ISSN (electrónico): 1699-5198 - ISSN (papel): 0212-1611 - CODEN NUHOEQ S.V.R. 318

ARÁN

Nutrición Hospitalaria

Trabajo Original

Epidemiología y dietética

Protective effect of dietary micronutrients on gastric cancer risk among Jordanians

Efecto protector de los micronutrientes de la dieta ante el riesgo de cáncer gástrico entre jordanos

Sabika Allehdan[1], Shatha S. Hammad[2], Razan M. Alatrash[3], Tareq Al-Jaberi[4], Ahmad Hushki[5], Shirin Yacoub[6], Mahammad Dahoud[6], Tahra Elobeid[7], Reema F. Tayyem[7]

[1]Department of Biology. College of Science. University of Bahrain. Zallaq, Kingdom of Bahrain. [2]Department of Nutrition and Food Technology. Faculty of Agriculture. University of Jordan. Amman, Jordan. [3]Department of Health Education. Jordan University Hospital. Amman, Jordan. [4]Department of General and Pediatric Surgery. Faculty of Medicine. Jordan University of Science and Technology. Irbid, Jordan. [5]Gastroenterology Division. King Hussein Cancer Center. Amman, Jordan. [6]Nursing Department. King Hussein Cancer Center. Amman, Jordan. [7]Department of Human Nutrition. College of Health Sciences. Qatar University. Doha, Qatar

Abstract

Objective: several dietary and non-dietary factors and genetic predisposition may play an important role in gastric carcinogenesis. The findings about associations between micronutrients and gastric cancer (GC) is still inconsistent. This study aimed to investigate the effect of dietary micronutrients on gastric cancer risk.

Methods: a case-control study comprised of 173 GC (107 males: 66 females) patients and 313 (190 males: 123 females) population-based controls matched for age, occupation, and marital status. Demographics, medical history, physical activity, and nutrient intake information were collected using reliable interview-based questionnaires. Information on dietary micronutrient intake was collected from the participants using a validated food frequency questionnaire (FFQ). Multinomial logistic regression was used to calculate Odds ratios (ORs) and their corresponding 95 % confidence intervals (CIs) and evaluate associations between dietary micronutrients and GC risk.

Results: GC was inversely associated with the consumption of vitamin A, beta-carotene, vitamins D, E, K, B2, B3, B6, B12, and C, folate, chromium, iodine, and selenium. Additionally, a protective effect was observed for consumption of calcium, copper, iron, magnesium, phosphate, sodium, and zinc. In almost all the micronutrients, the second tertile showed a more pronounced reduction in GC risk as compared to the first tertile.

Conclusions: our data support favorable effects of dietary consumption of some vitamins and minerals against GC risk.

Keywords:

Case-control study. Gastric cancer. Micronutrients. Vitamins. Minerals.

Received: 24/11/2022 • Accepted: 26/05/2023

Acknowledgments: the authors would like to express their thanks to the Deanship od Scientific Research at The Hashemite University for funding the research projects. We would like to thank Dr Narmeen Al-Awwad for her support in the administrative work at The Hashemite University. This publication was supported by Qatar University Internal Grant No. Project QUST-2-CHS-2023-1492. The findings achieved herein are solely the responsibility of the authors.

Conflict of interests: the authors declare that they have no conflict of interest.

Authorship: RT and TA were responsible for the study conception and design and responsible for development of the methodology. SA, TA, AH, SY and MD were responsible for the acquisition of data. RT, SA, RA and SH were responsible for the analysis and interpretation of data. SA, SH, TE and RT were responsible for drafting the manuscript. All authors were responsible for reviewing and/or revising the manuscript.

Artificial intelligence: the authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Allehdan S, Hammad SS, Alatrash RM, Al-Jaberi T, Hushki A, Yacoub S, Dahoud M, Elobeid T, Tayyem RF. Protective effect of dietary micronutrients on gastric cancer risk among Jordanians . Nutr Hosp 2024;41(1):163-174

DOI: http://dx.doi.org/10.20960/nh.04547

Correspondence:

Reema Tayyem Tayyem. Department of Human Nutrition. College of Health Sciences. Qatar University. Doha 2713 Qatar
e-mail: reema.tayyem@qu.edu.qa

©Copyright 2024 SENPE y ©Arán Ediciones S.L. Este es un artículo Open Access bajo la licencia CC BY-NC-SA (http://creativecommons.org/licenses/by-nc-sa/4.0/).

Resumen

Objetivo: varios factores dietéticos y no dietéticos y predisposiciones genéticas pueden jugar un papel importante en la carcinogénesis gástrica. Los hallazgos sobre las asociaciones entre los micronutrientes y el cáncer gástrico (CG) aún son inconsistentes.

Métodos: este estudio tuvo como objetivo investigar el efecto de los micronutrientes sobre el riesgo de cáncer gástrico. Métodos: Un estudio de casos y controles comprendió 173 pacientes con GC (107 hombres: 66 mujeres) y 313 (190 hombres: 123 mujeres) controles basados en la población emparejados por edad, ocupación y estado civil. La información demográfica, el historial médico, la actividad física y la ingesta de nutrientes se recopilaron mediante cuestionarios confiables basados en entrevistas. La información sobre la ingesta de micronutrientes en la dieta se recopiló de los participantes mediante un cuestionario de frecuencia de alimentos (FFQ) validado. Se utilizó la regresión logística multinomial para calcular las razones de probabilidad (OR) y sus correspondientes intervalos de confianza (IC) del 95 % y evaluar las asociaciones entre los micronutrientes de la dieta y el riesgo de GC.

Resultados: la GC se asoció inversamente con el consumo de vitamina A, betacaroteno, vitaminas D, E, K, B2, B3, B6, B12 y C, folatos, cromo, yodo y selenio. Adicionalmente, se observó un efecto protector para el consumo de calcio, cobre, hierro, magnesio, fosfato, sodio y zinc. En casi todos los micronutrientes, el tercer tercil mostró una reducción más pronunciada del riesgo de CG en comparación con el primer tercil en hombres. Por el contrario, el segundo tercil exhibió un nivel de protección significativamente marcado en comparación con el primer tercil en mujeres.

Conclusiones: nuestros datos respaldan los efectos favorables del consumo dietético de algunas vitaminas y minerales para el riesgo de desarrollar cáncer gástrico

Palabras clave:

Estudio de casos y controles. Cáncer gástrico. Micronutrientes. Vitaminas. Minerales.

INTRODUCTION

Gastric cancer (GC) is one of the most common causes of cancer-related mortality worldwide. Globally, GC is the fourth leading cause of cancer mortality in males and females in 2020, based on global cancer statistics produced by the International Agency for Research on Cancer (1). GCs are primarily classified into two topographic subsites: cardia GC and non-cardia GC (2,3). The cardia GC arises in the region closest to the esophageal-gastric junction, and thus, share epidemiological features with esophageal cancer. The non-cardia GC arises in the distal portions of the stomach (2-4). These two subsites of GC were more prevalent in Eastern/Southeastern Asia countries. Men had higher rates than women for both GC subsites but specifically for cardia GC (male-to-female ratio of 3:1). Even though the incidence of non-cardia cancer has been dropping over the last years in most countries, but the incidences of cardia GC have remained constant or increased (5).

GC is a heterogeneous malignant disease and numerous factors are involved in its pathogenesis (6). Major GC risk factors include environmental factors like age, *Helicobacter pylori* (*H. pylori*) and Epstein-Barr virus (EBV) infection, race, sex, obesity, gastroesophageal reflux, tobacco, alcohol, diet, and genetic factors (6-8). The environmental factors like diet and lifestyle may positively or negatively affect the pathogenesis of GC (9-11), thus modifying these factors may control the risk of GC and reduce its incidence rate.

Epidemiological studies that examined dietary intake and plasma levels of various micronutrients and GC have reported inconsistent results (12,13). Vitamin C, vitamin E, retinol, and selected carotenoids have protective effects against gastric carcinogenesis (11,14,15). A few case-control studies showed that high intake of folate was inversely associated with the risk of GC (12,16,17), but findings from another case-control study did not support that finding (13). Data on the effect of intake of other minerals on the risk of GC is limited and generally inconclusive (13,18,19). Given the observed different results in the previous studies, the present study aimed to investigate the association between micronutrients intake and risk of GC in a case-control study conducted in Jordan.

