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Histologic and racial/ethnic patterns of appendiceal cancer among young patients

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ABSTRACT

Background: Appendiceal cancer (AC) incidence among individuals age<50 years (early-onset AC) is rising with unknown etiologies. Distinct clinicopathologic/ demographic features of early-onset AC remain unexplored. We compared patterns of AC among individuals by age of disease-onset.

Methods: Using the NIH/NCI's SEER program data, we identified individuals age 20+ years diagnosed with AC from 2007-2016. Cochran-Armitage trend tests and multinomial logistic regression models were used to examine age-related differences in clinicopathologic/demographic features of AC.

Results: We identified 8,851 patients with AC during the 10-year study period. Histological subtype, tumor grade, stage, sex and race/ethnicity all significantly differed by age of AC-onset. After adjustment for race/ethnicity, sex, stage, insurance status, and tumor grade, young patients were 82% more likely to be Hispanic (OR=1.82, 95%CI=1.48-2.25, P<0.001) and four-fold more likely to be American Indian or Alaska Native (OR=4.02, 95%CI=1.77-9.16, P=0.0009) compared with late-onset cases. Early-onset AC patients were also two-fold to 3.5-fold more likely to be diagnosed with neuroendocrine tumors of the appendix (goblet cell carcinoid: OR=1.96, 95%CI=1.59-2.41, P<0.0001; carcinoid: OR=3.52, 95%CI=2.80-4.42,P<0.0001) compared to patients with late-onset AC. Among patients with neuroendocrine tumors, early-onset cases were also 45-61% less likely to present with high grade (III-IV) tumors.

Conclusion: Approximately one in every three patients with AC is diagnosed before age 50 years in the US. AC in young patients is classified by distinct histologic and demographic features.

Impact: Early-onset AC determinants can inform discovery of risk factors and molecular biomarkers of AC in young patients, with implications for AC prevention, detection and treatment.

KEYWORDS

Appendix, appendiceal cancer, early-onset, young-onset.

INTRODUCTION

In 2020, an estimated 333,680 cases of cancers of the digestive system will be diagnosed in the United States—of which 2.3% (7,600 cases) include appendiceal carcinomas and other rare digestive system tumors.[1] As a rare malignancy, with an age-adjusted incidence rate of 0.12 per 1,000,000 person years,[2] little is currently known about the risk factors and etiologies of appendiceal cancer. Among patients of all ages diagnosed with appendiceal carcinomas, incidence rates have been increasing over the last two and a half decades with causes unexplained.[3,4] Strikingly, as the overall incidence of malignant appendix tumors has risen over the last two decades in the United States by 232%, rates have also increased from older to younger generations. However, rates of appendectomies have remained stable over this period—suggesting that the rising AC incidence is likely not related to an increase in diagnosis of incidental, asymptomatic tumors.[4] Given this changing landscape of appendiceal cancer, a better understanding of disease patterns specific to young patients is needed to inform discovery of risk factors and biomarkers for disease prevention and early detection. Consequently, the study of appendix cancer by age of disease-onset—using nationally representative data from the National Institutes of Health/National Cancer Institute's (NIH/NCI) Surveillance, Epidemiology, and End Results (SEER) Program—provides a unique opportunity to examine differences in clinical and demographic features between early-onset and late-onset cases that may inform a better understanding of this rare malignancy, particularly for young patients.

MATERIALS AND METHODS

Data Sources and Study Population

Patients were identified using the NIH/NCI's SEER program that collects data from 18 population-based cancer registries that cover approximately 28% of the United States population.[5,6] A case listing session was run on the SEER 18 incidence dataset in SEER*Stat to collect demographic and clinicopathologic characteristics on appendiceal cancer cases. A total of 8,930 patients age 20 years and older were diagnosed with a pathologically-confirmed appendiceal tumor (C18.1) from years 2007 to 2016. The analysis was restricted to cases diagnosed between 2007 and 2016 as 2007 is the first year for which individual-level insurance status data were available in SEER. Histological subtypes other than adenocarcinoma, carcinoid and signet ring cell carcinoma were not included in this analysis (n=79 cases excluded). Our final cohort was comprised of 8,851 patients age 20 years and older at first appendiceal cancer diagnosis. This study was exempt from IRB approval as SEER datasets are publicly available.

