

## Omission of breakfast and risk of gastric cancer in Mexico

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groups, a multivariate sub-analysis was performed in subjects  $\geq 39$  years of age and in females and males separately.

**RESULTS:** In the univariate analysis, we found an association between GC and education to primary level or below, low socioeconomic status, the use of dental prostheses, omission of breakfast, consumption of very hot food and drink, addition of salt to prepared foods, consumption of salt-preserved foods and the pattern of alcohol consumption. We found protection against GC associated with the use of mouthwash, food refrigeration and regular consumption of fruit and vegetables. In the multivariate sub-analysis with subjects of  $\geq 39$  years, the omission of breakfast was identified as a risk factor for GC.

**CONCLUSION:** Our study suggests an association between the omission of breakfast and the failure to refrigerate food with GC in the Mexican population.

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**Key words:** Gastric cancer; Questionnaire; Risk factors; Omission of breakfast

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### Abstract

**AIM:** To investigate factors associated with gastric cancer (GC) in the Mexican population using a validated questionnaire.

**METHODS:** We designed and validated in Spanish a Questionnaire to Find Factors Associated with Diseases of the Digestive Tract using GC as a model. A cross-sectional study using 49 subjects, with confirmed histopathological GC diagnosis, and 162 individuals without GC participated. Odds ratio and 95% CIs were estimated in univariate and multivariate analysis adjusted for possible confounding factors. In order to match age

### INTRODUCTION

It has been estimated that, since 1990, gastric cancer (GC)

has become the second most common form of cancer in the world, even though its incidence has decreased gradually in recent decades, especially in those countries with greatest resources<sup>[1]</sup>. Since 1980, the rate of mortality of GC in Mexico has shown an increasing trend, albeit with no significant changes, and it remains the second most common cause of death by cancer<sup>[2]</sup>. According to the latest report of the Histopathological Register of Malignant Tumors in Mexico, GC is the third most common cancer in men and the fifth in women<sup>[3]</sup>. In Mexico, there are few reports detailing the survival of patients with GC, and the stages at which they are diagnosed: two studies carried out in third-level reference hospitals indicate that 2%<sup>[4]</sup> and 3%<sup>[5]</sup> of cases are diagnosed in early stages, while Japan and the United States report 33.7% and 17.1%, respectively<sup>[6]</sup>. The evidence suggests that the factor which determines patient survival is the stage at which the disease is diagnosed. Sanitary intervention should begin at the stage at which the disease is diagnosed, and it is reasonable to expect greater GC patient survival if the cancer is detected at an early stage. In Mexico, unfortunately, the scarcity of data concerning the incidence by stages and prevalence of GC makes it difficult to justify programs of early detection.

It is currently accepted that GC is a process involving multiple factors, from environmental to genetic, the interaction of which influences the development and progression of the disease. The established GC risk factors are diverse, but they can be grouped. Nutritional factors: high consumption of salt, smoked food, hot spicy dishes, nitrite-rich food or water, high carbohydrate and fat ingestion, and low consumption of milk, fruit, fresh vegetables, selenium, vitamins A, C and E<sup>[7]</sup>. Also high consumption levels of tobacco and alcohol, although these GC risks remain controversial<sup>[8]</sup>. Bacterial and viral infections such as: *Helicobacter pylori* (*H. pylori*)<sup>[9]</sup>, mycoplasma<sup>[10]</sup> and Epstein-Barr viral infections<sup>[11]</sup>. Precursor conditions: for example chronic atrophic gastritis<sup>[12]</sup>, Barrett's esophagus<sup>[13]</sup>, intestinal metaplasia<sup>[14]</sup>, dysplasia<sup>[15]</sup> and Ménétrier's disease<sup>[16]</sup>; Accumulation of genetic changes including: p53<sup>[17]</sup>, E-cadherin<sup>[18]</sup>, c-myc<sup>[19]</sup> and microsatellite alterations<sup>[20]</sup>. Certain dietary habits in Mexico have been linked to the development of GC, such as the consumption of salt, processed meats and vegetables<sup>[21]</sup>, alcoholic beverages<sup>[22]</sup>, capsaicin<sup>[23]</sup>, polyphenols, nitrates and nitrites<sup>[24]</sup>.

