RESEARCH ARTICLE

Racial and Socioeconomic Disparities in Malignant Carcinoid Cancer Cause Specific Survival: Analysis of the Surveillance, Epidemiology and End Results National Cancer Registry

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Abstract

Background: This study hypothesized living in a poor neighborhood decreased the cause specific survival in individuals suffering from carcinoid carcinomas. Surveillance, Epidemiology and End Results (SEER) carcinoid carcinoma data were used to identify potential socioeconomic disparities in outcome. Materials and Methods: This study analyzed socioeconomic, staging and treatment factors available in the SEER database for carcinoid carcinomas. The Kaplan-Meier method was used to analyze time to events and the Kolmogorov-Smirnov test to compare survival curves. The Cox proportional hazard method was employed for multivariate analysis. Areas under the receiver operating characteristic curves (ROCs) were computed to screen the predictors for further analysis. Results: There were 38,546 patients diagnosed from 1973 to 2009 included in this study. The mean follow up time (S.D.) was 68.1 (70.7) months. SEER stage was the most predictive factor of outcome (ROC area of 0.79). 16.4% of patients were un-staged. Race/ethnicity, rural urban residence and county level family income were significant predictors of cause specific survival on multivariate analysis, these accounting for about 5% of the difference in actuarial cause specific survival at 20 years of follow up. Conclusions: This study found poorer cause specific survival of carcinoid carcinomas of individuals living in poor and rural neighborhoods.

Keywords: Carcinoid carcinomas - socioeconomic disparities - SEER registry - cause specific survival

Asian Pac J Cancer Prev, **14 (12)**, 7117-7120

Introduction

The Surveillance Epidemiology and End Results (SEER) cancer registry data have been extensively used to model prognostic models for carcinoid carcinoma. Carcinoid carcinomas are a heterogeneous group of carcinomas most commonly occur in small intestine, rectum and lung, but it could occur in a large variety of anatomic sites (Landry et al., 2008a; 2008b; 2009; Albores-Saavedra et al., 2009; Bilimoria et al., 2009; Bowen et al., 2009; Albores-Saavedra et al., 2010; Eltawil et al., 2010; Modlin et al., 2010; Mullen and Savarese, 2011; Yendamuri et al., 2011; Turaga et al., 2012). SEER data have been a particularly important source for identifying socioeconomic disparities in treatment outcomes in some cancers (Martinez et al., 2012a; 2012b; Saeed et al., 2012). It may be a common assumption that lower socioeconomic status will lead to poorer outcome in cancer treatments in general. However, it is important to ascertain and quantify these impacts of socioeconomic factors so that they could be appropriately considered in future clinical trials. To this end, this study was the first to assess the impact of living in low income neighborhoods on cause specific survival of carcinoid carcinomas using SEER data. The hypothesis here was residing in lower socioeconomic counties and poor rural areas of residence were independent predictors of poorer cause specific survival of carcinoid carcinomas. Receiver operating characteristic curves (ROC) (Cheung, 2012) was used to explore the predictors for this study. Multivariate analysis was performed to assess the independent effects of socioeconomic factors on cause specific survival of carcinoid carcinomas.

Materials and Methods

SEER is a public use database that can be used for analysis with no internal review board approval needed. This study analyzed socioeconomic, staging and treatment factors available in the SEER database for malignant carcinoid carcinomas focusing on socioeconomic disparities. Kaplan-Meier method was used to analyze the time to event data. Kolmogorov-Smirnov test was used to compare survival curves. Cox proportional hazard method was used for multivariate analysis. The area under the receiver operating characteristic curve (ROC) was computed. ROC curves were used to mine SEER data and construct accurate and efficient prediction models (Cheung et al., 2001a, b; Cheung, 2012). The data were obtained from SEER 18 database. SEER*Stat (http://seer.

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cancer.gov/seerstat/) was used for listing the cases. SEER 'ICD-O-3 Hist/behav, malignant'=' 8240/3: Carcinoid tumor, malignant' was used in this analysis. 'SEER cause-specific death classification' was used in this study. All statistics and programming were performed in Matlab (www.mathworks.com). For univariate and multivariate analysis the following coding was used: SEER stage (0=local/regional, 1=distant/unavailable stage); race (0=not African American, 1=African American); rural-urban status of county of residence (0=urban, 1 =rural); county level % college graduate (0=more than 35%, 1= less/equal 35%), the percentage was obtained by dividing SEER variable '% At least bachelors degree 2000' by 100; county level family income (0= higher/equal $50000/year, 1 = lower than $50000/year), the income was obtained from multiplying SEER variable 'Median family income (in tens) 2000' by 10.

