

Epidemiologic Analysis of Gastric Carcinoma in the Western Region of Nepal

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Abstract

Background

Gastric cancer is among the most common malignancies in Asia, comprising 74% of all global cases. Identifying the environmental risk factors may possibly shed more light on effective treatment and the prevention of this disease. The aim of our study is to document different histologic types of gastric cancer as per age, sex and ethnic groups in the patients in Nepal, to know the frequency of different gross and microscopic subtypes (according to Lauren's classification) of tumor and to find out the association of H. pylori and other major risk factors with gastric cancer.

Materials and Methods

The present study is a hospital based retrospective study done in the Department of Pathology, Manipal Teaching Hospital, Pokhara, Nepal, from Jan 1999 to July 2010. All the endoscopic biopsies and gastrectomy specimens from patients with diagnosed gastric carcinoma were reviewed and the clinical and other data were analyzed.

Results

In this study period, a total of 1223 cases related to stomach were received in Department of Pathology. Considering the

inclusion and exclusion criteria, a total of 397 cases - 315 cases of endoscopic biopsy and 82 cases of gastrectomy - were included in the study. In our study, the most affected age group and caste were 61-70 years (47.36%, CI 42.44% to 52.27%) and Gurungs (32%, CI 27.16% to 36.32%). The commonest gross and microscopic types were Borrmann's type IV (40%, CI 29.63% to 50.86%) and intestinal type (53%, CI 47.99% to 57.81%). Gastric antrum was the most affected site (70%, CI 65.26% to 74.29%). Among the cases with H pylori, antrum (62.5% CI 45.73% to 79.27%) was found to be the commonest site. Among all cases in Gurung, Chhetri and Brahmin communities, we retrieved data regarding risk factors in 93, 65 and 50 cases respectively. Significant relationship was found between the three risk factors studied and the ethnic groups. Smoked meat and alcohol were found to be associated with gastric carcinoma more in Gurungs and Chhetris than in Brahmins ($p=0.0001$). On the contrary, cases among Brahmins are found to more associated with smoking than Gurungs and Chhetris ($p=0.0001$).

Conclusion

Gastric carcinoma is a common malignancy in this part of world. The most high risk group includes elderly males with history of alcoholism and smoked meat consumption in Gurung community and with history of smoking from Brahmin family. We advise that regular endoscopic surveillance should be done at least in high risk group for the early detection of cancer.

Key Words

Gastric Carcinoma, Ethnicity, Risk Factors, Epidemiology, Helicobacter pylori, Nepal

Background

Gastrointestinal cancers account for a large fraction of human neoplasms. They are almost without exception incurable when gross metastases exist¹. Gastric carcinoma is a worldwide disease. In 1990, it was the second most common cancer in the world with an estimated 800,000 new cases every year, 60% of them being in developing countries². The areas of highest incidence include Eastern Asia, South America and Eastern Europe and those of lower incidence include North America, North Europe, most parts of Africa and South Eastern Asia^{3, 4}. However, there has been a steady decline in its incidence and mortality over the past several decades³. Its incidence has markedly decreased in developed countries but remains high in countries like Japan and Chile; Japan having the highest incidence worldwide^{3,5}. In 2008, it has come down to become the 6th commonest cancer worldwide (Age Standardized Rate (ASR) = 14.1%) with an estimated 1,000,000 cases⁶. It is the 4th commonest cancer in males and 5th in females. Interestingly, 74% of all global cases are from Asia, where gastric carcinoma is the 3rd commonest cancer (ASR 18.5%) including both genders, the 2nd commonest cancer in males and the 4th in females⁶.

The exact cancer prevalence rate in Nepal is unknown due to the lack of a population based national cancer registry. However, every year at least 17,000 new cancer cases are estimated and the figure is expected to go up considerably in the future⁷. According to the present data from Nepal, it is the 5th commonest cancer (ASR 8.2%) including both genders, 3rd in males and 6th in females⁵.

