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ASSOCIATIONS OF DURATION, INTENSITY, AND QUANTITY OF SMOKING WITH RISK OF GASTRIC

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Abstract:
Objectives: To investigate the associations between smoking habits (duration, intensity, and quantity) and the risk of developing GIM.

Materials and Methods: For this cross-sectional study, we enrolled 180 patients of both genders. Among them, 69 individuals presented with GIM, while 111 participants served as controls without GIM. Each participant completed standardized questionnaires and underwent a study endoscopy, including gastric mapping biopsies. The diagnosis of GIM was confirmed by identifying intestinal metaplasia in any non-cardia gastric biopsy. The study duration was 6 month from (August, 2023 to January, 2024) and was conducted at Pakistan Institute of Medical Sciences Hospital Islamabad.

Results: The mean age of all enrolled 102 patients was 46.08±11.7 years with mean BMI of 25.46±5.13 kg/m2. Among the participants, 62 (60.8%) were male, while the remaining 40 (39.2%) were female. Current smokers showed a twofold increased risk for gastric intestinal metaplasia compared to those who never smoked (odds ratio [OR] 2.452, 95% confidence interval [CI] 1.23-3.64). Additionally, among individuals with a history of smoking, both increasing duration and total dose were significantly linked to a higher risk of developing gastric intestinal metaplasia. However, among former smokers, the risk of gastric intestinal metaplasia declined progressively over time, reaching a level comparable to that of never smokers after 15 years of smoking cessation.

Conclusion: The study concluded that there is strong association between the associations between smoking habits (duration, intensity, and quantity) and the risk of developing GIM.

Key words: Gastric intestinal metaplasia; tobacco; gastric cancer, Quantity of Smoking

INTRODUCTION:

Gastric intestinal metaplasia (GIM) is a preneoplastic lesion of the stomach, characterized by the replacement of the normal gastric epithelium with intestinal-type epithelium.(1) It is considered a precursor to gastric cancer, which remains a significant global health burden.(2) While the etiology of GIM is multifactorial, smoking has been suggested as a potential risk factor. However, the specific associations between different aspects of smoking behavior (duration, intensity, and quantity) and the risk of GIM remain unclear. GIM is considered a premalignant condition, as it increases the risk of developing gastric cancer over time. This risk is estimated to be 6–9 times higher, underscoring the importance of identifying and managing GIM as a premalignant condition to mitigate the risk of gastric cancer development. Tobacco smoking is known as a well-established risk factor for gastric cancer, contributing to the development of tumors in both the cardia and non-cardia regions of the stomach.(3, 4) However, the relationship between the quantity of smoking (i.e., the total amount of tobacco consumed) and GIM risk remains less explored in the literature. Few studies have specifically addressed this aspect, with inconsistent findings reported. Some studies suggest a positive association between higher cumulative tobacco consumption and increased GIM risk, while others fail to establish a significant relationship after adjusting for confounding factors such as age, gender, and dietary habits.(5-7)

By systematically examining the effects of smoking duration, intensity, and quantity on GIM development, the study aims to contribute to a better understanding of this important precursor to gastric cancer and inform preventive efforts aimed at reducing its incidence and mortality.

Objective: To investigate the associations between smoking habits (duration, intensity, and quantity) and the risk of developing GIM.

MATERIALS AND METHODS:

Study Design: cross-sectional study.

Study setting: Pakistan Institute of Medical Sciences Hospital Islamabad.

Duration of the study: Duration of the study was 6 month (August, 2023 to January, 2024).

Inclusion Criteria:

- Individuals who are current or former smokers.
- Patients of age 20-70 years.

Exclusion Criteria:

- Patients with previous gastroesophageal surgery.
- Patients with a history of gastroesophageal cancer, active lung, colon, breast or stomach cancer and significant liver disease.

Methods:

This cross sectional study was conducted at Pakistan Institute of Medical Sciences Hospital Islamabad. from August, 2023 to January, 2024, following the approval of the hospital's ethical committee. A total of 180 patients were enrolled and an inform consent were obtained from the patient/guardian. Participants were initially asked if they had smoked more than 100 cigarettes, including hand-rolled cigarettes, cigars, or pipes, at any point in their lifetime. Those who answered affirmatively were then further queried about their smoking history, including the age at which they began smoking, if and when they ceased smoking, and the total duration of their smoking habit. Additionally, participants were asked to recall whether they smoked during each decade of life (10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years old), as well as the amount they typically smoked per day during these periods. Ever smokers were characterized as individuals who reported having consumed more than 100 cigarettes in their lifetime, including both current smokers and

former smokers who had quit at least one year before study enrollment. The duration of smoking was determined by subtracting the age of smoking initiation from either the age of permanent cessation (for former smokers) or the reference age (for current smokers). Smoking intensity was assessed by quantifying the average number of cigarettes smoked per day.