MATERIALS AND METHODS

STUDY DESIGN AND PARTICIPANTS

This case-control study was performed in Jordan from March 2015 to August 2018. A total of 173 GC cases and 313 controls agreed to participate in this study. The cases were recruited from King Hussein Cancer Center, oncology clinics at King Abdullah University Hospital, Jordan University Hospital, and Al-Bashir Hospital. The controls were community based and they were hospital workers, patient visitors, patient escorts, university students, and university workers. The controls were comparable to the cases accordance with sex, age, occupation, and marital status. The proportion of cases to controls in this study was 1:1.

Inclusion criteria consist of being Jordanian aged ≥ 18 years, able to communicate verbally, and free of any chronic diseases that require dietary interventions. Individuals who were critically ill, unable to communicate verbally, pregnant or breastfeeding mothers, and diagnosed with cancer for more than six months or being affected by GC as a second cancer were excluded from this study.

The study protocol was approved by the Institutional Review Board Ethics Committee of the King Hussein Cancer Center (IRB No. 15 KHCC 03, Amman, Jordan), King Abdullah University Hospital, Jordan University Hospital, and Al-Bashir Hospital. Prior to participation in this study, all participants were asked to give a signed written informed consent. The study was conducted based on the Declaration of Helsinki.

DATA COLLECTION

Demographic, health, physical activity, and dietary information was collected by trained nutritionists using structured questionnaires. Personal questionnaire includes data about age, gender, marital status, education, occupation, family income/month, smoking, family history of GC, and history of stomachache and stomach ulcers.

ANTHROPOMETRIC MEASUREMENTS

Trained Nutritionists measured body weight and height for all study participants using standardized techniques and calibrated scales. Body weight was measured to the nearest 0.1 kg using a calibrated scale (Seca, Germany) while participants wore minimal clothing and without shoes, Height was measured to the nearest 0.1 cm with the participant in the full standing position without shoes using a calibrated stadiometer (Seca, Germany). Body mass index (BMI) was computed as weight in kilograms divided by height in squared meters (20).

PHYSICAL ACTIVITY QUESTIONNAIRE

The physical activity level of the study participants was assessed using a validated seven-day Physical Activity Recall (PAR) questionnaire. The seven-Day PAR is a structured and validated questionnaire that relies on the participant's recall of frequency, intensity, time, and type of physical activity performed over a seven-day period (21). Daily number of hours expended in sleeping and different physical activity levels were taken and transformed into metabolic equivalents (MET). Based on the scoring instructions, sleeping was assigned a value of 1.0 MET, light activity a value of 1.5 METs, moderate activity a value of 4.0 METs, and for a very hard activity a value of 7.0 METs or greater (22). Physical activity was computed as the time (minutes) spent to each activity multiplied by the equivalent MET for that activity and multiplied again by the number of days that the activity was undertaken per week period, as stated in the following equation: (MET level x minutes of activity/day x days per week) (21).

DIETARY ASSESSMENT

Dietary intake of micronutrients was assessed by a validated Arabic quantitative FFQ (23). The FFQ questions examined the data dealing with the participant's dietary history. The FFQ assessed intake of 112 food items: 21 items of vegetables; 21 items of fruits and juices; 17 items of meat such as red meat; 12 items of cereals and legumes; nine items of milk and dairy products; four items of soups and sauces; five items of drinks; nine items of snacks and sweets; and 14 items of herbs and spices. The study participants were interviewed face-to-face by trained nutritionists and asked the participants to recall how frequently, on average, during the last year they had consumed one standard serving of specific food items in 10 classes (1-6 times/year 7-11 times/year, 1 time/month, 2-3 times/month, 1 time/week, 2 times/week, 3-4 times/week, 5-6 times/week, 1 day, 2 or more/day). The portion sizes of each food item were categorized according to commonly used portion sizes into small, medium, and large. Food models and standard measuring tools were used to help participants in determining the consumed portion size of foods precisely. Dietary analysis software (Food Processor SQL version 10.1.129; ESHA, Salem, OR, USA) was used to estimate dietary micronutrients intake, however, that software was modified to include nutritional data about Jordanian cuisine (24).

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM Corporation, Armonk, NY, USA). The statistically significant level was placed at $p < 0.05$. Data was represented as mean ± standard error of mean (SEM) for normally distributed continuous variables Independent Sample *t*-test was used to detect differences in normally distributed continuous variables between GC group and control group. Frequencies and percentages were calculated to describe categorical variables were represented as frequencies and percentages. *Pearson chi*-square was used to find differences in sociodemographic characteristics such as marital status, education, and employment status, and health characteristics such as smoking family history of GC, and personal history of stomachache and stomach ulcer between GC group and control group.

Median (33.3^{rd}-66.7^{th} percentile) was used for non- normally distributed data (micronutrients intake). *Mann-Whitney U* test was used to identify differences in intakes of micronutrients between GC cases and controls.

Intakes of micronutrients were modeled using tertiles of distribution in the study participants with the first tertile being the lowest intake and the third tertile the highest. Odds ratios (ORs) and their corresponding 95 % confidence intervals (95 % CIs) of GC according to different tertiles of daily micronutrient intake were calculated using a multinomial logistic regression model. All models were adjusted for all potential cofactors like total caloric intake, age, gender, marital status, education, BMI, smoking, period of smoking, family history of gastric cancer, personal history of gastric ulcer, and physical activity (MET-min/week) which were reported as risk factors of GC in previous studies (25-27). Linear logistic regression model was used to compute *p*-value for trend.

RESULTS

Table I gives distribution of 173 GC cases and 313 controls according to gender, anthropometric measurements, socio-demographic and health characteristics. No differences were seen between cases and controls in age, height, marital status, and medical history of chronic diseases. Control males were significantly more active than GC males (3406.6 ± 222.4 vs. 1851.6 ± 192.8, $p < 0.001$). Pre-diagnosis weight and BMI were significantly higher in GC males compared to control males ($p < 0.05$), whereas current weight and BMI were significantly lower in cases of both sexes ($p < 0.001$). The participants with a family history (beyond the second degree) of GC was significantly more frequent in GC group compared to the controls ($p < 0.001$). GC cases had a higher incidence of gastric ulcers and gastric ache than the control group ($p < 0.001$). GC patients consumed more energy than controls ($p < 0.001$).

Table I. Socio-demographic and health characteristics of 173 gastric cancer cases and 313 controls based on gender

