CASE STUDY

Association between retinol intake and risk of gastric cancer: a case-control study in a Korean population

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ABSTRACT

Objectives: Gastric cancer has the fifth highest incidence among cancers in the world and is the most common cancer in South Korea. Several studies suggested a protective role of retinol in oesophageal, liver, lung, and breast cancer, while this effect was still inconsistent in gastric cancer.

Methods: We conducted a case-control study that included 415 cases and 830 controls at the National Cancer Center Hospital in Korea. Dietary information of the participants was collected using a validated semi-quantitative food frequency questionnaire (SQFFQ) covering 106 food items. A multivariate logistic regression model was performed to investigate the association between retinol intake and risk of gastric cancer.

Results: The highest consumption of retinol intake was significantly associated with lower odds of gastric cancer in the total subjects (odds ratio (OR)=0.58, 95% confidence interval (CI)=0.37–0.89), and among women (OR = 0.43, 95% CI = 0.21–0.89), but not among men (OR = 0.72, 95% CI = 0.41–1.26). After stratifying by Helicobacter pylori (H. pylori) infection, we identified a reduced risk of gastric cancer when consuming the highest level of retinol intake only among H. pylori-positive patients. This trend was demonstrated in the subgroups of current drinkers and those who had not smoked without adjustment for H. pylori infection.

Conclusion: Retinol intake was proved as a protective factor against gastric cancer, and this effect remained among women and patients with H. pylori infection even after adjustment for multivariable.

***Keywords**: Gastric cancer, retinol, case-control study, Korean population.*

INTRODUCTION

According to GLOBOCAN 2020 statistics, gastric cancer remains important cancer worldwide and is responsible for over one million new cases in 2020 and an estimated 769,000 deaths (equating to one in every 13 deaths globally), ranking fifth for incidence and fourth for mortality globally (1). In South Korea, with an estimated almost 30,000 cases, gastric cancer is also the most common cancer and is the leading cause of cancer morbidity in men (16.3%) (2). Alcohol, foods preserved by salting, grilled or barbecued meat and fish, and

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low fruit intake were reported as risk factors for gastric cancer, while citrus fruit decreased the risk of stomach cardia cancer (3). However, the relationship between retinol and risk of gastric cancer is inconclusive (4-8).

Retinol is one of the preformed vitamin A in the human diet, which is present in foods of animal origin, such as liver, kidney, dairy products, and egg (9). Retinol and its metabolites (retinoids) have essential roles in the regulation of cell proliferation and differentiation, and they also modulate immune responses (10). To date, many studies have been conducted to investigate the association between retinol and the incidence of specific forms of cancer, such as oesophageal (11, 12), breast cancer (13), liver (14-16), and lung cancer (15). Nevertheless, evidence about the role of retinol intake in gastric cancer risk reduction was inconsistent. While many studies suggested an inverse association (4, 5) other studies reported that there was no relationship between retinol and reduced risk of gastric cancer incidence (6-8). Therefore, we conducted this study to examine whether retinol intake is a protective factor against gastric cancer development.

METHODS

Study design: A case-control study. This study is subsequent research of several studies previously conducted on the association between nutrient or food consumption and the risk of gastric cancer (17-22).

Study site and time: To conduct this study, participants were recruited at the National Cancer Center Hospital in Korea between March 2011 and December 2014. Patients who had been newly diagnosed with early gastric cancer, defined as gastric cancer confined to the mucosa/submucosa, regardless of lymph node metastasis (23) within the preceding three months at the Center for Gastric cancer of National Cancer Center Hospital in South Korea (KNCC) were eligible for enrollment. The control subjects were selected from people without cancers who underwent health examinations at the Center for Cancer Prevention and Detection at the same hospital. Both case and control subjects with several diseases that might have influenced their diet habit (those who had been diagnosed with cancer during the past 5 years, diabetes mellitus, or severe systemic/mental disease) and women who were pregnant or currently breastfeeding at the time of the investigation were excluded. Control subjects diagnosed with gastric or duodenal ulcer during the examination were excluded. All subjects had no history of previous Helicobacter pylori treatment.

