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Vitamins and Stomach Cancer: A Hospital Based Case-Control Study in Iran

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ABSTRACT

Background: This study investigated the association between vitamins intakes and risk of gastric cancer (GC) among Iranian population. M**ethods:** In this hospital-based case-control study, 178 pathologically confirmed GC patients and 276 healthy controls were interviewed to answer a valid diet history questionnaire. Unconditional logistic regression, in which potential confounders were taken into account, was applied to determine the association of vitamin intakes and odds of GC in total population and in stratums of body mass index (BMI), helicobacter pylori (H-pylori) infection, and smoking. **Results:** GC was directly associated with vitamin D (OR 1.59; CI 95% 1.07, 2.36) and cobalamin (OR 1.25; CI 95% 1.08, 1.44). Thiamin (OR 0.50; 95%CI 0.30, 0.83), pantothenic acid (OR 0.71; 95%CI 0.58, 0.87), folate (OR 0.99; 95%CI 0.99, 0.99) and vitamin E (OR 0.98; 95%CI 0.96, 0.99) were inversely associated with GC. In 231 H-pylori infected participants, consumption of thiamin (OR 0.3; 95% CI 0.59, 0.86), pyridoxine (OR 0.52; 95%CI 0.31, 0.85), and folate (OR 0.99; 95%CI 0.99, 0.99) reduced GC risk. In H-pylori negative participants, only vitamin E (OR 0.96; 95%CI 0.93, 0.99) reduced the risk and vitamin D (OR 1.99; 95%CI 1.18, 3.36), riboflavin (OR 1.91; 95%CI 1.37, 2.66), pantothenic acid (OR 1.34; 95%CI 1.13, 1.64), biotin (OR 1.03; 95%CI 1.01, 1.05), and cobalamin (OR 1.36; 95%CI 1.13, 1.64) increased the risk. In BMI stratums, only vitamin D (OR 1.81; 95%CI 1.07, 3.08) was associated with the risk of GC among normal weight participants. Vitamin E was associated with lower risk of GC in ever smokers (OR 0.97; 95%CI 0.95, 0.99) and thiamin (OR 0.41; 95%CI 0.19, 0.86) and niacin (OR 0.93; 95%CI 0.87, 0.99) were associated with lower risk in never smokers. Positive associations were observed by increasing vitamin D (OR 2.08; 95%CI 1.12, 3.85) and cobalamin (OR 1.33; 95%CI 1.08, 1.65) in never smokers. **Conclusion:** This study provided support for a possible protective effect of vitamin E, thiamin, pantothenic acid, and folate on GC risk. Vitamin D and cobalamin intake increased the risk.

Keywords: *Vitamin; Stomach cancer; Nutrition; Dietary Intake; Hospital-based case-control study*

Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer related death in both sexes worldwide (Fock, 2014). Its incidence has substantially

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decreased in developed countries, but it remained a major public health problem in developing countries, such as Iran. GC remained an important public health burden in Iran and its incidence rate is higher than the global average (Alireza *et al.*, 2005). Its age standardized incidence rate in Iran was 26.1 in 100,000 men and 11.1 in women (Mehrabian *et al.*, 2010), and 7300 new cases (10.5 per 100000 individual) are diagnosed annually (Akbari *et al.*, 2008).

Although medical and surgical treatment have significantly improved the gastrointestinal cancers surveillance (Guyot *et al.*, 2005, Ono *et al.*, 2009); total survival rate of GC has not shown any significant improvement in two past decades (Kong *et al.*, 2014). Therefore, primary prevention and early detection are the most sensible strategies in GC control (Lambert *et al.*, 2012). It is clear that prevention requires identification of risk factors (Lee and Derakhshan, 2013).

