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Pediatric Salivary Gland Carcinoma: Incidence and survival trends based on 1973-2013 SEER data

By

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Master of Public Health

Epidemiology

_____

Michael Goodman, MD, MPH

Committee Chair

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B.S., University of North Carolina at Chapel Hill, 2011

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An abstract of

A thesis submitted to the Faculty of the
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Abstract

Pediatric Salivary Gland Carcinoma: Incidence and survival trends based on 1973-2013 SEER data

By Anuja Mathur

Introduction: Salivary Gland Carcinoma (SGC) is a rare type of cancer affecting the parotid, submandibular, sublingual, and minor glands. There are few epidemiologic studies focusing on the malignancy among pediatric patients. The purpose of this study was to examine SGC incidence and survival in persons under 20 years of age.

Methods: Eligible cases (n= 433) were selected from the Surveillance, Epidemiology, and End Results (SEER) registries for the period 1973- 2013. Incidence of SGC was examined across demographic groups and over time. Associations of age at diagnosis, sex, race/ethnicity, year of diagnosis, histology, stage and site with survival were analyzed by Kaplan Meier curves and Cox proportional hazards models.

Results: Most patients were between 10-19 years old (89.4%) and Non-Hispanic Whites (58.9%). The most common SGC site was the parotid gland (86.6%), most common histology was mucoepidermoid neoplasm (43%) and the majority of tumors were localized (69.3%). Females and older children had a significantly higher age-adjusted incidence rate compared to males or children 0-9 years of age, respectively, but there was no difference by race. A diagnosis within the last 10 years, having a rare histological type, and a distant stage were associated with survival, while survival did not differ by age, sex, and primary site.

Conclusions: While females and older children had higher incidence rates, they do not have significantly different survival outcomes. Histological type and stage could be useful prognostic factors, and further studies are needed to elucidate these differences.

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BACKGROUND

Salivary Glands

The salivary glands (SG) are exocrine organs located in the neck area. The major function of the SG are to secrete saliva. This allows lubrication of the inside of the mouth, washing away of bacteria and debris, and help with speech and mastication (1). Additionally, the molecular composition of saliva (99% water, 1% combination of electrolytes and proteins) provides a seromucosal covering to protect oral tissues from foreign agents, maintaining oral health (2). Saliva also helps with digestion by rounding food particles and providing enzymes, such as lipase and amylase (2) . The SG are classified as major or minor glands, with the former further subdivided into the parotid, submandibular and sublingual groups. The major SG use salivary duct tubes to drain 90% of the saliva into the different areas of the mouth. The parotid glands release saliva into the back of the mouth, the submandibular SG drain under the tongue and produce 70% of the saliva, and the sublingual glands drain into the ducts that open in the floor of the mouth (1). The minor SG are found abundantly throughout the mouth and throat, as well as in the lips and inner cheek (3).

Salivary Gland Carcinoma (SGC)

The majority of SGC (80%) occur in the parotid gland, and another 8-15% originate in the submandibular gland (4). Between 21 and 37% of these tumors are malignant (5), but the percentage is dependent on the location of the tumor. In the parotid 80% are benign, submandibular 50%, and minor salivary glands 20% (6).

SG tumors have a very diverse histopathology, with almost 40 types classified (7). The most common benign SG tumor is pleomorphic adenoma, while the most common malignant

type is mucoepidermoid carcinoma. The latter tends to affect the parotid gland and accounts for 35% of all SGC. Another common type of SGC is adenocarcinoma, which originates in the gland cells; other histologic forms (e.g. basal cell adenocarcinoma, squamous cell carcinoma, epithelial- myoepithelial carcinoma) are relatively rare (8).

Typically, benign SG tumors present as swelling in the relevant gland and are painless. If the tumor is malignant, there may be intermittent pain or neurological symptoms that lead to nerve weakness and facial palsy or paralysis. However, clinical presentation varies by histological type (9).