Sample size and sampling: A total of 1,727 participants (500 cases and 1,227 controls) agreed to participate in the study. Among them, 26 cases and 30 controls were excluded as a result of an incomplete self-administered questionnaire or semiquantitative food frequency questionnaire (SQFFQ); furthermore, five cases and ten controls were excluded due to an implausible total energy intake (< 500 kcal or ≥ 4000 kcal). Then, the cases and controls were frequently matched at a ratio of 1:2 based on the distribution of age within 5 years and sex. Finally, a total of 415 cases and 830 matched controls were selected. All participants agreed to participate in this study and provided written informed consent, and the study protocol was approved by the Institutional Review Board (IRB) of the National Cancer Center (IRB Number: NCCNCS-11-438).

Data collection: Participants in this study completed a structured questionnaire about demographic characteristics and lifestyle factors by themselves. To collect the information on dietary intake, a

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trained interviewer used a 106-item semi-quantitative food frequency questionnaire (SQFFQ). It was confirmed and reported that the SQFFQ is valid and reproducible (24) . The SQFFQ contains nine categories regarding the frequency of food consumption (never or rarely, once a month, 2–3 times a month, once or twice a week, 3–4 times a week, 5–6 times a week, once a day, twice a day, and 3 times a day), and three categories regarding portion sizes (small, medium, and large) for each food item consumed during the past 12 months. The dietary data were then analyzed in Computer-Aided Nutritional Analysis Program 4.0 (CAN-PRO 4.0, The Korean Nutrition Society, Seoul, Korea). To ascertain H. pylori infection status, a rapid urease test (Pronto Dry; Medical Instruments Corporation, Solothurn, Switzerland) and histological evaluation were conducted.

Data analysis: The general characteristics between the case and control subjects were compared by using Student's t-test for continuous variables and chi-square test for categorical variables. Retinol consumption of each food group was adjusted for total energy intake using the linear residual regression method. The levels of retinol intake was categorized into quartiles according to the distribution of retinol among the control group. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated across the quartiles of the retinol intake using the multivariate logistic regression model adjusting for age, sex, body mass index (BMI), family history of gastric cancer, smoking status, regular exercise, education, occupation, monthly income, alcohol consumption, married status, total energy intake, and H. pylori infection. The lowest quartile of dietary retinol was used as the reference. Additionally, through stratifying by smoking, alcohol consumption, and H. pylori infection, potential effect modification of the association between the dietary retinol and risk of gastric cancer was examined. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA), and a two-sided p-value less than 0.05 was considered statistically significant.

RESULTS

Table 1 describes the general characteristics of the study participants included 415 gastric cancer cases and 830 controls. Means age and BMI of this study population were reported at 54 years old and 24 kg/m^2, respectively. The percentages of family history of gastric cancer, H. pylori infection, and current smokers are significantly higher in the case group compared with the controls ($p < 0.05$). After stratifying by gender, the results were consistent except for the proportion of FHGC among female case and control groups, which was not different significantly. However, the gastric cancer cases reported a lower level of education, less likely to be high-income group, and a lower frequency of doing physical activities than the control group, even when stratified by sex ($p < 0.05$). In addition, a limited level of retinol intake was observed in the gastric cancer group compared with the controls ($p < 0.001$), and this trend was remained unchanged among ($p < 0.05$) and women ($p < 0.001$).

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Table 1. Demographic characteristics of the study participants