A hospital based study done in Nepal showed that 8.8% of all cancers treated by radiotherapy in Pokhara were GIT malignancies⁸. Endoscopic biopsy is widely regarded as the most sensitive and specific diagnostic tool for gastric cancer³. Neoplasms of various parts of the gastrointestinal tract have a marked variation of distribution. These variations are according to race, gender, age, the part of the gastrointestinal tract affected, geographical region of the world and other exogenous risk factors^{9,10}. Identifying the environmental risk factors may possibly shed more light on effective treatment and the prevention of these diseases. The aim of our study was to document different histologic types of gastric cancer as per age, sex and ethnic groups in the patients, to know the frequency of different gross and microscopic subtypes (according to Lauren's classification) of tumor and to find out the association of H. pylori and other major risk factors with gastric cancer.

Materials and Methods

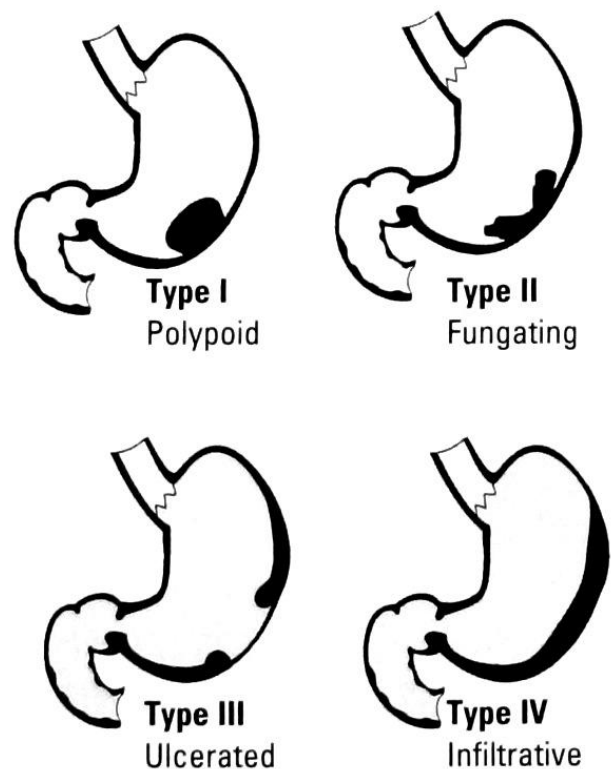
The present study is a hospital based retrospective study done in the Department of Pathology, Manipal Teaching Hospital, Pokhara, Nepal in a period from Jan 1999 to July 2010. All the endoscopic biopsies and gastrectomy specimens in patients with diagnosed gastric carcinoma were reviewed and analyzed. Patients' data were retrieved from the records of the Department of Pathology and also Department of Medical Records, Manipal Teaching Hospital. The parameters analyzed were age, gender, ethnicity, risk

factors, gross and microscopic types. For gross morphological types, Borrmann classification was followed (Fig 1). All biopsy tissues were fixed in 10% formalin, processed routinely and stained in Hematoxylin & Eosin and Giemsa stain for H. pylori.

Cases excluded from the study were (a) tumors with extensive areas of necrosis and no viable or normal looking tissues (b) cases where the site of biopsy is unclear, not mentioned by endoscopist or could not be identified histologically (c) other types of gastric malignancies (e.g., lymphoma, gastrointestinal stromal tumor etc).

The data collected was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and EPI Info 3.5.1 Windows Version. Chi- square test and Z-test was used to compare the significance difference or relationship between two variables. A p-value of <0.05 (two-tailed) was used to establish statistical significance.

Fig 1: Borrmann Classification - schematic representation³



Results

In this study period, a total number of approximately 25000 biopsies have been received in the Department of Pathology. Among these, there were a total of 1223 cases related to stomach (Table 1). Majority of endoscopic biopsies were found to be nonmalignant while all of gastrectomy specimens were found to be malignant. Considering the inclusion and exclusion criteria, a total of 397 cases, including 315 cases of endoscopic biopsy and 82 cases of gastrectomy were included in the study.

Table 1: Frequency of endoscopic biopsy and gastrectomy cases

Frequency of Cases	Endoscopic biopsy	Gastrectomy specimen	Total
Total cases	1137	86	1223
Malignant cases	340	86	426
Included in the study	315	82	397

Table 2 shows age wise frequency of all the studied cases. There is a sharp increase in incidence after 50 years of age and highest number is seen in the age group 51-70 years. Males are more commonly affected than females in a M:F ratio of 1.8:1 (Table 3).

