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Epidemiologic, Endoscopic and Histopathological Profile of Oesophagal Cancers of a High-Risk Region of Southern Kashmir-India

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ABSTRACT

Aim and Background: Kashmir Valley especially its southern region is a high-risk region for upper Gastrointestinal (GIT) cancers. This study, the first of its kind from this region was undertaken to determine the epidemiological, endoscopic, and histopathological profile of oesophageal cancer (OC) from this region. **Methods:** This multicentric, retrospective, observational hospital-based study was conducted at three government district hospitals of southern Kashmir viz Anantnag, Kulgam, and Shopian from 2003 to 2022. Patients were subjected to endoscopy using GIF- Olympus Endoscope after overnight fasting of 12 hours. Growths located between 1 and 5cm above the Gastro-Oesophageal junction (GEJ) were taken as oesophageal growths and included in this study whereas growths located from 1cm below GEJ were excluded from this study as they were taken as gastric growths. 4-6 Biopsies were taken from the oesophageal growth and subjected to rapid urease test and histopathological examination. The patient details like presenting symptoms, age, sex, residence, socioeconomic status, dietary habits, smoking habits, ultrasonography findings, endoscopic findings, and histopathological reports were analysed. Contrast-Enhanced Computed Tomography (CECT) abdomen/chest wherever available was also done. **Results:** In our study, there were 1,723 cases of oesophagal cancer, comprising 1,122 males (65.12%) and 601 females (34.88%) in the age group of 35-80 years (median age 61 years). The majority of the patients, 1,354 (78.58%), were in the age group of 45-65 years. A total of 1,335 patients (77.48%) were smokers using either hookah, cigarettes, or both. Additionally, 1,126 patients (65.35%) belonged to a low socioeconomic status. The primary presenting symptom was dysphagia, observed in 1,408 patients (81.71%).H. pylori infection was identified in 323 patients (18.74%) using the Rapid Urease Test. Cervical esophageal growths were observed in 63 patients (3.66%), upper thoracic esophageal growths in 254 patients (14.74%), middle thoracic in 843 patients (48.92%), and lower thoracic growths in 563 patients (32.67%). The most common histology was squamous cell carcinoma (SCC), observed in 1,136 patients (65.93%), while 587 patients (34.07%)

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had adenocarcinoma. **Conclusion:** Kashmir Valley, especially its southern province, is a highly prevalent upper GIT cancer region. Lower Oesophageal Cancers are more common in our study population which is primarily squamous cell carcinoma whereas the incidence of adenocarcinoma is also rising. Although the exact reason for this high prevalence is largely unknown, unique food habits, low socioeconomic conditions, smoking, genetic predisposition, and some other unknown factors have an essential role in its pathogenesis.

Keywords: Adenocarcinoma, Endoscopy, Oesophageal cancer, Histopathology, Squamous Cell Carcinoma.

INTRODUCTION

Upper gastrointestinal tract (GIT) cancers are the most common GIT cancers worldwide [1,2]. Some regions show a higher incidence rate of OC e.g. Iran, China, South Africa, USSR whereas some areas show a higher incidence of gastric cancer e.g. USA, Japan, Chile [3-7]. In India, there is a marked difference in the incidence of GIT cancers between the north and south regions because of the diversity in food habits amongst the various regions of the country. The Age Standardised Rate (ASR) of OC is 6.5 per lakh population amongst males and 4.2 per lac population in females in India. 47,000 new cases of OC and 42,000 deaths because of OC are reported annually in India [8]. A higher incidence of OC has been found in Karnataka, Tamil Nadu, Kerala and Assam [9,10].

Kashmir being a part of the "Asian Oesophageal Cancer Belt" is endemic for OC. The incidence of OC and gastric cancer in Kashmir is 3-6 times higher than in the rest of India and the incidence rate of OC has been 22.6 per lakh population in men and 11.5 per lakh in women. Although the reasons for the high prevalence of OC in Kashmir are unknown, the population's unique personal, dietary, economic, and social habits have a definite role in the pathogenesis of this disease. Various genetic factors, environmental factors, and some still unknown etiological factors also have a role in the pathogenesis of this disease. High prevalence of chronic Esophagitis, dysplasia, and high prevalence of H.pylori-associated chronic gastritis in a normal healthy population and peptic ulcer disease patients may also predispose to OC [11-18].

