.3	0.650	21.6 ± 24.9	21.5 ± 23.2	0.956
Chinese cabbage	22.3 ± 118.0	32.7 ± 142.8	0.172	20.7 ± 132.2	34.0 ± 164.8	0.217	25.1 ± 85.7	30.3 ± 88.5	0.564
Lettuce	7.2 ± 10.1	9.3 ± 15.5	0.004	6.1 ± 8.8	7.6 ± 10.7	0.039	9.1 ± 11.9	12.4 ± 21.4	0.040
Onion	14.5 ± 8.7	15.0 ± 9.2	0.375	13.4 ± 7.6	14.3 ± 8.6	0.166	16.4 ± 10.2	16.3 ± 10.2	0.887
Mustard leaf kimchi	10.5 ± 61.5	14.2 ± 118.4	0.469	8.1 ± 62.4	8.2 ± 58.9	0.990	14.9 ± 59.8	25.4 ± 183.1	0.377
Green onion	4.8 ± 3.0	5.0 ± 3.3	0.410	4.9 ± 3.01	5.1 ± 3.3	0.410	4.7 ± 2.9	4.8 ± 3.5	0.811
Fruits	136.0 ± 165.8	191.8 ± 209.1	< 0.001	115.5 ± 149.4	152.0 ± 163.5	0.002	174.1 ± 187.4	266.0 ± 259.0	< 0.001
Mandarins	16.0 ± 26.3	23.2 ± 44.9	< 0.001	12.9 ± 22.6	14.6 ± 23.4	0.319	21.8 ± 31.5	39.2 ± 66.0	< 0.001
Strawberries	5.2 ± 8.7	8.8 ± 15.8	< 0.001	4.3 ± 7.7	6.7 ± 11.2	< 0.001	7.0 ± 10.0	12.6 ± 21.4	< 0.001
Orange juice	8.9 ± 22.2	20.8 ± 56.1	< 0.001	6.4 ± 14.2	16.9 ± 54.8	< 0.001	13.6 ± 31.6	28.0 ± 57.8	0.001
Watermelon	13.4 ± 21.7	21.0 ± 69.4	0.004	11.3 ± 21.2	15.3 ± 36.5	0.050	17.5 ± 22.2	31.8 ± 105.6	0.028
Apples	30.4 ± 57.1	52.3 ± 89.7	< 0.001	23.8 ± 49.1	42.7 ± 77.3	< 0.001	42.7 ± 68.1	70.2 ± 107.0	0.001
Persimmons	17.4 ± 110.5	20.3 ± 57.6	0.617	17.2 ± 133.6	12.9 ± 43.3	0.603	17.8 ± 41.9	34.1 ± 75.5	0.004
Bananas	10.5 ± 26.5	20.3 ± 40.9	< 0.001	7.3 ± 16.0	15.2 ± 28.9	< 0.001	16.4 ± 38.5	29.8 ± 55.8	0.004
Citrus tea	23.6 ± 142.9	58.5 ± 729.7	0.184	11.8 ± 62.8	18.1 ± 67.4	0.201	45.5 ± 225.0	133.7 ± 1228.9	0.237

[1]Adjusted for total energy intake using the residuals method; [2]P values were calculated with the t test.

cabbage (P < 0.001), lettuce (P = 0.004), mandarins (P < 0.001), strawberries (P < 0.001), orange juice (P < 0.001), watermelon (P = 0.004), apples (P < 0.001), and bananas (P < 0.001) than the control group. Compared with the control group, the men and women in the case group also consumed less vitamin C, cabbage, lettuce, fruits, strawberries, orange juice, watermelon, apples, and bananas. Some gender differences in vitamin C-contributing food consumption were found in both the case and control groups. The men in the case group consumed more energy (P < 0.001) and fewer starches (P = 0.005), potatoes (P = 0.035), sweet potatoes (P = 0.030), and green peppers (P = 0.044) than the control group. The women in the case group consumed fewer mandarins (P < 0.001) and persimmons (P = 0.004) than the women in the control group.