Characteristics **Case** **(n = 415)**		**Total (n = 1,245)**			**Men (n = 810)**			**Women (n = 435)**		
		Control (n = 830)	**p-value**[a]	**Case (n = 270)**	**Control (n = 540)**	**p-value**[a]	**Case (n = 145)**	**Control (n = 290)**	**p-value**[a]	
BMI	Mean ± SD	23.81 ± 3.23	23.95 ± 2.94	0.452	24.2 ± 2.9	24.4 ± 2.7	0.390	23.0 ± 3.6	23.1 ± 3.1	0.839
	< 25	282 (67.9)	564 (67.9)	1	169 (62.6)	331 (61.3)	0.721	113 (77.9)	233 (80.3)	0.556
	>= 25	133 (32.1)	266 (32.1)		101 (37.4)	209 (38.7)		32 (22.1)	57 (19.7)	
Educational status	Middle school or less	142 (34.2)	119 (14.3)	**< 0.001**	91 (33.7)	71 (13.2)	**< 0.001**	51 (35.2)	48 (16.5)	**< 0.001**
	High school	174 (41.9)	253 (30.5)		112 (41.5)	140 (25.9)		62 (42.8)	113 (39.0)	
	College or more	97 (23.4)	426 (51.3)		66 (24.4)	301 (55.7)		31 (21.4)	125 (43.1)	
	Missing	2 (0.5)	32 (3.9)		1 (0.4)	28 (5.2)		1 (0.6)	4 (1.4)	
Family history of gastric cancer	No	333 (80.2)	725 (87.3)	**< 0.001**	210 (77.8)	464 (85.9)	**0.002**	123 (84.8)	261 (90.0)	0.114
	Yes	82 (19.8)	103 (12.5)		60 (22.2)	74 (13.7)		22 (15.2)	29 (10.0)	
	Missing	0	2 (0.2)		0	2 (0.4)		0	0	
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)	
	Missing	0	3 (0.4)		0	3 (0.6)		0	0	
H. pylori infection	Negative	33 (7.9)	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 (58.5)		252 (93.3)	333 (61.7)		130 (89.7)	153 (52.7)	
	Missing	0	24 (2.9)		0	20 (3.7)		0	4 (1.4)	
Smoking status	Non-smoker	167 (40.3)	384 (46.3)	**< 0.001**	39 (14.5)	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 (30.9)	162 (19.5)		121 (44.8)	157 (29.1)		7 (4.8)	5 (1.7)	
	Missing	1 (0.1)	0		0	0		1 (0.7)	0	
Monthly average gross income	< 200	133 (32.0)	149 (17.9)	**< 0.001**	85 (31.5)	85 (15.7)	**< 0.001**	48 (33.1)	64 (22.1)	**0.010**
	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)	
	Missing	38 (9.2)	67 (8.1)		24 (8.8)	55 (10.2)		14 (9.6)	12 (4.1)	

Characteristics **Case (n = 415)**		**Total (n = 1,245)**			**Men (n = 810)**			**Women (n = 435)**		
		Control (n = 830)	**p-value[a]**	**Case (n = 270)**	**Control (n = 540)**	**p-value[a]**	**Case (n = 145)**	**Control (n = 290)**	**p-value[a]**	
Job	Professional administrative	70 (16.8)	156 (18.8)		59 (21.8)	117 (21.7)		11 (7.5)	39 (13.4)	
	Office, sale, service	104 (25.1)	128 (15.4)		83 (30.7)	111 (20.6)		21 (14.5)	17 (5.9)	
	Laborer, agricultural	122 (29.4)	266 (32.0)	**< 0.001**	81 (30.0)	203 (37.6)	**0.010**	41 (28.3)	63 (21.7)	**0.002**
	Others, unemployed	117 (28.2)	277 (33.4)		46 (17.1)	106 (19.6)		71 (49.0)	171 (59.0)	
	Missing	2 (0.5)	3 (0.4)		1 (0.4)	3 (0.5)		1 (0.7)	0	
Retinol intake[b] (µg/day)		65.6 ± 44.3	79.4 ± 51.7	**< 0.001**	65.2 ± 44.0	73.6 ± 46.9	**0.015**	66.2 ± 44.9	90.1 ± 58.3	**< 0.001**

[a]*p-values were calculated using the chi-square test for categorical variables and the t test for continuous variables. Significance at p value<0.05.*

[b]*Retinol intake was adjusted for total energy intake using the residual method.*

Table 2 shows the ORs and corresponding 95% CIs of gastric cancer according to quartiles of total dietary retinol. An inverse association between retinol intake and gastric cancer risk was seen in the highest level of retinol compared to the lowest level (OR=0.39; 95% CI=0.27–0.56; *p*-trend<0.001). After adjusted for multiple variables, this relationship was still significant (OR=0.58; 95% CI=0.37–0.89; *p*-trend=0.015). Among men, the highest retinol consumption was inverse associated with gastric cancer incidence compared to the lowest level (OR=0.50; 95% CI=0.32–0.79; *p*-trend=0.005), but this trend was null after adjusting for multiple variables (OR=0.72; 95% CI=0.41–1.26; *p*-trend=0.346). However, this association in female participants was remained in the crude model (OR=26; 95% CI=0.14–0.48; *p*-trend <0.001) and in the fully adjustment model (OR=0.43; 95% CI=0.21–0.89; *p*-trend=0.011).