Variable	Male (*n* = 297) (61.1 %)		*p*-value*	Female (*n* = 189) (38.9 %)		*p*-value*
	Control (*n* = 190) (60.7 %) Mean ± SEM	Case (*n* = 107) (61.8 %) Mean ± SEM		Control (*n* = 123) (39.3 %) Mean ± SEM	Case (*n* = 66) (38.2 %) Mean ± SEM	
Age (years)	55.1 ± 0.89	55.0 ± 1.2	0.952	52.7 ± 1.6	52.3 ± 1.1	0.832
Pre-diagnosis weight (kg)	82.3 ± 1.7	89.8 ± 1.9	0.009	161.1 ± 0.63	160.4 ± 0.93	0.533
Current weight (kg)	83.5 ± 1.2	74.0 ± 1.7	< 0.001	77.0 ± 1.4	65.0 ± 1.9	< 0.001
Height (cm)	172.3 ± 0.49	172.4 ± 0.70	0.883	75.3 ± 1.3	77.8 ± 2.4	0.333
Pre-diagnosis BMI (kg/m^2)	27.7 ± 0.56	30.2 ± 0.70	0.006	29.2 ± 0.53	29.9 ± 0.83	0.482
Current BMI (kg/m^2)	28.1 ± 0.41	24.9 ± 0.64	< 0.001	29.7 ± 0.52	25.3 ± 0.76	< 0.001
Monthly Income (JD)	539.9 ± 44.9	751.7 ± 114.5	0.042	635.1 ± 60.0	517.1 ± 61.3	0.219
Physical activity (MET-min/week)**	3406.6 ± 222.4	1851.6 ± 192.8	< 0.001	3285.8 ± 296.9	2768.9 ± 207.9	0.234
Total energy intake (Kcal/day)	2568.2 ± 63.0	3441.8 ± 101.9	< 0.001	2285.5 ± 66.0	2911.6 ± 120.5	< 0.001
	***n* (%)**	***n* (%)**		***n* (%)**	***n* (%)**	
Marital status						
Married	177 (93.2 %)	103 (96.3 %)	0.654	96 (78.0 %)	45 (68.2 %)	0.224
Single	5 (2.6 %)	1 (0.9 %)		14 (11.4 %)	7 (10.6 %)	
Divorced	4 (2.1 %)	1(0.9 %)		3 (2.4 %)	2 (3.0 %)	
Widowed	4 (2.1 %)	2 (1.2 %)		10 (8.1 %)	12 (18.2 %)	
Educational level						
Illiterate	5 (2.6 %)	5 (4.7 %)	0.782	5 (7.6 %)	13 (10.6 %)	0.024
Primary school	53 (27.9 %)	30 (28.0 %)		24 (36.4 %)	27 (22.0 %)	
High school diploma	52 (27.4 %)	24 (22.4 %)		19 (30.3 %)	20 (16.3 %)	
College diploma	28 (14.7 %)	17 (15.9 %)		8 (12.1 %)	29 (23.6 %)	
Bachelor's degree	43 (22.5 %)	26 (24.3 %)		8 (12.1 %)	28 (22.8 %)	
Master's degree	8 (4.2 %)	3 (2.8 %)		1 (1.5 %)	5 (4.1 %)	
Doctorate	1 (0.53 %)	2 (1.9 %)		0 (0 %)	1 (0.8 %)	
Employment status						
Employee	113 (59.5 %)	71 (66.7 %)	0.325	39 (31.7 %)	12 (18.2 %)	0.046
Non-employee	77 (40.5 %)	36 (33.6 %)		84 (68.3 %)	54 (81.8 %)	
Family history of gastric cancer						
Yes	2 (1.1 %)	10 (9.3 %)	< 0.001	3 (2.4 %)	7 (10.6 %)	0.017
No	188 (98.9 %)	97 (90.7 %)		120 (97.6 %)	59 (89.4 %)	
Presence of chronic diseases						
Yes	97 (51.1 %)	46 (43.0 %)	0.367	60 (49.2 %)	29 (43.9 %)	0.497
No	93 (48.9 %)	61 (57.0 %)		63 (50.8 %)	37 (56.1 %)	
Smoking						
Yes	84 (44.5 %)	49 (45.8 %)	0.017	15 (12.2 %)	7 (10.6 %)	0.008
No	106 (55.5 %)	58 (54.2 %)		108 (87.8 %)	59 (89.4 %)	
Presence of stomachache						
Yes	8 (4.2 %)	28 (26.2 %)	< 0.001	6 (4.9 %)	20 (30.3 %)	< 0.001
No	182 (95.8 %)	79 (73.8)		117 (69.7 %)	46 (69.7 %)	
Presence of stomach ulcer						
Yes	2 (1.1 %)	49	< 0.001	3 (2.4 %)	27 (40.9 %)	< 0.001
No	188 (98.9 %)	58		120 (97.6 %)	39 (58.1 %)	

*p *values calculated by sample* t*-test for continuous variables and Pearson Chi-square for categorical variables.* p *value < 0.05 was considered statistically significant.*
***MET: metabolic equivalents-minutes/week.*

Table II displays the median daily intakes, the 33.3rd, and 66.7th percentile of micronutrients of GC cases and controls based on gender. The consumption of vitamin A, *beta*-carotene, vitamins B1, B2, B3, B6, B12, C, D, E, folate, calcium, chromium, copper, iodine, iron, magnesium, phosphate, potassium, selenium, sodium, and zinc was significantly higher in GC males compared to control males ($p < 0.05$), except fluoride. However, the GC females had significantly higher intakes of vitamin A, vitamins B1, B3, C, E, folate, calcium, chromium, copper, iodine, iron, magnesium, potassium, and zinc when compared to the control females ($p < 0.05$).

Table III shows the association between intake of selected vitamins and the risk of GC. There were significant negative linear trends for the risk of GC with increasing consumption of vitamins A, E, K, *beta*-carotene, and folate. Compared to the lowest tertile, the highest intakes of vitamin A (OR, 0.26; 95 % CI 0.12-0.57, *p*-value for trend = 0.001); *beta*-carotene (OR, 0.42; 95 % CI, 0.20-0.86, *p*-value for trend = 0.019); vitamin D (OR, 0.47; 95 % CI, 0.23-0.95, *p*-value for trend = 0.031), vitamin E (OR, 0.06; 95 % CI 0.02-0.18, *p*-value for trend < 0.001), folate (OR, 0.39; 95 % CI 0.19-0.79, *p*-value for trend < 0.001), and vitamin K (OR, 0.40; 95 % CI 0.20-0.80, *p*-value for trend = 0.006) were inversely associated with risk of GC. Statistically significant protective effect was observed for moderate consumption (T2 vs. T1) of vitamin B2 (OR, 0.36; 95 % CI, 0.18-0.75, *p*-value for trend < 0.001), vitamin B3 (OR, 0.28; 95 % CI, 0.12-0.62, *p*-value for trend < 0.001), vitamin B6 (OR, 0.29; 95 % CI, 0.13-0.60, *p*-value of trend < 0.001), vitamin B12 (OR, 0.48; 95 % CI, 0.24-0.96, *p*-value for trend < 0.001), and vitamin C (OR, 0.34; 95 % CI, 0.15-0.65, *p*-value for trend < 0.001) on GC risk.

Table II. Micronutrients intake of 173 gastric cancer cases and 313 controls participating in a case-control study

Micronutrients	Crude micronutrients intake Median (33rd-67th)			Crude micronutrients intake Median (33rd-67th)		
	Male (*n* = 297)			Female (*n* = 189)		
	Control (*n* = 190)	Case (*n* = 123)	*p*-value*	Control (*n* = 107)	Case (*n* = 66)	*p*-value*
Vitamin A (IU)	6275.3 (5272.0-7505.4)	8559.6 (6432.0-9599.2)	< 0.001	5292.6 (4235.2-6630.6)	7343.5 (5973.9-8656.3)	< 0.001
Beta-carotene (µg)	942.5 (759.6-1251.2)	1336.5 (955.7-1577.5)	< 0.001	951.1 (764.7-1329.7)	1130.5 (894.7-1403.3)	0.131
Vitamin B1 (mg)	1.7 (1.5-2.0)	2.2 (2.0-2.5)	< 0.001	1.2 (0.98-1.4)	1.4 (1.1-1.6)	0.023
Vitamin B2 (mg)	1.6 (1.4-1.9)	1.6 (1.3-1.9)	< 0.001	1.5 (1.3-1.8)	1.6 (1.3-1.9)	0.350
Vitamin B3 (mg)	19.2 (16.0-22.2)	24.7 (22.5-27.2)	< 0.001	16.1 (13.3-18.6)	18.3 (15.5-20.5)	0.046
Vitamin B6 (mg)	1.4 (1.2-1.8)	1.7 (1.5-1.9)	0.001	1.3 (1.0-1.5)	1.3 (1.1-1.5)	0.290
Vitamin B12 (µg)	3.3 (2.5-4.5)	4.7 (3.9-5.7)	< 0.001	2.9 (2.2-3.6)	3.2 (2.4-4.4)	0.343
Vitamin C (mg)	133.6 (108.3-170.3)	181.1 (135.8-211.7)	0.001	134.8 (109.9-158.7)	162.8 (122.3-215.8)	0.010
Vitamin D (µg)	1.5 (0.96-2.7)	2.6 (1.5-3.9)	0.002	1.4 (0.75-2.4)	2.0 (1.3-3.2)	0.115
Vitamin E (α-tocopherol) (mg)	7.0 (6.3-8.1)	10.2 (8.7-11.6)	< 0.001	6.8 (5.9-7.7)	9.3 (8.3-10.6)	< 0.001
Folate (µg)	358.2 (303.7-414.6)	479.9 (414.2-560.7)	0.003	303.4 (263.1-360.1)	372.3 (312.0-429.2)	0.003
Vitamin K (µg)	139.7 (107.7-198.5)	173.3 (127.8-263.5)	0.038	140.4 (91.8-187.9)	154.6 (121.0-252.8)	0.101
Calcium (mg)	828.3 (677.8-1030.0)	1187.6 (1042.5-1316.5)	< 0.001	756.5 (646.8-940.6)	986.1 (710.0-1177.7)	< 0.001
Chromium (µg)	1.8 (1.5.2.3)	2.8 (2.2-3.5)	< 0.001	1.7 (1.3-2.2)	2.7 (2.3-3.3)	< 0.001
Copper (mg)	0.73 (0.63-0.87)	1.1 (00.88-1.2)	< 0.001	0.65 (0.55-0.78)	0.81 (0.68-0.94)	< 0.001
Fluoride (mg)	1.2 (0.63-1.2)	1.2 (0.77-1.5)	0.071	1.1 (0.53-1.2)	0.86 (0.55-1.2)	0.868
Iodine (µg)	47.6 (34.5-73.6)	73.0 (52.1-92.1)	< 0.001	42.9 (31.4-63.9)	54.2 (40.4-76.1)	0.028
Iron (mg)	13.1 (11.3-15.7)	17.0 (15.0-19.6)	< 0.001	11.9 (9.8-13.6)	13.2 (11.6-16.2)	0.005
Magnesium (mg)	199.0 (171.3-237.2)	276.5 (246.9-309.4)	< 0.001	187.7 (154.8-218.0)	222.0 (187.2-248.3)	0.006
Phosphate (mg)	856.4 (696.5-1036.2)	1178.3 (1012.0-1300.8)	< 0.001	769.4 (624.3-919.3)	813.7 (709.4-1002.8)	0.077
Potassium (mg)	2653.5 (2253.4-3105.9)	3381.7 (2930.9-3821.7)	< 0.001	2491.9 (2080.3-2915.9)	2747.2 (2418.9-3172.0)	0.042
Selenium (µg)	79.2 (67.3-91.4)	99.6 (82.7-111.5)	< 0.001	64.2 (52.6-72.3)	67.2 (53.6-79.4)	0.255
Sodium (mg)	3227.4 (2743.3-3865.1)	3760.4 (3160.6-4492.4)	0.007	2781.3 (2365.4-3269.7)	2896.2 (2462.2-3357.1)	0.407
Zinc (mg)	6.7 (5.8-7.8)	9.7 (8.7-11.2)	< 0.001	5.9 (5.2-7.4)	7.2 (5.8-8.3)	0.022