Vitamin C intake and the risk of gastric cancer

Table 3 reports the ORs and corresponding 95%CIs for vitamin C intake. Vitamin C intake exhibited was negatively associated with gastric cancer in both the unadjusted model [OR (95%CI): 0.53 (0.40-0.71), P for trend < 0.001] and the adjusted model (family history of gastric cancer, education level, job, household income, smoking status, and regular exercise; 0.64 (0.46-0.88), P for trend = 0.007. However, the association was marginally significant after an additional adjustment for *H. pylori* status [0.71 (0.50-1.00), P for trend = 0.052]. No protective effect of vitamin C was observed in either gender as a result of the adjusted model.

The results were stratified by *H. pylori* status and sex in the present study. In the crude model, vitamin C intake was a protective factor against gastric cancer for participants infected with *H. pylori* [0.62 (0.45-0.87), P for trend = 0.006]. However, the association was weakened after an adjustment for confounding factors [0.74 (0.51-1.08), P for trend = 0.116]. No effect of vitamin C intake on the gastric cancer incidence was observed for both either men or women infected with *H. pylori* (data not shown).

Vitamin C - contributing food consumption and the risk of gastric cancer

Table 4 shows the association between vitamin C-contributing food consumption and the gastric cancer risk. Overall, the consumption of total fruit [0.57 (0.41-0.81)], sweet potatoes [0.62 (0.44-0.87)], cabbage [0.45 (0.32-0.63)], Chinese cabbage [0.58 (0.41-0.81)], lettuce [0.67 (0.49-0.93)], strawberries [0.56 (0.40-0.78)], orange juice [0.61 (0.44-0.85)], watermelon [0.69 (0.50-0.95)], apples [0.60 (0.43-0.85)], persimmons [0.56 (0.40-0.78)], and bananas [0.40 (0.29-0.57)] protects against gastric cancer based on the results of the adjusted model.

Table 3 ORs and 95%CIs of gastric cancer by tertiles of dietary vitamin C

	Range (mg/d)	No. of controls/cases	Model Ⅰ OR (95%CI)	Model Ⅱ OR (95%CI)	Model Ⅲ OR (95%CI)
Total (n = 1245)					
T1	< 80.14	276/186	1	1	1
T2	80.14-120.67	277/130	0.70 (0.53-0.92)	0.81 (0.59-1.10)	0.81 (0.58-1.12)
T3	≥ 120.67	277/99	0.53 (0.40-0.71)	0.64 (0.46-0.88)	0.71 (0.50-1.00)
P for trend[1]			< 0.001	0.007	0.052
Men (n = 810)					
T1	< 73.18	180/107	1	1	1
T2	73.18-110.59	180/93	0.87 (0.62-1.23)	1.11 (0.75-1.64)	1.07 (0.70-1.61)
T3	≥ 110.59	180/70	0.65 (0.45-0.94)	0.78 (0.52-1.18)	0.91 (0.59-1.41)
P for trend			0.022	0.229	0.659
Women (n = 435)					
T1	< 91.70	96/69	1	1	1
T2	91.70-139.52	97/45	0.65 (0.40-1.03)	0.81 (0.48-1.36)	0.85 (0.49-1.48)
T3	≥ 139.52	97/31	0.45 (0.27-0.74)	0.57 (0.32-1.00)	0.61 (0.34-1.12)
P for trend			0.002	0.051	0.109

[1]Trends were calculated using the median intake for each dietary vitamin C category as a continuous variable: Model Ⅰ: Unadjusted; Model Ⅱ: Adjusted by first-degree family history of gastric cancer, education level, job, household income, smoking status, regular exercise; Model Ⅲ: Additionally adjusted for *H. pylori* infection.