A challenge to diagnosing SGC is the diversity of histologic types and primary sites. Additionally, there is heterogeneity within the same tumor mass, further complicating optimal diagnosis (4). Diagnosed cancers are assigned a grading scale, which provides information on how abnormal the cells look compared to their normal state and how quickly the disease is spreading or growing.

While benign tumors can usually be treated effectively with surgery, treatment for malignant tumors depends on the specific type of cancer and its progression. For relatively early disease, a total removal of the affected gland (e.g. parotidectomy) is usually indicated (5). If the cancer is deemed inoperable then radiation treatment is used. In addition, radiotherapy may be used post-surgery to prevent recurrence (5).

Epidemiology of SGC

Current estimates of global SGC incidence range from 0.4 to 2.6 cases per 100,000 people per year (9). In the United States, the annual rate of SGC is about 1.5 per 100,000 individuals, which accounts for 6% of all head and neck tumors (4).

Data from the Surveillance, Epidemiology and End Results (SEER) program show that incidence differs by race, with an age-adjusted rates of 1.33 per 100,000 among Whites and 1.23 per 100,000 among Blacks. SGC incidence is also higher in men than in women (1.77 vs 1.03 per 100,000/year) (10). Both sexes show a gradually increasing rate of SGC since 1973, with an estimated annual percent increase of 0.5 for men and 0.7 for women.

The annual age-adjusted SGC mortality in the United States is 0.25 deaths per 100,000 people. From 2000-2006 there was an annual decrease in mortality of approximately 1.2%, but since 2006 this trend has reversed. Age-adjusted mortality rates are higher among males (0.39 per 100,000 people) than females (0.14 per 100,000 people) according to 2013 data.

While tobacco and alcohol use are important risk factors for head and neck cancers in general, they have not been linked to SGC specifically (11). Other risk factors hypothesized to play a role in SGC etiology include occupational exposure to silica dust, use of kerosene as cooking fuel, and previous history of radiation therapy as well as certain dietary patterns (11).

Salivary Gland Cancer in Pediatric Patients

The data on SGC in children and adolescents are sparse. With respect to primary site, pediatric SGC are similar to those of adults, with 88% of tumors found in the parotid gland, 5% in the submandibular glands, and 7% in minor SG. The immunohistochemical and molecular profiles of SGC are also similar in children and adults (12). SG tumors in children are more likely to be malignant (13); pediatric SG carcinomas are reported to include a greater proportion of low-grade tumors (14).

To date, only two studies examined population- based data SGC characteristics in children and adolescents (13). In one study, the authors analyzed SEER data for 1988-2001 and

included only patients 18 years old or younger. They described the clinical characteristics for 113 cases, but were unable to see the effects of different pathological factors on survival due to small sample size (15). In another study, the authors expanded the SEER data to 1973-2006 and compared SGC characteristics of 263 patients who were diagnosed under the age of 20 years to those of adults. While this study offered several useful observations, it was still limited by the relatively small number of pediatric cases.

There are important unanswered questions related to the prognostic factors of SGC that may play a role within the pediatric age group. The most current SEER data allow addressing of these questions because they include an additional seven years and greatly increases the number of pediatric SGC cases from what was available in the earlier reports. With these considerations in mind, the purpose of the present study was to assess how different clinical and prognostic factors may differ across patient- and disease-related characteristics of SGC patients diagnosed before the age of 20 years.

METHODS

Data Extraction

Data were obtained from the SEER program for the years 1973-2013. Incident cases of SGC diagnosed among patients of pediatric age (0-19 years) were selected for analyses using International Classification of Disease-Oncology (ICD-O) primary site codes (C07.9, C08.0, C08.9). Patients were excluded if they were of unknown age or above the age of 19, not actively followed by SEER, had a benign neoplasm, only had an autopsy- or death certificate-based SGC diagnosis, or had SGC that followed a previous cancer diagnosis.

