Epidemiology and Outcomes of Young-Onset Esophageal Adenocarcinoma: An Analysis from a Population-Based Database

Don C. Codipilly, Tarek Sawas, Lovekirat Dhaliwal, Michele L. Johnson, Ramona Lansing, Kenneth K. Wang, Cadman L. Leggett, David A. Katzka, and Prasad G. Iyer

ABSTRACT

Background: Esophageal adenocarcinoma is a lethal cancer with rising incidence. There are limited data in younger (<50 years) patients with esophageal adenocarcinoma. We aimed to assess time trends in the incidence and outcomes of "young-onset" esophageal adenocarcinoma using a population-based database.

Methods: We queried the Surveillance, Epidemiology, and End Results 9 database to identify patients with esophageal adenocarcinoma between 1975 and 2015. Patients were stratified into three age strata: <50, 50 to 69, and ≥70 years. Staging was stratified as localized, regional, and distant. Trends in incidence, disease stage, and survival were assessed in three periods (1975–89, 1990–99, and 2000–2015). Univariate and multivariate models were created to identify predictors of mortality.

Results: Esophageal adenocarcinoma incidence has increased in patients <50 years of age, with an annual percentage change of 2.9% (95% confidence interval, 1.4%–4.4%) from 1975 to 2015. Young-onset esophageal adenocarcinoma presented at more advanced stages (regional + distant) compared with older patients (84.9% vs. 67.3%; $P < 0.01$), with increasing proportion of advanced stages over the study period. These patients also experienced poorer 5-year esophageal adenocarcinoma–free survival compared with older patients (22.9%% vs. 29.6%; $P < 0.01$), although this finding was attenuated on stage-stratified analysis.

Conclusions: Young-onset esophageal adenocarcinoma, while uncommon, is rising in incidence. Concerningly, the proportion of advanced disease continues to increase. Young-onset esophageal adenocarcinoma also presents at more advanced stages, resulting in poorer esophageal adenocarcinoma–free survival.

Impact: Patients with esophageal adenocarcinoma younger than 50 years present at more advanced stages with higher esophageal adenocarcinoma–specific mortality compared with older peers. Current diagnostic and management strategies for young-onset esophageal adenocarcinoma may need to be reevaluated.

Introduction

The incidence of esophageal adenocarcinoma has been rising rapidly over the last 4 decades, and approximately 17,650 esophageal cancer cases were expected to be diagnosed in the United States in 2019 (1, 2). Barrett esophagus, a form of intestinal metaplasia in which the normal esophageal squamous epithelium is replaced by columnar epithelium, is the only known precursor lesion for the development of esophageal adenocarcinoma (3). The risk of malignant transformation for dysplastic Barrett esophagus is dramatically increased compared with the general population, and can be as high as 7% per year for patients who have Barrett esophagus with high-grade dysplasia (4).

Gastroenterological societies have advocated for endoscopic screening for Barrett esophagus in those with chronic gastroesophageal reflux and other risk factors (5, 6). Age greater than 50 years is one of the risk factors for Barrett esophagus and is based on studies showing an increase in the incidence of Barrett esophagus diagnosed on endoscopy done in the 5th and 6th decade (7). The median age of esophageal adenocarcinoma diagnosis is the 6th decade. Hence, esophageal adenocarcinoma is relatively uncommon before the age of 50 years, and data on the incidence, stage distribution, and outcomes of this segment of patients with esophageal adenocarcinoma are relatively limited.

A recent report of patients at a single tertiary care center demonstrated that younger patients (less than age 50) presented with advanced cancers (stages III and IV) at higher rates than patients ages 50 to 69 years (77.1% compared with 61.4%; $P < 0.001$; ref. 8). Furthermore, survival outcomes were also poorer in this younger cohort of patients. Other studies have also reported that a small proportion of esophageal adenocarcinoma cases are diagnosed in patients younger than 50 years (9–11). However, most were from tertiary care centers, making them subject to referral bias, and therefore, their conclusions may not be generalizable to the entire population.

In this study, we aimed to further understand the epidemiology, including trends in incidence (using annual percent change, APC), stage at presentation, and survival outcomes (cancer free and overall), of young-onset esophageal adenocarcinoma (patients <50 years old at diagnosis) over the last 4 decades, in comparison with older patients, using a population-based national cancer database.

