

# Esophageal Cancer: An Updated Surveillance Epidemiology and End Results Database Analysis

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## Abstract

**Background:** Esophageal cancer is the sixth leading cause of cancer-related deaths and the eighth most common cancer worldwide with a 5-year survival rate of less than 25%. Here we report the incidence, risk factors and treatment options that are available currently, and moving into the future.

**Methods:** We retrospectively analyzed the Surveillance Epidemiology and End Results (SEER) database made available by the National Cancer Institute in the USA. Specifically we extracted data from the years 2004 - 2015.

**Results:** In total we identified 23,804 patients with esophageal adenocarcinoma and 13,919 patients with esophageal squamous cell carcinoma. Males were at an increased risk of developing both types of esophageal cancer when compared to females. Most cases of adenocarcinoma were diagnosed as poorly differentiated grade III (42%), and most cases of squamous cell carcinoma were diagnosed as moderately differentiated grade II (39.5%). The most common stage of presentation for both adenocarcinoma (36.9%) and squamous cell (26.8%) carcinoma was stage IV. The worst outcomes for adenocarcinoma were noted with grade III tumors (hazard ratio (HR): 1.56, 95% confidence interval (CI): 1.44 - 1.68, P value: < 0.01), stage IV tumors (HR: 3.58, 95% CI: 3.33 - 3.85, P value: < 0.01) and those not treated with surgery (HR: 2.54, 95% CI: 2.44 - 2.65, P value: < 0.01). For squamous cell carcinoma, the worst outcomes were noted with grade III tumors (HR: 1.35, 95% CI: 1.23 - 1.49, P value: < 0.01), stage IV tumors (HR: 2.12, 95% CI: 1.94 - 2.32, P value: < 0.01).

**Conclusions:** The incidence of esophageal adenocarcinoma in the

USA is steadily on the rise. Conversely, the incidence of squamous cell carcinoma has been continually declining. While white males had an increased incidence of both types of esophageal cancer, a higher proportion of African Americans suffered from squamous cell carcinoma. Despite the wide spread use of proton pump inhibitors, adenocarcinoma continues to be a major public health concern.

**Keywords:** Esophageal cancer; Adenocarcinoma; Squamous cell carcinoma; Chemotherapy; Radiotherapy

## Introduction

Esophageal cancer is a type of malignancy characterized by its high mortality rate, poor prognosis at the time of diagnosis and significant variations in incidence, mortality, and histopathology based on geographic region. This disease is the sixth cause of cancer-related deaths and the eighth most common cancer worldwide with a 5-year survival rate of less than 25% [1]. An estimated 17,650 cases of esophageal cancer will be diagnosed each year in the USA, from which 16,080 deaths are expected [2]. Squamous cell carcinoma and adenocarcinoma represent the vast majority of esophageal cancers. The most common type of esophageal cancer is squamous cell carcinoma, but esophageal carcinoma is in epidemiological transition, with a dramatic increase in the incidence of esophageal adenocarcinoma (EAC) during the last 40 years [3].

EAC is quickly becoming the most prevalent form of esophageal cancer in the developed world. Indeed in 2012, one study found that its incidence rate was highest in Northern and Western Europe, Northern America, and Oceania. In contrast, the lowest incidence rates were found in developing countries, namely, in Eastern and Southeastern Asia, and sub-Saharan Africa [4]. Not only has its incidence rate steadily been on the rise, but also, over the past 25 years the rate at which it has been rising is the highest of any other malignancy in the USA [5]. Regarding gender and racial distribution, historically, EAC is more common in males when compared to females (7:1 ratio), and its incidence rate is higher in whites when compared to blacks [6]. Risk factors for EAC may be divided into genetic and non-genetic components. In recent literature clustering of EAC within several families has suggested the presence of a genetic component in EAC. The identification of this subset of patients has given rise to the term "familial EAC", which

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is also referred to as “familial Barrett’s esophagus (BE)”. Familial EAC is defined as the presence of two or more family members diagnosed with BE, EAC or gastroesophageal junction EAC (EJEAC) [7]. Studies have shown that familial cases of EAC tend to develop at a younger age, and are less strongly associated with other risk factors for EAC [8]. In 2016, further supporting the theory of a genetic component, Fecteau et al were able to identify a germline mutation associated with a subset of patients with EAC [9]. Non-genetic risk factors are better established in the development of EAC and include BE, gastroesophageal reflux disease (GERD), obesity, and tobacco smoking [8].