Due to the fact that GC is preceded by a long period of latency, it is possible to perform interventions during this stage which allow the prevention of manifestation of the disease<sup>[25]</sup>. In this context, we have designed and validated a Questionnaire to Find Factors Associated with Diseases of the Digestive Tract (QUFA-DT<sup>®</sup>), utilizing GC as a model. We propose that the QUFA-DT<sup>®</sup> could be a valuable instrument for future selection of Mexican patients to undergo gastroendoscopy for the early diagnosis of GC.

## MATERIALS AND METHODS

### Characteristics of the study

This was a cross-sectional analytical study approved by the ethics committee (official minute JE/035/07) of the "Dr. Miguel Dorantes Mesa", third-level reference Hospital of the Health Services of Veracruz State, Mexico. The study complied fully with the principles of the Declaration of Helsinki of the World Medical Association, 2002.

### Subjects involved

Patients with a confirmed histopathological diagnosis of GC, as reported in the Hospital records of 2008 and 2009, were invited to participate with informed consent. Sixty-five patients, all advanced GC cases, were identified within the hospital records, of whom 16 had already died. Among the blood bank donors at the same Hospital, 162 apparently healthy individuals were selected, i.e. individuals free of any chronic pathology, who had no clinical history of cancer. Relatives of the GC patients who participated in the study were excluded. Blood bank donors were recruited from May 2009 to January 2010.

### Data collection

A rapid application instrument called QUFA-DT<sup>®</sup> was designed and validated in Spanish. This instrument gathers sociodemographic information regarding lifestyle, clinical history, factors associated with the development of tumors of the mouth, stomach, colon and rectum. The development of the QUFA-DT<sup>®</sup> took place in the following steps: (1) systematic review of the literature in English and Spanish; (2) production of the instrument; (3) evaluation by a panel of six experts; (4) application with a sample of 49 people with GC, and 162 without GC; and (5) statistical analysis.

### Statistical analysis

In the univariate analysis, proportions and means were compared by  $\chi^2$  and Student's *t* test, respectively. Risks were estimated by odds ratio (OR) and 95% CI. Multivariate analysis was carried out by logistic regression adjusted by the conditional forward method. The dependent variable was GC diagnosis, while covariates were age, sex, use of mouthwash, use of dental prosthesis, food refrigeration, omission of breakfast, consumption of very hot food or drinks, addition of salt to prepared food and consumption of highly salted foods. In order to match age groups, a multivariate sub-analysis was performed in subjects  $\geq 39$  years of age and in females and males separately. In this case, the dependent variable was GC diagnosis and the covariates were omission of breakfast, dental prosthesis use and food refrigeration. Statistical significance was considered to be  $P \leq 0.05$ . Analyses were performed using SPSS software version 18 and Epidat version 3.1.

**Table 1** General characteristics of the subjects *n* (%)

	Total ( <i>n</i> = 211)	With GC ( <i>n</i> = 49)	Without GC ( <i>n</i> = 162)
Sex			
Male	152 (72.0)	23 (46.9)	129 (79.6)
Female	59 (28.0)	26 (53.1)	3 (20.4)
Age (yr) <sup>1</sup>	40.2 ± 16.1	62.1 ± 10.7	33.5 ± 10.7
Minimum	18	39	18
Maximum	83	83	64
Histopathological classification			
Diffuse adenocarcinoma	–	26 (53.1)	–
Intestinal adenocarcinoma	–	21 (42.8)	–
Lymphoma	–	2 (4.1)	–
Marital status			
Single	56 (26.5)	6 (12.2)	50 (30.9)
Married	90 (42.7)	27 (55.1)	63 (38.9)
Living with a partner	46 (21.8)	5 (10.2)	41 (25.9)
Divorced	8 (3.8)	1 (2.0)	7 (4.3)
Widowed	11 (5.2)	10 (20.4)	1 (0.6)
Education level			
No formal education	26 (12.3)	14 (28.6)	12 (7.4)
Primary	66 (31.3)	26 (53.1)	40 (24.7)
Secondary	49 (23.2)	4 (8.2)	45 (27.8)
Bachelors	23 (10.9)	0 (0.0)	23 (14.2)
Professional technical	1 (0.5)	0 (0.0)	1 (0.6)
Graduate	45 (21.3)	5 (10.2)	40 (24.7)
Postgraduate	1 (0.5)	0 (0.0)	1 (0.6)
Place of work <sup>2</sup>			
Without employment	51 (24.2)	27 (55.1)	24 (14.8)
Rural	57 (27.0)	12 (24.5)	45 (27.8)
Urban	103 (48.8)	10 (20.4)	93 (57.4)
Socioeconomic status <sup>3</sup>			
Low	134 (63.5)	42 (85.7)	92 (56.8)
Medium	67 (31.8)	4 (8.2)	63 (38.9)
High	10 (4.7)	3 (6.1)	7 (4.3)

