BRIEF ARTICLE

Age, smoking and overweight contribute to the development of intestinal metaplasia of the cardia

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Abstract

AIM: To assess the role of *Helicobacter pylori* (*H. pylori*), gastroesophageal reflux disease (GERD), age, smoking and body weight on the development of intestinal metaplasia of the gastric cardia (IMC).

METHODS: Two hundred and seventeen patients scheduled for esophagogastroduodenoscopy were enrolled in this study. Endoscopic biopsies from the esophagus, gastroesophageal junction and stomach were evaluated for inflammation, the presence of *H. pylori* and intestinal metaplasia. The correlation of these factors with the presence of IMC was assessed using logistic regression.

RESULTS: IMC was observed in 42% of the patients. Patient age, smoking habit and body mass index (BMI) were found as potential contributors to IMC. The risk of developing IMC can be predicted in theory by combining these factors according to the following formula: Risk of IMC = a + s - 2B where a = 2,...6 decade of age, s = 0 for non-smokers or ex-smokers, 1 for < 10 cigarettes/d, 2 for > 10 cigarettes/d and B = 0 for BMI < 25 kg/m^2 (BMI < 27 kg/m^2 in females), 1 for BMI > 25 kg/m^2 (BMI > 27 kg/m^2 in females). Among potential factors associated with IMC, *H. pylori* had borderline significance (P = 0.07), while GERD showed no significance.

CONCLUSION: Age, smoking and BMI are potential factors associated with IMC, while *H. pylori* and GERD show no significant association. IMC can be predicted in theory by logistic regression analysis.

INTRODUCTION

The development of gastric cancer involves an interplay of bacterial, host, and environmental facts, including dietary factors, lifestyle factors and *Helicobacter pylori* (*H. pylori*)[1-3].

The worldwide incidence of gastric cancer has declined over the recent decades[4]. Part of this decline is due to the recognition of risk factors such as *H. pylori* infection and other environmental risk factors[3,5]. Despite the overall decline in gastric cancer, there has been a significant increase in the incidence of cancer of the gastric cardia[6]. The shift from distal to proximal stomach may be due to the decrease in the distal cancers.

However, it has also been proposed that adenocarcinomas at the cardia represent a different entity of antral gastric adenocarcinomas[7]. Indeed, environmental factors or chemical carcinogens may be more strongly associated with cardia carcinomas compared with more distal gastric carcinoma[8]. On the other hand, the proximal gastric carcinomas differ from distal gastric carcinomas as they are not associated with a severe form of gastritis characterized by atrophy and/or intestinal metaplasia[9,10].

Carcinomas of the gastric cardia appear to be similar to those associated with Barrett's esophagus, with which they share some demographic features[9]. Several studies indicated that obesity satisfies several criteria for a causal association with gastroesophageal reflux disease (GERD) and some of its complications, including erosive esophagitis, and esophageal adenocarcinoma[11-13]. Therefore, obesity could represent an important factor in the development of cardia carcinoma.

The development of cardia carcinoma seems to be preceded by intestinal metaplasia, which is secondary to chronic inflammation[1,14-16]. However, the etiology of intestinal metaplasia of the gastric cardia (IMC) remains controversial. To our knowledge, no study has evaluated the effects of age, smoking and body weight on IMC. Thus, our aim was to set up a cross-sectional study to examine these the role of these factors, and also *H. pylori* and GERD. To evaluate the incidence of IMC and the respective role of these factors on the development of IMC at a particular point in time, we enrolled a population of outpatients with upper gastrointestinal (GI) endoscopy scheduled for various reasons.

MATERIALS AND METHODS

Study design and population
The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by our institutional Ethics committee (Commission Centrale d'Ethique) (Controlled-trials.com, Number IS-RCTN15324190, www.con trolled-trials.com). This was an investigator-initiated study with no involvement of industry.

Inclusion criteria
All outpatients scheduled for an elective upper GI endoscopy were eligible for inclusion in the study. Exclusion criteria were: age < 18 years, pregnancy, patients unable to give their own consent, a previous history of upper GI surgery, severe bleeding diathesis (platelet count < 50 000/mm^3, prothrombin rate < 50%), psychiatric diseases, allergy to lidocaine. All patients signed an informed consent form.

