

## The increasing incidence of esophageal squamous cell carcinoma in women in Turkey

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**Background/aim:** This study assessed the trend changes in the histological types of esophageal cancer in a 25-year period in eastern Turkey.

**Materials and methods:** We searched all cases of esophageal cancer from 1990 to 2015 according to their histological diagnosis and sex, grouping the patients in 5-year time periods to evaluate time trends.

**Results:** We identified 1462 cases of esophageal cancer. In terms of patient make-up, 742 were male and 720 were female. In general, 75.86% of the patients had squamous cell carcinoma (SCC), 19.56% of the patients had adenocarcinoma (ADC), and the remaining 4.58% patients were found to have other histopathologic disorders. While the SCC to ADC ratio was 1.76 between 1990 and 1994, this rate increased to 8.73 between 2010 and 2014; during these periods, the male to female ratio decreased from 1.43 to 0.86. Between these two periods, statistically significant changes were observed of SCC and the number of female patients ( $P < 0.001$ ,  $P = 0.008$ , respectively).

**Conclusion:** While the incidence of esophagus ADC and the number of male patients increased recently in Western countries, the number of female patients and SCC cases increased in our region in the last 25 years.

**Key words:** Esophageal cancer, squamous cell carcinoma, adenocarcinoma, epidemiology

### 1. Introduction

The epidemiology of esophageal cancer has been a growing area of interest in recent years. The research on epidemiologic variations has played an important role in making esophageal cancer the 8th most commonly diagnosed of all cancer types (1). Along with geographical localization, race, sex, socioeconomic status, and dramatic changes are linked to two main histological types: squamous cell carcinoma (SCC) and adenocarcinoma (ADC) (2,3). SCC and ADC are the most frequent primary esophageal malignancies, and their epidemiological characteristics vary greatly. While the incidence of ADC has increased in Western countries, especially with males in the last 50 years, the incidence of ADC has remained stable in Turkey (2,3). In the United States, ADC has been the most common subtype of esophageal cancer since 1990 (4). SCC has been the dominant type of esophageal cancer in Western and Asian countries. The rapid increase of ADC is believed to be associated with the increase in the prevalence of gastroesophageal reflux—the major determinant factor for it being obesity—and developments in medicine with increasing awareness. Also, despite the

rapid increase of ADC following gastroesophageal reflux in Western countries, no increase has been observed in Asia (5).

Although there is no present reliable number for its incidence, mainly because of insufficient cancer reports in Turkey, it is a known fact that this cancer type has frequently been seen in the eastern part of Turkey. Erzurum, located in the east of the country, has the highest rates of esophageal cancer in the country, and the most prevalent subtype of esophageal cancer is SCC (6–8). The aim of this study was to verify the trend changes in the histological types of esophageal cancer in a 25-year period in the east of Turkey.

### 2. Materials and methods

We searched through the endoscopy and pathology records of Atatürk University Hospital for all cases of esophageal cancer from January 1990 to December 2014. Our hospital is a reference center for the east of Turkey, covering approximately 2 million people. We recorded the age and sex of the patients and the histological type. We excluded patients with an endoscopic diagnosis of

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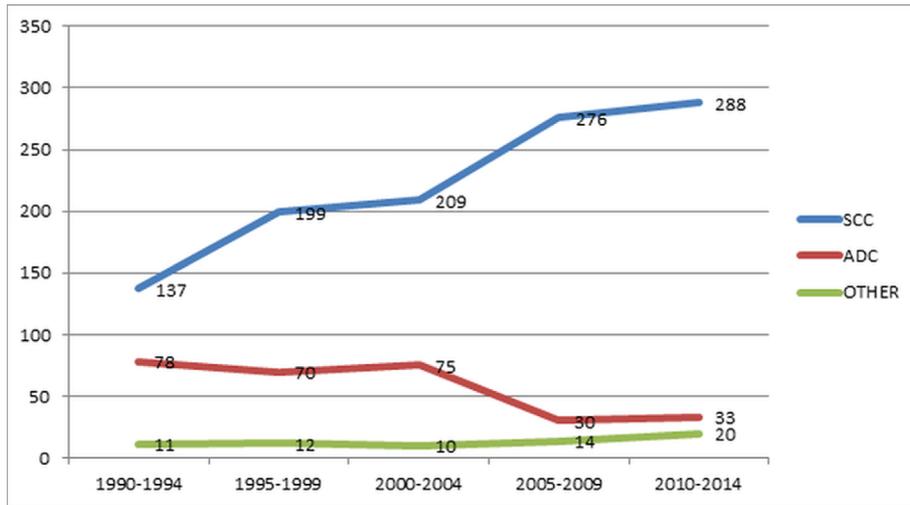
esophageal cancer but no histological confirmation. We also excluded the cases of patients who had tumors in the pharynx or stomach. We grouped the patients in 5-year time periods to evaluate time trends.

