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ALIMENTARY FACTORS IN THE DEVELOPMENT OF GASTRIC INTESTINAL METAPLASIA IN FUNCTIONAL DYSPEPTIC PATIENTS

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ABSTRACT – ***Context*** - Intestinal metaplasia of the stomach is a lesion in which metaplasia of gastric epithelial cells occurs for an intestinal phenotype. Gastric intestinal metaplasia is a lesion associated with an increase in the risk of gastric carcinoma development. Epidemiologic studies indicate a relation between dietary habits and stomach cancer development, some habits increasing the risk for it, and others have a protective effect, suggesting that antioxidants, such as vitamins A, C, and E, decrease the risk of this type of cancer. The relationship of these alimentary factors and intestinal metaplasia is unknown. ***Methods*** - It is a case-control, observational study in which 320 patients with functional dyspepsia, divided in two groups, were assessed. The case I group (individuals with intestinal metaplasia) had their dietary pattern compared to that of the control group, constituted of individuals similar to those in the case group but without intestinal metaplasia, through a food frequency questionnaire. ***Results*** - The analysis of the dietary pattern of functional dyspeptic patients with intestinal metaplasia, and its comparison with those without intestinal metaplasia, showed a higher frequency of canned and smoked foods consumption in the first group and, on the other hand, a higher consumption of fruits and vegetables in patients without intestinal metaplasia. No effect of salt consumption was detected. ***Conclusions*** - The results obtained in this study suggest changes in the diet, with a decrease in the consumption of smoked and canned foods, and an increase in the consumption of fruits and vegetables, can lead to a diminution of gastric intestinal metaplasia cases.

HEADINGS – Metaplasia. Intestines. Stomach. Dyspepsia. Food habits.

INTRODUCTION

The functional gastrointestinal illnesses are recognized public health problems. They are characterized by a series of conditions and chronic gastrointestinal symptoms that cannot be explained by structural alterations or possible identification by the currently clinical available tests[1, 28]. The term dyspepsia is used to define recurrent or persistent symptoms of discomfort and/or pain in the upper abdomen[1, 28].

The etiological factors involved in the genesis of the gastric cancer are not entirely known. Epidemiological studies demonstrate the importance of ambiental factors, especially alimentary, in its pathogenesis. A factor that has been investigated in gastric oncogenesis is the infection by *Helicobacter pylori* leading to chronic gastritis, atrophy of the mucosa and intestinal metaplasia; having, thus, participation in the chain of events leading to gastric cancer[6, 21, 23].

The alimentary factors of increased risk more are salty diets, smoked fish, high nitrate content (the nitrates are converted in carcinogenic nitrates by the intestinal bacteria)[12, 17, 29].

Raw vegetable consumption, citric fruits and breads with high fiber are associated to a lesser risk of gastric cancer. The ascorbic acid and β-carotene, found in fruits and vegetables, act as antioxidants and the ascorbic acid also can prevent the nitrates conversion into nitrites[4, 17].

The atrophic chronic gastritis and the intestinal metaplasia (IM) are associated with this neoplasm. The pre-neoplastic states, such as atrophic chronic gastritis and intestinal metaplasia would evolve into dysplasia and this for the cancer in about 10% of the cases, after many years[14, 18].

The IM of the stomach is an injury that consists of the transdifferentiation of the gastric epithelial cells into an intestinal phenotype. The gastric IM is

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considered a pre-neoplastic injury that is associated with an increased risk of gastric carcinoma[5, 22].

The process of intestinal differentiation that occurs in the gastric mucosa is dependent of the expression of the gene homeobox CDX2 - a factor of crucial transcription for the intestinal differentiation in such a way in its normal localization, the intestine, as in other tissues[19, 26].

Free radicals are produced by chemical modifications of proteins, lipids, carbohydrates and nucleotides, resulting in a variety of biological consequences, including injury, mutations, carcinogenesis, impaired immune system, diseases and cell death[8, 11, 21].

The continuous production of free radicals during the metabolic processes led to the development of many mechanisms of antioxidant defense to limit the intracellular levels and to hinder the induction of damages[10, 21, 27].

The antioxidant substances are a heterogeneous group consisting of vitamins, minerals, pigments and other vegetal composites; are also enzymes, acting these as blocking agents of the harmful effects of the free radicals[24, 25, 30, 31].

There are also indications that a diet consisting of fresh vegetables and fruits is protective in numerous studies suggesting that antioxidants such as vitamins A, C and E, reduce the risk of gastric cancer[4, 11].

