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ORIGINAL ARTICLE

# Frequency of Precancerous Lesions in Endoscopic Gastric Biopsies in Chronic Gastritis

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## ABSTRACT

**Objective:** To determine the frequency of precancerous lesions in endoscopic gastric biopsies of patients with chronic gastritis.

**Study Design:** A case series.

**Place and Duration of Study:** Department of Histopathology, Liaquat National Hospital, Karachi, from July 2008 to January 2009.

**Methodology:** Over 6 months, 375 endoscopic gastric biopsies of patients with age group of 15 – 65 years having endoscopic chronic gastritis were included. From final biopsy report, basic information like patient demographics and presence of precancerous lesions i.e. activity (chronic active gastritis), atrophy (atrophic gastritis), intestinal metaplasia and dysplasia were recorded on proforma. Results were described as proportions and frequency.

**Results:** The frequency of precancerous lesions in endoscopic gastric biopsies of patients with chronic gastritis in Karachi was markedly high. Most common lesion was chronic active gastritis as depicted by activity (48.3%); dysplasia (1.3%) was the least common. Proportion of more aggressive precancerous lesions were markedly higher in older age group (> 40 years).

**Conclusion:** The precancerous lesions are frequent in endoscopic gastric biopsies of patients with chronic gastritis.

**Key words:** *Precancerous lesion. Atrophy. Metaplasia. Dysplasia. Activity. Chronic gastritis. Endoscopic gastric biopsy.*

## INTRODUCTION

Gastric carcinoma ranks second in cancer deaths worldwide due to late presentation, poor treatment options and aggressive disease course.[1] Having particularly high mortality rates in Asia, South America and Central Europe, it is twice as common in males as in females.[2] There is great emphasis on early detection of precancerous conditions because full blown carcinoma has a depressing outlook.[3] Studies in Pakistan have also reported a high prevalence of gastric carcinoma and its precancerous lesions but none as yet reported prevalence of precancerous lesions with special emphasis on patients of chronic gastritis.[4,5]

Gastric carcinogenesis is a multistep process with intervening precancerous lesions, providing opportunity to decrease mortality by halting this process and early detection of stomach cancer.[6,7] According to Correa's model of carcinogenesis, gastric carcinogenesis is a multistep process. The precancerous lesions implicated in these steps are potentially reversible changes.[3,6] So the clinician should look for these lesions, as to detect the abnormality at reversible stage rather than permitting the lesions to become full blown cancer. Gastric carcinoma pathogenesis is supposed to be the result of a mixture of environmental factors, including *Helicobacter pylori (H. pylori)* infection, excessive salt intake, low vegetable and fruit intake and the accumulation of specific genetic alterations.[3,6] *H. pylori* prevalence rate is high in Pakistan, India and Bangladesh particularly in paediatric population. Once acquired, this bacterium is able to establish lifelong relationship with its host.[7]

The problem in the set-up is that gastric cancer is often diagnosed at advanced stages leading to a very poor prognosis. Few centres put stress on early detection of gastric carcinoma in potential candidates. An expanded and long-term precancerous process, lasting for decades, precedes most gastric cancers. It includes the following sequential steps: chronic active gastritis, multifocal atrophy, intestinal metaplasia, and intra-epithelial neoplasia (dysplasia).[5,7] An early diagnosis and treatment of *H. pylori* infection with chronic gastritis is a prudent investment and the goal of *H. pylori* treatment is complete elimination of organism. This includes triple therapy which combines two or more antibiotics with an anti-secretory agent.[8-10]

Based on the frequency of precancerous lesions, specific recommendations for obtaining biopsies in such patients can achieve an early detection of precancerous gastric lesions and hence a favourable outcome through

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either treatment or prevention of progression of precancerous lesions.

The aim of this study was to determine the frequency of precancerous changes in gastric biopsy specimens obtained through endoscopy from patients having chronic gastritis and dyspeptic symptoms for 6 months who had not responded to targeted medical therapy.

## METHODOLOGY

This prospective case series was conducted at Liaquat National Hospital, Karachi, from July 2008 to January 2009. Specimens were collected by employing non-probability purposive sampling technique. Sample size was calculated as 375, at p = 58%, d = 5% and confidence level = 95%. Patients belonging to either gender, whose endoscopic gastric biopsies had been received were enrolled after verbal informed consent was taken. Duplicate samples from same patient or samples from patients with a known carcinoma, ulcer, polyp and pernicious anaemia or from patients on known calcium antagonists, nitrates, theophyllines, bisphosphonates, corticosteroids and non-steroidal anti-inflammatory drugs were excluded. All samples were processed as per standard guidelines including steps of fixation by 10% formalin, dehydration by increasing concentration of ethyl alcohol (70%, 80% and 90%), clearing by xylene and final preservation by paraffin wax and then stained with routine Hematoxylin and Eosin (H & E) stain for evaluation. Data was collected on proforma including patient's demographics like age and gender and by microscopic examination, presence of activity, activity with *Helicobacter pylori*, atrophy, metaplasia and dysplasia.