Materials and Methods

The Surveillance, Epidemiology, and End Results (SEER) database is a comprehensive, national database, which is maintained by the NIH, and contains deidentified data for the incidence and outcomes for a

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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number of cancers, including esophageal adenocarcinoma. We utilized the SEER 9 release, which incorporates data from 18 geographic regions in the United States with a catchment area of approximately 35% of the U.S. population (12). Data were obtained through SEER*-Stat version 8.3.6 software (13). Data were included on patients diagnosed over 40 years (1975–2015), except for survival outcomes, where data were included from 1975 to 2011 to allow at least 5 years of follow-up after diagnosis. In addition, a subset analysis of 1-year survival outcomes was done for patients diagnosed from 2011 to 2015.

Data abstraction and patient classification

SEER 9 cases were limited to histologically confirmed cases of esophageal adenocarcinoma utilizing International Classification of Diseases for Oncology (ICD-O-3)/World Health Organization 2008 site recodes for the esophagus, with confirmation of the diagnosis with ICD-O-3 codes 8140–8389 (adenomas and adenocarcinomas), with exclusion of nonmalignant cases. Cases with an unknown stage at diagnosis, unknown age at diagnosis, diagnosis based only on autopsy report at death, and without histologic confirmation of esophageal adenocarcinoma were excluded. Demographic variables, including age at diagnosis, gender, race (as white, black, or other), and year of diagnosis, were retrieved. Stage was recoded on the basis of SEER historic stages (as localized, regional, and distant). Localized disease was disease confined to the boundaries of the esophagus, regional disease included either direct extension of tumor to adjacent structures or regional lymph nodes, and distant disease included all metastatic disease (14). A sensitivity analysis utilizing the American Joint Commission on Cancer (AJCC) staging system (version 6 for 2004–2009 and version 7 for 2010–2015) was also used to stratify outcomes for localized T1 disease (T1N0M0), disease with positive regional nodes (TXNXM0), and metastatic disease (TXNXM1). From the time period of 2010 to 2015, AJCC version 7 data were available and used to compare outcomes stratified by T1a status. Survival time and cause of death were recorded, with appropriate censoring at last follow-up. The SEER 9 database does not record cancer recurrence, but does provide data on whether death was due to esophageal adenocarcinoma. As such, the outcome of esophageal adenocarcinoma–free survival was defined as either not dying by the end of follow-up or dying from a cause other than esophageal adenocarcinoma. First-line surgical or endoscopic treatment modalities are available after 1998 and were collected utilizing SEER site-specific therapy codes (localized therapies, 10–29; surgery, including partial and total esophagectomy, 30–98; and no surgery, 0). Age at diagnosis was stratified into the following categories to effectively compare across age groups: 1, age less than 50; 2, age 50 to 69; 3, age greater than or equal to 70.

Statistical analysis

Age-standardized incidence, standardized to 2000 U.S. census data, was calculated utilizing SEER*Stat software. APC in incidence, presented as an average of the percent change over the time period of interest, was calculated utilizing the weighted least squares method, with the Tiwari modification for confidence intervals (CI; refs. 15, 16). Significance testing for the APC was tested against the null hypothesis of no change (APC = 0). ANOVA was used to assess for changes in continuous values (means), followed by multiple stepwise comparisons to identify significant differences. For categorical variables, we utilized χ^2 analysis. Univariate and multivariate Cox proportional hazard models were created to identify predictors of survival. As the variables incorporated into our study were predetermined, we used a two-sided alpha level of 0.05 as our threshold for statistical significance. This alpha level has been used in other epidemiologic studies of esophageal adenocarcinoma utilizing the SEER database (1, 17). JMP (SAS Software) was used for the analysis.

This study was exempt from review by the Mayo Clinic (Rochester, MN) Institutional Review Board given the use of deidentified data in this analysis.

Results

Incidence-based outcomes

We identified 34,443 cases of esophageal adenocarcinoma diagnosed from 1975 to 2015 that were included in the incidence analysis, and basic demographics are displayed in **Table 1**. Young-onset esophageal adenocarcinoma has a strong male predominance: 90% of all esophageal adenocarcinoma cases in those <50 years were men in 1975 and this proportion remained high at 86.4% in 2015.