We considered a further analysis to stratify these confounding factors among case and control groups. Table 3 demonstrates the ORs and corresponding 95% CIs of gastric cancer according to quartiles of dietary retinol after stratified by H. pylori infection. An inverse relationship between retinol intake and gastric cancer was identified in the participants whose H. pylori result was positive (OR=0.54; 95% CI=0.34–0.86; *p*-trend=0.018), whereas there was no association in subjects without H. pylori infection.

Table 4 shows the relationship between total retinol intake and risk of gastric cancer when stratifying by alcohol consumption. Among non-drinker, the relationship between the highest quartile of retinol intake and reduced risk of gastric cancer was only seen without multivariate adjustment (OR=0.37; 95% CI=0.19–0.72; *p*-trend=0.004). However, current drinkers who consumed the highest retinol level could decrease the risk of gastric cancer compared to those who consumed the lowest category even after adjusted for general character variables without H. pylori infection (OR=0.57; 95% CI=0.33–0.97; *p*-trend=0.039). There was no association reported in the former drinker.

Table 5 expresses the association between retinol intake and risk of gastric cancer after stratifying by smoking status of the study population. Overall, the higher consumption of retinol related to a reduced risk of gastric cancer was only demonstrated in the non-smoker group after adjusting for multiple variables without H. pylori infection (OR=0.47; 95% CI=0.25–0.87; *p*-trend=0.017).

Table 2. Association between retinol intake (categorized into quartiles) and risk of gastric cancer

Retinol (µg/day)	Controls	Cases	Model 1 ORs (95% CIs)	Model 2 ORs (95% CIs)	Model 3 ORs (95% CIs)
Total (n = 1,245)					
Q1 (<41.4)	208 (25.1)	144 (34.7)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	207 (24.9)	107 (25.8)	0.75 (0.55–1.02)	0.88 (0.61–1.25)	0.97 (0.67–1.43)
Q3 (68.7 - <102.5)	207 (24.9)	108 (26.0)	0.75 (0.55–1.03)	0.97 (0.68–1.39)	1.04 (0.71–1.53)
Q4 (≥102.5)	208 (25.1)	56 (13.5)	0.39 (0.27–0.56)	0.53 (0.35–0.80)	0.58 (0.37–0.89)
p-trend			**< 0.001**	**0.004**	**0.015**
Men (n = 810)					
Q1 (<41.4)	146 (27.0)	95 (35.2)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	146 (27.0)	69 (25.5)	0.73 (0.49–1.07)	0.86 (0.55–1.35)	0.93 (0.57–1.51)
Q3 (68.7 - <102.5)	137 (25.4)	70 (25.9)	0.79 (0.53–1.16)	1.05 (0.67–1.66)	1.11 (0.68–1.80)
Q4 (≥102.5)	111 (20.6)	36 (13.4)	0.50 (0.32–0.79)	0.71 (0.41–1.21)	0.72 (0.41–1.26)
p-trend			**0.005**	0.313	0.346
Women (n = 435)					
Q1 (<41.4)	62 (21.4)	49 (33.8)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	61 (21.0)	38 (26.2)	0.79 (0.45–1.37)	0.92 (0.49–1.71)	1.09 (0.56–2.12)
Q3 (68.7 - <102.5)	70 (24.1)	38 (26.2)	0.69 (0.40–1.18)	0.73 (0.39–1.36)	0.80 (0.40–1.58)
Q4 (≥102.5)	97 (33.5)	20 (13.8)	0.26 (0.14–0.48)	0.35 (0.18–0.70)	0.43 (0.21–0.89)
p-trend			**< 0.001**	**0.002**	**0.011**

Model 1: Crude model.