Kashmir Valley lies in the northernmost region of India between latitudes 33o 20'-34o 40' N and longitudes 73o 40'-75o 40' E characterized by a temperate climate. The valley's altitude ranges from 1073-5236 m above sea level. The total population of the valley is 6.9 million, and the southern districts of Kashmir (Anantnag, Kulgam, Shopian, and Pulwama) comprise 47.94% of the area and 33.71% of the population of Kashmir (Figure 1) with the majority of the population being Muslims (https://censusindia.gov.in/) [19].

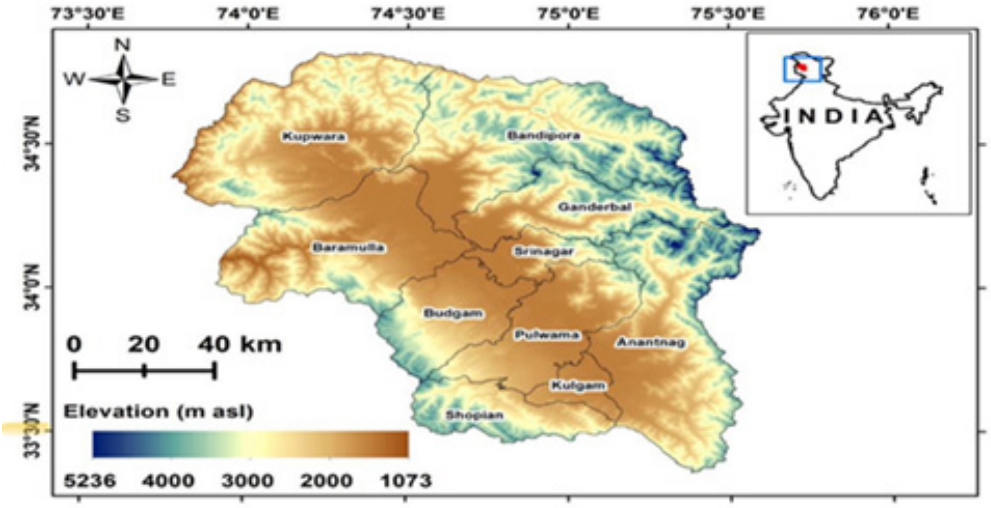

Figure 1. Location of the Kashmir Valley (Inset map: India political boundary with red dot in the North indicating Kashmir Valley). The 4 districts (Anantnag, Kulgam, Pulwama, Shopian) lie towards the Southern most part of valley. Background data: Shuttle Radar Topography Mission (SRTM)Digital Elevation Model of Kashmir Valley.

This Southern region of Kashmir Valley has a high incidence of OC and the present research is the first large retrospective study from this region undertaken to determine the epidemiological, clinical, endoscopic, and histopathological profile of OC. Furthermore, this study highlights some possible etiopathological causes of OC in the region.

METHODS

This multicentric, retrospective, observational hospital-based study was conducted at three government district hospitals of southern Kashmir viz Anantnag, Kulgam, and Shopian from 2003 to 2022. Patients were subjected to endoscopy using GIF- Olympus Endoscope after overnight fasting of 12 hours. The oesophageal growths were assessed by their location, shape and size. Growths located between 1 and 5cm above the Gastro-Oesophageal junction (GEJ) were taken as oesophageal growths and included in this study whereas growths located from 1cm below GEJ were excluded from this study as they were taken as gastric growths. 4-6 Biopsies were taken from the oesophageal growth and subjected to rapid urease test and histopathological examination. The histopathological report was taken as the "*Gold standard*" for diagnosis of oesophageal cancers. The patient details like presenting symptoms, age, sex, residence, socioeconomic status, dietary habits, smoking habits, ultrasonography findings, endoscopic findings, and histopathological reports were analyzed. Contrast-Enhanced Computed Tomography (CECT) abdomen/chest wherever available were also noted. A well-informed written consent for performing the endoscopic procedure and for obtaining biopsy tissue was obtained. Human experimentation guidelines laid by the "Declaration of Helsinki" were followed in this study.

RESULTS

There were 1723 patients with OC, males 1122 (65.11%), and females 601 (34.89%) with male to female ratio of 1.8:1 (Figure 2). The median age of the patients was 61 years (Range 35-80 years). The majority of patients 1354 (78.58%), were in the age group of 45-65years. 1335 patients (77.48%) were smokers using either hookah or cigarettes or both. 1126 patients (65.35%) belonged to low socioeconomic status (Kuppusswami class 4 and 5) [20]. Various characteristics of these patients are given in Table 1. The district-wise distribution of the patients is shown in Figure 3. The most common presentation of OC was dysphagia (81.71%). Other clinical features of these patients are given in Table 2. 68 patients presented with metastatic lesions in the lung, liver and bones. On subsequent upper GI endoscopy, they had OC.