Clinical, Pathologic and Demographic Characteristics

Demographic variables examined included: patient sex, age at diagnosis, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic/Spanish/Latino, Asian or Pacific Islander, American Indian or Alaska Native), insurance status (insured, any Medicaid, uninsured), marital status (married, single/unmarried, divorced/separated, widowed) and US region. US region was grouped by SEER registry, where metropolitan Detroit and Iowa were categorized as the Midwest, Connecticut and New Jersey as the Northeast, Greater Georgia, Rural Georgia, Louisiana and Kentucky as the South; and Alaska Natives, Utah, Seattle (Puget Sound), Hawaii, New Mexico, and California (including San Jose-Monterey, San Francisco-Oakland, and Los Angeles) as the West.

Clinical and pathological variables examined included: histological subtype, American Joint Commission on Cancer (AJCC) clinical stage, tumor grade, receipt of surgery, and history of previous cancer. Appendiceal carcinomas were classified into mucinous (ICD-O-3 Histology: 8470/8480/8481) and non-mucinous (ICD-O-3 Histology: 8010/8020/8140/8144/8210/8211/8213/8220/8255/8260/8261/8262/8263/8323/8440/8460/8560/8576) adenocarcinoma, goblet cell carcinoid (ICD-O-3 Histology: 8013/8243/8244/8245/8246/8574), other carcinoid (ICD-O-3 Histology: 8240/8241/8249), and signet ring cell carcinoma (ICD-O-3 Histology: 8490) histological subtypes.

Statistical Analysis

To assess clinicopathologic and demographic patterns between patients diagnosed with early-onset appendiceal cancer (age<50 years at diagnosis) and late-onset appendiceal cancer (age 50+ years at diagnosis), we compared differences in characteristics by age of disease-onset group (early-onset vs late-onset) and by 5-year age groups (20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90+ years) using chi-square tests and *t*-tests for categorical and continuous variables, respectively. Cochran-Armitage trend tests were used to examine trends in the distribution of clinicopathologic and demographic features by 5-year age groups.

To quantify associations between clinicopathologic and demographic features and age of disease-onset group, multivariable logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs) where the reference outcome category was individuals diagnosed with late-onset appendiceal cancers. Associations between clinicopathologic and demographic characteristics and age of disease-onset group were assessed in models adjusted for: race/ethnicity, sex, AJCC clinical stage,

histological subtype, insurance status, and tumor grade, based on patients having complete co-variate information. Data were analyzed using SAS v9.4 statistical software (SAS Institute; Cary, NC). All tests were two-sided and *P*<0.05 was considered to be statistically significant.

RESULTS

A total of 8,851 individuals age 20 years and older were diagnosed with a first primary appendiceal cancer over the 10-year study period. Clinicopathologic and demographic features of individuals by age of disease-onset group are described in Table 1. Nearly one in every three individuals (30.8%) with appendiceal cancer were diagnosed before age 50 years (early-onset disease). Mean age at cancer diagnosis was 37.5 years (std, 8.8 years) among patients with early-onset appendiceal cancer and 64.9 years (std, 10.2 years) for patients with late-onset disease.

The distribution of patient sex and race/ethnicity by age of appendiceal cancer-onset (5-year groups) is illustrated in Figure 1 (Table S1). Women comprised 54.5% of the population of individuals diagnosed with appendiceal cancer, and the proportion of women was higher among individuals diagnosed in younger age groups (P-trend<0.001) (Table 1, Figure 1A, Table S1). While women consistently accounted for 56-59% of cases age 20-49 years at diagnosis, the proportion of cases diagnosed among women fell to 51-53% of individuals age 60-89 years (Table S1). By race/ethnicity, every one in ten patients with appendiceal cancer was non-Hispanic black (9.6%) or Hispanic (10.7%). The proportion of Hispanic and American Indian or Alaska Native individuals was higher in younger age groups (P-trends<0.001), whereas the proportion of non-Hispanic black individuals did not differ by 5-year age group (P-trend=0.99) (Figure 1B). Compared with individuals age 50-54 years at diagnosis, the

proportion of patients who were Hispanic nearly doubled among 20-24 year-old patients (9.5% vs 17.9% of the population, respectively) (Table S1). In contrast, Asian or Pacific Islanders accounted for 6.1% of late-onset appendiceal cancer patients compared with 4.4% of early-onset cases—with the proportion of cases gradually increasing across 5-year age groups (P<0.001; P-trend<0.001). Other demographic features, including insurance status, marital status, and geographic region also statistically significantly differed by age of appendiceal cancer-onset (P<0.01) (Table 1 and Table S1).

