



Epidemiology of Adenosquamous Carcinomas

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Abstract

Background: Adenosquamous carcinomas (ASCs) are a very rare histology containing cancer cells with both glandular-like (adeno) and squamous cell histologies, comprising typically a fraction of a percent of all solid tumors. The bulk of the literature on ASCs is comprised of case reports and small series, with the general finding that ASCs tend to have worse outcomes than either of their parent histologies. However, there is a lack of pan site-comparative studies in the literature that compare ASC clinicodemographic and survival outcomes with those of conventional adenocarcinomas (ACs) and squamous cell carcinomas (SCCs).

Methods: In this study, we summarize these outcomes in eight primary sites, comprising 92.7% of all ASC cases diagnosed from 1975 to 2020 in the Surveillance, Epidemiology, and End Results (SEER) database.

Results: Lung ASCs comprise 51.5% of all ASC cases, accounting for 1.1% of all lung cancer cases, followed by uterine/cervical cancers at 29.7% of all ASC cases, translating into 1.8% of all cancers in this site. In descending order, the remaining 20% of ASCs arise in pancreatic, oral cavity, biliary, esophageal, colorectal, and gastric sites, comprising between 0.1% and 0.7% of all cancers in these sites. Apart from pancreatic and oral cavity cancers, ASC tumors tended to favor higher rates of regional or distant disease at presentation with poor tumor differentiation compared to either AC or SCC histologies. After multivariable

analysis, adjusting for age, sex, detection stage, grade differentiation, surgery, chemotherapy, and radiotherapy, except for oral cavity cancers, ASCs tended to have worse overall survivals compared to ACs (hazard ratios: 1.1 - 1.6) and SCC (1.0 - 1.3), with colorectal ASCs having the worse overall survival compared to colorectal ACs, with a hazard ratio of 1.4 (95% confidence interval: 1.3 - 1.6).

Conclusions: Overall, these results suggest that ASC outcomes are site specific, and in general, tend to have worse outcomes than non-variant ACs and SCCs even after correction for common clinical and epidemiological factors. These cancers have a poorly understood but unique tumor biology that warrants further characterization.

Keywords: Cancer; Chemotherapy; Demographics; Histopathology; Outcomes; Radiotherapy; Surgery

Introduction

Adenosquamous carcinomas (ASCs) are a rare histological class of cancer that contain both squamous cells and glandular-like (adeno) cells [1, 2]. In certain cancers, this histology has been associated with more aggressive disease than either parent histology [3]. These cancers are recognized by the International Classification of Diseases for Oncology (ICD)-0-3 classification as a unique entry (8560/3) under the broader umbrella of Complex Epithelial Neoplasms [4]. The World Health Organization varies the formal definition of ASCs slightly based on tumor site, where for lungs, each of the squamous and adenocarcinoma components must constitute at least 10% of the tumor, and for gastrointestinal malignancies, the squamous component constitutes at least 25% of the tumor [1, 2].

Given that these cancers comprise less than 1% of all total carcinomas, most of the literature on ASCs is limited to case reports or small series [5, 6]. There are no studies that systematically and robustly compare ASCs to nonvariant histologies, which limits the ability of researchers and clinicians to make meaningful comparisons to conventional adenocarcinomas (ACs) and squamous cell carcinomas (SCCs) [7]. The systematic examination and characterization of the epidemiological and clinical behavior of this histology requires the resources only available through a population-level database [8].

The Surveillance, Epidemiology, and End Results (SEER) database is an amalgamation of population-based cancer registries maintained by the National Cancer Institute, encompassing 47.9% of the United States population with its most recent release [9]. As one of the oldest population-level cancer

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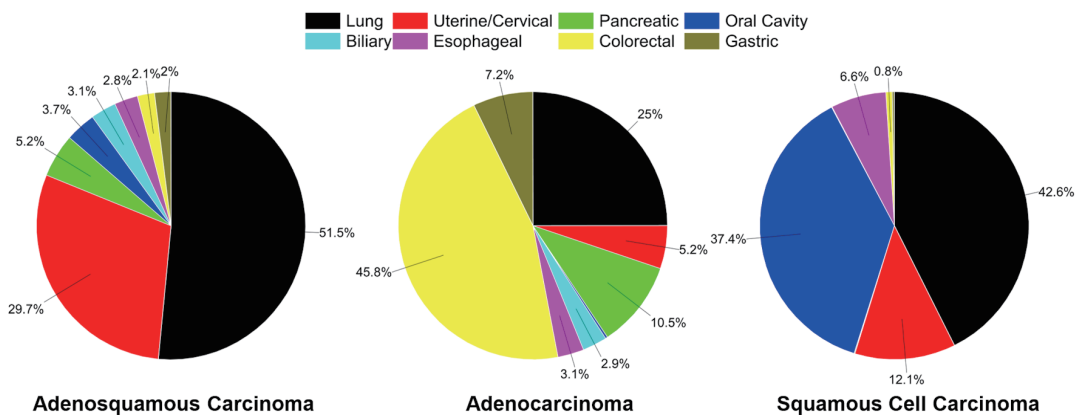


Figure 1. Distribution of cancers in SEER, 1975 - 2020 for sites analyzed. Distribution of adenosquamous carcinoma cases in all major sites examined (total of 26,525 cases (92.7% of all adenosquamous carcinoma cases in SEER)) (left). Distribution of all conventional adenocarcinoma cases in sites examined (total of 1,535,527 cases) (middle). Distribution of all conventional squamous cell carcinoma cases in sites examined (total of 588,802 cases) (right).

registries, it is a well-respected resource for investigating correlations between histopathological data with patient outcomes across all cancer sites with nearly 50 years of data capture [10]. In this site-stratified analysis, we use the SEER database to overcome the limitations imposed by cancer rarity to investigate the clinicopathological characteristics and survival outcomes of ASCs compared to nonvariant ACs and SCCs across all major locations. This investigation provides a thorough epidemiological description and characterization of this poorly understood rare cancer histology.

Materials and Methods

Patient selection

The National Cancer Institute's SEER database composed from 18 SEER cancer registries was employed using data from 1975 to 2020, as previously described [11-17]. Data release from the SEER database does not require informed patient consent or review by an institutional review board. The SEER database was accessed and searched in compliance with signed user agreements [17]. A complete outline of exclusion criteria and its effects on case counts is presented here (Supplementary Material 1, www.wjon.org). Definitions of variables analyzed are presented here (Supplementary Material 2, www.wjon.org). We limited our analysis to sites with at least 400 cases of undifferentiated carcinomas, which captures 92.7% of all cases (Supplementary Material 3, www.wjon.org). We compared demographic and outcomes data for ASCs to site-matched ACs and SCCs. All cases listed in SEER have at least a tissue biopsy reviewed by a pathologist to confirm the histological diagnosis [17].

Statistical analysis

All selected data from 18 SEER cancer registries were imported into Stata 15.1 (StataCorp LLC, College Station, TX, USA)

for statistical analysis following case listing downloading using SEER*Stat 8.4.2 (Surveillance Research Program, National Cancer Institute, Calverton, MD, USA). A complete case analysis was completed after variable definition, as previously described (Supplementary Material 1, 2, www.wjon.org) [11-17].

Baseline patient characteristics were compared with the *t* and Chi-squared tests for continuous and categorical variables, respectively. Univariate and multivariable Cox proportional hazard regression was used to determine the association of mortality with cancer histology type, adjusting for age, sex, race, detection stage, grade differentiation, surgery, chemotherapy, and radiotherapy. All hazard ratios (HRs) were calculated with 95% confidence intervals. Use of surgery, chemotherapy, and radiotherapy as treatment variables were binary. All P values were two-sided, with a threshold of 0.05 to determine statistical significance. Survival curves were plotted using the Kaplan-Meier method, with P values for survival curves generated by the log rank test. Graphs were plotted using Origin Pro 2022 (OriginLab Corporation, Northampton, MA, USA). Using SEER 18 (2000 - 2020) data with SEER*Stat 8.4.2, incidence rates were calculated and age-adjusted to the 2000 United States standard population with the age variable recode < 1-year-olds. Cause-specific survival and relative survival were calculated with the same dataset and software and were both age standardized to the International Cancer Survival Standard 1-Age 15+ variable via the actuarial method, and Ederer II cumulative expected method for relative survival.

Results

Analysis of ASCs by anatomical site

Subsections are presented in order of anatomical site by the percentage of ASC cases in that site relative to all cases of ASC presented (92.7% of all cases of ASC in the SEER database) (Fig. 1). Within each subsection, we first present a demographics table with all included cancer cases for that site, followed by nonvariant AC and SCC cases, and then the ASC cases.

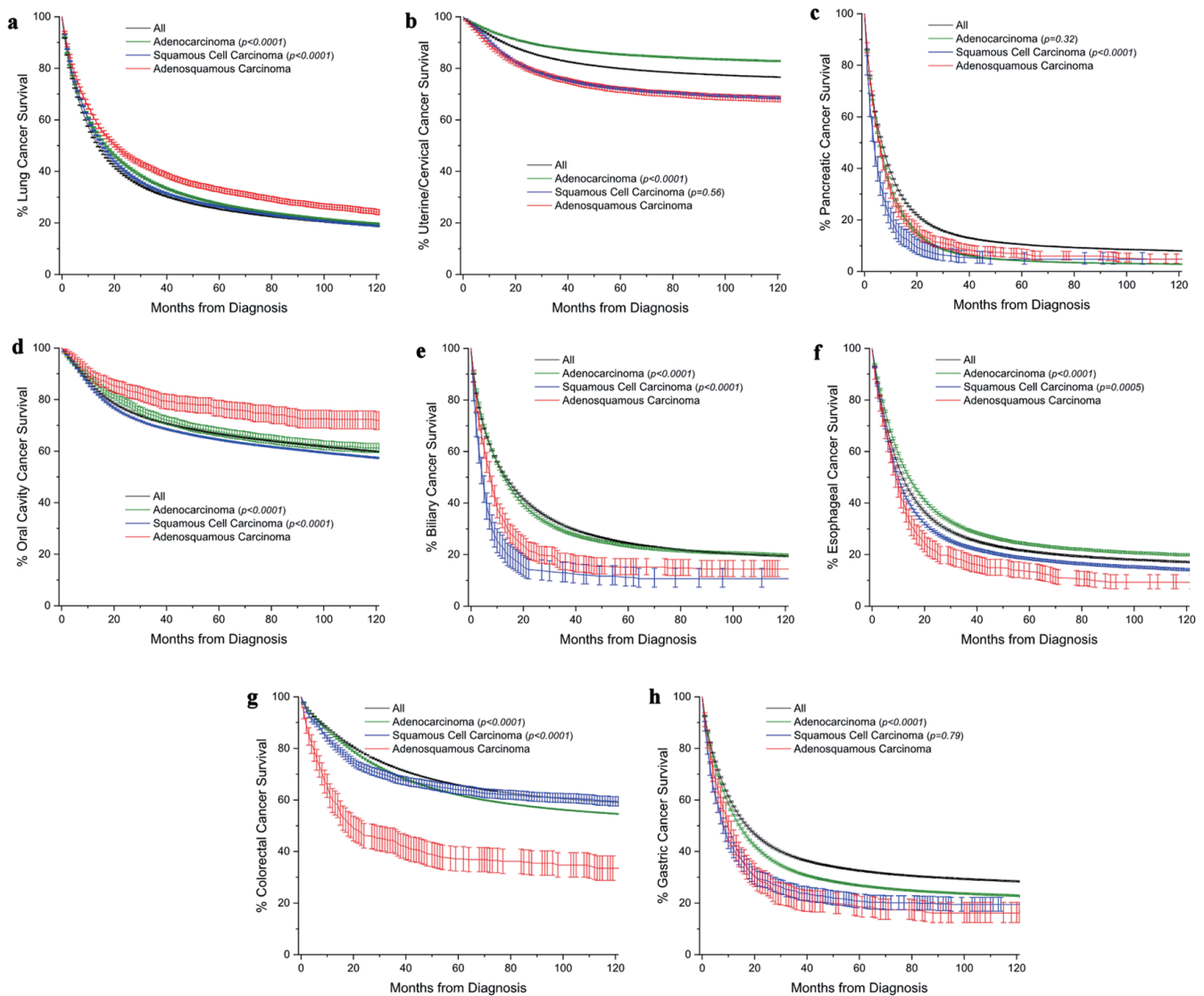


Figure 2. Kaplan-Meier survival curves comparing overall survival of adenosquamous carcinomas patients to those with either conventional adenocarcinomas or squamous cell carcinomas. The black line represents a comparative survival curve for all malignancies within that site. (a) Lung cancer. (b) Uterine/cervical cancer. (c) Pancreatic cancer. (d) Oral cavity cancer. (e) Biliary cancer. (f) Esophageal cancer. (g) Colorectal cancer. (h) Gastric cancer. All survival curves are shown with 95% confidence interval. Among subtypes, pairwise statistical comparisons by the log-rank test are shown relative to adenosquamous carcinomas.