Table 2: Distribution of cases according to age

Age range	Number of cases	Percentage	CI
21-30	5	1.26	(0.16, 2.36)
31-40	9	2.27	(0.8, 3.73)
41-50	19	4.79	(2.67, 6.89)
51-60	143	36	(31.3, 40.74)
61-70	188	47.36	(42.44, 52.27)
71+	33	8.31	(5.6, 11.03)
Total	397		

Table 3: Distribution of cases according to gender

Gender	Number of cases	Percentage	Ratio	p value
Male	254	64	1.8	0.001**
Female	143	36	1.0	
Total	397			

** Statistically significant (p value<0.05)

Among the different castes, Gurungs are much more commonly affected with 32% of all cases (Table 4). They are closely followed by Chhetri and Brahmins comprising 21% and 15% respectively.

Table 4: Distribution of cases according to caste

Caste	Number of cases	Percentage	CI
Gurung	126	32	(27.16, 36.32)
Chhetri	83	21	(16.91, 24.91)
Brahmin	60	15	(11.59, 18.64)
Magar	29	7	(4.75, 9.86)
Newar	28	7	(4.53, 9.57)
Other castes	71	18	(14.11, 21.65)
Total	397		

Table 5: Site wise distribution of all cases included in the study

Site	Number of cases	Percentage	CI
Antrum	277	70	(65.26, 74.29)
Corpus	78	20	(15.74, 23.56)
Fundus	28	7	(4.53, 9.57)
Cardia	14	3	(1.71, 5.34)
Total	397		

Antrum was found to be the site of carcinoma in 70% of cases, thus being the most common site (Table 5). Gross morphologic types were studied in all 82 gastrectomy cases (Table 6) according to Borrmann's type. Type IV was the commonest type with 33 cases (40% of all 82 cases). Microscopically, all cases were divided as per Lauren's classification and it was found that 210 cases (53%) were of intestinal type (Table 7).

Table 6: Gross morphological distribution of all gastrectomy cases

Borrmann's Gross types and Descriptions	Number of cases	%	CI
Type I Polypoid protruding growth.	0	--	--
Type II Fungating growth. with discrete sharply defined borders	22	27	(17.24, 36.42)
Type III Ulcerated and infiltrating with no discrete borders in ulcer	27	33	(22.76, 43.10)
Type IV Diffuse infiltrating, linitis plastica	33	40	(29.63, 50.86)
Total	82		

Table 7: Microscopic types - distribution of all cases included in the study

Microscopic types (Lauren's classification)	Number of cases	Percentage (n = 82)	CI
Intestinal	210	53	(47.99, 57.81)
Diffuse	123	31	(26.43, 35.53)
Mixed type	64	16	(12.50, 19.74)
Total	397		

H. pylori was associated with 32 cases i.e. 8% of all carcinoma cases (Table 8).

Table 8: Association of H pylori and its relation to site of carcinoma

H. Pylori association with cancer (N = 32, 8% of total cases)

Site of carcinoma	Number of cases	Percentage	CI
Antrum	20	62.5	(45.73, 79.27)
Corpus	11	34.4	(17.92, 50.83)
Cardia	1	3.1	(0, 9.15)
Fundus	0	0	--
Total	32		

Table 9: Caste-wise Assessment of major risk factors

	Gurung	Chhetri	Brahmin	p value
Total cases	126	83	60	
Data available for risk factor	93	65	50	
Smoked meat				0.0001**
Yes	68	41	18	
No	25	24	32	
Alcohol				0.0001**
Yes	72	39	19	
No	21	26	31	
Smoking				0.0001**
Yes	32	25	36	
No	61	40	14	

** Statistically significant (p value<0.05)

Among all cases in Gurung, Chhetri and Brahmin communities, we could retrieve data on risk factors in 93, 65 and 50 cases respectively. Significant relationship was found between the three risk factors studied and ethnic groups (Table 9). Smoked meat was found to be associated with gastric carcinoma in Gurungs, Chhetris and Brahmins in 73%, 63%, and 36% cases respectively. Similarly alcohol consumption was found to be associated more commonly with Gurungs (77%) and Chhetris (60%) than among Brahmins (38%). On the contrary, cases among Brahmins (72%) are found to more associated with smoking than Gurungs (34%) and Chhetris (38%).