Despite the increasing incidence of EAC in the west, esophageal squamous cell carcinoma (ESCC) continues to be the most prevalent type of esophageal cancer worldwide accounting for 90% of all esophageal cancers each year [10]. Geographically, in contrast to EAC, ESCC is more commonly seen in developing countries. Specifically the highest rates were observed in Eastern and South-East Asia, followed by sub-Saharan Africa, and Central Asia [4]. Similar to EAC, cases of ESCC are more commonly seen in males when compared to females with a ratio of 2.7 [4]. Regarding ethnicity, ESCC has a higher incidence in blacks when compared to other races (White, Pacific Islanders, American Indian or Alaskan Natives) [11]. Risk factors for ESCC include low socioeconomic status, tobacco smoking and alcohol consumption (which when combined, exert a synergistic effect on increasing risk). Diet also plays a significant role in developing ESCC. Namely, consumption of hot beverages, nitrosamine (seen in processed meats), red meat, and micronutrient deficiencies (beta-carotene, folate, vitamin C, vitamin E and riboflavin) have all been linked with a higher risk of ESCC [12]. Achalasia, a motility disorder of the esophagus also confers an increased risk [13]. Establishing a genetic component in the development of ESCC has been a controversial topic. Two studies conducted in China and in the Turkmen population in Iran, both endemic areas of ESCC, showed that a positive family history conferred an increased risk of developing ESCC [14, 15]. Other studies have contradicted these findings. Dhillon et al conducted a population-based study in the USA that found no such link between family history and ESCC [16].

Overall, the 5-year survival rate of esophageal cancer, of all types, remains poor at approximately 20% [17]. Despite its poor prognosis, significant strides in cancer treatment have resulted in a decreased mortality over the past four decades. When analyzing survival rates of esophageal cancer by type, EAC has a better prognosis when compared to ESCC. One study published in 2003, analyzed survival trends of EAC and ESCC from mid 1970s to the late 1990s. The study found that the relative 5-year relative survival rate of EAC increased from 5.7 to 13.6 during the study period. Similarly, the 5-year relative survival rate of ESCC increased from 4.5 to 11.8 [18].

The primary aim of this study was to analyze incidence rate, mortality rate and yearly incidence trend using data extracted from the Surveillance, Epidemiology and End Results (SEER) registry for the time period of 2004 - 2015. This registry is compiled by the National Cancer Institute and represents approximately 28% of the US population.

## Materials and Methods

This is a retrospective cohort study in which we extracted data from the SEER registry for the time period of 2004 - 2015. This registry is compiled by the National Cancer Institute and represents approximately 28% of the US population. Specifically we used the SEER 18 database, which includes patient data from Alaska, Connecticut, Detroit, Atlanta, greater Georgia, rural Georgia, San Francisco-Oakland, San Jose-Monterey, greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Mexico, New Jersey, Seattle-Puget Sound and Utah [19, 20].

All patients who were diagnosed with cancer located in the esophagus as per the International Classification of Diseases for Oncology, third edition (ICD-0-3) from 2004 - 2015 were identified and included in our study. Exclusion criteria included patients under the age of 20 years and over the age of 85 years. Additionally we excluded patients that did not have a confirmed pathologic diagnosis of esophageal cancer.