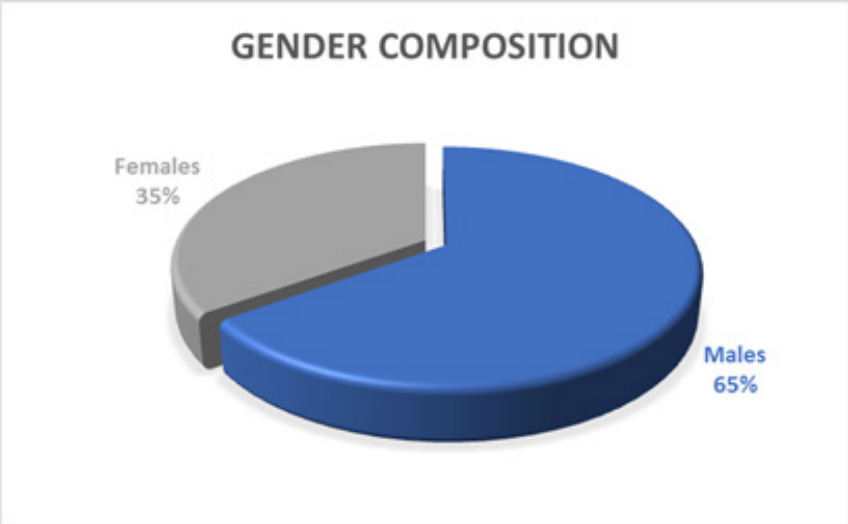

Figure 2. Gender composition of Oesophageal Cancer.

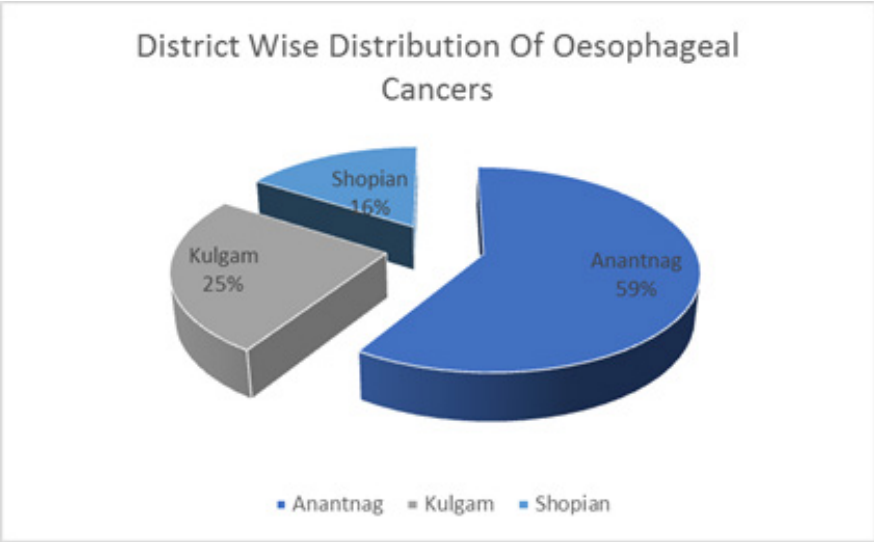

Figure 3. District Wise Distribution Of Oesophageal Cancer.

Table 1. Characteristics of the study patients

Charateristics	OC (N=1723)
Median Age (Range)	61 yrs (35-80yrs)
Males	1122(65.11%)
Females	601(34.89%)
Male: Female	1.8:1
Anantnag District	1017
Kulgam District	431
Shopian District	275
Smokers	1065 (61.81%)
Low socioeconomic status	1179(68.42%)

Table 2. Clinical Features of Patients*

Symptoms	OC (N=1723)
Loss of appetite	418(24.26%)
Dysphagia	1260(73.12%)
Post Prandial Distension	397(23.04%)
Epigastric Pain	317(18.39%)
Recurrent Vomitting	439(25.47%)
GI Bleeding (Malena Hematemesis)	68(3.94%)
Anaemia	223 (12.94%)

*Many patients had more than one symptoms.