The second table presents both univariate and multivariable HRs for cause-specific mortality according to the same demographic, histopathological, and treatment variables as the first table, comparing ASCs to the other cancer categories.

To provide a visual overview across all cancer sites, Kaplan-Meier survival curves with 95% confidence intervals are also presented (Fig. 2).

Lung cancer

ASC comprised a minority of lung cancer cases at 1.1% but represented just over half (51.5%) of all ASC tumors (Table 1, Fig. 1). Age of diagnosis was overall similar among all cancer

subtypes in the 68 - 70 years old range (Table 1). Compared to males, female cases were slightly lower for ASC (44.3%) and SCC (35.9%), but the same for AC (50%). ASC tended to be diagnosed at an earlier stage (26.1%), in contrast to AC (19.9%) but very similar to SCC (24.5%). Notably, ASC tumors were more frequently poorly differentiated (44.9%) compared to AC (26.1%) and SCC (32.8%). About half of the ASC patients underwent surgical resection, contrasted with about a quarter for both AC and SCC. Furthermore, patients with AC and SCC underwent chemotherapy (41.0% and 35.4%, respectively) and radiotherapy more frequently (39.4% and 46.7%, respectively) than patients with ASC (34.3% for chemotherapy and 53.9% for radiotherapy). Survival was significantly better at all points for ASC patients. Median survival was 16.6 months compared

to 13.7 months for AC and 13.5 months for SCC (Table 1). In comparison to AC and SCC lung cancers, ASC had an unadjusted HR of 0.87 (95% confidence interval 0.85 - 0.89) to AC and 0.84 (0.82 - 0.86) to SCC, but after multivariable analysis correcting for age, sex, race, detection stage, grade, and use of surgery, chemotherapy, and radiotherapy, the HRs were 1.14 (1.11 - 1.16), and 1.08 (1.05 - 1.10), respectively (Table 2).

Uterine/cervical cancer

ASC represented 1.8% of uterine/cervical cancer cases and 29.7% of all ASC cases (Table 3, Fig. 1). The mean age at presentation for ASC was 55.7 years old, which was 4.7 years older compared to SCC but 5.1 years younger than AC (Table 3). ASC tended to be detected at a localized stage more frequently than SCC (52.1% vs. 46.5%, respectively), but less often when compared to AC (74.6%). Further, ASC presented with distant disease more frequently (14.9%) than AC and SCC (7.7% and 11.3%, respectively). Notably, ASC tumors were more frequently poorly differentiated (44.0%) compared to AC (17.3%) and SCC (28.6%). Seventy-eight percent of ASC patients underwent surgical resection, contrasting with 85.6% for AC and 54.2% for SCC. Patients with ASC and SCC underwent chemotherapy (26.0% and 37.0%, respectively) and radiotherapy more frequently (56.0% and 57.1%, respectively) compared to individuals diagnosed with AC, where the rates were lower (9.1% for chemotherapy and 32.2% for radiotherapy). ASC survival rates closely matched SCC rates, which at 10 years was significantly worse compared to AC patients (about 66% vs. about 78%, respectively) (Table 3). In comparison to AC and SCC uterine/cervical cancers, ASC had a HR of 1.06 (1.01 - 1.11) and 1.18 (1.13 - 1.23), respectively, after multivariate analyses (Table 4).

Pancreatic cancer

ASC histology constituted 0.5% of all pancreatic cancers and 5.2% of all ASCs (Table 5, Fig. 1). Age of presentation was similar among ASC, AC, or SCC (about 68 years old), as well as sex distribution (about 52% males) (Table 5). ASC tumors were less likely to present as distant disease (49.6%) than either AC or SCC (57.9% vs. 62.1%, respectively). However, these tumors presented with higher rates of poor grade differentiation than either AC or SCC (33.7%, vs. 15.0% and 30.8%, respectively). ASC patients had significantly higher surgery rates at 36.2% compared to AC at 13.3% and SCC at 8.3%. Median survival for ASC and AC patients was similar at just under 6 months, compared to about 4 months for SCC patients (Table 5). In comparison to AC, ASC had an equivalent unadjusted HR of 0.97 (0.91 - 1.03) to AC and 0.77 (0.68 - 0.86) to SCC, but after multivariable analysis, the HRs were 1.25 (1.18 - 1.34), and 1.16 (1.02 - 1.31), respectively (Table 6).

Oral cavity cancer

As a collective group, ASCs comprised 0.4% of all oral cavity

cancers and 3.7% of all ASCs (Table 7, Fig. 1). These cancers had about the same average age of onset at about 63 - 64 years across all three histologies (Table 7). ASC tumors were similar to AC tumors with a male prevalence in the mid-50% range, whereas for SCC tumors, 72.6% of cases were in male patients. ASC tumors were most often detected as localized disease 53.2% of the time, compared to 38.8% and 30.6% of AC and SCC tumors, respectively. AC tumors had higher rates of poor differentiation at 34.7% than either SCC or ASC tumors (23.9% vs. 25.3%, respectively), though ASC tumors had a very high rate of unknown grade differentiation at 43.9%. ASC tumors were treated with surgery 84.0% of the time, similar to AC at 78.0%, vs. 55.4% of time for the SCC, while SCC tumors were more likely treated with chemotherapy (35.5% vs. about 14% for AC and ASC), with similar rates of radiotherapy in the 50-60% range for all histologies. Ten-year survival rates were about 15% higher for ASC tumors than either AC or SCC tumors (Table 7). This translated into overall better HR for mortality for ASC vs. AC, though not statistically significant after multivariable adjustment at 0.88 (0.76 - 1.02), and for ASC vs. SCC 0.75 (0.66 - 0.86) (Table 8).

Biliary tract cancer

As a collective group, ASCs comprised 0.3% of all biliary tract cancers and 3.1% of all ASCs (Table 9, Fig. 1). These cancers had about the same average age of onset at about 68 - 69 years old across all three histologies (Table 9). ASC tumors were more similar to SCC tumors with a female rate at about 65%, whereas for AC tumors, 56.2% of cases were in female patients. ASC tumors were most often detected as regional disease 44.7% of the time, compared to 39.4% and 34.2% of AC and SCC tumors, respectively, with higher rates of poor differentiation at 43.8% compared to 36.9% and 39.8%. ASC tumors were treated with surgery 76.9% of the time, which was much higher than AC at 51.3% or SCC at 42.4%. Chemotherapy and radiotherapy use rates were statistically identical across all histologies. Median survival for ASC patients was about 8 months, compared to about 11 months for AC patients and 4 months for SCC patients (Table 9). This translated into overall worse mortality HR for ASC compared to AC at 1.56 (1.43 - 1.71), but equivalent to SCC 0.93 (0.80 - 1.09) (Table 10).

Esophageal cancer

ASC histology constituted 0.7% of all esophageal cancers and 2.8% of all ASCs (Table 11, Fig. 1). The age of presentation was similar among ASC, AC, and SCC (about 66 - 67 years old). Sex distribution towards males was similar for ASC and AC at 82.3% and 86.1% respectively, but lower for SCC at 65.1% (Table 11). ASC tumors were most likely to present as distant disease (41.4%), compared to 38.0% for AC and 28.3% for SCC. Additionally, ASC tumors presented with higher rates of poor grade differentiation than either AC or SCC (60.0%, vs. 37.3% and 33.8%, respectively). ASC

Table 1. Demographics and Clinical Characteristics for Lung Cancer by Histology

Lung	All	Adenocarcinoma	Squamous	Adenosquamous	P value
N (%)	1,124,192 (100)	357,273 (31.8)	226,774 (20.2)	12,498 (1.1)	
Age (years) (%)					
0 - 14	180 (< 1)	5 (< 1)	2 (< 1)	0 (0.0)	< 0.001
15 - 29	1,393 (0.1)	248 (0.1)	86 (< 1)	10 (0.1)	
30 - 49	48,725 (4.3)	18,354 (5.1)	5,840 (2.6)	540 (4.3)	
50 - 69	496,997 (44.2)	166,617 (46.6)	96,877 (42.7)	5,489 (43.9)	
70 - 89	576,897 (51.3)	172,049 (48.2)	123,969 (54.7)	6,459 (51.7)	
Mean (SD)	69.0 (10.7)	68.2 (10.8)	69.9 (9.6)	68.9 (10.4)	< 0.001
Median	70	69	71	70	
Sex (%)					
Male	603,851 (53.7)	178,466 (50.0)	145,474 (64.1)	6,960 (55.7)	< 0.001
Female	520,341 (46.3)	178,807 (50.0)	81,300 (35.9)	5,538 (44.3)	
Race (%)					
White	938,501 (83.5)	288,603 (80.8)	190,397 (84.0)	10,391 (83.1)	< 0.001
Black	111,668 (9.9)	37,065 (10.4)	24,883 (11.0)	1,216 (9.7)	
Other	74,023 (6.6)	31,605 (8.8)	11,494 (5.1)	891 (7.1)	
Detection stage (%)					
Localized	222,677 (19.8)	71,010 (19.9)	55,571 (24.5)	3,265 (26.1)	< 0.001
Regional	260,684 (23.2)	73,042 (20.4)	75,034 (22.1)	4,127 (22.0)	
Distant	573,501 (51.0)	202,024 (56.5)	86,151 (38.0)	4,844 (38.8)	
Unstaged	67,330 (6.0)	11,191 (3.1)	10,018 (4.4)	262 (2.1)	
Grade differentiation (%)					
Well	49,946 (4.4)	20,356 (5.7)	5,284 (2.3)	124 (1.0)	< 0.001
Moderate	151,654 (13.5)	63,230 (17.7)	57,028 (25.1)	2,445 (19.6)	
Poor	310,089 (27.6)	93,380 (26.1)	74,361 (32.8)	5,614 (44.9)	
Unknown	612,503 (54.5)	180,307 (50.5)	90,101 (39.7)	4,315 (34.5)	
Surgery (%)					
Yes	260,926 (23.2)	92,593 (25.9)	62,602 (27.6)	6,247 (50.0)	< 0.001
No	863,266 (76.8)	264,680 (74.1)	164,172 (72.4)	6,251 (50.0)	
Chemotherapy (%)					
Yes	433,894 (38.6)	146,491 (41.0)	80,278 (35.4)	4,284 (34.3)	< 0.001
No	690,298 (61.4)	210,782 (59.0)	146,496 (64.6)	8,214 (65.7)	
Radiotherapy (%)					
Yes	430,333 (38.3)	140,587 (39.4)	106,011 (46.7)	4,491 (35.9)	< 0.001
No	693,859 (61.7)	216,686 (60.6)	120,763 (53.3)	8,007 (64.1)	
Incidence rate (95% CI)					
All	565 (564 - 566)	179 (178 - 180)	109.5 (109.0 - 110.0)	5.9 (5.8 - 6.0)	-
Male	675 (673 - 677)	198 (197 - 199)	155.6 (154.8 - 156.5)	7.4 (7.2 - 7.6)	
Female	482 (481 - 484)	165 (164 - 166)	73.2 (72.7 - 73.8)	4.8 (4.7 - 5.0)	
CSS (95% CI)					
1-year	47.8 (47.6 - 47.9)	52.9 (52.7 - 53.1)	52.8 (52.5 - 53.1)	57.6 (56.4 - 58.7)	-
2-year	33.6 (33.5 - 33.8)	38.7 (38.5 - 38.9)	37.3 (37.1 - 37.6)	42.7 (41.5 - 43.8)	

Table 1. Demographics and Clinical Characteristics for Lung Cancer by Histology - (continued)

Lung	All	Adenocarcinoma	Squamous	Adenosquamous	P value
5-year	21.7 (21.6 - 21.9)	24.0 (23.8 - 24.2)	24.2 (24.0 - 24.5)	30.0 (28.9 - 31.2)	
10-year	16.1 (16.0 - 16.3)	17.1 (16.9 - 17.3)	17.4 (17.2 - 17.7)	22.4 (21.2 - 23.5)	
Median (months)	10.9	13.7	13.5	16.6	
RS (95% CI)					-
1-year	44.2 (44.1 - 44.3)	50.0 (49.8 - 50.2)	48.7 (48.5 - 49.0)	54.4 (53.3 - 55.5)	
2-year	29.7 (29.6 - 29.8)	35.3 (35.1 - 35.5)	32.4 (32.2 - 32.7)	38.6 (37.5 - 39.7)	
5-year	16.8 (16.7 - 16.9)	19.5 (19.4 - 19.7)	17.5 (17.3 - 17.8)	23.2 (22.2 - 24.2)	
10-year	9.5 (9.4 - 9.5)	11.0 (10.8 - 11.1)	8.4 (8.2 - 8.6)	13.0 (12.1 - 13.9)	
Median (months)	9.4	12.0	11.4	14.3	

P < 0.05 for all comparisons between adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma comparisons. Incidence rates were expressed per 100,000. CSS: cause-specific survival; RS: relative survival; CI: confidence interval; SD: standard deviation.

patients had similar surgery rates at 33.1% compared to AC at 32.9%. SCC tumors had higher rates of radiotherapy use at 63.2%, compared to about 55% for the other two histologies. Median survival for ASC and SCC patients was similar at 8 - 10 months, compared to about 14 months for AC patients (Table 11). After multivariable analysis, ASC patients had worse mortality HR at 1.30 (1.19 - 1.42) compared to AC patients, and similarly to SCC patients at 1.21 (1.10 - 1.32) (Table 12).