For this study, 250 consecutive patients scheduled for upper GI endoscopy for a variety of conditions were recruited over a 2.5-year period. Among them, 217 accepted the study protocol (acceptance rate of 86%). Endoscopy was performed in the left lateral position after local anesthesia using a 10% xylocaine spray with the patient under conscious sedation using midazolam as reported previously[17]. A standard endoscopy was performed, including retroflexion in the stomach (Table 1).

Endoscopic biopsies
Each patient had 2 biopsies performed in the esophagus 2 cm above the Z-line, 4 biopsies at the esophagogastric junction, 2 biopsies in the cardia located within 10 mm below the Z-line, 2 biopsies in the fundus (greater and lesser curvature), 2 biopsies in the antrum (greater and lesser curvature), and one biopsy in the angulus. In the case of Barrett's esophagus, 4 biopsies were performed every cm in the Barrett's segment. All biopsy specimens were fixed in 0.5% formaldehyde solution and stained with haematoxylin eosin, Giemsa, and Gomori-aldehyde-fuschin. Two experienced GI pathologists (BH, MB), who were blinded to the clinical diagnosis, analyzed the biopsies. The diagnosis of IMC was reserved for patients with intestinal metaplasia detected in biopsy specimens sampled from the macroscopically normal-appearing gastroesophageal junction.

Study variables and data collection
As previously defined by Vakil *et al*[18], clinically significant GERD was diagnosed when reflux of the gastric contents caused troublesome symptoms and/or complications. It was considered negative if there were no such symptoms (Score 0), positive if the patient presented symptoms once a month (Score 1) or more than once a month (Score 2).

The presence of a hiatus hernia was defined as widening of the muscular hiatal tunnel and circumferential laxity of the phrenoesophageal membrane[19], allowing a portion of the stomach to slide into the thorax.

Smoking habit (never smoking: score 0; past smoker: score 1; current smoker < 1 pack per day: score 2; current smoker > 1 pack per day: score 3), body mass index (BMI) and age were recorded.

Endoscopic biopsies from the esophagus, the Z-line, the cardia, the fundus and the antrum were histologically evaluated for the following criteria: (1) Acute and chronic inflammation using a visual analogue scale from 0 to 3 as proposed by Dixon *et al*[20] in an updated Sydney system, 0 being none and 3 being marked; (2) Absence or presence of incomplete (types Ⅰ, Ⅱ) or complete (type Ⅲ) intestinal metaplasia as defined by Filipe *et al*[21]; and (3) Absence or presence of *H. pylori*.

Barrett's esophagus was defined as "a change in the distal esophageal epithelium of any length that can be recognized as metaplastic mucosa at endoscopy and confirmed to have intestinal metaplasia by biopsy of the tubu-

Table 1 Characteristics of the cohort study group *n* (%)

	Total	Men	Women	*P* value	OR (95% CI)
No. of patients (%)	217	97 (45)	120 (55)		
Age (yr)	45.3 ± 15.3	49.9 ± 16.5	43.3 ± 13.5		
Reason for endoscopy[1]					
Epigastric pain	62 (29)	31	31	NS	
Barrett's esophagus	26 (12)	20	6	0.01	4.94 (1.9-12.8)
Reflux grade 1	17 (8)	6	11	NS	
Reflux grade 2	141 (65)	69	72	NS	
Dyspepsia	9 (4)	3	6	NS	
Dysphagia	2 (1)	2	0	NS	
Gastric bypass	48 (22)	7	41	0.01	0.15 (0.06-0.35)
Anemia	5 (2)	2	3	NS	
Celiac disease suspicion	7 (3)	4	3	NS	
Ulcer follow-up	8 (4)	6	2	NS	
Helicobacter antibiogram	4 (2)	1	3	NS	
Personal history of reflux	141 (65)	69	72	NS	
Tobacco use					
Non smoker	119 (55)	46	73	NS	
Past smoker	11 (5)	5	6	NS	
Current smoker all	87 (40)	46	41	NS	
Current smoker 0.5 p/d	48 (22)	27	21	NS	
Current smoker > 1.0 p/d	39 (18)	19	20	NS	
BMI	29.8 ± 10.6	32.4 ± 11.5	27.7 ± 7.7		
PPI users	96 (44)	52	44	NS	
NSAID users	37 (17)	20	17	NS	