Upper GI Endoscopy revealed cervical oesophageal growths in 63 patients (3.66%), upper thoracic oesophageal growths in 254 patients (14.74%), middle thoracic in 843 patients (48.92%) and lower thoracic growths in 563 patients (32.67%) (Figure 4).On endoscopy the majority of the oesophageal growths 1344 (78%) were polypoid type, whereas 379 (22%) were ulcerative friable growths(Figure 5 & 6). 678 patients (39.34 %) had two-thirds of the oesophageal lumen occluded and the endoscope could not be passed beyond the growth. Helicobacter Pylori was found positive in 323 (18.74%) patients on rapid urease test. Histopathologically 1136 (65.93%) had squamous cell carcinoma whereas 587 (34.07%) had adenocarcinoma (Figure 7 a & 7b).

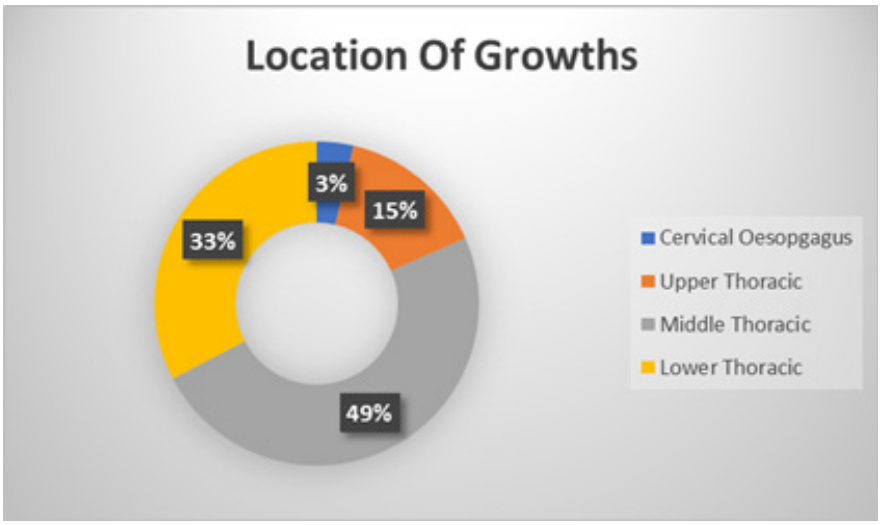

Figure 4. Location Of Oesophageal growths.

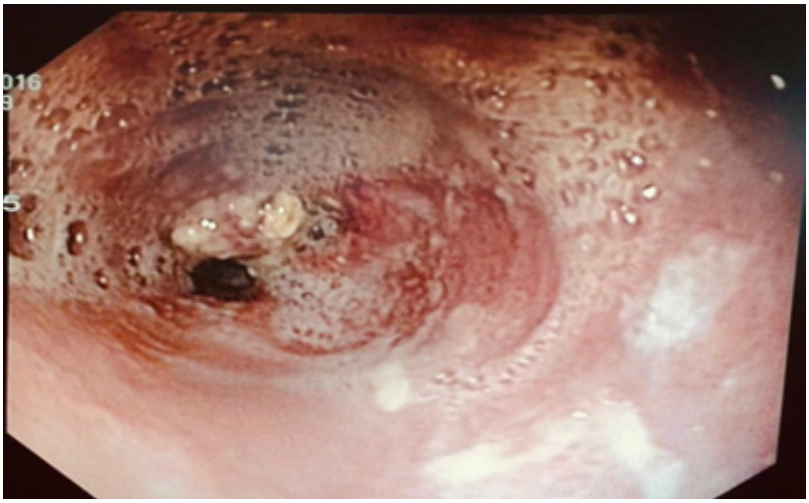

Figure 5. Polypid growth at lower Oesophagus.

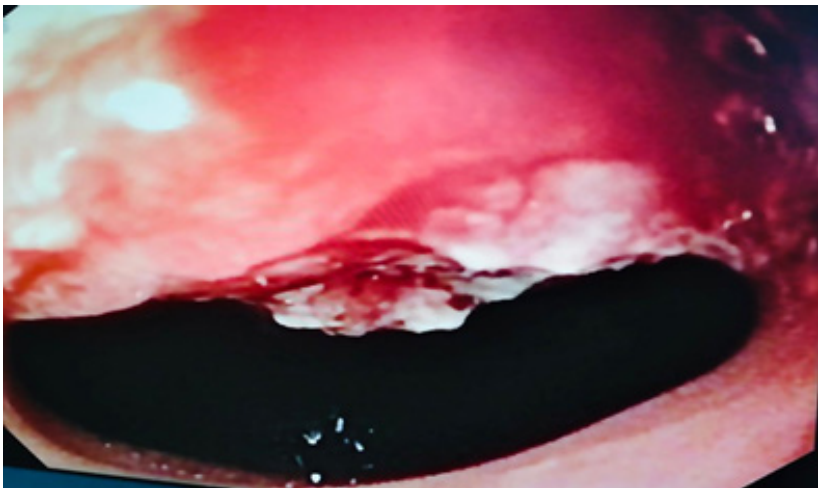

Figure 6. Ulcerative Growth at Gastroesophageal Junction.