Table 4 ORs and 95%CIs of gastric cancer by the highest tertile of vitamin C contributing food consumption

	Total (n = 1245)	*P* for trend[2]	Men (n = 810)	*P* for trend	Women (n = 435)	*P* for trend
Potatoes and starches						
Model Ⅰ OR[1] (95%CI)	0.74 (0.54-1.59)	0.020	0.55 (0.37-0.82)	0.001	0.97 (0.60-1.57)	0.996
Model Ⅱ OR (95%CI)	0.72 (0.52-1.01)	0.028	0.55 (0.36-0.85)	0.003	0.94 (0.55-1.60)	0.889
Model Ⅲ OR (95%CI)	0.85 (0.59-1.21)	0.277	0.65 (0.41-1.03)	0.042	1.01 (0.57-1.79)	0.891
Total vegetable consumption						
Model Ⅰ OR (95%CI)	0.87 (0.66-1.16)	0.366	0.91 (0.64-1.31)	0.593	0.86 (0.54-1.37)	0.549
Model Ⅱ OR (95%CI)	0.91 (0.66-1.25)	0.575	1.01 (0.67-1.52)	0.955	0.83 (0.49-1.39)	0.496
Model Ⅲ OR (95%CI)	0.96 (0.68-1.34)	0.800	1.09 (0.71-1.68)	0.744	0.82 (0.47-1.43)	0.494
Total fruit consumption						
Model Ⅰ OR (95%CI)	0.41 (0.30-0.56)	< 0.001	0.52 (0.36-0.75)	0.001	0.34 (0.21-0.57)	< 0.001
Model Ⅱ OR (95%CI)	0.57 (0.41-0.81)	0.002	0.73 (0.49-1.10)	0.148	0.52 (0.30-0.92)	0.032
Model Ⅲ OR (95%CI)	0.59 (0.41-0.85)	0.005	0.73 (0.47-1.13)	0.179	0.57 (0.31-1.05)	0.089
Potatoes						
Model Ⅰ OR (95%CI)	0.82 (0.61-1.10)	0.114	0.60 (0.41-0.87)	0.003	1.19 (0.73-1.93)	0.444
Model Ⅱ OR (95%CI)	0.79 (0.57-1.09)	0.105	0.55 (0.36-0.85)	0.003	0.99 (0.57-1.70)	0.867
Model Ⅲ OR (95%CI)	0.91 (0.64-1.29)	0.458	0.65 (0.41-1.02)	0.034	1.10 (0.61-1.97)	0.572
Sweet potatoes						
Model Ⅰ OR (95%CI)	0.57 (0.42-0.77)	< 0.001	0.54 (0.37-0.80)	< 0.001	0.71 (0.44-1.16)	0.244
Model Ⅱ OR (95%CI)	0.62 (0.44-0.87)	0.002	0.60 (0.39-0.92)	0.003	0.68 (0.39-1.18)	0.196
Model Ⅲ OR (95%CI)	0.69 (048-1.00)	0.018	0.66 (0.42-1.05)	0.016	0.76 (0.42-1.37)	0.294
Korean cabbage kimchi						
Model Ⅰ OR (95%CI)	1.08 (0.81-1.43)	0.547	0.90 (0.63-1.28)	0.572	1.47 (0.91-2.39)	0.087
Model Ⅱ OR (95%CI)	1.08 (0.79-1.48)	0.629	0.91 (0.61-1.35)	0.693	1.41 (0.81-2.43)	0.163
Model Ⅲ OR (95%CI)	1.11 (0.80-1.55)	0.511	0.99 (0.65-1.51)	0.976	1.27 (0.71-2.28)	0.342
Green pepper						
Model Ⅰ OR (95%CI)	0.85 (0.64-1.14)	0.252	0.78 (0.54-1.12)	0.141	0.99 (0.60-1.62)	0.894
Model Ⅱ OR (95%CI)	0.87 (0.64-1.20)	0.328	0.74 (0.49-1.12)	0.090	0.99 (0.57-1.72)	0.973
Model Ⅲ OR (95%CI)	0.81 (0.57-1.13)	0.167	0.67 (0.44-0.04)	0.037	0.93 (0.51-1.68)	0.844
Radish						
Model Ⅰ OR (95%CI)	0.97 (0.72-1.31)	0.599	0.89 (0.62-1.28)	0.468	1.22 (0.72-2.06)	0.870
Model Ⅱ OR (95%CI)	0.92 (0.67-1.28)	0.348	0.90 (0.60-1.35)	0.489	1.16 (0.65-2.07)	0.799
Model Ⅲ OR (95%CI)	0.98 (0.69-1.39)	0.495	0.92 (0.60-1.43)	0.578	1.27 (0.68-2.35)	0.893
Spinach						
Model Ⅰ OR (95%CI)	0.77 (0.58-1.03)	0.173	0.62 (0.44-0.90)	0.024	0.93 (0.58-1.51)	0.923
Model Ⅱ OR (95%CI)	0.80 (0.58-1.09)	0.283	0.66 (0.45-0.99)	0.071	1.02 (0.59-1.77)	0.851
Model Ⅲ OR (95%CI)	0.86 (0.61-1.20)	0.532	0.78 (0.51-1.20)	0.360	0.94 (0.52-1.70)	0.821
Radish kimchi						
Model Ⅰ OR (95%CI)	0.82 (0.62-1.10)	0.193	0.69 (0.48-0.99)	0.038	1.33 (0.80-2.22)	0.592
Model Ⅱ OR (95%CI)	0.82 (0.59-1.12)	0.195	0.70 (0.47-1.05)	0.090	1.21 (0.69-2.11)	0.937
Model Ⅲ OR (95%CI)	0.80 (0.57-1.12)	0.192	0.73 (0.47-1.13)	0.142	1.06 (0.58-1.94)	0.816