P value indicates results of the comparison of male and female patients. [1]Patients may have more than one pathology. OR: Odds ratio; BMI: Body mass index; PPI: Proton pump inhibitor; NSAID: Non steroidal antiinflammatory drug; NS: Not significant.

lar esophagus"[22]. Short segment Barrett's esophagus was considered if metaplasia extended < 3 cm into the tubular esophagus or long segment Barrett's esophagus if metaplasia extended > 3 cm into the tubular esophagus. Patients taking nonsteroidal anti-inflammatory drugs and/or proton pump inhibitors (PPI) during the last month before inclusion and continuously for more than 6 mo were defined as regular non steroidal antiinflammatory drug or PPI users.

Statistical analysis

The analysis of group variables was studied primarily using cross-tabulation analysis (Fischer's exact test). The Kruskal-Wallis test was used to test equality of the population. Multivariate analysis of predictors of IMC was performed by linear logistic regression. To accomplish this goal, a model was created that included all predictor variables. Multiple logistic regression analysis was used to develop an equation to predict a logit transformation of the probability of IMC based on risk factors that included in the equation: age (years), BMI (kg/m^2), smoking habit, sex, reflux disease and hiatal hernia. Age and BMI, were modeled as continuous variables, and sex was modeled as a categorical variable (0 = male and 1 = female). The final mathematical equation provided an estimate of a subject's likelihood of having IMC. *P* values < 0.05 were interpreted as statistically significant. *P* values > 0.05 were taken as non significant (NS). SPSS advanced models 10.0 was used for statistical analysis.

RESULTS

A total of 217 patients were enrolled in the current study.

Table 1 presents the characteristics of the group according to the sex distribution. There were no significant differences among the two groups except a higher frequency of Barrett's esophagus in men and a higher rate of gastric bypass in women. BMI exceeded 25 kg/m^2 in 54 males (56%) and 27 kg/m^2 in 61 females (51%). Because our surgical team has a long lasting program of bariatric surgery[23], a substantial number of patients evaluated for gastric bypass (22%) was included but the mean BMI in the overall cohort was < 30 kg/m^2. Epigastric pain and gastroesophageal reflux were the major causes for endoscopy. Of note, almost half of the patients was taking a PPI and 45% of the patients were past or current tobacco users.

Endoscopy was normal in 36% of the patients whereas erosive esophagitis and hiatus hernia were the main endoscopic findings in our population (Table 2). Barrett's esophagus was histologically confirmed in 13% of the patients. *H. pylori* was present in the gastric biopsies of 70 patients (32%).

We analyzed the potential relationship between the presence of *H. pylori* and various factors including GERD, Barrett's esophagus, hiatus hernia, tobacco use, sex and BMI (Table 3). There were statistically more patients infected by *H. pylori* with a normal esophagogastric junction (45%) than with long (16%) or short segment Barrett's esophagus (11%) (*P* < 0.05). Patients with a hiatus hernia were less frequently infected by *H. pylori* than patients without (*P* < 0.05). Current tobacco users were more frequently infected by *H. pylori* than non or past smokers (*P* < 0.05).

Table 2 Results of upper gastrointestinal endoscopy *n* (%)				
	Total	**Men**	**Women**	***P* value**
No. of patients	217	97	120	
Normal	79 (36)	43	36	NS
Esophagitis[1]	26 (12)	14	12	NS
Hiatus hernia[1]	60 (28)	36	24	NS
Short segment Barrett's	9 (4)	6	3	NS
Long segment Barrett's	19 (9)	11	8	NS
Esophageal tumor	4 (2)	3	1	NS
Gastric ulcer	4 (2)	3	1	NS
Gastric tumor	1 (0.5)	1	0	NS
Gastritis	9 (4)	5	4	NS
Duodenal ulcer	3 (1)	2	1	NS
Duodenal atrophy	2 (1)	1	1	NS
Other	1 (0.5)	1	0	NS
H. pylori				
Positive	70 (32)	33	37	NS
Negative	147 (68)	64	83	NS

P value indicates results of the comparison of male and female patients.
[1]Patients may have more than one pathology. NS: Not significant; *H. pylori*: *Helicobacter pylori*.

