Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Christopher L. Ellington Date

Adenoid Cystic Carcinoma of the Head and Neck; Incidence and survival trends based on 1973-2007 SEER data

By

Christopher L. Ellington

Master of Science in Public Health

Epidemiology

_____ [Chair's signature]

Dr. Michael Goodman MD/MPH

Committee Chair

Adenoid Cystic Carcinoma of the Head and Neck; Incidence and survival trends based on 1973-2007 SEER Data

By

Christopher L. Ellington

Bachelor of Science

Emory University

2009

Thesis Committee Chair: Dr. Michael Goodman MD, MPH

An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Science in Public Health]
in Epidemiology

2011

Abstract

Adenoid Cystic Carcinoma of the Head and Neck; Incidence and survival trends based on 1973-2007 SEER Data

By Christopher L. Ellington

Introduction:
Adenoid Cystic Carcinoma (ACC) is a rare tumor of minor salivary, parotid, and submandibular glands. The biological behavior of the disease is poorly understood, and treatment strategies have yet to be standardized. The long-term prognosis continues to be poor, with an estimated 10-year survival of under 60%. Population-based studies examining ACC are scarce. We aimed to analyze incidence rates and survival outcomes for patients diagnosed ACC of the head and neck (ACCHN) using national population-based data.

Materials and Methods:
Data were obtained from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Newly diagnosed ACCHN cases reported to SEER from 1973 through 2007 were categorized according to their sex, race, age, year of diagnosis, marital status, treatment interventions, primary tumor site, and disease stage. Incidence of ACCHN and post-diagnosis survival were examined over time and compared across different demographic and disease-related categories.

Results:
We have identified 3026 patients with ACCHN between 1973 and 2007. The mean age at diagnosis among those cases was 57.4 years (range: 11–99 years). Analyses of incidence data demonstrated a decline in ACCHN rates between 1973 and 2007, noted across all sexes and races with no detectable inflexion points. The overall 5-year, 10-year, and 15-year survival outcomes for ACCHN patients were 90.3%, 79.9%, and 69.2% respectively. Females, patients with localized disease, and younger patients were found to have significantly better survival across all time periods (all comparison-specific log rank p-values <0.001). Multivariate analyses revealed better prognosis among women compared to men (hazard ratio [HR] = 0.72; 95% confidence interval [CI]: 0.64-0.81), among married compared to unmarried individuals (HR = 0.85; 95% CI: 0.75-0.97), and in those who had surgery of the primary tumor site (HR = 0.50; 95% CI: 0.42-0.61).

Conclusion:
The overall incidence of ACC seems to be on the decline. Survival outcomes based on age and stage of disease categories are consistent with clinical literature on ACC. The noted differences in survival based on gender, marital status, and treatment intervention require further investigation.

Adenoid Cystic Carcinoma of the Head and Neck; Incidence and survival trends based on 1973-2007 SEER Data

By

Christopher L. Ellington

Bachelor of Science

Emory University

2009

Thesis Committee Chair: Dr. Michael Goodman MD, MPH

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
in Epidemiology

2011

Table of Contents

Introduction:

Adenoid Cystic Carcinoma (ACC) is a rare malignant tumor that originates within secretory glands and accounts for a substantial portion of minor salivary, parotid, and submandibular gland malignancies [26, 27]. Although this cancer typically arises within the salivary glands of the head and neck, other sites of origin have been found in the ceruminous glands, lacrimal glands, and excretory glands of the genital tract. It has been noted throughout literature that ACC tumors progress slowly and can often be found growing along nerve tracts; however, the exact biologic mechanisms and the lifecycle of the disease are still poorly understood. Due in a large part to these knowledge gaps, treatment therapies for ACC have yet to be standardized.

In an effort to more fully understand the course and behavior of the disease, many studies have focused on identifying specific prognostic factors for ACC. These indicators include site of origin [13], tumor size [26], advanced stage at diagnosis [4, 25], distant metastases [19], solid histological pattern [9, 19], presence of tumors in lymph nodes [22], and perineural invasion [31].

Currently, the most common course of treatment for ACC is surgical excision, which is typically followed by radiotherapy of the surgical bed [8, 24, 33]. ACC appears to be sensitive to radiotherapy, and the addition of postoperative RT has significant benefits for local control [19, 20]. Numerous phase I and II studies have been conducted to determine the efficacy of systemic therapies to manage reoccurrence and metastasis. Both single-agent and combination chemotherapy regimens have been tested with extremely variable and inconsistent results [24]. Evidence from these studies for systemic single agent therapies is strongest for platinum, 5-fluorouracil and anthracyclines, while combination chemotherapies using platinum, anthracyclines and

alkylating agent regimens seem to have the best overall response. Regardless, the noted beneficial duration with these traditional chemotherapy approaches has been reportedly short in a majority of cases— usually 5 to 13 months [3, 5, 16, 28].

