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Prevalence of Family History of Cancer among Gastric Cancer Patients at Brazilian National Cancer Institute

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Abstract

Background: Gastric cancer is the third most incident malignancy and the fifth leading cause of death in the world. In Brazil, it is the fourth most common tumour in men and the fifth in women. Familial aggregation of this tumour is being studied and discussed by experts. **Aim:** Determine the frequency of family history of cancer in patients with gastric cancer, suggesting familial aggregation or increased risk for hereditary cancer syndromes. **Methods:** This is a retrospective cross-sectional study carried out from January 2011 to March 2015 at the Department of Abdominal and Pelvic Surgery of the Brazilian National Cancer Institute (INCA). Data were collected from electronic medical records and analyzed using SPSS Statistics® version 20. **Results:** 873 patients with gastric adenocarcinoma were analyzed. A family history of cancer was reported by 451 patients (51.6%), which reported cancer in 878 relatives, of which 110 (12.6%), reported having more than three relatives with any type of cancer. The most prevalent malignancies among these relatives were gastric cancer (21.3%) and breast cancer (9.5%). **Conclusion:** Most of the patients had cancer family history, being gastric cancer the most common. The high percentage of cancer family history confirms the importance of collecting this information, whose lack reflects professional negligence, as family history study can serve as a low-cost tool, favoring prevention and early diag-

nosis, situations where morbidity and mortality are smaller, thus reducing health costs and assistance and preserving lives.

Keywords

Stomach Neoplasms, Family History, Hereditary, Aggregation, Hospital Records, Cross-Sectional Studies

1. Introduction

Gastric cancer is a national and worldwide public health problem [1], prevalent in developing countries, becoming the fifth most prevalent malignancy and the third in mortality in the world, affecting about twice the men [2]. In Brazil, it is the fourth most incident in men and the fifth in women. For the biennium 2016/2017, it is estimated 12,920 new cases in men and 7600 in women [3].

There are many factors associated with this type of cancer, such as: smoking, alcohol consumption, sedentarism, obesity, diet poor in fibers and rich in food preservers (sodium, nitrate and nitrite), infections such as those caused by *Helicobacter pylori* or Epstein-Barr virus, presence of comorbidities (atrophic gastritis, pernicious anemia), in addition to familial aggregation and hereditary factors [4] [5].

Familial cancer aggregation or "familial cancer" is evidenced by the familial recurrence of some common types of cancer, without a definite pattern of inheritance and high frequency of multiple tumours and at an early age, etiologically caused by a combination of environmental and genetic factors (risk-modifier polymorphisms). Hereditary cancer syndromes, in turn, include hundreds of relatively rare inherited syndromes and of monogenic etiology [5].

A small percentage of gastric tumours occur as part of hereditary predisposition syndromes. In addition to the Hereditary Diffuse Gastric Cancer (HDGC), the main responsible syndromes are Lynch, Peutz-Jeghers, Li-Fraumeni, Cowden, Familial Adenomatous Polyposis (FAP), MUTYH-Associated Polyposis (MAP) and Juvenile Polyposis [6].

There are specific features within a family that suggests the possibility of hereditary cancer syndrome, associated genetic mutations. Among these features there are: cancer diagnosed at early age; autosomal dominant inheritance (successive affected generations); several cases of cancer linked to an individual (breast cancer and ovarian cancer or colon cancer and endometrial cancer); a family member or more than one primary cancer; bilateral cancer in paired organs; occurrence of more than one rare tumour in a family (sarcomas, brain tumors) and male breast cancer [7].

Knowledge of the cancer family history and checking the consistence of this information in daily clinical practice is an important support tool for the genetic counseling of families at risk, hence the importance of knowing it by collection

and, if possible, confirmation of the information obtained. Documentation of the family health history is the basis of any risk assessment and implementation of preventive measures [7] [8].