Data were analyzed with SPSS 20 at a significance level of  $P < 0.05$ . Chi-square and Fisher's exact test tested the associations between age, sex, and histological type. We assessed the trends over time through the Mantel trend test.

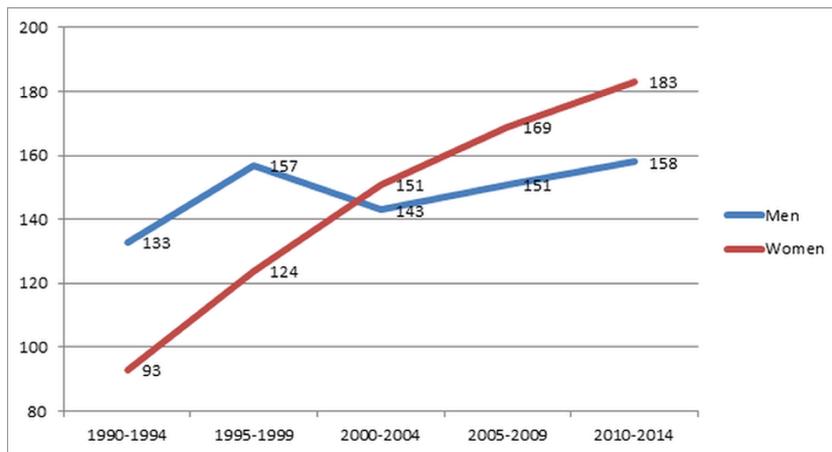
**3. Results**

A total of 42,652 patients underwent upper gastrointestinal endoscopy and esophageal cancer was detected in 1462 (3.43%) of them during a period of 25 years. Seven hundred and forty-two of the patients were male (50.75%) and 720 were female (49.25%). Their ages were between 13 and 96 years (mean:  $60.85 \pm 12.43$ ). The mean age for the males and the females was  $61.27 \pm 12.28$  (30–96) and

$60.46 \pm 13.53$  (13–89), respectively. While the male to female ratio was 1.43 (133/93) between 1990 and 1995, it was 0.86 (158/183) between 2010 and 2014. There was female dominance in the group below 50 years old and male dominance in the group above 50 years old. In the group below 30 years old, there were 17 females and 2 males. The number of cases intensified in the 5th and 6th decades. In general, 1109 (75.86%) of the patients had SCC, 286 (19.56%) of the patients had ADC, and the remaining 67 (4.58%) patients were found to have other histopathologic diseases. While the SCC to ADC ratio was 1.76 (137/78) between 1990 and 1994, this rate increased to 8.73 (288/33) between 2010 and 2014. During these periods, the male to female ratio decreased from 1.43 (133/93) to 0.86 (158/183). Figure 1 shows the steady trend of SCC and ADC during the 25-year period. Figure 2 shows the trend of males and females along the same 25-year period. Between these two periods, statistically



**Figure 1.** Time trends in histological types of esophageal cancer between 1990 and 2015.



**Figure 2.** Time trends in esophageal cancer of the sexes between 1990 and 2015.

significant changes were observed in SCC and the number of female patients ( $P < 0.001$ ,  $P = 0.008$ , respectively). Table 1 shows significant changes in the mean age or the distribution of the disease by sex and histological type over the 25-year period. The mean ages in SCC and ADC were  $59.9 \pm 13.7$  and  $64.0 \pm 13.4$ , respectively ( $P = 0.041$ ). The male to female ratios in SCC and ADC were 0.95 and 1.60, respectively ( $P < 0.001$ ). In our study, SCC presented the highest frequency between 45 and 74 years of age, and ADC was present more frequently between 60 and 74 years of age. Table 2 shows the demographics and histological type distribution.