Cabbage						
Model Ⅰ OR (95%CI)	0.34 (0.25-0.46)	< 0.001	0.37 (0.26-0.53)	< 0.001	0.33 (0.19-0.55)	< 0.001
Model Ⅱ OR (95%CI)	0.45 (0.32-0.63)	< 0.001	0.50 (0.34-0.75)	0.004	0.45 (0.25-0.81)	0.016
Model Ⅲ OR (95%CI)	0.50 (0.35-0.72)	0.001	0.53 (0.35-0.82)	0.015	0.54 (0.29-1.00)	0.094
Chonggak kimchi						
Model Ⅰ OR (95%CI)	0.83 (0.62-1.10)	0.215	0.69 (0.48-0.99)	0.038	1.33 (0.80-2.20)	0.589
Model Ⅱ OR (95%CI)	0.83 (0.60-1.04)	0.253	0.69 (0.46-1.04)	0.077	1.21 (0.69-2.11)	0.933
Model Ⅲ OR (95%CI)	0.81 (0.58-1.13)	0.244	0.72 (0.47-1.11)	0.113	1.06 (0.58-1.94)	0.818
Zucchini						
Model Ⅰ OR (95%CI)	1.01 (0.76-1.35)	0.898	0.96 (0.67-1.37)	0.772	1.38 (0.84-2.25)	0.195
Model Ⅱ OR (95%CI)	1.09 (0.79-1.51)	0.783	0.99 (0.66-1.48)	0.846	1.87 (1.06-3.28)	0.026
Model Ⅲ OR (95%CI)	1.11 (0.78-1.56)	0.749	1.97 (0.63-1.50)	0.784	1.82 (1.00-3.30)	0.045
Chinese cabbage						
Model Ⅰ OR (95%CI)	0.64 (0.47-0.86)	< 0.001	0.53(0.36-0.78)	< 0.001	0.80 (0.49-1.31)	0.342
Model Ⅱ OR (95%CI)	0.58 (0.41-0.81)	< 0.001	0.49(0.32-0.76)	< 0.001	0.72 (0.41-1.25)	0.115
Model Ⅲ OR (95%CI)	0.62 (0.44-0.89)	< 0.001	0.57(0.36-0.90)	0.005	0.67 (0.37-1.22)	0.092
Lettuce						
Model Ⅰ OR (95%CI)	0.64 (0.48-0.86)	0.008	0.58 (0.41-0.82)	0.013	0.77 (0.47-1.26)	0.301
Model Ⅱ OR (95%CI)	0.67 (0.49-0.93)	0.026	0.58 (0.39-0.86)	0.023	0.79 (0.45-1.36)	0.365
Model Ⅲ OR (95%CI)	0.68 (0.48-0.95)	0.031	0.58 (0.38-0.88)	0.023	0.78 (0.43-1.40)	0.337
Onion						
Model Ⅰ OR (95%CI)	1.06 (0.79-1.42)	0.817	0.90 (0.62-1.30)	0.436	1.21 (0.73-1.99)	0.539
Model Ⅱ OR (95%CI)	1.09 (0.79-1.51)	0.693	0.84 (0.56-1.27)	0.320	1.33 (0.76-2.33)	0.344
Model Ⅲ OR (95%CI)	1.13 (0.80-1.59)	0.572	0.90 (0.58-1.40)	0.524	1.27 (0.71-2.30)	0.457
Mustard leaf Kimchi						
Model Ⅰ OR (95%CI)	0.84 (0.62-1.12)	0.099	0.87 (0.60-1.25)	0.220	0.66 (0.40-1.08)	0.207
Model Ⅱ OR (95%CI)	0.76 (0.55-1.06)	0.018	0.84 (0.56-1.27)	0.089	0.60 (0.34-1.04)	0.076
Model Ⅲ OR (95%CI)	0.76 (0.54-1.08)	0.038	0.90 (0.58-1.40)	0.180	0.57 (0.32-1.04)	0.093
Green onion						
Model Ⅰ OR (95%CI)	1.03 (0.76-1.38)	0.909	0.92 (0.64-1.33)	0.527	1.21 (0.73-2.01)	0.612
Model Ⅱ OR (95%CI)	1.02 (0.73-1.41)	0.807	0.94 (0.62-1.42)	0.588	1.11 (0.64-1.95)	0.731
Model Ⅲ OR (95%CI)	1.01 (0.71-1.44)	0.744	0.94 (0.60-1.46)	0.582	1.18 (0.65-2.13)	0.650