*p *values were calculated by* Mann-Whitney U *test and* p *value < 0.05 was considered statistically significant.*

Table III. Adjusted odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) of association of intake of selected vitamins and risk of gastric cancer among Jordanian

Vitamin	OR (95 % CI)[a]			*p*-value of trend
	T1[b]	T2	T3	
Vitamin A (IU)	*1*	*0.52 (0.20-1.03)*	*0.26 (0.12-0.57)*	*0.001*
No. of cases/control	59/106	57/104	57/103	
Beta-carotene (µg)	*1*	*0.72 (0.37-1.41)*	*0.42 (0.20-0.86)*	*0.019*
No. of cases/control	58/104	58/105	57/104	
Vitamin B1 (mg)	*1*	*0.36 (0.18-0.75)*	*0.10 (0.04-0.28)*	*< 0.001*
No. of cases/control	48/102	65/104	60/107	
Vitamin B2 (mg)	*1*	*0.28 (0.12-0.62)*	*0.02 (0.01-0.08)*	*< 0.001*
No. of cases/control	57/112	58/87	58/114	
Vitamin B3 (mg)	*1*	*0.34 (0.19-0.83)*	*0.07 (0.03-0.20)*	*< 0.001*
No. of cases/control	59/106	57/104	57/103	
Vitamin B6 (mg)	*1*	*0.29 (0.13-0.60)*	*0.04 (0.02-0.13)*	*< 0.001*
No. of cases/control	58/95	60/116	55/102	
Vitamin B12 (µg)	***1***	*0.48 (0.24-0.96)*	*0.14 (0.06-0.33)*	*< 0.001*
No. of cases/control	60/105	56/105	57/103	
Vitamin C (mg)	*1*	*0.34 (0.15-0.65)*	*0.13 (0.05-0.31)*	*< 0.001*
No. of cases/control	57/104	59/105	57/104	
Vitamin D (µg)	*1*	0.82 (0.42-1.63)	*0.47 (0.23-0.95)*	*0.031*
No. of cases/control	57/106	60/102	56/105	
Vitamin E (α-Tocopherol) (mg)	*1*	0.71 (0.35-1.42)	*0.06 (0.02-0.18)*	*< 0.001*
No. of cases/control	55/105	60/104	58/104	
Folate (µg)	*1*	*0.10 (0.039-0.26)*	*0.39 (0.19-0.79)*	*< 0.001*
No. of cases/control	59/106	55/104	57/103	
Vitamin K (µg)	*1*	*0.39 (0.34-1.29)*	*0.40 (0.20-0.80)*	*0.006*
No. of cases/control	59/106	57/104	57/103	

[a]*Adjusted for caloric intake, age, gender, marital status, education, BMI, smoking, period of smoking, family history of gastric cancer, medical history of gastric ulcer, and physical activity. The control group was considered the reference group for analysis.* [b]*Reference tertile.*

The adjusted ORs of GC for different tertiles of intake of vitamins categorized based on gender are presented in table IV. There were significant inverse association between GC risk and high dietary intake of vitamin A (OR, 0.12; 95 % CI, 0.04-0.36, *p*-value for trend < 0.001); beta-carotene (OR, 0.35; 95 % CI, 0.13-0.92, *p*-value for trend = 0.038); vitamin B1 (OR, 0.17; 95 % CI, 0.05-0.59, *p*-value for trend = 0.006), vitamin B3 (OR, 0.13; 95 % CI 0.03-0.46, *p*-value for trend = 0.002), vitamin B12 (OR, 0.25; 95 % CI 0.08-0.75, *p*-value for trend = 0.013), folate (OR, 0.12; 95 % CI 0.03-0.42, *p*-value for trend = 0.033), and vitamin K (OR, 0.39; 95 % CI 0.15-0.98, *p*-value for trend = 0.038) in male group. In contrast, the higher dietary vitamin C intake (OR the highest vs. the lowest tertile = 0.27, 95 % CI: 0.00-0.08, *p*-value for trend = 0.038) was associated with reduction of GC in female group. Negative relationships were revealed for moderate dietary intakes of vitamin B1 (OR 0.13; 95 % CI: 0.04-0.46, *p*-value for trend = 0.033), vitamin B6 (OR 0.23; 95 % CI: 0.07-0.75, *p*-value for trend = 0.001), vitamin C (OR 0.27; 95 % CI: 0.08-0.9, *p*-value for trend = 0.033), and folate (OR 0.27; 95 % CI: 0.09-0.85, *p*-value for trend < 0.001) in female group.

Table V gives adjusted ORs of GC for the highest versus the lowest tertile of intake of selected minerals. Comparing the highest tertile to the lowest tertile, odds of GC risk reduced significantly for intake of chromium (OR, 0.26; 95 % CI, 0.12-0.57, *p*-value for trend < 0.001), iodine (OR, 0.42; 95 % CI 0.20-0.86, *p*-value for trend = 0.033) and selenium (OR, 0.17; 95 % CI 0.07-0.42, *p*-value for trend < 0.001). The protective effect was also found for moderate consumption as the middle tertile compared to the lowest tertile of calcium (OR, 0.42; 95 % CI, 0.20-0.86, *p*-value for trend < 0.001), copper (OR, 0.21; 95 % CI, 0.10-0.45, *p*-value for trend < 0.001), iron (OR, 0.38; 95 % CI, 0.19-0.82, *p*-value for trend = 0.019), magnesium (OR, 0.15; 95 % CI, 0.07-0.34, *p*-value for trend < 0.001), phosphate (OR, 0.27; 95 % CI, 0.12-0.58, *p*-value for trend < 0.001), sodium (OR, 0.24.; 95 % CI, 0.11-0.54, *p*-value for trend < 0.001),

and zinc (OR, 0.32; 95 % CI, 0.15-0.68, *p*-value for trend < 0.001) on GC risk. However, the consumption of fluoride and potassium showed null associations with risk of GC.

Table VI shows the relationships between GC and intake of selected minerals classified based on gender. GC was negatively associated with chromium, with an OR of 0.26 (95 % CI = 0.09-0.70) for the middle, iron, with an OR 0.06 (95 % CI = 0.01-0.25) for the middle, and magnesium, with an OR of 0.29 (95 % CI = 0.11-0.83) for the middle versus lowest tertile of intake in male group. Likewise, the high consumption of calcium, chromium, copper, magnesium, phosphate, potassium, selenium, sodium and zinc was inversely associated with GC in males. Whereas great reduction in risk of GC was seen in females who consumed calcium (OR the middle vs. the lowest tertile = 0.32, 95 % CI: 0.11-0.97, *p*-value for trend < 0.001) and selenium (OR the middle vs. the lowest tertile = 0.31, 95 % CI: 0.11-0.87, *p*-value for trend = 0.001). The moderate and high intakes of calcium, iron, magnesium, phosphate, selenium, and sodium were inversely associated with GC in females ($p < 0.05$). An inverse relationship was detected for highest intake of zinc (OR = 0.03, 95 % CI: 0.00-0.15, *p*-value for trend < 0.001).