In total 37,723 patients met our inclusion criteria and were studied in our cohort. We extracted baseline demographic characteristics including, age, sex, race, and geographic location. Race was classified into White, Black, Hispanic, Asian/Pacific Islander, or Alaskan/Native Indian. Tumor characteristics were also extracted and included histology, tumor size, tumor grade, tumor stage, and tumor location. The American Joint Committee on Cancer Classification (AJCC) 2004 was used to sub-classify tumor stage. Treatment information was extracted and categorized into surgical treatment, chemotherapy or radiotherapy.

SEER\*Stat statistical software was used to calculate incidence rates, mortality rates and yearly incidence trends that spanned 11 years (2004 - 2015) [20, 21]. STATA software version 15 was used to create multivariate Cox proportional hazard regression models. Given the nature of the SEER database, all patient information is de-identified and not made available to researchers accessing this database. Because of this, our study was exempt from Institutional Review Board (IRB) approval.

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## Results

### Demographic characteristics

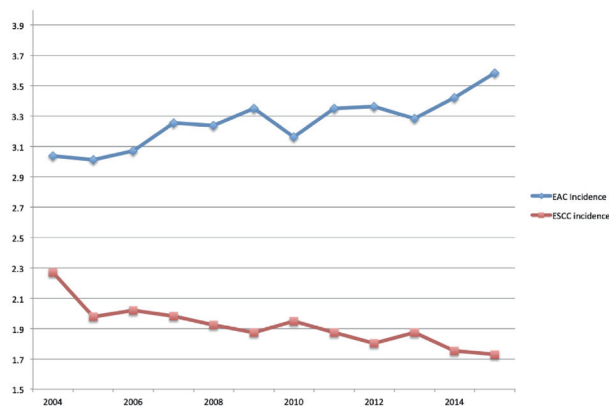
A total of 39,842 patients were included in our study. The mean age for all esophageal cancer patients was  $65.7 \pm 10$  years. The mean age for adenocarcinoma and squamous cell carcinoma patients was  $65.4 \pm 10$  and  $66.3 \pm 10$  years, respectively (Table 1). The overall age adjusted incidence rate for all esophageal

**Table 1.** Baseline Demographic Characteristics of Esophageal Adenocarcinoma and Squamous Cell Carcinoma

Variable	Total EAC (n, %)	Total ESCC (n, %)
Sex		
Male	20,700 (86.96%)	9,156 (65.78%)
Female	3,104 (13.04%)	4,763 (34.22%)
Race		
White	20,951 (88.01%)	7,754 (55.71%)
Black	649 (2.73%)	3,649 (26.22%)
Hispanic	1,612 (6.77%)	1,148 (8.25%)
Asian or Pacific Islander	417 (1.75%)	1,257 (9.03%)
American Indian/Alaskan Native	124 (0.52%)	92 (0.66%)
Unknown	51 (0.21%)	19 (0.14%)
Region		
Pacific Coast	10,098 (42.42%)	5,940 (42.68%)
East	9,553 (40.13%)	6,286 (45.16)
Northern Plains	2,959 (12.43%)	1,274 (9.15%)
Southwest	1,167 (4.90%)	378 (2.72%)
Alaska	27 (0.11%)	41 (0.29%)

EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma.

cancer patients from 2004 - 2015 was 5.8 per 100,000. The overall age adjusted incidence rate for adenocarcinoma and squamous cell carcinoma from 2004 - 2015 was 3.2 and 1.9 per 100,000 respectively (Fig. 1). Males composed 79.3% of all cancer patients, 86.9% of adenocarcinoma patients, and 65.7% of squamous cell carcinoma patients. Whites had a higher proportion of adenocarcinoma when compared to squamous cell carcinoma (88.01% vs. 55.71%). Blacks however had a higher proportion of squamous cell carcinoma when compared to adenocarcinoma (26.22% vs. 2.73%). With each progressive year the incidence of squamous cell carcinoma trended down (nadir: 1.729 per 100,000). Conversely, the incidence of adenocarcinoma trended up with each progressive year (peak: 3.5 per 100,000).