Mandarins						
Model Ⅰ OR (95%CI)	0.60 (0.44-0.80)	0.001	0.79 (0.55-1.12)	0.356	0.42 (0.25-0.71)	0.002
Model Ⅱ OR (95%CI)	0.74 (0.53-1.04)	0.061	0.97 (0.66-1.44)	0.941	0.60 (0.34-1.07)	0.101
Model Ⅲ OR (95%CI)	0.71 (0.50-1.01)	0.038	0.95 (0.62-1.44)	0.961	0.54 (0.29-0.99)	0.061
Strawberries						
Model Ⅰ OR (95%CI)	0.44 (0.33-0.60)	< 0.001	0.40 (0.27-0.58)	< 0.001	0.39 (0.23-0.67)	0.001
Model Ⅱ OR (95%CI)	0.56 (0.40-0.78)	0.001	0.49 (0.32-0.74)	0.001	0.52 (0.29-0.93)	0.026
Model Ⅲ OR (95%CI)	0.61 (0.43-0.86)	0.009	0.50 (0.32-0.79)	0.004	0.57 (0.30-1.07)	0.065
Orange juice						
Model Ⅰ OR (95%CI)	0.43 (0.32-0.59)	< 0.001	0.36 (0.25-0.53)	< 0.001	0.50 (0.30-0.85)	0.006
Model Ⅱ OR (95%CI)	0.61 (0.44-0.85)	0.003	0.47 (0.30-0.71)	0.001	0.83 (0.46-1.51)	0.294
Model Ⅲ OR (95%CI)	0.65 (0.46-0.94)	0.014	0.49 (0.31-0.77)	0.002	0.98 (0.52-1.86)	0.677
Watermelon						
Model Ⅰ OR (95%CI)	0.59 (0.44-0.78)	0.003	0.61 (0.43-0.87)	0.032	0.63 (0.39-1.02)	0.117
Model Ⅱ OR (95%CI)	0.69 (0.50-0.95)	0.065	0.71 (0.48-1.06)	0.211	0.72 (0.42-1.24)	0.309
Model Ⅲ OR (95%CI)	0.65 (0.46-0.92)	0.043	0.67 (0.44-1.03)	0.132	0.71 (0.40-1.27)	0.292
Apples						
Model Ⅰ OR (95%CI)	0.40 (0.29-0.54)	< 0.001	0.38 (0.26-0.55)	< 0.001	0.43 (0.26-0.71)	0.005
Model Ⅱ OR (95%CI)	0.60 (0.43-0.85)	0.006	0.57 (0.37-0.87)	0.026	0.64 (0.37-1.11)	0.204
Model Ⅲ OR (95%CI)	0.64 (0.45-0.92)	0.028	0.53 (0.34-0.83)	0.013	0.82 (0.46-1.47)	0.705
Persimmons						
Model Ⅰ OR (95%CI)	0.49 (0.36-0.66)	< 0.001	0.62 (0.43-0.89)	0.026	0.40 (0.24-0.66)	0.002
Model Ⅱ OR (95%CI)	0.56 (0.40-0.78)	0.001	0.72 (0.48-1.08)	0.151	0.46 (0.26-0.80)	0.018
Model Ⅲ OR (95%CI)	0.55 (0.38-0.78)	0.001	0.67 (0.44-1.03)	0.086	0.45 (0.25-0.82)	0.028
Bananas						
Model Ⅰ OR (95%CI)	0.32 (0.24-0.44)	< 0.001	0.33 (0.22-0.47)	< 0.001	0.26 (0.15-0.46)	< 0.001
Model Ⅱ OR (95%CI)	0.40 (0.29-0.57)	< 0.001	0.41 (0.27-0.62)	< 0.001	0.34 (0.19-0.63)	0.001
Model Ⅲ OR (95%CI)	0.44 (0.31-0.63)	< 0.001	0.41 (0.27-0.64)	0.001	0.44 (0.23-0.83)	0.014
Citrus tea						
Model Ⅰ OR (95%CI)	0.64 (0.48-0.87)	0.002	0.56 (0.38-0.81)	0.001	0.81 (0.49-1.34)	0.281
Model Ⅱ OR (95%CI)	0.78 (0.56-1.09)	0.048	0.68 (0.44-1.04)	0.017	1.00 (0.57-1.76)	0.669
Model Ⅲ OR (95%CI)	0.83 (0.59-1.18)	0.161	0.71 (0.45-1.11)	0.040	1.14 (0.63-2.09)	0.992