Data was stored in Statistical Package for Social Sciences (SPSS) Windows version 10.0 statistical package. To determine significance of any difference in age between patients with and without the precancerous conditions, T-test was used. To determine significance of difference in gender between patients with and without the precancerous conditions, Chi-square test was used. P-value of less than 0.05 was considered significant; 95% confidence interval was computed for proportion of specific precancerous lesion.

## RESULTS

A total of 375 patients were included in this study fulfilling the inclusion criteria. None of the biopsies was inadequate for histopathological evaluation. Patients' mean age was 41.3 ± 13.3 years ranging from 16 – 75 years. There was an equal distribution of gender seen. Chronic active gastritis was encountered in most cases (n = 181, 48.3%), strongly associated with the presence of *Helicobacter pylori* organisms, where *Helicobacter pylori* were seen in 175 (96.6%) biopsies out of the 181 cases of chronic active gastritis. Atrophy was present in 9.6% biopsies whereas intestinal metaplasia was found in fewer number i.e. in 31 (8.3%) biopsies. Dysplasia, which was the least common lesion, was present in only 5 (1.3%) patients. Some biopsies exhibited more than one lesion. Precancerous lesions were found in 232 (61.9%) biopsies out of 375 biopsies. Mean (±SD) age of precancerous positive patients was 42.2 ± 13.1 years and precancerous negative patients was 39.7 (±13.6), insignificant difference found to be p = 0.078, (min – max = 16 – 65 years). Out of 232 positive cases, 160 (69%) patients had age between 31 – 60 years. Gender distribution of precancerous lesions was also noted and the proportion of precancercous lesion positivity was significantly higher in males (p = 0.003, Figure 1). Other biopsy findings with respect to gender are shown in Table I. Proportion of chronic active gastritis depicted by activity was also significantly high in males. However, proportion difference of atrophy was statistically insignificant between gender, out of 36 cases, 20 (55.6%) were males and 16 (44.4%) were females. Proportion of intestinal metaplasia in accordance with gender was again significantly high in males. Among the dysplasia cases, 3 (60%) were females and 2 (40%) were males. Biopsy findings with respect to age groups (i.e. ≤ 40 years and > 40 years) are detailed in Table II. Proportion of chronic active gastritis was significantly high in age group ≤ 40 years at p < 0.05. The percentage of dysplasia was significantly high in age group > 40

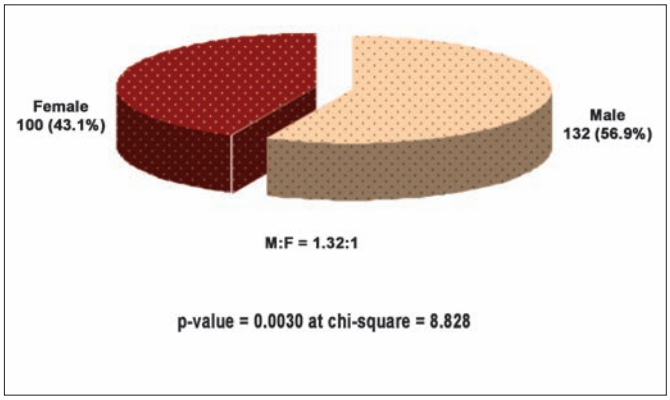


**Figure 1:** Gender distribution of precancercous lesions (n = 232).

**Table I:** Gender distribution of other biopsy findings in patients with chronic gastritis (n = 375).

| | Male | Female | p-values |
|---|---|---|---|
| Activity (chronic active gastritis) | 103 (56.9%) | 78 (43.1%) | **0.0084+ |
| Activity and *Helicobacter pylori* | 98 (56.3%) | 76 (43.7%) | **0.0200 |

**At chi-square = 6.935 + Significant, **At chi-square = 5.411 + Significant.*

**Table II:** Endoscopic gastric biopsies finding of chronic gastritis in age (n = 375).

| | Age (years) ≤ 40 | Age (years) ≥ 40 | p-values* |
|---|---|---|---|
| Activity(Chronic active gastritis) | 105 (58%) | 76 (42%) | **0.002+ |
| Activity and *Helicobacter pylori* | 101 (58%) | 73 (42%) | **0.002+ |
| Dysplasia | 0 | 5 (100%) | 0.0617 n.s |

years with all the cases of dysplasia having age more than 40 years. The proportion of atrophy was again high in age > 40 years, out of 36 cases, 33 (91.7%) cases had age > 40 years while only 3 (8.3%) cases had age ≤ 40 years. Proportion of intestinal metaplasia was also significantly high in age > 40 years, out of 31 biopsies, 28 (90.3%) cases had age > 40 years and only 3 (9.7%) cases had ≤ 40 years.