Information available for each eligible patient included age at diagnosis, sex, year of diagnosis, tumor histology, stage and site. Age at diagnosis was categorized as 0-9 vs. 10-19 years and race/ethnicity was categorized as Non-Hispanic White, Non-Hispanic Black, Hispanic, and Unknown/Other. The last category includes American Indian/AK natives, Asian/Pacific Islanders, and unknown races. The Hispanic designation included Spanish, Hispanic and Latino identifiers.

To assess temporal changes in disease presentation and survival, year of diagnosis was categorized as 1973 – 1993, 1994 – 2003, and 2004 – 2013. Tumor histology was grouped as mucoepidermoid, acinar cell, and other. The latter included adenocarcinomas, myomatous neoplasms, and other less frequent histologic types. SEER Historic Stage A was used in all analyses to overcome the problem of multiple changes in disease staging over the years and to achieve data consistency across the entire study period.

Statistical Analysis

Distributions of patient- and disease-related characteristics were examined both overall and across two age groups (0-9 and 10-19 years). Incidence rates were estimated as the number of new cases per 100,000 person-years and age-adjusted using the 2000 US standard population. The rates were compared in the two age groups of interest as well as by race and sex. The results of these comparisons were expressed as rate ratios (RRs) and the corresponding 95% confidence intervals (CIs) as described previously (16). Secular changes in pediatric SGC incidence rates (age-adjusted for 2000 US population) were examined by computing the annual percent change (APC) over a forty-year study period using data from the nine original SEER registries. APC was calculated using the weighted least squares method with year of diagnosis used as the independent variable.

Survival analyses were conducted by evaluating the interval from the date of diagnosis until either date of death, the end of follow up at 15 years' post-diagnosis or the date of the study cutoff (December 31, 2013). Kaplan Meier curves were generated for crude survival analysis and the log-rank test was used for comparison across groups. Multivariable Cox proportional hazards model was used to examine the association between age group and survival, adjusted for sex, year of diagnosis, histology, SEER stage and site and stratified by race/ethnicity. The proportional hazards assumption was evaluated by inspecting log-log plots for each variable in the model. For variables that violated this assumption, stratified Cox models were used. The results of the multivariate analyses were expressed as adjusted hazard ratios (HRs) and their 95% CIs.

Descriptive data analyses and examination of rates were performed using SEER*Stat software version 8.1.2, and Joinpoint Regression Program version 4.0.4 (both available from NCI, Bethesda, MD). Multivariable analyses were carried out using SAS statistical software 9.3

(Cary, North Carolina). The cut-point for statistical significance was a two-sided alpha error of 0.05 for all analyses.

RESULTS

There were 433 pediatric SGC cases reported to SEER from 1973 through the end of 2013. The mean age at diagnosis of the study population was 14.2 years and 11% of patients (n=48) were under the age of 10 years. As shown in Table 1, 59% of the population were female (n = 256). The most common racial/ethnic group were Non-Hispanic Whites (59%, n = 255), followed by Hispanics (17.8%, n = 77). Nearly half of the patients (49%) were diagnosed in the most recent decade (2004–2013). Most tumors originated in the parotid gland (87%) and nearly half (43%) were classified as mucoepidermoid neoplasms. Among cases with documented stage, 69% had localized disease.

As shown in Table 2, SGC rates among females were 50% greater than the corresponding rates among males (RR: 1.51, 95% CI: 1.17, 1.95). While overall incidence of pediatric SGC was low, children 10-19 years of age had a seven times higher incidence relative to the younger age group. No significant difference was found by race.

As shown in Figure 1, the incidence of pediatric SGC has been increasing over time with a statistically significant APC of 1.6 (95% CI: 0.5, 2.8). The increase appeared to be gradual between 1973-2013 with no identifiable inflexion points.