Table IV. Adjusted odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) of association of intake of selected vitamins among Jordanian based on gender

Vitamin	Male (*n* = 297)				Female (*n* = 189)			
	OR (95 % CI)[a]			*p*- value of trend	OR (95 % CI)[a]			*p*-value of trend
	T1[b]	T2	T3		T1[b]	T2	T3	
Vitamin A (IU)	*1*	0.46 (0.18-1.19)	*0.12 (0.04-0.36)*	*< 0.001*	1	0.80 (0.28-2.28)	0.82 (0.24-2.75)	0.683
No. of cases/control	34/51	33/65	40/74		23/52	24/39	19/32	
Beta-carotene (µg)	*1*	0.64 (0.26-1.55)	*0.35 (0.13-0.92)*	*0.038*	1	0.72 (0.26-1.98)	0.46 (0.14-1.46)	0.194
No. of cases/control	32/64	35/65	40/61		25/40	23/40	18/43	
Vitamin B1 (mg)	*1*	0.78 (0.29-2.11)	*0.17 (0.05-0.59)*	*0.006*	1	*0.13 (0.04-0.46)*	*0.02 (0.00-0.16)*	*< 0.001*
No. of cases/control	26/52	40/63	41/75		34/55	25/41	7/27	
Vitamin B2 (mg)	*1*	0.71 (0.25-2.05)	*0.07 (0.02-0.29)*	*< 0.001*	1	*0.02 (0.00-0.15)*	--------	*< 0.001*
No. of cases/control	19/58	42/54	46/78		39/56	16/33	11/34	
Vitamin B3 (mg)	*1*	0.85 (0.31-2.33)	*0.13 (0.03-0.46)*	0.002	1	0.15 (0.04-0.54)	0.01 (0.00-0.11)	*< 0.001*
No. of cases/control	21/49	36/66	50/75		36/66	21/38	9/31	
Vitamin B6 (mg)	*1*	0.40 (0.14-1.10)	*0.03 (0.01-0.15)*	*< 0.001*	1	*0.23 (0.07-0.75)*	*0.10 (0.02-0.47)*	*0.001*
No. of cases/control	26/54	39/69	42/67		29/48	21/47	16/28	
Vitamin B12 (µg)	*1*	0.71 (0.27-1.86)	*0.25 (0.08-0.75)*	*0.013*	1	*0.39 (0.14-1.08)*	*0.06 (0.01-0.28)*	*0.001*
No. of cases/control	23/55	37/64	47/71		34/48	19/41	13/34	
Vitamin C (mg)	*1*	0.49 (0.19-1.28)	*0.09 (0.03-0.30)*	*0.008*	1	*0.27 (0.08-0.97)*	*0.29 (0.1-0.84)*	*0.033*
No. of cases/control	32/65	41/56	34/69		25/39	18/49	23/35	
Vitamin D (µg)	1	0.58 (0.23-1.46)	*0.39 (0.15-1.01)*	*0.048*	1	1.77 (0.61-5.13)	0.67 (0.23-1.95)	*0.491*
No. of cases/control	31/56	38/68	38/66		25/49	22/34	19/40	
Vitamin E (α-tocopherol) (mg)	*1*	0.63 (0.24-1.63)	*0.04 (0.01-0.18)*	*< 0.001*	1	0.56 (0.20-1.58)	*0.06 (0.01-0.33)*	*0.003*
No. of cases/control	33/56	35/66	39/68		25/48	25/38	16/37	
Folate (µg)	*1*	0.52 (0.20-1.39)	*0.12 (0.03-0.42)*	0.001	1	*0.27 (0.09-0.85)*	*0.06 (0.01-0.29)*	*< 0.001*
No. of cases/control	23/49	37/68	47/73		34/54	20/36	12/33	
Vitamin K (µg)	1	0.73 (0.29-1.81)	*0.39 (0.15-0.98)*	0.038	1	0.77 (0.29-2.06)	0.61 (0.21-1.80)	0.380
No. of cases/control	33/57	35/67	39/66		24/46	22/37	20/40	

[a]Adjusted for caloric intake, age, marital status, education, BMI, smoking, period of smoking, family history of gastric cancer, personal history of gastric ulcer, and physical activity. The control group was considered the reference group for analysis. [b]Reference tertile.

Table V. Adjusted odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) of association of intake of selected minerals among 173 gastric cancer cases and 313 controls participating in a case-control study

Mineral	OR (95 % CI)[a]			*p*-value of trend
	T1[b]	T2	T3	
Calcium (mg)	*1*	*0.42 (0.20-0.86)*	*0.08 (0.31-0.21)*	*< 0.001*
No. of cases/control	59/106	57/104	57/103	
Chromium (µg)	*1*	0.56 (0.28-1.11)	0.26 (0.12-0.57)	
No. of cases/control	56/107	61/101	56/105	
Copper (mg)	*1*	*0.21 (0.10-0.45)*	*0.04 (0.02-0.12)*	*< 0.001*
No. of cases/control	59/104	54/103	60/106	
Fluoride (mg)	*1*	0.80 (0.40-1.56)	0.68 (0.36-1.30)	0.135
No. of cases/control	60/116	55/90	58/107	
Iodine (µg)	*1*	0.62 (0.31-1.25)	*0.42 (0.20-0.86)*	*0.033*
No. of cases/control	59/106	57/103	57/104	
Iron (mg)	*1*	*0.38 (0.19-0.82)*	*0.04 (0.01-0.133)*	*< 0.001*
No. of cases/control	58/106	58/102	57/105	
Magnesium (mg)	*1*	*0.15 (0.07-0.34)*	*0.02 (0.004-0.06)*	*< 0.001*
No. of cases/control	59/106	58/104	56/103	
Phosphate (mg)	*1*	*0.27 (0.12-0.58)*	*0.02 (0.006-0.06)*	*< 0.001*
No. of cases/control	59/106	57/103	57/104	
Potassium (mg)	*1*	0.84 (0.41-1.70)	0.77 (0.390-1.50)	0.659
No. of cases/control	57/106	57/104	57103	
Selenium (µg)	*1*	*0.58 (0.29-1.20)*	*0.17 (0.07-0.42)*	*< 0.001*
No. of cases/control	*59/106*	*57/104*	*57/103*	
Sodium (mg)	*1*	*0.24 (0.11-0.54)*	*0.02 (0.01-0.07)*	*< 0.001*
No. of cases/control	59/106	57/104	57/103	
Zinc(mg)	*1*	*0.32 (0.15-0.68)*	*0.08 (0.03-0.20)*	*< 0.001*
No. of cases/control	59/103	57/100	57/110	

[a]Adjusted for caloric intake, age, gender, marital status, education, BMI, smoking, period of smoking, family history of gastric cancer, personal history of gastric ulcer, and physical activity. The control group was considered the reference group for analysis. [b]Reference tertile.