GC is a complex and multifactorial disease (Piazuelo and Correa, 2013). Helicobacter pylori (H-pylori) is recognized as a main risk factor for GC (Fock, 2014). However, only 1% of individuals affected with H-pylori develop GC (Fock, 2014). Genetic factors (González *et al.*, 2013), tobacco smoking (Sasco *et al.*, 2004), and heavy alcohol drinking (Duell *et al.*, 2011, Tramacere *et al.*, 2011) are also considered as provoking factors. Diet is a modifiable risk factor for GC (Thomson *et al.*, 2003). The effect of nutritional intake on GC development has been investigated in several studies (Berretta *et al.*, 2012, Buiatti *et al.*, 1990, Gonz *et al.*, 1994, Hansson *et al.*, 1994, López-Carrillo *et al.*, 1999, Marmot *et al.*, 2007, Mayne *et al.*, 2001, Palli *et al.*, 2001, Qiu *et al.*, 2005). Intake of salty foods and red or processed meat might provoke formation of GC enhancing factors (Liu and Russell, 2008, Malekzadeh, 2013). In this regard, fruit and vegetable intakes are explored as protecting factors (Liu and Russell, 2008).

Some studies have investigated the association of several vitamins intakes with GC; however, they ended to inconclusive results and there is still an open question (Berretta *et al.*, 2012). Vitamin D intake has been considered as a risk factor of several cancers (Goyal *et al.*, 2019). This vitamin has a substantial role in immune system and could modify tumor microenvironment. Several studies have reported the association of vitamin D intake or status with gastrointestinal cancers (Camara and Brandao, 2019, Goyal *et al.*, 2019). Moreover, higher intake of antioxidant components, such as vitamin C and E is proposed to reduce GC in some studies but these associations need more clarification (Key *et al.*, 2020, Rawla and Barsouk, 2019). The most important group of vitamins in GC etiology is vitamins which are involved in One-carbon metabolism. It is considered that lower intake of these B vitamins or lower serum levels could initiate tumorigenic reaction. Several studies examined the association of folate, cobalamin or pyridoxine intakes with GC (Miranti *et al.*, 2017, Xiao *et al.*, 2014). American cancer society and world cancer fund, in their recent review, reported that there are limited evidence on the association between GC and vitamin intake (Rock *et al.*, 2020). Accordingly, the data of a hospital based case-control study conducted in cancer institute of Iran were used to provide further evidence on the relation of vitamins intake and GC.

Materials and Methods

Study protocol: It is a hospital-based case-control study conducted in Cancer Institute of Iran between May 2010 and June 2012. Cancer Institute of Iran is a referral teaching hospital which is located in Imam Khomeini complex in Tehran, capital city of Iran. The standard questionnaire which includes questions related to socio-demographic characteristics of participants was completed by face-to-face interview. Interviewers were trained bachelors of health. Blood samples were obtained in both cases and controls for evaluation of H-pylori infections status. IgG antibody were evaluated in serum samples by ELISA kits and the seropositivity > 0.87 was considered positive.

Participants: Cases were histopathologically confirmed GC patients. All newly admitted patients, who were 40 years or older, were asked to take part the study if they fulfill the inclusion

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criteria. The main criterion was no more than six month of cancer diagnosis and no previous diagnosis of any cancers. Controls were frequently matched to cases by 5-year age group, sex, and geographic area. They were healthy people who came to visit their relatives in the hospital.

Dietary assessment: A trained nutritionist interviewed the participants by Persian version of Diet History Questionnaire (DHQ). Its validity was reported previously (Toorang *et al.*, 2019). Complete description of this DHQ and its analysis process was explained elsewhere (Toorang *et al.*, 2019). The questionnaire questions were about consumption of 146 foods and mixed dishes in the preceding year. Moreover, it covers information on cooking methods and adding oil or sauces during cooking. It is clear that, interviewers reminded the patients to recall their dietary habits before the presence of cancer symptoms. Daily intakes of foods were computed in a program made by authors in STATA. Food intakes were converted to energy and nutrients intakes using food composition table in Access program. The translated version of McCance and Widdowson's Food composition table was used (Dorosti and Tabatabaei, 2007) and integrated with Iranian food composition table (Movahedi and Roosta, 2000) in case of special Iranian food which were not covered by the mentioned food composition table.