The correlation between the presence of reflux symptoms, and Barrett's esophagus, hiatus hernia, tobacco use, sex, age and BMI was shown in Table 4. All patients with short segment Barrett's esophagus and 90% of patients with long segment Barrett's esophagus had significant reflux ($P < 0.01$). The presence of reflux was not statistically significantly associated with the presence of hiatus hernia or increased BMI.

IMC was observed in 92 patients (42%), 48 were men and 44 were female, and the mean age was 27.3 years. IMC was not statistically associated (although there was a tendency) with the presence of *H. pylori* ($P > 0.05$), whereas *H. pylori* was strongly associated with the presence of inflammation of the cardia (carditis) since 82% of patients infected with *H. pylori* had carditis compared with 30% in the group without *H. pylori* infection ($P < 0.001$). Furthermore, there was a strong relationship between IMC and metaplasia found in other gastric areas, including the antrum and the corpus of the stomach. This relationship was not present in patients with Barrett's esophagus. BMI was found to be significantly lower and age significantly greater in patients with IMC than in patients with normal cardia mucosa. *H. pylori* played a pivotal role in the development of metaplasia of the antrum and the fundus, with an odds ratio reaching 7.4 and 11.2 respectively compared with patients not infected with *H. pylori* (Table 5).

GERD was not significantly associated with acute and chronic inflammation of the gastroesophageal junction, and it was not associated with the presence of IMC (borderline significance 0.06) (Table 5). Compared with patients with either short or long segment Barrett's esophagus, patients with IMC had significantly fewer GERD symptoms.

In univariate analysis, age, BMI and tobacco use were statistically significantly associated with IMC (Table 5). Using logistic regression analysis, the presence of IMC could be predicted by the patient's age, smoking habit
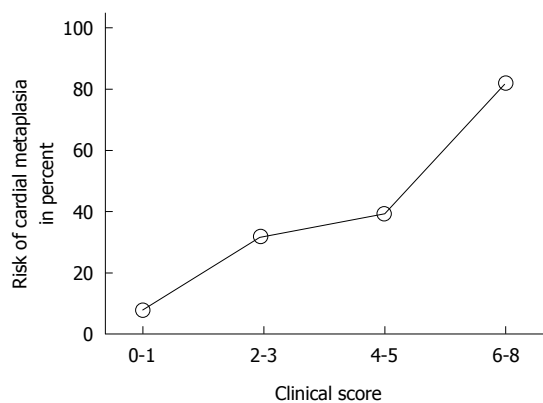

Figure 1 The curve indicates the actual risk (with standard deviation) of cardia metaplasia as a function of the personal clinical score.

and the absence of overweight according to the following formula: Risk score of IMC = a + s - 2B where a = 2,… 6 decade of age, s = 0 for non-smokers or ex-smokers, 1 for < 10 cigarettes per day, 2 for > 10 cigarettes per day, and B = 0 for BMI < 25 kg/m^2 (BMI < 27 kg/m^2), 1 for BMI > 25 kg/m^2 (BMI > 27 kg/m^2) for males (females), respectively. In the presence of these factors, *H. pylori* had only a borderline significance ($P = 0.07$) and would contribute only 1 point on the above scale which ranges from 0 to 8. Therefore, for a 50-year-old patient smoking 15 cigarettes per day and with a BMI of 26 kg/m^2, the theoretical risk of having IMC is 5. The data of 82 patients with IMC were analyzed to obtain the actual frequency in percent of IMC as a function of the calculated risk score for a given patient using the above equation (Figure 1). Finally, the presence of *H. pylori* was associated with severe acute and chronic inflammation in the antrum ($P < 0.01$), corpus ($P < 0.01$) and in the Z-line area ($P < 0.01$).

DISCUSSION

During the last few decades there has been a marked increase in the incidence of adenocarcinoma of the esophagogastric junction in Western countries in contrast to the reduction in incidence of distal gastric cancer. Most observers believe that this is the consequence of an increased rate of adenocarcinoma of the distal esophagus and a decreased incidence of distal gastric cancer related to *H. pylori* eradication. If the above-mentioned epidemiologic relationships are correct, this could indicate that the so-called cardia adenocarcinomas are not related to *H. pylori* infection but to other factors, and eventually may not be considered to be "gastric" cancers.

