Original Paper

The Influence of Risk Factors to the Prevalence of Gastric Mucosal Atrophy, Intestinal Metaplasia and Dysplasia in Oltenia Region

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ABSTRACT **Background &aims** Gastric atrophy and intestinal metaplasia represent the most important premalignant lesions in gastric carcinogenesis (risk 1.1% / year). Although H. pylori infection has a major role, the prevalence and severity of mucosal atrophy and intestinal metaplasia at Helicobacter positive patients is variable, which suggest other factors except H. pylori infection may play an important role. **Method.** We performed a prospective, case-control study at patient admitted in a tertiary care unit (I[st] Medical Clinic, Emergency Hospital Craiova) and examined by endoscopy during 3 years. We selected 1432 patients with chronic gastrites or gastropathies by endoscopic examination; atrophy and intestinal metaplasia were confirmed by pathologic exam. We analyzed the prevalence of risk factors by comparing patients with atrophy and intestinal metaplasia with patients without these abnormalities. **Results**The presence of IgG anti-HP antibodies was associated with increased risk of superficial (OR=1.711) and atrophic gastritis (OR=1.744). At patients with gastric atrophy diagnosed by endoscopy, OR has statistical significant risk for age above 50 years (OR=8.54, CI 95% 2.95-14.42), for rural residence (OR=2.47), smoking habit (8,821) and alcohol consumption, whereas NSAID use was associated with some protective effect. For intestinal metaplasia, a statistically significant risk was noted above 60 years, rural residence (OR=3.25), smoking habit (2, 8947) and alcohol consumption. Endoscopic-diagnosed atrophy has proved a mild to moderate sensibility for the detection of atrophy at pathological examination. **Conclusions** Helicobacter pylori infection, age, rural residence, smoking habit and alcohol consumption were associated with increased risk of gastric atrophy and intestinal metaplasia.

KEY WORDS *gastritis, gastric atrophy, intestinal metaplasia, Helicobacter pylori, NSAID, chromoendoscopy*

Introduction

Gastric mucosal atrophy and intestinal metaplasia represent the most important premalignant lesions in gastric carcinogenesis. (1), (2). Annual examination of patients with atrophy and metaplasia reveal a medium risk of 1.1% / year (3). The monitoring permit an earlier diagnosis of gastric carcinoma compared with symptomatic patients examined by endoscopy (67% in I and II stage compared with 23% at patients above 40 years with dyspeptic symptoms), and 5 years-survival was also superior (50% vs. 10%) (3). The severity of gastric mucosal atrophy and intestinal metaplasia at Helicobacter positive patients is variable from one country to other, (4), (5), which suggest other factors except H. pylori infection may play an important role in progression toward atrophy and intestinal metaplasia

Patients and method

We performed a prospective, case-control study at patient admitted in a tertiary center (I[st] Medical Clinic, Emergency Hospital Craiova) and examined by upper digestive endoscopy during 3 years (2004-2006). The endoscopy represents first examination for the selection of the patients. We noted all macroscopic abnormalities suggestive for the diagnosis of gastritis (using Sydney system) (6), (7), (8), (9), (10), (11) and a classification propose for Japanese Society for the study of gastritis (12). Form 3616 upper digestive endoscopies, we selected 1432 patients with chronic gastrites or gastropathies. The diagnosis of gastric mucosal atrophy was made by vascular sub mucosal pattern visibility, by pale appearance of the mucosa and by reduced thickness of the mucosa (*figure 1, 2*).

Intestinal metaplasia (*figure 3, 5*) was sometime very difficult to diagnose by endoscopy. In the literature endoscopic appearance of intestinal metaplasia is characterized as „nodular gray-type abnormality with cobblestone appearance in antral region" (12).

Many endoscopists know that is very difficult to visualize by macroscopic exam, without the use of chromoendoscopy and/or biopsy. For improving the diagnosis of intestinal metaplasia, we use in many cases methylene blue chromoendoscopy (*figure 4, 6*).