Since the positive family history is a recognized risk factor for several chronic diseases like cancer, knowing the family history is important to program the monitoring of people at increased risk of developing malignant tumours and in some cases, in the prevention. This study aimed to determine the frequency of the cancer family history in gastric adenocarcinoma patients suggestive of familial aggregation or at increased risk of syndromes.

2. Methods

Retrospective sectional study, carried out at the Abdomino-Pelvic Surgery Division of Brazilian National Cancer Institute, after approval on the Institutional Review Board (IRB) of the Brazilian National Cancer Institute.

Data were collected from electronic medical records of all the patients admitted for treatment of gastric adenocarcinoma in the period from January 1st, 2011 to March 13th, 2015 resulting in a sample of 873 cases. All the patients with another histologic type of gastric cancer were excluded from this work and also, patients under 18 years old.

For data collection, we used a structured questionnaire with the variables: gender, age, color (according to the classification of the Brazilian Institute of Geography and Statistics-IBGE), educational level, marital status, household income, Performance Status based on the Eastern Cooperative Oncology Group-ECOG assigned at the time of hospital admission, blood type and Rh factor, smoking (defined as anyone who smokes at least 1 cigarette per day for 6 months or more), alcohol intake (an alcohol drinker as anyone who drinks beer, wine and/or hard liquor for at least 3 times per week during 6 months or more), *Helicobacter pylori* infection, tumor location, histopathological type and degree of cell differentiation, Lauren classification (microscopic), Borrmann classification (macroscopic), presence of signet ring cells, tumor staging (TNM) based on the 7th edition of the International Union Against Cancer-American Joint Committee on Cancer and cancer history family. We considered first-degree (parents, children, and full siblings) and second-degree relatives (grandparents, aunts/uncles, nieces/nephews, grandchildren, and half siblings).

The data bank was elaborated using SPSS Statistics^{TM} version 20 (Statistical Package for the Social Sciences*)*. Descriptive analysis was conducted with absolute and relative frequencies, standard deviation, mean and median.

3. Results

Sociodemographic status of the patients of our sample is shown in **Table 1**. Most of the patients in the study were male (61.4%), with ages ranging between 23 and 99 years (B = 63.7 years; median = 64 years; SD ± 12.5), light brown (42.4%), married (64.4%), with low education (77%) and low household income (32.9%).

Table 1. Sociodemographic characteristics of patients admitted for gastric for treatment of gastric adenocarcinoma (n = 873) at the Brazilian National Cancer Institute. Rio de Janeiro, 2015.

Variable	n	%
Gender		
Female	337	38.6
Male	536	61.4
Age		
23 - 40	37	4.2
41 - 60	279	32.0
61 - 99	557	63.8
Colour		
White	366	41.8
Light Brown	370	42.4
Black	130	15.0
Yellow/Oriental	2	0.2
Not informed	5	0.6
Marital Status		
Unmarried	99	11.3
Married/Consensual Union	562	64.4
Divorced/Separated	68	7.8
Widow	140	16.0
Not informed	4	0.5
Educational level		
None	502	57.5
Elementary	170	19.5
High School	137	15.7
Higher Education	38	4.3
Post graduate	6	0.7
Not informed	20	2.3
Household income		
None	51	5.8
Up to 01 minimum wage	287	32.9
01 - 02 minimum wages	246	28.2
03 - 05 minimum wages	163	18.7
06 - 10 minimum wages	23	2.6
>10 minimum wages	11	1.3
Not informed	92	10.5
Total	**873**	**100**

With regard to data related to patients's clinical information, (Table 2), most patients had their symptoms started between 3 and 6 months prior to the admission date for oncologic treatment at the institution (26.5%) and they also had ECOG-Perfomance Status I (54.1%). Most of them were smokers (49.8%), drank

Table 2. Clinical characteristics of patients admitted for treatment of gastric adenocarcinoma (n = 873) at Brazilian National Cancer Institute. Rio de Janeiro, 2015.