When comparing changes in standardized incidence from 1975 to 2015, there has been an increase in all three age groups (**Fig. 1A**). The largest increase has occurred in patients over the age of 70 (APC = 5.4; 95% CI, 3.9–6.9; $P < 0.01$). The annual incidence of esophageal adenocarcinoma in those <50 years of age has also increased by more than three-fold from 0.08/100,000 in 1975 to 0.27/100,000 in 2015

Table 1. Basic demographics of esophageal adenocarcinoma cases, 1975–2015 ($N = 34,443$).

		<50	50–69	≥70	Total
Gender	Male	2,442 (88.3%)	15,750 (89.2%)	11,503 (82.0%)	29,695 (86.2%)
	Female	323 (11.7%)	1,900 (10.8%)	2,525 (18.0%)	4,748 (13.8%)
Race	White	2,578 (93.2%)	16,699 (94.6%)	13,468 (96.0%)	32,745 (95.1%)
	Black	84 (3.0%)	532 (3.0%)	247 (1.8%)	863 (2.5%)
	Other/unknown	103 (3.7%)	419 (2.4%)	313 (2.2%)	835 (2.3%)
Stage	Localized	460 (16.6%)	4,047 (22.9%)	4,590 (3.3%)	9,098 (26.4%)
	Regional/distant	2,305 (83.4%)	13,603 (77.1%)	9,438 (67.2%)	25,345 (73.6%)
Year of diagnosis	1975–1989	168 (10.4%)	895 (55.4%)	551 (34.2%)	1,614 (4.7%)
	1990–1999	371 (9.1%)	1,986 (48.8%)	1,715 (42.1%)	4,072 (11.8%)
	2000–2015	2,226 (7.7%)	14,769 (51.4%)	11,762 (40.9%)	28,757 (83.5%)
Receipt of chemotherapy[a]		1,331 (74.0%)	8,634 (67.4%)	5,056 (47.0%)	15,021 (59.2%)
Receipt of radiotherapy[a]		963 (53.5%)	6,948 (54.2%)	4,974 (46.3%)	12,885 (50.8%)
Receipt of surgical or endoscopic therapy[a]		607 (33.7%)	4,742 (37.0%)	2,448 (22.8%)	7,797 (30.7%)
Total		2,765 (8.0%)	17,650 (51.2%)	14,028 (40.8%)	34,442

[a]Data presented only for patients diagnosed from 2004 to 2015.

(**Fig. 1B**; Supplementary Table S1). Similarly, an increase in the incidence of regional and distant disease affecting those younger than 50 years during the same time period accounted for most of the overall increase in esophageal adenocarcinoma within that age group (APC = 3.6; 95% CI, 2.0–5.2; $P < 0.01$; **Fig. 1C**; Supplementary Fig. S1A).

The proportion of esophageal adenocarcinoma diagnosed in patients <50 years (as a fraction of all incident esophageal adenocarcinoma) remains small overall (<10%). It also appears to have decreased over time (from 10.7% in 1975–1989 to 7.7% in 2000–2015; $P < 0.0001$; Supplementary Fig. S2), likely due to the rather steep