All patients underwent endoscopy with gastric mapping biopsies. The procedure for participants undergoing a study endoscopy with gastric mapping biopsies usually comprises several sequential steps. First, the endoscopy facility is prepared, ensuring the availability of necessary instruments, proper calibration of endoscopic equipment, and preparation of sedation or anesthesia medications. Participants are then prepared for the procedure, receiving instructions on fasting, medication restrictions, and an explanation of the procedure's details, followed by obtaining informed consent. During the endoscopy procedure, participants are escorted to the endoscopy suite, where sedation or anesthesia is administered as needed. The endoscope is carefully inserted into the mouth and advanced through the esophagus, stomach, and duodenum for a comprehensive examination of the gastric mucosa, with gastric mapping techniques used to obtain biopsies from multiple stomach regions. Post-procedure care involves monitoring vital signs, providing instructions on diet and activity, and scheduling follow-up appointments. Biopsy specimens are labeled and transported to the pathology laboratory for histological analysis, evaluating the presence of GIM and other abnormalities, with findings documented in pathology reports for each participant.

During histological analysis, biopsy specimens were embedded in paraffin and sectioned into 5-sections for staining, including hematoxylin and eosin, and alcian blue at pH 2.5. The assessment of GIM severity was independently conducted by two pathologists unaware of endoscopic findings. Discrepancies were resolved by a third pathologist. GIM cases exhibited intestinal metaplasia on at least one non-cardia gastric biopsy, while controls lacked GIM. Pathologists used the Operative Link for Gastric Intestinal Metaplasia (OLGIM) criteria for standardized severity assessment.

RESULTS:

The mean age of all 102 enrolled patients was 46.08 ± 11.7 years, with a mean BMI of 25.46 ± 5.13 kg/m^2 (Table 1). Among the case patients, there were 58 (84.1%) males and 11 (15.9%) females, while in the control group, there were 95 (85.6%) males and 16 (14.4%) females, resulting in a p-value of 0.78. Regarding age distribution, among case patients, there were 23 (33.3%), 39 (56.5%), and 7 (10.1%) individuals in the age groups of 20-40 years, 41-60 years, and >60 years, respectively. In contrast, among control patients, there were 33 (29.7%), 64 (57.7%), and 14 (12.6%) individuals in the corresponding age groups, with a p-value of 0.81.

In terms of BMI categories, among case patients, there were 4 (5.8%), 38 (55.1%), and 9 (13.0%) individuals categorized as Underweight, Normal weight, and Overweight, respectively. Conversely, among control patients, there were 2 (1.8%), 61 (55.0%), and 18 (16.2%) individuals in the respective BMI categories, with a p-value of 0.50.

Table 3 presents the unadjusted and adjusted odds ratios for associations between smoking-related variables and the risk of gastric intestinal metaplasia, while Table 4 delineates the associations between smoking status and the risk of gastric intestinal metaplasia, stratified by age group and gender.

Table 1: Mean age of all enrolled Patient *(n=180)*

Variables	**Mean±SD**
Age (Years)	46.08±11.7
BMI	25.46±5.13

Table 2: Characteristics of controls and gastric intestinal metaplasia cases *(n=180)*

	Group		P-value
	Cases	Control	
Gender			
Male	58(84.1%)	95(85.6%)	
Female	11(15.9%)	16(14.4%)	0.78
Age group			
20-40 years	23(33.3%)	33(29.7%)	
41-60 years	39(56.5%)	64(57.7%)	0.81
>60 years	7(10.1%)	14(12.6%)	
BMI, kg/m2			
Underweight	4(5.8%)	2(1.8%)	
Normal weight	38(55.1%)	61(55.0%)	
Overweight	9(13.0%)	18(16.2%)	0.50
Obesity	18(26.1%)	30(27.0%)	
Smoking status			
Never	23(33.3%)	24(21.6%)	
Former	29(42.0%)	60(54.1%)	0.17
Current	17(24.6%)	27(24.3%)	

Table 3: Unadjusted and adjusted odds ratios for associations between smoking-related variables and risk of gastric intestinal metaplasia

		Controls	Cases	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Smoking status	Never	24	23	1.00 (ref)	1.00 (ref)
	Former	60	29	1.983(0.962-4.08)	1.45(0.94-3.12)
	Current	27	17	1.522(0.661-3.504)	2.452(1.23-3.64)
Age at smoking initiation (years)					
	<20	22	19	1.753(0.835-3.682)	1.93(0.855-3.692)
	21-25	67	33	1.118(0.463-2.699)	1.118(0.463-2.699)
	>25	22	17	1.158(0.563-2.559)	1.08 (0.56-2.70)
Smoking duration (years)					
	≤20	15	15	1.595(0.708-3.597)	1.432(0.604-3.496)
	21–40	67	42	2.417(0.905-6.453)	2.237(0.415-5.253)
	>40	29	12	1.000(0.810-1.341)	1.120(0.711-1.441)
Smoking intensity (cigarettes/day)					
	≤10	16	37	0.643(0.315-1.312)	0.456(0.235-1.262)
	11-15	39	58	0.494(0.196-1.248)	0.393(0.196-1.248)
	>15	14	16	2.312(0.94-3-3.546)	2.451(1.65-3-2.834)
Smoking cessation (years)					
	≤15	20	17	1.61(0.756-3.432)	1.52(0.643-3.322)
	15.01–30	72	38	1.15(0.448-2.970)	1.21(0.421-2.540)
	>30	19	14	1.17(0.342-2.876)	1.20(0.332-2.656)

Table 4: Associations between smoking status and risk of gastric intestinal metaplasia, stratified by age group and gender.

