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Original Article

Retrospective Analysis of Risk Factors in Cases of Biopsy Proven Carcinoma Esophagus in an Urban Indian Population

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Abstract

Aims and Objectives: Carcinoma (Ca) esophagus is a life-threatening malignancy in Indian scenario, due to late-stage presentation and limited treatment options. Rampant tobacco and alcohol use have seen a rise in the incidence of squamous cell Ca esophagus. Accurate identification and description of risk factors are critical to the implementation of preventive measures. The data in this regard are lacking in our country.

Materials and Methods: This was a retrospective study conducted at a tertiary care center in Southern India. 103 patients with biopsy-proven esophageal Ca presenting over a period of 22 months were studied. The data regarding smoking and alcohol consumption, history of gastroesophageal reflux disease (GERD), *Helicobacter pylori* infections as assessed by rapid urease test during endoscopy and documentation suggestive of tylosis were collected by means of a questionnaire and analysis of existing medical documents. No therapeutic or diagnostic interventions were made based on the data collected.

Results: Smokers were more likely to develop squamous cell Ca (82.1%, $P = 0.04$, $Z = 1.74$) as well as adenocarcinoma (41%, $P = 0.01$, $Z = 5.18$). Alcohol consumption was more likely to develop both squamous cell Ca (39%, $P = 0.01$, $Z = 1.73$) and adenocarcinoma. Smoking, GERD, and *H. pylori* infection had a significantly higher association with adenocarcinoma than with the squamous cell Ca while alcohol use and caustic injury had a higher association with squamous cell Ca.

Conclusion: A systematic analysis of risk factors shows that smoking and alcohol are strongly associated with both histopathological subtypes of this malignancy. Other risk factors were *H. pylori* infection, GERD, caustic injury, and tylosis.

Key words: Alcohol, Carcinoma esophagus, Gastroesophageal reflux disease, *Helicobacter pylori,* Risk factors, Smoking

INTRODUCTION

Carcinoma (Ca) esophagus is a common malignancy of the upper gastrointestinal tract, carrying high mortality. It is unique because two distinct histopathological types are seen in the Indian setting, squamous cell, and adenocarcinoma. Despite the therapeutic interventions, case fatality for established Ca esophagus is about 90%.[1] The mortality is even higher among women.[2] Evidence suggests the high prevalence of adenocarcinoma in developed countries and that of squamous cell Ca in developing countries like ours. The prevalence of these two subtypes is dependent on pre-existing risk factors and geographical locations. Due to high mortality in the Ca esophagus, the importance of prevention cannot be overemphasized. The detailed study of the risk factors is, therefore, imperative to effectively implement the preventive and screening measures. The important risk factors are as follows:

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Tobacco

Nearly 90% of squamous cell cancers of the esophagus may be attributed to smoking, with a demonstrable dose-dependent increase in risk; an increase in risk with increasing duration and quantity of smoking.[1,3] Cigarette smoking also confers a two-fold risk of adenocarcinoma in patients who smoke more than one pack per day.[4,5] Second-

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hand smoke is also associated with this malignancy.[2] Furthermore, evidence now confirms the increased risk of Barrett's esophagus in smokers.

Alcohol

Nearly 80% of cases of squamous cell cancers are attributable to alcohol consumption, with a well-established dose-dependent relationship.[5]

Diet and Nutrition

The protective effect of raw fruits and vegetables has been established.[6,7] Vitamins A, C, and E, selenium, carotenoids, and fiber, all have a role in the prevention of carcinogenesis.[8,9] Selenium deficiency has been known to cause cancer of the esophagus, as so has consumption of pickled, smoked, and processed foods.[10,11] In India, this risk factor has been difficult to elucidate due to the diverse and unpredictable dietary habits.

Obesity

Body mass index (BMI) has been shown to increase the risk of adenocarcinoma.[12] The risk of Ca esophagus is up to seven-fold higher in patients with high BMIs.[13]

Socioeconomic Status

Income, education, and occupation have been shown to increase the risk for esophageal cancer, probably due to working/exposed to the more carcinogenic environment (chemical/viral) coupled with nutritional deficiency.[14,15]

Gastroesophageal Reflux Disease (GERD) and Barrett's Esophagus

GERD and Barrett's esophagus are the strongest risk factors for adenocarcinoma esophagus.[16,17] Long-term reflux causes Barrett's esophagus which is a malignant precursor for cancer. The frequency, severity, and chronicity are associated with a 2–16-fold higher risk.