Results

There were 38,546 patients included in this study (Figure 1). The follow up (S.D.) was 68.1 (70.7) months. 55% of the patients were female. The mean (S.D.) age was 60.5 (14.7) years. Less than 1% of patients were younger than 20 years old. Small intestine, rectum and lung malignant carcinoid carcinomas constituted about 65% of the carcinoid cancer cases. There was no statistically significant difference in female to male risk in cause specific death. Poorly differentiated and anaplastic carcinoid cancers had about 45% risk of dying from the disease. 86.9% of the tumors were not graded. SEER stage model (localized, regional, distant, un-staged/others) was the most predictive highly predictive model (ROC area or 0.79). Regional carcinoid carcinoma was an aggressive disease, there was a 13.7% absolute risk of carcinoid carcinoma death despite treatments even for early stage

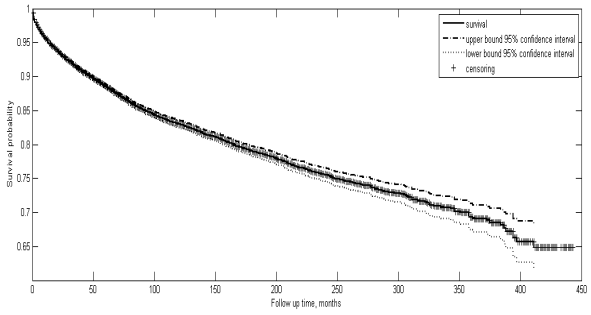

Figure 1. A Kaplan Meier Cause Specific Survival Plot of SEER Carcinoid Cancer Patients

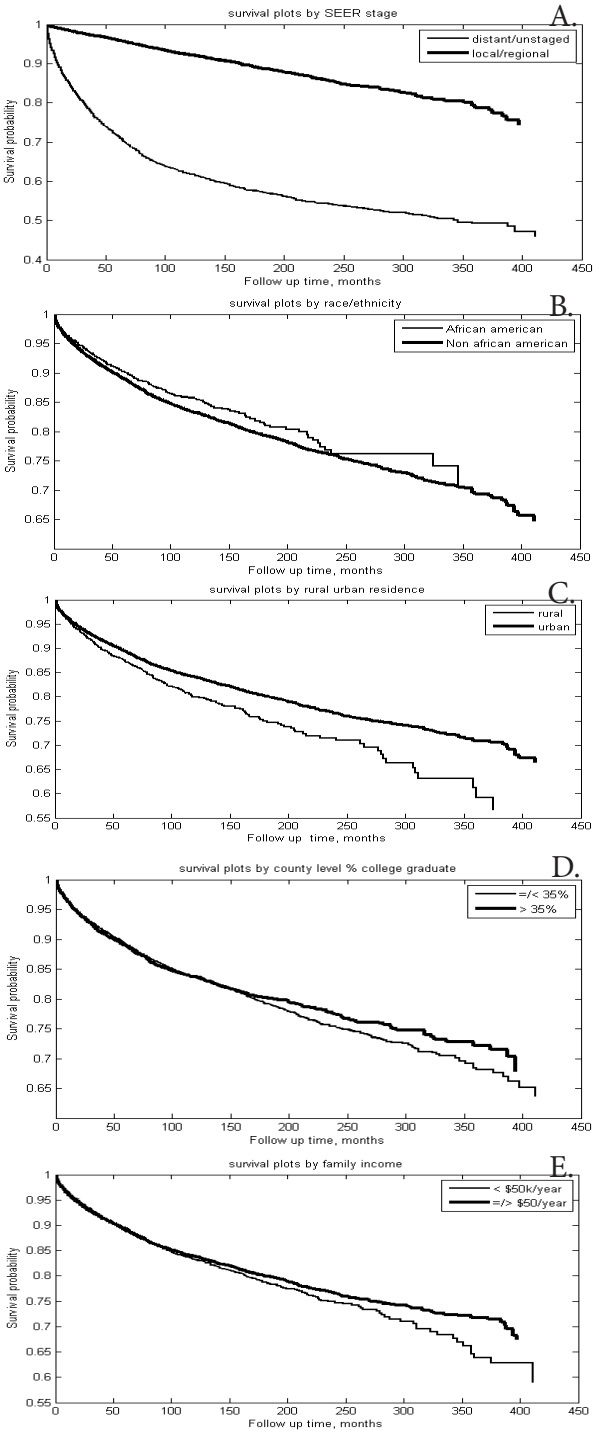

Figure 2. Kolgomorov-Smirnov's Tests of Predictors for Carcinoid Specific Death. A) SEER stage; B) race; C) rural urban residence; D) county level % college graduate; and E) county level family income

Table 1. Univariate Kolmogorov-Smirnov 2-Sample Tests and Multivariate Cox proportional Hazard Regression of Cause Specific Survival of Carcinoid Cancers. The Result h of Kolmogorov-Smirnov Test Statistics k was 1 if the Test Rejected the null Hypothesis at the 5% Significance level; 0 otherwise. S.e. are the Standard Errors of Cox Proportional Hazards Coefficients Beta. Test Probability p<0.05 was Statistically Significant

