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Descriptive epidemiology of esophageal carcinoma in the Ohio Cancer Registry

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Abstract

Background—Etiologic factors and demographics in esophageal cancer have not been fully characterized at a population-level. This study aimed to compare incidence rates of esophageal adenocarcinoma (EAC) and squamous cell carcinoma (ESCC) by race. Other aims were to evaluate the impact of race, age, gender, and histology on presenting stage; and to describe tobacco use history in EAC as documented in a cancer registry.

Methods—Invasive esophageal cancer cases reported to Ohio's cancer registry 1998–2002 were identified. Incident staged EAC and ESCC cases were analyzed for factors associated with metastatic disease.

Results—930 ESCC and 1,801 EAC cases were identified. African-Americans had higher ESCC incidence than whites (5.0 versus 1.3 cases/100,000/year). However, whites had higher EAC incidence (3.3 versus 0.8 cases/100,000/year). 77% of EAC cases with available tobacco history were reported in tobacco users. In univariate analyses, race, age, gender, and histology differed significantly by stage. 31% of patients ≥ aged 65 presented with distant stage, versus 26% of those < 65 ($p<0.001$). 32% of African-Americans had distant stage, versus 34% of whites ($p=0.048$). In logistic regression modeling, male gender [OR 1.76, CI(1.15, 2.67)] and age < 75 [OR 1.95, CI(1.21, 3.15)], but not race, predicted distant stage ESCC. Distant stage EAC was associated with age < 56 [OR 1.82, CI(1.39, 2.38)] but not significantly associated with African-American race ($p=0.062$) for the sample size available.

Conclusions—Whites had higher EAC rates, and African-Americans had higher ESCC rates. African-Americans were not more likely than whites to present with metastatic ESCC.1

Keywords

esophagus; adenocarcinoma; squamous cell carcinoma; esophageal neoplasm; neoplasm staging; neoplasm metastasis; incidence; tobacco; smoking; race

[1]Cancer incidence data used in this study were obtained from the Ohio Cancer Incidence Surveillance System, Ohio Department of Health (ODH), a registry participating in the National Program of Cancer Registries of the Centers for Disease Control and Prevention (CDC). Use of these data does not imply ODH or CDC either agrees or disagrees with any presentations, analyses, interpretations or conclusions. Information about the OCISS can be obtained at: http://www.odh.ohio.gov/odhprograms/svio/ci_surv/ci_surv1.aspx.

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CONFLICT OF INTEREST: none declared

Introduction

The incidence of esophageal cancer has risen rapidly over the past several decades, with a sharp increase in the incidence of esophageal adenocarcinoma (EAC) over that of esophageal squamous cell carcinoma (ESCC) [1]. Risk factors for EAC include obesity, white race, male gender, and Barrett's esophagus [2,3]. While tobacco use is a strong risk factor for ESCC, its role in the development of EAC is less clear. Although some studies have suggested that tobacco exposure is linked to EAC [4,5], others have found no association [6,7].

While relatively uncommon, esophageal cancer is usually fatal, with a relative 5-year survival rate of only 16% in the United States [8]. Survival is worse in African-Americans, who tend to present at a later stage. However, within a given stage, 5-year survival is lower in African-Americans than in whites [8].

Given the rising incidence of EAC and prior evidence for demographic factors in esophageal cancer, the primary goal of this study was to compare age-adjusted incidence rates of adenocarcinoma and squamous cell carcinoma by race and gender. Other aims were to investigate the impact of race, age, gender, and histology on stage at presentation; and to describe tobacco use history as reported for cases of esophageal adenocarcinoma. We used data from the state cancer registry of Ohio to address these aims.

Materials and Methods

The Ohio Cancer Incidence Surveillance System (OCISS) state cancer registry of the Ohio Department of Health was established in 1991. By state law, all primary malignancies except for non-melanoma skin cancers and carcinoma in situ of the cervix diagnosed in Ohio residents on or after January 1, 1992, are required to be reported to OCISS. Data regarding cases of esophageal cancer diagnosed 1998–2002 were requested from the OCISS. The North American Association of Central Cancer Registries (NAACCR) awarded the OCISS Silver Certification for the high quality of its incidence data for all years of this study period. NAACCR evaluates cancer registry data annually based on data quality index indicators including case ascertainment completeness, data timeliness, and degree of missing demographic data and assigns certification status of "Gold," "Silver," or "Other with Feedback" accordingly. The following data elements were obtained from the OCISS: age at diagnosis, gender, race, histology, history of previous malignancy, stage, date of diagnosis, tobacco use, and anatomical site of the cancer. Race was documented in the registry as assigned by provider report. A data user's agreement was submitted to the OCISS, and data was maintained on a password-protected computer. Because of the lack of patient identifiers and the inability to obtain informed consent, the study was deemed exempt from formal Institutional Review Board (IRB) approval at University Hospitals Case Medical Center.