Ethical considerations: The research protocol was approved by Ethics Committee of Tehran University of Medical Science (no.17198) and was in accordance with the Declaration of Helsinki Ethical Principles. All the participants signed an informed written consent after oral description of the study protocol.

Data analysis: Odd ratios (OR) and 95% confidence intervals (CIs) of GC according to energy adjusted intakes of vitamins were reported using unconditional multiple logistic regression models. The residual method explained by Willett was used to adjust vitamin intakes based on energy intakes (Willett *et al.*, 1997). Two models were considered, including model A which was adjusted for age, sex, and energy and model B which was adjusted for age, sex, smoking, H-pylori, and residential place. Stratified OR and 95% CIs of GC according to energy adjusted intakes of vitamins in different Strata of H-pylori infection, body mass index (BMI), and smoking status were also reported. All statistical analyses were carried out using STATA 14 (State Corp., College station, TX).

Results

A total of 188 GC patients and 284 controls were recruited in this study. People with implausible energy intakes (± 2SD) were considered as under and over-reporting and were excluded from analysis. Finally, 178 GC patients and 276 controls were selected. General characteristics of the participants are shown in **Table 1**. Most of the participants in both groups were men (132, 74.2% in the case group and 176, 63.8% in the control group). GC patients smoked more (45.5% vs. 38.8%, P = 0.001) had lower education level, so that 62.4% of the participants in the case group and 26.1% in the control group were illiterate. Obesity was more frequent in cases, so that BMI in 57.3% of the participants in the case group and 48.6% the control group was over 25 kg/m^2 or more.

Table 2 shows daily intakes of vitamins in GC patients and controls. It also represents ORs for the case group compared to the control group in two different models: A, partially adjusted (age, sex, and energy) and B, fully adjusted (age, sex, energy, education, ever smoking, H-pylori, and residence). GC patients consumed slightly more vitamin A (1250 vs. 1198 µg/day), vitamin D (1.7 vs. 1.6 µg/day), riboflavin (3.6 vs. 3.2 mg/day), pantothenic acid (8.6 vs. 8.4 mg/day), biotin (54.7 vs. 53.8 µg/day), folate (446.9 vs. 440.9 µg/day), and cobalamin (4.8 vs. 4.1 µg/day). In full adjusting model, GC showed a positive association with vitamin D (OR 1.59; 95%CI 1.07, 2.36) and cobalamin (OR 1.25; 95%CI 1.08, 1.44). An inversely significant association was found for vitamin E (OR 0.98; 95%CI 0.96, 0.99), thiamin (OR 0.50; 95%CI 0.30, 0.83), pantothenic acid

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(OR 0.71; 95%CI 0.58, 0.87), and folate (OR 0.99; 95%CI 0.99, 0.99).

Table 3 shows ORs and the corresponding 95% CIs of vitamin intakes in three subgroups according to H-pylori infection, BMI, and smoking status. In 231 H-pylori infected participants, consumption of thiamin (OR 0.3; 95% CI 0.59, 0.86), pyridoxine (OR 0.52; 95%CI 0.31, 0.85), and folate (OR 0.99; 95%CI 0.99, 0.99) was associated with lower risk of GC; however, only vitamin E intake reduced the risk (OR 0.96; 95%CI 0.93, 0.99) in H-pylori negative subjects. Vitamin D (OR 1.99; 95%CI 1.18, 3.36), riboflavin (OR 1.91; 95%CI 1.37, 2.66), pantothenic acid (OR 1.34; 95%CI 1.13, 1.64), biotin (OR 1.03; 95%CI 1.01, 1.05), and cobalamin (OR 1.36; 95%CI 1.13, 1.64) consumption increased the risk of GC in this group.