**Figure 1.** Annual incidence rate of esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC).

### Tumor characteristics

Most cases of esophageal cancer were diagnosed as adenocarcinoma (59.7%), followed by squamous cell carcinoma (34.9%), and signet ring cell carcinoma (2.9%). At time of diagnosis most cases of adenocarcinoma were poorly differentiated (42.04%). Squamous cell carcinoma was mostly moderately differentiated (39.5%) at time of diagnosis. Most cases of both adenocarcinoma and squamous cell carcinoma were diagnosed as stage IV (36.9% and 26.8%, respectively). Adenocarcinoma was mainly located in the lower esophagus (78.9%), whereas the middle esophagus was the most common location for squamous cell carcinoma (39.1%) (Table 2).

### Treatment

Regarding treatment, most cases of esophageal cancers were treated with chemotherapy (61.7%), followed by radiotherapy (55.4%). Surgery was performed in only 26.6% of all patients with esophageal cancer. Patients with adenocarcinoma were more likely to undergo surgical resection when compared to squamous cell carcinoma (32.9% vs. 15.9%). Both adenocarcinoma and squamous cell carcinoma patients underwent combined radiotherapy and chemotherapy at similar rates (45.8% vs. 50.4%). Adenocarcinoma patients underwent combined surgical resection and chemotherapy at a higher rate than patients with squamous cell carcinoma (20.1% vs. 9.3%). Similarly, triple therapy with surgery, radiotherapy and chemotherapy was seen more frequently in adenocarci-

**Table 2.** Tumor Characteristics for Esophageal Adenocarcinoma and Squamous Cell Carcinoma

Variable	Total EAC (n, %)	Total ESCC (n, %)
<b>Tumor grade</b>		
Well differentiated; grade I	1,227 (5.15%)	651 (4.68%)
Moderately differentiated; grade II	7,987 (33.55%)	5,500 (39.51%)
Poorly differentiated; grade III	10,007 (42.04%)	4,881 (35.07%)
Undifferentiated; anaplastic; grade IV	279 (1.17%)	106 (0.76%)
Unknown	4,304 (18.09%)	2,781 (19.98%)
<b>Stage</b>		
Stage I	4,009 (16.84%)	1,988 (14.28%)
Stage II	4,039 (16.97%)	2,748 (19.74%)
Stage III	4,355 (18.30%)	3,091 (22.21%)
Stage IV	8,806 (36.99%)	3,731 (26.81%)
Unknown	2,595 (10.90%)	2,361 (16.96%)
<b>T staging</b>		
T1	6,932 (29.12%)	3,631 (26.09%)
T2	2,265 (9.52%)	1,234 (8.87%)
T3	7,002 (29.42%)	3,581 (25.73%)
T4	2,442 (10.26%)	2,269 (16.30%)
Unknown	5,163 (21.69%)	3,204 (23.02%)
<b>N staging</b>		
N0	13,014 (54.67%)	7,763 (55.77%)
N1	10,790 (45.33%)	6,156 (44.23%)
<b>Location</b>		
Upper esophagus	288 (1.21%)	2,643 (18.99%)
Middle esophagus	1,846 (7.75%)	5,444 (39.11%)
Lower esophagus	18,785 (78.92%)	3,755 (26.98%)
Overlapping lesion	2,885 (12.12%)	2,077 (14.92%)
<b>Surgery</b>		
Surgery performed	7,831 (32.90%)	2,214 (15.91%)
No surgery performed	15,973 (67.10%)	11,705 (84.09%)
<b>Radiation</b>		
Radiation given	12,440 (52.26%)	8,515 (61.18%)
No radiation given	11,364 (47.74%)	5,404 (38.82%)
<b>Chemotherapy</b>		
Chemotherapy given	14,830 (62.30%)	8,384 (60.23%)
No chemotherapy given	8,974 (37.70%)	5,535 (39.77%)

EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma.

noma patients than in the squamous cell carcinoma population (17.8% vs. 8.4%).