Because of the debated roles of different clinical factors in the emergence of malignant neoplasia of the gastric cardia, and because many reports have stated that IMC precedes the development of cardiac cancer, our study was aimed at assessing the respective roles of *H. pylori*, GERD, age, smoking habit and body weight on the development of IMC in a large group of patients. To this end our cross-sectional study enrolled outpatients scheduled for upper GI endoscopy for various reasons and specifi-

Table 3 Relationship between the presence of *Helicobacter pylori* and reflux, Barrett's esophagus, hiatus hernia, tobacco, sex and body mass index *n* (%)

	Total	*H. pylori* negative	*H. pylori* positive	*P* value	OR (95% CI)
H. pylori	217	147	70		
Reflux = 0	59 (27)	36 (61)	23 (39)	NS	
Reflux = 1	17 (8)	11 (65)	6 (35)	NS	
Reflux = 2	141 (65)	100 (71)	41 (29)	NS	
Short segment Barrett's	9 (4)	8 (89)	1 (11)	NS	
Long segment Barrett's	19 (9)	16 (84)	3 (16)	NS	
Normal gastroesophageal junction	189 (87)	122 (65)	67 (45)	0.01	4.58 (1.33-15.73)
Hiatus hernia					
Absent	157 (72)	100 (64)	57 (36)	0.04	2.06 (1.03-4.13)
Present	60 (28)	47 (78)	13 (22)	0.03	0.49 (0.24-0.98)
Tobacco					
Non smoker	119 (55)	85 (71)	34 (29)	NS	
Past smoker	11 (5)	9 (82)	2 (18)	NS	
Current smoker (all)	87 (40)	53 (61)	36 (39)	0.03	1.88 (1.08-3.35)
Current smoker 0.5 p/d	48 (22)	26 (54)	22 (46)	0.03	5.2 (1.1-4.12)
Current smoker > 1.0 p/d	39 (18)	27 (69)	12 (31)	NS	
Age					
Mean age	45.3	46.57	42.78	0.06	
Sex					
Male	97 (45)	64 (66)	33 (34)	NS	
Female	120 (55)	83 (69)	37 (31)	NS	
Body Mass Index					
Mean BMI	29.8	30.6	28.1	NS	

P value indicates results of the comparison of *H. pylori* positive patients and *H. pylori* negative patients. OR: Odds ratio; BMI: Body mass index; NS: Not significant; *H. pylori*: *Helicobacter pylori*.

Table 4 Relationship between reflux and Barrett's esophagus, hiatus hernia, tobacco use, sex, age and body mass index *n* (%)

	Total	Reflux			*P* value
		Grade 0	Grade 1	Grade 2	
No. of patients	217	59	17	141	
Short segment Barrett's	9 (4)	1 (11)	0	8 (89)	0.010
Long segment Barrett's	19 (9)	1 (5)	1 (5)	17 (90)	0.010
Normal gastroesophageal junction	189 (87)	59 (31)	16 (9)	114 (60)	0.002
Hiatus hernia					
Absent	157 (72)	49 (31)	13 (8)	94 (61)	0.060
Present	60 (28)	10 (17)	4 (7)	46 (76)	NS
Tobacco					
Non smoker	119 (55)	32 (27)	13 (11)	74 (62)	NS
Past smoker	11 (5)	1 (10)	1 (10)	9 (80)	NS
Current smoker all	87 (40)	26 (29)	11 (13)	51 (48)	NS
Current smoker 0.5 p/d	48 (22)	14 (29)	7 (15)	27 (56)	NS
Current smoker > 1.0 p/d	39 (18)	12 (30)	3 (8)	24 (62)	NS
Sex					
Male	97 (45)	22 (23)	6 (6)	69 (71)	NS
Female	120 (55)	37 (31)	11 (9)	72 (60)	NS
Age					
Mean age	45.3	42	45.2	46.8	0.080
Body Mass Index					
Mean BMI	29.8	27.9	33.1	30.2	0.080

BMI: Body mass index; NS: Not significant.