<sup>1</sup>mean ± SD; <sup>2</sup>Rural: working outside the town; urban: working in the town; <sup>3</sup>Monthly household income: low ≤ \$376 USD; medium \$377 to \$979 USD; high ≥ \$980 USD. GC: Gastric cancer.

## RESULTS

With a response rate of 100%, a total of 211 subjects were included in this study. The general characteristics of the study population are shown in Table 1.

All subjects were interviewed face to face by two qualified interviewers, with the majority completing the QUFA-DT<sup>®</sup> in less than 20 min. Possible factors associated with GC are detailed in Table 2, where it can be seen that associations exist between the development of GC and schooling to primary level or below, low socioeconomic status, use of dental prostheses, omission of breakfast, consumption of very hot food and drinks, consumption of salt-preserved foods and pattern of alcohol consumption.

In contrast, protection against GC was found to be associated with the use of mouthwash, food refrigeration and regular consumption of fruit and vegetables. No associations were found between development of GC and the habitual use of tobacco, or the consumption of alcohol and of capsaicin, in comparison to abstinence.

In the multivariate analysis, we found in the adjusted

model that only the omission of breakfast ( $P = 0.004$ ), use of dental prosthesis ( $P = 0.017$ ), and lack of food refrigeration ( $P = 0.005$ ) were associated with GC (Table 3). In contrast, in the multivariate sub-analysis with subjects ≥ 39 years of age, omission of breakfast was identified as the sole risk factor for GC in women (OR, 7.0, 95% CI = 1.45-33.80), men (OR, 5.25, 95% CI = 1.02-27.0) and in general (OR, 6.06, 95% CI = 1.74-21.14).

## DISCUSSION

Although GC is the second leading cause of cancer death in Mexico<sup>[2]</sup>, there are no data with which to support programs of prevention, detection and control of this disease. Information is scarce regarding factors associated with GC in the population of Mexico<sup>[21-24]</sup> and there is a lack of validated instruments to identify such risks. This study proposes an instrument called QUFA-DT<sup>®</sup> which can be used in the search for factors associated with this disease.

The results of the multivariate analysis of factors potentially associated with GC suggest an increased risk of GC development in people with a primary or lower educational level and low socioeconomic status, which is consistent with the results of previous studies<sup>[26,27]</sup>. While we found that regular consumption of alcohol, but not tobacco, has an association with GC risk, we believe that this data is inconclusive. It is clear that international reports regarding both of these factors in relation to GC are still controversial<sup>[18,28]</sup>.

The use of a dental prosthesis was identified as a risk factor for GC in the adjusted multivariate model. However, this result can be treated with caution given that age may act as a confounding factor; in our study, patients with GC had a higher mean age than those free of the disease, and this higher mean age could reasonably be expected to imply a greater probability of requiring such prosthesis. To our knowledge, there have been no reports concerning the association of this variable with GC, although it has been reported for oral cancer<sup>[29]</sup>. Further testing is therefore required to confirm this association.

In the multivariate adjusted model, we also found an association between GC and the lack of food refrigeration, which again is consistent with the findings of previous studies<sup>[30,31]</sup>. Interestingly, in countries with a documented decrease in GC, this has been attributed in part to the use of refrigeration for preserving food<sup>[31,32]</sup>. Unfortunately, a considerable percentage of households in Veracruz do not have adequate conditions for food hygiene: only 68.2% have refrigerators, 73.5% have piped water and 50.5% have drains connected to a public network<sup>[33]</sup>. It is striking that the percentage of households with a television set (85.9%) is higher than that of households with refrigerators (68.2%)<sup>[33]</sup> and that 20% of houses still have dirt floors<sup>[33]</sup>. These socioeconomic data for our state, Veracruz, acquire major relevance in explaining the reasons why those patients skipped break-