[1]OR for the association with the lowest tertile group compared with the highest tertile group; [2]Trends were calculated using the median intake for each category of vitamin C-contributing food consumption as a continuous variable: Model Ⅰ: Unadjusted; Model Ⅱ: Adjusted by first-degree family history of gastric cancer, education level, job, household income, smoking status, regular exercise; Model Ⅲ: Additionally adjusted for *H. pylori* infection.

Inverse associations between cabbage, strawberry, and banana consumption and gastric cancer risk were also observed for both men and women. Some different protective factors were found between genders. Starches, potatoes, sweet potatoes, spinach, Chinese cabbage, lettuce, orange juice, and apples decreased the risk of gastric cancer in men, and fruits and persimmons decreased the risk of gastric cancer in women. In particular, zucchini consumption increased the gastric cancer risk in women [1.87 (1.06-3.28)].

DISCUSSION

In our study, we found a negative association between vitamin C intake and gastric cancer in the crude model and the adjusted model. The association became less apparent after an additional adjustment for *H. pylori* status. After adjustment for confounders, vitamin C intake showed no protective effect for participants infected with *H. pylori*. The consumption of cabbage, strawberries, and bananas had inverse associations with gastric cancer risk based on the results of the overall adjusted model and for both genders.

The association between vitamin C intake and the risk of gastric cancer is supported by many observational and meta-analysis studies. In a meta-analysis of 11 observational studies, a dose-response analysis was conducted for vitamin C intake (100 mg/d), which showed a significant reduction in the risk of gastric cancer [RR (95%CI): 0.74 (0.69-0.79)][6]. An inverse association between the intake of vitamin C and the risk of gastric cancer was consistent among case-control studies[7-13] and cohort studies[14,15]. For example, in a Spanish study, the strongest protective effects were observed for vitamin C from fruits and vegetables[12]. Another case-control study in Italy reported that increased vitamin C consumption exhibited an inverse relationship to the risk of gastric cancer[13]. Our result is consistent with a cohort study from Netherlands that reported that an inverse association between vitamin C and the risk of gastric carcinoma was found in age- and gender-adjusted analyses. However, this association became weaker and was of borderline significance in the multivariate analysis (which included age, gender, smoking history, education, stomach disorders, and family history of gastric cancer) [RR (95%CI): 0.70 (0.50-1.00)][14]. Therefore, it appears that vitamin C is among the most consistent protective factors against gastric carcinogenesis. This protective effect may be related to the antioxidant effects of vitamin C, free radical scavenger effects, and the inhibition of nitrosamine formation[30,31]. Another biological explanation for the inverse association is the direct action of vitamin C on the growth of *H. pylori*[32]. However, no clear protective effect of vitamin C intake was observed in participants infected with *H. pylori* in our study.

In contrast, some observational studies did not successfully demonstrate a significant association between vitamin C intake and gastric cancer. Two case-control studies conducted in Mexico and Italy that included a small number of participants, showed no protective effect of vitamin C[16,17]. The Shanghai Women's and Men's Health study showed that none of the dietary nutrients examined, including vitamin A, vitamin C, vitamin E, carotene, retinol, selenium, or folic acid, were associated with the distal gastric cancer risk among men or women[18].