Variable	n	%
Smoking		
Yes	435	49.8
No	338	38.7
Not Informed	100	11.5
Alcohol intake		
Yes	456	52.2
No	317	36.3
Not Informed	100	11.5
ECOG Performance Status		
0	88	10.1
I	472	54.1
II	119	13.6
III	31	3.6
IV	6	0.6
Not informed	157	18.0
Blood Type		
O+	279	31.8
O−	23	2.6
A+	225	25.8
A−	26	3.0
AB+	25	2.9
AB−	2	0.2
B+	75	8.6
B−	4	0.5
Not informed	214	24.6
Time from symptom onset		
<3 months	108	12.4
3 - 6 months	231	26.5
7 - 9 months	97	11.1
10 - 12 months	139	15.9
>12 months	120	13.7
Not Informed	178	20.4
***H. pylori* infection**		
Yes	120	13.7
No	213	24.4
No informed	540	61.9
Total	**873**	**100**

alcoholic drinks (52.2%) and had blood type O+ (31.8%). As for the *Helicobacter pylori* infection, most records (61.9%) did not include any information about the presence of this infectious agent.

As to the anatomopathololological characteristics (**Table 3**), most of the tumours affected the distal third of the stomach (30.8%) with some affecting the middle and distal parts (24.6%), with histopathological diagnosis of poorly differentiated adenocarcinoma (59.36%), with signet-ring cell (40%), Borrmann III (29.3%), stage IV (22.5%). Of 873 cases in this sample, 105 were classified according to Lauren's classification as the diffuse type gastric cancer (12%).

Cancer family history (**Table 4**) was reported by 451 patients (51.6%), of which reported of 878 relatives, 551 of first-degree and 327 of second-degree. Of these 451 patients, 110 (12.6%) reported having more than three relatives with any type of cancer. Among them, the most prevalent neoplasia were gastric cancer (21.3%) and breast cancer (9.5%).

4. Discussion

Sociodemographic characteristics of this study are in accordance with those described in the literature. Gastric cancer affects men more frequently than women, usually over 40 years of age, with a peak incidence ranging between 50 and 70 years, being more prevalent in groups of low socioeconomic status and low educational level [9] [10] [11] [12]. Low socioeconomic status is a variable also associated with other risk factors as high salt intake, *Helicobacter pylori* infection, and greater difficulty in accessing health services, which results in diagnostic delay, reducing patients' survival and quality of life [13].

Considering clinical and anatomopathological data, our findings corroborate those of the literature [4] [9] [10] [11] [13]. The most common blood group was the group O (34.4%), as found by Yaghoobi *et al.* (68.1%) [14]. However, in other studies the group A+ was the most common [16] [17] [18].

The research shows a high percentage of lack of fulfillment in some variables of interest, similar to those of the clinical and anatomopathological features, affecting some statistical analysis of the study. Statistical analysis is not only a fundamental tool to disclose epidemiological and clinical profile of the diseases, but also plays a pivotal role on the elaboration of indicators, analysis of trends, and indication of priorities and, consequently, planning of actions [19] [20].

Our results show a high percentage of cancer reference in the family history, since more than 50% (n = 451) reported having at least one relative with cancer and 110 patients (24.4%) reported having more than three relatives with any type of malignancy. It is well known that about 90% of gastric tumour cases are sporadic and only 10% have familial aggregation of cancer [21] [22]. Kawasaki *et al.* (46.4%) [23], Minami *et al.* (26.1%) [24], Bernini *et al.* (18.5%) [25], Yu *et al.* (9.61%) [26], La Vechia *et al.* (12.6%), [27] e Dhillon *et al.* (11.1%) [28] also reported high familial aggregation of cancer. In addition, 51.6% of patients reported cancer family history in first and second-degree relatives. Bernini *et al.* (70, 8%) [25], Kawasaki *et al.* (46.4%) [23] and Yu *et al.* (35.6%) [26] also reported

Table 3. Anatomopathological characteristics of patients admitted for treatment of gastric adenocarcinoma (n = 873) at Brazilian National Cancer Institute. Rio de Janeiro, 2015.