The overall 15-year survival was 93%. Kaplan-Meier curves and log-rank tests were initially used to determine the difference in survival by age, sex, race/ethnicity, year of diagnosis, histology, stage and site. Figure 2 shows no significant difference in survival by age, sex, race/ethnicity and year of diagnosis. The Kaplan-Meier curves comparing survival across tumor characteristics are presented in Figure 3. There was a significant difference by histology, with mucoepidermoid and acinar tumors having better survival relative to other less common

histologic types. More advanced stage was also associated with worse prognosis. There was no apparent association between survival and tumor site.

In the multivariable survival analysis, the proportional hazards assumptions were met for all variables except race/ethnicity. For this reason, the final Cox survival model was stratified on race/ethnicity. As shown in Table 3, the final Cox model demonstrated no significant differences in survival by sex, age, or tumor site. Patients diagnosed in the last two decades had a significantly better survival than those diagnosed in the earliest study period (1973 – 1993). Patients with mucoepidermoid or acinar cell neoplasms had significantly better prognosis than those diagnosed with tumor of other histologic types. The most pronounced difference in survival was observed between distant and localized SGC (HR= 10.4; 95% CI: 3.53, 30.56). By contrast, there was no discernable survival difference between localized and regional disease.

DISCUSSION

Rare malignancies such as pediatric SGC are difficult to study because of the challenges associated with the assembling a cohort of sufficient size. For this reason, most previous publications of SGC in children are case reports or relatively small single institution based clinical series (17) (18) (14).

Two population-based studies of pediatric SGC were conducted previously. The earlier of the two studies used 1988-2001 SEER data and included 113 pediatric patients with the mean diagnosis age of 13 years (15). Most tumors were mucoepidermoid carcinomas and the majority originated in the parotid gland. All patients were treated with a superficial or total parotidectomy, with modifications as required, and 27% received adjuvant postoperative radiation therapy. Overall survival was 153 months with a 94.2% survival rate during a 163-month follow up (15).

The second study examined SEER data from 1973 through the end of 2006 and compared 263 pediatric SGC patients to their adult case counterparts (13). The clinical characteristics in the two groups were similar. However, the 10-year overall survival among children and adolescents was higher than that in adults (94% vs. 46%). The main distinguishing features of pediatric cases were earlier stage and lower grade. Other factors associated with worse prognosis across both age groups included male sex, lymph node involvement, distant stage, higher grade, and larger tumor size (13). However, the within-pediatric age group analyses were not conducted due to relatively few cases in this category.

Our study builds on the previous research by extending the case finding and the observation period through the end of 2013. This almost doubled the sample size and permitted additional within-cohort analyses. We found that among pediatric patients there was a significant

difference in incidence rates by sex and age, but not race. We also observed that survival of pediatric SGC patients improved in the last decade, and confirmed previous observations that relatively rare histologic types carry less favorable prognosis.

The interpretation of our findings requires understanding of the strengths and limitations of the SEER data. As previously noted elsewhere, the population-based design of the SEER program allows assembling historical cohorts of patients with rare cancers (19). Further, the population-based identification of cases increases the generalizability of findings and the active follow-up of cases facilitates survival analyses.

The main limitations of this study pertain to the lack of data on certain important clinical and demographic variables such as details of treatment, recurrence, health insurance and socioeconomic status. Another important data item that may need to be considered is the effect of provider- and facility-related characteristics, which may be of critical importance as determinants of diagnostic and treatment quality (including pathology and surgery). Thus, both cancer registry-based and institution-based studies provide useful complementary information that may contribute to the evidence despite their respective strengths and limitations (20).

Even with a relatively large sample such as ours, several of the variables were lacking necessary detail due to sparse data within specific subgroups. For example, tumor site was categorized as parotid gland versus other. Similarly, data on histologic type were presented using relatively crude categories where some of the less common types had to be included in single group. As the SEER program continues to expand and the data for additional years become available, it will be important to extend the present analyses by including greater level of detail on clinical features and demographic characteristics of SGC patients.