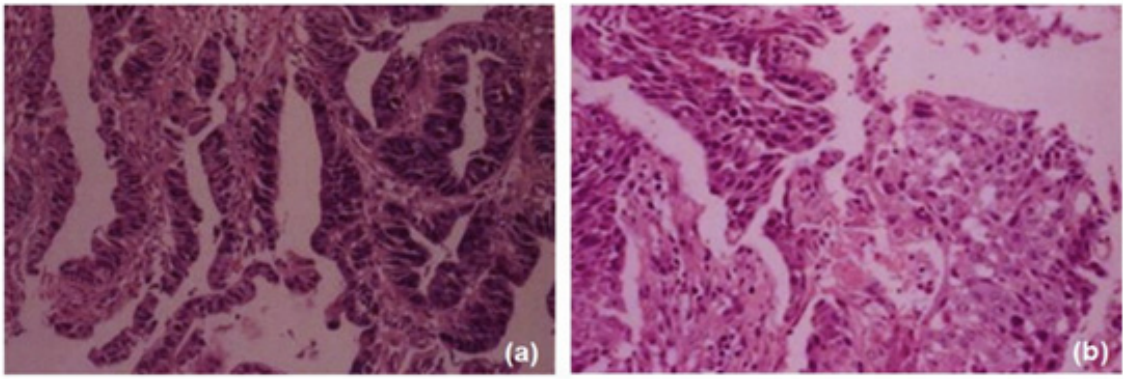

Figure 7. Low Grade Adenocarcinoma Oesophagus (a), Squamous Cell Carcinoma Oesophagus (b).

DISCUSSION

Oesophageal Cancer is the eighth most common cancer in the world. Globally 6 lakh people are diagnosed with OC every year. Fifty per cent of the world's OC are diagnosed in China whereas the lowest rates of OC are found in Central America, western and middle Africa. The various risk factors advocated in the pathogenesis of OC are poor nutritional status, low vegetable and fruit intake, alcoholism, smoking, intake of hot beverages and excessive consumption of red meat. The prevalence of OC varies from continent to continent and from region to region within a country because of diverse food habits. The etiopathogenesis of GIT cancers including OC is multifactorial but it is well-known that dietary habits have an important role to play.

Kashmir has a 3-6 times higher incidence of OC than the rest of the country. The pattern of prevalence, incidence, and histopathology of OC of Kashmir is also different from other states because there are a lot of social, cultural, religious, dietary habits, and environmental differences in our region and the rest of the country which include consumption of salt-tea, spicy food intake, high rice consumption, hot food intake, hot beverages and foods, sundried fish, smoked fish, high-calorie intake of non-vegetarian food (wazwan). The direct relation between the concentration of nitrosamines and other well-known carcinogens with the etiopathogenesis of gut cancers, including OC, has been proven by many studies. Though the actual reason for the high incidence of OC in this region is unknown, one of the hypotheses may be that hot beverages and other hot food items may cause mucosal injuries, especially at the GE junction. High salt intake along with the presence of nitrosamine carcinogens in above mentioned commonly used foods may transform inflamed mucosa into dysplasia, metaplasia and anaplasia through the process of mutagenesis [21-31].

The other reason for this markedly significant difference could be a higher incidence of chronic esophagitis (74.7%) and dysplasia (7.5%) amongst the Kashmiri population [16]. Furthermore, being in proximity to the "Asian oesophageal cancer belt" (which extends from the southern shore of the Caspian Sea in Iran through the Soviet Union, Central Asia,

and Mongolia to northern China), the epidemiological risk factors may be the same for Kashmir as well [12].