It has also been noted that long follow-up is necessary to detect recurrence in patients with ACC. To address this issue, the routine use of radiologic examinations, especially magnetic resonance imaging, in the postoperative period may help discover changes indicative of recurrent ACC anywhere from months to years before they are clinically evident [23]. The use of fluoro-deoxy glucose (FDG)-PET has also been used during the radiotherapy planning process in an attempt to delineate the primary tumor volume, and to theoretically provide a more effective dose within the target volume while minimizing the dose to surrounding critical structures [10].

In addition to more traditional chemotherapy regimens, encouraging responses have been reported for intra-arterial (IA) neoadjuvant chemotherapy—especially in the most advanced stage patients and in situations when surgery is not feasible. However, the IA neoadjuvant strategy is associated with substantial toxicity and should still be considered investigational [15]. Molecular targeted agents may also have a role, although the agents tested to date in several ACC studies have yet to produce a viable tumor reducing treatment. So far, one of the most promising targets remains to be c-KIT, which reportedly has a high expression ranging from 78%-100% [15, 18, 30]. A better understanding of the biology and molecular pathenogenesis of ACC will be crucial to the future success of targeted agents for this disease.

Although studies have reported moderate success for treating metastatic disease with various systemic therapies, no clear treatment option has emerged to improve the long term survival of ACC patients. In addition to the rarity of ACC, much of the difficulty has been linked to its propensity for local recurrence and distant metastasis; often years after the initial presentation of disease [25].

The population-based data pertaining to ACC are scarce. In our study, we aimed to assess the incidence and survival outcomes for patients diagnosed with ACC in the last three decades and to search for patterns suggestive of risk factors or changes in prognoses. Because of mounting evidence that ACC has a rather distinct molecular pathogenesis compared to other malignant salivary gland tumors, we have decided to focus only on analysis of ACC disease of the head and neck (ACCHN). Using data from a large nationwide cancer surveillance program, we analyzed ACCHN incidence according to various patient and disease-related characteristics, and examined frequency and determinants of survival following diagnosis.

Methods:

Data were obtained from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. SEER data collection began in the early 1970's and includes 17 registries that account for roughly a quarter of the US population. For the purpose of this study, SEER Historic Stage A was used in all analysis. SEER Historic Stage A field is produced by recoding extent of disease (EOD) information collected by SEER into a single stage variable consistent across all time periods.

We selected all cases coded as cancers of the lip, tongue, salivary gland, floor of mouth, gum and other mouth, nasopharynx, tonsil, oropharynx, hypopharynx, or other oral cavity and pharynx sites with a microscopically-confirmed histologic type of adenoid cystic carcinoma (M-8200/3) diagnosed from 1973 through 2007. We examined temporal trends of ACCHN incidence rates (age-adjusted for US standard population) by sex, race, and stage at diagnosis. The race variable was dichotomized as 'white' and 'black' and other race categories were excluded from the analysis due to insufficient number of observations (274 total cases). Sex was also treated as a dichotomous variable, and age at diagnosis was divided into tertiles at cut-points of 50 yrs and 66 yrs. Lastly, marital status was categorized as "Married" and "Single" (including individuals who have never married, widowed, divorced, and are legally married but separated).

Results from the trend analyses were expressed as the average annual percent change (AAPC) over the 35-year study period. AAPC was used to measure the change in rates over time and was calculated by fitting a least squares regression line to the natural logarithm of the rates, using the calendar year as a regressor variable. Differences between trends for two time periods were tested for statistical significance by comparing the difference in regression coefficients divided by the standard error of that difference

with a T-distribution with degrees of freedom defined as the sum of the years in both time periods minus 4 [14].