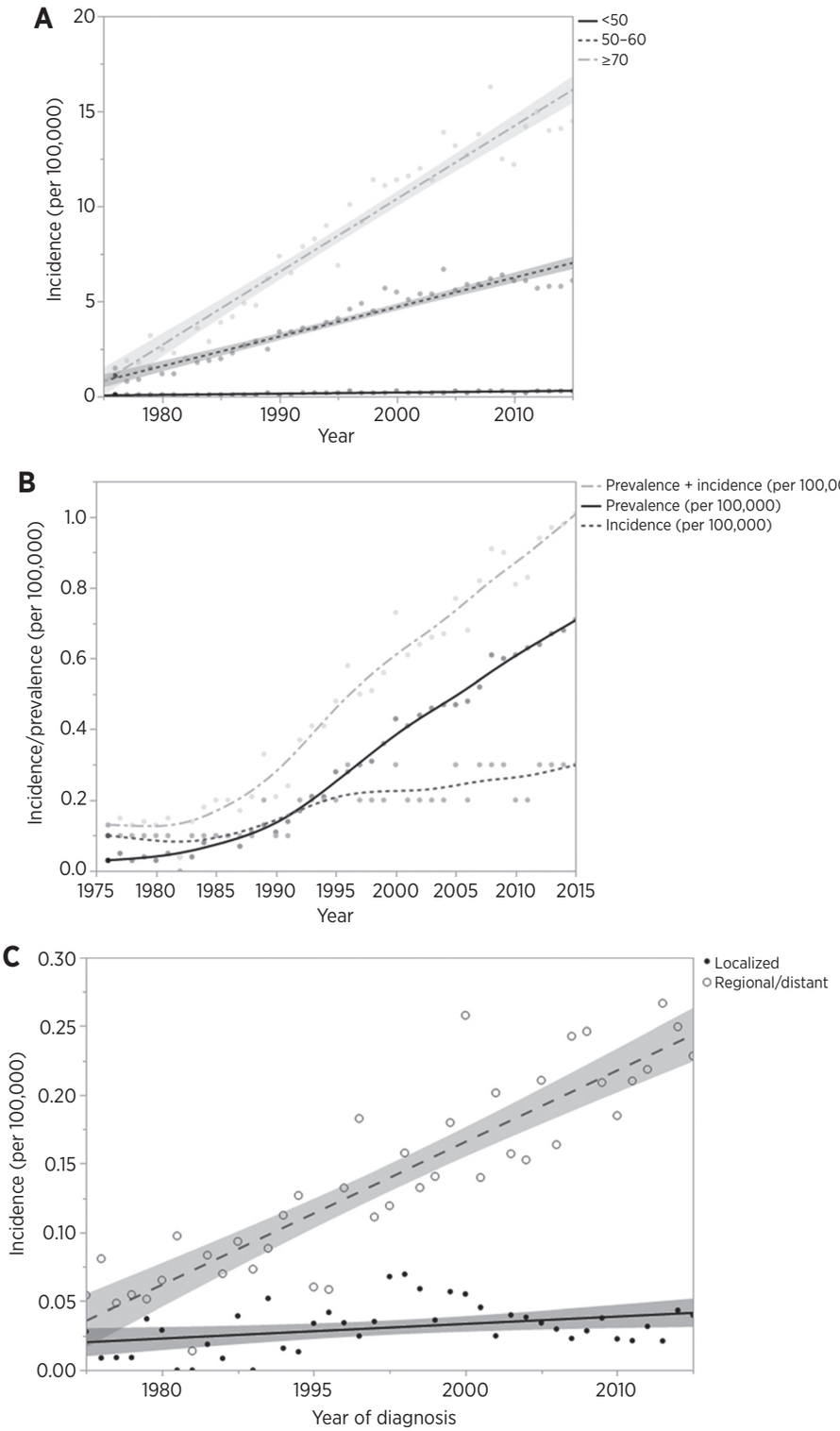

Figure 1.

A, Incidence of esophageal adenocarcinoma by age groups, from 1975 to 2015 (per 100,000). **B,** Prevalence and incidence of young-onset esophageal adenocarcinoma, from 1975 to 2015 (per 100,000). **C,** Incidence by stage at diagnosis in patients with young-onset esophageal adenocarcinoma (age <50), from 1975 to 2015.

rise in the incidence of esophageal adenocarcinoma in those ≥70 years old. There was a corresponding rise in the proportion of esophageal adenocarcinoma diagnosed in patients older than 70 years (from 33.9% in 1975–1989 to 40.9% in 2000–2015; $P < 0.01$). The proportion of disease burden in patients ages 50 to 69 years has remained relatively stable (55.4% in 1975–1989 and 55.6% in 2000–2015; $P > 0.05$).

Notably, young-onset esophageal adenocarcinoma presented at more advanced stages when compared with both groups of older patients (**Table 2A**). In the time period from 2000 to 2015, regional/distant disease made up 84.9% of young-onset esophageal adenocarcinomas, compared with 77.6% of esophageal adenocarcinomas in patients ages 50 to 69 and 67.8% of esophageal adenocarcinomas in those over age 70 years ($P < 0.01$). Somewhat concerning was the observation that the proportion of patients with young-onset esophageal adenocarcinoma presenting with regional/distant disease has also increased over time (1975–1989: 81.8%; 1990–1999: 75.5%; and 2000–2015: 84.9%; $P < 0.01$; **Table 2A**), at a rate faster than the older age groups. Ordinal logistic regression analysis confirmed this observation (Supplementary Fig. S1A–S1C; F test for difference among regression lines <0.01).