Cases of invasive esophageal cancer diagnosed 1998–2002 were included, the most recent years for which data with reliable race information was available. Cases of lymphoma, carcinoma in situ, or cases without tissue confirmation were excluded. Stage at diagnosis was reported as localized, regional, or distant. Although the OCISS is not part of the Surveillance, Epidemiology, and End Results (SEER) program, the SEER summary stage variable was used because not all the data elements employed in the AJCC algorithm have been validated. Therefore, stage was localized if the tumor was confined to its site of origin and regional if the tumor had spread to adjacent organs by direct extension and/or had spread to regional lymph nodes. Classification of histologic variants into EAC and ESCC subtypes was made based upon consultation with Dr. Joseph Willis, gastrointestinal pathologist at University Hospitals Case Medical Center. The following International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes were classified as esophageal adenocarcinoma: 8140, 8143, 8144,

8211, 8255, 8260, 8262, 8323, 8480, 8481, and 8490. The following ICD-O-3 codes were classified as esophageal squamous cell carcinoma: 8032, 8051, 8070, 8071, 8072, 8073, 8074, 8076, 8083, and 8094. ICD-O-3 codes for less differentiated histologies or uncommon histologies which could be inadvertently misclassified were categorized as other: 8000, 8010, 8012, 8020, 8041, 8046, 8050, 8075, 8145, 8240, 8246, 8560, 8720, 8890, and 8935.

Incidence Rates

The total number of cases of histologically confirmed invasive esophageal cancers was determined, as well as the total number of invasive EAC or ESCC cases further stratified by race and gender. Given the paucity of cases diagnosed in younger patients, cases were categorized into 4 age groups: < 55 years old, 55–64 years old, 65–74 years old, and > 74 years old. Age-specific rates were calculated for these age groups and incidence rates adjusted for age with direct standardization using U.S. Census 2000 data regarding the Ohio population. 95% confidence intervals (95% CI) were obtained using a 1-sample proportions test without continuity correction.

Tobacco Use

Tobacco use history was reported to the OCISS by providers as any of the following categories: no history of tobacco use; current cigarette use; current pipe or cigar use; current snuff, chewing tobacco, or smokeless tobacco use; current use of a combination of the previously listed categories of tobacco; and previous use of tobacco. Current tobacco users were defined as those using tobacco of any form at the time of diagnosis or who had quit within the past year. Former tobacco users were patients who had quit over a year prior to cancer diagnosis. Because the vast majority of current tobacco users were cigarette smokers, current tobacco use in the form of cigarettes, cigars, pipe smoking, snuff, chew, or smokeless tobacco, or any combination of these forms was grouped together.

Analysis of Stage at Presentation

Cases with history of previous malignancy were excluded from analysis of stage at presentation because metastases from prior cancers might inadvertently affect stage. Unstaged cases and cases with missing race information were excluded. Due to the small number of cases with race reported as “Asian” or “Other,” analysis was limited to major race groups (African-American or white). Cases were grouped by stage (localized, regional, or distant) and further stratified by race, histology, age, and gender.

Statistical Methods

Pearson’s chi-square test and Fisher’s exact test were used to compare proportions. Analysis of variance was used to compare continuous variables among groups. Analysis of stage at presentation was conducted separately for ESCC and EAC. For each histology, race, gender, and age were evaluated in univariate analyses with contingency tables and univariate logistic regression models. Variables that were found on univariate analysis to be associated with significant (p values < 0.20) differences in stage at presentation were entered into a multivariate logistic regression model. Variables that were no longer statistically significant (p values ≥ 0.20) in the multivariate model based on the likelihood ratio test were removed in a stepwise fashion from the model. Age at diagnosis was then examined for linearity in the logit by categorizing age by quartiles and refitting the model with categorized age variables. Based on a nonlinear increase noted in the estimated coefficients for multivariate logistic regression models for both histologies between 2 groups of age categories, age was dichotomized as appropriate and the models refit with the dichotomized age variables. Outside of the context of logistic regression modeling, p values of 0.05 or smaller were considered to be significant. Data were analyzed with R for Windows, version 2.1.1 (R Foundation for Statistical

Computing, Vienna, Austria). SAS software, version 9.1 for Windows (SAS Institute Inc., Cary, North Carolina) was used to perform logistic regression using the SAS PROC LOGISTIC statement.