Tylosis

Tylosis is also known as palmoplantar keratoderma or Howel–Evans syndrome, this condition, though rare, is an established risk factor for Ca esophagus.[18-22]

MATERIALS AND METHODS

Study Population

A total of 103 patients with biopsy-proven Ca esophagus, presenting to our center over 22 months were studies and a retrospective analysis of the risk factors for Ca esophagus was performed. The data from the patients regarding smoking and alcohol consumption, history of GERD (heart burn, retrosternal discomfort, regurgitation or water brash), *Helicobacter pylori* infections (as assessed by rapid urease test during endoscopy), and documentation suggestive of tylosis were collected by means of a questionnaire and analysis of existing medical documents. No therapeutic or diagnostic interventions were made based on the data collected herein unless when deemed so by the investigators. For example, current smokers were counseled to quit smoking and skin consultation was accorded to patients having palmoplantar keratoderma.

Study Design

The study was a single center, retrospective cross-sectional observational study lasting 22 months. Since every patient received treatment according to the existing standard of care, written consent was waived.

Study Outcomes

The prevalence of etiological risk factors such as consumption of tobacco and alcohol, history of GERD, tylosis, and *H. pylori* was studied in patients with biopsy-proven esophageal Ca.

Statistical Analysis

The Z test for proportions was used to compare the relative proportions of patients with various risk factors.

RESULTS

Smokers were more likely to develop squamous cell Ca (82.1 %, $P = 0.04$, $Z = 1.74$) as well as adenocarcinoma (41%, $P = 0.01$, $Z = 5.18$). Alcohol consumption was more likely to develop both squamous cell Ca (39%, $P = 0.01$, $Z = 1.73$) and adenocarcinoma. Smoking, GERD, and *H. pylori* infection had a significantly higher association with adenocarcinoma than with the squamous cell Ca while alcohol use and caustic injury had a higher association with squamous cell Ca.

Table 1 shows the association of BMI with the occurrence of esophageal Ca. Smoking and alcohol are major contributing risk factors for squamous cell and adenocarcinoma of the esophagus. Smoking was specifically associated with squamous cell Ca (82.1 %, $P = 0.04$, $Z = 1.74$). Alcohol use was also found to be higher in squamous cell Ca and

Table 1: Distribution of patients according to the BMI

BMI (%)	Groups (%)		Total (%)
	Squamous cell carcinoma	Adenocarcinoma	
22–25	19 (48.7)	22 (35.5)	41 (40.6)
25–28	18 (46.2)	25 (40.3)	43 (42.6)
28–31	2 (5.1)	14 (22.6)	16 (15.8)
31–34	0 (0.0)	1 (1.6)	1 (1.0)
Total	39	62	101
Average	25.1795	26.2346	25.8272

BMI: Body mass index

Table 2: Positive association of various risk factors in patients of esophageal carcinoma

Risk factor associated with esophageal carcinoma (Total number 101)	Type of esophageal carcinoma		Total Number patients having a positive association
	Squamous cell carcinoma (Total No. 39)	Adeno carcinoma (Total No. 62)	
	Number (%)	Number (%)	Number (%)
Tobacco use	32 (8201)	41 (66.1)	73 (72.3)
Alcohol use	39 (100)	32 (51.6)	71 (70.3)
GERD	05 (12.8)	17 (27.4)	22 (21.8)
Helicobacter pylori infection	10 (25.6)	30 (48.4)	40 (39.6)
Barrett's esophagus	02 (5.1)	8 (12.9)	10 (9.9)
Tylosis	00 (0.0)	00 (0.0)	00 (0.0)
Caustic injury	04 (10.3)	00 (0.0)	4 (4.0)
Prior aerodigestive malignancy	03 (7.7)	2 (3.2)	05 (5.0)
Achalasia cardia	03 (7.7)	08 (12.9)	11 (10.9)

GERD: Gastroesophageal reflux disease

Table 3: Composite results proportions of various risk factors in squamous cell carcinoma and adenocarcinoma. (The test used is Z test of proportions).

Parameters	Groups		Proportion in SCC (P1)	Proportion in AdCa (P2)	Z Statistic	*P* value	Significance	Higher association with
	SCC	AdCa						
Smoking	32	41	0.82	0.66	1.74	0.04	S	AdCa
Alcohol	39	32	1.00	0.52	5.18	0.01	S	SCC
GERD	5	17	0.13	0.27	−1.73	0.04	S	AdCa
Helicobacter pylori	10	30	0.26	0.48	−2.28	0.01	S	AdCa
Barrett's esophagus	2	8	0.05	0.13	−1.27	0.01	NS	
Caustic injury	4	0	0.10	0.00	2.57	0.01	yes	SCC
Prior aerodigestive malignancy	3	2	0.08	0.03	1.01	0.15	NS	
Achalasia	3	8	0.08	0.13	−0.82	0.2	NS	

AdCa: Adenocarcinoma, SCC: Squamous cell carcinoma, S: Significant, NS: Not significant, GERD: Gastroesophageal reflux disease

about half of the patients with adenocarcinoma were found to be consumers of alcohol. GERD found in up to 39% (95% confidence interval [CI], $P = 0.04$) in patients with squamous cell Ca and in 62% (95% CI, $P = 0.05$) in patients with adenocarcinoma.