In conclusion, our study demonstrated a gradual but significant increase in pediatric SGC incidence rates over the last four decades. The risk is more pronounced in females and in older children and adolescents. The prognosis of patients diagnosed and treated in the more recent decade appears to have improved compared to earlier periods. Survival appears to be lower among patients diagnosed with tumors of less common histologic types, but it is unclear which specific histology is associated with the worst prognosis. Future studies using additional years or more expanded data (e.g., based on all 50 state cancer registries) are needed to address this and other knowledge gaps about pediatric SGC.

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TABLES AND FIGURES

Table 1. Demographic and disease characteristics of pediatric SGC patients by age group; SEER 1973-2013

Patient Characteristics	Overall	Age 0 - 9 years	Age 10 - 19 years
	433 (100%)	48 (11.1%)	387 (89.4%)
Sex			
Female	256 (59.1)	32 (7.4)	224 (51.7)
Male	177 (40.9)	16 (3.7)	161 (37.2)
Race/Ethnicity			
Non-Hispanic White	255 (58.9)	26 (6.0)	229 (52.9)
Non-Hispanic Black	62 (14.3)	16 (3.7)	46 (10.6)
Hispanic [a]	77 (17.8)	5 (1.2)	72 (16.6)
Other/Unknown [b]	39 (9.0)	#	38 (8.8)
Year of Diagnosis			
1973-1993	104 (24.0)	17 (3.9)	87 (20.1)
1994-2003	115 (26.6)	10 (2.3)	105 (24.3)
2004-2013	214 (49.4)	21 (4.9)	193 (44.6)
Site			
Parotid Gland	375 (86.6)	41 (9.5)	334 (77.1)
Other	58 (13.4)	7 (1.6)	51 (11.8)
Histology			
Mucoepidermoid neoplasm	186 (43.0)	19 (4.4)	167 (38.6)
Acinar cell neoplasm	152 (35.1)	12 (2.8)	140 (32.3)
Other	95 (22.0)	17 (3.9)	78 (18.0)
Stage [c]			
Localized	289 (69.3)	26 (6.2)	263 (63.1)
Regional	105 (25.2)	15 (3.6)	90 (21.6)
Distant	23 (5.5)	5 (1.2)	18 (4.3)

[a] Spanish-Hispanic-Latino
[b] Includes American Indian/AK Native, Asian/Pacific Islander, and Unknown
[c] Missing 16 cases (2 from ages 0-9, 8 from 10-14, 6 from 15-19)
Numbers suppressed

Table 2. Age-standardized incidence rates [a] of pediatric SGC from 1973-2013 SEER data [b]

Variable	Cases	Adjusted Rate (CL)	Rate Ratio (CL)
Sex			
Male	106	0.7 (0.6, 0.8)	*ref*
Female	153	1.1 (0.9, 1.2)	1.51 (1.17, 1.95)*
Age			
0 – 9 years	30	0.2 (0.1, 0.3)	*ref*
10 – 19 years	229	1.5 (1.3, 1.7)	7.38 (5.03, 11.18)*
Race			
White	197	0.9 (0.8, 1.0)	*ref*
Black	37	0.9 (0.6, 1.3)	1.05 (0.72, 1.50)
Other/Unknown	25	0.8 (0.5, 1.2)	0.95 (0.60, 1.44)