Table VI. Adjusted odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) of association of intake of selected minerals among based on gender

Mineral	Male (*n* = 297)				Female (*n* = 189)			
	OR (95 % CI)[a]			*p*- value of trend	OR (95 % CI)[a]			*p*-value of trend
	T1[b]	T2	T3		T1[b]	T2	T3	
Calcium (mg)	1	0.51 (0.19-1.39)	*0.12 (0.03-0.41)*	*< 0.001*	1	*0.32 (0.11-0.97)*	*0.04 (0.01-0.21)*	*< 0.001*
No. of cases/control	26/58	38/63	43/69		31/45	19/41	16/37	
Chromium (µg)	1	*0.26 (0.09-0.70)*	*0.15 (0.05-0.45)*	*< 0.001*	1	1.64 (0.58-4.70)	0.54 (0.17-1.72)	0.275
No. of cases/control	37/55	34/70	36/65		19/50	27/31	20/42	
Copper (mg)	1	0.36 (0.13-1.01)	*0.07 (0.02-0.26)*	*< 0.001*	1	0.07 (0.02-0.28)	0.01 (0.0-0.06)	0.429
No. of cases/control	24/127	37/63	46/0		33/83	20/40	13/0	
Fluoride (mg)	1	0.71 (0.27-1.86)	1.05 (0.44-0.08)	0.908	1	1.11 (0.40-3.11)	0.32 (0.10-1.05)	0.076
No. of cases/control	33/60	30/61	44/69		25/47	25/29	16/47	

(Continues on next page)

Table VI (cont.). Adjusted odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) of association of intake of selected minerals among based on gender

Mineral	Male (*n* = 297)				Female (*n* = 189)			
	OR (95 % CI)[a]			*p*- value of trend	OR (95 % CI)[a]			*p*-value of trend
	T1[b]	T2	T3		T1[b]	T2	T3	
Iodine (µg)	1	0.43 (0.15-1.22)	0.43 (0.17-1.10)	0.082	1	1.1 (0.41-2.95)	0.45 (0.15-1.37)	0.178
No. of cases/control	31/59	35/64	41/67		26/45	22/39	18/39	
Iron (mg)	1	*0.06 (0.01-0.25)*	0.68 (0.24-1.86)	*< 0.001*	1	*0.19 (0.06-0.67)*	*0.04 (0.01-0.21)*	*< 0.001*
No. of cases/control	23/50	39/50	39/63		34/55	*19/39*	*13/29*	
Magnesium (mg)	1	*0.29 (0.11-0.83)*	*0.05 (0.01-0.20)*	*< 0.001*	1	*0.06 (0.01-0.27)*	*0.03 (0.0-0.03)*	*< 0.001*
No. of cases/control	24/56	38/65	45/69		32/47	20/39	14/37	
Phosphate (mg)	1	0.61 (0.22-1.71)	*0.05 (0.01-0.23)*	*< 0.001*	1	*0.07 (0.02-0.32)*	*0.003 (0.0-0.03)*	*< 0.001*
No. of cases/control	21/56	40/63	46/71		36/48	17/40	13/35	
Potassium (mg)	1	0.68 (0.27-1.72)	*0.25 (0.10-0.66)*	*0.003*	1	3.89 (1.22-12.4)	2.52 (0.75-8.44)	0.060
No. of cases/control	44/57	36/64	27/69		15/46	21/40	30/37	
Selenium (µg)	1	1.14 (0.40-3.24)	*0.20 (0.06-0.69)*	*0.005*	1	*0.31 (0.11-0.87)*	*0.11 (0.02-0.54)*	*0.001*
No. of cases/control	50/82	36/60	21/48		9/24	21/44	36/55	
Sodium (mg)	1	0.35 (0.11-1.10)	*0.02 (0.00-0.08)*	*< 0.001*	1	*0.09 (0.02-0.36)*	*0.01 (0.0-0.10)*	*< 0.001*
No. of cases/control	26/52	39/62	42/76		31/51	18/42	17/30	
Zinc (mg)	1	0.37 (0.14-1.01)	*0.11 (0.03-0.39)*	< 0.001	1	0.52 (0.17-1.58)	*0.03 (0.0-0.15)*	< 0.001
No. of cases/control	22/52	38/72	47/66		35/58	19/28	12/37	

[a]Adjusted for caloric intake, age, marital status, education, BMI, smoking, period of smoking, family history of gastric cancer, personal history of gastric ulcer, and physical activity. The control group was considered the reference group for analysis. [b]Reference tertile.

DISCUSSION

The association between the consumption of a healthy diet that is rich in fruits and vegetables and GC is previously documented; however, the evidence is controversial regarding the association between micronutrients and GC risk (28). Here, we observed several significant favorable effects of micronutrients against the risk of GC.

Lunet *et al.* (28) found no association between vitamin C, E, or carotenoids with the risk of GC; however, these results were adjusted for *H. pylori* infection which has a causal association with GC (28). Other studies reported protective effects of the antioxidant vitamins; A, C, and E on gastric carcinogenesis (29-31). This effect of antioxidant vitamins is confirmed by a systemic review and a meta-analysis of prospective and well-designed observational studies and relevant evidence (11,32). These vitamins may modify the pathogenesis of GC by their antioxidant capacity, free-radical scavenging capacity, and by reducing the risk of *H. pylori* infection (29,33). Specifically, vitamin C inhibits the conversion of nitrites to carcinogenic N-nitroso compounds; therefore, protects gastric mucosa (29,33,34).

The association between gastric carcinogenesis and vitamin D is controversial. Neither dietary vitamin D consumption nor vitamin D-related genes modulated GC risk in the Korean population (35). Although a systematic review of evidence found no association between GC risk and dietary vitamin D or its serum level (36), other case-control and cross-sectional studies, including the current study, found a beneficial effect of vitamin D on GC risk (12,37). Yet, vitamin D has an anticancer activity against various cancers, and it has been documented to reduce the risk of *H. pylori* infection (35,38). To the best of our knowledge, no previous study reported the association between dietary vitamin K and GC risk. Vitamin K is associated with the consumption of plant-based foods that are rich in many other nutrients and non-nutrients components which could underly the protective effect of high vitamin K consumption observed in this study.

An Italian case-control study found no significant relationships between GC risk and the intake of iron, calcium, potassium, and zinc (13). Another hospital-based study showed inverse associations between GC and consumption of potassium and iron (18). Sodium intake has been related to an increased risk of GC in several epidemiological studies (13,18,39). Conversely, we detected a negative GC risk with moderate consumption of sodium and no association with higher consumption. Also, our results did not show any significant association with potassium intake. The negative impact of high sodium intake on GC incidence has been previously documented in one study instead of other studies (28). High dietary sodium irritates gastric mucosa, induces its inflam-

mation and damage, incites *H. pylori* infection, and increases the risk of gastric carcinogens (34). However, here, the median daily intake of sodium for cases and control was found to be less than 3500 mg per day which is not considered high compared to Western, European, and East Asian countries where sodium consumption may reach up to 13 g per day (40,41).

Our results suggest a protective effect of high consumption of B vitamins on the risk of GC. The association between dietary intake of B vitamins and GC is debatable. One-carbon metabolism nutrients (folate, vitamin B6, vitamin B2, and vitamin B12) are essential for DNA methylation, and insufficient intake of these nutrients potentially could encourage carcinogenesis (42,43). Thiamine and niacin are coenzymes in several cellular functions (43). Thiamine may affect cancer risk through several mechanism such as protein expression, oxidative stress, inflammation, and cellular metabolism (44), while niacin may influence cancer risk through its antioxidant activity (18). The current evidence is not consistent on the link between GC risk with the consumption of folate, vitamin B6, or vitamin B12 (43,44,45). Similarly, the associations of thiamine/niacin and cancer risk is yet to be defined (18,46,47). However, Miratni et al. (42) found that low serum concentrations of vitamin B12 augmented the risk of GC by 5.8 folds. Thus, the association could be obvious when habitual intake is not sufficient to support health. Also, several factors may interfere with the bioavailability of B vitamins including smoking, alcohol intake, some medications, as well as gut microbiota. Well-nourished individuals may not benefit from high consumption of B vitamins to reduce the risk of gastric carcinogenesis (43).

Evidence regarding the effect of dietary minerals on the incidence of GC is scarce and inconsistent (49,50,51). To our knowledge, no available evidence reported the effect of dietary fluoride, copper, or chromium on GC. Nevertheless, consistent with our results, gastric carcinogenesis might be suppressed by high dietary intake of some minerals including selenium and zinc which play essential roles in oxygen species-scavenging activity (51,52,53); magnesium and calcium which are required for overall homeostasis and health (54); and iron (53) where its low serum levels and a higher rate of iron deficiency anemia were found to augment GC risk (55-57). The latter evidence indicates the influence of mineral status on the risk of GC where iron deficiency anemia could increase DNA damage and oxidative stress (56). Another evidence suggested a higher risk of GC in case of a high-iron diet, where it is suggested to induce tumorigenesis by the effect of dysregulated iron metabolism on iron-modulated function (58). Also, different dietary sources may have variable impacts on disease risk, for example, heme iron was found to be associated with a higher risk for GC which could be provoked by other components or processing methods (48). Concerning iodine, a protective effect on GC of high dietary iodine was observed, which is consistent with a previous report of a high incidence of goiter among GC patients and is supported by the antioxidant activity of iodine (59). Previous studies showed lower intake of phosphorus among GC patients (13,60), here, we found protective effects against GC of moderate consumption of phosphorus.