Model 2: Adjusted for age, body mass index, family history of gastric cancer, smoking status, regular exercise, education, occupation, monthly income, alcohol consumption, married status, and total energy intake.

Model 3: Additionally adjusted for Helicobacter pylori infection.

Table 3. Association between retinol intake (categorized into quartiles) and risk of gastric cancer stratified by Helicobacter pylori infection

Retinol (µg/day)	Controls	Cases	Model 1 ORs (95% CIs)	Model 2 ORs (95% CIs)
Negative (n = 353)				
Q1 (<41.4)	71 (22.2)	9 (27.3)	1.00	1.00
Q2 (41.4 - <68.7)	85 (26.6)	12 (36.3)	1.11 (0.44–2.79)	1.81 (0.61–5.35)
Q3 (68.7 - <102.5)	79 (24.7)	6 (18.2)	0.60 (0.20–1.77)	0.85 (0.23–3.12)
Q4 (≥102.5)	85 (26.5)	6 (18.2)	0.56 (0.19–1.64)	0.84 (0.23–3.02)
p-trend			0.177	0.502

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Retinol (µg/day)	Controls	Cases	Model 1 ORs (95% CIs)	Model 2 ORs (95% CIs)
Positive (n = 868)				
Q1 (<41.4)	131 (26.9)	135 (35.3)	1.00	1.00
Q2 (41.4 - <68.7)	115 (23.7)	95 (24.9)	0.80 (0.56–1.15)	0.89 (0.60–1.34)
Q3 (68.7 - <102.5)	123 (25.3)	102 (26.7)	0.81 (0.56–1.15)	1.07 (0.71–1.61)
Q4 (≥102.5)	117 (24.1)	50 (13.1)	0.42 (0.28–0.63)	0.54 (0.34–0.86)
p-trend			**< 0.001**	0.018

Model 1: Crude model.

Model 2: Adjusted for age, body mass index, family history of gastric cancer, smoking status, regular exercise, education, occupation, monthly income, alcohol consumption, married status, and total energy intake.

Table 4. Association between retinol intake (categorized into quartiles) and risk of gastric cancer stratified by alcohol consumption

Retinol (µg/day)	Controls	Cases	Model 1 ORs (95% CIs)	Model 2 ORs (95% CIs)	Model 3 ORs (95% CIs)
Non-drinker (n = 355)					
Q1 (<41.4)	62 (26.3)	39 (32.8)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	57 (24.2)	32 (26.9)	0.89 (0.49–1.61)	1.18 (0.59–2.35)	1.28 (0.61–2.70)
Q3 (68.7 - <102.5)	48 (20.3)	32 (26.9)	1.06 (0.58–1.93)	1.43 (0.71–2.87)	1.48 (0.69–3.19)
Q4 (≥102.5)	69 (29.2)	16 (13.4)	0.37 (0.19–0.72)	0.53 (0.24–1.14)	0.63 (0.28–1.43)
p-trend			**0.004**	0.088	0.213
Ex-drinker (n = 101)					
Q1 (<41.4)	15 (25.0)	17 (41.4)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	12 (20.0)	7 (17.1)	0.52 (0.16–1.65)	0.13 (0.02–1.04)	0.05 (0.01–1.25)
Q3 (68.7 - <102.5)	15 (25.0)	9 (22.0)	0.53 (0.18–1.56)	0.48 (0.07–3.56)	0.12 (0.01–2.27)
Q4 (≥102.5)	18 (30.0)	8 (19.5)	0.39 (0.13–1.16)	0.11 (0.02–0.84)	0.09 (0.01–1.32)
p-trend			0.122	0.070	0.138
Current drinker (n = 290)					
Q1 (<41.4)	131 (24.5)	88 (34.6)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	138 (25.8)	68 (26.8)	0.73 (0.49–1.09)	0.88 (0.56–1.39)	0.92 (0.57–1.49)
Q3 (68.7 - <102.5)	144 (27.0)	66 (26.0)	0.68 (0.46–1.02)	0.83 (0.53–1.31)	0.89 (0.55–1.44)
Q4 (≥102.5)	121 (22.7)	32 (12.6)	0.39 (0.25–0.63)	0.57 (0.33–0.97)	0.58 (0.33–1.02)
p-trend			0.001	0.039	0.065

Model 1: Crude model.