Discussion

Gastric carcinoma is one of the most common malignancies worldwide and is among the top five malignancies encountered at Manipal Teaching Hospital⁸. Among all the histopathological tissues received in the Department of Pathology, approximately 5% cases were related to gastric pathology. We have reported a total of 426 cases of gastric malignancy (1.7% of all cases and 35% of all gastric tissue) in the study period. As per our exclusion criteria, 397 cases were included in the study.

Gastric carcinoma is extremely rare before the age of 30 years and most patients are above 50 years of age^{3,5}. Though a steady decline in the incidence and mortality rates of gastric carcinoma has been observed worldwide over the past several decades, the absolute number of new cases per year is increasing mainly because of the aging of the

population¹¹. In our study, majority of the patients (331 cases, 83%) were in the age range of 51 to 70 years. This finding corroborates well with international trends. However, cases of gastric carcinoma in young and even in children are recorded in world literature and we found 5 cases in the age group of 21-30 years^{12,13}. As seen in other international studies, males are clearly affected more commonly, nearly two times more than females in our data³.

All gastric carcinomas arise from foveolae; in most instances, in a back ground of chronic atrophic gastritis with intestinal metaplasia^{14,15}. The most frequent site of stomach cancer is the distal stomach i.e., the antro-pyloric region³. Carcinomas of the body or the corpus are located mostly along the greater or lesser curvature^{3,5}. In our study, the distal stomach (antrum) was also seen to be the primary site in 70% of cases followed by the body or corpus (20%).

Grossly, gastric carcinomas show a wide variation⁵. Dysplasias may present as a flat lesion, difficult to detect on conventional endoscopy³. The gross appearances of advanced carcinoma include flat, ulcerated, or fungating tumor growing into the gastric lumen and deeply invasive tumor growing through the wall of the stomach^{5,16}. Borrmann classified the gross appearance of advanced carcinomas into 4 types based on the proportion of exophytic and endophytic components^{3,5,17}. Fig. 1 shows the schematic representation of four gross morphological types described by Borrmann³. Types II and III are common³. Diffuse type (Type IV) spread superficially in the mucosa and submucosa producing flat lesions with or without ulceration. With extensive infiltration, a linitis plastica or leather bottle stomach results. In our study, we analyzed 82 gastrectomy cases. We found type IV (diffuse infiltrating) to be the most common constituting 40% of 82 cases. However, combined type II and III comprise 60%. We did not find any nonulcerated polypoid type (type I) in our study. Type IV has been found to be an independent prognostic factor by other studies¹⁸. More studies from this country on this aspect are invited. Depending of the relative proportion of mucin and fibrosis, the tumor may have fleshy, fibrous or gelatinous appearance^{3,5}.

Microscopically, this carcinoma has been divided into two major categories by Lauren in 1965¹⁹. Lauren classification has been found useful in evaluating the natural history of gastric carcinoma³. According to Lauren Classification, the main two types are "intestinal" and "diffuse" type. Tumors that contain approximately equal quantities of both components are called "mixed" type and carcinomas too undifferentiated to fit into any category are placed in "indeterminate" type³. Intestinal carcinomas form recognizable glands ranging from poorly to moderately differentiated and well differentiated. On the other hand, diffuse type consists of poorly cohesive cells diffusely infiltrating the gastric wall with minimal gland formation^{3,5}. This type is currently known as "signet ring" carcinoma as most of the cells contain intracytoplasmic mucin giving the cell the typical signet ring appearance^{3,5}. According to the original study by Lauren, intestinal type comprised 53% and

diffuse type comprised 33%. In our study, the findings are closely similar with intestinal type being 53% and diffuse type 31%.