Although H. pylori infection has been strongly implemented in the pathogenesis of peptic ulcer disease of this region 32, the association of this organism with OC has not been found of any significance ($p<0.01$). Many other studies have also reported similar findings [33-35]. Smoking has been found globally as a major risk factor in the pathogenesis of OC along with excess alcohol intake. Though our population is non-alcoholic the majority of them were found to be smokers. Smoking increases acid reflux by decreasing sphincteric tone which causes reflux esophagitis and if not treated leads to Barett's oesophagus (which is a precancerous condition) in the presence of various other risk factors in some genetically susceptible persons [36]. Patients with gastro-oesophageal reflux disease(GERD) and Barett's oesophagus have a five-fold risk and 30-fold risk of developing Oesophageal Adenocarcinoma respectively [37].

Though the use of sun-dried foods, smoked foods, and other preserved foods has markedly decreased in our population during the last four decades and the consumption of fresh vegetables, salads, and fruits has increased significantly throughout the world, the prevalence of OC and other GIT cancers have not shown any significant decline. The reason could be the scarcity of natural food products and food adulteration. The fruits and vegetables are ripened and grown using various growth-promoting chemicals, which may have an additional carcinogenic effect by enhancing apoptosis due to nucleic acid damage. The use of chemicals for promoting the growth and development of various poultry products may also have a carcinogenic effect on human beings [38-40].

The quality and quantity of food consumed is a crucial factor as most of the patients in our study were from Kandi belts, where food quality and quantity are always compromised because of low socioeconomic status. Low socioeconomic status has been an additional important etiological factor for the high prevalence of OC and other GIT cancers worldwide. Genetic predisposition and some environmental factors in people who have a deficiency of various micronutrients, macronutrients, and trace elements due to lack of adequate food consumption may lead to the development of GIT cancers, including OC. Low levels of selenium, low zinc levels and low folic acid have been found to increase the risk of OC by enhancing the carcinogenic effect of nitrosamines and overexpression of cyclooxygenase 2 (COX 2) [41-45].

Oesophageal cancer is considered to be the disease of the elderly population, with a majority of patients being more than 60 years [23], however, our study observed that an appreciable percentage of patients (42.23%) of OC were middle-aged (<50 years). Similarly, the proportion of involvement of the female gender is higher than reported by various global studies. This early involvement and higher prevalence of OC among females is unknown but could be attributed to their activities in agriculture, horticulture, and sericulture-based occupation where they get exposed to various chemicals (carcinogens) like rodenticides, insecticides, pesticides, fungicides etc. This could be also a reason for the narrowing of male to female ratio amongst the OC.

Though the majority of OC are squamous cell carcinomas, the incidence of adenocarcinomas is increasing globally. In our study, a significant number of patients had adenocarcinoma which could be attributed to the high prevalence of GERD, Oesophageal Dysplasia and high prevalence of H. Pylori infection in the Peptic Ulcer Disease (PUD) and asymptomatic population.

Because of ignorance, carelessness, apprehensions of invasive endoscopic procedures, and irrational use of proton pump inhibitors, most patients were diagnosed with an advanced stage of disease (stage III). Similar observations have been reported in other studies.

CONCLUSION

Kashmir is a highly endemic region for Oesophageal Cancers due to unique food habits, low socioeconomic status, and various adverse environmental and genetic factors besides some still unknown reasons. Since the improvement of socioeconomic conditions has not changed the prevalence of the disease, there is a need for primordial prevention and early genetic evaluation besides surveillance and screening of populations with high-risk factors for the development of the disease. There is a need for the propagation of health education amongst the community to address various risk factors of the disease and thereby decrease the incidence of this miserable disease in the region.

REFERENCES

1. Kamangar F, Dores GM, Anderson WF. (2023). Patterns of Cancer Incidence, Mortality, and Prevalence Across Five Continents: Defining Priorities to Reduce Cancer Disparities in Different Geographic Regions of the World. J Clin Oncol. 41(34):5209-5224.
2. Corley DA, Buffler PA. (2001). Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database. Int J Epidemiol. 30(6):1415-1425.
3. Mahboubi E, Kmet J, Cook PJ, Day NE, Ghadirian P, Salmasizadeh S. (1973). Oesophageal cancer studies in the Caspian Littoral of Iran: the Caspian cancer registry. Br J Cancer. 28(3):197-214.