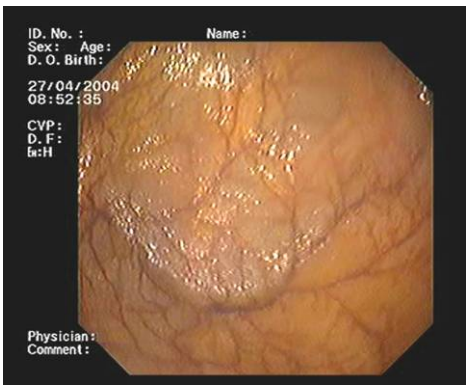

Figure 1 Female, 74 year-old. Typical endoscopic aspect of gastric atrophy: thick, pale gastric mucosa with visible vascular pattern

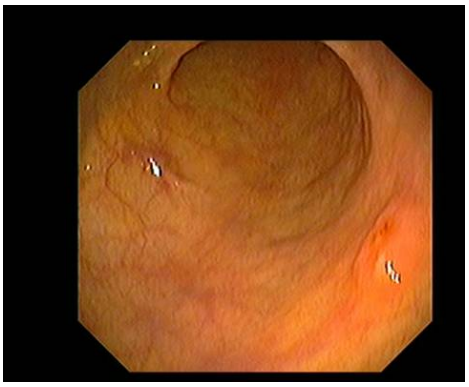

Figure 2 male, 56 years. Mucosal atrophy at the level of gastric corpus. Small, erosive, protrusive lesion observed concomitant

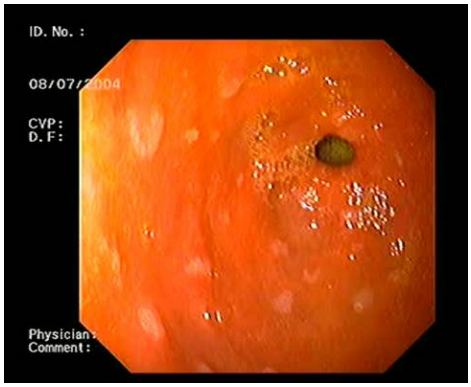

Figure 3 Male, 63 years. Intestinal metaplasia presumed at endoscopy – protrusive, gray-appearance lesions into the antral region of the stomach.

We analyzed some of the known risk factors for atrophy and intestinal metaplasia:

- Age, gender, urban or rural residence
- Non-steroidal anti-inflammatory use, although the information obtained were subjective and biased by some factors such educational level, memory et al;
- Smoking habit, alcohol and coffee consumption were also noted;
- Previous gastric of biliary surgery, because of association between reflux gastropathy and atrophy. We are noted the time of surgical intervention, the type of the operation;
- Pathology exam was performed in all cases of gastrites or gastropathies. We perform two antral biopsies, two from gastric corpus and one from gastric angulus; also we perform biopsies from suspicious lesions.
- The presence of Helicobacter pylori infection was made by rapid urease test, by microbiological examination (Giemsa staining) (figure 7) and by serology.

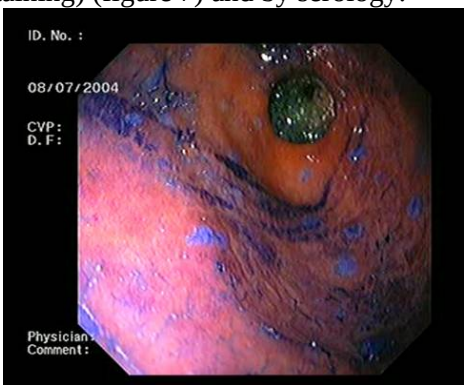

Figure 4 Same case, examination after methylene blue staining. Multiple colored lesions; pathology shows the presence of intestinal metaplasia).

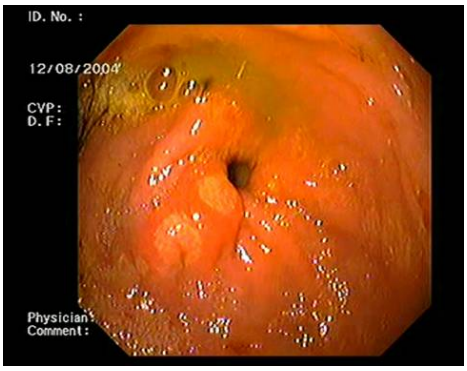

Figure 5 Female, 48 years. Biliary reflux. Two small lesions suggestive for intestinal metaplasia with prepiloric location.