In the present study, totally 235 (51.8%) participants were overweight or obese (BMI ≥ 25 kg/m^2). In this stratum, there was no significant association between vitamin intakes and risk of GC. Among normal weight participants defined as BMI < 25 kg/m^2 (n = 212), only vitamin D intake affected the risk of GC (OR 1.81; 95%CI 1.07, 3.08).

Vitamin E reduced the risk of GC (OR 0.97; 95%CI 0.95, 0.99) in ever smokers. Thiamin (OR 0.41; 95%CI 0.19, 0.86) and niacin (OR 0.93; 95%CI 0.87, 0.99) reduced the risk of GC in never smokers. A positive association was observed with increasing intakes in vitamin D (OR 2.08; 95%CI 1.12, 3.85) and cobalamin (OR 1.33; 95%CI 1.08, 1.65) intakes in never smoker.

Table 1. Characteristics of the participants in the case-control study of gastric cancer and vitamin intake.

Characteristics	Cases (n=178)	Control (n=276)	P-value[a]
Age (year)	60.8 ± 12.0[b]	53.2 ± 11.9	<0.001
Gender (Males)	132 (74.2)[c]	176 (63.8)	0.021
Education level			
Illiterate	111 (62.4)	72 (26.1)	<0.001
Literate	67 (37.6)	204 (73.9)	
Smoking			
Never smokers	97 (54.5)	191 (69.2)	0.001
Ever smokers	81 (45.5)	85 (30.8)	
Body mass index (kg/m^2)			
< 25	76 (42.7)	142 (51.4)	0.068
>= 25	102 (57.3)	134 (48.6)	
H-pylori infection			
Positive	110 (61.8)	121 (43.8)	<0.001
Negative	68 (38.2)	155 (56.2)	
Residential places			
Capital city	93 (52.3)	140 (50.7)	0.753
Others	85 (47.7)	136 (49.3)	

[a]: Chi-square test for categorical variables and independent student's *t-test* for continuous variables; [b]: Mean ± SD; [c]: n (%)

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Table 2. Daily intake of vitamins and OR and 95% CIs of gastric cancer.

Vitamins	Cases (n=178)	Controls (n=276)	Model A[a]		Model B[b]	
			OR	95%CI	OR	95%CI
Vitamin A (µg)	1250.02 ± 636.70	1197.80 ± 607.12	1.00	0.99-1.00	1.00	0.99-1.00
Carotene (µg)	5634.72 ± 3630.24	5635.63 ± 3571.34	0.99	0.99-1.00	1.00	0.99-1.00
Vitamin D(µg)	1.71 ± 0.63	1.66 ± 0.69	1.05	0.77-1.43	1.59	1.07-2.36
Vitamin E (mg)	24.42 ± 14.19	29.48 ± 19.56	0.97	0.96-0.99	0.98	0.96-0.99
Thiamin (mg)	2.09 ± 0.44	2.17 ± 0.54	0.67	0.43-1.05	0.50	0.30-0.83
Riboflavin (mg)	3.56 ± 1.23	3.24 ± 1.42	1.18	1.01-1.38	0.87	0.63-1.21
Niacin (mg)	17.58 ± 7.26	18.57 ± 7.23	0.98	0.95-1.01	0.98	0.95-1.02
Pantothenic acid (mg)	8.62 ± 2.13	8.38 ± 2.37	1.04	0.95-1.14	0.71	0.58-0.87
Pyridoxine(mg)	2.47 ± 0.51	2.52 ± 0.65	0.79	0.55-1.14	0.79	0.53-1.19
Biotin(µg)	54.65 ± 19.14	53.78 ± 23.57	1.00	0.99-1.01	1.00	1.00-1.02
Folate(µg)	446.91 ± 98.47	440.85 ± 114.03	1.00	0.99-1.00	0.99	0.99-0.99
Cobalamin(µg)	4.77 ± 1.71	4.05 ± 1.79	1.29	1.14-1.46	1.25	1.08-1.44
Ascorbic acid (mg)	224.51 ± 98.23	227.57 ± 109.13	0.99	0.99-1.00	0.99	0.99-1.00

[a]: Age, sex, and energy adjusted; [b]: age, sex, energy, Education, Ever sSmoking, H-pylori, and residential adjusted

Table 3. ORs and 95% CIs of gastric cancer for vitamins intakes for participants in different strata of H-pylori infection , body mass index, and smoking status.