A sensitivity analysis utilizing the AJCC staging system versions 6 (2004–2009) and 7 (2010–2015) was also congruent with the above findings, and demonstrated that in the time period from 2004 to 2015, patients less than 50 years of age were significantly more likely to present with metastatic disease, and less likely to present with localized T1 disease, than their older counterparts (Supplementary Table S2; $P < 0.01$). From 2010 to 2015, AJCC version 7 staging was available to stratify outcomes by T1a status. During this time period, fewer (9.2%) patients younger than 50 years of age were diagnosed with T1a disease, compared with 12.3% of patients ages 50 to 59 years ($P < 0.01$) and 13.3% of patients older than 70 years ($P < 0.01$).

Survival outcomes

We identified 25,813 cases of esophageal adenocarcinoma that were included in the final survival analysis (1975–2011). Across all age groups, 5-year esophageal adenocarcinoma–free survival has improved from 1975 to 2011 (**Table 2B**). However, patients younger than 50 had the lowest rates of 5-year esophageal adenocarcinoma–free survival compared with older cohorts in the time period from 2000 to 2011 (age <50, 22.9%; ages 50–69, 29.6%; and age ≥70, 29.6%; $P < 0.01$; **Table 2B**; **Fig. 2**). This trend toward lower 5-year esophageal adenocarcinoma–free survival was mirrored in earlier time periods as well. As shown in **Table 2B**, when analyzing survival stratified by stage at diagnosis, results appeared similar, with younger patients having poorer 5-year esophageal adenocarcinoma–free survival compared with patients over age 50 (apart from those diagnosed with localized disease, in which 5-year esophageal adenocarcinoma–free survival in those <50 was worse compared with those ages 50–69).

In contrast, overall 5-year survival was significantly better in those <50 years old compared with patients over 70, but was significantly worse compared with patients ages 50 to 69 (for time period 2000–2011, age <50: 19.7%; ages 50 to 69: 21.4%; and age ≥70: 12.3%; $P < 0.01$). This trend of superior overall survival in patients ages 50 to 69 compared with other age cohorts has persisted since 1975 (Supplementary Table S3). As shown in Supplementary Table S3, when analyzing survival by stage of diagnosis, results remained consistent, with superior 5-year overall survival in patients ages 50 to 69 compared with the other age groups over the time periods studied.

Univariate and multivariate predictors of 5-year esophageal adenocarcinoma–specific mortality are shown in **Table 3**. Univariate predictors of higher esophageal adenocarcinoma–related mortality included age less than 50, diagnosis of regional or distant disease, and diagnosis prior to 1990. However, on multivariate analysis adjusted by gender, age, race, stage at diagnosis, and year of diagnosis, esophageal adenocarcinoma–specific mortality was higher in patients older than 50 years ($P = 0.03$). The determinant of this effect appears to be stage at diagnosis, as construction of a model excluding stage (but incorporating the other aforementioned characteristics) demonstrated poorer mortality outcomes in the younger cohorts compared with those older than 50 years (Supplementary Table S4). Multivariate analysis also demonstrated poorer outcomes for females, patients with regional/distant disease, and patients diagnosed prior to 1990. There

Table 2A. Incidence of localized and advanced-stage esophageal adenocarcinoma by age and year of diagnosis (%).

	<50 years			50–69 years			≥70 years		
	1975–1989	1990–1999	2000–2015	1975–1989	1990–1999	2000–2015	1975–1989	1990–1999	2000–2015
N	168	371	2,226	895	1,986	14,769	551	1,715	11,762
% localized	18.2	24.5	15.1	21.3	27.5	22.4	39.9	36.8	32.2
% regional/distant	81.8	75.5	84.9	78.7	72.5	77.6	67.1	63.3	67.8

Note: Denominator is total esophageal adenocarcinoma cases in age group.

Table 2B. Esophageal adenocarcinoma survival outcomes by age and year of diagnosis.

	<50 years			50–69 years			≥70 years		
	1975–1989	1990–1999	2000–2011	1975–1989	1990–1999	2000–2011	1975–1989	1990–1999	2000–2011
	5-year EAC-free survival (%)								
N	168	371	1,644	895	1,986	10,206	551	1,715	8,276
Total	10.3	20.5	22.9	13.8	21.8	29.6	13.0	21.6	29.6
Localized	35.3	53.5	63.2	37.1	47.9	66.2	22.1	38.8	50.9
Regional/distant	4.3	9.7	14.7	7.0	11.1	17.6	8.2	9.6	17.2

Note: A cutoff of 2011 was used to allow for a potential of 5 years of follow-up. Denominator is total cases within each age group.
Abbreviation: EAC, esophageal adenocarcinoma.