Model 2: Adjusted for age, body mass index, family history of gastric cancer, smoking status, regular exercise, education, occupation, monthly income, alcohol consumption, married status, and total energy intake.

Model 3: Additionally adjusted for Helicobacter pylori infection.

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Table 5. Association between retinol intake (categorized into quartiles) and risk of gastric cancer stratified by smoking status

Retinol (µg/day)	Controls	Cases	Model 1 ORs (95% CIs)	Model 2 ORs (95% CIs)	Model 3 ORs (95% CIs)
Non-smoker (n = 551)					
Q1 (<41.4)	92 (24.0)	58 (34.7)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	90 (23.4)	44 (26.3)	0.78 (0.48–1.26)	0.85 (0.49–1.46)	1.02 (0.56–1.83)
Q3 (68.7 - <102.5)	97 (25.3)	42 (25.2)	0.69 (0.42–1.12)	0.88 (0.51–1.53)	0.98 (0.54–1.77)
Q4 (≥102.5)	105 (27.3)	23 (13.8)	0.35 (0.20–0.61)	0.47 (0.25–0.87)	0.53 (0.28–1.01)
p-trend			**0.002**	**0.017**	**0.039**
Ex-smoker (n = 403)					
Q1 (<41.4)	75 (26.4)	39 (32.8)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	64 (22.5)	28 (23.5)	0.84 (0.47–1.52)	1.28 (0.63–2.62)	1.47 (0.68–3.14)
Q3 (68.7 - <102.5)	76 (26.8)	32 (26.9)	0.81 (0.46–1.43)	0.83 (0.42–1.64)	0.88 (0.42–1.84)
Q4 (≥102.5)	69 (24.3)	20 (16.8)	0.56 (0.30–1.05)	0.62 (0.29–1.35)	0.68 (0.30–1.55)
p-trend			0.072	0.143	0.223
Current smoker (n = 290)					
Q1 (<41.4)	41 (25.3)	47 (36.7)	1.00	1.00	1.00
Q2 (41.4 - <68.7)	53 (32.7)	35 (27.3)	0.58 (0.32–1.05)	0.80 (0.39–1.67)	0.78 (0.36–1.70)
Q3 (68.7 - <102.5)	34 (21.0)	33 (25.8)	0.85 (0.45–1.60)	1.12 (0.51–2.47)	1.16 (0.50–2.71)
Q4 (≥102.5)	34 (21.0)	13 (10.2)	0.33 (0.16–0.72)	0.46 (0.17–1.21)	0.48 (0.17–1.38)
p-trend			**0.018**	0.226	0.336

Model 1: Crude model.

Model 2: Adjusted for age, body mass index, family history of gastric cancer, smoking status, regular exercise, education, occupation, monthly income, alcohol consumption, married status, and total energy intake.

Model 3: Additionally adjusted for Helicobacter pylori infection.

DISCUSSION

The current study suggested an inverse association between retinol intake and the risk of gastric cancer. The participants who consumed the highest intake of retinol had a 40-60% lower risk of gastric cancer compared to those who consumed the lowest quartile of retinol intake.

Findings from our study are consistent with the results in Larsson's study (4) and Jenab's study (5), in which a relationship between retinol intake and reduced risk of gastric cancer was observed. A meta-analysis of Wu et al (6) indicated a marginally inverse association was found between retinol intake or blood retinol level and gastric cancer. However, their detailed data on retinol intake was not available from each study, which might reduce the accuracy of the results. In Pelucchi's study (7), they had no information on H. pylori infection, and it might be a reason for their inconsistent results with other studies. Fortunately, our study considered that problem to performed further analyses, then an inverse association was observed in the subjects with H. pylori infection. In other words, a higher intake of retinol could decrease the occurrence of gastric cancer specifically in patients with H. pylori infection.