Clinicopathologic features, including histological subtype, tumor stage, and grade, also differed by age of appendiceal cancer diagnosis (Figure 1 and Table S1). Overall, 43.6% of patients were diagnosed with neuroendocrine tumors (carcinoid or goblet cell carcinoid) of the appendix (Table 1), and the proportions of neuroendocrine tumors increased with younger age (P-trends ≤0.01). The highest proportion of carcinoid tumors was observed among individuals age 20-24 years at appendix cancer diagnosis (n=227, 76.7%) (Figure 1C and Table S1). Notably, the proportion of cases with goblet cell carcinoid tumors rose from 15.9% of cases among 20-24 year-old patients, up to 25.8% of 45-49 year-olds, and peaking at 26.2% of cases among 55-59 year-old patients—before dropping down to approximately 15% of cases among individuals age 75 years and older at diagnosis (Table S1). In contrast, epithelial tumors of the appendix (mucinous adenocarcinoma, non-mucinous adenocarcinoma, signet ring cell) yielded increasing trends by age. Mucinous adenocarcinomas comprised 4.1% of tumors among individuals age 20-24 years, rising to 30.6% of cases among 50-54 year olds, up to 36.7% of cases among individuals at 70-74 years at diagnosis (Table S1). Signet ring cell and non-mucinous adenocarcinoma patterns followed similar patterns. As the proportion of cases diagnosed with epithelial tumors of the appendix rose with increasing age, the proportion of patients with stage II-IV tumors also significantly

increased by 5-year groups (all P-trend<0.001) (Figure 1D and Table S1). By tumor stage, 30.4% of patients with early-onset appendiceal cancer were diagnosed with AJCC stage 0-I tumors compared with 17.6% of late-onset cases (P<0.001) (Table 1).

Nearly half of patients with early-onset appendiceal cancer (47.3%) had well-differentiated tumors versus less than one-third of late-onset cases (29.2%; P<0.001; P-trend<0.001) (Table 1, Figure 1E, Table S1). Decreasing trends for well differentiated tumors were observed by 5-year age groups, as the highest proportion of well differentiated tumors were observed among patients aged 20-24 years (67.6%)—which consistently decreased down to 24.1% of cases among 80-84 year olds (Table S1). In parallel, the proportions of poorly differentiated and undifferentiated tumors consistently increased with patient age. History of previous cancer also differed by age of appendiceal cancer-onset, as patients diagnosed with late-onset appendiceal cancer more frequently presented with previous cancer diagnoses compared with early-onset cases (20.5% vs 5.3%, respectively; P<0.001; P-trend<0.001) (Table 1).

To investigate associations between clinicopathologic and demographic features and age of disease-onset among patients diagnosed with appendiceal cancer, we used multinomial logistic regression models (Table 2). Individuals diagnosed with early-onset appendiceal cancer were 20% less likely to be diagnosed with stage II disease (OR=0.80, 95%CI 0.66-0.98, P=0.03), and 18% to 50% less likely to be diagnosed with higher grade tumors (grade II: OR=0.82, 95%CI 0.69-0.97, P=0.02; grade III: OR=0.72, 95%CI 0.57-0.02, P=0.008; grade IV: OR=0.50, 95%CI 0.30-0.82, P=0.006) compared with late-onset cases after adjustment for patient race/ethnicity, AJCC clinical stage, histological subtype, and insurance status. Young patients were 82% more likely to be Hispanic (OR=1.82, 95%CI 1.48-2.25, P<0.001) and four-fold more likely to be

American Indian or Alaska Native (OR=4.02, 95%CI 1.77-9.16, P=0.0009) compared with late-onset cases (Table 2). By histological subtype, early-onset appendiceal cancer cases were more likely to be diagnosed with neuroendocrine tumors of the appendix, including carcinoid and goblet cell carcinoid tumors (goblet cell carcinoid: OR=1.96, 95%CI 1.59-2.41, P<0.0001; carcinoid: OR=3.52, 95%CI 2.80-4.42, P<0.0001) compared to patients with late-onset appendiceal cancer.