Variable	n	%
Tumour location		
Proximal	40	4.6
Middle	160	18.3
Distal	269	30.8
Proximal and middle	60	6.9
Proximal and distal	5	0.6
Middle and distal	215	24.6
3 thirds	82	9.4
Not informed	42	4.8
Cell differentiation grade		
Poorly differentiated	520	59.6
Moderately differentiated	283	32.4
Well differentiated	39	4.5
Not informed	31	3.5
Presence of signet-ring cells		
Yes	349	40.0
No	10	1.1
Not informed	514	58.9
Lauren's classification		
Diffuse	105	12.0
Intestinal	88	10.1
Mixed	10	1.1
Not informed	670	76.8
Borrmann's classification		
I	25	2.9
II	110	12.6
III	256	29.3
IV	154	17.6
V	6	0.7
Not informed	322	36.9
Staging (TNM)		
0	4	0.5
I A	51	5.8
I B	34	3.9
IIA	50	5.7
IIB	41	4.7
IIIA	43	4.9
IIIB	52	6.0
IIIC	69	7.9
IV	196	22.5
Not informed	333	38.1
Total	**873**	**100**

Table 4. Distribution of the tumours in the first-degree and second-degree relatives (n = 878) of the patients admitted for treatment of gastric adenocarcinoma at the Brazilian National Cancer Institute. Rio de Janeiro, 2015.

Type of cancer	Firs-degree relative (n)	%	Second-degree relative (n)	%
Gastric	124	22.5%	63	19.3%
Breast	57	10.3%	26	8.0%
Prostate	49	8.9%	15	4.6%
Colorectal	41	7.4%	22	6.7%
Head and Neck[1]	39	7.1%	41	12.5%
Lung	33	6.0%	18	5.5%
Cervical	29	5.3%	19	5.8%
Esophageal	24	4.4%	5	1.5%
Hematological	27	4.9%	5	1.5%
Liver	16	2.9%	6	1.8%
Skin	13	2.4%	12	3.7%
2 types of cancer[2]	12	2.2%	1	0.3%
CNS	12	2.2%	10	3.1%
Gallbladder	8	1.5%	1	0.3%
Pancreas	8	1.5%	1	0.3%
Bone	8	15%	6	1.8%
Kidney	8	1.5%	1	0.3%
Penis	3	0.5%	1	0.3%
Vagina	3	0.5%	0	0.0%
Bladder	2	0.4%	2	0.6%
Testicle	2	0.4%	0	0.0%
Ovary	1	0.2%	3	0.9%
Vulva	1	0.2%	1	0.3%
Spleen	0	0.0%	1	0.3%
Unknown site	31	5.6%	67	20.5%
Total	**551**	**100%**	**327**	**100%**

[1]Head and Neck: Mouth, Laryngeal. [2]First degree relative: Breast + Laryngeal (n = 3), Bladder + Skin (n = 1), Breast + Skin (n = 1), Breast + Liver (n = 1), Gastric + Prostate (n = 1), Gastric + Cervical (n = 1), Gastric + Lung (n = 1), Skin + HN (n = 1), Intestine+Prostate (n = 1), Prostate+Lung (n = 1). Second degree relative: Intestine + Laryngeal (n = 1).

high percentages. These studies are from Italy, Japan and China respectively. In Italy, the problem was related to the genetic susceptibility to the ethnicity. In Japan and China, it was associated with the high incidence of gastric cancer in these countries.