**4. Discussion**

Esophageal cancer is a major health problem around the world. It is the 8th most commonly diagnosed cancer and the 6th most common cause of cancer deaths worldwide (9). It is endemic in many parts of the world, particularly in developing nations, where it is the 4th most common cause of cancer deaths (9). Esophageal cancer is the 8th most common cancer in the world, with more than 456,000 new cases and 400,000 deaths annually (10). An important characteristic of esophageal cancer is that its prevalence may differ between some geographical regions; indeed, it may even differ between very close locations in

the same geographical region. The incidence of esophageal cancer represents one of the widest variations, with a sixty-fold difference between high- and low-incidence regions (11). However, the incidence rates for esophageal cancer have increased worldwide. While there is no exact incidence rate determined for our country, it has mostly been observed in the east of Turkey. Upper gastrointestinal system tumors are more frequent in the eastern region of the country for both males and females. Esophageal cancer was the 2nd most commonly diagnosed cancer in the eastern region according to a study (12). Our study is the first to be carried out in Turkey that evaluates time trends in the incidence rates of esophageal cancer according to sex and histopathology between 1990 and 2014.

SCC and ADC are the most frequently seen primary esophageal malignancies, and they have quite different epidemiologic characteristics. Surgical series between 1926 and 1976 indicated that ADC is not common and accounts for 0.8%–3.7% of all esophageal cancers (3,13,14). The incidence of SCC has been increasing progressively in Western countries since the 1970s (15,16). ADC is the most rapidly increasing solid malignancy and has climbed to the 7th position of deaths caused by cancer (17). The incidence of ADC in white males in the United States was 0.5–0.9/100,000 in the 1970s, but later, during the next

**Table 1.** Time trends in age, sex, and histological types of esophageal cancer between 1990 and 2015.

	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014	Total	P trend over time
Sex	226	281	294	320	341	1462	P = 0.008
Male (n, %)	133 (58.85)	157 (55.87)	143 (48.64)	151 (47.18)	158 (46.33)	742 (50.75)	
Female (n, %)	93 (41.15)	124 (44.13)	151 (51.36)	169 (52.82)	183 (53.67)	720 (49.25)	
Mean age (±SD)	55.08 ± 11.83	56.71 ± 12.5	60.89 ± 12.91	61.81 ± 13.90	67.13 ± 13.01	60.85 ± 12.43	
Male (±SD)	57.15 ± 9.69	56.81 ± 10.7	61.08 ± 13.13	61.94 ± 14.82	68.68 ± 12.22	61.27 ± 12.28	
Female (±SD)	53.56 ± 12.71	56.62 ± 12.6	60.17 ± 12.04	61.91 ± 13.29	65.47 ± 13.65	60.46 ± 13.53	
Histopathological type							
SCC (n, %)	137 (60.62)	199 (70.82)	209 (71.09)	276 (86.25)	288 (84.46)	1109 (75.86)	P < 0.001
ADC (n, %)	78 (34.51)	70 (24.91)	75 (25.51)	30 (9.37)	33 (9.68)	286 (19.56)	
Other (n, %)	11 (4.87)	12 (4.27)	10 (3.40)	14 (4.38)	20 (5.86)	67 (4.58)	

**Table 2.** Sex and histological type distribution.

	Male	Female	M/F	Total
SCC	541	568	0.95	1109
ADC	176	110	1.60	286
Other	25	42	0.595	67
Total	742	720		1462

two decades, it increased to 3.2–4.0/100,000 (18–20). A similar increase was also observed in the United Kingdom, Australia, Northern Europe, and Iceland (16,21,22). The rate of SCC to ADC was 4.7:1 in white males in 1975. It decreased to 2.1:1 in 1995 and, after that, it rapidly decreased to 0.43:1 between 1996 and 1998 (20,23). In the mid-1990s, ADC surpassed SCC, which was then the most common esophageal cancer (1,20). The reason behind this increase remains unclear. The incidence of SCC among white males decreased with the increase in the incidence of ADC (18,24). On the other hand, the incidence of ADC did not change in Asian countries or in the Asian population living in the United States (24–30). SCC is still the most frequent histopathological disorder (29). The incidence of ADC in Asian countries is quite low and, especially in East Asian countries, the incidence of SCC is higher than that of ADC. SCC is the dominant type of esophageal cancer, especially in China, Hong Kong, Taiwan, Korea, and Japan (25–31). However, the incidence of SCC is relatively stable or slightly decreasing in the rest of the world (31). In the many studies on this subject conducted in Turkey, where Asia meets Europe, the incidence of SCC was reported to be higher than that of ADC (6,7,12). Considering the data gathered from the 1462 cases diagnosed in our hospital over the last 25 years, we noticed that despite the data about American and European countries, the SCC/ADC ratio increased from 1.76 to 8.73 in the 5-year time periods of 1990–1994 and 2010–2014.