Given these distinct histology patterns by age of appendix cancer-onset, we next sought to explore clinical and demographic patterns of early-onset appendiceal cancer by histological subtype classification (epithelial tumors/adenocarcinomas and neuroendocrine tumors) (Table 3). Among patients with epithelial tumors of the appendix, individuals younger than age 50 were two-fold more likely to be Hispanic (OR=1.99, 95%CI 1.53-2.58, P<0.0001) and were 75% more likely to be diagnosed with stage IV disease (OR=1.75, 95%CI 1.26-2.43, P=0.0008) in adjusted models. However, tumor grade was not associated with early-onset disease. Young patients were also 31% less likely to be diagnosed with non-mucinous adenocarcinomas of the appendix compared with late-onset cases (OR=0.69, 95%CI 0.56-0.86, P=0.0008). Similar to patients with epithelial tumors, young patients diagnosed with neuroendocrine tumors of the appendix were also more likely to be Hispanic (OR=1.58, 95%CI 1.11-2.24, P=0.01). Unique to cases with neuroendocrine tumors, however, young patients were less likely to be diagnosed with advanced stage disease (stage II: OR=0.47, 95%CI 0.35-0.63, P<0.0001; stage IV: OR=0.41, 95%CI 0.24-0.70, P=0.001), and were 45% to 61% less likely to be diagnosed with high-grade tumors (grade III: OR=0.55, 95%CI 0.35-0.86, P=0.008; grade IV: OR=0.39, 95%CI 0.15-1.00, P=0.049). Young patients were also 24% less likely to be diagnosed with goblet cell carcinoid tumors compared

with patients age 50 years and older at appendix cancer diagnosis (OR=0.76, 95%CI 0.59-0.97, P=0.03) (Table 3).

DISCUSSION

Our study of 8,851 individuals diagnosed with appendiceal cancer age 20 years and older in the United States between 2007 and 2016 identified distinct clinicopathologic and demographic patterns among patients younger than age 50 years at diagnosis compared with cases diagnosed at age 50 years and older. We observed individuals with early-onset appendiceal cancer were more likely to be diagnosed with neuroendocrine tumors of the appendix compared with late-onset cases. Early-onset appendiceal cancer cases were also more likely to be Hispanic, American Indian or Alaska Native. Moreover, among patients diagnosed with neuroendocrine tumors, young individuals were less likely to be diagnosed with high grade tumors or with advanced stage disease. These findings are novel as this study is the first to compare clinicopathologic and demographic features among individuals diagnosed with appendiceal cancer by age of disease-onset and to characterize distinct clinical features of early-onset appendiceal cancer.

The burden of malignant appendiceal tumors continues to rise, particularly among young patients, with underlying etiologies unknown. Recently, the most pronounced increase in disease incidence was reported for neuroendocrine tumors among patients younger than age 50 years.[4] Strikingly, here we observed that individuals diagnosed with early-onset disease were two-fold to four-fold more likely to be diagnosed with neuroendocrine tumors of the appendix compared with cases age 50 years and older at diagnosis. Previous reports suggest that intestinal carcinoid tumors—

including carcinoid tumors of the appendix[8]—have a higher incidence among patients who are obese (BMI: 30+ kg/m^2). Work by Lu and colleagues also noted that obesity was also a predictor of cancer diagnosis among individuals undergoing appendectomy.[9] Indeed, over the last several decades obesity rates have continued to rise worldwide[10] such that nearly half of cancers diagnosed among individuals younger than age 65 are obesity-related.[11] Moreover, among adolescents and young adults (AYAs; age 18-39 years) diagnosed with cancer, reports from contemporary single institution studies have noted that nearly two in every three AYAs are overweight/obese at cancer diagnosis.[12] Body fatness predominantly results from physical inactivity and chronic excessive caloric intake, although metabolic changes and hereditary factors are also contributors to excess adiposity.[13-15] Consequently, although the underlying factors responsible for these distinct patterns of appendiceal cancer among young patients are currently unknown, differences in adiposity and other health behaviors are likely contributors to the observed variation in disease patterns. Further epidemiologic study is warranted to identify risk factors of appendiceal cancer among all ages, as well as early-onset appendiceal cancer-specific risk factors.

