Original Article

Family history of gastric cancer in dyspeptic patients referred for endoscopic screening

Histórico familiar de câncer gástrico em pacientes dispépticos indicados à triagem endoscópica

Antecedentes familiares de cáncer gástrico en pacientes dispépticos derivados a triaje endoscópico

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Abstract

Objective: To identify first-degree relative history of gastric cancer in patients with dyspeptic symptoms receiving care at a public endoscopy service.

Methods: A cross-sectional study, performed with dyspeptic patients referred for an upper gastrointestinal endoscopy. The association between the family history of gastric cancer and the findings of the endoscopic examination was verified using the Chi-square or Fisher tests, and its effect was shown using odds ratio and confidence interval in univariate and multivariate analyses. Logistic regression was used to analyze the data.

Results: Among the 751 dyspeptic patients enrolled, 44 (5.9%) had a family history of gastric cancer, mostly females (70.5%) aged 45 years or older (56.8%). Patients with a family history of gastric cancer were more likely to have no endoscopic diagnosis of peptic ulcer (p=0.05; OR=2.33; CI=0.99-5.48). In addition, higher chances of gastric mucosal changes (p=0.05; RC=1.06; CI=1.04-1.08) and Helicobacter pylori infection (p=0.04; RC=1.79; CI=0.94-3.39) were found, even after adjusting the analyses.

Conclusion: The endoscopic gastric mucosal changes and Helicobacter pylori infection in patients with dyspeptic symptoms showed an independent association with family history of gastric cancer. Therefore, it is necessary to develop health care protocols for better investigation and surveillance of gastric cancer relatives, as well as health education actions to guide patients regarding screening and prevention of gastric cancer.

Resumo

Objetivo: Identificar o histórico familiar de primeiro grau de câncer gástrico em pacientes com sintomas dispépticos atendidos em um serviço público de endoscopia.

Métodos: Estudo transversal, realizado com pacientes dispépticos que tinham indicação para realizar o exame de endoscopia digestiva alta. A associação entre o histórico familiar de câncer gástrico e os resultados do exame endoscópico foi verificada por meio dos testes de *Qui-quadrado* ou *Fisher*, e medida seu efeito por meio da razão de chance e intervalo de confiança em analises uni e multivariadas. Utilizou-se regressão logística na análise dos dados.

Resultados: Observou-se que dos 751 pacientes dispépticos investigados, 44 (5,9%) possuíam histórico familiar de câncer gástrico, destes a maioria era do sexo feminino (70,5%), com idade maior ou igual a 45 anos (56,8%). Os pacientes com histórico familiar de câncer gástrico tinham maiores chances de não apresentarem diagnostico endoscópico de úlcera péptica (p=0,05; RC=2,33; IC=0,99-5,48). Além de maiores chances de alterações na mucosa gástrica (p=0,05; RC=1,06; IC=1,04-1,08) e infecção pela *Helicobacter pylori* (p=0,04; RC=1,79; IC=0,94-3,39) mesmo após ajustes nas análises.

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Conflitos de interesse: nada a declarar.

Conclusão: A alteração endoscópica da mucosa gástrica e a infecção pela *Helicobacter pylori* em pacientes com sintomas dispépticos, mostraram associação independente com o histórico familiar de câncer gástrico. Diante disso, faz-se necessário a elaboração de protocolos de assistência à saúde para melhor investigação e vigilância dos familiares de câncer gástrico, bem como ações de educação em saúde para orientar os pacientes a respeito do rastreio e prevenção do câncer gástrico.

Resumen

Objetivo: Identificar los antecedentes familiares de primer grado de cáncer gástrico en pacientes con síntomas dispépticos atendidos en un servicio público de endoscopía.

Métodos: Estudio transversal llevado a cabo con pacientes dispépticos que habían sido derivados a realizar un estudio de endoscopía digestiva alta. La relación entre los antecedentes familiares de cáncer gástrico y los resultados del estudio endoscópico fue verificada mediante la prueba χ^2 de Pearson o *de Fisher*, y su efecto fue medido a través de la razón de momios y del intervalo de confianza en análisis uni y multivariados. Se utilizó la regresión logística en el análisis de los datos.