Results

3,262 cases of esophageal cancer were reported to the OCISS between 1998 and 2002. After excluding lymphoma (n=4), carcinoma in situ (n=75), and cases lacking tissue confirmation (n=208), there were 2,975 cases. This included 1,801 cases of invasive adenocarcinoma, of which 93.7% (n=1,688) occurred in whites and 2.4% (n=43) in African-Americans; and 930 cases of invasive squamous cell carcinoma, of which 69.7% (n=648) occurred in whites and 27.6% (n=257) in African-Americans. An additional 244 esophageal cancer cases with other histologies were reported. The mean age at diagnosis was 67.4 (standard deviation, 11.9). Overall, 76.1% of cases occurred in males.

Incidence Rates

The overall age-adjusted incidence rate including all cases of tissue-confirmed invasive esophageal cancer was 5.3 cases per 100,000 per year (95% CI 4.8, 5.7). The incidence rate of EAC was 3.2 cases per 100,000 per year (95% CI 2.9, 3.5), twice the rate of ESCC at 1.6 cases per 100,000 per year (95% CI 1.4, 1.9). Age-adjusted incidence rates by histologic subtype, gender, and race are shown in Table I. ESCC incidence was higher among African-Americans than whites. However, EAC incidence was higher among whites than African-Americans, with the highest incidence rate in white males. Stratum-specific incidence rates of invasive EAC in African-American females were not calculated due to small numbers potentially causing unstable rates.

Tobacco Use

Information regarding tobacco use was available for 70.8% (n=2,109) of cases including all histologies. Of these, 48.1% (n=1,015) were current tobacco users, 32.2% (n=679) were former users, and 19.7% (n=415) were never users. Among 1,299 EAC cases with available tobacco history, 43.6% occurred in current tobacco users, 33.7% occurred in prior users, and 22.7% occurred in never users. Thus 77.3% of EAC cases occurred in past or current tobacco users, similar to the 80.3% rate of tobacco use among all histologies combined.

Among 694 cases of ESCC with tobacco history reported, 56.6% were current users, 28.5% were prior users, and 14.8% were never users. Compared with cases with available tobacco history, cases with missing information for smoking history were similar across age, gender, and major race groups; however, cases of non-white, non-African-American or missing race were more likely to have missing tobacco data. Supposing that tobacco history were biased towards tobacco users, and all EAC cases with missing tobacco history data were assumed to have occurred in never users, tobacco use would still have been associated with 55.7% of EAC cases.

Analysis of Factors Associated with Stage at Presentation

434 cases with history of prior malignancy were excluded to avoid potential misclassification of esophageal cancer stage due to metastases from a previous malignancy. An additional 215 cases with less common histologies (non-EAC or non-ESCC), 545 unstaged cases, and 29 cases for which race was not reported were excluded. Seven cases for which race was reported as “Asian” or “Other” were not included in the analysis. The remaining 1,745 staged cases of EAC and ESCC that occurred among whites or African-Americans were analyzed. 30.2% (n=527) of these cases were localized, compared with 36.2% (n=632) with regional disease and 33.6% (n=586) with distant disease. The mean age in the localized stage group was 67.5

years, compared to 65.5 years in the regional group and 63.9 in the distant group. Mean age differed by stage at presentation ($p < 0.001$ by ANOVA). The patient population was primarily male (78.7%) and white (89.2%). On univariate analysis, race, gender, and histology differed significantly by stage at presentation. These differences in stage at presentation by gender and race persisted within the ESCC subgroup, but not the EAC subgroup. Among whites, males were more likely to present with distant disease than females. Among African-Americans, a higher proportion of males presented with distant disease than females, but this difference was not statistically significant ($p=0.36$).