The etiology of esophageal cancer is multifactorial. While the most important etiologic factors are smoking and alcohol in the United States and in European countries, factors associated with nutrition are more common in developing countries (1,2). Tobacco and alcohol abuse are major risk factors for SCC, whereas the use of tobacco is a moderately established risk factor for ADC. Obesity, gastroesophageal reflux disease, and Barrett's esophagus have been established as strong risk factors for ADC of the esophagus (1–3). A study conducted in our clinic concerning the etiology of esophageal cancer in our region revealed that the educational levels and incomes of the patients were low and that most of them were living in villages working as farmers. There was no statistically significant difference with the control group in terms of alcohol and tobacco abuse. We determined that the risk factors for the development of esophageal cancer, common in our region, are as follows: low income and educational level; excessive consumption of hot tea; excessive consumption of moldy cheese, which produces many carcinogenic mycotoxins; insufficient consumption of fresh fruits and vegetables, which have antioxidant and anticancer effects; the presence of similar diseases within the family; and exposure to smoke, especially for women when they are cooking. In conclusion, we think

that tobacco and alcohol abuse are not an important factor in our region; instead, nutritional, environmental, and genetic factors are important in the etiology of the disease. However, epidemiologic studies with larger samples on this subject in our region are necessary.

Esophageal cancer is seen more frequently in men around the world. In the first series of collective studies done in 1952, the female to male ratio was 1/20, while this rate is between 1/2 and 1/4 in recent publications. While it is more frequent in men in North America and Europe, it affects males and females equally in countries where it has a high prevalence such as China, Japan, and Singapore (25–27,29,30). It was reported to be more common in women than men in Mazordaran Province of Iran (32). The male to female ratio was close to one, with a slight male dominance ( $742/720 = 1.03$ ). However, the interesting fact is that the male to female ratio in the 1990–1994 period was 1.43; in contrast, this rate decreased to 0.86 in the 2010–2014 period. The number of female patients has increased progressively since 1990 in our studies, and female patients have surpassed the number of male patients since 2000. Today, the incidence of SCC is higher in males than females around the world (2). It was proven that males are affected 3 to 4 times more than females, regardless of their race (33). Males are affected 6 to 8 times more than females in ADC (3,4,34). Our study suggests that SCC is more common in women while ADC is more common in men.

Esophageal cancer is extremely rare in people below 40, and its rate increases every decade (6). Generally, the disease is more prevalent in the 5th and 6th decades (6). In the United States, many patients with SCC are treated in the 6th and 7th decades, while ADC peaks in males at 75–79 and females at 80–84 years old (2). The mean age at diagnosis is 68 in the group of patients recorded since 1988 in the SEER database (35). The incidence is increasing in our country during middle age. According to the data gathered by the WHO, the mean life expectancy in our country has shown significant improvements in the last 30 years. Male to female life expectancy increased from 63/67 to 72/78. The life expectancy at birth for US citizens was 76 in males and 81 in females in 2012. In concordance with that, the mean age at diagnosis increased from 55 (in the 1990–1994 period) to 64. Also, we noticed that females are affected with the disease earlier than males, and patients with SCC were 4 years younger.

In conclusion, while the incidence of esophageal adenocarcinoma increased in Western countries, the incidence of SCC had a significant increase in our country in the last 25 years. The number of female patients has surpassed the number of male patients since 2000. SCC was more common in females while ADC was more common in males. Females were affected with the disease

at a younger age than males. Further epidemiological research, both in terms of descriptive studies and analytical investigations, is needed to confirm our observations and

related considerations. Investigation of these changes may contribute to understanding and preventing the occurrence, early diagnosis, and treatment of esophageal cancer.

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