**Survival and clinical predictors**

One- and 5-year cause specific survival for EAC was 54.4% and 23.4% respectively, with a median survival of 15 months

(Table 3, Fig. 2). One- and 5-year cause specific survival for ESCC was 43.8% and 18.9% respectively, with a median survival of 10 months (Table 3, Fig. 3). For patients with adenocarcinoma, Cox proportional hazard regression analysis revealed worse outcomes with lesions located in the middle esophagus (hazard ratio (HR): 1.20, confidence interval (CI): 1.03 - 1.39, P value: 0.01); tumor grade III (HR: 1.56, CI: 1.44 - 1.68); tumor stage IV (HR: 3.58, 3.33 - 3.85, P value:



**Table 3.** Survival of Patients with Esophageal Adenocarcinoma and Squamous Cell Carcinoma

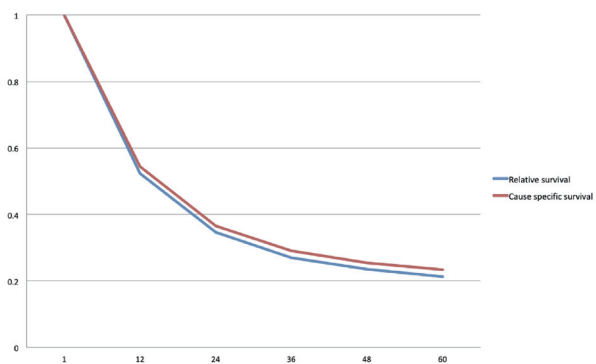
Survival	EAC	ESCC
Relative		
1-year	52.3%	41.4%
5-year	21.3%	15.9%
Median	13 months	9 months
Cause-specific		
1-year	54.4%	43.8%
5-year	23.4%	18.9%
Median	15 months	10 months

EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma.

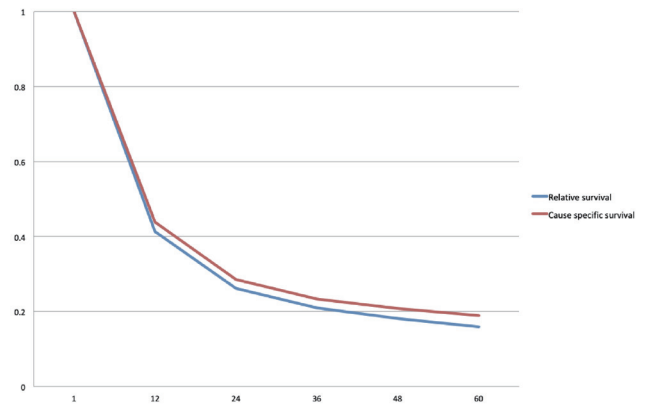
< 0.05) and those that did not undergo surgery (HR: 2.54, CI: 2.44 - 2.65, P value: < 0.05) (Table 4). In the squamous cell carcinoma population, worse outcomes were seen in African Americans (HR: 1.11, CI: 1.06 - 1.16, P value: < 0.05), lesions located in the lower esophagus (HR: 1.12, CI: 1.06 - 1.19, P value: < 0.05), tumor grade III (HR: 1.35, CI: 1.23 - 1.49, P value: < 0.05), tumor stage IV (HR: 2.17, CI: 1.94 - 2.32, P value: < 0.05), and those that did not undergo surgery (HR: 2.37, CI: 2.22 - 2.52, P value: < 0.05) (Table 5).

**Discussion**

Based on our findings, the incidence of adenocarcinoma is steadily increasing, while that of squamous cell carcinoma is steadily decreasing. At the tail end of our study in 2015, the incidence rate of adenocarcinoma was at an all-time high. In contrast, the incidence of squamous cell carcinoma was at an all-time low. In 2010 there was a downtrend in the incidence of adenocarcinoma, but this trended back up in subsequent years. Despite its decreasing incidence in the USA, squamous cell carcinoma continues to be the most common type of esophageal cancer worldwide. This may be due to the decreasing rates of tobacco use and increasing rates of BS [22].