Resultados: Se observó que de los 751 pacientes dispépticos investigados, 44 (5,9 %) tenían antecedentes familiares de cáncer gástrico, de los cuales la mayoría era de sexo femenino (70,5 %), de 45 años o más (56,8 %). Los pacientes con antecedentes familiares de cáncer gástrico tenían mayores chances de no presentar diagnóstico endoscópico de úlcera péptica (p=0,05; RC=2,33; IC=0,99-5,48). Además de mayores probabilidades de alteraciones en la mucosa gástrica (p=0,05; RC=1,06; IC=1,04-1,08) e infección por *Helicobacter pylori* (p=0,04; RC=1,79; IC=0,94-3,39), inclusive después de ajustes en los análisis.

Conclusión: La alteración endoscópica de la mucosa gástrica y la infección por *Helicobacter pylori* en pacientes con síntomas dispépticos mostraron relación independiente con los antecedentes familiares de cáncer gástrico. Ante este escenario, es necesaria la elaboración de protocolos de atención a la salud para una mejor investigación y observación de los familiares de cáncer gástrico, así como también acciones de educación en salud para orientar a los pacientes sobre la detección y prevención del cáncer gástrico.

Introduction

Gastric cancer (GC) is the sixth most common neoplasia throughout the world, and the third leading cause of cancer-related death.[1] The incidence of GC is declining in developed countries due to appropriate health interventions, but high morbidity and mortality rates still remain in developing countries.[2]

Multiple factors are associated with increased risk of GC, such as: low socioeconomic status, advanced age, poor eating habits, alcoholism, smoking, family history of cancer, Epstein-Barr and Helicobacter pylori infections, and premalignant lesions of the stomach.[3,4] Due to the multifactorial nature of GC, prevention relies on accurate identification of risk factors, the underlying causes of this disease, and appropriate management of these factors.[5]

H. pylori infection and family history of gastric cancer have been reported as important risk factors for the development of GC worldwide.[6,7] H. pylori eradication has been defined as a strategy to prevent GC, according to a World Health Organization (WHO) publication in 2014.[8] Studies have shown consistent evidence that eradication of *H. pylori* reduces the risk of GC, depending on the severity and extent of gastric mucosal damage at the time of eradication, and recommend treatment of all infected individuals.[9-11]

Family members of GC patients have higher rates of *H. pylori* infection than people in the general population, and precancerous histological changes of the stomach are more severe in this group.[12,13] Both GC patients and their relatives share risk factors, including genetic characteristics and exposure to H. pylori in the environment. This bacterium can be easily transmitted between individuals, as it can be found in feces, saliva, and dental plaque, favoring the concentration of infection among family members and people living in the same environment.[14,15]

Although a family history is a recognized risk factor for GC, the molecular basis of familial aggregation and intrafamilial transmission of *H. pylori* are unclear. Familial gastric cancer usually indicates only a positive family history, whereas hereditary gastric cancer suggests alterations in specific genes.[16] Despite current recommendations for monitoring and eradication of *H. pylori* among family members of patients with GC, the strategies for monitoring, screening, and interval surveillance in this high-risk group have not been well established by global guidelines.[15,17]

Identification of high-risk individuals is important for surveillance and prevention of GC. Proper

diagnosis and treatment of gastric mucosal lesions at early stages can reduce GC-related mortality, and contribute to effective treatments with lower costs and increased survival.[18] Current guidelines recommend timely endoscopic screening of patients with dyspeptic symptoms to detect possible organic diseases causing symptoms, especially to rule out upper gastrointestinal malignancies.[6]

Therefore, investigating and knowing the family history of gastric cancer in patients with dyspeptic symptoms is important for developing prevention and control strategies for GC, and also to know the most susceptible populations, contributing to the development of surveillance, treatment, and early detection protocols for GC. Therefore, this study aimed to identify the first-degree family history of gastric cancer in patients with dyspeptic symptoms treated at a public endoscopy service.

Methods

This was a cross-sectional study conducted in a public endoscopy service, located in northeastern Brazil, with patients presenting dyspeptic symptoms who were referred for upper gastrointestinal endoscopy (UGIE). The sample was calculated using a formula for an infinite population. A prevalence of 50% was adopted as it provides a maximum sample size, confidence level of 95% ($Z\alpha$=1.96), and sampling error of 5%. For better representativeness, the sample size was increased by 10% (n=751 patients with dyspeptic symptoms).