Because histology differed by stage at presentation, logistic regression modeling to evaluate factors associated with distant stage at presentation was conducted separately for ESCC and EAC. The results of univariate logistic regression modeling for each histology are displayed (Table II). Among ESCC cases, race was not found to be associated with distant stage at presentation. Among EAC cases, male gender was not found to be significantly associated with presentation with distant stage. For both histologies, increasing age was associated with a decreased risk of distant stage at presentation. These results persisted in multivariate logistic regression models for each histology (Tables III and IV). Male gender and age < 75 years (not being in the top age quartile) were both associated with distant stage. Patients in the lowest age quartile (age < 56 years) were 1.82 times more likely to present with distant stage, controlling for African-American race. While African-American race was associated with distant stage EAC at presentation, this association was not statistically significant ($p = 0.062$).

Discussion

In this study, EAC incidence rates were higher among whites than African Americans, especially among males. However, ESCC incidence was higher among African-Americans. This pattern is consistent with a prior study by Kubo and Corley analyzing Surveillance, Epidemiology, and End Results (SEER) data from 1992 to 1998, which used the 1970 U.S. standard population to calculate age-adjusted incidence rates [9]. In that study, the incidence rate of EAC was 4.2 cases/100,000/year among white males and 2.0 cases/100,000/year among white Hispanic males. The rate of ESCC among African-American males was 8.8 cases/100,000/year. While the current study did not distinguish between Hispanic and non-Hispanic ethnicity, the rate of ESCC among African-American males (8.2 cases/100,000/year) was similar to the findings by Kubo and Corley.

Over 75% of EAC cases with available tobacco history occurred in current or prior smokers. According to 2005 Behavioral Risk Factor Surveillance System (BRFSS) data for Ohio, 53% of respondents 55 and older were current or past smokers, suggesting that smoking rates among EAC cases may be higher than in a similar age group in the general Ohio population [10]. However, smoking history was ascertained differently between the BRFSS survey and the OCISS registry, with different definitions of current tobacco use. Also, BRFSS respondents were more likely to be female than OCISS cases, and female respondents in the BRFSS survey were less likely than males to have ever smoked. Therefore, a direct comparison of BRFSS survey data to the current study is difficult. At any rate, although the current study is limited by missing tobacco use information, it provides interesting results in light of evidence from case-control studies linking tobacco use with EAC [4,11,12].

Similar to prior data suggesting that African-Americans typically present with distant disease while whites most commonly present with regional disease [8], in the current study, among EAC cases, African-American race was associated with distant stage in a logistic regression model, although this association was not statistically significant ($p = 0.062$). However, because the vast majority of esophageal carcinomas occurring among African-Americans were ESCC, overall African-Americans were more likely to present with regional than distant disease.

Among whites, the proportion of cases presenting with regional disease and distant disease were more similar. A prior study by Younes et al. evaluating SEER data from 1973 to 1998 found that white race was associated with a decreased risk for Stage IV disease [13]. However, that study did not exclude cases with other histologies besides adenocarcinoma and squamous cell carcinoma and did not analyze factors associated with metastatic disease separately for ESCC and EAC. These prior studies presumably did not exclude cases with a history of prior malignancy, which theoretically could have affected esophageal cancer staging. The current study suggests that racial disparities in presenting stage may be less severe than previously noted, at least among ESCC cases; alternatively, non-whites could have been systematically understaged.

Females in the current study were more likely to present with localized disease and less likely to present with distant disease than males. Upon further stratification by histology, this distinction only persisted among cases of ESCC and not for EAC. Among ESCC cases, both female gender and increasing age were associated with a decreased risk for distant disease in a logistic regression model. Of note, female gender and age ≥ 65 were associated with decreased risk for Stage IV disease in the SEER analysis by Younes et al, but cases of all histologies were evaluated together [13]. That study also found that male gender was associated with poorer survival.

Differences in stage by gender and by age could be due to females and older individuals being more likely to seek medical attention. Although gender differences could partially result from socioeconomic factors associated with better access to healthcare among women, there is no a priori reason to believe that males would have had a lower socioeconomic status than females. On the other hand, older patients may have been less likely to have metastatic disease at presentation due to better health care access, such as insurance coverage under Medicare.

This study had several limitations. First, some gastric cardia adenocarcinomas could have been misclassified as esophageal carcinomas, and vice versa. Without a centralized pathology review process, the accuracy of cancer site and histologic type data may vary by hospital. In addition, because the OCISS registry is limited to Ohio, results may not necessarily be applicable to other states. Although obesity is a risk factor for esophageal adenocarcinoma, body mass index information was not available in this dataset.