This study aimed to evaluate the potential relationship between these dietary factors and the development of gastric intestinal metaplasia in functional dyspeptic subjects.

METHODS

Delineation

A case-control, observational, longitudinal, analytical study, in which a group I cases (individuals with intestinal metaplasia) has its dietary patterns compared to the group of individuals similar to the case group, called the control (without intestinal metaplasia) through a questionnaire of food frequency.

Population and sample

Functional dyspeptic patients were evaluated at The HEROES (Helicobacter Eradication Relief of Dyspeptic Symptoms) trial was a randomized double-blind, placebo-controlled clinical trial. The study was conducted in a single academic hospital, the Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil. The local institutional review board approved the trial protocol. Written informed consent was obtained from all patients prior to enrollment The research project (05-422) and informed consent were approved, on 21/12/2005, by the Scientific and Research Committee and Ethics in Health Research Group and Graduate Hospital de Clínicas de Porto Alegre.

Inclusion criteria

Included patients with more than 18 years of age with the clinical criteria for functional dyspepsia according to Rome III Consensus, which includes pain or discomfort centered in the upper abdomen for a period equal to or greater than 3 months, or with normal endoscopies or only with endoscopic gastritis according to Sydney classification[15].

Any diagnosis of metaplasia was confirmed histologically. Three biopsy specimens were obtained from the body of the stomach, three from the antrum, and two from the incisura angularis. One specimen from each anatomical region was used for the urease test, and the others were used for histologic examination by two pathologists.

Description of methods for assessment of dietary patterns

The evaluation of the alimentary pattern was performed using the Frequency Questionnaire Food Consumption, a qualitative instrument, which includes a list of foods, and we analyzed the frequency of daily intake, 3-4 times a week, 1-2 times a week, less than once a week, less than in a month or never.

Statistical analysis

The variables were divided into two groups where daily and 3-4 times per week were considered high intake, and 1-2 times a week, less than once a week, less than in a month or never were considered low intake.

Continuous variables were expressed as means and standard deviations and comparison groups were analyzed using the *t* test for independent samples. Qualitative variables expressed as percentages and comparisons analyzed using Fisher's exact test. All tests two-tailed, and $P<0.05$ were considered statistically significant. Multivariate analysis with logistic regression was obtained.

RESULTS

We evaluated 320 patients with functional dyspepsia, 70 of these patients had intestinal metaplasia, which corresponds to 21% of the population studied.

In Table 1 we list the pattern of food consumption by patients with and without intestinal metaplasia.

Salt intake was subjected to qualitative assessment by having patients taking them offered three response options, which were: little, moderate or high salt intake; 55% of patients with intestinal metaplasia rated their salt consumption as moderate, the patients without intestinal metaplasia chose this same alternative in the proportion of 61%, this difference was not significant according to Fisher's exact test.

TABLE 1. Pattern of food consumption by patients with and without intestinal metaplasia

Frequency of consumption		Group		n	OR
		Without metaplasia	With metaplasia		
Food 1	Low consumption	81	33	114	1,861 (1,089-3,181)
	High consumption	169	37	206	
Total		250	70	320	
Food 2	Low ingestion	168	57	225	2,140 (1,117-4,094)
	High consumption	82	13	95	
Total		250	70	320	
Food 3	Low ingestion	101	42	143	2,213 (1,293-3,788)
	High consumption	149	28	177	
Total		250	70	320	
Food 4	Low ingestion	181	55	236	1,398 (0,746-2,617)
	High consumption	69	15	84	
Total		250	70	320	
Food 5	Low ingestion	234	24	258	28,031 (13,884-56,588)
	High consumption	16	46	62	
Total		250	70	320	
Food 6	Low ingestion	193	47	240	0,604 (0,339-1,073)
	High consumption	57	23	80	
Total		250	70	320	
Food 7	Low ingestion	236	57	293	0,260 (0,118-0,575)
	High consumption	14	13	27	
Total		250	70	320	
Food 8	Low ingestion	127	18	145	3,032 (1,687-5,444)
	High consumption	121	52	173	
Total		250	70	320	

Food 1: fruits in general; Food 3: green vegetables; Food 5: smoked foods; Food 7:canned foods;
Food 2: citric fruits; Food 4: yellow vegetables; Food 6:embedded foods ; Food 8: cheeses;
OR: odds ratio

It was noted that the consumption of alcohol and tobacco were also surveyed showing no statistical differences between the groups surveyed.