**Table 2 Association between sociodemographic characteristics, habits, diet and pathological history of gastric cancer *n* (%)**

	With GC (49) <sup>1</sup>	Without GC (162) <sup>1</sup>	OR (95% CI)	<i>P</i> value
Education level				
Higher than primary	9 (18.4)	110 (67.9)	1	
Primary or below	40 (81.6)	52 (32.1)	9.40 (4.25-20.81)	< 0.0001
Socioeconomic level				
Medium-high	7 (14.3)	70 (43.2)	1	
Low	42 (85.7)	92 (56.8)	4.57 (1.93-10.77)	0.0002
Use of tobacco <sup>2</sup>				
Non-smoker	27 (55.1)	87 (53.7)	1	
Smoker-ex-smoker	22 (44.9)	75 (46.3)	0.95 (0.50-1.80)	0.99
Pattern of tobacco consumption <sup>3</sup>				
Occasional	15 (30.6)	54 (33.3)	1	
Habitual	7 (14.3)	22 (13.6)	1.15 (0.41-3.19)	0.49
Consumption of alcohol <sup>4</sup>				
Non-consumer	20 (40.8)	57 (35.2)	1	
Consumer-ex-consumer	29 (59.2)	105 (64.8)	0.79 (0.41-1.51)	0.47
Pattern of alcohol consumption <sup>5</sup>				
Occasional	21 (72.4)	101 (96.2)	1	
Habitual	8 (27.6)	4 (3.8)	9.62 (2.65-34.90)	0.0001
Use of mouthwash				
No	46 (93.9)	127 (78.4)	1	
Yes	3 (6.1)	35 (21.6)	0.24 (0.07-0.81)	0.014
Use of dental prosthesis				
No	31 (63.3)	158 (97.5)	1	
Yes	18 (36.7)	4 (2.5)	22.94 (7.26-72.42)	< 0.0001
Refrigeration of food				
Yes	24 (49.0)	137 (84.6)	1	
No	25 (51.0)	25 (15.4)	5.71 (2.82-11.54)	< 0.0001
Omission of breakfast				
No	14 (28.6)	137 (84.6)	1	
Yes	35 (71.4)	25 (15.4)	13.70 (6.46-29.07)	< 0.0001
Consumption of very hot food or drinks				
No	43 (87.8)	159 (98.1)	1	
Yes	6 (12.2)	3 (1.9)	7.40 (1.78-30.79)	0.006
Addition of salt to prepared food <sup>6</sup>				
No	32 (65.3)	138 (85.2)	1	
Yes	17 (34.7)	24 (14.8)	3.05 (1.47-6.34)	0.002
Consumption of fruit <sup>7</sup>				
Rare	29 (59.2)	64 (39.5)	1	
Frequent	20 (40.8)	98 (60.5)	0.45 (0.23-0.86)	0.015
Consumption of vegetables <sup>7</sup>				
Rare	31 (63.3)	69 (42.6)	1	
Frequent	18 (36.7)	93 (57.4)	0.43 (0.22-0.88)	0.011
Consumption of salt-preserved foods				
No	29 (59.2)	129 (79.6)	1	
Yes	20 (40.8)	33 (20.4)	2.70 (1.36-5.35)	0.004
Consumption of capsaicin				
No	11 (22.4)	26 (16.0)	1	
Yes	38 (77.6)	136 (84.0)	0.66 (0.30-1.46)	0.30
Family history of gastric cancer				
No	44 (89.8)	159 (98.1)	1	
Yes	5 (10.2)	3 (1.9)	6.02 (1.39-26.19)	0.018

<sup>1</sup>Total may vary due to lost values; <sup>2</sup>Smoker: Consumes cigarettes currently or consumed prior to diagnosis of gastric cancer (GC); Ex-smoker: Has not consumed cigarettes for at least one year before the interview or on diagnosis of GC; non-smoker: does not consume cigarettes; <sup>3</sup>Occasional: Only smokes on special occasions which occur infrequently; habitual: Smokes one or more times per week; <sup>4</sup>Consumer: Consumes alcohol at the time of the interview or prior to diagnosis with GC; Ex-consumer: Has not consumed alcohol for at least one year before the interview or on diagnosis of GC; Non-consumer: Does not consume alcohol; <sup>5</sup>Occasional: Only consumes alcohol on special occasions which occur infrequently; Habitual: Consumes alcohol one or more times per week; <sup>6</sup>Addition of salt to prepared foods, during the course of meals; <sup>7</sup>Rare: Consumption of less than seven portions per week; Frequent: Consumption of seven or more portions per week.