Overall incidence rates of appendiceal cancer are comparable across all ages among blacks and whites.[16,17] Aligned with these findings, we observed no differences in the likelihood of early-onset appendiceal cancer diagnosis between whites and blacks. However, compared to late-onset appendix cancer cases, we did find that young patients with appendix tumors were more likely to be Hispanic as well American Indian or Alaska Natives. As racial/ethnic demographics continue to shift in the United States,[18] it is important to note these findings are aligned with previous reports demonstrating that Hispanic individuals are more likely to be diagnosed with gastrointestinal cancers, including cancers of the colorectum and stomach, at younger ages compared with other

racial/ethnic groups.[19-21] Moreover, across all racial/ethnic groups, American Indian/Alaska Natives have one of the highest cigarette smoking prevalence rates.[22,23] Together with potential differences in environmental exposures, including microbiome composition, and gene-environment interactions across racial/ethnic groups, these results support further study of appendiceal cancer by race/ethnicity in order to investigate how these individual-level factors may contribute to marked disparities in disease burden.

Use of high-quality data from the population-based SEER registry is a strength of this study as it allowed for a large number of pathologically-verified appendiceal cancer cases to be identified. Limitations are acknowledged in the availability of individual-level data regarding characteristics (e.g. incidental finding of appendiceal cancer for appendicitis, co-morbidities, environmental exposures, body fatness) that may be associated with age-related differences in appendiceal cancer. Given that race/ethnicity in SEER is based on self-identification, it is subject to misclassification. Moreover, the World Health Organization Classification of Tumors of the Digestive System summary[24] classifies behaviors of low-grade appendiceal mucinous neoplasms (LAMN) as non-invasive or uncertain (as to whether benign or malignant). To date, completeness of data on LAMNs varies significantly in SEER. SEER also lacks information about pseudomyxoma peritonei and the clinical context in which a tumor was discovered (e.g. incidental diagnosis). As a result, it is not possible to include these malignancies in this analysis or to assess whether these may be contributing to differences in appendiceal cancer histology by age.

Our findings raise the possibility that the observed clinical and demographic patterns by age of disease-onset may be attributed to differences in tumor biology

between early-onset and late-onset appendiceal cancer cases. However, this study does not provide complete data on molecular characteristics of appendiceal cancer cases. Nonetheless, our recent study investigating molecular features of appendiceal tumors by age of disease-onset supports these observations, as we discovered that appendiceal tumors in young patients harbor a distinct spectrum of somatic cancer gene mutations compared with late-onset cases.[25] Using clinical-grade targeted sequencing data, young patients harbored unique mutation patterns in *PIK3CA, GNAS, SMAD3* and *TSC2* compared with late-onset cases—providing initial evidence to suggest that early-onset appendix cancer harbors a distinct disease biology. Furthermore, as recent studies have shed light on distinct molecular profiles between cancers of the appendix and colorectum,[26-29] additional research is warranted to understand appendiceal cancer carcinogenesis and develop appendiceal cancer-specific prevention strategies and clinical management guidelines.

Together, this population-based cohort study represents the first reporting of clinical and demographic patterns of appendiceal cancer cases by age of disease-onset in the United States. Approximately one in every three patients diagnosed with appendiceal cancer was diagnosed before age 50 years. Appendiceal cancer in young patients is classified by distinct clinicopathologic and demographic features, including sex, race/ethnicity, and histological subtypes. As such, further study of lifestyle-related factors, environmental exposures and familial history of disease are warranted to better understand the unique burden of appendix cancer among young patients. Early-onset appendiceal cancer determinants can inform discovery of risk factors and molecular biomarkers of appendix cancer in young patients, with implications for disease prevention, detection and treatment.

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TABLES

Table 1. Summary of demographic and clinical characteristics by age of diagnosis among individuals with appendiceal cancer: Surveillance, Epidemiology and End Results (SEER) 18, 2007-2016.