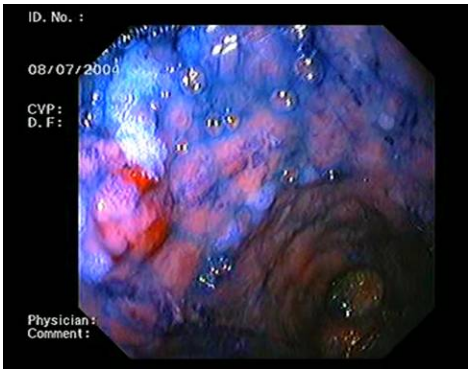

Figure 6 Female, 59 years. Diffuse intestinal metaplasia observed after methylene blue staining. Small, post-biopsy bleeding.

The presence of atrophy and intestinal metaplasia was confirmed by pathological examination (*figure 7, 8, 9, 10*).

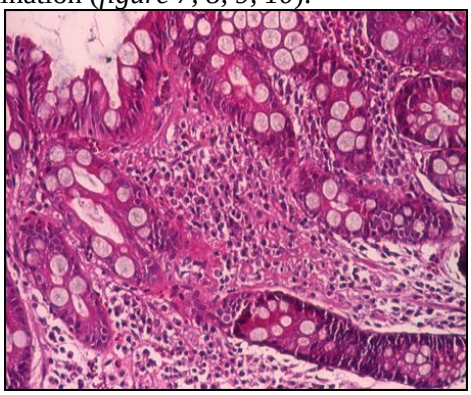

Figure 7 Male, 46 years. Gastric mucosa with presence of H. pylori, severe intestinal metaplasia and abundant inflammatory infiltrate with lymphocytes and plasma cells into the chorion, acute inflammatory infiltrate into the glandular lumen.

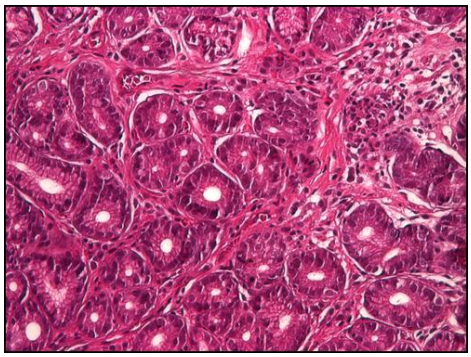

Figure 8 Female, 57 years. Chronic atrophic gastritis, mild interstitial inflammatory infiltrate. Periglandular fibrosis.

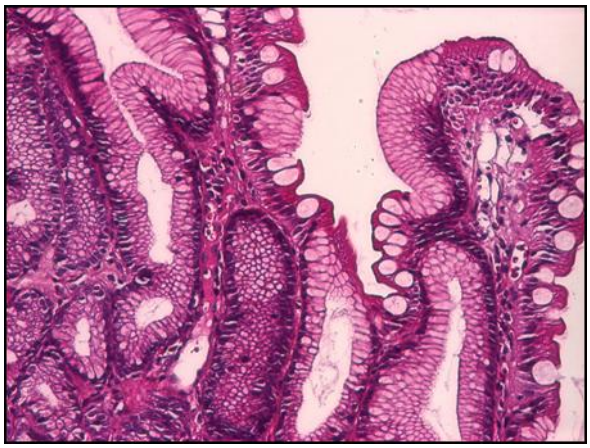

Figure 9 Male, 43 years. Focal metaplasia.

For the statistical analysis we are selected a group of patients for comparison. Patients were selected by normal endoscopic exam and by absence of atrophy. We analyzed also the difference between the subgroup of patients with superficial non-atrophic gastritis and patients with gastric mucosal atrophy, in order to evaluate the difference between risk factors toward atrophy progression.

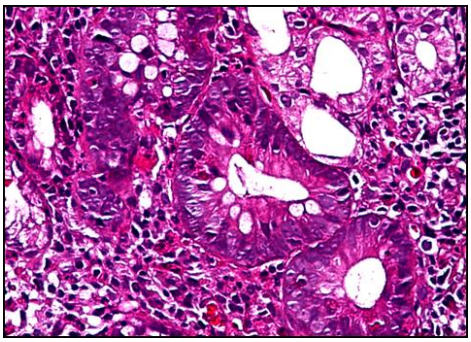

Figure 10 Male, 65 years. Moderate dysplasia with focal metaplasia areas; inflammatory infiltrate into the chorion.