fast (see below). The need to keep foods refrigerated in our state is accentuated by the climatic conditions. The average annual temperature, excluding the mountain-

ous areas of “Cofre de Perote” and “Pico de Orizaba”, ranges between 25-27 °C, with maximum temperatures in the warmest month between 33-35 °C and minimum

**Table 3 Association of the variables included in the multivariate analysis**

	Non-adjusted model			Adjusted model		
	OR	95% CI	P value	OR	95% CI	P value
Use of dental prosthesis	9.44	1.26-70.78	0.029	9.68	1.51-61.97	0.017
Use of mouthwash	0.10	0.01-1.01	0.051	-	-	-
Omission of breakfast	6.65	1.94-22.79	0.003	5.21	1.70-16.00	0.004
Non-refrigeration of foods	4.18	0.99-17.60	0.051	6.58	1.78-24.32	0.005
Consumption of very hot food and drinks	11.81	0.86-162.85	0.065	-	-	-
Addition of salt to prepared food	2.29	0.56-9.49	0.25	-	-	-
Consumption of salt-preserved foods	4.75	1.14-19.73	0.032	-	-	-

Multivariate analysis conducted using logistic regression adjusted, by the forward conditional method, for the following variables: use of mouthwash, consumption of very hot food and drinks, addition of salt to prepared food and consumption of salt-preserved foods.

temperatures in the coldest month between 14-20 °C<sup>[34]</sup>, while cumulative annual rainfall is  $\geq 1000$  mm<sup>[34]</sup>. We believe that, due to social and climatic conditions, for a significant percentage of households in Veracruz it is difficult to follow the recommendations of the World Health Organization (WHO) for the safe handling of food. As proposed by the WHO, the five keys to safer food are: keep food at safe temperatures; refrigerate cooked and perishable food preferable below 5 °C; use safe water and raw materials; cook food thoroughly; separate raw and food cooked and keep hands, utensils and surfaces clean<sup>[35]</sup>.

In the univariate analysis, the consumption of very hot food or drinks, or of foods preserved in salt, and the addition of salt to prepared foods were associated with GC, however, no such association was observed in the adjusted multivariate analysis. Consumption of foods preserved in salt and the addition of salt to prepared foods have been reported as risk factors for GC<sup>[36]</sup>, however, further investigations are needed to determine the association between these variables and the development of GC. On the other hand, we found an association between protection against GC and the regular consumption of fruit and vegetables, consistent with the findings of previous studies<sup>[7,30]</sup>.

We found that the omission of breakfast has a strong association with GC, which is evident in the adjusted model and in the sub-analysis by gender in subjects aged  $\geq 39$  years. This finding appears to have a precedent in reports that claim that irregular eating is associated with GC<sup>[30,37]</sup>. It was also reported in these studies that overeating and eating quickly are factors associated with GC<sup>[30,37]</sup>. We believe that the reasons why those patients skipped breakfast are probably associated with their low socioeconomic status and level of education. Unfortunately, in our country a considerable percentage of Mexicans have lived for generations under conditions of poverty. In our experience, validation of the questionnaire was a very complex labor, since a considerable percentage of those patients surveyed found it difficult to understand questions, apparently simple to us. Others were surprised when we explained to them some of the common factors associated with the development

of GC. We hypothesize that the omission of breakfast causes alteration of the natural stomach environment which may promote a precursor condition and/or susceptibility to bacterial or viral infections. As is known, irregular eating, especially skipping breakfast, has been associated with gastric ulcer development<sup>[38]</sup> and a history of gastric ulcer has been linked to Epstein-Barr virus-associated GC<sup>[39]</sup>. Interestingly, skipping breakfast correlates with Epstein-Barr virus-associated GC in male patients<sup>[39]</sup>. Additionally, the consumption of strong alcoholic beverages before breakfast has been associated with risk of GC<sup>[40]</sup>. While, Western-style breakfast has been associated with protection against GC<sup>[41]</sup>.