			Age of Appendiceal Cancer Diagnosis				*P**	
	Total		Early-Onset (<50 years)		Late-Onset (50+ years)		Value	Trend**
Characteristic	N	%	N	%	N	%		
Total	8851		2729	30.8	6122	69.2		
Age at Diagnosis							--	
20-29 Years	621	7.0	621	22.8				--
30-39 Years	771	8.7	771	28.3				--
40-49 Years	1337	15.1	1337	49.0				--
50-59 Years	2191	24.8			2191	35.8		--
60-69 Years	2044	23.1			2044	33.4		--
70-79 Years	1263	14.3			1263	20.6		--
80-89 Years	545	6.2			545	8.9		--
90+ Years	79	0.9			79	1.3		--
Mean, Years (SD)	56.4	(16.0)	37.5	(8.8)	64.9	(10.2)	--	
Race/Ethnicity							<0.001	
Non-Hispanic White	6444	72.8	1872	68.6	4572	74.7		<0.001
Non-Hispanic Black	847	9.6	249	9.1	598	9.8		0.99
Hispanic/Spanish/Latino	951	10.7	422	15.5	529	8.6		<0.001
Asian or Pacific Islander	490	5.5	119	4.4	371	6.1		<0.001
American Indian or Alaska Native	51	0.6	27	1.0	24	0.4		<0.001
Unknown	68	0.8	40	1.5	28	0.5		
Sex							<0.001	<0.001
Female	4824	54.5	1580	57.9	3244	53.0		
Male	4027	45.5	1149	42.1	2878	47.0		
Insurance Status							<0.001	

Insured	7273	82.2	2036	74.6	5237	85.5		<0.001
Any Medicaid	939	10.6	396	14.5	543	8.9		<0.001
Uninsured	352	4.0	175	6.4	177	2.9		<0.001
Unknown	287	3.2	122	4.5	165	2.7		
Marital Status							<0.001	
Married	5008	56.6	1329	48.7	3679	60.1		<0.001
Single/Unmarried	1855	21.0	998	36.6	857	14.0		<0.001
Divorced/Separated	856	9.7	207	7.6	649	10.6		0.03
Widowed	636	7.2	9	0.3	627	10.2		<0.001
Unknown	496	5.6	186	6.8	310	5.1		
US Region							0.01	
Midwest	862	9.7	242	8.9	620	10.1		0.02
Northeast	1639	18.5	508	18.6	1131	18.5		0.67
South	2103	23.8	703	25.8	1400	22.9		0.001
West	4247	48.0	1276	46.8	2971	48.5		0.57
AJCC Stage							<0.001	
0-I	1906	21.5	830	30.4	1076	17.6		<0.001
II	2093	23.6	475	17.4	1618	26.4		<0.001
III	742	8.4	184	6.7	558	9.1		<0.001
IV	1519	17.2	353	12.9	1166	19.0		<0.001
Unknown	2591	29.3	887	32.5	1704	27.8		
Histological Subtype							<0.001	
Mucinous Adenocarcinoma	2589	29.3	604	22.1	1985	32.4		<0.001
Non-Mucinous Adenocarcinoma	1875	21.2	314	11.5	1561	25.5		<0.001
Signet Ring Cell	528	6.0	125	4.6	403	6.6		<0.001
Carcinoid	1950	22.0	1097	40.2	853	13.9		<0.001
Goblet Cell Carcinoid	1909	21.6	589	21.6	1320	21.6		0.01
Grade							<0.001	
I (Well Differentiated)	3077	34.8	1290	47.3	1787	29.2		<0.001
II (Moderately Differentiated)	2265	25.6	533	19.5	1732	28.3		<0.001
III (Poorly Differentiated)	1114	12.6	229	8.4	885	14.5		<0.001
IV (Undifferentiated)	171	1.9	29	1.1	142	2.3		<0.001
Unknown	2224	25.1	648	23.7	1576	25.7		
Previous Cancer							<0.001	<0.001
None	7453	84.2	2584	94.7	4869	79.5		
Yes	1398	15.8	145	5.3	1253	20.5		

*_P_-value calculations do not include unknown values. **_P_-trend calculated using 5-year age groups (20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90+years).

Abbreviations: std, standard deviation; AJCC, American Joint Committee on Cancer.

Table 2. Multivariable logistic regression for demographic and clinical features by age of appendiceal cancer diagnosis: SEER18, 2007-2016.