4. Yang CS. (1980). Research on esophageal cancer in China: a review. Cancer Res. 40(8 Pt 1):2633-2644.
5. Warwick GP. (1973). Some aspects of the epidemiology and etiology of oesophageal cancer with particular emphasis on the Transkei, South Africa. Adv Cancer Res. 17:81-229.
6. Devesa SS, Silverman DT. (1978). Cancer incidence and mortality trends in the United States: 1935-74. J Natl Cancer Inst. 60(3):545-571.
7. Ferlay J, Shin HR, Bray F, et al. Peter Boyle, Bernard, Levin, editors. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No.10. Lyon, France: International Agency for Research in Cancer 2010. Available at: http://www.globocan.iarc.fr. World Cancer Report 2008 IARC; 2008.
8. Globocon. (2008). Accessed online at: http://globocon.iarc
9. Chitra S, Ashok L, Anand L, Srinivasan V, Jayanthi V. (2004). Risk factors for esophageal cancer in Coimbatore, southern India: a hospital-based case-control study. Indian J Gastroenterol. 23(1):19-21.
10. Desai BP, Bojes JI, Vohra CV, et al. (1969). Carcinoma of the esophagus in India. Cancer.23:979-989.
11. Khan NA, et al. (2004). Clinicopathologic profile of carcinoma oesophagus and oesophagogastric junction in Kashmir.JK practitioner. 11(3):182-185.
12. Rasool S, Ganai BA, Sameer AS, Masood A. (2012). Esophageal cancer: associated factors with special reference to the Kashmir Valley. Tumori Journal. 98(2):191-203.
13. Romshoo GJ, Malik GM, Bhat MY, Rather AR, Basu JA, Qureshi KA. (1998). Helicobacter pylori associated antral gastritis in peptic ulcer disease patients and normal healthy population of kashmir, India. Diagn Ther Endosc. 4(3):135-139.
14. Romshoo GJ, Malik GM, Basu JA, Bhat MY, Khan AR. (1999). Prevalence of Helicobacter pylori Infection in Peptic Ulcer Patients of Highly Endemic Kashmir Valley. Diagn Ther Endosc. 6(1):31-36.
15. Khan NA, Teli MA, Mohib-Ul Haq M, Bhat GM, Lone MM, Afroz F. (2011). A survey of risk factors in carcinoma esophagus in the valley of Kashmir, Northern India. J Cancer Res Ther. 7(1):15-18.
16. Khuroo MS, Zargar SA, Mahajan R, Banday MA. (1992). High incidence of oesophageal and gastric cancer in Kashmir in a population with special personal and dietary habits. Gut. 33(1):11-15.
17. Siddiqi M, Tricker AR, Preussmann R. (1988). The occurrence of preformed N-nitroso compounds in food samples from a high risk area of esophageal cancer in Kashmir, India. Cancer Lett. 39(1):37-43.
18. Goswami KC, Khuroo MS, Zargar SA, Pathania AG. (1987). Chronic esophagitis in a population (Kashmir) with high prevalence of esophageal carcinoma. Indian J Cancer. 24(4):232-241.
19. Rashid I, Parray AA, Romshoo SA. (2019). Evaluating the Performance of Remotely Sensed Precipitation Estimates against In-Situ Observations during the September 2014 Mega-Flood in the Kashmir Valley. Asia-Pacific Journal of Atmospheric Sciences. 55(2):209-219.
20. Kuppuswamy B. (1981). Manual of socioeconomic status (Urban). Delhi: Manasayan.
21. Malhotra SL. (1967). Geographical distribution of gastrointestinal cancers in India with special reference to causation. Gut. 8(4):361-372.
22. Purushottam AG, Kailash KS, Deepak BP. (2014). Study of socioeconomic determinants of oesophageal cancer at a tertiary care Teaching hospital of western Maharashtra, India. South Asian J Cancer. 3(1):54-56.
23. National Cancer registry. (1988). Annual report 1988 population based cancer registries in Bombay, Bangalore and Madras. New Delhi: Indian Council of Medical Research.
24. Abdi-Rad A, Ghaderi-sohi S, Nadimi-Barfroosh H, Emami S. (2006). Trend in incidence of gastric adenocarcinoma by tumor location from 1969-2004: a study in one referral center in Iran. Diagn Pathol. 1:5.
25. Correa P. (1987). Modulation of gastric carcinogenesis: Updated model based on intragastricnitrosetion. In: Bartsch H, O Neill I, Schulte-Hermann R, eds. Relevance of N-nitroso compounds to human cancer: exposure and mechanisms. IARC Scientific Publication no. 84. Lyon: IARC. pp. 485-491.
26. Tricker AR, Siddiqi M, Preussmann R. (1988). Occurrence of volatile N-nitrosamines in dried chilies. Cancer Lett. 38(3):271-273.
27. Siddiqi M, Tricker AR, Preussmann R. (1988). The occurrence of preformed N-nitroso compounds in food samples from a high risk area of esophageal cancer in Kashmir, India. Cancer Lett. 39(1):37-43.
28. Siddiqi M, Tricker AR, Preussmann R. (1988). Formation of N-nitroso compounds under the simulated gastric condition from Kashmir foodstuff. Cancer Lett. 39(3):259-265.