Colorectal cancer

ASC histology constituted 0.1% of all colorectal cancers and 2.1% of all ASCs (Table 13, Fig. 1). ASC patients had a mean age of presentation of 64.6 years, while AC patients were older at 67.5 years, and SCC patients were younger at 62.9 years (Table 13). There was a female bias at 52.1% for ASC, increased to 66.7% for SCC, but decreased to 47.4% for AC tumors. ASC tumors were most likely to present as distant dis-

Table 2. Univariate and Multivariable Cox-Proportional Hazard Ratios (HRs) of Mortality for Lung Cancer

Lung	Adenosquamous vs. adenocarcinoma		Adenosquamous vs. squamous	
	Univariate, HR (95% CI)	Multivariable, HR (95% CI)	Univariate, HR (95% CI)	Multivariable, HR (95% CI)
Adenosquamous histology	0.87 (0.85 - 0.89)	1.14 (1.11 - 1.16)	0.84 (0.82 - 0.86)	1.08 (1.05 - 1.10)
Age (per 10 years)	1.051 (1.047 - 1.055)	1.067 (1.062 - 1.071)	1.08 (1.07 - 1.09)	1.05 (1.04 - 1.06)
Sex				
Female	0.78 (0.77 - 0.79)	0.81 (0.80 - 0.82)	0.87 (0.86 - 0.88)	0.88 (0.87 - 0.89)
Race				
Black	1.08 (1.07 - 1.10)	0.97 (0.96 - 0.99)	1.16 (1.14 - 1.18)	1.00 (0.99 - 1.02) ^a
Other	0.93 (0.91 - 0.94)	0.77 (0.76 - 0.78)	1.10 (1.08 - 1.13)	0.95 (0.93 - 0.97)
Detection stage				
Regional	2.16 (2.13 - 2.19)	2.28 (2.25 - 2.32)	2.00 (1.97 - 2.03)	2.03 (2.00 - 2.06)
Distant	6.05 (5.97 - 6.13)	4.79 (4.72 - 4.86)	4.76 (4.69 - 4.83)	3.65 (3.59 - 3.71)
Unstaged	3.56 (3.47 - 3.52)	2.31 (2.25 - 2.37)	2.96 (2.86 - 3.04)	1.84 (1.79 - 1.89)
Grade differentiation				
Moderate	1.42 (1.39 - 1.45)	1.36 (1.32 - 1.39)	0.87 (0.84 - 0.90)	0.96 (0.93 - 1.00) ^a
Poor	2.46 (2.41 - 2.51)	1.73 (1.69 - 1.77)	1.05 (1.01 - 1.09)	1.04 (1.00 - 1.07)
Unknown	3.26 (3.19 - 3.33)	1.41 (1.38 - 1.44)	1.48 (1.43 - 1.53)	0.93 (0.90 - 0.97)
Surgery (yes)	0.244 (0.241 - 0.247)	0.395 (0.389 - 0.400)	0.267 (0.263 - 0.270)	0.319 (0.314 - 0.324)
Chemotherapy (yes)	1.33 (1.32 - 1.34)	0.635 (0.629 - 0.641)	1.16 (1.15 - 1.18)	0.66 (0.65 - 0.67)
Radiotherapy (yes)	1.45 (1.44 - 1.46)	1.03 (1.02 - 1.04)	1.42 (1.41 - 1.44)	0.89 (0.88 - 0.90)

P < 0.05 relative to reference unless noted by ^aP ≥ 0.05. Reference categories: sex (Male), race (White), detection stage (Localized), grade differentiation (Well), surgery (no), radiotherapy (no), and chemotherapy (no). CI: confidence interval.

Table 3. Demographics and Clinical Characteristics for Uterine/Cervical Cancer by Histology

Uterus/cervix	All	Adenocarcinoma	Squamous	Adenosquamous	P value
N (%)	400,543 (100.0)	74,765 (18.7)	64,391 (16.1)	7,206 (1.8)	
Age (years) (%)					
0 - 14	43 (< 1)	1 (< 1)	0 (0.0)	0 (0.0)	< 0.001
15 - 29	7,539 (1.9)	886 (1.2)	4,034 (6.3)	217 (3.0)	
30 - 49	83,563 (20.9)	14,070 (18.8)	29,498 (45.8)	2,345 (32.5)	
50 - 69	209,049 (52.2)	39,016 (52.2)	22,344 (34.7)	3,174 (44.0)	
70 - 89	100,349 (25.1)	20,792 (27.8)	8,515 (13.2)	1,470 (20.4)	
Mean (SD)	59.6 (13.9)	60.8 (13.5)	50.4 (15.3)	55.7 (15.1)	< 0.001
Median	60	62	49	56	
Race (%)					
White	326,288 (81.5)	65,547 (87.7)	48,509 (75.3)	5,945 (82.5)	< 0.001
Black	37,776 (9.4)	3,891 (5.2)	9,112 (14.2)	568 (7.9)	
Other	36,479 (9.1)	5,327 (7.1)	6,770 (10.5)	693 (9.6)	
Detection stage (%)					
Localized	258,276 (64.5)	55,762 (74.6)	29,930 (46.5)	3,752 (52.1)	< 0.001
Regional	83,626 (20.9)	9,809 (13.1)	24,731 (38.4)	2,156 (29.9)	
Distant	42,433 (10.6)	5,786 (7.7)	7,266 (11.3)	1,077 (14.9)	
Unstaged	16,208 (4.0)	3,408 (4.6)	2,464 (3.8)	221 (3.1)	
Grade differentiation (%)					
Well	115,050 (28.7)	28,758 (38.5)	3,556 (5.5)	568 (7.9)	< 0.001
Moderate	98,038 (24.5)	22,567 (30.2)	17,940 (27.9)	1,886 (26.2)	
Poor	91,240 (22.8)	12,950 (17.3)	18,407 (28.6)	3,203 (44.4)	
Unknown	96,215 (24.0)	10,490 (14.0)	24,488 (38.0)	1,549 (21.5)	
Surgery (%)					
Yes	333,390 (83.2)	63,980 (85.6)	34,884 (54.2)	5,678 (78.8)	< 0.001
No	67,153 (16.8)	10,785 (14.4)	29,507 (45.8)	1,528 (21.2)	
Chemotherapy (%)					
Yes	83,350 (20.8)	6,778 (9.1)	23,795 (37.0)	1,872 (26.0)	< 0.001
No	317,193 (79.2)	67,987 (90.0)	40,596 (63.0)	5,334 (74.0)	
Radiotherapy (%)					
Yes	136,342 (34.0)	24,045 (32.2)	36,777 (57.1)	4,037 (56.0)	< 0.001
No	264,201 (66.0)	50,720 (67.8)	27,614 (42.9)	3,169 (44.0)	
Incidence rate (95% CI)					
All	175 (174 - 176)	17.1 (17.0 - 17.4)	26.6 (26.4 - 26.8)	2.27 (2.20 - 2.35)	-
Female	331 (330 - 332)	32.6 (32.2 - 33.0)	51.7 (51.3 - 52.2)	4.39 (4.26 - 4.53)	
CSS (95% CI)					
1-year	91.3 (91.2 - 91.4)	90.4 (90.1 - 90.8)	88.3 (88.0 - 88.6)	87.0 (85.9 - 88.1)	-
2-year	85.9 (85.7 - 86.0)	85.7 (85.3 - 86.2)	79.5 (79.1 - 79.9)	78.8 (77.4 - 80.1)	
5-year	79.0 (78.9 - 79.2)	80.4 (79.9 - 80.9)	70.7 (70.2 - 71.1)	69.5 (67.9 - 71.1)	
10-year	75.6 (75.4 - 75.8)	77.7 (77.2 - 78.2)	67.0 (66.5 - 67.5)	65.9 (64.2 - 67.6)	
Median (months)	-	-	-	-	
RS (95% CI)					
					-

Table 3. Demographics and Clinical Characteristics for Uterine/Cervical Cancer by Histology - (continued)

Uterus/cervix	All	Adenocarcinoma	Squamous	Adenosquamous	P value
1-year	89.6 (89.5 - 89.7)	88.4 (88.0 - 88.8)	86.7 (86.4 - 87.0)	85.8 (84.6 - 86.9)	
2-year	83.1 (83.0 - 83.3)	82.6 (82.2 - 83.1)	76.8 (76.4 - 77.3)	76.6 (75.1 - 77.9)	
5-year	73.3 (73.1 - 73.4)	74.2 (73.6 - 74.7)	65.5 (65.0 - 66.0)	64.9 (63.2 - 66.5)	
10-year	63.9 (63.7 - 64.1)	65.6 (65.0 - 66.2)	57.9 (57.3 - 58.4)	56.8 (55.0 - 58.5)	
Median (months)	-	-	-	-	

P < 0.05 for all comparisons between adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma comparisons. Incidence rates were expressed per 100,000. CSS: cause-specific survival; RS: relative survival; CI: confidence interval; SD: standard deviation.

case (42.3%), compared to 22.3% for AC and 17.8% for SCC. Additionally, ASC tumors presented with much higher rates of poor grade differentiation than either AC or SCC (61.5%, vs. 17.1% and 32.0%, respectively). Therapeutic modality use for ASC patients was similar to AC patients, apart from increased chemotherapy for ASC patients (46.5% vs. 36.5%). Median survival for ASC patients was about 17 - 20 months, while median survival was not reached in either the AC or SCC groups (Table 13). After multivariable analysis, ASC patients had worse mortality HR at 1.44 (1.28 - 1.63) compared to AC patients, and similarly to SCC patients at 1.26 (1.08 - 1.47) (Table 14).