While several other factors may contribute to the risk of GC such as *H. pylori* infection, host susceptibility, environmental exposures, and other dietary components such as phytochemicals and fat, the findings of this study may aid in increasing awareness of population and health care members toward the avoidance or encouragement of the consumption of specific micronutrients.

STUDY STRENGTHS AND LIMITATIONS

This case-control study has several strengths including the adjustment of statistical analyses for many substantial confounders is believed to strengthen our findings by eliminating the effects of these variables on GC risk. Compliance with the questionnaire was high with an eminent response rate of > 95 %. On the other hand, it is worth mentioning the limitations of this research including some questionnaire-inherited limitations that cannot be excluded; nevertheless, these factors were attenuated by precautionary measures. The accuracy of dietary recall tools is affected by possible recall bias and estimation errors; however, their effects were lessened using a validated FFQ along with food models and measuring tools to enhance the accuracy of portion size estimation. The used FFQ includes cultural foods, commonly used portion sizes for each food item, and accounted for seasonal variations for a more precise estimation of participants' dietary history. Also, differential recall bias may have influenced the dietary data due to knowledge of the disease status as well as due to the possibility that cases might have changed diet due to their disease or corresponding symptoms; yet, the inclusion of recently diagnosed patients could have reduced such bias. Another limitation is the lack of biochemical levels of these micronutrients; however, further research is warranted to investigate the effect of their serum levels on the pathogenesis of GC. Also, the interviewers were not blinded for the diagnosis of the participants (i.e., cases and control); nevertheless, all interviewers were well-trained and treated the participants professionally and identically, regardless of their case and control status. Moreover, the body composition of the study participants was not measured, however, the body composition is an important factor when it comes to investigate correlation between dietary factors and cancer due to most cancer patients have wasting, which includes muscle loss whether or not there is also fat loss.

CONCLUSION

The findings of this study support the advantageous effects of moderate consumption of micronutrients on GC risk which can be achieved by a balanced, healthy diet. GC was inversely associated with the consumption of vitamin A, beta-carotene, vitamins D, E, K, B2, B3, B6, B12, and C, folate, chromium, iodine and selenium. Additionally, a protective effect was observed for consumption of calcium, copper, iron, magnesium, phosphate, sodium, and zinc. Increasing the population's awareness toward the health benefits of micronutrients and regarding their dietary

sources would reduce GC-related morbidity and mortality. Further research is required to confirm our findings and elucidate the underlying mechanisms of these associations.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49. DOI: 10.3322/caac.21660
2. McColl KE, Going JJ. Aetiology and classification of adenocarcinoma of the gastro-oesophageal junction/cardia. Gut 2010;59:282-4. DOI: 10.1136/gut.2009.186825
3. Mukaisho K, Nakayama T, Hagiwara T, Hattori T, Sugihara H. Two distinct etiologies of gastric cardia adenocarcinoma: interactions among pH, Helicobacter pylori, and bile acids. Front Microbiol 2015;6:412. DOI: 10.3389/fmicb.2015.00412
4. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol 2019;14(1):26-38. DOI: 10.5114/pg.2018.80001
5. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut 2015;64(12):1881-8. DOI: 10.1136/gutjnl-2014-308915
6. Cheng XJ, Lin JC, Tu SP. Etiology and Prevention of Gastric Cancer. Gastrointest Tumors 2016;3:25-36. DOI: 10.1159/000443995
7. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet 2016;388:2654-64. DOI: 10.1016/S0140-6736(16)30354-3
8. Karimi *p*, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014;23:700-13. DOI: 10.1158/1055-9965.EPI-13-1057
9. Akbarpour E, Sadjadi A, Derakhshan MH, Roshandel G, Alimohammadian M. Gastric cancer in Iran: an overview of risk factors and preventive measures. Arch Iran Med 2021;24:556-67. DOI: 10.34172/aim.2021.79
10. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharmaceutical research 2008;25:2097-116. DOI: 10.1007/s11095-008-9661-9
11. Kong P, Cai Q, Geng Q, Wang J, Lan Y, Zhan Y, et al. Vitamin intake reduce the risk of gastric cancer: meta-analysis and systematic review of randomized and observational studies. PLoS One 2014;9:e116060. DOI: 10.1007/s11095-008-9661-9
12. La Vecchia C, Ferraroni M, D'Avanzo B, Decarli A, Franceschi S. Selected micronutrient intake and the risk of gastric cancer. Cancer Epidemiol Biomarkers Prev 1994;3:393-8.
13. Pelucchi C, Tramacere I, Bertuccio P, Tavani A, Negri E, La Vecchia C. Dietary intake of selected micronutrients and gastric cancer risk: an Italian case-control study. Ann Oncol 2009;20:160-5.
14. Jenab M, Riboli E, Ferrari P, Friesen M, Sabate J, Norat T, et al. Plasma and dietary carotenoid, retinol and tocopherol levels and the risk of gastric adenocarcinomas in the European prospective investigation into cancer and nutrition. Br J Cancer 2006;95:406-15. DOI: 10.1093/annonc/mdn536
15. Jenab M, Riboli E, Ferrari P, Sabate J, Slimani N, Norat, T, et al. Plasma and dietary vitamin C levels and risk of gastric cancer in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). Carcinogenesis 2006;27:2250-7. DOI: 10.1093/carcin/bgl096
16. Liu W, Zhou H, Zhu Y, Tie C. Associations between dietary folate intake and risks of esophageal, gastric and pancreatic cancers: an overall and dose-response meta-analysis. Oncotarget 2017;8:86828-42. DOI: 10.18632/oncotarget.18775
17. Tio M, Andrici J, Cox MR, Eslick GD. Folate intake and the risk of upper gastrointestinal cancers: a systematic review and meta-analysis. J Gastroenterol Hepatol 2014;29:250-8. DOI: 10.1111/jgh.12446
18. Lazarević K, Nagorni A, Bogdanović D, Rančić N, Stošić L, Milutinović S. Dietary micronutrients and gastric cancer: hospital based study. Cent eur j med 2011; 6:783-7. DOI: 10.2478/s11536-011-0079-0
19. Lee DH, Anderson KE, Folsom AR, Jacobs DR Jr. Heme iron, zinc and upper digestive tract cancer: the Iowa women's health study. Int J Cancer 2005;117:643-7. DOI: 10.1002/ijc.21215
20. Lee R, Nieman D. Nutritional Assessment. 6th ed. New York, NY, USA: McGraw-Hill Companies, Inc.; 2013. p. 176.
21. Sallis JF, Haskell WL, Wood PD, Fortmann SP, Rogers T, Blair SN, et al. Physical activity assessment methodology in the Five-City Project. Am J Epidemiol 1985;121:91-106. DOI: 10.1093/oxfordjournals.aje.a113987
22. Thompson JK, Jarvie GJ, Lahey BB, Cureton KJ. Exercise and obesity: etiology, physiology, and intervention. Psychol Bull 1982;91:55-79. DOI: 10.1037/0033-2909.91.1.55
23. Tayyem RF, Abu-Mweis SS, Bawadi HA, Agraib L, Bani-Hani K. Validation of a food frequency questionnaire to assess macronutrient and micronutrient intake among Jordanians. J Acad Nutr Diet 2014;114:1046-1052. DOI: 10.1016/j.jand.2013.08.019
24. Takruri H. Al-Ismail K. Tayyem R. Al-Dabbas M. Composition of Local Jordanian Food Dishes. 1st ed. Dar Zuhdi; Amman, Jordan: 2020.
25. Al-Awwad N, Allehdan S, Al-Jaberi T, Hushki A, Albtoush Y, Bani-Hani K, et al. Dietary and lifestyle factors associated with gastric and pancreatic cancers: a case-control study. Prev Nutr Food Sci 2021;26:30-9. DOI: 10.3746/pnf.2021.26.1.30
26. Nomura AM, Hankin JH, Kolonel LN, Wilkens LR, Goodman MT, Stemmermann GN. Case-control study of diet and other risk factors for gastric cancer in Hawaii (United States). Cancer Causes Control. 2003;14:547-58. DOI: 10.1023/A:1024887411846
27. Toorang F, Sasanfar B, Hekmatdoost A, Narmcheshm S, Hadji M, Ebrahimpour-Koujan S, et al. Macronutrients intake and stomach cancer risk in iran: a hospital-based case-control study. J Res Health Sci 2021;21:e00507. DOI: 10.34172/jrhs.2021.38
28. Lunet N, Valbuena C, Carneiro F, Lopes C, Barros H. Antioxidant vitamins and risk of gastric cancer: a case-control study in Portugal. Nutr Cancer 2006;55:71-7. DOI: 10.1207/s15327914nc5501_9
29. Qiu JL, Chen K, Zheng JN, Wang JY, Zhang LJ, Sui LM. Nutritional factors and gastric cancer in Zhoushan Islands, China. World J Gastroenterol 2005;11:4311-6. DOI: 10.3748/wjg.v11.i28.4311
30. Hoang BV, Lee J, Choi IJ, Kim YW, Ryu KW, Kim J. Effect of dietary vitamin C on gastric cancer risk in the Korean population. World J Gastroenterol 2016;22:6257-67. DOI: 10.3748/wjg.v22.i27.6257
31. Larsson SC, Bergkvist L, Näslund I, Rutegård J, Wolk A. Vitamin A, retinol, and carotenoids and the risk of gastric cancer: a prospective cohort study. Am J Clin Nutr 2007;85:497-503. DOI: 10.1093/ajcn/85.2.497
32. Li P, Zhang H, Chen J, Shi Y, Cai, J, Yang J, et al. Association between dietary antioxidant vitamins intake/blood level and risk of gastric cancer. Int J Cancer 2014;135:1444-53. DOI: 10.1002/ijc.28777
33. Vahid F, Davoodi SH. Nutritional factors involved in the etiology of gastric cancer: a systematic review. Nutr Cancer 2021;73:376-90. DOI: 10.1080/01635581.2020.1756353
34. Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. Gastric Cancer 2007;10:75-83. DOI: 10.1007/s10120-007-0420-0
35. Eom SY, Yim DH, Kim DH, Yun HY, Song YJ, Youn, SJ, et al. Dietary vitamin D intake and vitamin D related genetic polymorphisms are not associated with gastric cancer in a hospital-based case-control study in Korea. J Biomed Res 2018;32:257-63. DOI: 10.7555/JBR.32.20170089
36. Khayatzadeh S, Feizi A, Saneei P, Esmaillzadeh A. Vitamin D intake, serum Vitamin D levels, and risk of gastric cancer: a systematic review and meta-analysis. J Res Med Sci 2015;20:790-6. DOI: 10.4103/1735-1995.168404
37. Kwak JH, Paik JK. Vitamin D status and gastric cancer: a cross-sectional study in Koreans. Nutrients 2020;12:2004. DOI: 10.3390/nu12072004
38. Yang L, He X, Li L, Lu C. Effect of vitamin D on Helicobacter pylori infection and eradication: a meta-analysis. Helicobacter 2019;24:e12655. DOI: 10.1111/hel.12655
39. D'Elia L, Galletti F, Strazzullo P. Dietary salt intake and risk of gastric cancer. Cancer Treat Res 2014;159:83-95. DOI: 10.1007/978-3-642-38007-5_6
40. Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. J Gastroenterol Hepatol 2008;23:351-65.
41. Hasenegger V, Rust P, König J, Purtscher AE, Erler J, Ekmekcioglu C. Main sources, socio-demographic and anthropometric correlates of salt intake in Austria. Nutrients 2018;10:311. DOI: 10.1111/j.1440-1746.2008.05314.x
42. Miranti EH, Stolzenberg-Solomon R, Weinstein SJ, Selhub J, Männistö S, Taylor PR, et al. Low vitamin B_{12} increases risk of gastric cancer: A prospective study of one-carbon metabolism nutrients and risk of upper gastrointestinal tract cancer. Int J Cancer 2017;141:1120-9. DOI: 10.1002/ijc.30809
43. Dugué PA, Bassett JK, Brinkman MT, Southey MC, Joo JE, Wong EM, et al. Dietary Intake of Nutrients Involved in One-Carbon Metabolism and Risk of