**Figure 2.** Kaplan-Meier curve for cause specific and relative survival for esophageal adenocarcinoma (EAC).



**Figure 3.** Kaplan-Meier curve for cause specific and relative survival for esophageal squamous cell carcinoma (ESCC).

Demographically we found that African American patients had a disproportionately increased risk of developing squamous cell carcinoma. This is consistent with current literature, which suggests that African American race is an independent risk factor for the development of squamous cell carcinoma [10]. Additionally African Americans have a higher likelihood of mortality when compared to other races [23]. A theory to explain this staggering disparity could be centered on socioeconomic status. Present day squamous cell carcinoma has higher rates among populations in developing countries that have predominantly low socioeconomic status [10]. Additionally, smoking, alcohol and poor diet are known risk factors for the development of squamous cell carcinoma, and are all risk factors that are less likely to be present in affluent, predominantly Caucasian populations. This is compounded by the innate distrust of doctors that exists within the African American community. One study in particular found that that African Americans are more likely to be diagnosed with squamous cell carcinoma at a later stage when compared to other races [24]. This suggests a reluctance to seek timely evaluation and subsequent treatment that would result in a decreased mortality rate.

As mentioned previously, our study found that the incidence rate of adenocarcinoma has steadily been on the rise. Current data are ambiguous regarding where this trend is heading in upcoming years. A study conducted by Njei et al analyzing the SEER database from 1973 - 2009 had findings similar to our study, concluding that rates of adenocarcinoma increased with each progressive decade [25]. Patel et al published a similar study more recently, which analyzed the incidence rates of esophageal cancer from 2001 - 2015 using the United States cancer statistics database. According to their data, the incidence rate of adenocarcinoma after initially rising has begun to trend down [26]. If our findings hold true into the upcoming decade, it represents a distinct problem moving forward. In particular the use of proton pump inhibitors may come under more scrutiny. Coleman et al and Soest et al published research concerning the incidence rates of BE in the UK and the Netherlands respectively. Despite increasing rates of endoscopic evaluation, their data showed that the incidence of BE nearly tripled from 1997 - 2002 [27, 28]. This suggests that despite the widespread use of proton pump inhibitors, BE

**Table 4.** Hazard Ratios for Esophageal Adenocarcinoma

Variable	Hazard ratio	95% Confidence interval	P value
Age at diagnosis	1.012	1.010 - 1.013	0.000
Sex			
Male	1.00		
Female	0.932	0.892 - 0.975	0.002
Race			
White	1.00		
Black	1.091	0.996 - 1.194	0.061
Hispanic	1.023	0.963 - 1.086	0.450
Asian/Pacific Islander	0.862	0.769 - 0.967	0.012
American Indian/Alaskan	1.143	0.929 - 1.407	0.205
Location			
Upper esophagus	1.00		
Middle esophagus	1.202	1.037 - 1.395	0.014
Lower esophagus	1.123	0.977 - 1.291	0.101
Overlapping lesion	1.177	1.019 - 1.361	0.027
Tumor size	0.999	0.999 - 1.000	0.812
Grade			
Grade I	1.00		
Grade II	1.226	1.134 - 1.325	0.000
Grade III	1.563	1.447 - 1.689	0.000
Grade IV	1.404	1.204 - 1.637	0.000
Unknown	1.117	1.029 - 1.212	0.008
Stage			
Stage I	1.00		
Stage II	1.962	1.821 - 2.115	0.000
Stage III	2.447	2.247 - 2.666	0.000
Stage IV	3.587	3.336 - 3.857	0.000
Unknown	1.669	1.539 - 1.809	0.000
T - stage			
T1	1.00		
T2	0.765	0.713 - 0.820	0.000
T3	0.895	0.848 - 0.945	0.000
T4	1.109	1.041 - 1.182	0.001
Unknown	1.171	1.108 - 1.238	0.000
N - stage			
N0	1.00		
N1	1.078	1.039 - 1.118	0.000
Unknown			
Surgery			
Surgery performed	1.00		
No surgery performed	2.545	2.443 - 2.652	0.000
Radiation			
Radiation given	1.00		