	Kolmogorov-Smirnov tests		Cox proportional regression			
	h	p	k	beta	s.e.	p
SEER stage (0=local/regional, 1=distant/unstaged)	1.000	8.94E-74	0.839	1.817	0.032	0.000
Race (0=not African American, 1=African American)	1.000	1.30E-04	0.178	-0.098	0.046	0.033
Rural-urban status of county of residence (0=urban, 1 =rural)	0.000	1.96E-01	0.109	0.116	0.047	0.015
County level %college graduate (0=more than 35%, 1= less/equal 35%)	1.000	3.80E-03	0.166	-0.016	0.040	0.681
County level family income (0 = higher/equal $50k/year, 1= lower than $50k/year)	0.000	8.91E-01	0.053	0.107	0.036	0.003

cancer. Un-staged patients had risk of cause specific deaths placed between regional and distant SEER stages. Given its accurate predictive value, the SEER stage was used for further univariate and multivariate analysis.

Figure 2a shows the Kaplan Meier survival curve of malignant carcinoid carcinomas by SEER stage. There was a large difference (30%) in long term cause specific survival between the local/regional and distant/un-staged patients. This difference was statistically significant (Table 1). Race and ethnicity (Figure. 2b), as well as county level % college graduate (Figure. 2d) were important univariate predictors of cause specific survival, but rural-urban residence (Figure. 2c) and county level family income (Figure. 2e) were not on univariate analysis (Table 1). To account for the large and confounding biological effects of SEER stage, these socioeconomic factors were analyzed under Cox proportional hazard multivariate analysis. Race and ethnicity (favoring African American patients), rural-urban residence (favoring urban residents) and county level family income (counties with family income more or equal to $50k/year) were significant predictors of carcinoid carcinoma cause specific survival (Table 1). These socioeconomic factors account for about 5% difference in the actuarial cause specific survival at 20 years of follow up.

Discussion

The cause specific survival rates for carcinoid carcinoma are about 70% (Figure. 1). Thus there is room for improvement for malignant carcinoid carcinomas. This study used receiver operating characteristic curve (Cheung, 2012) to analyze SEER carcinoid carcinoma outcome data. Surveillance Epidemiology and End Results (SEER) (http://seer.cancer.gov/) is a public use cancer registry of United States of America (US). SEER is funded by National Cancer Institute and Center for Disease Control to cover 28% of all oncology cases in US. SEER started collecting data in 1973 for 7 states and cosmopolitan registries. Its main purpose is through collecting and distributing data on cancer, it strives to decrease the burden of cancer. SEER data are used widely as a bench-mark data source for studying cancer outcomes in US and in other countries. The extensive and uniform coverage by the SEER data is ideal for identifying the disparities (Cheung, 2012) in oncology outcome and treatment in different geographical and cultural areas for cancers.

This study screened the ROC models (Hanley and McNeil, 1982) of a long list of potential explanatory factors and selected SEER stage as the most predictor pretreatment factor for further analysis. SEER stage was used in this study in order to use the decades of follow up data in SEER. Unlike other staging systems, SEER staging has been consistent over decades, it abstracts the staging into simple but important stages for cancer progression: localized, regional and distant. ROC was used as a screening tool for the predictors in this study because it took into account both sensitivity and specificity of the prediction. Ideal model would have a ROC area of 1 and a random model is expected to have an area of 0.5 (Hanley and McNeil, 1982). As a point of reference combined use of prostate specific antigen, digital examination and Gleason score was only associated with 0.75 ROC area (Cheung et al., 2001a; 2001b), therefore, the 0.79 ROC area of SEER stage could be considered very high.

Univariate analysis was then performed to screen the predictors for multivariate analysis. To account for the large biological effects of SEER stage (Figure. 2a and Table 1), these socioeconomic factors were analyzed under Cox proportional hazard multivariate analysis. Race and ethnicity was statistically significant under univariate and multivariate analysis favoring African American race (Figure 2b and Table 1). Other studies have noted racial disparities in epidemiology of carcinoid tumors (Konishi et al., 2006) suggesting a possible genetic differences in the racial distribution and outcome of carcinoid carcinomas and it worth further investigations. Rural-urban residence (favoring urban residents) (Figure. 2c) and county level family income (counties with family income more or equal to $50k/year) (Figure. 2e) were not statistically significant predictors on univariate analysis (Table 1) but they were highly significant and independent predictors after accounting for cofounding effects of the SEER stage (Table 1).

In conclusion, this study found SEER stage as the most predictive pretreatment factor, and significant socioeconomic disparities of about 5% at 20 years of follow up in the cause specific survival of carcinoid carcinomas.

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