DISCUSSION

Intestinal metaplasia, has been studied mainly in a descriptive ways. Although said to be a precancerous condition, a functional link between intestinal metaplasia and carcinogenesis remains speculative. However, intestinal metaplasia has been considered a risk factor for the development of intestinal-type gastric adenocarcinoma. It is known that genetic, environmental and food are involved. However, a precancerous lesion takes about 20 years to develop into the severe form. Thus, the most effective measure to reduce the risk factors in relation to food is a balanced diet starting early, in childhood[19, 22].

As shown in Table 1 (food 1 and 2) can be observed that a high frequency of consumption of fruits in general and citrus fruit, these foods have a protective effect on relation to the development of intestinal metaplasia, as evidenced by the OR = 1.861 CI = 1.089 to 3.181.

Studies have shown that diets rich in vegetables and fruits is associated with low incidence of chronic degenerative diseases, such as some types of cancer (lung, breast, prostate) and cardiovascular diseases, photoprotective effects, as well as the effects of feminine hormone replacement therapy[4, 11, 20].

It is widely known that the consumption of vegetables helps to reduce the risk of gastric cancer. However, the incidence rates of gastric cancer remain high in some populations, such as Japan and Korea, despite a high intake of total vegetables. This may be due to the fact that Japanese and Koreans consume vegetables mainly processed as salted

or pickled vegetables instead of fresh vegetables[2, 9]. In our study we evaluated the frequency of intake of green and yellow vegetables, and it was observed that the high frequency of consumption of green vegetables denoted an inverse correlation to the development of intestinal metaplasia, as evidenced in Table 1 (food 3), however in yellow vegetables (food 4) there were no significant differences between the groups.

In a population-based study conducted by Kim et al.[9] they analyzed the consumption of fresh vegetables and of pickled vegetables, relating them to the risk of gastric cancer[9]. It was observed that a high intake of fresh vegetables was significantly associated with a decreased risk of gastric cancer, but that a high intake of pickled vegetables was significantly associated with an increased risk. The results of this 2010 study show that a high intake of pickled vegetables may increase the risk for gastric cancer and suggest that a high intake of fresh vegetables is important for reducing the risk of gastric cancer. In our study, we found the frequency of consumption of individuals, although there were no significant differences between groups in relation to consumption of canned food in general (Table 1 food 7) and the development of intestinal metaplasia.

The most consistent inverse association which can be detected in epidemiological studies, refers to a higher consumption of fruits and vegetables, especially dark green color and yellow-orange, or high serum β-carotene, and low rates of cancer[3, 7, 13].

In the present study, we found a significantly higher risk of developing intestinal metaplasia in patients whose food intake frequency of smoking foods was high, v.g., daily, or about 3-4 times a week, as seen in Table 1 (food 5).

Among the foods identified as those that increase the risk are primarily the smoked foods, cured meats and other foods preserved in salt.

Foods with high nitrate content, foods cured, tinned, with dyes or conserved in salt are factors of risk for this type of cancer. Other factors as the conservation of foods and the water ingestion from wells that also contain high nitrate concentration are related with the incidence of stomach cancer[16, 30].

More recently begun to be recognized the potential carcinogenic effects of nitrosamines and nitrosamides, generically called N-compounds, substances formed in the interaction between a group of secondary nitrogen (which can be an amine or amide, a urea or an alkyl-ring peptide) and a nitrite. The evidence that the populations most at risk for gastric cancer have diets rich in substrates for the process of endogenous N-compounds triggered the interest in the evaluation of these substances in the genesis of gastric cancer[6].

The N-nitroso compounds, the main source for most people, the endogenous formation, a process that can be inhibited by polyphenols. A case-control study in Mexico City in 2004-2005, including 257 cases with gastric cancer (histologically confirmed) and 478 controls was conducted to estimate the risk of gastric cancer in relation to individual and combined consumption of polyphenols and precursors N-compounds[6]. The intake of polyphenols, nitrate and nitrite were estimated by a food frequency questionnaire. High intake of secoisolariciresinol and coumestrol cinnamic acids were associated with a reduction of about 50% in the risk of gastric cancer. A high intake of total nitrite and nitrate and nitrite animal doubled the risk of gastric cancer.