Gastric Cancer: A Prospective Study. Nutr Cancer 2019;71:605-14. DOI: Dietary Intake of Nutrients Involved in One-Carbon Metabolism and Risk of Gastric Cancer: A Prospective Stud
44. Xiao Q, Freedman ND, Ren J, Hollenbeck AR, Abnet CC, Park Y. Intakes of folate, methionine, vitamin B6, and vitamin B12 with risk of esophageal and gastric cancer in a large cohort study. Br J Cancer 2014;110:1328-33. DOI: 10.1038/bjc.2014.17
45. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst 2010;102:1344-53. DOI: 10.1093/jnci/djq289
46. Lu'o'ng KV, Nguyễn LT. The role of thiamine in cancer: possible genetic and cellular signaling mechanisms. Cancer Genomics & Proteomics 2013;10:169-85.
47. Narmcheshm S, Sasanfar B, Hadji M, Zendehdel K, Toorang F, Azadbakht L. Patterns of nutrient intake in relation to gastric cancer: a case control study. Nutr Cancer 2022;74:830-9. DOI: 10.1080/01635581.2021.1931697
48. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey SM, Li B. The Linxian trials: mortality rates by vitamin-mineral intervention group. Am J Clin Nutr 1995;62:1424S-1426S. DOI: 10.1093/ajcn/62.6.1424S.
49. Jakszyn P, Agudo A, Lujan-Barroso L, Bueno-de-Mesquita HB, Jenab M, Navarro C, et al. Dietary intake of heme iron and risk of gastric cancer in the European prospective investigation into cancer and nutrition study. Int J Cancer 2012;130:2654-63. DOI: 10.1002/ijc.26263
50. González CA, Sala N, Rokkas TN. Gastric cancer: epidemiologic aspects. Helicobacter 2013;18:34-8. DOI: 10.1111/hel.12082
51. Nakaji S, Fukuda S, Sakamoto J, Sugawara K, Shimoyama, T, Umeda, T, et al. Relationship between mineral and trace element concentrations in drinking water and gastric cancer mortality in Japan. Nutr Cancer 2001;40:99-102. DOI: 10.1207/S15327914NC402_4
52. Gong HY, He JG, Li BS. Meta-analysis of the association between selenium and gastric cancer risk. Oncotarget 2016;7:15600-5. DOI: 10.18632/oncotarget.7205
53. Pakseresht M, Forman D, Malekzadeh R, Yazdanbod A, West RM, Greenwood DC, et al. Dietary habits and gastric cancer risk in north-west Iran. Cancer Causes Control 2011;22:725-36. DOI: 10.1007/s10552-011-9744-5
54. Shah SC, Dai Q, Zhu X, Peek RM, Jr, Smalley W, Roumie C, Shrubsole MJ. Associations between calcium and magnesium intake and the risk of incident gastric cancer: A prospective cohort analysis of the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study. Int J Cancer 2020;146:2999-3010. DOI: 10.1002/ijc.32659
55. Cook MB, Kamangar F, Weinstein SJ, Albanes D, Virtamo J, Taylor PR, et al. Iron in relation to gastric cancer in the Alpha-tocopherol, Beta-carotene Cancer Prevention Study. Cancer Epidemiol Biomarkers Prev 2012;21:2033-42. DOI: 10.1158/1055-9965.EPI-12-0799
56. Fonseca-Nunes A, Agudo A, Aranda N, Arija V, Cross AJ, Molina E, et al. Body iron status and gastric cancer risk in the EURGAST study. Int J Cancer 2015;137:2904-14. DOI: 10.1002/ijc.29669
57. Tang GH, Hart R, Sholzberg M, Brezden-Masley C. Iron deficiency anemia in gastric cancer: a Canadian retrospective review. Eur J Gastroenterol Hepatol 2018;30:1497-501. DOI: 10.1097/MEG.0000000000001251
58. Kim JL, Lee DH, Na YJ, Kim BR, Jeong YA, Lee SI, et al. Iron chelator-induced apoptosis via the ER stress pathway in gastric cancer cells. Tumour Biol 2016;37:9709-19. DOI: 10.1007/s13277-016-4878-4
59. Gulaboglu M, Yildiz L, Celebi F, Gul M, Peker K. Comparison of iodine contents in gastric cancer and surrounding normal tissues. Clin Chem Lab Med 2005;43:581-4. DOI: 10.1515/CCLM.2005.101
60. Cornée J, Pobel D, Riboli E, Guyader M, Hémon B. A case-control study of gastric cancer and nutritional factors in Marseille, France. Eur J Epidemiol 1995;11:55-65. DOI: 10.1007/BF01719946