Results

Helicobacter pylori infection plays an important role in chronic superficial gastritis and into the evolution toward mucosal atrophy. In our study, we evaluate HP infection by the measurement of IgG anti-HP antibody, by rapid urease test and by microbiological examination of tissue gastric sample provided by biopsy.

The prevalence of IgG anti HP antibodies is outlined in table 1.

Table I Analysis of patients by HP serology

Gastritis	Serology + (%)	Serology - (%)	OR	CI 95%
Superficial gastropathy	(96) 68.09	(45) 31.93	**1.711**	**1.09 - 2.685**
Atrophic gastropathy	(137) 68.52	(63) 31.48	**1.744**	**1.159 - 2.623**
Controls	(111) 55.55	(89) 44.45	-	-

The presence of IgG anti-HP antibodies was associated with increased risk of superficial (OR=1.711) and atrophic gastritis (OR=1.744) (statistically significant in both cases).

The prevalence of active infection with *Helicobacter pylori* detected by rapid urease test or microbiological exam of tissue sample is outlined in table 2, together with confidence interval 95%.

Table II Analysis of patients by local status of Helicobacter pylori

Gastritis	Local status + (%)	Local status - (%)	OR	CI 95%
Superficial gastropathy	60 (45.45)	72 (54.55)	**1.563**	**0.62 – 3.936**
Atrophic gastropathy	21 (40.38)	31 (59.62)	**1.27**	**0.457 – 3.527**
Controls	16 (34.78)	30 (65.22)	-	-

The active presence of Helicobacter pylori infection at gastric mucosa was associated with moderate risk of superficial gastritis and atrophy but, because the confidence interval was not above 1, this risk didn't achieve statistical significance.

Because endoscopic diagnosis of gastric mucosal atrophy was non identical with pathological diagnosis, we evaluate the subgroups of patients with non-atrophic vs. atrophic gastritis (by pathology and by endoscopy) with positive and negative serology, respectively (table 3).

Table III Analysis of patients by the presence or absence of H.pylori

Study groups	OR	CI 95%
Atrophy vs. non-atrophy (endoscopic diagnosis)	1.02	0.52 – 2.003
Atrophy vs. non-atrophy (pathological diagnosis)	**1.456**	**0.513-4.134**
Atrophy vs. control (endoscopic diagnosis)	**1.745**	**0.922 – 3.304**
Atrophy vs. control (pathological diagnosis)	**2.205**	**1.076 – 4.517**

The presence of IgG anti-HP antibodies was associated with moderate and statistically significant risk of gastric atrophy diagnosed by pathology (OR 2.205) if we compared with controls, but if we compare the subgroups of non-atrophic and atrophic gastropathy, statistical significance is lost.

Because of multifactorial etiology of gastric atrophy, we tried to evaluate the impact of some of demographic and toxic factors to the progression toward atrophy and intestinal metaplasia, which are the main lesions intermediary to gastric carcinoma.

Sex ratio reveal an almost unitary rapport between males and females for atrophy groups, diagnosed either by endoscopy (91 males and 109 females) or by pathology (40 males and 43 females), with some predominance of females. The patients with non-atrophic gastropathy have equal sex ratio (237 males and 237 females at endoscopy, 29 males and 29 females by pathology respectively).

We noted a small predominance of urban residence at patients with gastric mucosal atrophy, but urban residence was predominant also in patients with superficial, non-atrophic gastritis and also in controls.

Mean age was greater for atrophic groups vs. non-atrophic gastritis, for endoscopic-made diagnosis (63.27 vs. 50.9 years) and pathological-made diagnosis respectively (57.7952 vs. 51.9138 yrs.). Greater differences for endoscopic groups was explained by longer time needed for severe atrophy, because generally endoscopic exam diagnose usually advanced cases of atrophy compared with pathology.

Table IV Risk factors for mucosal atrophy analyzed in study group and controls

	Atrophy (endoscopy)	Gastritis without atrophy (endoscopy)	Atrophy (pathology)	Gastritis without atrophy (pathology)
Males	91	237	40	29
Females	101	237	43	29
Urban residence	105	291	41	41
Rural residence	95	183	42	17
Smoker	66	132	38	7
Ex smoker	35	72	21	12
Non-smoker	99	270	24	39
Above 20	54	110	30	7
Below 20	47	94	29	12
Alcohol drinker	75	172	36	18
Non-alcohol drinker	125	302	47	40
Coffee consumption	70	193	34	28
Non-coffee	128	281	49	30
NSAID consumption	43	135	21	28
Non-NSAID	156	338	62	30
Serology +	37	96	33	17
Serology -	17	45	12	9

The group of patients without gastric atrophy has a greater percent of non-smokers, while smokers and ex-smokers were prevalent in group of patients with gastric atrophy. The proportion of patients who smoke a number of cigarettes above 20 was greater only at patients with atrophy diagnosed by pathology.