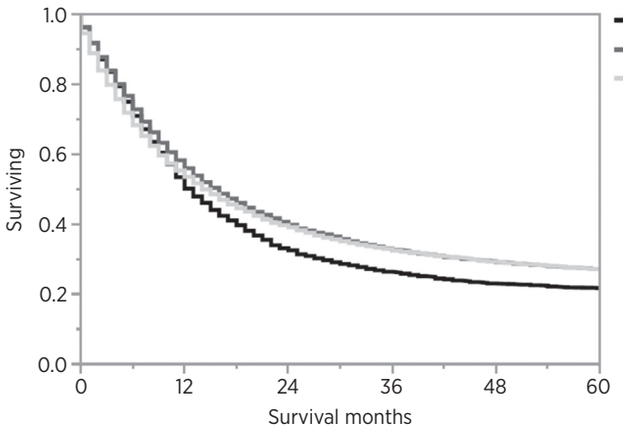

Figure 2.
Kaplan–Meier survival curve for 5-year esophageal adenocarcinoma–free survival (<50 vs. older cohorts: log-rank < 0.0001).

was a trend toward poorer survival in African Americans compared with whites, although this did not meet our *a priori* level of significance. Esophageal adenocarcinoma–related mortality has continued to improve for each time period compared with the preceding time period.

Univariate and multivariate predictors of 5-year overall mortality are shown in Supplementary Table S5. Females appear to have poorer survival compared with males on both univariate and multivariate analyses. Other predictors of poor 5-year overall mortality included age >50, African-American race, regional/advanced disease, and diagnosis prior to 1990.

Supplementary Table S6 shows 1-year survival data for patients diagnosed from 2011 to 2015. One-year esophageal adenocarcinoma–free survival was significantly lower in patients younger than 50 years (51.9%) compared with patients ages 50 to 69 years (57.9%; $P < 0.01$) and ≥70 years (54.2%; $P < 0.01$). Overall 1-year survival was similar between patients aged <50 (48.7%) and those ages 50 to 69 (50.6%; $P > 0.05$), but significantly higher compared with patients ≥70 years (37.9%; $P < 0.01$).

Surgical and endoscopic treatment modalities

Data for endoscopic therapy are available from 1998. During the time period from 1998 to 2015, of patients with localized disease, only 7.4% of those <50 years were treated with endoscopic therapies compared with 11.2% ($P = 0.05$) of those ages 50 to 60 and 14% of patients ≥70 years of age ($P < 0.01$; Supplementary Table S7). In a sensitivity analysis of T1a lesions, for which data were available from 2010 to 2015, receipt of endoscopic eradication therapy (EET) as first-line treatment modality appeared to be highest in the oldest age group (age <50, 27.4%; ages 50–69, 37.5%; and age ≥70, 43.3%; $P < 0.01$). Rates of surgical resection for localized disease were similar among patients <50 years of age (44.8%) compared with those ages 50 to 69 (45.2%; $P = 0.25$), but were significantly higher compared with patients ≥70 years of age (20.5%; $P < 0.01$; Supplementary Table S7). This trend persisted in a sensitivity analysis of patients with T1a lesions diagnosed from 2010 to 2015, with patients older than 70 significantly less likely to undergo surgery (13.3%) compared with the younger cohorts (age <50, 35.5% and ages 50–69, 32.9%; $P < 0.0001$).

Table 3. Predictors of esophageal adenocarcinoma–specific mortality (HR > 1 = increased mortality).

	HR (95% CI range)			
	Univariate	***P***	**Multivariate[a]**	***P***
Gender				
Male	Reference		Reference	
Female	1.05 (1.01–1.10)	0.02	1.08 (1.04–1.13)	<0.01
Age				
<50	Reference		Reference	
≥50	0.88 (0.83–0.93)	<0.01	1.06 (1.00–1.11)	0.03
Race				
White	Reference		Reference	
Black	1.17 (1.06–1.30)	<0.01	1.09 (0.99–1.21)	0.08
Other	1.12 (1.01–1.24)	0.03	1.05 (0.95–1.17)	0.31
Stage				
Localized	Reference		Reference	
Regional	1.99 (1.90–2.08)	<0.01	2.00 (1.91–2.10)	<0.01
Distant	4.89 (4.68–5.10)	<0.01	5.02 (4.81–5.25)	<0.01
Year of diagnosis				
1975–1989	Reference		Reference	
1990–1999[b]	0.75 (0.70–0.80)	<0.01	0.83 (0.78–0.89)	<0.01
2000–2011[b]	0.61 (0.58–0.65)	<0.01	0.60 (0.56–0.63)	<0.01

Note: Model adjusted for variables in table.
[a]Multivariate model incorporates all variables in the table.
[b]Statistically significant comparison to each other.