Observed survival (OS; the proportion of patients surviving beyond a given interval) and relative survival (RS; calculated by dividing the observed survival among cancer patients by the expected survival in the general population with the same age, race, and sex) were analyzed according to patient sex and race. The 5yr, 10yr, and 15yr RS estimates were evaluated across three time periods: 1973-1982, 1983-1992, and 1993 through 2007. The follow up data in survival analyses extended through the end of 2007. The crude survival analyses were based on Kaplan-Meier methods using a log-rank test of significance to assess the differences between curves. Multivariate analysis was performed using Cox proportional hazards models to evaluate the association between survival and potential risk factors after adjusting for all potential risk factors. The proportional hazards assumption was evaluated using graphical log(-log), time-dependent variable, and goodness of fit methods. If the proportional hazards assumptions were violated, the adjusted associations were examined using extended Cox survival models. The results of multivariate analyses were expressed as adjusted hazard ratios (HRs) accompanied by the corresponding 95% confidence intervals (CIs).

All data analyses were performed using SEER*Stat, JoinPoint and SAS statistical software (National Cancer Institute, Bethesda, MD and SAS Institute Inc.).

Results:

A total of 3026 cases of head and neck adenoid cystic carcinoma were reported to SEER between 1973 and 2007. Among these cases, the mean age at diagnosis was 57.39 years (Range: 11 – 99 years), with 613 of these cases reported from 1973-1982, 639 cases from 1983-1992, 1009 cases from 1993 and 2002, and 765 cases from 2003-2007. As shown in Table 1, men and women represented 40.98% (N = 1,240) and 59.02% (N = 1,786) of the sample, respectively. The majority of cases were white (N = 2,471; 81.66%), with blacks being the second largest group (N = 286; 9.45%). Patients with localized or regional disease accounted for 45.3% (N = 1372) and 36.38% (N = 1044) respectively, whereas 11.57% (N=317) had distant metastases. Salivary gland primary tumors were the majority (57.98%), followed by oral cavity tumors including lip and oral tongue (36.91%), with oropharynx and nasopharynx accounting for 4.56% (Table 1).

Analyses of incidence data demonstrated a decline in ACCHN rates between 1973 and 2007, noted across all sexes and races with no detectable inflexion points (Figures 1-8). The decline was more apparent for localized ACCHN than for regional and distant disease.

The overall 5yr, 10yr, and 15yr survival estimates for ACCHN patients were 90.34%, 79.88%, and 69.22% respectively (Table 2). The Kaplan-Meier survival curves differed significantly in men and women (Log-rank 45.64; $p < .0001$), with females having a better survival outcome. There were no significant differences in survival curves based on race.

The multivariate analysis controlled for potential covariates, which included age, race, sex, stage at diagnosis, year of diagnosis, primary site, radiation therapy, and surgery of primary site. The proportional hazards assumption was not satisfied for age

and stage at diagnosis, and all further multivariable analysis was stratified on these variables using a 'no-interaction' model.

As shown in Table 3, the multivariate analyses revealed better prognosis among women compared to men (HR=0.72; 95% CI: 0.64-0.81) and among married individuals compared to a combined group that included never married, widowed, divorced, and separated (HR = 0.85; 95% CI: 0.75-0.97). The only clinical factor related to better survival was surgery of primary site, which demonstrated a reduced HR of 0.50 (95% CI: 0.42-0.61). The corresponding results for other covariates in the model, including radiation therapy, race, site of primary tumor, and year of diagnosis, did not show any significant departures from the null (Table 3).

Discussion:

Our findings indicate that the overall incidence of disease for ACC of the head and neck continues to decline, most notably in the less advanced stages of disease. This observation cannot be attributed to change in the frequency of unstaged cases, which remained relatively stable over the years. The survival data are consistent with current literature that indicates a high rate of recurrent disease after 5 years since initial diagnosis. Among the patients diagnosed with ACCHN, women and persons who are currently married tended to have better survival outcomes. Although the association between better survival and marital status is a well-described phenomenon reported across several cancer sites, the reasons for observed gender differences in our study require exploration [2, 12, 32]. Surgery of the primary site was the only demonstrated clinical intervention to have a survival benefit for patients diagnosed with ACCHN. As we used a rather crude staging system, the latter finding probably indicates that surgically treated ACCHN in these data represent either the less advanced (i.e. operable) disease, or the higher quality of care. It is likely that surgery will remain the primary treatment option until more consistently successful radiation or chemotherapeutic options are developed.