According to several studies, Helicobacter pylori (H. pylori) infection, alcohol, and smoking consumption were reported as the main risk factors of gastric cancer incidence (4-5) . H. pylori infection is the main risk factor of gastric cancer (25-27) because it causes persistent inflammation in the human stomach, and gastric inflammation nearly always precedes the development of peptic ulceration and is a critical component in initiating the multi-step progression towards gastric carcinogenesis (28). In addition, H. pylori infection also impairs nutrient absorption, then many micronutrients were lower among H. pylori (+) individuals than H. pylori (-) individuals, significantly for β-carotene, folate, and retinol (29). Retinol was known as a type of retinoid – which was proved to prevent chemically induced gastric mucosal damage without inhibiting gastric acid secretion (30). Therefore, we might assume that the participants with H. pylori infection who consumed a high retinol intake may protect their stomach significantly. Besides, in this study, a smaller sample size of the participants without H. pylori infection compared to those who had been infected with H. pylori might be a limitation to observed a significant association between higher retinol intake and reduced risk of gastric cancer.

An investigation among gastric cancer patients in Korea reported that intake of retinol significantly higher in women than those in men (31). This result is quite similar to our finding in the current study. After stratifying by sex, the association between retinol intake and gastric cancer was consistent only among women. This difference could be reasonable that women consuming dietary retinol at a level high enough to identify a significant association with a decreased risk of gastric cancer.

Smoking was also a known risk factor for gastric cancer (27, 32, 33). Therefore, we should consider it as a confounder in the interpretation of our results. In detail, patients consuming a high intake of retinol who were current smokers could be difficult to identify a reduced risk of gastric cancer significantly because of this confounder. However, in patients without smoking status, an inverse association between dietary retinol and gastric cancer might be observed more apparent.

Several studies suggested a positive association between alcohol consumption and risk of gastric cancer (34-36). Ethanol is metabolized by alcohol dehydrogenases (ADH), catalase or cytochrome P450 2E1 (CYP2E1) to acetaldehyde, which is then further oxidized to acetate by aldehyde dehydrogenase (ALDH). Acetaldehyde has been classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen to humans. Alcohol stimulates the uptake of carcinogens and their metabolism and also changes the composition of enteric microbes in a way to enhance the aldehyde level (37). In addition, alcohol consumption has been associated with the inhibition of retinol metabolism (38), declines in hepatic levels of retinol (39), and the breakdown of retinol through cross-induction of degradative enzymes (40). Therefore, the subjects who consumed alcohol may have a similar consequence as H. pylori infected patients about retinol deficiency, and we may explain for an inverse association between the highest of retinol intake and gastric cancer observed only in the subgroup of current-drinker participants.

The current study has some strengths included: (1) a comprehensive and validated FFQ to investigate the relationship between retinol intake and gastric cancer risk; (2) collecting information about H. pylori infection of the participants and taking into account it as a confounding factor in the interpretation of results; (3) the first case-control study among Korean population examining dietary retinol as a protective factor of gastric cancer.

Besides, we also have several limitations when conducting this study. First, our study was hospital-based population research, so the control group could not represent for general Korean population. Second, a small sample size might not be sufficient to identify a significant association between retinol intake and reduced

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risk of gastric cancer after stratifying multiple confounders.

CONCLUSION

A reduced risk of gastric cancer when consuming a higher level of retinol intake was observed among the Korean population. After stratifying by sex, this relationship was significant only in women. Furthermore, dietary retinol was reported as a protective factor against gastric cancer only among H. pylori-positive subjects, non-smokers, and current drinkers. Future large-scale prospective cohort studies examining the potential preventive role of total retinol or dietary retinol to gastric cancer incidence are needed.

Author contribution statement

A.Q.B. and J.S.K. designed and conducted the research; J.L., I.J.C., Y.-I.K.: collect the data; A.Q.B., J.L., and M.G. analyzed the data; A.Q.B. wrote the manuscript draft; J.S.K. revised the manuscript. All authors: read and approved the final paper.

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