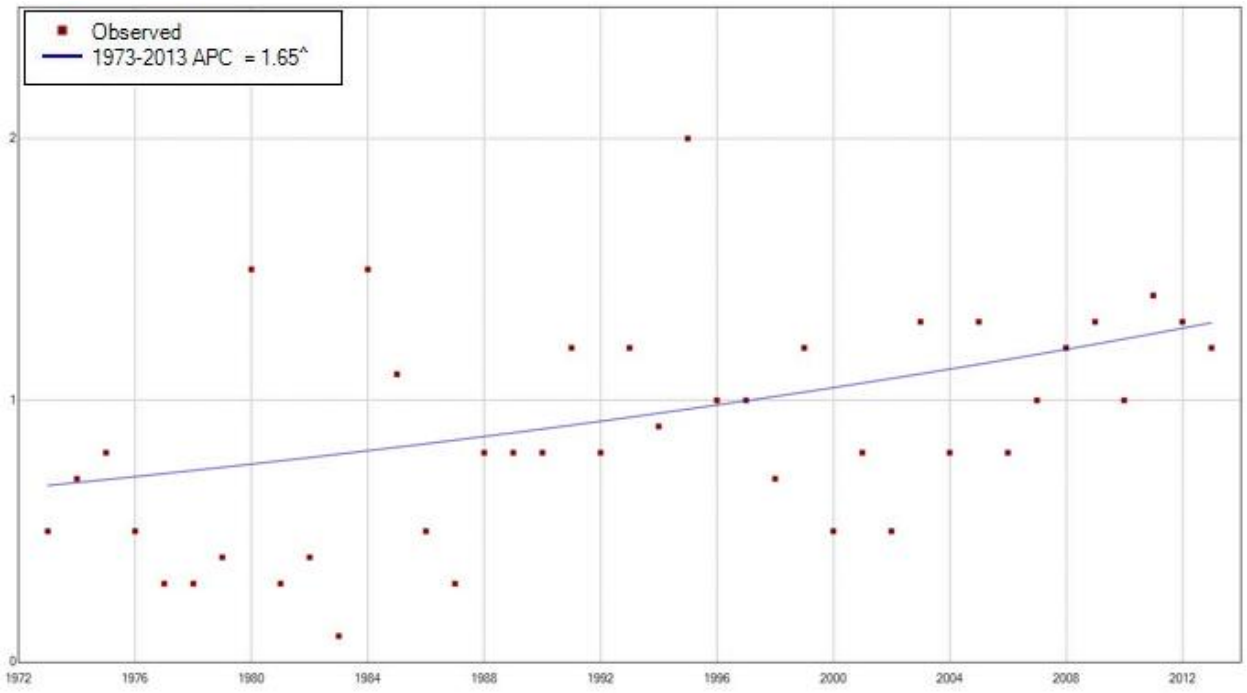
[a] Per 1,000,000 person-years; Standardized to 2000 US Population;
[b] SEER9 Registry Data
CL: Confidence limits (95%), lower and upper, on rate
* Statistically significant difference

Table 3. Multivariate analyses of the association between patient and disease characteristics and pediatric SGC mortality

Characteristic	Hazard Ratio	95% Confidence Interval	
Sex			
Male	*ref*		
Female	0.53	0.24	1.19
Age			
0 to 9	*ref*		
10 to 19	1.26	0.45	3.55
Year of Diagnosis			
1973-1993	*ref*		
1994-2003	0.5	0.19	1.29
2004-2013	0.31*	0.11	0.86
Site			
Parotid Gland	*ref*		
Other	1.15	0.44	3.04
Histology			
Mucoepidermoid neoplasm	*ref*		
Acinar cell neoplasm	0.58	0.11	3
Other	5.0*	1.87	13.42
Stage [a]			
Localized	*ref*		
Regional	1.93	0.75	4.99
Distant	10.38*	3.53	30.56

[a] Missing 16 cases (2 from ages 0-9, 8 from 10-14, 6 from 15-19)
*Statistically significant difference

Figure 1. Changes in pediatric SGC incidence over the study period; SEER 1973-2013*



* SEER9 Registry Data

Figure 2. Kaplan-Meier Survival Curves evaluating the association of demographic factors (age, sex, race/ethnicity and year of diagnosis) with SGC survival; SEER 1973-2013