Gastric cancer

ASC histology constituted 0.3% of all gastric cancers and 2.0% of all ASCs (Table 15, Fig. 1). ASC patients had an ear-

lier mean age of presentation of 65.6 years old, compared to 68.5 years old for AC patients and 67.3 years old for SCC patients (Table 15). There was a strong male bias at 72.2% for ASC, compared to 66.5% for AC and 70.9% for SCC tumors. ASC tumors were most likely to present as distant disease at 43.0%, compared to 37.6% for AC and 41.4% for SCC. Similarly, ASC tumors presented with much higher rates of poor grade differentiation than either AC or SCC (63.9%, vs. 47.8% and 41.5%, respectively). Therapeutic modality use for ASC patients was similar to AC patients (surgery 54.9% vs. 48.6%, respectively), compared to 26.2% for SCC patients. ASC patients had the highest rates of chemotherapy use at 50.9%, compared to 41.0% for AC and 44.0% for SCC. Radiotherapy use was similar for ASC and SCC patients (33.4% vs. 38.7%). Median survival for ASC patients was about 9 - 10 months, compared to 14 - 17 months for AC patients and 7 - 8 months for SCC patients (Table 15). After multivariable

Table 4. Univariate and Multivariable Cox-Proportional Hazard Ratios (HRs) of Mortality for Uterine/Cervical Cancer

Uterus/cervix	Adenosquamous vs. adenocarcinoma		Adenosquamous vs. squamous	
	Univariate, HR (95% CI)	Multivariable, HR (95% CI)	Univariate, HR (95% CI)	Multivariable, HR (95% CI)
Adenosquamous histology	1.99 (1.90 - 2.08)	1.06 (1.01 - 1.11)	1.02 (0.97 - 1.06) ^a	1.18 (1.13 - 1.23)
Age (per 10 years)	1.36 (1.34 - 1.38)	1.34 (1.32 - 1.35)	1.29 (1.28 - 1.30)	1.12 (1.11 - 1.14)
Race				
Black	2.56 (2.43 - 2.70)	1.49 (1.41 - 1.57)	1.36 (1.31 - 1.41)	1.20 (1.15 - 1.24)
Other	1.04 (0.98 - 1.10) ^a	1.00 (0.94 - 1.06) ^a	0.89 (0.85 - 0.93)	0.82 (0.78 - 0.86)
Detection stage				
Regional	5.11 (4.91 - 5.32)	3.02 (2.89 - 3.16)	4.93 (4.75 - 5.12)	3.24 (3.10 - 3.39)
Distant	19.5 (18.7 - 20.2)	8.79 (8.38 - 9.22)	16.8 (16.1 - 17.5)	10.6 (10.1 - 11.1)
Unstaged	4.35 (4.07 - 4.65)	2.07 (1.92 - 2.22)	4.85 (4.53 - 5.20)	2.96 (2.75 - 3.18)
Grade differentiation				
Moderate	2.43 (2.31 - 2.56)	1.77 (1.68 - 1.87)	1.77 (1.64 - 1.92)	1.26 (1.16 - 1.36)
Poor	7.76 (7.39 - 8.15)	3.50 (3.31 - 3.69)	2.57 (2.38 - 2.77)	1.56 (1.45 - 1.69)
Unknown	4.71 (4.45 - 4.97)	2.21 (2.08 - 2.34)	1.51 (1.40 - 1.64)	1.12 (1.04 - 1.21)
Surgery (yes)	0.162 (0.156 - 0.167)	0.35 (0.34 - 0.37)	0.233 (0.227 - 0.240)	0.44 (0.43 - 0.46)
Chemotherapy (yes)	5.15 (4.97 - 5.34)	1.25 (1.20 - 1.31)	2.24 (2.17 - 2.30)	0.84 (0.82 - 0.87)
Radiotherapy (yes)	2.41 (2.33 - 2.48)	1.04 (1.00 - 1.07)	3.13 (3.03 - 3.23)	1.02 (0.98 - 1.06)

P < 0.05 relative to reference unless noted by ^aP ≥ 0.05. Reference categories: race (White), detection stage (Localized), grade differentiation (Well), surgery (no), radiotherapy (no), and chemotherapy (no). CI: confidence interval.

Table 5. Demographics and Clinical Characteristics for Pancreatic Cancer by Histology

Pancreas	All	Adenocarcinoma	Squamous	Adenosquamous	P value
N (%)	250,034 (100.0)	149,409 (59.8)	530 (0.2)	1,273 (0.5)	
Age (years) (%)					
0 - 14	94 (< 1)	1 (< 1)	0 (0.0)	0 (0.0)	0.66
15 - 29	696 (0.3)	94 (0.1)	0 (0.0)	0 (0.0)	
30 - 49	14,416 (5.8)	7,915 (5.3)	33 (6.2)	70 (5.5)	
50 - 69	105,829 (42.3)	68,078 (45.6)	220 (41.5)	564 (44.3)	
70 - 89	128,999 (51.6)	73,321 (49.1)	277 (52.3)	639 (50.2)	
Mean (SD)	68.9 (11.8)	68.4 (11.1)	68.6 (11.5)	68.4 (10.5)	0.91
Median	70	69	70	70	
Sex (%)					
Male	128,060 (51.2)	77,717 (52.0)	282 (53.2)	671 (52.7)	0.76
Female	121,974 (48.8)	71,692 (48.0)	248 (46.8)	602 (47.3)	
Race (%)					
White	203,422 (81.4)	121,475 (81.3)	403 (76.0)	1,027 (80.7)	0.032
Black	26,897 (10.8)	16,531 (11.1)	74 (14.0)	140 (11.0)	
Other	19,715 (7.9)	11,403 (7.6)	53 (10.0)	106 (8.3)	
Detection stage (%)					
Localized	26,418 (10.6)	11,737 (7.9)	30 (5.7)	112 (8.8)	< 0.001
Regional	68,912 (27.6)	43,426 (29.1)	133 (25.1)	488 (38.3)	
Distant	129,160 (51.7)	86,543 (57.9)	329 (62.1)	632 (49.6)	
Unstaged	25,544 (10.2)	7,703 (5.2)	38 (7.2)	41 (3.2)	
Grade differentiation (%)					
Well	14,289 (5.7)	5,895 (3.9)	14 (2.6)	6 (0.5)	< 0.001
Moderate	31,406 (12.6)	19,930 (13.3)	42 (7.9)	148 (11.6)	
Poor	34,609 (13.8)	22,413 (15.0)	163 (30.8)	429 (33.7)	
Unknown	169,730 (67.9)	101,171 (67.7)	311 (58.7)	690 (54.2)	
Surgery (%)					
Yes	44,939 (18.0)	19,802 (13.3)	45 (8.5)	461 (36.2)	< 0.001
No	205,095 (82.0)	129,607 (86.7)	485 (91.5)	812 (63.8)	
Chemotherapy (%)					
Yes	105,126 (42.0)	75,021 (50.2)	219 (41.3)	703 (55.2)	< 0.001
No	144,908 (58.0)	74,388 (49.2)	311 (58.7)	570 (44.8)	
Radiotherapy (%)					
Yes	34,417 (13.8)	24,021 (16.1)	86 (16.2)	207 (16.3)	0.98
No	215,617 (86.2)	125,388 (83.9)	444 (83.8)	1,066 (83.7)	
Incidence rate (95% CI)					
All	123.6 (123.1 - 124.1)	71.2 (70.9 - 71.7)	0.23 (0.21 - 0.25)	0.63 (0.59 - 0.66)	-
Male	140.3 (139.4 - 141.1)	82.1 (81.5 - 82.8)	0.28 (0.24 - 0.32)	0.73 (0.67 - 0.79)	
Female	109.7 (109.1 - 110.4)	62.3 (61.8 - 62.8)	0.19 (0.16 - 0.22)	0.54 (0.50 - 0.59)	
CSS (95% CI)					
1-year	32.0 (31.8 - 32.2)	28.0 (27.7 - 28.3)	17.7 (13.5 - 22.4)	27.7 (24.7 - 30.8)	-
2-year	17.6 (17.4 - 17.8)	11.5 (11.3 - 11.7)	7.2 (4.5 - 10.7)	13.4 (11.1 - 16.0)	

Table 5. Demographics and Clinical Characteristics for Pancreatic Cancer by Histology - (continued)

Pancreas	All	Adenocarcinoma	Squamous	Adenosquamous	P value
5-year	9.6 (9.4 - 9.7)	3.9 (3.8 - 4.0)	3.3 (1.6 - 6.2)	6.7 (4.9 - 8.8)	
10-year	7.3 (7.1 - 7.4)	2.6 (2.5 - 2.7)	3.3 (1.6 - 6.2)	4.7 (3.0 - 7.0)	
Median (months)	5.9	5.7	3.7	5.9	
RS (95% CI)					-
1-year	30.3 (30.0 - 30.5)	26.6 (26.3 - 26.9)	16.4 (12.5 - 20.9)	26.5 (23.6 - 29.5)	
2-year	16.1 (16.0 - 16.3)	10.5 (10.4 - 10.7)	6.4 (4.0 - 9.7)	12.4 (10.2 - 14.8)	
5-year	8.1 (7.9 - 8.2)	3.3 (3.1 - 3.4)	2.7 (1.2 - 5.2)	5.7 (4.1 - 7.6)	
10-year	5.1 (5.0 - 5.3)	1.7 (1.6 - 1.9)	2.7 (1.2 - 5.2)	3.2 (1.9 - 5.1)	
Median (months)	5.4	5.4	3.6	5.7	

P < 0.05 for all comparisons between adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma comparisons. Incidence rates were expressed per 100,000. CSS: cause-specific survival; RS: relative survival; CI: confidence interval; SD: standard deviation.

analysis, ASC patients had worse mortality HR at 1.24 (1.11 - 1.38) compared to AC patients, but equivalent to SCC patients at 1.11 (0.96 - 1.27) (Table 16).

Discussion

This study is the most comprehensive comparative analysis of ASCs to site-matching parent nonvariant ACs and SCC histologies. Because these cancers comprise less than 0.3%

of all malignancies, the literature on this histology is extremely sparse. There is a pressing need to better understand the underlying tumor biology, as several reports have suggested that the incidence of these malignancies is rising [18, 19]. Gathered primarily from limited series, the prevailing understanding of ASC clinical behavior is that patients with these malignancies have more aggressive disease progression compared to site-matched ACs or SCCs [20, 21]. However, outside of a systematic examination of a population-level registry, the epidemiological factors that may be contributing

Table 6. Univariate and Multivariable Cox-Proportional Hazard Ratios (HRs) of Mortality for Pancreatic Cancer

Pancreas	Adenosquamous vs. adenocarcinoma		Adenosquamous vs. squamous	
	Univariate, HR (95% CI)	Multivariable, HR (95% CI)	Univariate, HR (95% CI)	Multivariable, HR (95% CI)
Adenosquamous histology	0.97 (0.91 - 1.03) ^a	1.25 (1.18 - 1.34)	0.77 (0.68 - 0.86)	1.16 (1.02 - 1.31)
Age (per 10 years)	1.116 (1.110 - 1.122)	1.084 (1.079 - 1.091)	1.13 (1.08 - 1.19)	1.11 (1.06 - 1.17)
Sex				
Female	0.98 (0.97 - 0.99)	0.96 (0.95 - 0.97)	0.96 (0.86 - 1.07) ^a	1.01 (0.91 - 1.12)
Race				
Black	1.05 (1.03 - 1.07)	1.05 (1.03 - 1.07)	1.18 (1.00 - 1.39)	1.16 (0.98 - 1.38) ^a
Other	0.97 (0.95 - 0.99)	0.94 (0.92 - 0.96)	0.88 (0.73 - 1.08) ^a	0.95 (0.78 - 1.16) ^a
Detection stage				
Regional	1.06 (1.03 - 1.08)	1.32 (1.29 - 1.36)	1.07 (0.86 - 1.34) ^a	1.43 (1.14 - 1.79)
Distant	2.16 (2.11 - 2.21)	2.16 (2.11 - 2.21)	2.40 (1.94 - 2.98)	2.03 (1.63 - 2.54)
Unstaged	1.54 (1.49 - 1.60)	1.15 (1.11 - 1.19)	1.67 (1.21 - 2.30)	0.91 (0.65 - 1.27) ^a
Grade differentiation				
Moderate	1.06 (1.03 - 1.10)	1.26 (1.22 - 1.30)	0.72 (0.42 - 1.23) ^a	1.01 (0.58 - 1.73) ^a
Poor	1.48 (1.43 - 1.53)	1.57 (1.52 - 1.62)	0.91 (0.55 - 1.53)	1.11 (0.65 - 1.87) ^a
Unknown	1.60 (1.55 - 1.64)	1.25 (1.21 - 1.29)	1.41 (0.85 - 2.35)	1.17 (0.70 - 1.98) ^a
Surgery (yes)	0.36 (0.35 - 0.37)	0.43 (0.42 - 0.44)	0.32 (0.28 - 0.37)	0.36 (0.31 - 0.43)
Chemotherapy (yes)	0.56 (0.55 - 0.57)	0.525 (0.518 - 0.532)	0.55 (0.50 - 0.62)	0.52 (0.46 - 0.58)
Radiotherapy (yes)	0.61 (0.60 - 0.62)	0.93 (0.91 - 0.94)	0.66 (0.57 - 0.76)	0.88 (0.76 - 1.10) ^a

P < 0.05 relative to reference unless noted by ^aP ≥ 0.05. Reference categories: sex (Male), race (White), detection stage (Localized), grade differentiation (Well), surgery (no), radiotherapy (no), and chemotherapy (no). CI: confidence interval.