Data are available from 1975 to 2015 in regards to receipt of chemotherapy or radiotherapy as primary treatment modality. However, well over half of patients have "unknown" status for these outcomes and presentation of the remaining numbers may not present informative trends. However, acknowledging the importance of treatment options in patients with esophageal adenocarcinoma, we did a multivariate analysis of patients diagnosed from 2004 to 2015, in whom treatment information was reliably available, and found poorer esophageal adenocarcinoma–free survival in those without treatment (Supplementary Table S8).

Discussion

In this large population-based study on the epidemiology and outcomes of "young-onset" esophageal adenocarcinoma over the last 4 decades, we make the following observations. While this subset continues to constitute a small proportion of all esophageal adenocarcinomas (<10%), its incidence has increased by more than 200% over the last few decades. Young-onset esophageal adenocarcinoma also presents at more advanced stages, along with a worrying trend of increasing proportion of advanced-stage presentation over time, compared with older age groups. Finally, while young-onset esophageal adenocarcinoma was associated with lower esophageal adenocarcinoma–free survival, this appeared to be a reflection of the advanced stage at presentation.

Several findings in our study mirror trends in young-onset colorectal cancer. Patients younger than 50 years also make up approximately 5% to 10% of all colorectal cancers. Over the last 30 years, the incidence of young-onset colorectal cancer has increased by 2% per year (2, 18–20). These patients are also more likely to present with more advanced-stage disease (21–23). Cancer-specific mortality appears to be increased in young-onset colorectal cancer in a number of studies, even in stage-stratified analyses (24–31).

Some investigators have reported similar findings. Sawas and colleagues, in a single-center study from a quaternary referral center susceptible to referral bias, reported a higher proportion of advanced stages (stage III and IV disease) and poorer esophageal adenocarcinoma–free survival in younger (<50 years) compared with older patients. (8) In another recent study utilizing the National Cancer Database, the authors found that patients with esophageal adenocarcinoma ages 18 to 57 years had the highest proportion of metastatic disease at presentation (34%; ref. 32). Esophageal adenocarcinoma–free survival was unfortunately not reported in this cohort (33). This is an inpatient database, not population-based database, and hence, may have been biased by sicker hospitalized patients. Our study demonstrates that the increased burden of advanced disease in young patients is not due to referral bias, but a true population-based phenomenon with adverse survival outcomes.

There is no clear explanation for the higher proportion of advanced disease in younger patients, and further study is required to identify biologic, genetic, and environmental factors that may underlie this observation. A potential hypothesis is that "young-onset esophageal adenocarcinoma" may involve rapid transition from intestinal metaplasia to esophageal adenocarcinoma, driven by an increase in signaling molecules that are active in the intestine, such as Wnt/β-catenin, Notch, and TGFβ (34), or this may be esophageal adenocarcinoma that is potentially driven by a process independent of intestinal metaplasia. Poorer survival in patients without Barrett esophagus or intestinal metaplasia on esophageal adenocarcinoma specimens has been reported recently (35). Unfortunately, the SEER 9 database does not contain histology data regarding the presence of intestinal metaplasia. While a genetic sequencing analysis of esophageal adenocarcinoma in patients younger than 40 years compared with patients older than 68 years found no difference in mutational load, the two most commonly mutated genes were *TP53* and *P16* in both age cohorts (36). As such, the similar survival noted on multivariate and stage-stratified analysis suggests the esophageal adenocarcinoma affecting younger populations is no different from that seen in older age groups, and may reflect the inability to identify early-stage disease in this population. The delay in diagnosis of esophageal adenocarcinoma may be due to several factors, including lack of clinical suspicion (for malignancy) in young patients presenting with dysphagia, lack of screening and surveillance recommendations for Barrett esophagus in those younger than 50 years, as well as the fact that younger individuals, in general, are less likely to seek care compared with older individuals (37).

