

## RESEARCH COMMUNICATION

# Geographical Variation in the Epidemiology of Esophageal Cancer in Pakistan

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### Abstract

**Study objectives:** To evaluate whether factors such as the geographic area of residence, sex, and anatomic subsite of esophagus can prognosticate the histologic subtype of esophagus cancer.

**Design:** To study the major histologic subtypes of esophagus cancer stratified by various factors through multivariate analyses using morphology as the dependent factor and gender, province, and subsite of esophagus as independent factors.

**Setting:** A tertiary care cancer hospital situated in the city of Lahore in Pakistan.

**Patients:** Three hundred and thirty five patients diagnosed either with esophageal squamous cell carcinoma or adenocarcinoma, from December 1994 to April 2004, were included. Subjects were residents of either Punjab or the Northwest Frontier Province in Pakistan.

**Main results:** An excessive likelihood of development of squamous cell carcinoma versus adenocarcinoma was established for the Northwest Frontier Province as compared to Punjab (odds ratio 2.7, 95 percent confidence interval: 1.2, 6.2,  $p = 0.02$ ), and in the upper-third of the esophagus relative to the lower-third of the organ (odds ratio 8.8, 95 percent confidence interval: 2.8, 28.3,  $p < 0.001$ ).

**Conclusions:** This histologic variation may be explained by environmental and lifestyle factors peculiar to geographical regions.

**Key Words:** Esophagus - geographic area of residence - sex - site of origin - squamous cell carcinoma.

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### Introduction

Cancer of the esophagus is the sixth most frequent cancer worldwide with about 412,000 new cases occurring every year. The total number of deaths due to esophageal cancer amounted to 337,500 out of a total of 6.2 million cancer deaths worldwide in 2000 (Stewart and Kleihues, 2003). Risk of esophagus cancer shows marked geographic variability with the highest incidences measured in the Peoples Republic of China, the Caspian region of Iran, South Africa, and France. In these regions, the annual age-specific incidence rates are as high as 100 new cases per 100,000 population (Stewart and Kleihues, 2003; Heath et al., 2001; Islami et al., 2004)

According to a recent release by the Surveillance, Epidemiology, and End Results (SEER) Program, the estimated annual percent change (EAPC) for esophagus cancer in the US, from 1992 to 2001, among white males

was 1.87 and for females, it was - 0.24 (SEER, 2004). For white males, the EAPC was significantly different from zero ( $p < 0.05$ ). The high incidence of esophageal adenocarcinoma (AC) has recently surpassed the incidence of squamous cell carcinoma (SCC) among white males, but this change is not evident among African-American men (Gammon et al., 1998; Chalasani et al., 1998; Devesa et al., 1997). Among white females, rates of esophageal AC have also risen but are much lower than those among white males, whereas, the rates for esophageal SCC among women have remained constant.

In Pakistan, as reported by a population-based cancer registry in the country in Karachi South, esophagus cancer was the sixth commonest malignancy among males, and fifth commonest one among females, for the time period extending from 1995 to 1999 (Bhurgri, 2001). In males, the age-standardized incidence rate (ASIR) was measured to be 6.2 per 100,000 persons, and among females, it was 7.0

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per 100,000 population (Bhurgrri, 2001).

At the Shaukat Khanum Memorial Cancer Hospital and Research Center, (SKMCH and RC), located in Lahore, Pakistan, cancer of the esophagus accounted for nearly 1.9 percent of the total malignancies registered or diagnosed at the hospital from December 1994 to April 2004. It also ranked as the fifteenth commonest invasive malignancy seen at the hospital with a high frequency among male (55%) versus female (45%) patients. Because of its location, the vast majority of patients coming to this tertiary care facility belonged to the Northwest Frontier Province (NWFP) and Punjab.

**Patients and Methods**

Cases were selected by reviewing the pathology reports in the medical records department of the hospital. Of the three hundred and eighty four endoscopically diagnosed esophageal malignancies, 171 were located in the lower-third, 122 in the middle-third, and 91 in the upper-third of the esophagus. Among these, 328 were histologically confirmed esophageal SCCs, and 87 were adenocarcinomas. These malignancies were classified according to the International Classification of Diseases for Oncology, Ninth Revision, Clinical Modification (ICD-9-CM). However, since stage of the disease was not a part of this study, the authors did not collect any information on this parameter. Further, as the hospital caters mostly to patients living in the provinces of Punjab and NWFP, only those subjects whose geographic area of residence was either the NWFP or Punjab were selected for the study; these were 118 and 217 in numbers respectively and accounted for 87 percent of the cases. Therefore, the total number of patients in the study was 335. As it was a retrospective review of charts, complete information on risk factors was not available and,



**Figure 1. Pakistan (shaded in grey), with Neighboring Countries.** NWFP, Punjab, Balochistan, Sindh, Northern areas, and Azad Jammu and Kashmir are separate regions.

therefore, possible factors playing a role in the etiology of the disease were not included. Analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 10.0. P values were considered significant at an alpha level of 0.05. The study was approved by the local scientific review committee.