The results regarding tobacco use particularly merit further discussion due to their inherent limitations. Because tobacco data from the OCISS registry is based on provider report, documentation may not necessarily be consistent or accurate. Indeed, a prior study comparing Missouri cancer registry data on smoking history to interviews found that the concordance for never- versus ever-smoking status was only 83% [14]. Former tobacco users could have been misclassified as never users. However, misclassification of former tobacco users as never tobacco users would have led to an even higher proportion of tobacco-associated EAC cases than was found in the current study. Tobacco analysis in the current study was also limited by incomplete tobacco history reporting, with 29% of tobacco data missing. This rate of missing information regarding tobacco use was higher than the rates of 10%–15% reported in previous studies of cancer registry data [14,15]. However, in the current study, cases with missing data regarding tobacco use were similar to those with available tobacco history with respect to gender, age, and major race groups. Although cases of non-white, non-African-American or missing race were more likely to have missing tobacco data, these cases made up a small percentage (3.3%) of all the cases. Finally, tobacco analysis was complicated by a lack of detailed information regarding degree of exposure and potential bias of reporting towards smokers.

The current study suggests that patients with EAC may have higher smoking rates than the general population. Like other studies, this study demonstrates higher EAC incidence rates in whites and higher ESCC incidence rates in African-Americans. African-American race was associated with distant stage EAC at presentation, but this difference was not statistically significant ($p = 0.062$). This study also found that male gender and younger age were associated with increased risk for distant stage ESCC. These effects could be related to socioeconomic factors, but further research is needed to explore this possibility.

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Table I

Age-adjusted Incidence Rates of ESCC and EAC by Race and Gender[†]

Race	ESCC [95% CI] (n = 930)	EAC [95% CI] (n = 1,801)
White	1.3 [1.1, 1.5] (n = 648)	3.3 [3.0, 3.7] (n = 1,688)
Male	1.9 [1.6, 2.1] (n = 407)	6.4 [5.9, 6.9] (n = 1,403)
Female	0.8 [0.7, 1.0] (n = 241)	1.0 [0.8, 1.2] (n = 285)
African-American	5.0 [4.6, 5.5] (n = 257)	0.8 [0.7, 1.0] (n = 43)
Male	8.2 [7.7, 8.7] (n = 176)	1.4 [1.2, 1.7] (n = 32)
Female	2.8 [2.5, 3.1] (n = 81)	NA (n = 11)

[†] Cases per 100,000 per year

Incidence rates were adjusted for age with direct standardization using U.S. Census 2000 data regarding the Ohio population. Total number of cases for each histology is greater than the sum of cases in African-Americans and whites due to small numbers of cases in patients of other or unknown race.

NA, not applicable due to small numbers of cases.

95% CI, 95% confidence interval.

ESCC, esophageal squamous cell carcinoma.

EAC, esophageal adenocarcinoma.

Table II

Factors Associated with Distant Stage Disease in Univariate Logistic Regression Models

Factor	Coefficient Estimate	Odds Ratio (95% CI)	p value
ESCC			
Age	−0.017	0.98 (0.97, 1.00)	0.05
African-American Race	−0.034	0.97 (0.64, 1.45)	0.87
Male Gender	0.620	1.86 (1.23, 2.82)	0.003
EAC			
Age	−0.020	0.98 (0.97, 0.99)	0.0001
African-American Race	0.756	2.13 (1.00, 4.52)	0.05
Male Gender	0.251	1.29 (0.92, 1.80)	0.14

ESCC, esophageal squamous cell carcinoma. EAC, esophageal adenocarcinoma.

Table III

Factors Associated with Distant Stage ESCC in a Multivariate Logistic Regression Model

Factor	Coefficient Estimate	Odds Ratio (95% CI)	p value
Age < 75 years†	0.670	1.95 (1.21, 3.15)	<0.01
Male Gender	0.563	1.76 (1.15, 2.67)	<0.01

† Compared with Age ≥ 75 years. ESCC, esophageal squamous cell carcinoma. 95% CI, 95% confidence interval.

Table IV

Factors Associated with Distant Stage EAC in a Multivariate Logistic Regression Model

Factor	Coefficient Estimate	Odds Ratio (95% CI)	p value
Age < 56 years°	0.598	1.82 (1.39, 2.38)	<0.0001
African-American Race	0.724	2.06 (0.97, 4.41)	0.062

° Compared with Age ≥ 56 years. EAC, esophageal adenocarcinoma. 95% CI, 95% confidence interval.