H. pylori has been implicated as an etiologic factor in gastric carcinoma through development of chronic gastritis²⁰. Strong evidence has been shown in prospective cohort studies that presence of *H. pylori* antibodies in serum poses a significant increased risk of carcinoma²¹. *H. pylori* causes these sequential stages of disease progression – chronic gastritis, multifocal atrophy, intestinal metaplasia and intraepithelial neoplasia. Gastritis and atrophy lead to elevated pH altering the colonizing bacterial flora. These bacteria activate reductases that form nitrite from food nitrate. This nitrite reacts with amines, amides and ureas producing carcinogenic N-nitroso compounds^{22,23}. *H. pylori* however are mainly seen in normal mucosa and are absent in areas with intestinal metaplasia where neoplasia originates³. In our study, we searched for *H. pylori* in both the neoplastic and non-neoplastic mucosa in all 397 malignant cases. We found presence of *H. pylori* only in 32 cases (8%). However, it is premature to come to any conclusion and there is scope of further study to assess the association of *H. pylori* with gastric carcinoma in this part of the world. A follow-up meta-analysis of 42 studies carried out by Eslick GD et al showed a significant relationship between *H. pylori* and gastric cancer²⁴. Several studies reported that *H. pylori* infection for 10 or more years poses a significantly increased risk for carcinoma²⁵. So, ideally, cases with *H. pylori* associated gastritis should be prospectively followed up for adequate period to correctly assess its association with carcinogenesis. Several studies have been done regarding prevalence of genetic strains of *H. pylori* in different ethnic groups. As it was found that *H. pylori* has evolved together with its host, the subpopulation of *H. pylori* serves as a surrogate marker for estimating anthropological and demographic migrations. Manjulata Devi S et al have shown in their study that the important *H. pylori* strains prevalent in India share more ancestral similarity with their European counterparts rather than African and East Asian strains²⁶. Farhana K et al has studied the genetics of *H. pylori* strain in high altitude low populated Himalayan terrain like Ladakh and found it to be distinct and less virulent than the strains in East Asian countries like China and Japan²⁷. Shalome C et al also has found in their study among different ethnic groups in New Zealand that there are ethnic group specific *H. pylori* strains²⁸. Western Nepal being geographically located in sub-Himalayan terrain may show presence of some unique *H. pylori* strains reflecting its geo-climatic and anthropological nature. Studies have also been carried out with respect to responsiveness and resistance of different strains of *H. pylori* to different medication regimens.

Among other risk factors, the most consistent association is diet. This is especially true for intestinal carcinoma³. Salt intake, smoked meat, smoked fish, pickled vegetables, chili peppers, alcohol and tobacco are found to incur high risk^{3, 29}. In our study, we classified the incidence of gastric carcinoma in different castes and also tried to find out the

importance of smoked meat, alcohol and smoking as risk factors. According to an estimation by the World Health Organization (WHO), 38.4 % of the total population of Nepal above 15 years of age smoke, of which 48.4% are males and 28.7% are females³⁰. NY Sung et al had carried out a prospective study in Korean population and found strong association of smoking and alcohol consumption with gastric carcinoma. He further states than combined smoking and alcohol poses a higher risk as synergistic effect³¹. Despite a high incidence in many Asian nations, population-based studies indicate that Asian-American patients have improved gastric cancer survival compared with other races and ethnicities³²⁻³⁵. However, the categorization of Asian ethnicities as a single race appears inappropriate, given that Asians are a culturally diverse mix of people that differ widely in country of origin, immigration patterns, socioeconomic status, and lifestyle factors³⁶⁻³⁸. Nevertheless, epidemiologic studies often aggregate these diverse populations without mention of the specific ethnic subgroups. The flaw in this practice was recently underscored by a report from Kwong et al., who observed wide variations in cancer incidence and mortality among the five most prevalent Asian-American subgroups, namely Korean, Japanese, Chinese, Vietnamese, and Filipino³⁹. These observations highlight the need to carefully examine gastric cancer outcomes among the different Asian ethnicities. In Nepal, we found that Gurungs are more commonly affected followed by Chhetris and Brahmins comprising 32%, 21% and 15% respectively.

Conclusion

Gastric carcinoma is a common malignancy in this part of world. There is need of further follow up cohort studies regarding carcinogenic property of *H. pylori* and prevalence of its different strains in different ethnic groups in the sub-Himalayan belt. This may help in understanding the pathogenesis of gastritis and gastric cancer as well as the responsiveness and resistance of different anti-helicobacter regimens. The most high risk group includes elderly males with history of alcoholism & smoked meat consumption from Gurung community and with history of smoking from Brahmin family. There is obvious scope of further studies on gastric carcinoma in other parts of this country and to also assess the other risk factors in this population. However, we advise that regular endoscopic surveillance should be done at least in the high risk group for the early detection of cancer.

Conflict of Interests

The authors do not have any conflict of interest arising from the study.

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