Vitamins	H-pylori infection[a]				Body mass index (kg/m^2)[b]				Smoking[c]			
	Positive (n=231)		Negative (n=223)		< 25 (n=218)		>=25 (n=236)		Ever (n=166)		Never (n=288)	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Vitamin A (µg)	0.99	0.99-1.00	1.00	0.99-1.00	0.99	0.99-1.00	0.99	0.99-1.00	1.00	0.99-1.00	1.00	0.99-1.00
Carotene (µg)	0.99	0.99-1.00	1.00	0.99-1.00	0.99	0.99-1.00	0.99	0.99-1.00	1.00	0.99-1.00	1.00	0.99-1.00
Vitamin D (µg)	1.17	0.69-1.97	1.99	1.18-3.36	1.81	1.07-3.08	1.12	0.74-1.98	1.31	0.80-2.16	2.08	1.12-3.85
Vitamin E (mg)	0.99	0.97-1.00	0.96	0.93-0.99	0.99	0.98-1.01	0.99	0.98-1.01	0.97	0.95-0.99	1.00	0.98-1.02
Thiamin (mg)	0.30	0.59-0.86	1.24	0.61-2.54	0.99	0.49-2.03	0.83	0.44-1.56	0.65	0.33-1.28	0.41	0.19-0.86
Riboflavin (mg)	0.98	0.79-1.22	1.91	1.37-2.66	0.93	0.72-1.20	1.07	0.83-1.38	1.26	0.98-1.61	1.14	0.87-1.47
Niacin (mg)	0.97	0.92-1.02	1.01	0.96-1.07	0.98	0.92-1.04	1.01	0.97-1.06	1.02	0.98-1.07	0.93	0.87-0.99
Pantothenic acid (mg)	0.92	0.81-1.04	1.34	1.13-1.64	1.01	0.88-1.17	1.03	0.89-1.20	1.06	0.92-1.22	1.02	0.88-1.19
Pyridoxine (mg)	0.52	0.31-0.85	1.81	0.93-3.50	1.09	0.66-1.80	1.22	0.69-2.14	0.99	0.58-1.67	0.67	0.36-1.25
Biotin (µg)	0.99	0.98-1.01	1.03	1.01-1.05	0.99	0.98-1.02	1.00	0.98-1.02	1.02	1.00-1.04	1.00	0.98-1.02
Folate (µg)	0.99	0.99-0.99	1.00	1.00-1.00	0.99	0.99-1.00	1.00	0.99-1.00	1.00	0.99-1.00	0.99	0.99-1.00
Cobalamin (µg)	1.17	0.97-1.41	1.36	1.13-1.64	0.86	0.68-1.22	0.97	0.81-1.19	1.24	1.05-1.47	1.33	1.08-1.65
Ascorbic acid (mg)	0.99	0.99-1.00	1.00	0.99-1.00	1.00	0.99-1.00	1.00	0.99-1.00	0.99	0.99-1.00	0.99	0.99-1.00

[a]: Age, sex, energy, education, ever smoking, and residential adjusted; [b] Age, sex, energy, education, ever smoking, H-pylori, and residential adjusted; [c] Age, sex, energy, education, H-pylori, and residential adjusted

Discussion

This hospital based case control study figured out that GC was directly associated with riboflavin and cobalamin consumption in model A, and vitamin D and cobalamin in the model B. Thiamin, pantothenic acid, and folate intake reduced the risk of GC in model B and vitamin E was inversely associated with GC in both models. There was no significant association between vitamin A, carotene, and ascorbic acid intake with GC in the models.