29. Wang XQ, Terry PD, Yan H. (2009). Review of salt consumption and stomach cancer risk: Epidemiological and biological evidence. World J Gastroenterol. 15(18):2204-2213.

30. Sehgal S, Gupta BB, Dhār MK. (2012). Risk factors and survival analysis of oesophageal cancer in the population of Jammu, India. Indian J Cancer. 49(2):245-250.

31. Hussain S, Ali M, Jeelani R, Abbas M. (2019). Cancer Burden in High Altitude Kargil Ladakh: Ten Year Single Centre Descriptive Study. Int J Cancer Treat. 2(2):4-10.

32. RomshooGJ, Malik GM, Basu JA, Bhat MU, Khan AR. (1999). The prevalence of Helicobacter pylori infection in peptic ulcer patients of highly endemic Kashmir valley-a preliminary study. Diagnostic and therapeutic endoscopy. 6:31-36.

33. Malik GM, Kadla S, Mubarik M, Hussain T, Jeelani G, Basu J, et al. (1997). Helicobacter pylori infection in endoscopic biopsy specimens of gastric cancer: a preliminary evaluation in a high risk population of kashmir valley. Diagn Ther Endosc. 4(1):35-42.

34. Islami F, Kamangar F. (2008). Helicobacter pylori and esophageal cancer risk: a meta-analysis. Cancer Prev Res (Phila). 1(5):329-338.

35. Rubenstein JH, Taylor JB. (2010). Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther. 32(10):1222-1227.

36. Edgren G, Adami HO, Weiderpass E, Nyrén O. (2013). A global assessment of the oesophageal adenocarcinoma epidemic. Gut. 62(10):1406-1414.

37. He Z, Zhao Y, Guo C, Liu Y, Sun M, Liu F, et.al. Prevelence and risk factors for esophageal squamous cell cancer and precursor lesions in Anyang, China : A population based endoscopic survey. Br.J.Cancer 2010; 103:1085-1088.

38. Filazi A, Yurdakok-Dikmen B, Kuzukiran O, Sireli UT. (2017). Chemical Contaminants in Poultry Meat and Products. Poult Sci. 15:171.

39. Filazi A, Yurdakok-Dikmen B, Kuzukiran O, Sireli UT. (2017). Chemical Contaminants in Poultry Meat and Products, Poultry Science, Milad Manafi, Intech Open, DOI: 10.5772/64893. Available at: https://www.intechopen.com/books/poultry-science/chemical-contaminants-in-poultry-meatand-products.

40. Daly JM, Karnell LH, Menck HR. (1996). National Cancer Data Base report on esophageal carcinoma. Cancer. 78(8):1820-1828.

41. Islami F, Poustchi H, Pourshams A, Khoshnia M, Gharavi A, Kamangar F, et al. (2020). A prospective study of tea drinking temperature and risk of esophageal squamous cell carcinoma. Int J Cancer. 146(1):18-25.

42. Islami F, Pourshams A, Nasrollahzadeh D, Kamangar F, Fahimi S, Shakeri R, et.al. (2009). Tea drinking habits and esophageal cancer in a high-risk area in Northern Iran: population based case control study. BMJ. 338:b929.

43. Steevens J, van den Brandt PA, Goldbohm RA, Schouten LJ. (2010). Selenium status and the risk of esophageal and gastric cancer subtypes: the Netherlands cohort study. Gastroenterology. 138(5):1704-1713.

44. Abnet CC, Lai B, Qiao YL, Vogt S, Luo XM, Taylor PR, et al. (2005). Zinc concentration in esophageal biopsy specimens measured by x-ray fluorescence and esophageal cancer risk. J Natl Cancer Inst. 97(4):301-306.

45. Xiao Q, Freedman ND, Ren J, Hollenbeck AR, Abnet CC, Park Y. (2014). Intakes of folate, methionine, vitamin B6, and vitamin B12 with risk of esophageal and gastric cancer in a large cohort study. Br J Cancer. 110(5):1328-1333.