Table 7. Demographics and Clinical Characteristics for Oral Cavity Cancer by Histology

Oral cavity	All	Adenocarcinoma	Squamous	Adenosquamous	P value
N (%)	249,224 (100.0)	3,863 (1.6)	199,190 (79.9)	888 (0.4)	
Age (years) (%)					
0 - 14	677 (0.3)	9 (0.2)	58 (< 1)	4 (0.5)	< 0.001
15 - 29	3,502 (1.4)	65 (1.7)	1,174 (0.6)	15 (1.7)	
30 - 49	34,002 (3.6)	557 (14.4)	24,397 (12.2)	114 (12.8)	
50 - 69	134,349 (53.9)	1,750 (45.3)	111,842 (56.1)	419 (47.2)	
70 - 89	76,694 (30.8)	1,482 (38.4)	61,719 (31.0)	336 (37.8)	
Mean (SD)	62.4 (13.4)	63.8 (14.5)	63.1 (31.0)	63.7 (14.5)	< 0.001
Median	63	65	63	66	
Sex (%)					
Male	173,732 (69.7)	2,240 (58.0)	144,537 (72.6)	472 (53.2)	< 0.001
Female	75,492 (30.3)	1,623 (42.0)	54,653 (27.4)	416 (46.8)	
Race (%)					
White	209,572 (84.1)	3,195 (82.7)	170,640 (85.7)	731 (82.3)	< 0.001
Black	20,512 (8.2)	390 (10.1)	15,952 (8.0)	84 (9.5)	
Other	19,140 (7.7)	278 (7.2)	12,598 (6.3)	73 (8.2)	
Detection stage (%)					
Localized	81,048 (32.5)	1,499 (38.8)	60,949 (30.6)	472 (53.2)	< 0.001
Regional	118,479 (47.5)	1,290 (33.4)	100,544 (50.5)	275 (31.0)	
Distant	35,025 (14.1)	790 (20.5)	27,525 (13.8)	113 (12.7)	
Unstaged	14,672 (5.9)	284 (7.4)	10,172 (5.1)	28 (3.2)	
Grade differentiation (%)					
Well	32,962 (13.2)	389 (10.1)	27,681 (13.9)	88 (9.9)	< 0.001
Moderate	78,898 (31.7)	942 (24.4)	70,941 (35.6)	185 (20.8)	
Poor	61,523 (24.7)	1,340 (34.7)	47,510 (23.9)	225 (25.3)	
Unknown	75,841 (30.4)	1,192 (30.9)	53,058 (26.6)	390 (43.9)	
Surgery (%)					
Yes	143,820 (57.7)	3,013 (78.0)	110,288 (55.4)	746 (84.0)	< 0.001
No	105,404 (42.3)	850 (22.0)	88,902 (44.6)	142 (16.0)	
Chemotherapy (%)					
Yes	82,274 (33.0)	568 (14.7)	70,643 (35.5)	118 (13.3)	< 0.001
No	166,950 (67.0)	3,295 (85.3)	128,547 (64.5)	770 (86.7)	
Radiotherapy (%)					
Yes	144,488 (58.0)	1,989 (51.5)	118,348 (59.4)	461 (51.9)	< 0.001
No	104,736 (42.0)	1,874 (48.5)	80,842 (40.6)	427 (48.1)	
Incidence rate (95% CI)					
All	111.1 (110.7 - 111.6)	1.63 (1.57 - 1.69)	87.2 (86.7 - 87.6)	0.44 (0.41 - 0.47)	-
Male	167.2 (166.3 - 168.0)	2.10 (2.00 - 2.20)	136.3 (135.5 - 137.1)	0.49 (0.44 - 0.54)	
Female	62.8 (62.3 - 63.3)	1.26 (1.19 - 1.33)	44.4 (44.0 - 44.8)	0.39 (0.35 - 0.43)	
CSS (95% CI)					
1-year	85.9 (85.7 - 86.1)	87.1 (85.6 - 88.4)	85.0 (84.8 - 85.2)	89.5 (86.7 - 91.8)	-
2-year	77.5 (77.3 - 77.7)	78.7 (76.9 - 80.4)	75.8 (75.6 - 76.1)	85.3 (82.0 - 88.0)	

Table 7. Demographics and Clinical Characteristics for Oral Cavity Cancer by Histology - (continued)

Oral cavity	All	Adenocarcinoma	Squamous	Adenosquamous	P value
5-year	68.5 (68.3 - 68.8)	66.8 (64.6 - 68.8)	66.7 (66.4 - 66.9)	78.5 (74.6 - 81.8)	
10-year	62.1 (61.8 - 62.4)	61.0 (58.6 - 63.2)	60.1 (59.8 - 60.5)	74.3 (69.8 - 78.1)	
Median (months)	-	-	-	-	
RS (95% CI)					-
1-year	82.7 (82.5 - 82.9)	85.0 (83.4 - 86.4)	81.6 (81.4 - 81.8)	87.4 (84.4 - 89.8)	
2-year	72.6 (72.3 - 72.8)	74.6 (72.7 - 76.4)	70.7 (70.4 - 73.3)	81.4 (77.9 - 84.4)	
5-year	58.8 (58.5 - 59.1)	87.8 (56.0 - 60.3)	56.6 (56.3 - 56.9)	70.0 (65.8 - 73.8)	
10-year	45.1 (44.8 - 45.4)	76.0 (43.2 - 47.9)	42.4 (42.0 - 42.7)	59.1 (54.2 - 63.6)	
Median (months)	96.5	93.0	85.6	-	

P < 0.05 for all comparisons between adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma comparisons. Incidence rates were expressed per 100,000. CSS: cause-specific survival; RS: relative survival; CI: confidence interval; SD: standard deviation.

to this perception cannot be well characterized.

From this analysis, we demonstrate site-specific variabilities in the behaviors of ASCs. Among the gastrointestinal tract malignancies, esophageal, gastric, and biliary tumors have slightly earlier ages of onset than either parent histology (about 1 - 3 years), identical for pancreatic cancer, and averaged between the histologies for colorectal cancer (median age AC 69 years old, SCC 63 years old, ASC 66 years old). With respect to stage at detection, ASCs of the lung, pancreas, oral cavity,

and biliary tract tended to present with less distant disease, whereas uterine/cervical, esophageal, colorectal, and gastric cancers presented more often with distant disease than ACs or SCCs. The notable outlier was colorectal cancers, where ASCs presented with distant disease 42.3% of the time, nearly double that of the other histologies (AC 22.3%, SCC 17.8%). Except for oral cavity cancers, the grade differentiation was poor, nearly twice as often for ASCs at all other sites compared to ACs and SCCs. Taken all together, the unadjusted mortality HRs

Table 8. Univariate and Multivariable Cox-Proportional Hazard Ratios (HRs) of Mortality for Oral Cavity Cancer

Oral cavity	Adenosquamous vs. adenocarcinoma		Adenosquamous vs. squamous	
	Univariate, HR (95% CI)	Multivariable, HR (95% CI)	Univariate, HR (95% CI)	Multivariable, HR (95% CI)
Adenosquamous histology	0.70 (0.60 - 0.81)	0.88 (0.76 - 1.02) ^a	0.60 (0.52 - 0.68)	0.75 (0.66 - 0.86)
Age (per 10 years)	1.28 (1.23 - 1.33)	1.24 (1.19 - 1.29)	1.20 (1.19 - 1.21)	1.24 (1.23 - 1.25)
Sex				
Female	0.59 (0.53 - 0.65)	0.79 (0.71 - 0.88)	1.07 (1.05 - 1.08)	1.10 (1.08 - 1.11)
Race				
Black	0.98 (0.83 - 1.16)	1.18 (1.00 - 1.40)	1.99 (1.95 - 2.04)	1.72 (1.68 - 1.76)
Other	0.81 (0.66 - 1.00)	0.79 (0.64 - 0.97)	1.11 (1.08 - 1.15)	1.06 (1.03 - 1.09)
Detection stage				
Regional	4.03 (3.48 - 4.67)	2.70 (2.31 - 3.15)	2.16 (2.11 - 2.20)	2.25 (2.20 - 2.30)
Distant	9.57 (8.22 - 11.1)	5.02 (4.23 - 5.95)	4.45 (4.34 - 4.55)	4.50 (4.39 - 4.62)
Unstaged	3.40 (2.70 - 4.29)	1.99 (1.56 - 2.54)	2.51 (2.42 - 2.59)	1.93 (1.86 - 2.00)
Grade differentiation				
Moderate	2.55 (1.85 - 3.51)	2.21 (1.60 - 3.05)	1.67 (1.63 - 1.71)	1.34 (1.31 - 1.38)
Poor	8.89 (6.56 - 12.1)	4.71 (3.45 - 6.45)	1.64 (1.59 - 1.68)	1.16 (1.13 - 1.19)
Unknown	4.15 (3.04 - 5.66)	2.61 (1.91 - 3.58)	1.37 (1.33 - 1.41)	0.94 (0.92 - 0.97)
Surgery (yes)	0.26 (0.24 - 0.29)	0.38 (0.34 - 0.44)	0.484 (0.477 - 0.492)	0.52 (0.51 - 0.53)
Chemotherapy (yes)	3.00 (2.67 - 3.37)	1.04 (0.91 - 1.19) ^a	1.18 (1.16 - 1.20)	0.68 (0.67 - 0.69)
Radiotherapy (yes)	1.85 (1.66 - 2.05)	0.96 (0.86 - 1.08)	1.37 (1.35 - 1.39)	0.85 (0.83 - 0.86)

P < 0.05 relative to reference unless noted by ^aP ≥ 0.05. Reference categories: sex (Male), race (White), detection stage (Localized), grade differentiation (Well), surgery (no), radiotherapy (no), and chemotherapy (no). CI: confidence interval.

Table 9. Demographics and Clinical Characteristics for Biliary Tract Cancer by Histology

Biliary	All	Adenocarcinoma	Squamous	Adenosquamous	P value
N (%)	218,928 (100.0)	41,976 (19.2)	450 (0.2)	749 (0.3)	
Age (years) (%)					
0 - 14	1,392 (0.6)	1 (< 1)	0 (0.0)	0 (0.0)	0.23
15 - 29	1,064 (0.5)	90 (0.2)	0 (0.0)	0 (0.0)	
30 - 49	15,632 (7.1)	2,556 (6.1)	35 (7.8)	46 (6.1)	
50 - 69	111,391 (50.9)	16,888 (40.2)	184 (40.9)	333 (44.5)	
70 - 89	89,449 (40.9)	22,441 (53.5)	231 (51.3)	370 (49.4)	
Mean (SD)	65.9 (12.9)	69.3 (11.8)	68.3 (11.8)	68.5 (11.4)	0.041
Median	66	71	70	69	
Sex (%)					
Male	139,293 (63.6)	18,403 (43.8)	164 (36.4)	258 (34.4)	< 0.001
Female	79,635 (36.4)	23,573 (56.2)	286 (63.6)	491 (65.6)	
Race (%)					
White	160,585 (73.4)	33,504 (79.8)	335 (74.4)	600 (80.1)	0.039
Black	22,737 (10.4)	3,531 (8.4)	51 (11.3)	70 (9.3)	
Other	35,606 (16.3)	4,941 (11.8)	64 (14.2)	79 (10.5)	
Detection stage (%)					
Localized	73,131 (33.4)	7,489 (17.8)	44 (9.8)	100 (13.4)	< 0.001
Regional	65,390 (29.9)	16,530 (39.4)	154 (34.2)	335 (44.7)	
Distant	51,708 (23.6)	14,588 (34.8)	225 (50.0)	299 (39.9)	
Unstaged	28,699 (13.1)	3,369 (8.0)	27 (6.0)	15 (2.0)	
Grade differentiation (%)					
Well	18,412 (8.4)	3,876 (9.2)	21 (4.7)	14 (1.9)	< 0.001
Moderate	35,006 (16.0)	12,125 (28.9)	115 (25.6)	188 (25.1)	
Poor	28,836 (13.2)	10,489 (25.0)	135 (30.0)	328 (43.8)	
Unknown	136,674 (62.4)	15,486 (36.9)	179 (39.8)	219 (29.2)	
Surgery (%)					
Yes	64,309 (29.4)	21,527 (51.3)	191 (42.4)	576 (76.9)	< 0.001
No	154,619 (70.6)	20,449 (48.7)	259 (57.6)	173 (23.1)	
Chemotherapy (%)					
Yes	73,858 (33.7)	14,544 (34.6)	149 (33.1)	284 (37.9)	0.14
No	145,070 (66.3)	27,432 (65.4)	301 (66.9)	465 (62.1)	
Radiotherapy (%)					
Yes	24,015 (11.0)	6,488 (15.5)	67 (14.9)	126 (16.8)	0.56
No	194,913 (89.0)	35,488 (84.5)	383 (85.1)	623 (83.2)	
Incidence Rate (95% CI)					
All	111.6 (111.1 - 112.1)	19.5 (19.3 - 19.7)	0.19 (0.17 - 0.22)	0.32 (0.29 - 0.35)	-
Male	156.1 (155.2 - 156.9)	19.7 (19.4 - 20.0)	0.17 (0.14 - 0.20)	0.24 (0.21 - 0.28)	
Female	73.4 (72.9 - 74.0)	19.4 (19.1 - 19.7)	0.22 (0.19 - 0.25)	0.38 (0.34 - 0.42)	
CSS (95% CI)					
1-year	47.7 (47.5 - 48.0)	47.7 (47.1 - 48.3)	19.8 (15.1 - 24.9)	33.1 (28.7 - 37.7)	-
2-year	34.3 (34.1 - 34.6)	31.8 (31.2 - 32.4)	10.2 (6.7 - 14.5)	18.4 (14.8 - 22.4)	