Antioxidant vitamins could protect mucosa from oxidative stress associated with H-pylori, high salt consumption and nitrate and nitrite intake (Terry *et al.*, 2000). Although the antioxidant activity of vitamin C has been well described (Padayatty *et al.*, 2003), in the present study, there was no significant association between vitamin C intake and GC; however, some studies (Kong *et al.*, 2014, Pakseresht *et al.*, 2011) have reported its protective effect.

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It is generally believed that, nutrients, such as folate, riboflavin, pyridoxine, and cobalamin affect DNA methylation by regulating the levels of S-adenosyl-L-homocysteine and S-adenosyl-L-methionine (Stefanska *et al.*, 2012). Given that the main cause of carcinogenesis is aberrations in gene expression and protein function is caused by both genetic and epigenetic modifications, it is indicated that these nutrients could protect cells from acrogenous pathways. In this study, cobalamin (B12) consumption increased the risk of GC, but thiamin (B1), pantothenic acid (B5), and folate intake decreased the risk. Dietary vitamin B12 is derived exclusively from animal food; therefore, it seems that cobalamin is a marker for consumption of animal protein in the study population. Several studies have suggested that animal protein can increase the risk of GC.

Based on the results, vitamin E intake is inversely associated with GC risk. The results are in agreement with some studies (Kong *et al.*, 2014, Pelucchi *et al.*, 2008) but not others (Mayne *et al.*, 2001, Pakseresht *et al.*, 2011). The most well-recognized function of vitamin E is preventing the cyclic propagation of lipid peroxidation (Kline *et al.*, 2007). Alfa –tocopherol (one form of vitamin E) acts as a free radical scavenger (Yamauchi, 1997) and anticarcinogen through its ability to prevent the formation of N-nitrosamines which have been suggested to be important factors in the etiology of GC. Furthermore, this vitamin seems to play an immune modulatory role and is capable of increasing natural killer cell activity (Mergens *et al.*, 1980).

The OR (95% CI) of Thiamin and GC risk was 0.5(0.3-0.83), which indicates that thiamin reduced the risk. The dietary intake of thiamine and cancer risk has provided conflicting results. Thiamin appears to have both cancer-promoting and anticancer properties, which vary in relation to both genomic and non-genomic factors. It has been hypothesized that excess thiamine supplementation may be a factor for increased cancer incidence in western countries compared to other countries (Boros, 2000). In contrast, Asian and African countries principally consume foods that are high in thiaminase, which may reduce thiamin exposure. Possible pathways which explain the association of thiamin with cancers include the solute carrier transporter (SLC19) gene, transketolase, transcription factor p53, and poly (ADP-ribose) polymerase-1 gene (Carraher *et al.*, 2015). The data on the association of thiamin intake and GC are limited. It has been suggested that thiamin can reduce cancer cell proliferation (Hanberry *et al.*, 2014).

The study results suggest that pantothenic acid consumption can reduce risk of GC. Pantethine affects cellular fatty acid metabolism; moreover, it displays anti-inflammatory properties by maintaining the asymmetric distribution of cell membrane phosphatidyl serine, resulting in the prevention of cellular response to pro-inflammatory factors (Penet *et al.*, 2008). A large number of studies did not report any association between B5 consumption and GC risk (Mayne *et al.*, 2001, Pakseresht *et al.*, 2011, Ren *et al.*, 2016).