The odds ratio of about 2 times was observed among individuals with low consumption of cinnamic acids, secoisolariciresinol and coumestrol and high intake of nitrate or nitrite animal, compared with a high intake of polyphenols and nitrate low consumption of animals or nitrite, respectively[6].

By analysis of Table 1 (food 6 and 7), regarding the frequency of consumption of embedded foods and canned foods, there was no statistical significance between the groups with and without metaplasia.

In this study, a relationship between salt intake and intestinal metaplasia was not observed, since, in both groups, most patients rated their daily salt consumption as moderate, with this, there were no significant differences between them.

Work done by Dias-Neto et al.[2], sought the association between salt intake and precancerous lesions and how they can help to clarify the causal relationship to gastric cancer. They systematically reviewed 17 articles addressing the association between dietary salt exposure and gastric intestinal metaplasia and performed a meta-analysis. Exposure to salt was estimated by evaluating the consumption of salty foods, preference for salty foods, salt use and urinary excretion of sodium. The odds ratio of 1.68 with (CI) = 0.98 to 2.90, I (2) = 55.4% for the association between salted salty/and intestinal metaplasia (four studies) and OR was 1.53 (95% CI = 0.72 to 3.24, I (2) = 76.8%), preferably salt. There was a positive association but not statistically significant between intestinal metaplasia and urinary sodium excretion.

The preference for salty meals may increase the risk of developing stomach cancer. Evaluating more than 2.2 million Koreans ages 30 to 80, researchers found that a diet high in salt can increase by 10% the chances of developing the disease. In the study, 9,620 men and 2,773 women who had the disease prefer a saltier diet[9].

CONCLUSIONS

We found that foods such as canned and smoked have higher consumption in patients with intestinal metaplasia,

indirectly supporting the hypothesis that they can act as potential carcinogens.

Patients without intestinal metaplasia have a significantly higher consumption of fruits and vegetables in general.

Cheese consumption, showed a greater tendency to consumption in patients with metaplasia, in contrast patients without metaplasia had a larger trend in the consumption of legumes.

In relation to the consumption of salt our results do not corroborate a role in the process of gastric intestinal metaplasia.

We conclude that dietary modification by reducing the intake of foods such as smoked and canned, as well as the increased intake of fruits, may represent a practical strategy to prevent gastric cancer by decreasing case of intestinal metaplasia.

Further investigation of these associations in prospective cohort studies are needed.

Taborda AG, Prolla JC. Fatores alimentares envolvidos no desenvolvimento de metaplasia intestinal em dispépticos funcionais. Arq Gastroenterol. 2012;49(3):208-13.

RESUMO – ***Contexto*** - A metaplasia intestinal do estômago é uma lesão onde ocorre a metaplasia das células epiteliais gástricas para um fenótipo intestinal. A metaplasia intestinal gástrica é considerada uma lesão associada ao aumento do risco de desenvolvimento de carcinoma gástrico. Estudos epidemiológicos indicam uma relação entre hábitos alimentares e o risco de desenvolvimento de câncer de estômago: tanto podendo ter efeito carcinogênico gástrico, como fator protetor, sugerindo que os antioxidantes como as vitaminas A, C e E diminuem o risco desse tipo de câncer. Não se conhece a influência desses fatores alimentares na metaplasia intestinal gástrica. ***Material*** - Trata-se de estudo caso-controle, observacional, para o qual foram avaliados 320 pacientes com dispepsia funcional, separados em dois grupos, um grupo de casos I (indivíduos com metaplasia intestinal) teve seus hábitos alimentares comparados aos do grupo de casos-controle (sem metaplasia intestinal), através de um questionário de frequência de consumo alimentar. ***Resultados*** - Ao analisarmos o padrão alimentar dos pacientes dispépticos funcionais com metaplasia intestinal e compará-lo com o padrão daqueles que não possuem metaplasia intestinal, constatou-se que os pacientes com metaplasia intestinal consomem mais alimentos como os enlatados e defumados, enquanto os pacientes sem metaplasia intestinal apresentam consumo expressivamente maior de frutas em geral e vegetais. Diferença no padrão de consumo de sal não foi identificada. ***Conclusões*** - Através dos resultados obtidos no presente estudo podemos supor que a modificação da dieta, por meio da diminuição na ingestão de alimentos como defumados e enlatados e acréscimo na ingestão de frutas e vegetais pode levar a diminuição de casos de metaplasia intestinal.

DESCRITORES – Metaplasia. Intestinos. Estômago. Dispepsia. Hábitos alimentares.

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