**Table 4.** Hazard Ratios for Esophageal Adenocarcinoma - (continued)

Variable	Hazard ratio	95% Confidence interval	P value
No radiation given	0.917	0.884 - 0.950	0.000
Chemotherapy			
Chemotherapy given	1.000		
No chemotherapy given	1.689	1.622 - 1.758	0.000

**Table 5.** Hazard Ratios for Esophageal Squamous Cell Carcinoma

Variable	Hazard ratio	95% Confidence interval	P value
Age at diagnosis	1.005	1.003 - 1.007	0.000
Sex			
Male	1.00		
Female	0.833	0.800 - 0.0868	0.000
Race			
White	1.00		
Black	1.117	1.068 - 1.169	0.000
Hispanic	0.937	0.872 - 1.006	0.076
Asian/Pacific Islander	0.893	0.833 - 0.956	0.001
American Indian/Alaskan	1.061	0.836 - 1.346	0.623
Location			
Upper esophagus	1.00		
Middle esophagus	1.126	1.068 - 1.188	0.000
Lower esophagus	1.127	1.063 - 1.195	0.000
Overlapping lesion	1.210	1.132 - 1.293	0.000
Tumor size	1.000	0.999 - 1.000	0.400
Grade			
Grade I	1.00		
Grade II	1.322	1.200 - 1.457	0.000
Grade III	1.358	1.231 - 1.497	0.000
Grade IV	1.169	0.923 - 1.480	0.194
Unknown	1.161	1.048 - 1.285	0.004
Stage			
Stage I	1.00		
Stage II	1.266	1.158 - 1.384	0.000
Stage III	1.431	1.287 - 1.592	0.000
Stage IV	2.127	1.945 - 2.326	0.000
Unknown	1.273	1.152 - 1.407	0.000
T-stage			
T1	1.00		
T2	0.816	0.745 - 0.893	0.000
T3	0.946	0.880 - 1.017	0.133
T4	1.346	1.241 - 1.460	0.000
Unknown	1.064	0.984 - 1.150	0.116
N-stage			

**Table 5.** Hazard Ratios for Esophageal Squamous Cell Carcinoma - (continued)

Variable	Hazard ratio	95% Confidence interval	P value
N0	1.00		
N1	1.045	0.998 - 1.094	0.060
Unknown			
Surgery			
Surgery performed	1.00		
No surgery performed	2.370	2.226 - 2.52	0.000
Radiation			
Radiation given	1.00		
No radiation given	1.319	1.258 - 1.384	0.000
Chemotherapy			
Chemotherapy given	1.00		
No chemotherapy given	1.840	1.755 - 1.930	0.000

continues to thrive.

When analyzing factors impacting survival, most of our findings are consistent with current literature. For both squamous cell carcinoma and adenocarcinoma we found that grade III, stage IV, and lack of treatment with surgery or chemotherapy conferred a higher risk for mortality. Conversely, we found that tumor size had no statistical significance on impacting mortality in either squamous cell carcinoma or adenocarcinoma. This goes against current literature, which suggests increasing tumor size in esophageal cancer is associated with increased mortality. In a retrospective study by Haisley et al, they found that increased tumor length resulted in a 20% increased risk of mortality (HR: 1.206; P value: 0.03) [29]. This study however was limited by lack of power evidenced by their small sample size (n = 98). Another study published by Valmasoni et al also suggests tumor size (greater than 3 cm) increases risk of mortality, but their study only reached statistical significance in patients with squamous cell carcinoma (HR: 1.47; P value: 0.01) [30]. More studies should be pursued in order to elucidate the importance of tumor size on survival in these patients.