	Early-Onset vs Late-Onset Appendiceal Cancer Cases*		
Observational Study Estimate	OR	(95% CI)	*P*
Race/Ethnicity			
Non-Hispanic White	Ref		
Non-Hispanic Black	1.03	(0.82-1.29)	0.83
Hispanic/Spanish/Latino	1.82	(1.48-2.25)	<0.0001
Asian or Pacific Islander	1.15	(0.86-1.55)	0.35
American Indian or Alaska Native	4.02	(1.77-9.16)	0.0009
Sex			
Male	Ref		
Female	1.07	(0.93-1.22)	0.36
Insurance Status			
Insured	Ref		
Any Medicaid	1.45	(1.17-1.78)	0.0005
Uninsured	2.56	(1.87-3.50)	<0.0001
AJCC Stage			
0-I	Ref		
II	0.80	(0.66-0.98)	0.03
III	0.87	(0.69-1.11)	0.27
IV	0.95	(0.75-1.19)	0.63
Grade			
I (Well Differentiated)	Ref		
II (Moderately Differentiated)	0.82	(0.69-0.97)	0.02
III (Poorly Differentiated)	0.72	(0.57-0.92)	0.008
IV (Undifferentiated)	0.50	(0.30-0.82)	0.006
Histological Subtype			
Mucinous Adenocarcinoma	Ref		
Non-Mucinous Adenocarcinoma	0.67	(0.54-0.82)	0.0002
Signet Ring Cell	1.24	(0.87-1.76)	0.23
Carcinoid	3.52	(2.80-4.42)	<0.0001
Goblet Cell Carcinoid	1.96	(1.59-2.41)	<0.0001

*Adjusted for patient race/ethnicity, sex, AJCC clinical stage, histological subtype, insurance status, and tumor grade, as appropriate.
OR, odds ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.

Table 3. Multivariable logistic regression for demographic and clinical features by age of appendiceal cancer diagnosis and histological subtype classification: SEER18, 2007-2016.

	Early-Onset vs Late-Onset Appendiceal Cancer Cases*					
	Epithelial Tumors/ Adenocarcinoma			Neuroendocrine Tumors		
Observational Study Estimate	OR	(95% CI)	*P*	OR	(95% CI)	*P*
Race/Ethnicity						
Non-Hispanic White	Ref			Ref		
Non-Hispanic Black	1.16	(0.87-1.55)	0.31	0.87	(0.61-1.25)	0.45
Hispanic/Spanish/Latino	1.99	(1.53-2.58)	<0.0001	1.58	(1.11-2.24)	0.01
Asian or Pacific Islander	1.13	(0.79-1.61)	0.52	1.42	(0.80-2.52)	0.23
American Indian or Alaska Native	3.96	(1.52-10.31)	0.005	3.51	(0.71-17.31)	0.12
Sex						
Male	Ref			Ref		
Female	0.98	(0.82-1.18)	0.85	1.15	(0.93-1.42)	0.19
Insurance Status						
Insured	Ref			Ref		
Any Medicaid	1.31	(0.97-1.76)	0.08	1.66	(1.22-2.25)	0.001
Uninsured	2.25	(1.49-3.39)	0.0001	3.31	(1.96-5.60)	<0.0001
AJCC Stage						
0-I	Ref			Ref		
II	1.53	(1.12-2.10)	0.008	0.47	(0.35-0.63)	<0.0001
III	1.39	(0.95-2.03)	0.10	0.77	(0.55-1.07)	0.12
IV	1.75	(1.26-2.43)	0.0008	0.41	(0.24-0.70)	0.001
Grade						
I (Well Differentiated)	Ref			Ref		
II (Moderately Differentiated)	0.85	(0.68-1.05)	0.14	0.88	(0.67-1.16)	0.37
III (Poorly Differentiated)	0.93	(0.69-1.25)	0.62	0.55	(0.35-0.86)	0.008
IV (Undifferentiated)	0.64	(0.36-1.14)	0.13	0.39	(0.15-1.00)	0.049
Histological Subtype						
Mucinous Adenocarcinoma	Ref			--		
Non-Mucinous Adenocarcinoma	0.69	(0.56-0.86)	0.0008	--		
Signet Ring Cell	1.02	(0.71-1.47)	0.92	--		
Carcinoid	--			Ref		