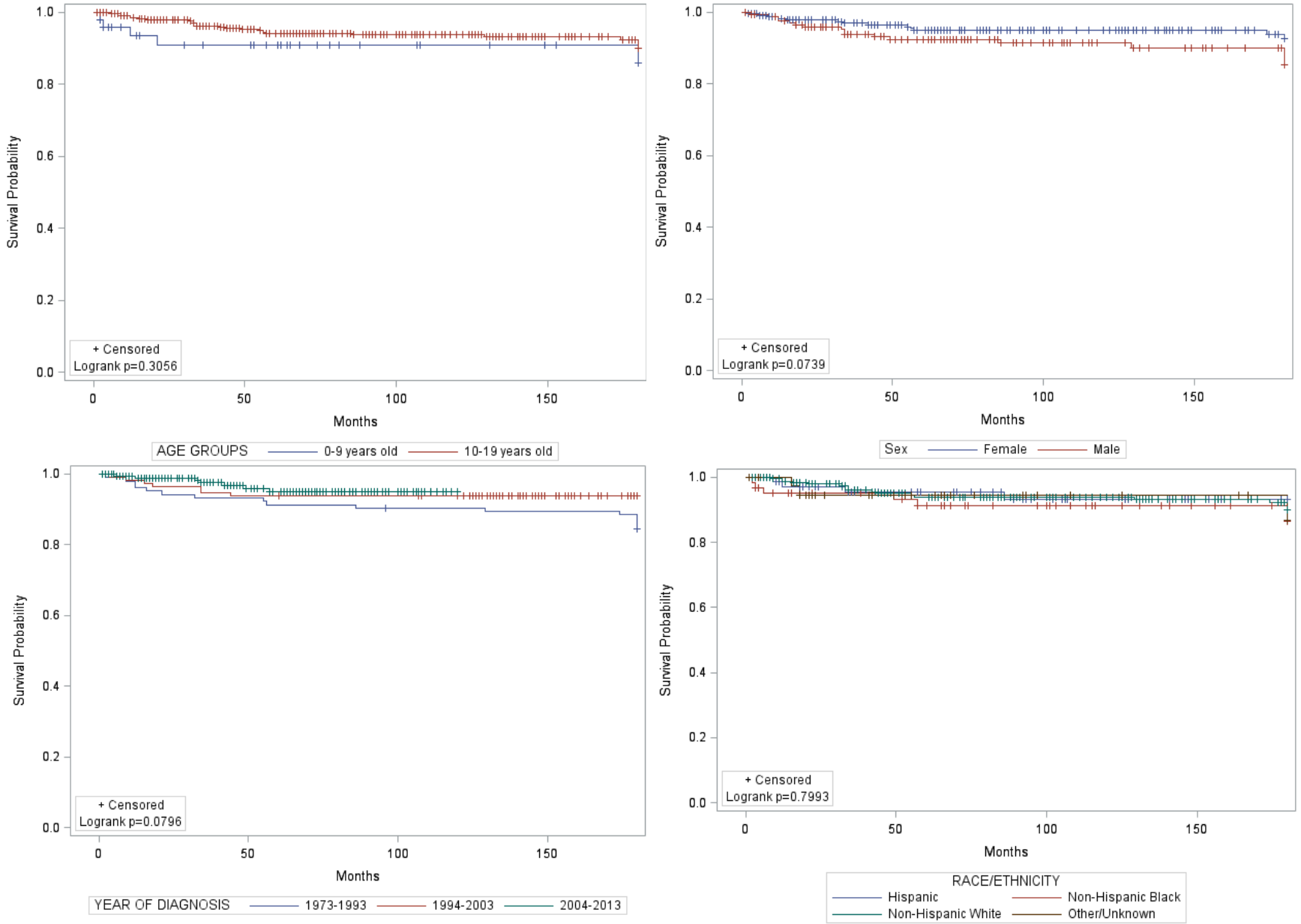


Figure 3. Kaplan-Meier Survival Curves evaluating the association of tumor-related factors (stage, histology and site) with SGC survival SEER 1973-2013