There has only been one other similar population-based study by Lloyd et al that examined survival trends for ACC [17]. Both studies concluded that gender plays a role in survival, and that traditional radiation therapy does not significantly affect patient survival outcomes. However, the two studies meaningfully differ both on selection criteria and methods of analysis. Since ACC is such a rare cancer and registry data is scarce, Lloyd et al also included cribriform histologic type carcinomas and expanded the selection of primary sites to include skin of the head and neck, the upper respiratory system (the nose, nasal cavity, middle ear, paranasal sinuses, and larynx), the eye, and the thyroid gland. While the larger sample size may increase statistical power, the cases

examined in the Lloyd et al study represent a more heterogeneous group of malignancies than those included in our analyses. Additionally, we included an examination of incidence rates for various subpopulations of ACCHN, which was not included in the Lloyd et al study.

A more comprehensive interpretation of study results requires understanding the strengths and limitations of SEER data. Disease registries such as SEER provide a large, reliable source of data with sufficient statistical power to examine even rare cancers such as ACC. Furthermore, population-based, as opposed to institution-based, studies have the added benefit of greater external validity. On the other hand, our study is limited by the relatively limited number of variables and the level of detail available for each case. These limitations are particularly evident with regards to relevant clinical or treatment information. For this study, the lack of information about comorbidities, the type of surgery, and the chemo- and/or radiation therapies may preclude us from drawing more definitive conclusions. Another limitation of our analysis is the use of Historic Summary Stage A versus more recent and more detailed staging criteria such as those from the American Joint Committee on Cancer. Due to these study limitations, the next rational step to study ACCHN will likely involve cooperative clinical trials from several institutions in order to accumulate adequate samples of cases to assess more definitive risk factors and novel treatment therapies.

In summary, the incidence of ACCHN appears to be on the decline across all study populations. As reported in the earlier literature, patient survival drops off considerably after 5yrs and appears to change over time depending on patients' age and stage. Future analyses may examine the relation of age and stage to survival using time-dependent models. We also found evidence that ACCHN survival may be associated with sex, marital status, and surgery of the primary site. Additional research aimed at understanding the mechanisms underlying these associations is warranted.

References:

1. Armstrong, J. G., L. B. Harrison, et al. (1990). "Malignant tumors of major salivary gland origin. A matched-pair analysis of the role of combined surgery and postoperative radiotherapy." Arch Otolaryngol Head Neck Surg **116**(3): 290-293.

2. Abern MR, Dude AM, Coogan CL. "Marital status independently predicts testis cancer survival- an analysis of the SEER database." Urol Oncol. 2010 Sep 25. PubMed PMID: 20870430.

3. Belani, C. P., M. A. Eisenberger, et al. (1988). "Preliminary experience with chemotherapy in advanced salivary gland neoplasms." Med Pediatr Oncol **16**(3): 197-202.

4. Ciccolallo, L., L. Licitra, et al. (2009). "Survival from salivary glands adenoid cystic carcinoma in European populations." Oral Oncol **45**(8): 669-674.

5. Dodd, R. L. and N. J. Slevin (2006). "Salivary gland adenoid cystic carcinoma: a review of chemotherapy and molecular therapies." Oral Oncol **42**(8): 759-769.

6. Fordice, J., C. Kershaw, et al. (1999). "Adenoid cystic carcinoma of the head and neck: predictors of morbidity and mortality." Arch Otolaryngol Head Neck Surg **125**(2): 149-152.

7. Garden, A. S., R. S. Weber, et al. (1995). "The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation." Int J Radiat Oncol Biol Phys **32**(3): 619-626.

8. Ghosal, N., K. Mais, et al. (2010). "Phase II study of cisplatin and imatinib in advanced salivary adenoid cystic carcinoma." Br J Oral Maxillofac Surg.

9. Goepfert, H., M. A. Luna, et al. (1983). "Malignant salivary gland tumors of the paranasal sinuses and nasal cavity." Arch Otolaryngol **109**(10): 662-668.

10. Haresh, K. P., R. Prabhakar, et al. (2008). "Adenoid cystic carcinoma of the trachea treated with PET-CT based intensity modulated radiotherapy." J Thorac Oncol **3**(7): 793-795.

11. Huang, M., D. Ma, et al. (1997). "Factors influencing survival rate in adenoid cystic carcinoma of the salivary glands." Int J Oral Maxillofac Surg **26**(6): 435-439.

12. Johnson TV, Master VA. "Decreased cancer survival in individuals separated at time of diagnosis: Critical period for cancer pathophysiology?" Cancer. 2010 Dec 1; 116(23): 5564; author reply 5564. Dio: 10.1002/cncr.25265. PubMed PMID: 20665485.

13. Khafif, A., Y. Anavi, et al. (2005). "Adenoid cystic carcinoma of the salivary glands: a 20-year review with long-term follow-up." Ear Nose Throat J **84**(10): 662, 664-667.