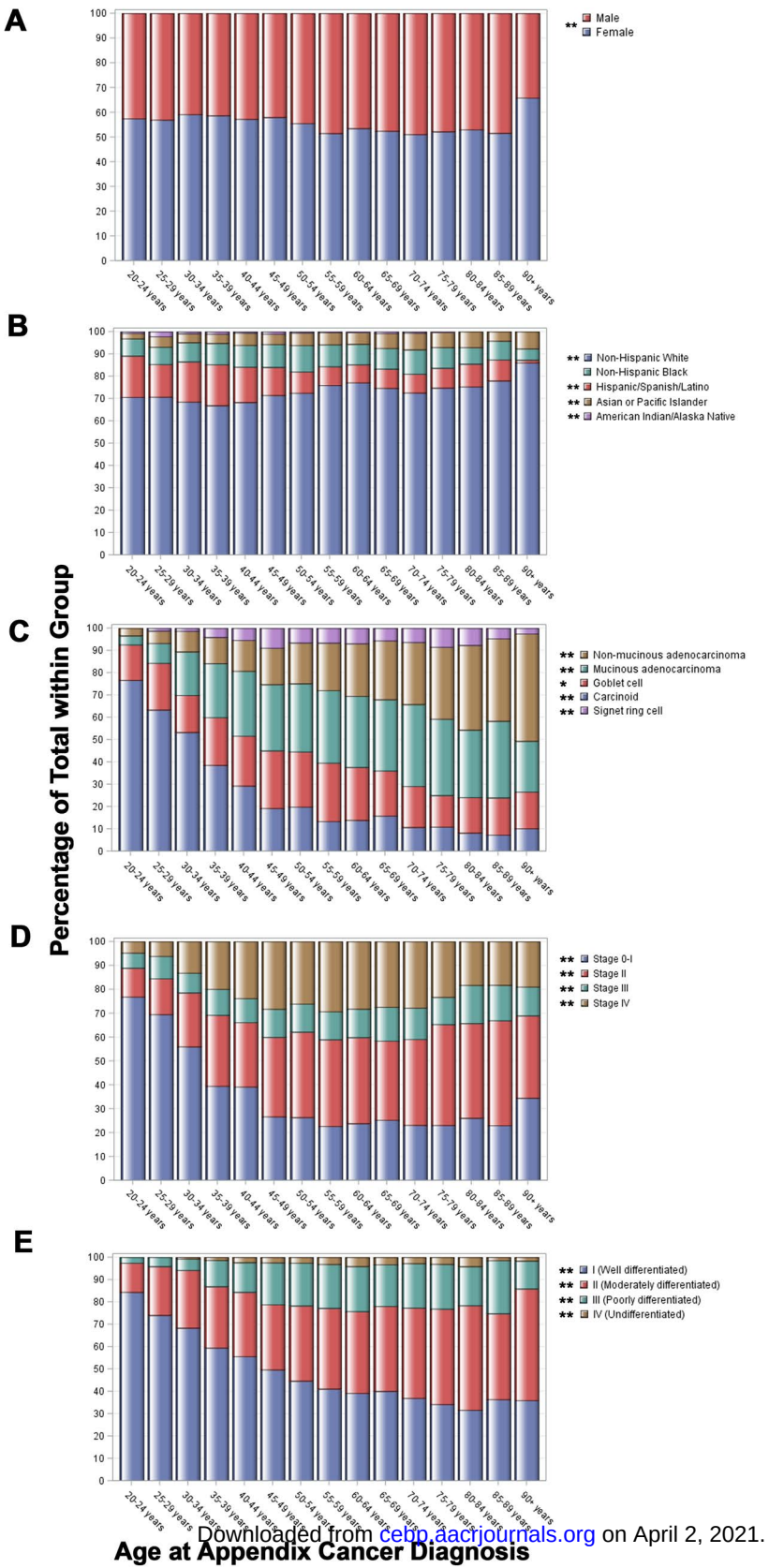
Goblet Cell Carcinoid	--	0.76	(0.59-0.97)	0.03

*Adjusted for patient race/ethnicity, sex, AJCC clinical stage, histological subtype, insurance status, and tumor grade, as appropriate.
OR, odds ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.

FIGURE LEGENDS

Figure 1. Clinicopathologic and demographic patterns among patients with appendiceal cancer by age of disease-onset. Proportions of patients, grouped by age at diagnosis (5-year groups) for patient (A) sex and (B) race/ethnicity, (C) histological subtype, (D) American Joint Committee on Cancer (AJCC) clinical stage, and (E) tumor grade. Asterisks indicate: **P*-trend≤0.01; **P-trend<0.001.

Figure 1.



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