			Adjusted OR (95% CI)	
		Never smokers	Former smokers	current smokers
Age smoker	20-40 years	1.00 (ref)	1.86 (0.76–4.29)	2.43 (1.36–4.25)
	41-60 years	1.00 (ref)	1.33 (0.65–1.54)	1.54 (1.12–2.76)
	>60 years	1.00 (ref)	1.54 (0.44–3.23)	2.11 (0.69–5.43)
Gender				
	Male	1.00 (ref)	1.33 (1.02–1.75)	1.66 (1.23–2.55)
	Female	1.00 (ref)	0.64 (0.07–3.34)	2.54 (0.43–12.0)

Discussion:

Gastric intestinal metaplasia is a condition where the normal lining of the stomach is replaced by tissue that is similar to the lining of the intestine. The correlation between smoking and gastric intestinal metaplasia underscores the importance of smoking cessation in reducing the risk of developing gastrointestinal diseases, including stomach cancer. This finding suggests that individuals who smoke are more likely to develop GIM, and the risk increases with the duration and intensity of smoking. The present study aim was to investigate the associations between smoking habits (duration, intensity, and quantity) and the risk of developing GIM. The current study revealed that smoking constitutes a substantial risk factor for GIM. Furthermore, the risk of developing GIM was observed to escalate with longer durations of smoking and higher pack-years of smoking exposure. Tobacco smoking is a well-established risk factor for gastric cancer. In 2002, the International Agency for Research on Cancer (IARC) reached the conclusion that there is ample evidence to support the assertion that tobacco smoking directly causes gastric cancer.(8) Smoking was associated with approximately a 1.5-fold higher risk of gastric cancer. This suggests that individuals who smoke are 1.5 times more likely to develop gastric cancer compared to non-smokers. According to a meta-analysis of 40 studies,(9) smoking was correlated with an approximately 1.5-fold increase in the risk of gastric cancer. Furthermore, it was estimated that approximately 11% of all gastric cancer cases globally could be attributed to tobacco smoking. The findings of the present study underscore the importance of tobacco control measures in reducing the burden of gastric cancer. Smoking cessation interventions and public health campaigns aimed at reducing tobacco use could potentially decrease the incidence of gastric cancer and improve public health outcomes. There is evidence suggesting that the risk of smoking on gastric cancer may be higher for males than females, although the exact reasons for this difference remain unclear.(4) In our study the male patients were dominant. The cumulative exposure to cigarette smoke emerges as a pivotal determinant in gastric cancer risk. Research indicates an inverse relationship between the duration since quitting smoking and the likelihood of developing gastric cancer, suggesting that the longer an individual refrains from smoking, the lower their risk becomes. Nomura et al.'s study sheds light on this inverse correlation. They discovered that individuals who had quit smoking more than 21 years before assessment exhibited a notably reduced excess risk of gastric cancer compared to those who had quit within the past 10 years. Quitting smoking not only mitigates immediate health hazards linked to tobacco use but also diminishes the long-term likelihood of gastric cancer development. The relationship between smoking and the development of gastric intestinal metaplasia (GIM), as well as its potential role in later events such as progression from GIM to cancer, has been subject to uncertainty. Previous investigations exploring the association between smoking and GIM have yielded conflicting findings. While certain studies indicate smoking as a risk factor for GIM development, others have failed to establish a significant association. Some studies (10, 11) have indeed suggested smoking as a potential risk factor for GIM. However, it's worth noting that other studies (7) did not find a significant association between smoking and GIM. In a study conducted by Robert W. Kneller,(11) the role of tobacco consumption was examined to offer insights into other environmental and genetic factors involved in the process of gastric carcinogenesis. As in the present study it was shows that smoking is associated with increased risk for GIM. In an Italian study,(6) it was discovered that participants currently smoking more than 20 cigarettes per day exhibited a 4-fold increased risk of gastric intestinal metaplasia (GIM) compared to a 2-fold elevated risk observed in participants smoking fewer than 20 cigarettes per day or former smokers. This finding underscores the dose-dependent relationship between tobacco consumption and the risk of GIM. Individuals with higher daily cigarette consumption were at significantly greater risk of developing GIM compared to those who smoked fewer cigarettes per day or had quit smoking. Tobacco smoke has been shown to decrease concentrations of vitamin C in the gastric mucosa.(12) Vitamin C plays a crucial role in protecting the gastric mucosa from oxidative damage and inflammation.(13) Therefore, reduced levels of vitamin C can compromise the gastric defense mechanisms, making the mucosa more susceptible to injury and inflammation.(14)

Conclusion:

It was concluded that there is strong association between the associations between smoking habits (duration, intensity, and quantity) and the risk of developing GIM. Cigarette smoking represents a notable risk factor for gastric intestinal metaplasia. Moreover, our findings highlight the duration of smoking as a particularly influential determinant of this risk.

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