Participants were randomly selected according to the established eligibility criteria. Inclusion criteria included: patients at least 18 years of age, of both sexes, with indication for upper digestive endoscopy. Exclusion criteria were: use of antibiotics or gastric antisecretory agents in the two weeks prior to the UGIE exam, pregnant or lactating women, conditions associated with gastric physiology disorders such as vagotomy, previous surgery for gastric resection, and pyloric stenosis.

Data collection was performed from October of 2015 to February of 2018, in the waiting room of the endoscopy service. Patient recruitment was performed in the waiting room of the UGIE exam, after the objectives and methodology of the research were explained. Those who agreed signed the Terms of Free and Informed Consent form, and were interviewed. The instrument used for data collection was a form containing identification data, socioeconomic and clinical characteristics, and data on first-degree family history of gastric cancer.

Endoscopic diagnoses were accessed in the patient's medical record. Detection of *H. pylori* was accomplished by means of the rapid urease test during the upper digestive endoscopy examination. The rapid urease test is based on the production of urease by the bacteria, for indirect diagnosis of the presence of *H. pylori*.[19]

The data were analyzed using SPSS for Windows software, version 22.0 (SPSS Inc., Chicago, IL). First, the Kolmogorov-Smirnov test was applied to assess the normality of quantitative variables, which were presented by means of descriptive statistics (mean and standard deviation). Correlations between the study variables were calculated using the Chi-square or Fisher's tests. The significance level was defined as p-value ≤ 0.05. The dependent variable was family history of gastric cancer and the independent variables were the results of the upper digestive endoscopy and the presence of *H. pylori* infection. Logistic regression analysis was used to determine the relationship between the dependent variable and the simultaneous set of independent variables.

National and international standards for ethics in research involving human subjects were respected. This study was approved by the Research Ethics Committee of the institution responsible for the study with opinion number 1,304,308.

Results

We analyzed 751 patients with dyspeptic symptoms receiving care in a public endoscopy service, with a predominance of females (68.3%); ages ranged from 18 to 91 years, with a mean age of 43.43 (standard deviation of 16.42); 66.7% were married;

67.2% had a monthly family income of more than one time the minimum wage (R$ 1851.41); 50.3% were educated for more than eight years; 82% identified as nonsmokers; 67.5% were not consumers of alcohol, and 94.1% had no history of gastric cancer in their family.

In this study, patients with dyspeptic symptoms older than 45 years were more likely to be married (p<0.0001; OR= 2.87; CI: 2.07 - 3.98), educated for eight years or less (p<0.0001; OR= 2.93; CI: 2.40 - 3.58), and smokers (p<0.0001; OR= 1.58; CI: 1.35 - 1.85). Patients aged 45 years or younger were more likely to consume alcohol (p=0.02; OC = 1.44; CI: 1.05 - 1.97) and present endoscopic gastric mucosal changes (p=0.01; OC = 2.31; CI: 1.20 - 4.45), and less likely to have esophagitis (p=0.004; OC = 0.61; CI: 0.44 - 0.85). There was no association between age and family history of gastric cancer, as can be seen in table 1.

Table 1. Distribution of socioeconomic and clinical characteristics of patients with dyspeptic symptoms receiving care at a public endoscopy service, according to age

Variables	Age		p-value	OR	CI 95%
	<= 45 n=413 n (%)	>45 n=338 n (%)			
Sex					
Female	278(67.4)	235 (69.6)	0.51	1.1	0.81-1.51
Marital status					
Married	234(56.7)	267(78.9)	<0.0001*	2.87	2.07-3.98
Income					
≥ 1 minimum wage	284(68.8)	221(65.3)	0.32	0.85	0.63-1.16
Level of education					
≤ 8 years	125(30.2)	253(74.8)	<0.0001*	2.93	2.40-3.58
Smoker					
Yes	48(11.6)	87(25.7)	<0.0001*	1.58	1.35-1.85
Alcoholic					
Yes	149(36.1)	95(28.1)	0.02*	1.44	1.05-1.97
Family history of gastric cancer					
Yes	19(4.6)	25(7.3)	0.1	0.6	0.32-1.11
Alteration in Gastric Mucosa					
Yes	35(8.4)	13(3.8)	0.01*	2.31	1.20-4.45
Infection by *H. pylori*					
Yes	220(53.2)	176 (52.1)	0.74	1.04	0.78-1.39
Gastritis					
Yes	323(78.2)	270(79.8)	0.57	0.9	0.63-1.28
Peptic Ulcer					
Yes	27(6.5)	33(9.7)	0.1	0.64	0.38-1.09
Esophagitis					
Yes	90(21.7)	105(31.1)	0.004*	0.61	2.06-2.41