## DISCUSSION

Gastric cancer often presents at an advanced stage and at that stage most patients have very short survival.[18] The global incidence of gastric cancer is still quite high with approximately 870,000 new cases and 650,000 deaths per year. The estimated current incidence of gastric cancer is approximately 16.2/100,000 persons/ year.[19] Gastric cancer in Karachi fall into the archetype of a low risk developing country pattern, but increasing incidence has been reported recently. This is most marked in males above 40 years of age.[20] The process of carcinogenesis engages a slow but continuous stepwise progression from active gastritis leading to adenocarcinoma.[21,18] Intestinal-type GC typically arises in the setting of chronic active gastritis, usually caused by *Helicobacter pylori* and develops through intermediate stages.The chronic aggression to the gastric epithelia eventually causes the appearance of preneoplastic lesions and increases the risk of gastric cancer. It has become evident that *Helicobacter pylori* eradication by antibiotic treatment combined with proton pump inhibitor (PPI) serves as the primary chemo-prevention strategy to reduce gastric cancer incidence. Moreover, the eradication therapy reduces gastric cancer incidence in patients without any precancerous lesions at the baseline and is most effective before the development of atrophic gastritis.[22]

In this study, atrophic gastritis and intestinal metaplasia were assessed separately, in conformity with the updated Sydney system.[23] In order to prevent misclassification, the less advanced lesions that were indefinite for dysplasia were classified as reactive atypia, rather than dysplasia. In this study, the precancerous lesions were seen more frequently in males. This possibly represents same etiological factors (ecological, genetic and life-style factors like smoking etc.) for precancerous lesions and gastric carcinoma in males, as the incidence of gastric carcinoma is also increasing significantly in male population of Karachi.[20] This may be because some proposed causative factors for premalignant lesions, such as smoking and tobacco use, are more prevalent in males. In international studies, frequency of precancerous lesions increases with increasing age, however, precancerous lesions present in patients over 60 years of age, was only 7.3% of total in this study. The likely explanation for this is that out of a total 375 biopsies, only 25 patients were more than 60 years of age, so the age distribution of precancerous lesions could not reach statistical significance due to small number of patients falling in that age group. However, age is known as an important factor governing the histological progression.[3]

The most common lesion was chronic active gastritis and the additional significant finding of spiral bacterium *Helicobacter pylori* signifies the chronic aggression by *H. pylori* to the gastric mucosa which finally results in the appearance of preneoplastic lesions and increases the risk of gastric cancer.

In most of the other studies of this sort, patients with symptoms of dyspepsia were selected, whereas, the authors were more focused and wanted to be target specific so that only those patients with symptoms of dyspepsia were included that showed endoscopic chronic gastritis. However, the present results were in concordance with those seen in other international studies, most probably because most patients with symptoms of dyspepsia show signs of endoscopic gastritis.[24,25]

Limitations of this study include confounders such as biopsy sampling and focal nature of the precancerous lesions which may alter results subject to sampling error. The fact that the population in this study lived in a relatively open society and had varying living conditions or habits, may enhance the effects of other mixed factors such as intake of fresh vegetables, salt consumption, water intake. Unfortunately, the intra-gastric distribution of pre-malignant lesions could not be evaluated in this study because the data regarding the exact site of biopsy and number of biopsies taken from each compartment within the stomach was not available. Therefore, for the evaluation of pre-malignant lesions, a more extensive biopsy sampling may be required.

This study provides important insight into precancerous lesions and that precancerous lesions are common in patients with chronic gastritis. *Helicobacter pylori* associated chronic active gastritis is the most common pre-malignant gastric lesion. It can, therefore, be assumed that all subsequent stages have a background of chronic active inflammation of the gastric mucosa. It was also found that advanced precancerous gastric lesions increase with age (> 40 years) depicting age as an important factor. In addition, there was gender predilection and the lesions were more commonly seen in males. It is recommended that gastric biopsy histological evaluation should be done in all patients with chronic gastritis. Follow-up and preventive strategies in patients with established pre-malignant lesions is highly recommended.

## CONCLUSION

Precancerous lesions were encountered with significant frequency in patients with endoscopic chronic gastritis. Based on these findings, it is proposed that it is a

rational approach to get biopsies from patients with endoscopic chronic gastritis, which can allow us to detect precancerous lesions thus providing opportunity to apply primary chemo-preventive strategies along with lifestyle changes and halt initial steps of the gastric carcinogenic cascade.

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