Based on the results, vitamin D intake is associated with higher risk of GC, which is in agreement with some studies (Giovannucci *et al.*, 2006), but some studies showed different results (La Vecchia *et al.*, 1994, Pelucchi *et al.*, 2008). Several studies have hypothesized that the nutritional status of vitamin D and serum levels of vitamin D may be important in risk of GC; however, the results are inconsistent (Abnet *et al.*, 2010, Chen *et al.*, 2007, Khayatzadeh *et al.*, 2015). In the present study, increased consumption of dietary vitamin D was associated with a significantly higher risk of GC. In Abnet study, lower levels of serum 25(OH)D was protective against upper GI tract cancers in Asian subjects (Abnet *et al.*, 2010). Several biologic pathways have been suggested for possible associations between higher vitamin D status and increased cancer risk. It is assumed that vitamin D could induces phase I metabolizing enzymes under certain conditions (Kutuzova and DeLuca, 2007), and it can modulate both proliferative and antiproliferative effects on preneoplastic lesions. It should be noted that UVB (Ultra Violet) generated vitamin D was not considered; therefore, serum

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level of vitamin D was not assessed and the estimated intake was not necessarily a perfect assessment of vitamin D status.

In H-pylori positive subjects, consumption of Thiamin, Pyridoxine, and folate were inversely associated with GC. Published data suggest that infection of H-pylori can reduce the level of Thiamin, Pyridoxine, and folate (Franceschi *et al.*, 2014, Tamura *et al.*, 2002, Testerman *et al.*, 2006, Uruha *et al.*, 2011), so increased consumption can reduce the deficiency caused by H-pylori.

In H-pylori negative subjects, only vitamin E consumption was associated with lower risk and vitamin D, riboflavin, pantothenic acid, biotin, and cobalamin consumption increased the risk of GC. In this group, it is obvious that H-pylori did not exist and could not affect serum levels of vitamin D, riboflavin, pantothenic acid, biotin, and cobalamin. A new study suggest that vitamin D has a role in eradication of H-pylori (Hu, 2017), so in the absence of H-pylori, vitamin D can act as carcinogen, as mentioned in the previous section. It was mentioned that cobalamin consumption may be an indicator of animal dietary patterns; the association of vitamin D with GC could be explained in the same way.

Vitamin E was associated with lower risk of GC in ever smokers. There is evidence that cigarette smoking alters vitamin E requirements (Bruno and Traber, 2005). Increasing vitamin E consumption can replenish body stores and enhance antioxidant capacity and it could prevent carcinogenesis in this way.

Exposure to cigarette can reduce vitamin D in the blood (Brot *et al.*, 1999), so in the ever smokers no significant association was found between vitamin D and GC. In this stratum, vitamin D consumption may retrieve body vitamin D store and in the never smokers there is no need to replenish body stores and excess vitamin D can lead to cancer.

Thiamin and niacin consumption decreased risk of GC in never smokers. Thiamin was associated with lower risk of GC in never smokers, but not in ever smokers. It could be assumed that in smokers, higher amount of vitamins is needed to decrease risk of GC. However, it should be mentioned that sample size was too small in ever smoking group which could lead to wider confidence interval and insignificant results.

This study has several relevant strengths. The first is using a validated diet history questionnaire (Toorang *et al.*, 2019). The second strength of the study is assessing several cofounders which let us to adjust their effects on the studied associations. Nevertheless, we should mention limitation of this study. The most important weak point of the study is using a foreign food composition table. It is clear that food compositions are not the same in different regions. However, it is inevitable, since there is not any comprehensive national food composition table in Iran. The second limitation stems from the case control design of the study which is supposed to recall bias.

Conclusion

This study provided support for a possible protective effect of vitamin E, thiamin, pantothenic acid, and folate on GC risk. Vitamin D and cobalamin intake increased the risk. Further studies are suggested to assess the role of food dietary patterns in relation with GC.

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Conflict of interest

There is no potential conflict of interest.

Authors' contributions

Toorang F and Zendehdel K designed the study. Amini N developed the non-dietary questionnaire. Sasanfar B and Hadji M supervised primary data collection and training the interviewers. Mortazavi M and Narmcheshm S did data cleaning and primary analysis. Toorang F analyzed the data and wrote the draft under the supervision of Zendehdel K. All authors reviewed the final version of the manuscript.

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