Table 9. Demographics and Clinical Characteristics for Biliary Tract Cancer by Histology - (continued)

Biliary	All	Adenocarcinoma	Squamous	Adenosquamous	P value
5-year	21.7 (21.5 - 22.0)	20.0 (19.5 - 20.6)	7.4 (4.4 - 11.4)	13.1 (9.8 - 16.8)	
10-year	17.1 (16.9 - 17.3)	16.6 (16.1 - 17.2)	7.4 (4.4 - 11.4)	12.6 (9.3 - 16.3)	
Median (months)	10.7	10.9	4.2	7.9	
RS (95% CI)					-
1-year	43.9 (43.7 - 44.1)	44.5 (43.9 - 45.1)	18.0 (13.7 - 22.8)	31.9 (27.6 - 36.3)	
2-year	29.9 (29.7 - 30.1)	28.3 (27.7 - 28.8)	8.1 (5.1 - 11.8)	16.8 (13.4 - 20.6)	
5-year	16.7 (16.5 - 16.9)	15.6 (15.1 - 16.1)	5.8 (3.4 - 9.3)	9.9 (7.1 - 13.1)	
10-year	11.0 (10.8 - 11.2)	10.2 (9.8 - 10.7)	5.8 (3.4 - 9.3)	7.7 (5.1 - 10.9)	
Median (months)	8.9	9.6	3.9	7.4	

P < 0.05 for all comparisons between adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma comparisons. Incidence rates were expressed per 100,000. CSS: cause-specific survival; RS: relative survival; CI: confidence interval; SD: standard deviation.

for ASCs compared to ACs were higher for uterine/cervical, biliary tract, esophageal, colorectal, and gastric cancers (about 1.3 - 2.2), equivalent for pancreatic cancer, and lower for lung and oral cavity cancers (about 0.7 - 0.9). Compared to SCCs, unadjusted mortality HRs were higher for esophageal and colorectal cancers (about 1.2 - 2.2), equivalent for uterine/cervical and gastric cancers, and lower for lung, pancreatic, oral cavity, and biliary tract cancers (about 0.7 - 0.8). However, after multivariable adjustment for sex, race, detection stage, grade differentiation,

surgery, chemotherapy, and radiotherapy, except for oral cavity cancers, ASCs in all other sites had higher mortality HRs than ACs or SCCs (apart from biliary tract and gastric SCCs, which were equivalent). This finding implies that apart from oral cavity cancers, ASC histology may be an independent predictor of poorer prognosis compared to conventional ACs and SCCs.

The etiology of ASCs is poorly understood. Leading ideas include a predominant adenocarcinoma histology that undergoes a subsequent metaplasia, or in other cases, an underlying

Table 10. Univariate and Multivariable Cox-Proportional Hazard Ratios (HRs) of Mortality for Biliary Tract Cancer

Biliary	Adenosquamous vs. adenocarcinoma		Adenosquamous vs. squamous	
	Univariate, HR (95% CI)	Multivariable, HR (95% CI)	Univariate, HR (95% CI)	Multivariable, HR (95% CI)
Adenosquamous histology	1.40 (1.28 - 1.52)	1.56 (1.43 - 1.71)	0.74 (0.64 - 0.85)	0.93 (0.80 - 1.09) ^a
Age (per 10 years)	1.10 (1.08 - 1.11)	1.08 (1.07 - 1.09)	1.12 (1.06 - 1.20)	1.10 (1.03 - 1.17)
Sex				
Female	1.06 (1.04 - 1.09)	1.06 (1.04 - 1.09)	0.98 (0.84 - 1.13) ^a	1.04 (0.90 - 1.21) ^a
Race				
Black	1.05 (1.01 - 1.10)	1.06 (1.01 - 1.11)	1.22 (0.98 - 1.53) ^a	1.05 (0.84 - 1.32) ^a
Other	0.94 (0.90 - 0.98)	0.96 (0.92 - 1.00) ^a	0.97 (0.79 - 1.21) ^a	0.91 (0.73 - 1.13) ^a
Detection stage				
Regional	1.36 (1.31 - 1.42)	1.61 (1.55 - 1.68)	1.48 (1.17 - 1.88)	1.92 (1.50 - 2.45)
Distant	3.56 (3.42 - 3.70)	3.06 (2.93 - 3.19)	2.59 (2.04 - 3.28)	2.99 (2.31 - 3.86)
Unstaged	2.50 (2.37 - 2.64)	1.41 (1.33 - 1.49)	2.19 (1.41 - 3.40)	1.86 (1.19 - 2.91)
Grade differentiation				
Moderate	1.28 (1.22 - 1.35)	1.26 (1.20 - 1.32)	0.96 (0.63 - 1.47) ^a	0.88 (0.57 - 1.35) ^a
Poor	2.11 (2.00 - 2.22)	1.87 (1.78 - 1.97)	1.26 (0.83 - 1.91) ^a	1.16 (0.76 - 1.77) ^a
Unknown	2.82 (2.68 - 2.96)	1.42 (1.35 - 1.50)	1.62 (1.07 - 2.47)	1.06 (0.69 - 1.64) ^a
Surgery (yes)	0.33 (0.32 - 0.34)	0.385 (0.372 - 0.398)	0.42 (0.37 - 0.49)	0.48 (0.40 - 0.58)
Chemotherapy (yes)	0.95 (0.93 - 0.98)	0.66 (0.65 - 0.68) ^a	0.72 (0.62 - 0.83)	0.57 (0.49 - 0.67)
Radiotherapy (yes)	0.82 (0.79 - 0.84)	1.01 (0.98 - 1.05)	0.60 (0.50 - 0.72)	0.76 (0.63 - 0.93)

P < 0.05 relative to reference unless noted by ^aP ≥ 0.05. Reference categories: sex (Male), race (White), detection stage (Localized), grade differentiation (Well), surgery (no), radiotherapy (no), and chemotherapy (no). CI: confidence interval.

Table 11. Demographics and Clinical Characteristics for Esophageal Cancer by Histology

Esophagus	All	Adenocarcinoma	Squamous	Adenosquamous	P value
N (%)	92,290 (100.0)	44,971 (48.7)	35,215 (38.2)	683 (0.7)	
Age (years) (%)					
0 - 14	3 (< 1)	0 (0.0)	2 (< 1)	0 (0.0)	< 0.001
15 - 29	143 (0.2)	94 (0.2)	20 (0.1)	0 (0.0)	
30 - 49	5,857 (6.3)	3,128 (7.0)	1,966 (5.6)	52 (7.6)	
50 - 69	46,353 (50.2)	22,659 (50.4)	18,032 (51.2)	375 (54.9)	
70 - 89	39,934 (43.3)	19,090 (42.4)	15,195 (43.1)	256 (37.5)	
Mean (SD)	67.1 (11.3)	66.8 (11.5)	67.2 (10.8)	65.8 (10.7)	< 0.001
Median	67	67	67	66	
Sex (%)					
Male	71,029 (77.0)	38,740 (86.1)	22,933 (65.1)	562 (82.3)	< 0.001
Female	21,261 (23.0)	6,231 (13.9)	12,282 (34.9)	121 (17.7)	
Race (%)					
White	76,729 (83.1)	42,643 (94.8)	23,426 (66.5)	585 (85.7)	< 0.001
Black	10,225 (11.1)	1,164 (2.6)	8,181 (23.2)	58 (8.5)	
Other	5,336 (5.8)	1,164 (2.6)	3,608 (10.2)	40 (5.9)	
Detection stage (%)					
Localized	20,381 (22.1)	10,255 (22.8)	8,130 (23.1)	89 (13.0)	< 0.001
Regional	27,306 (29.6)	13,250 (29.5)	11,191 (31.8)	249 (36.5)	
Distant	31,335 (34.0)	17,074 (38.0)	9,966 (28.3)	283 (41.4)	
Unstaged	13,268 (14.4)	4,392 (9.8)	5,928 (16.8)	62 (9.1)	
Grade differentiation (%)					
Well	4,118 (4.5)	2,174 (4.8)	1,725 (4.9)	7 (1.0)	< 0.001
Moderate	25,982 (28.2)	13,110 (29.2)	12,152 (34.5)	79 (11.6)	
Poor	34,171 (37.0)	16,792 (37.3)	11,893 (33.8)	410 (60.0)	
Unknown	28,019 (30.4)	12,895 (28.7)	9,445 (26.8)	187 (27.4)	
Surgery (%)					
Yes	24,022 (26.0)	14,778 (32.9)	6,648 (18.9)	226 (33.1)	< 0.001
No	68,268 (74.0)	30,193 (67.1)	28,567 (81.1)	457 (66.9)	
Chemotherapy (%)					
Yes	49,701 (53.9)	26,358 (58.6)	17,993 (51.1)	392 (57.4)	< 0.001
No	42,589 (46.1)	18,613 (41.4)	17,222 (48.9)	291 (42.6)	
Radiotherapy (%)					
Yes	50,446 (54.7)	23,192 (51.6)	22,270 (63.2)	378 (55.3)	< 0.001
No	41,844 (45.3)	21,779 (41.4)	12,945 (36.8)	305 (44.7)	
Incidence rate (95% CI)					
All	42.9 (42.6 - 43.2)	22.8 (22.6 - 23.1)	13.8 (13.7 - 14.0)	0.29 (0.27 - 0.32)	-
Male	73.9 (73.3 - 74.5)	43.6 (43.1 - 44.0)	19.6 (19.3 - 19.9)	0.54 (0.49 - 0.59)	
Female	17.6 (17.3 - 17.8)	5.9 (5.7 - 6.1)	9.1 (8.9 - 9.3)	0.09 (0.07 - 0.11)	
CSS (95% CI)					
1-year	49.4 (49.0 - 49.8)	54.2 (53.7 - 54.8)	44.4 (43.7 - 45.2)	40.1 (35.2 - 44.8)	-
2-year	32.8 (32.4 - 33.2)	36.5 (36.0 - 37.1)	29.0 (28.3 - 29.7)	21.4 (17.4 - 25.7)	

Table 11. Demographics and Clinical Characteristics for Esophageal Cancer by Histology - (continued)

Esophagus	All	Adenocarcinoma	Squamous	Adenosquamous	P value
5-year	21.1 (20.7 - 21.5)	23.3 (22.8 - 23.8)	19.0 (18.4 - 19.6)	13.7 (10.3 - 17.7)	
10-year	17.2 (16.9 - 17.6)	19.3 (18.8 - 19.8)	14.9 (14.3 - 15.6)	9.6 (6.6 - 13.3)	
Median (months)	11.8	14.0	9.9	9.2	
RS (95% CI)					-
1-year	46.0 (45.6 - 46.4)	50.8 (50.3 - 51.4)	41.1 (40.3 - 41.8)	36.4 (31.8 - 40.9)	
2-year	29.2 (28.8 - 29.6)	32.8 (32.3 - 33.4)	25.4 (24.8 - 26.1)	18.1 (14.6 - 22.0)	
5-year	16.5 (16.1 - 16.8)	18.6 (18.2 - 19.1)	14.2 (13.7 - 14.8)	10.6 (7.8 - 13.9)	
10-year	10.5 (10.2 - 10.8)	12.5 (12.0 - 12.9)	8.1 (7.6 - 8.6)	6.4 (4.1 - 9.3)	
Median (months)	10.5	12.4	8.9	8.5	

P < 0.05 for all comparisons between adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma comparisons. Incidence rates were expressed per 100,000. CSS: cause-specific survival; RS: relative survival; CI: confidence interval; SD: standard deviation.

squamous metaplasia that experiences a malignant transformation secondary to persistent chronic inflammation [22-26]. Alternatively, these cancers may arise from pluripotent cancer stem cells capable of inducing malignant transformation of both histologies or transdifferentiation [6]. This theory is particularly intriguing, because if these cancers are more likely to be propagated by semi-quiescent cancer stem cells, which are well recognized to be chemotherapy and radiotherapy resistant, it might explain the higher rates of dedifferentiation and wors-

ened outcomes compared to conventional histologies [27, 28].