Caustic injury can cause cancer of the esophagus up to 40–50 years after the injury.[23-25] It was associated with squamous cell cancer (10.02%, 95% CI, $P = 0.01$). In our study, about 8–12% of patients had evidence of achalasia cardia. The risk of developing esophageal cancer after a prior aerodigestive malignancy is thought to be 4% per year. Between 3.5 and 7% (CI 95%, $P = 0.05$) patients in our study had prior history of aerodigestive malignancy.

Barrett's esophagus is a well-recognized risk factor for the development of esophageal cancer. However, only 0.12–0.33% (95% CI) with Barrett's esophagus go on to develop the malignancy. The association of Barrett's esophagus, prior aerodigestive malignancy[26] and caustic injury were not found to be significantly associated as an etiological risk factor. Association of various risk factors and their significance is shown in Tables 2 and 3.

Human papillomavirus (HPV) infection may contribute to the pathogenesis of esophageal squamous cell cancer in high-incidence areas in Asia and South Africa.[27-30] We did not study this as an etiological risk factor in our study.

DISCUSSION

Smoking and alcohol are major contributing risk factors for squamous cell and adenocarcinoma of the esophagus.[1,3,31] The incidence of adenocarcinoma was also found to be higher in smokers. Alcohol was also found to be higher in squamous cell Ca and about half of the patients with adenocarcinoma were found to be consumers of alcohol.

GERD is implicated as one of the strongest risk factors for the development of this malignancy. It was found in up to 39% (95% CI, $P = 0.04$) in patients with squamous cell Ca and in 62% (95% CI, $P = 0.05$) in patients with adenocarcinoma. *H. pylori* and its associated with Ca esophagus were demonstrated in this study. Although the cag A+ strains are well known to be associated with the development of cancer,[32,33] this aspect of *H. pylori* infection was not tested or analyzed in this study. Although infection by *H. pylori* cag A+ strains by itself may not increase the risk of squamous cell Ca, the concurrent presence of gastric atrophy and *H. pylori* infection has been reported to significantly increase the risk of squamous cell Ca.

Atrophic gastritis may promote bacterial overgrowth, leading to intragastric nitrosation, with the production of nitrosamines increasing the risk of esophageal squamous cell Ca. Caustic injury can cause cancer of the esophagus up to 40–50 years after the injury.[23-25] The majority of this found in the middle third of the esophagus. Only one in 10 were found to have this risk factor and were associated with squamous cell cancer (10.02%, 95% CI, $P = 0.01$).

Achalasia is an idiopathic esophageal motility disorder characterized by increased basal pressure in the lower esophageal sphincter, incomplete relaxation of this sphincter after deglutition, and aperistalsis of the body of the esophagus.[34-36] It is associated with 16–30-fold increase in Ca esophagus.[37-40] According to one series, the average duration for malignancy to manifest, following achalasia, was found to 17 years. In our study, about 8–12% of patients had this risk factor.

Barrett's esophagus is a well-recognized risk factor for the development of esophageal cancer. However, only 0.12–0.33% (95% CI) with Barrett's esophagus go on to develop the malignancy. This is thought to be the reason for lack of statistical coherence for this important risk factor. The risk of developing esophageal cancer after a prior aerodigestive malignancy is thought to be 4% per year. Between 3.5 and 7% (CI 95%, $P = 0.05$) patients had this risk factor. The association of Barrett's esophagus, prior aerodigestive malignancy[26] and caustic injury were not found to be significantly associated as an etiological risk factor.

HPV infection may contribute to the pathogenesis of esophageal squamous cell cancer in high-incidence areas in Asia and South Africa.[27-30] We did not study this as an etiological risk factor in our study.

CONCLUSION

Esophageal cancer has a poor prognosis. The morbidity and mortality associated with the condition, along with complications of surgical procedures and toxicity of chemotherapeutic agents add to the morbidity. A systematic analysis of risk factors shows that smoking and alcohol are strongly associated with both histopathological subtypes of this malignancy. Other risk factors such as *H. pylori* and GERD were also found to be associated (with statistical significance) with this dreaded malignancy. A detailed study of these risk factors would contribute to planning and implementation of preventive, public health education,[41-43] and screening[44-47] measures with a view toward early diagnosis and treatment.

Patient Safety

We wish to emphasize that history taking, clinical examination, and analysis of records were the key data collection tool, with all patients receiving existing standard of care as per the guidelines. Surgery, endoscopic mucosal resection, esophageal palliation and chemotherapy with epirubicin, cisplatin, and 5FU were administered patients as deemed by the medical oncologist. The technique of data collection through history taking ensured prompt emergency care and further referral as deemed necessary without any delay.

Limitations

This was a study based on history taking and an additional questionnaire regarding the presence or absence of etiological risk factors of Ca esophagus. We fully identify the drawbacks of analyzed parameters which were questionnaire-based, since patient-based accounts may often be biased with personal and social preferences in addition to memory lapses.

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