*Geographic Area of Residence*

Figure 1 is a map of Pakistan showing its neighboring countries and also all the provinces of Pakistan including Punjab and NWFP.

*Location of Malignancies*

Esophageal lesions were examined by the gastroenterologist at SKMCH and RC through endoscopy and stratified by their locations in the upper-, middle-, or lower-third of the esophagus. Lesions in the upper-third of the organ extended from the lower border of the cricoid cartilage, 16 cm. from the incisors to the level of tracheal bifurcation at 24 cm., those in the middle-third extended from 25 cm. to 32 cm., the approximate level of T9 vertebral body, and those in the lower-third extended from 33 cm. to the gastroesophageal junction at 40 cm.

*Statistical Methods*

Preliminary (bivariate) analyses were conducted to determine associations between the predictors under study and esophageal cancer subtype. These were followed by running the unconditional backward stepwise likelihood ratio (LR) logistic regression method to compute the magnitude of association between the selected variables and the endpoint of interest.

**Results**

Of the 335 cases selected for this study, there were 184 (54.9 percent) males and 151 (45.1 percent) females. Two hundred and sixty (77.6 percent) patients were diagnosed with SCC and 75 (22.4 percent) with AC of the esophagus. The mean age at presentation was 52 years (standard

**Table 1. Descriptive Result for Age and Weight for Selected Cases**

Variable	Mean	Min	Max	SD	Median	Mode
Age (year)	52	08	86	14	53	55
Weight (kg.)	51	25	94	14	49	47

**Table 2. Differences in Age Distributions for the Two Main Types of Esophagus Cancer**

Descriptive	Age (Years)	
	SCC	AC
Mean	51	55
Median	52	56
SD	14	14
Minimum	08	15
Maximum	86	82

**Table 3. Differences in Weight Distributions for The Two Main Types of Esophagus Cancer**

Descriptive	Weight SCC	(Kg.) AC
Mean	50	54
Median	49	51
SD	13	15
Minimum	25	29
Maximum	94	90

**Table 4. Frequencies of SCC and AC Stratified by Gender**

Gender	Histology		Total Count (%)
	SCC Count (%)	AC Count (%)	
Male	127 (69.0)	57 (31.0)	184 (100)
Female	133 (88.1)	18 (11.9)	151 (100)
Total	260 (77.6)	75 (22.4)	335 (100)

$X^2(1, N = 335) = 17.34, p < 0.001$

**Table 5. Frequencies of SCC and AC Stratified by The Geographic Area of Residence**

Province	Histology		Total Count (%)
	SCC Count (%)	AC Count (%)	
Punjab	161 (74.2)	56 (25.8)	217 (100)
NWFP	99 (83.9)	19 (16.1)	118 (100)
Total	260 (77.6)	75 (22.4)	335 (100)

$X^2(1, N = 335) = 4.14, p = 0.04$

**Table 6. Frequencies of SCC and AC Stratified by Anatomic Subsite**

Anatomic subsites for esophagus cancer	Histology		Total Count (%)
	SCC Count (%)	AC Count (%)	
Upper-third	78 (92.9)	06 (07.1)	84 (100)
Middle-third	90 (91.0)	09 (09.1)	99 (100)
Lower-third	92 (60.5)	60 (39.5)	152 (100)
Total	260 (100)	75 (100)	335 (100)

$X^2(2, N = 335) = 46.85, p < 0.001$

deviation (SD): 14), whereas, the average weight was 51 kilogram (kg.) with a SD of 14 (Table 1).

#### Age and Weight Distributions According to Histology

Study of age according to histology showed higher average age and weight in those with AC than with SCC (Tables 2 and 3). The mean age of the subjects with SCC was 51 (SD 14), whereas, of those who presented with AC was 55 (SD 14). The average weight of those with AC was 54 kg., and with SCC was 50 years, with standard deviations of 15 and 13, respectively. Also, the results for the analysis of variance conducted to determine the difference between the means for the two groups were not significant ( $p > 0.05$ ).