This study does have several limitations. Despite this project using a well-validated population level database with quality assurance metrics [10], the research is retrospective in nature, and therefore is prone to selection bias. In order to obtain sufficient numbers of ASC cases for meaningful descriptive and comparative analyses across all major disease sites, the entire span of SEER database is required, which requires us to limit our treatment variables to binary values. Unfortunately, this approach

Table 12. Univariate and Multivariable Cox-Proportional Hazard Ratios (HRs) of Mortality for Esophageal Cancer

Esophagus	Adenosquamous vs. adenocarcinoma		Adenosquamous vs. squamous	
	Univariate, HR (95% CI)	Multivariable, HR (95% CI)	Univariate, HR (95% CI)	Multivariable, HR (95% CI)
Adenosquamous histology	1.47 (1.35 - 1.60)	1.30 (1.19 - 1.42)	1.16 (1.07 - 1.27)	1.21 (1.10 - 1.32)
Age (per 10 years)	1.10 (1.09 - 1.11)	1.08 (1.07 - 1.09)	1.05 (1.04 - 1.07)	1.02 (1.01 - 1.03)
Sex				
Female	1.04 (1.01 - 1.08)	0.97 (0.93 - 1.00)	0.84 (0.81 - 0.86)	0.86 (0.84 - 0.89)
Race				
Black	1.16 (1.08 - 1.24)	1.05 (0.98 - 1.13) ^a	1.21 (1.17 - 1.24)	1.13 (1.09 - 1.16)
Other	0.99 (0.93 - 1.07) ^a	0.88 (0.82 - 0.95)	1.02 (0.98 - 1.06) ^a	0.97 (0.93 - 1.10) ^a
Detection stage				
Regional	1.92 (1.85 - 1.99)	2.22 (2.13 - 2.30)	1.21 (1.16 - 1.25)	1.44 (1.39 - 1.50)
Distant	4.59 (4.43 - 4.75)	3.84 (3.69 - 4.00)	2.36 (2.28 - 2.45)	2.34 (2.26 - 2.43)
Unstaged	2.95 (2.82 - 3.10)	1.86 (1.77 - 1.95)	1.60 (1.54 - 1.67)	1.26 (1.21 - 1.32)
Grade differentiation				
Moderate	1.54 (1.45 - 1.64)	1.27 (1.19 - 1.35)	1.17 (1.10 - 1.24)	1.16 (1.09 - 1.24)
Poor	2.23 (2.10 - 2.37)	1.68 (1.58 - 1.79)	1.33 (1.25 - 1.41)	1.24 (1.17 - 1.32)
Unknown	1.62 (1.52 - 1.73)	1.18 (1.10 - 1.25)	1.16 (1.09 - 1.24)	1.03 (0.96 - 1.10) ^a
Surgery (yes)	0.294 (0.286 - 0.302)	0.39 (0.37 - 0.40)	0.51 (0.49 - 0.53)	0.47 (0.45 - 0.49)
Chemotherapy (yes)	0.98 (0.96 - 1.01)	0.56 (0.54 - 0.58)	0.61 (0.60 - 0.63)	0.53 (0.51 - 0.55)
Radiotherapy (yes)	0.96 (0.94 - 0.98)	1.03 (1.00 - 1.06)	0.72 (0.70 - 0.74)	0.80 (0.78 - 0.83)

P < 0.05 relative to reference unless noted by ^aP ≥ 0.05. Reference categories: sex (Male), race (White), detection stage (Localized), grade differentiation (Well), surgery (no), radiotherapy (no), and chemotherapy (no). CI: confidence interval.

Table 13. Demographics and Clinical Characteristics for Colorectal Cancer by Histology

Colorectal	All	Adenocarcinoma	Squamous	Adenosquamous	P value
N (%)	976,218 (100.0)	654,583 (67.1)	4,099 (0.4)	499 (0.1)	
Age (years) (%)					
0 - 14	388 (< 1)	18 (< 1)	0 (0.0)	0 (0.0)	< 0.001
15 - 29	6,306 (0.6%)	2,517 (0.4)	14 (0.3)	7 (1.4)	
30 - 49	91,261 (9.3)	59,034 (9.0)	567 (13.8)	69 (13.8)	
50 - 69	417,273 (42.7)	276,839 (42.3)	2,237 (54.6)	217 (43.5)	
70 - 89	460,990 (47.2)	316,175 (48.3)	1,281 (31.3)	206 (41.3)	
Mean (SD)	67.1 (13.2)	67.5 (12.8)	62.9 (12.6)	64.6 (14.2)	< 0.001
Median	68	69	63	66	
Sex (%)					
Male	508,045 (52.0)	344,212 (52.6)	1,367 (33.3)	239 (47.9)	< 0.001
Female	468,173 (48.0)	310,371 (47.4)	2,732 (66.7)	260 (52.1)	
Race (%)					
White	797,944 (81.7)	535,324 (81.8)	3,535 (86.2)	416 (83.4)	< 0.001
Black	96,336 (9.9)	62,425 (9.5)	451 (11.0)	55 (11.0)	
Other	81,938 (8.4)	56,834 (8.7)	113 (2.8)	28 (5.6)	
Detection stage (%)					
Localized	382,652 (39.2)	211,323 (32.3)	1,563 (38.1)	68 (13.6)	< 0.001
Regional	349,452 (35.8)	272,190 (41.6)	1,172 (28.6)	208 (41.7)	
Distant	197,244 (20.2)	145,939 (22.3)	731 (17.8)	211 (42.3)	
Unstaged	46,870 (4.8)	25,131 (3.8)	633 (15.4)	12 (2.4)	
Grade differentiation (%)					
Well	100,493 (10.3)	50,960 (7.8)	205 (5.0)	8 (1.6)	< 0.001
Moderate	530,921 (54.4)	402,646 (61.5)	1,138 (27.8)	100 (20.0)	
Poor	156,586 (16.0)	111,890 (17.1)	1,310 (32.0)	307 (61.5)	
Unknown	188,218 (19.3)	89,087 (13.6)	1,446 (35.3)	84 (16.8)	
Surgery (%)					
Yes	832,886 (85.3)	560,355 (85.6)	1,293 (31.5)	414 (83.0)	< 0.001
No	143,332 (14.7)	94,228 (14.4)	2,806 (68.5)	85 (17.0)	
Chemotherapy (%)					
Yes	309,619 (31.7)	238,979 (36.5)	2,536 (61.9)	232 (46.5)	< 0.001
No	666,599 (68.3)	415,604 (63.5)	1,563 (38.1)	267 (53.5)	
Radiotherapy (%)					
Yes	117,214 (12.0)	91,656 (14.0)	2,611 (63.7)	101 (20.2)	< 0.001
No	859,004 (88.0)	562,927 (86.0)	1,488 (36.3)	398 (79.8)	
Incidence rate (95% CI)					
All	427 (426 - 428)	279 (278 - 280)	2.1 (2.0 - 2.2)	0.20 (0.18 - 0.22)	-
Male	492 (491 - 494)	328 (326 - 329)	1.5 (1.4 - 1.6)	0.22 (0.18 - 0.25)	
Female	373 (372 - 374)	240 (239 - 241)	2.6 (2.5 - 2.7)	0.19 (0.16 - 0.22)	
CSS (95% CI)					
1-year	84.6 (84.5 - 84.7)	84.2 (84.1 - 84.3)	81.2 (79.7 - 82.6)	61.3 (55.3 - 66.8)	-
2-year	77.1 (76.9 - 77.2)	75.6 (75.5 - 75.8)	72.0 (70.2 - 73.7)	47.2 (41.1 - 53.1)	

Table 13. Demographics and Clinical Characteristics for Colorectal Cancer by Histology - (continued)

Colorectal	All	Adenocarcinoma	Squamous	Adenosquamous	P value
5-year	65.3 (65.2 - 65.4)	61.7 (61.6 - 61.9)	63.9 (61.9 - 65.8)	35.7 (29.8 - 41.6)	
10-year	58.8 (58.6 - 58.9)	54.3 (54.1 - 54.5)	59.7 (57.6 - 61.8)	32.9 (27.0 - 38.9)	
Median (months)	-	-	-	20.3	
RS (95% CI)					-
1-year	81.0 (80.9 - 81.1)	80.5 (80.4 - 80.7)	77.7 (76.1 - 79.2)	58.7 (52.7 - 64.1)	
2-year	71.9 (71.8 - 72.0)	70.4 (70.3 - 70.6)	67.3 (65.5 - 69.0)	44.4 (38.5 - 50.1)	
5-year	55.8 (55.6 - 55.9)	52.4 (52.2 - 52.6)	55.8 (53.8 - 57.7)	32.0 (26.6 - 37.7)	
10-year	41.4 (41.2 - 41.5)	37.5 (37.3 - 37.6)	46.1 (43.9 - 48.2)	26.4 (21.0 - 32.0)	
Median (months)	80.3	67.3	94.5	17.0	

P < 0.05 for all comparisons between adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma comparisons. Incidence rates were expressed per 100,000. CSS: cause-specific survival; RS: relative survival; CI: confidence interval; SD: standard deviation.

does not allow for consideration of the effects of advances in therapeutic efficacy over the 45 years of data captured by SEER. Additionally, stage and grade classifications have subtle differences across different anatomical sites and have also evolved with temporal updates of tumor classification algorithms. Therefore, out of necessity to make consistent comparisons across all sites and over the evolution of formalized staging systems, this study is required to use very broad definitions out of necessity. However, despite these drawbacks, this project would not be

possible outside of a population-level registry given the extreme rarity of ASCs. By providing a standardized and systemic characterization of the clinicoepidemiological features of ASCs against nonvariant ACs and SCCs across all major sites, this study provides the comprehensive groundwork for future comparative studies that will be required to further delineate the tumor biology of this rare and poorly understood pathology. Such research will be necessary in order to implement effective and tailored treatment interventions for patients diagnosed with these cancers.