Table V Associated odds ratio for risk factors of mucosal gastric atrophy

Risk factor	Endoscopic-diagnosed atrophy	Atrophy diagnosed by pathology	Intestinal metaplasia	Dysplasia
	RR (CI 95%)	RR (CI 95%)	RR (CI 95%)	RR (CI 95%)
Sex F/M	1.11 (0.793-1.553)	1.075 (0.55-2.103)	0.9547 (0.84-1.06)	1.642 (0.12-3.16)
Residence R/U	*1.439 (1.031-2.008)*	*2.471 (1.214-5.028)*	*3.2558 (1.88-4.62)*	1.418 (0.35-2.49)
Smoker	1.364 (0.938-1.983)	*8.821 (3.401-22.881)*	*2.8947 (1.51-4.28)*	0.455 (0.17-0.73)
Ex-smoker	1.326 (0.833-2.11)	*2.844 (1.188-6.806)*	1.3233 (0.96-1.68)	2.75 (-2.07÷7.58)
No cigarettes>20	0.982 (0.609-1.584)	1.773 (0.613-5.133)	0.8182 (0.68-0.95)	4.59 ((-22.8÷32))
Alcohol drinking	0.342 (0.243-0.481)	1.702 (0.841-3.447)	*1.3750 (1.13-1.61)*	0.965 (0.43-1.49)
Coffee consumption	0.796 (0.564-1.123)	0.743 (0.378-1.461)	*0.5016 (0.47-0.53)*	0.4056 (0.29-0.2)
NSAID protection	1.449 (0.979-2.145)	*2.583 (1.272-5.247)*	*1.2500 (1.01-1.48)*	0.357 (0.29-0.43)

Regarding the consumption of alcohol and coffee, the majority of subjects were not consumers, especially in case of patients with non-atrophic forms of gastritis. Patients with mucosal atrophy have a lower prevalence of non-steroidial anti-inflammatory drugs (NSAID) consumption.

Univariate statistical analysis has tried to evaluate the main factors associated with increased risk of mucosal gastric atrophy, intestinal metaplasia and dysplasia (table 5).

We are evaluate the odds ratio for age as risk factor for gastric mucosal atrophy and intestinal metaplasia, by comparing patients below and above 30, 40, 50, 60 and 70 years.

At patients with gastric atrophy diagnosed by endoscopy, OR has statistical significant risk above 50 years (OR=8.54, CI 95% 2.95-14.42), while in gastric atrophy diagnosed by pathology statistical significance was notated above 40 years (OR=2.71, CI 95% 0.97-4.45). The main explanation is that endoscopic diagnosis of gastric atrophy was generally made in advanced cases, while pathology may diagnose early cases of atrophy.

Table VI Odds ratio in age groups for gastric atrophy (diagnosed by endoscopy)

Age (yrs)	OR	Lower limit CI 95%	Upper limit CI 95%
30	NS	NS	NS
40	NS	NS	NS
50	*8.5404*	2.9561	14.1248
60	*5.0503*	4.2007	5.8999
70	*4.0940*	3.2583	4.9297
80	NS	NS	NS

Table VII Odds ratio in age groups for gastric atrophy (diagnosed by pathology)

Age (yrs)	OR	Lower limit CI 95%	Upper limit CI 95%
30	NS	NS	NS
40	2.7083	0.9664	4.4503
50	*1.5346*	1.1951	1.8741
60	*1.5222*	1.2407	1.8037
70	NS	NS	NS

Table VIII Gastric atrophy in study group

	Atrophy diagnosed by pathology		
Endoscopic atrophy	Atrophy	Absence of atrophy	Total
Atrophy	44	6	50
Absence of atrophy	39	52	91
Total	83	58	141

For intestinal metaplasia, a statistically significant risk was noted only above 60 years. In these case however, because intestinal metaplasia need some time to go into dysplasia and to gastric carcinoma, it's very probable that the augmentation of risk after 60 years has not significant for risk of gastric carcinoma.