#### Distribution by Sex, Geographic area of Residence, and Subsite

Majority of the patients belonged to Punjab followed by the NWFP. Tables 4-6 display the frequencies of the two major types of esophageal malignancies stratified by sex, province, and anatomic subsite along with their corresponding chi-square results.

As seen in Table 4, there was a preponderance of SCC in both the male and female populations under study. However, there was a dominance of AC among males. The chi-square showed a statistically significant relationship between histology and sex ( $X^2(1, N = 335) = 17.34, p < 0.001$ ). The relationship between province and histology was represented by  $X^2(1, N = 335) = 4.14, p = 0.04$  (Table 5). When stratified by anatomic subsite, a marked dominance of SCC in all the segments of esophagus was seen (Table 6). A substantial relationship between anatomic subsite and morphology was also found ( $X^2(2, N = 335) = 46.85, p < 0.001$ ). However, the ratio of SCC to AC was 1.53 to 1 in the lower segment compared to 13 to 1 in the upper segment. No significant association between weight or age, and histology was found using the regression equation.

#### Multivariate Analysis

Preliminary tests performed as screening tests to evaluate relationships between different variables and morphology revealed associations between morphology, and gender, province, and anatomic subsites only. In the unconditional backward stepwise LR method, these three variables were entered simultaneously in the regression analysis in the first step. Of the three variables that were entered into the equation, two showed statistically significant associations with the possibility of development of SCC relative to AC of the esophagus. The corresponding odds of developing SCC versus AC were 2.7 times higher in NWFP than in Punjab (95% CI: 1.2, 6.2). The association between the upper-third of the organ and histology, revealed a significant OR of 8.8 (95% CI: 2.8, 28.1). However, the strength of association between gender and histology was not significant ( $p > 0.05$ ).

#### Discussion

Overall, cancer of the esophagus has a distinct geographic distribution with very high rates seen in South-Central Asia. The esophageal cancer belt, stretches eastward from Iran through Turkmenistan, northern Afghanistan, Uzbekistan, and Kazakhstan into Northern China and Mongolia (Kuska, 2001). This belt is characterized by very high, nearly epidemic rates of esophageal cancer in the world, with the subtype squamous cell carcinoma being more common than any other type seen in the region. In the areas lying in the cancer belt, although no proven precursor or causative factor has been identified for SCC, many factors have been implicated in the etiology of the disease. These include environmental factors as mineral content of the soil; dietary factors such as a diet low in animal protein, fruits, and

vegetables; and personal habits such as alcohol consumption and tobacco intake (Cortes and Villaseñor, 1997). Majority of the factors so far implicated in the etiology of the disease appear to act directly on the esophagus rather than systemically; these may account for the increased risk of SCC in the upper-third as opposed to the lower-third of the organ noted in our study (odds ratio 8.8, 95% CI: 2.8, 28.3,  $p < 0.001$ ). If proven so, this may imply that the disease can be prevented by primary means.

Also, an association between Human Papillomavirus (HPV) infection and development of esophageal cancer has been found in some countries including China, and the HPV detection rates may be highest in China and South Africa (Moradi et al., 2002). HPV may be implicated in the etiology of SCC in synergism with other factors but not alone by itself (Moradi et al., 2002).

Studies conducted in Pakistan have identified smoking, chewing paan (which is betel quid, a mixture of areca nut, lime, and other spices wrapped in a betel leaf), eating naswar (which is tobacco mixed with ash and kept in the buccal cavity between the lips and the alveolus), and inhaling snuff (tobacco powder) as high risk factors among esophageal cancer patients (Jamal et al., 1997; Afridi et al., 2000). Of these two studies, one found the risk of development of cancer of the esophagus to be 3.3-fold higher in those who were smokers compared to non-smokers and 2-times higher in naswar (snuff) users than in non-users (Afridi et al., 2000).

Our study has found the possibility of developing esophageal SCC higher in the residents of NWFP close to the high risk belt than in Punjab and in the upper-third of the organ. The weakness of the study is that it is a retrospective study and complete information on risk factors could not be pulled out of the files. Also, the data for this study have principally been obtained from a single institution. Therefore, it is not possible to derive specific explanations for morphology in terms of demographics and clinical findings. The strength of the report is that it has brought to our attention the fact the likelihood of experiencing esophageal SCC is high in the NWFP patients registering at our institution, and that Pakistan's Northwest Frontier Province lies close to the esophagus cancer belt of South-Central Asia. A prospective cohort or population-based study now needs to be conducted to confirm high-incidence rates of SCC among residents of NWFP, and whether the type of tobacco consumed and social customs typical to specific provinces can explain the differences noted here.

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