About 1% to 3% of diffuse gastric cancers are attributed to the CGDH syndrome [10]. Of 451 patients with cancer family history, 141 patients (31.26%) had at least one relative at any degree affected by gastric cancer. Relatives of individuals with gastric cancer of the diffuse type have a 7-fold increased risk of

developing the same disease, while relatives of individuals with the same intestinal type have a 1.4-fold increased risk of developing gastric adenocarcinoma compared with the remainder of the population [29]. A positive family history of gastric cancer is present in 10% to 15% [7] of cases, and is associated with a 1.5 to 3.5-fold increased risk of developing this neoplasia, compared with the general population [11]-[30]. Individuals with affected first-degree relatives have a 2 to 4-fold increased risk [30].

In the findings of our study, most of the reported tumours (35.3%) in the cancer family history affected some of the digestive tract organs (stomach, esophagus, liver, pancreas, colon and rectum). Due to the lack of documents that confirm consistent recorded information, it emphasizes that the patient presumed the tumour location. Despite the lack of a confirmed diagnosis, these data give rise to suspicion of cancer family risk in the sample used for this study. High percentages like this one in our study were also referred by Kawasaki *et al.* (70.9%) [23] and Yu *et al.* (74.9%) [26].

Gastric cancer was the most cited tumour by relatives of patients in the sample (n = 187; 21.3%). Bernini *et al.* (21.9%) [25], Kawasaki *et al.* (40, 9%) [23], Yu *et al.* (23, 8%) [26] and Minami *et al.* (26.1%) [24], also found high percentages of gastric cancer among relatives of patients in their studies. Dhillon *et al.* affirm that, even after adjusting for other risk factors, such as age, race, smoking and body mass index [28], the family history of gastric cancer increased the risk of developing this type of tumour in patients.

In our study, breast cancer was the second most common cancer diagnosed among the relatives (n = 83; 18.3%). It can be justified by its high incidence in Brazil and in the world [2] [3]. Breast and gastric cancer can also occur together in other syndromes non-CGDH, such as Li-Fraumeni, Cowden, Peutz-Jeghers and Lynch [31]. In our study, there was no evidence of relationship between breast cancer and HDGC syndrome since lobular histological type was not confirmed in the registered reports of patients and relatives.

The variable age also draw attention to possible investigations, since 37 patients were diagnosed with gastric cancer before age 40, representing 4.2% of the whole sample (n = 873), which met one of the criteria for suspictions of some hereditary cancer predisposition syndrome [32] [33].

Familial aggregation of cancer shows greater frequency of diffuse type gastric cancer than the intestinal type [29], which is confirmed in our study, since the diffuse-type of adenocarcinoma was diagnosed in 105 patients (12%). Of these, 12 cases were diagnosed before age 40, fulfilling thus one of the criteria for the CGDH syndrome [7]. It should be noted that missing data in this variable was observed in 76.8% (n = 670) of cases.

This study suffered from limitations for having collected retrospective and secondary data, as well as other studies [24] [25]. For example, we have failed to ascertain the age in which relatives were affected by cancer. Accuracy of the self-reported cancer family history is over 75% for first-degree relatives. However, it may not be so, as far as more distant relatives are concerned, with varia-

tions ranging between 50% and 80%, depending on the type of cancer [8]. Even then, this does not diminish the importance of family history collection, since a positive family history of cancer is necessary for referral of patients and their families to a Clinical Genetics unit in order to receive genetic counseling and specialized follow-up [7] [8] [9] [10].

5. Conclusions

We concluded that 51.6% of the patients had cancer family history in first or second-degree relatives. The reported tumours involved mostly digestive system organs (35.3%), confirming that family history of digestive system cancer can be a risk factor for gastric cancer, as well as association with lobular breast cancer history.

The high percentage of cancer family history confirms the importance of the data collection. Non-analysis of this information implies a professional negligence, since the family history study can serve as a low-cost tool, favoring prevention and early diagnosis, reducing morbidity, mortality and costs of health assistance and ultimately preserving lives.

Individuals at increased risk for cancer hereditary syndromes should receive specific attention from experts in Cancer Genetics Settings. The professional's view must be holistic and critical, since taking care of the patient means taking care of the family as a whole.

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