We analyzed the diagnosis accuracy of gastric mucosal atrophy and intestinal metaplasia by endoscopy, using as „gold standard" pathology examination of tissue samples from gastric mucosa. Results are noted in tables VIII and IX.

Table IX statistical value of endoscopy-diagnosed atrophy for the prediction of histological atrophy

	Statistical parameter	
Sn	Sensibility	0.530
Sp	Specificity	0.897
PPV	Positive predictive value	0.880
NPV	Negative predictive value	0.571
TPR	True Positive Rate	0.470
FNR	False Negative Rate	0.103

Another problem is related to accuracy of endoscopic examination for the diagnosis of intestinal metaplasia. We analyzed the sensibility, specificity and predictive value of endoscopic diagnostic of intestinal metaplasia. (Table X and XI).

Table X Intestinal metaplasia diagnosed by endoscopy and pathology

	Intestinal metaplasia confirmed by pathology		
Endoscopic suspicion of intestinal metaplasia	Present	Absent	Total
Present	6	1	7
Absent	92	181	273
Total	98	182	280

Table XI Statistical value of endoscopic diagnosed metaplasia for the prediction of pathology result

	Statistical parameter	
Sn	Sensibility	0.061
Sp	Specificity	0.995
PPV	Positive predictive value	0.857
NPV	Negative predictive value	0.663

Discussions

Gastric atrophy and intestinal metaplasia represents the most important lesions into the evolution of chronic gastrites, together with dysplasia. The main reason is close related to the sequences of gastric carcinogenesis (Correa model), which included superficial gastritis, atrophic gastritis, intestinal metaplasia and dysplasia as intermediary lesions. From these reasons, the prediction of atrophy and intestinal metaplasia, together with risk factors understanding, represent the subject of several studies.

The presence of HP infection is associated with increased risk of superficial and atrophic gastritis (relative risk 3.72- (13)). In most studies published was noted an increased prevalence of HP infection from superficial gastritis toward atrophy (12), while at patients with gastric carcinoma the frequency of local infection is moderately decreased (14). The main explanation is that in patients with gastric carcinoma mucosal gastric atrophy was so long and severe so Helicobacter pylori disappear from mucosa ("suicide effect") (14). IgG antibodies anti-HP may persist many months or even years after HP disappear from mucosa.

The significance of negative or positive serology as risk factors need to be carefully interpreted. Many patients with gastric atrophy, especially severe, have negative serology because of disappearance of the germ; a previous infection was therefore not excluded. There are many discussions in the literature about the role of Helicobacter as initiator or promoter of gastric carcinogenesis; we don't know exactly the moment of HP intervention. Today there is no method to tell us exactly the HP status many years before the atrophy is advanced. Because at least theoretically progression toward atrophy is associated with the disappearance of HP from mucosa, but the same result may came in favorable local evolution with complete cure of the infection.

In our study we noted a moderate but significant risk for HP infection for superficial gastropathy and severe atrophy diagnosed by endoscopy.

Many studies found an increased prevalence with age of gastric atrophy (15), (16), (17), patients above 60 years having a greater risk (18), (19). A similar trend was noted for intestinal metaplasia (20). In our study we noted an increased prevalence of gastric atrophy diagnosed by endoscopy and pathology above 40-50 years. There are many geographic variations in prevalence, even at same age, which is show in a comparative study in Sao Paolo and Lima (21); another study including subjects from China and Holland has noted a prevalence of 36% at Chinese patients below 30 years and just 7% at Netherlander patients of same age (17). A particular effect is noted in Japan where a reduction of HP prevalence was not accompanied by lower incidence of gastric atrophy, one study in 21 centers show even a greater prevalence ant lower age (38.5% below 20 years!) (13). An increased prevalence of gastric atrophy at lower ages may represent one of factors who explain the significant prevalence and incidence of gastric carcinoma, especially with antro-piloric location, in our country.

Rural residence was a risk factor in our study for gastric atrophy diagnosed by pathology (OR=2.47) and for intestinal metaplasia (OR=3.25). We didn't note a predisposition of any gender for atrophy or intestinal metaplasia. The relation between gastrites and gender is controversial; some studies didn't report any predisposition, but other studies indicated a higher prevalence of HP infection in males, some studies even in Romania (14), (22). Other studies suggest HP infection is much important for the development of gastric carcinoma in woman (23). The role of gender in gastric atrophy is also controversial, even gastric carcinoma is found more frequent in males; a study published in 2002 in Gut (18) failed to demonstrate a significant predisposition of gastric atrophy for any gender, but notated a favorable trend for males.