cally searched for the presence of IMC. The study then examined all the above mentioned variables to evaluate their respective role on the development of IMC at a particular point in time. For this purpose, each patient had endoscopic gastric and esophageal biopsies. We paid specific attention to the cardia area because the location and extent of the gastric cardia are controversial. Today, the vast majority of the data available on the cardia and cardia cancer are not comparable because of variations in the diagnostic criteria. Thus, to avoid any problem in "cardia" definition, we followed rigorous anatomist and endoscopist recommendations that defined the cardia as being the part of the stomach that lies around the orifice of the tubular esophagus, and which corresponds to the

Table 5 Factors associated with intestinal metaplasia of the cardia *n* (%)

	Total	Intestinal metaplasia		*P* value	OR (95% CI)
		Absent	Present		
No. of patients (%)	217	125 (58)	92 (42)		
Indications for endoscopy					
GERD[1]	141 (65)	106 (75)	35 (25)	NS	
Epigastric pain[1]	62 (29)	41 (66)	21 (34)	NS	
Gastric bypass	48 (22)	30 (63)	18 (37)	NS	
Results of endoscopy					
Normal	79 (36)	41 (52)	38 (48)	NS	
GERD	26 (12)	10 (38)	16 (62)	0.060	
Hiatus hernia	60 (28)	26 (43)	34 (57)	NS	
Barrett's esophagus	28 (13)	13 (46)	15 (54)	NS	
Other	29 (13)	17 (59)	12 (41)	NS	
H. pylori					
Positive	70 (32)	34 (49)	36 (51)		
Negative	147 (68)	91 (62)	56 (28)	0.060	
Reflux = 0	59 (27)	33 (56)	26 (44)		
Reflux = 1	17 (8)	15 (88)	2 (12)		
Reflux = 2[2]	141 (65)	77 (55)	64 (45)	0.060	
BMI	29.8 ± 10.6	31.61	27.33		
Age	45.3 ± 15.3	43.29	50.68		
Sex					
Male	97 (45)	55 (57)	42 (43)	NS	
Female	120 (55)	70 (58)	50 (42)	NS	
Tobacco use					
Non smoker	119	89	30		
Past smoker	11	8	3	0.500	0.6 (0.13-1.9)
Current smoker all	87	28	59	0.001	6.19 (3.4-11.2)
Current smoker 0.5 p/d	48	14	32	0.001	4.23 (2.1-8.5)
Current smoker > 1.0 p/d	39	12	27	0.010	4.33 (2.1-9.1)
Antrum metaplasia	19	5	14	0.010	4.31 (1.49-12.4)
Fundus metaplasia	9	1	8	0.001	11.8 (1.45-96.1)

P value indicates results of the comparison of patients with or without intestinal metaplasia of the cardia. [1]patients may have more than one reason for endoscopy; [2]data are missing. GERD: Gastroesophageal reflux disease; OR: Odds ratio; BMI: Body mass index; NS: Not significant; *H. pylori*: *Helicobacter pylori*.

point at which the tubular esophagus joins the saccular stomach[24-26].

In our study, IMC was histologically found in 92 patients (42%). Whereas *H. pylori* was present in 70 patients (32%), the distribution of *H. pylori* was similar in patients with or without IMC, suggesting that no significant relationship between *H. pylori* and IMC exists. We found that *H. pylori* was strongly associated with the presence of carditis without IMC, as previously reported. Indeed, Sotoudeh *et al*[3] found a significant relationship between carditis and *H. pylori* infection in an Iranian cohort of patients in which the infection rate was as high as 85% whereas our infection rate was close to 32%. In contrast to our study, Goldblum *et al*[10] found that not only was *H. pylori* associated with carditis but also with IMC. In our series there was a strong correlation between the presence of *H. pylori* and acute or chronic inflammation in biopsies taken at different sites of the stomach. This finding is consistent with several other eastern observations showing that carditis is more associated with *H. pylori* infection than with GERD. In our study, GERD was present in 141 patients (65%) and was not found to be significantly associated with IMC, whereas GERD was strongly associated with acute and chronic inflammation of the gastroesophageal junction, a feature already