*p ≤0.05; F= frequency; OR= Odds Ratio; 95% CI = 95% confidence interval

It was observed that 44 (5.9%) patients had a family history of gastric cancer, most of them were female (70.5%), aged 45 years or older (56.8%), with an income of more than one time the minimum wage (68.2%), more than eight years of education (52.3%), non-smokers (81.8%) and non-alcohol drinkers (59.1%). These socioeconomic factors were not associated with family history of gastric cancer, as shown in table 2.

Table 2. Association of socioeconomic factors with family history of gastric cancer in patients with dyspeptic symptoms

Variables		Family history of gastric cancer		Total	p-value
		Yes (n= 44) f(%)	No (n= 707) f(%)		
Sex	Male	13(29.5)	225(31.8)	238	0.448
	Female	31(70.5)	482(68.2)	513	
Age	≤ 45 years	19(43.2)	394(55.7)	413	0.072
	≥ 45 years	25(56.8)	313(44.3)	338	
Income	≤ 1 minimum wage	14(31.8)	232(32.8)	246	0.518
	≥ 1 minimum wage	30(68.2)	475(67.2)	505	
Marital status	Single	12(27.3)	238(33.7)	250	0.242
	Others	32(72.7)	469(66.3)	501	
Level of education	≤ 8 years	21(47.7)	357(50.5)	378	0.42
	≥ 8 years	23(52.3)	350(49.5)	373	
Smoker	Yes	8(18.2)	127(18.0)	135	0.551
	No	36(81.8)	580(82.0)	616	
Alcohol consumption	Yes	18(40.9)	226(32.0)	244	0.144
	No	26(59.1)	481(68.0)	507	

f= frequency

Patients with dyspeptic symptoms who reported a family history of gastric cancer were more likely to have altered gastric mucosa, and all of them showed altered esophagastroduodenoscopy results (p= 0.05; OR= 1.06; CI: 1.04 - 1.08), and also a higher chance of being infected with *H. pylori* (p= 0.04; OR= 1.79; CI: 0.94 - 3.39. The dyspeptic patients with a family history of gastric cancer had a higher chance of not having the diagnosis of peptic ulcer (p= 0.05; OR= 2.33; CI: 0.99 - 5.48), as demonstrated in table 3.

After multivariate analysis, patients with a family history of gastric cancer remained in the model with higher odds of having endoscopic gastric mucosal change (p< 0.0001; OR= 2.34; CI=1.10-5.51) and *H. pylori* infection (p=0.05; OR=1.89; CI=0.84-3.18).

Table 3. Association of endoscopic examination findings with the presence of family history of gastric cancer in patients with dyspeptic symptoms

Endoscopic findings		Family history of gastric cancer Yes (n= 44) f(%)	No (n= 707) f(%)	Total	p- value	RC	IC 95%
Gastric mucosal changes	Yes	44(100.0)	659(93.2)	703	0.05*	1.06	1.04 – 1.08
	No	00(0.0)	48(6.8)	48			
Infection by *H. Pylori*	Yes	29(65.9)	367(51.9)	396	0.04*	1.79	0.94 – 3.39
	No	15(34.1)	340(48.1)	355			
Gastritis	Yes	38(86.4)	555(78.5)	593	0.14	1.73	0.72 – 4.18
	No	06(13.6)	152(21.5)	158			
Antral gastritis	Yes	33(75.0)	478(67.6)	511	0.19	1.43	0.71 – 2.89
	No	11(25.0)	229(32.4)	240			
Body gastritis	Yes	2(4.5)	37(5.2)	39	0.59	0.86	0.20 – 3.70
	No	42(95.5)	670(94.8)	712			
Peptic Ulcer	Yes	7(15.9)	53(7.5)	60	0.05*	2.33	0.99 – 5.48
	No	37(84.1)	654(92.5)	691			
Esophagitis	Yes	10(22.7)	185(26.2)	195	0.38	0.83	0.40 – 1.71
	No	34(77.3)	522(73.8)	556			