Epidemiological data from the literature show a gastric carcinoma predisposition at patients with low socio-economic status and rural residence. But when we study the exact mechanisms which drive from these conditions toward atrophy to gastric carcinoma, the things got unclear. HP infection is more frequent in areas with low socio-economic status and, of course, in rural regions. But there are also a clear regional predisposition (geographic) related to development grade of the country or region. On the other hand, except for the prevalence of HP infection, it is very possible that other factors related to geographic/socio-economic status to have a role. For instance, the diet content in NaCl and other carcinogen agents appeared from improper manufacturing or storage may have a significant role.

In our study we notate a strong relation between smoking habit and pathological-diagnosed atrophy, but not with atrophy diagnosed by endoscopy (which is surprising!). The relation was notated even in case of ex-smokers, although the risk was smaller. In the literature, data related to smoking habit are contradicting, a close relation with gastric carcinoma is frequent stipulate into the literature, although the relation is weaker compared to other smoking-related cancers (24). We don't know what is the moment and place for smoking habit intervention in multistadial gastric carcinogenesis, some studies suggesting the importance of alcohol drinking smoking habit into the progression to atrophy and intestinal metaplasia (25).

Alcohol consumption was associated with mild or moderate risk of atrophy and intestinal

metaplasia, while coffee consumption showed contradicting results, suggesting even a protective effect, contrarian to the Eurohepygast study (18). The relation between atrophy and alcohol is controversial; Eurohepygast study demonstrate only a mild association with intermittent alcohol consumption (18), while another study conducted in Hong Kong show alcohol consumption as risk factor, OR being 1.67 (26). Some studies suggest a role of alcohol and smoking habit into the progression to atrophy and intestinal metaplasia (27). It is possible for alcohol consumption to be correlated with another diet factors (such as increased consumption of NaCl) rather than favoring factor for atrophy (confounding factor). Some studies suggest even a „disinfectant" effect to Helicobacter pylori (28), with a lower prevalence at consumers.

Coffee consumption was associated in Eurohepygast study with increased risk of atrophy (OR 2, 35), without any specific mechanism (18). It is also possible that other diet factors to play a major role. In our study we didn't noted any association with coffee consumption.

NSAID consumption was associated with some protective effect for atrophy and intestinal metaplasia. NSAID chronic use has a complex role into the carcinogenesis, even we don't know the exact moment for intervention in carcinogenesis; the mechanism seem related to the effect to tissue cycloxygenases and lipooxygenases.

Intestinal metaplasia was associated with rural residence, smoking habit and, with mild correlation, with alcohol consumption. Literature studies revealed as risk factors the persistence of HP infection, age above 45 years, male gender and alcohol consumption (26).

The analysis of risk factors for dysplasia was not possible because of relative small number of cases.

Endoscopic-diagnosed atrophy has proved a mild to moderate sensibility for the detection of atrophy at pathological examination, because the exam don't reveal early forms of atrophy. In exchange, endoscopy proved a high specificity (89, 7%), which correlate with a significant positive predictive value (88%). Data are similar to those with literature, a study published in 2003 in Endoscopy reveal a 67% sensitivity for aplatisation of gastric folds and 48% for the visualization of vascular pattern on the submucosa into the corpus , and 14% in antral region respectively, with a specificity between 85 and 91% (29).

Conclusions:

The presence of HP infection is associated with increased risk of superficial and atrophic gastritis;

In our study we noted an increased prevalence of gastric atrophy diagnosed by endoscopy and pathology above 40-50 years

We didn't observe a predisposition of atrophy or intestinal metaplasia for any gender<

Rural residence, smoking or ex-smoking habit and, with a mild significance, alcohol consumption were associated with risk of gastric mucosal atrophy;

Intestinal metaplasia was associated with rural residence, smoking habit and, with mild correlation, with alcohol consumption;

Endoscopic-diagnosed atrophy has proved a mild to moderate sensibility for the detection of atrophy at pathological examination, but a high specificity for the diagnosis.

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