reported by others[27,28]. Voutilainen *et al*[14] reported that there are two dissimilar types of chronic inflammation of the gastric cardiac mucosa that seem to occur: one existing in conjunction with chronic *H. pylori* infection and the other with normal stomach and erosive GERD. Patients with IMC also had significantly higher rates of metaplasia of other gastric areas. Therefore finding antral or corporeal metaplasia should alert the gastroenterologist to redo a biopsy of the cardia in a subsequent endoscopy. The absence of any correlation between the presence of IMC and Barrett's esophagus might indicate that IMC is a distinct entity from Barrett's esophagus as proposed by Golblum[16]. Similar inflammation and mucosal alteration in the antrum and the corpus should be regarded as a potential sign of predisposition to IMC. We found that the risk of having IMC was associated with increasing age since 70.5% of patients with IMC were > 40 years old, a feature also reported by McNamara *et al*[29] in a cohort of 36 patients with IMC. Among other factors associated with IMC, tobacco use was found to be strongly associated with the development of IMC and 68% of patients with IMC were smokers, data never reported before, to our knowledge. Indeed, Koizumi *et al*[5] reported an increased risk of IMC of 1.84 (1.39-2.43 95% CI) only for antral cancer in current smokers compared with subjects

who had never smoked. BMI was surprisingly found to be a protective factor: the greater the BMI the less it contributed to the risk of IMC. This specific point should be balanced by the fact that the majority of our population was under the threshold of obesity. This finding could seem controversial against the current literature that suggests a link between obesity, GERD and carcinoma[30].

Although a real prospective study design is needed to assess a prediction, our statistician has tried to find the best fitting model to describe the relationship between the presence of IMC and various predisposing factors. The final mathematical equation provided an evaluation (and not the risk) of a subject's likelihood of having IMC. In the current study, the presence of IMC could be predicted by age, smoking habit and low or normal BMI. The evaluation showed no association with GERD. *H. pylori* had only a borderline significance ($P = 0.07$) if any. Nevertheless, this point must be emphasized because recent studies have found two types of cardia cancer, one linked to *H. pylori*-associated atrophic gastritis, and the other associated with nonatrophic gastritis, resembling esophageal adenocarcinoma[7].

Although our study was not prospective, it gives results at a particular point in time, and points out the greater need for endoscopic surveillance of gastric cardia mucosal changes in individuals aged 40 and over. Regarding the epidemiology of adenocarcinoma of the esophagus and gastroesophageal junction, the patterns of each disease are sufficiently alike to implicate shared risk factors or even to represent a single neoplastic entity. Although studies at the molecular level have produced conflicting results, many have demonstrated the similarity between adenocarcinomas of the cardia and esophagus. Most important is the evidence that the overall survival is similar in patients with gastroesophageal junction and esophageal adenocarcinoma.

In summary, this study indicates that chronically inflamed gastric mucosa in the cardia area can be replaced by intestinal metaplasia, a finding which has been shown to precede the development of cardia cancer. Whereas esophageal adenocarcinomas are strongly associated with GERD and obesity and are inversely associated with *H. pylori*, we suggest that IMC is not convincingly associated with GERD, is inversely correlated with BMI and has a dubious association with the presence of *H. pylori,* but is associated with increased age and a smoking habit. A prospective study aimed at evaluating the true incidence and natural history of IMC is therefore clearly needed.

COMMENTS

Background
Development of carcinoma of the cardia seems to be preceded by intestinal metaplasia. Gastroesophageal reflux and *Helicobacter pylori* (*H. pylori*) infection are together believed to cause intestinal metaplasia of the cardia (IMC).

Research frontiers
Despite the overall decline in gastric cancer, there has been a significant increase in the incidence of cancer of the gastric cardia. Because the roles of different clinical factors in the emergence of cardia malignancy are still debated,

there is a need to carry out further studies aiming at defining the risk factors for developing IMC.

Innovations and breakthroughs
This cross-sectional study indicated that IMC is associated with increased age and smoking, but is not strongly associated with *H. pylori* infection and gastroesophageal reflux disease.

Applications
The study indicates there is a greater need for endoscopic surveillance of gastric cardia mucosal changes in individuals aged 40 and over.

Terminology
Intestinal metaplasia of the cardia represents a mucosal change of the gastric cardia that is secondary to chronic inflammation and that can be considered as a potential precursor of cancer.

Peer review
The paper is a well-written manuscript with an important topic in clinical epidemiology. The authors tried to study the risk factors for intestinal metaplasia of the cardia. In addition they compared these factors with the epidemiological criteria of patients with Barrett's esophagus. The results show that Barrett mucosa and IMC differed according their etiological factors.

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