In the present study, we failed to find a protective effect of vitamin C against gastric cancer in participants infected with *H. pylori*. At least three explanations for this finding should be considered. First, the consumption of fruits and vegetables, which are the main sources of vitamin C, is highly prevalent among the Korean population[33]. In our study, a difference between case and control groups was observed only for total fruit consumption. Therefore, if an association between vitamin C intake and gastric cancer truly exists, the small difference between the case and control groups in our study may have limited the statistical power to detect this association. Second, this finding may be related to the Korean habit of eating pickled or processed vegetables, which includes many types of kimchi. Kimchi is a fermented vegetable with a high concentration of salt and pepper, which are important risk factors for gastric cancer[3]. Moreover, a high dietary salt intake can exacerbate *H. pylori* infection in gastric cancer patients[34]. Therefore, it is not surprising that no difference in vegetable consumption was observed between the case and control groups, which may weaken the protective effect of vitamin C. Additionally, the exacerbating role of *H. pylori* infection may modify the true association between vitamin C intake and gastric cancer risk in the adjusted model. Therefore, the protective effect of vitamin C should be considered in the model without adjusting for *H. pylori* status. Finally, the amount of vitamin C consumed by the participants with *H. pylori* infection could explain this finding. A Korean case-control study reported that consuming over 170 mg/d of vitamin C could protect people with *H. pylori* infection against the risk of gastric cancer [0.10 (0.02-0.63)][10]. Hence, in our analysis, vitamin C doses of 120 mg/d may not be high enough to show protective effect of vitamin C in participants infected with *H. pylori*.

In the vitamin C-contributing food consumption analyses, our findings are consistent with a meta-analysis of prospective cohort studies that reported an inverse association between fruit intake and gastric cancer incidence [RR (95%CI): 0.82 (0.73-0.93)] that was stronger for follow-up periods of ≥ 10 years [0.66 (0.52-0.83)]; however, no such association was observed for vegetable consumption [0.88 (0.69-1.13)][35]. Another meta-analysis of 8 observational studies of Korean and Japanese populations also showed that an increased intake of fresh vegetables was significantly associated with a decreased risk of gastric cancer

[OR (95%CI): 0.62 (0.46-0.85)][36]. Other meta-analyses of observational studies have supported the protective effect of fruits and vegetables against gastric cancer[37-40]. Additionally, the protective effect of fruits and vegetables has been consistently reported in many other case-control studies[8,11,41-46] and prospective cohort studies[47-50]. However, some cohort studies did not find this association[51-54]. For example, our findings are inconsistent with a cohort study from Japan that reported non-significant associations for the consumption between fruit and vegetable consumption and gastric cancer incidence[54]. This finding is comparable with the results of the Netherlands Cohort Study, which showed inverse associations between gastric cancer and the consumption of total vegetables, pulses, raw leaf vegetables, total fruits, citrus fruits, and apples and pears in the crude analysis that became weaker or disappeared in the multivariate analysis[51].