*p ≤0.05; F= frequency; OR= Odds Ratio; CI 95% = 95% confidence interval

Discussion

The present study revealed that family history of gastric cancer was present in 5.9% of patients and the majority was female, aged 45 years or older. The influence of family history of gastric cancer on susceptibility to GC may differ according to sex. A review study showed that women with a first-degree family history of gastric cancer were associated with an increased risk of developing GC.[20]

The age limit for risk of developing CG may differ between the high and low risk regions, approximately 45 years and 50 years of age, respectively.[6] In individuals with family history the limit is 50 years of age, or about 10 years younger than the first degree relative at diagnosis.[7]

It was evident in this study that dyspeptic patients over 45 years of age were more likely to be married, have lower educational levels, and smoke. Advanced age,[3] low education[21] and smoking[22] are relevant risk factors for the development of CG. Thus, health actions must be developed to support discontinuation of smoking, by providing comprehensive assistance, appropriate to the age and education of patients, in order to prevent the onset of GC.

The current study showed that dyspeptic patients aged 45 years or younger were more likely to be alcohol users and have endoscopic gastric mucosal changes. Studies have suggested that excessive alcohol consumption is associated with an increased risk of CG.[23,24] Therefore, health actions that guide dyspeptic patients with gastric mucosal changes in reducing alcohol consumption may be favorable for GC prevention.

A well-established hypothesis for the development of GC arises from the progression of precursor lesions, in which chronic inflammation of the gastric mucosa (chronic gastritis) progresses to gastric cancer, including pre-neoplastic conditions such as atrophic gastritis, intestinal metaplasia and dysplasia.[25]

The most frequent endoscopic alteration in patients with a family history of gastric cancer was gastritis, and these patients had a greater chance of endoscopic alterations of the gastric mucosa, even after adjustments in the analysis. These data reinforce the need for endoscopic surveillance in this group of patients, as a preventive strategy.

Dyspeptic patients with family history of gastric cancer included in this study had higher chances of being infected with *H. pylori*, in uni- and multi-variate analyses. These data suggest intrafamilial transmission of the bacterium and reinforce the need for *H. pylori* eradication and confirmation of elimination of the infection, in order to control transmission and reduce long-term complications.

The form in which *H. pylori* is transmitted is still uncertain, suggesting that the main route is interpersonal transmission, whereas environmental transmission via contaminated water and food remains possible.[26] Studies show that the family environment seems relevant in person-to-person transmission, especially mother-to-child, as most *H. pylori* infections occur in childhood and result in the onset of gastric diseases in adulthood.[17,27]

Patients with a family history of gastric cancer showed a higher chance of not being diagnosed with peptic ulcer disease. These data are in agreement with a study by Nishizawa et al.,[28] who found that a first-degree family history of gastric cancer, absence of peptic ulcers, and advanced age were independent risk factors for gastric atrophy in patients infected with *H. pylori*.

The limitations of this study include a sample from a single endoscopy service. As this was a cross-sectional study, follow-up of the studied patients was not possible. The information about the family history of gastric cancer was collected based on the patients' memories, which could result in a memory bias.

Recognizing the relevant risk factors for the development of gastric cancer among patients with dyspeptic symptoms contributes to expanding and improving the role of public health nursing in education, practice, and research. It also supports efforts to develop policies and protocols for surveillance, treatment, and prevention of gastric cancer, especially for groups of patients at higher risk for developing the disease, such as family members of those with gastric cancer.

Conclusion

The study showed that patients with dyspeptic symptoms with a family history of gastric cancer were more likely to present changes in the gastric mucosa and infection by *H. pylori*, relevant risk factors for the development of gastric cancer. Considering the findings of this study, health care protocols for better investigation and surveillance of gastric cancer relatives are necessary, as well as health education actions to guide patients regarding screening for and prevention of gastric cancer.

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Collaborations

Rodrigues MCP, Lima VP, Monari FF, Silva RA, Teles LMR, Beserra EP, Lima MA e Serra MAAO contributed to the study design, data analysis and interpretation, article writing, relevant critical review of the intellectual content and approval of the final version to be published.

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