In this study we found that the lack of undergoing treatment with surgery for both squamous cell carcinoma and adenocarcinoma portended poorer outcomes. These findings have been validated by multiple studies. Using the SEER database from 1991 - 2002, Abrams et al showed that when compared to chemoradiation, esophagectomy resulted in higher rates of 3-year survival for both squamous cell carcinoma and adenocarcinoma [31]. Combining both chemoradiation and esophagectomy may be a more effective modality moving forward. Sjoquist et al conducted a meta-analysis containing data from 24 studies with a total of 4,188 patients. Through Cox proportional hazard ratios, they found that neoadjuvant chemoradiotherapy was superior to surgery alone in decreasing risk of mortality [32]. Despite the strong evidence, the implementation of such a treatment regimen may be impeded by cost-effectiveness. Salcedo et al conducted a study evaluating this issue. They found that chemoradiotherapy alone resulted in

less cost for more quality-adjusted life years when compared to chemoradiotherapy combined with surgery [33].

Present day screening for esophageal cancer is a point of contention for multiple reasons. Firstly, the cost-effectiveness of implementing a universal screening program has been deemed too burdensome and may also expose patients to harm without necessarily improving outcomes [34]. Notwithstanding, screening for BE to prevent EAC is a common practice in the USA for which there are established guidelines. In 2016 the American College of Gastroenterology (ACG) recommended screening male patients with chronic GERD symptoms (> 5 years), and two or more risk factors for BE or EAC [35]. Multiple studies have supported the cost-effectiveness of endoscopic screening in this population [36, 37]. Despite its cost-effectiveness and impact on reducing mortality, screening for BE is an imperfect science. This is mainly because 25% of BE cases are asymptomatic, thus exposing a sub-group of these patients to missed screening [38]. Another challenge of implementing a universal screening program exists with screening for ESCC. Currently guidelines for ESCC vary by region. In endemic areas, namely China, evidence suggests that screening for esophageal squamous dysplasia (a precursor to ESCC) is beneficial and cost effective in preventing the development of ESCC [39]. In non-endemic areas such as the USA, screening has only been shown to be beneficial in high-risk populations. These include patients with a history of head and neck cancers and those with tylosis, a hereditary dermatologic condition in which 95% of afflicted patients develop ESCC [40, 41].

Our study was hindered by multiple limitations. The first limitation is the retrospective nature of our study, which carries with its inherent weaknesses in design when compared to prospective studies. Another limitation exists within the SEER database itself. Specifically, it lacks information regarding exposure to risk factors (i.e. smoking, alcohol use, presence of BE) that would confound our findings. Strengths of using the SEER database in our study include adequate sample size and the low likelihood of patient selection bias that is associated



with single center studies.

In conclusion esophageal cancer present day continues to be a prevalent pathology and cause of mortality across all genders and demographic populations. Although rates of squamous cell carcinoma have steadily decreased, adenocarcinoma rates have risen and threaten to be major cause of concern moving into the future. Robust measures should be implemented to reduce exposure to risk factors. Further, initiatives targeting early screening in selected high-risk populations should be strongly considered.

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None to declare.

## Financial Disclosure

None to declare.

## Conflict of Interest

None of the authors have any financial conflict of interest.

## Informed Consent

Not applicable as this is a retrospective study that de-identifies patient information.

## Author Contributions

Eric Then, Michell Lopez, Saad Saleem and Vijay Gayam involved in conception and design; Eric Then, Michell Lopez, and Saad Saleem involved in interpretation of the data; Eric Then, Michell Lopez, and Vijay Gayam involved in drafting of the article; Vinaya Gaduputi, Tagore Sunkara and Andrea Culliford involved in revision of the article for important intellectual content; Vinaya Gaduputi, Tagore Sunkara and Andrea Culliford involved in final approval of the article.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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