The methods used to cook fruits and vegetables may play an important role in the relationship between fruit and vegetable consumption and gastric cancer risk. Some studies have reported that an increased consumption of pickled or processed vegetables increases the risk of gastric cancer[36,46,55-57]. A meta-analysis of 14 observational studies demonstrated that an increased intake of pickled vegetables was significantly associated with an increased risk of gastric cancer [OR (95%CI): 1.28 (1.06-1.53)][36]. Moreover, a Korean study reported that increased intake of salt-fermented fish and kimchi was associated with an elevated risk of early gastric cancer[46]. These findings explain the non-significant associations in our study because Koreans frequently consume processed vegetables, such as cooked, salted, or pickled vegetables, instead of fresh vegetables, and these often include a high concentration of salt. This increased salt consumption could weaken the protective effect of vegetables against gastric cancer.

Some strengths of the present study include the use of a comprehensive, validated FFQ to assess of the exposure to factors of interest. Additionally, we collected information from the participants about the prevalence of *H. pylori* infection, which an IARC monograph names as a cause of stomach cancer[19,20].

However, some potential limitations are also present in our hospital-based case-control study, such as selection and recall bias. Selection bias occurs in a case-control study when subjects in the "control" group are not truly representative of the population that is included in the case group. The hospital-based control group may not represent the Korean population. Moreover, the small number of participants in our study may not be sufficient to detect the protective effects of vitamin C and vitamin C-contributing foods on the gastric cancer risk. Finally, subgroup analyses by anatomical site (cardia *vs* non-cardia) or histological type (intestinal *vs* diffuse) would be helpful because these factors may modify the epidemiological characteristics of gastric cancer.

In conclusion, an inverse association was found between vitamin C and the risk of gastric cancer. Sufficient evidence is lacking to support the protective effect of vitamin C intake in participants infected with *H. pylori*. The total fruit consumption and some vitamin C-contributing foods showed a negative association with gastric cancer. Further studies that replicate our results in larger sample are required.

COMMENTS

Background

Vitamin C is one of the most common antioxidants in fruits and vegetables and it may exert a chemopreventive effect. However, the association between vitamin C intake and gastric cancer risk has been inconsistent among epidemiological studies.

Research frontiers

The authors conducted a case-control study to investigate the association between vitamin C, foods containing vitamin C consumption and gastric cancer risk.

Innovations and breakthroughs

Protective effect of vitamin C and some vitamin C-contributing foods against gastric cancer risk was observed in this study. Additionally, the authors collected information from the participants about the prevalence of *H. pylori* infection, which an IARC monograph names as a cause of stomach cancer. However, they failed to find a protective effect of vitamin C against gastric cancer in participants infected with *H. pylori.*

Applications

Results of this study support for using vitamin C and some vitamin C-contributing foods to protect people against gastric cancer risk.

Terminology

Dietary vitamin C intake has a chemopreventive effect, which may reduce gastric cancer risk. The normal metabolism in human body or exposure to well-known carcinogenesis can produce reactive oxygen species. At a cellular level, these species cause various mutations and other consequences in the DNA. Vitamin C plays a role in blocking carcinogenesis to protect cells from this damage and development of gastric cancer.

Peer-review

The manuscript by Hoang and colleagues describes the risk of gastric cancer as a function of vitamin C intake, an epidemiological study involving more than 1200 cases who participated in the study through questionaires and other tests. The study is well performed, and the manuscript is written in good and logical order easy for the reader to digest.

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