The human stomach is a specialized organ which produces a highly acid secretion, gastric acid, which beyond its physiological role in digestion, is one of the body's major non-specific defense mechanisms against infection<sup>[42]</sup>. Food intake is the strongest physiological stimulus to the secretion of gastric acid. It has been postulated that elderly patients are prone to develop severe bacterial infections due to their natural reduction in gastric acid secretion<sup>[42]</sup>. Malnutrition predisposes to gastritis and reduced acid secretion<sup>[42]</sup>. Interestingly, transgenic mice with impaired secretion of gastric acid develop intestinal metaplasia<sup>[43,44]</sup>, a precursor condition of GC<sup>[14]</sup>. In humans, a series of changes have been identified with respect to the mechanism of gastric carcinogenesis due to *H. pylori* infection: superficial gastritis, atrophic gastritis, intestinal metaplasia and carcinoma<sup>[45]</sup>. In this context, is probable that omission of breakfast, in combination with other risk factors, alters the secretion patterns of the stomach giving favorable conditions for colonization of pathogens, such as *H. pylori* or Epstein-Barr virus, which could promote gastric carcinogenesis.

In Veracruz State, it is necessary to implement programs of constant dissemination of healthy eating habits, comprising information on nutrition, portion size, regularity and speed of food consumption emphasizing the importance of not skipping breakfast. Such public health interventions could assist the prevention not only of GC, but other chronic degenerative diseases. For the planning and execution of these sanitary interventions it is mandatory to consider that in our state only 40%

of the population has access to public or private medical services<sup>[33]</sup> and this results in the poor demand for preventative public services and hence the lack of a preventative culture in our population<sup>[46]</sup>. As reported, clinical studies in humans have consistently found that dietary patterns characterized by a regular breakfast intake may improve risk factors for chronic disease<sup>[47]</sup>. Moreover, in children, not eating breakfast contributes to dietary inadequacies that are not compensated for at other meals<sup>[48,49]</sup>. In adolescence, a good quality breakfast has been associated with better mental health<sup>[50]</sup>.

Our study had certain limitations, such as possible memory bias that can change over time, and the relatively small sample size. However, we believe that its strengths are the proposal of an instrument in Spanish to search for factors associated with GC, and the type of analysis employed, which allowed adjustment for potential confounding factors.

In conclusion, our study suggests an association between the omission of breakfast and the failure to refrigerate food, with GC in the Mexican population. We propose an instrument of rapid application in order to identify factors associated with GC; this instrument could be of great value to public health.

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## COMMENTS

### Background

In Mexico gastric cancer (GC) is the third most common cancer in men and the fifth in women. Its prognosis is difficult as it is commonly diagnosed at an advanced stage. In tertiary level hospitals in this country only 2%-3% of GC are diagnosed in the early stages, and unfortunately there are no programs for early detection of GC. As is known, the factor which determines patient survival is the stage at which GC is diagnosed; thus sanitary intervention should begin at that stage and it is reasonable to expect greater GC patient survival if the cancer is detected an early stage.

### Research frontiers

In Mexico, unfortunately, the scarcity of data concerning factors associated with GC and prevalence of this disease makes it difficult to justify and develop programs of early detection. Application of questionnaires to identify subjects with exposure to GC risk factors is an important tool since it has been estimated that most GC cases are related to lifestyle and environmental factors, with a minor proportion attributed to genetic defects. Thus the authors developed and validated a Spanish questionnaire to find exposure to factors associated with GC in the Mexican population and we found that omission of breakfast and the failure to refrigerate food are associated with GC.

## Innovations and breakthroughs

To the authors' knowledge this is the first study conducted in Mexico that identifies the omission of breakfast as a factor associated with GC.

## Applications

Knowledge of factors associated with the evolution of GC and the development of an instrument to identify such factors is very useful for public health, especially in a country lacking a screening program for early detection of GC.

## Terminology

The authors investigate factors associated with the development of GC in the Mexican population using a questionnaire. They found that omission of breakfast and failure to refrigerate food are factors associated with GC. They propose a questionnaire as an instrument for future selection of Mexican patients to undergo gastroendoscopy for early diagnosis of GC.

## Peer review

It is a very interesting manuscript and suggested to be accepted as it is.

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