Table 14. Univariate and Multivariable Cox-Proportional Hazard Ratios (HRs) of Mortality for Colorectal Cancer

Colorectal	Adenosquamous vs. adenocarcinoma		Adenosquamous vs. squamous	
	Univariate, HR (95% CI)	Multivariable, HR (95% CI)	Univariate, HR (95% CI)	Multivariable, HR (95% CI)
Adenosquamous histology	2.15 (1.91 - 2.42)	1.44 (1.28 - 1.63)	2.20 (1.93 - 2.50)	1.26 (1.08 - 1.47)
Age (per 10 years)	1.109 (1.105 - 1.112)	1.204 (1.201 - 1.209)	1.21 (1.16 - 1.26)	1.18 (1.13 - 1.23)
Sex				
Female	0.94 (0.93 - 0.95)	0.935 (0.928 - 0.943)	0.69 (0.63 - 0.76)	0.74 (0.67 - 0.82)
Race				
Black	1.24 (1.22 - 1.25)	1.17 (1.16 - 1.19)	1.26 (1.09 - 1.46)	1.18 (1.02 - 1.37)
Other	0.90 (0.89 - 0.92)	0.92 (0.91 - 0.93)	1.19 (0.90 - 1.58) ^a	0.86 (0.65 - 1.14) ^a
Detection stage				
Regional	2.26 (2.23 - 2.29)	2.51 (2.48 - 2.54)	2.07 (1.80 - 2.38)	2.19 (1.90 - 2.53)
Distant	12.0 (11.0 - 12.2)	12.0 (11.9 - 12.2)	7.41 (6.46 - 8.50)	7.17 (6.20 - 8.28)
Unstaged	5.10 (5.00 - 5.21)	2.89 (2.83 - 2.96)	2.20 (1.85 - 2.61)	1.72 (1.44 - 2.06)
Grade differentiation				
Moderate	1.17 (1.15 - 1.19)	1.04 (1.02 - 1.06)	1.31 (1.01 - 1.71)	1.26 (0.96 - 1.64) ^a
Poor	1.92 (1.89 - 1.96)	1.48 (1.46 - 1.51)	1.73 (1.33 - 2.24)	1.40 (1.08 - 1.83)
Unknown	2.43 (2.38 - 2.48)	1.17 (1.15 - 1.20)	1.39 (1.07 - 1.81)	1.09 (0.84 - 1.43) ^a
Surgery (yes)	0.203 (0.201 - 0.205)	0.410 (0.405 - 0.414)	0.92 (0.83 - 1.02) ^a	0.72 (0.64 - 0.82)
Chemotherapy (yes)	1.41 (1.40 - 1.42)	0.75 (0.74 - 0.76)	0.59 (0.53 - 0.65)	0.64 (0.56 - 0.72)
Radiotherapy (yes)	1.08 (1.06 - 1.09)	1.12 (1.10 - 1.13)	0.48 (0.43 - 0.53)	0.68 (0.60 - 0.77)

P < 0.05 relative to reference unless noted by ^aP ≥ 0.05. Reference categories: sex (Male), race (White), detection stage (Localized), grade differentiation (Well), surgery (no), radiotherapy (no), and chemotherapy (no). CI: confidence interval.

Table 15. Demographics and Clinical Characteristics for Gastric Cancer by Histology

Gastric	All	Adenocarcinoma	Squamous	Adenosquamous	P value
N (%)	163,791 (100.0)	103,143 (63.0)	1,306 (0.8)	479 (0.3)	
Age (years) (%)					
0 - 14	45 (< 1)	3 (< 1)	0 (0.0)	0 (0.0)	< 0.001
15 - 29	1,149 (0.7)	493 (0.5)	4 (0.3)	2 (0.4)	
30 - 49	16,632 (10.2)	8,103 (7.9)	76 (5.8)	39 (8.1)	
50 - 69	66,842 (40.8)	41,002 (39.8)	632 (48.4)	257 (53.7)	
70 - 89	79,123 (48.3)	53,542 (51.9)	594 (45.5)	181 (37.8)	
Mean (SD)	67.2 (13.4)	68.5 (12.7)	67.3 (11.7)	65.6 (11.6)	< 0.001
Median	69	70	68	66	
Sex (%)					
Male	100,682 (61.5)	68,577 (66.5)	926 (70.9)	346 (72.2)	< 0.001
Female	63,109 (38.5)	34,566 (33.5)	380 (29.1)	133 (27.8)	
Race (%)					
White	118,825 (72.5)	74,681 (72.4)	951 (72.8)	371 (77.5)	< 0.001
Black	19,550 (11.9)	11,583 (11.2)	236 (18.1)	61 (12.7)	
Other	25,416 (15.5)	16,879 (16.4)	119 (9.1)	47 (9.8)	
Detection Stage (%)					
Localized	41,461 (25.3)	22,366 (21.7)	227 (17.4)	59 (12.3)	< 0.001
Regional	45,864 (28.0)	32,103 (31.1)	337 (25.8)	186 (38.8)	
Distant	58,576 (35.8)	38,774 (37.6)	541 (41.4)	206 (43.0)	
Unstaged	17,890 (10.9)	9,900 (9.6)	201 (15.4)	28 (5.8)	
Grade Differentiation (%)					
Well	9,547 (5.8)	4,779 (4.6)	64 (4.9)	3 (0.6)	< 0.001
Moderate	30,480 (18.6)	25,698 (24.9)	330 (25.3)	63 (13.2)	
Poor	75,552 (46.1)	49,344 (47.8)	542 (41.5)	306 (63.9)	
Unknown	48,212 (29.4)	23,322 (22.6)	370 (28.3)	107 (22.3)	
Surgery (%)					
Yes	81,339 (49.7)	50,124 (48.6)	342 (26.2)	263 (54.9)	< 0.001
No	82,452 (50.3)	53,019 (51.4)	964 (73.8)	216 (45.1)	
Chemotherapy (%)					
Yes	63,961 (39.1)	42,283 (41.0)	575 (44.0)	244 (50.9)	< 0.001
No	99,830 (60.9)	60,860 (59.0)	731 (56.0)	235 (49.1)	
Radiotherapy (%)					
Yes	31,035 (18.9)	22,608 (21.9)	505 (38.7)	160 (33.4)	< 0.001
No	132,756 (81.1)	80,535 (78.1)	801 (61.3)	319 (66.6)	
Incidence Rate (95% CI)					
All	73.7 (73.3 - 74.1)	43.6 (43.3 - 43.9)	0.57 (0.54 - 0.61)	0.19 (0.17 - 0.21)	-
Male	99.9 (99.2 - 100.7)	65.2 (64.7 - 65.8)	0.90 (0.83 - 0.97)	0.29 (0.26 - 0.34)	
Female	53.1 (52.6 - 53.5)	26.4 (26.1 - 26.7)	0.30 (0.27 - 0.34)	0.10 (0.08 - 0.12)	
CSS (95% CI)					
1-year	56.8 (56.5 - 57.1)	53.3 (52.9 - 53.7)	38.2 (34.6 - 41.8)	44.3 (38.2 - 50.3)	-
2-year	43.1 (42.7 - 43.4)	37.7 (37.3 - 38.1)	24.9 (21.7 - 28.2)	23.7 (18.6 - 29.2)	

Table 15. Demographics and Clinical Characteristics for Gastric Cancer by Histology - (continued)

Gastric	All	Adenocarcinoma	Squamous	Adenosquamous	P value
5-year	32.5 (32.1 - 32.8)	26.0 (25.7 - 26.4)	18.4 (15.4 - 21.6)	16.9 (12.5 - 22.0)	
10-year	28.5 (28.2 - 28.8)	22.3 (21.9 - 22.7)	17.1 (14.1 - 20.4)	14.0 (9.7 - 19.0)	
Median (Months)	16.6	13.7	7.7	10.3	
RS (95% CI)					-
1-year	53.5 (53.2 - 53.8)	49.9 (49.5 - 50.3)	35.3 (31.9 - 38.7)	41.4 (35.5 - 47.2)	
2-year	39.1 (38.8 - 39.4)	33.9 (33.5 - 34.3)	22.8 (19.8 - 25.9)	21.7 (16.9 - 26.8)	
5-year	26.5 (26.2 - 26.8)	20.7 (20.3 - 21.0)	14.6 (12.0 - 17.5)	14.7 (10.7 - 19.4)	
10-year	19.0 (18.8 - 19.3)	13.9 (13.6 - 14.3)	10.9 (8.5 - 13.6)	9.5 (6.1 - 13.9)	
Median (Months)	14.0	12.0	6.8	9.4	

P < 0.05 for all comparisons between adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma comparisons. Incidence rates were expressed per 100,000. CSS: cause-specific survival; RS: relative survival; CI: confidence interval; SD: standard deviation.

Supplementary Material

Suppl 1. Exclusion criteria and counts of all cases, ACs, SCCs, and ASCs from SEER (1975 - 2020).

Suppl 2. Variables in analysis. Categorization reflects final variable composition.

Suppl 3. Breakdown of ASC cases in SEER (1975 - 2020), both analyzed and not analyzed.

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None to declare.

Table 16. Univariate and Multivariable Cox-Proportional Hazard Ratios (HRs) of Mortality for Gastric Cancer

Gastric	Adenosquamous vs. adenocarcinoma		Adenosquamous vs. squamous	
	Univariate, HR (95% CI)	Multivariable, HR (95% CI)	Univariate, HR (95% CI)	Multivariable, HR (95% CI)
Adenosquamous histology	1.29 (1.16 - 1.44)	1.24 (1.11 - 1.38)	0.98 (0.87 - 1.12) ^a	1.11 (0.96 - 1.27) ^a
Age (per 10 years)	1.05 (1.04 - 1.06)	1.07 (1.06 - 1.08)	1.09 (1.04 - 1.15)	1.09 (1.03 - 1.14)
Sex				
Female	0.97 (0.95 - 0.98)	0.95 (0.93 - 0.96)	0.89 (0.78 - 1.01) ^a	0.88 (0.77 - 1.00) ^a
Race				
Black	0.97 (0.95 - 0.99)	0.98 (0.96 - 1.01) ^a	1.43 (1.22 - 1.66)	1.32 (1.13 - 1.54)
Other	0.74 (0.73 - 0.76)	0.82 (0.81 - 0.84)	1.09 (0.89 - 1.33) ^a	0.97 (0.79 - 1.19) ^a
Detection stage				
Regional	2.33 (2.27 - 2.39)	2.81 (2.74 - 2.89)	1.40 (1.16 - 1.70)	1.68 (1.37 - 2.05)
Distant	6.10 (5.95 - 6.26)	4.91 (4.77 - 5.05)	3.32 (2.76 - 4.00)	3.09 (2.52 - 3.77)
Unstaged	3.85 (3.72 - 3.98)	2.07 (2.00 - 2.15)	2.12 (1.68 - 2.68)	1.51 (1.18 - 1.92)
Grade differentiation				
Moderate	1.48 (1.41 - 1.55)	1.20 (1.15 - 1.26)	1.55 (1.10 - 2.17)	1.33 (0.94 - 1.87) ^a
Poor	2.08 (1.99 - 2.17)	1.60 (1.53 - 1.67)	2.07 (1.49 - 2.86)	1.72 (1.23 - 2.40)
Unknown	2.10 (2.01 - 2.20)	1.26 (1.21 - 1.32)	1.67 (1.19 - 2.34)	1.21 (0.86 - 1.70) ^a
Surgery (yes)	0.298 (0.293 - 0.303)	0.367 (0.360 - 0.375)	0.45 (0.40 - 0.51)	0.50 (0.42 - 0.58)
Chemotherapy (yes)	1.05 (1.03 - 1.07)	0.59 (0.57 - 0.60)	0.72 (0.64 - 0.81)	0.56 (0.49 - 0.64)
Radiotherapy (yes)	0.89 (0.87 - 0.91)	0.98 (0.96 - 0.99)	0.71 (0.63 - 0.80)	0.87 (0.76 - 0.99)

P < 0.05 relative to reference unless noted by ^aP ≥ 0.05. Reference categories: sex (Male), race (White), detection stage (Localized), grade differentiation (Well), surgery (no), radiotherapy (no), and chemotherapy (no). CI: confidence interval.

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Conflict of Interest

None to declare.

Informed Consent

Data release from the SEER database does not require informed patient consent.

Author Contributions

MGKB and VORS designed the study. MGKB conducted the SEER analysis. MGKB compiled the figures, and MGKB and CJR composed the tables. MGKB and VORS wrote the original draft, and all authors reviewed and edited the draft. KT supervised the project. All authors have read and agreed to the published version of the manuscript.

Data Availability

All data supporting the findings of this study are available within the article. Access to the SEER database is available via signed user agreements (<https://seer.cancer.gov/data/access.html>).

Abbreviations

AC: adenocarcinoma (conventional/nonvariant); ASC: adenosquamous carcinoma; CI: confidence interval; CSS: cause-specific survival; HR: hazard ratio; RS: relative survival; SD: standard deviation; SCC: squamous cell carcinoma (conventional/nonvariant); SEER: Surveillance, Epidemiology, and End Results

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