Some insight into the pathogenesis of this subset of esophageal adenocarcinoma may be garnered by evaluating traditional risk factors for Barrett esophagus. Central obesity has been strongly linked to the pathogenesis of Barrett esophagus, as visceral fat produces proinflammatory cytokines which can contribute to carcinogenesis (38–40). It is well known that obesity rates have dramatically increased in the United States over the last several decades (41–43). Furthermore, rates of current obesity appear to be higher in those ages 40 to 59 years compared with those more than 60 years of age (43). Mirroring these trends in obesity, the prevalence of another Barrett esophagus risk factor, gastroesophageal reflux disease, has also increased over the last decade, and may be partly explained by increased intraabdominal pressure as a result of obesity (44, 45). As such, rising rates of obesity and gastroesophageal reflux disease, affecting all age groups, but particularly those ages 40 to 59 years (46), may contribute to the burden of disease found in this age cohort (47).

On stage-stratified analysis, esophageal adenocarcinoma–free survival for localized disease in patients younger than 50 years was superior to those more than 70 years of age, but were poorer compared with patients ages 50 to 69 years. This may be due to differing therapeutic options, as younger patients were more likely to undergo esophagectomy (curative for T1 disease and also likely for T1b and T2 disease, which is also part of "localized disease"), whereas patients ages 50 to 69 years were more likely to undergo EET (which may not be curative for T1b or T2 disease). Furthermore, as mentioned previously, prior work has demonstrated the existence of a phenotype of esophageal adenocarcinoma without associated Barrett esophagus, which resulted in poorer esophageal adenocarcinoma–free survival outcomes (35). It is possible that younger patients may be more likely to carry this phenotype of esophageal adenocarcinoma, but unfortunately such information is not available in the SEER 9 database.

Our study has several strengths. We utilized the SEER 9 database, which is drawn from a significant sample of the U.S. population, therefore, avoiding the introduction of referral bias. This database regularly undergoes quality checks to ensure accuracy of included patient-level data, and has been the basis for a number of high-impact articles in many medical journals (48). In addition, we were also able to assess informative time trends. Hence, the use of the SEER 9 database strengthens the validity of our findings, and accurately assesses patient characteristics that would be encountered in clinical practice throughout the United States. Other strengths include the strict definition of esophageal adenocarcinoma, requiring histologic confirmation, the length of follow-up

(dating back to 1975), and exclusion of patients of unknown age and stage at diagnosis. Furthermore, we have constructed a multivariate model that takes into account several factors that could affect esophageal adenocarcinoma–free survival.

Limitations of this study include the lack of ability to thoroughly review individual case health records to confirm the stage of disease (as well as other demographic variables) at diagnosis. Although a trend toward poorer survival was found in African Americans in our multivariate analysis, the disproportionate ratio of white cases to other races makes it difficult to truly compare outcomes across races. Comorbidity information, which could be valuable in identifying a high-risk population, is unfortunately not available in the SEER 9 database. Notably, there is a SEER-Medicare linked database that includes comorbidity data, but unfortunately does not have information on patients younger than 65 years of age, which excludes the target cohort of this study. Information on chemotherapy and radiotherapy is clinically relevant, but given that therapy data were unknown for a large subset of the database, we did not include it in the primary analysis. However, in a subset analysis of patients in which these data are available, a lack of receipt of therapy was associated with poorer esophageal adenocarcinoma–free survival.

In conclusion, while young-onset esophageal adenocarcinoma remains uncommon, it presents disproportionately with advanced disease (with a worrisome trend of increase over the last 4 decades) and is associated with poorer 5-year esophageal adenocarcinoma–free survival compared with older cohorts. Concerningly, the proportion of advanced disease in this age group is steadily increasing. While it is unclear at this time what biologic, genetic, or environmental factors may influence these findings, until such factors are elucidated, reevaluation of our diagnostic and treatment strategies in this age group might need to be considered.

Authors' Disclosures

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Disclaimer

The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Authors' Contributions

D.C. Codipilly: Writing–original draft. **T. Sawas:** Data curation. **L. Dhaliwal:** Data curation. **M.L. Johnson:** Data curation. **R. Lansing:** Data curation. **K.K. Wang:** Data curation. **C.L. Leggett:** Data curation. **D.A. Katzka:** Data curation. **P.G. Iyer:** Writing–review and editing.

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