14. Kleinbaum, Kupper, and Muller. *Applied Regression Analysis and Other Multivariable Methods*. PWS-Kent, Boston, Mass., 2nd edition, 1988.

15. Le Tourneau, C., A. R. Razak, et al. (2010). "Role of chemotherapy and molecularly targeted agents in the treatment of adenoid cystic carcinoma of the lacrimal gland." Br J Ophthalmol.

16. Licitra, L., R. Cavina, et al. (1996). "Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma. A phase II trial of 22 patients." Ann Oncol **7**(6): 640-642.

17. Lloyd, S., J. B. Yu, et al. (2011). "Determinants and patterns of survival in adenoid cystic carcinoma of the head and neck, including an analysis of adjuvant radiation therapy." Am J Clin Oncol **34**(1): 76-81.

18. Locati, L. D., F. Perrone, et al. (2009). "Treatment relevant target immunophenotyping of 139 salivary gland carcinomas (SGCs)." Oral Oncol **45**(11): 986-990.

19. Matsuba, H. M., J. R. Simpson, et al. (1986). "Adenoid cystic salivary gland carcinoma: a clinicopathologic correlation." Head Neck Surg **8**(3): 200-204.

20. Miglianico, L., F. Eschwege, et al. (1987). "Cervico-facial adenoid cystic carcinoma: study of 102 cases. Influence of radiation therapy." Int J Radiat Oncol Biol Phys 13(5): 673-678.

21. Osborn, D. A. (1977). "Morphology and the natural history of cribriform adenocarcinoma (adenoid cystic carcinoma)." J Clin Pathol **30**(3): 195-205.

22. Perzin, K. H., P. Gullane, et al. (1978). "Adenoid cystic carcinomas arising in salivary glands: a correlation of histologic features and clinical course." Cancer **42**(1): 265-282.

23. Prokopakis, E. P., C. H. Snyderman, et al. (1999). "Risk factors for local recurrence of adenoid cystic carcinoma: the role of postoperative radiation therapy." Am J Otolaryngol **20**(5): 281-286.

24. Ross, P. J., E. M. Teoh, et al. (2009). "Epirubicin, cisplatin and protracted venous infusion 5-Fluorouracil chemotherapy for advanced salivary adenoid cystic carcinoma." Clin Oncol (R Coll Radiol) **21**(4): 311-314.

25. Spiro, R. H., A. G. Huvos, et al. (1979). "Adenoid cystic carcinoma: factors influencing survival." Am J Surg **138**(4): 579-583.

26. Spiro, R. H., L. G. Koss, et al. (1973). "Tumors of minor salivary origin. A clinicopathologic study of 492 cases." Cancer **31**(1): 117-129.

27. Spiro, R. H., H. T. Thaler, et al. (1991). "The importance of clinical staging of minor salivary gland carcinoma." Am J Surg **162**(4): 330-336.

28. Tsukuda, M., T. Kokatsu, et al. (1993). "Chemotherapy for recurrent adeno- and adenoidcystic carcinomas in the head and neck." J Cancer Res Clin Oncol **119**(12): 756-758.

29. van Herpen, C. M., L. D. Locati, et al. (2008). "Phase II study on gemcitabine in recurrent and/or metastatic adenoid cystic carcinoma of the head and neck (EORTC 24982)." Eur J Cancer **44**(17): 2542-2545.

30. Vila, L., H. Liu, et al. (2009). "Identification of c-kit gene mutations in primary adenoid cystic carcinoma of the salivary gland." Mod Pathol **22**(10): 1296-1302.

31. Vrielinck, L. J., F. Ostyn, et al. (1988). "The significance of perineural spread in adenoid cystic carcinoma of the major and minor salivary glands." Int J Oral Maxillofac Surg **17**(3): 190-193.

32. Wang L, Wilson SE, Steward DB, Hollenbeak CS. Marital status and colon cancer outcomes in US Surveillance, Epidemiology and End Results registries: Does marriage affect cancer survival by gender and stage? Cancer Epidemiol. 2011 Apr 3. PubMed PMID 21466984.

33. Wiseman, S. M., S. R. Popat, et al. (2002). "Adenoid cystic carcinoma of the paranasal sinuses or nasal cavity: a 40-year review of 35 cases." Ear Nose Throat J **81**(8): 510-514, 516-517.

Figures and Tables

Figure 1: Joinpoint analysis of ACCHN incidence by sex: All stages SEER 1973-2007

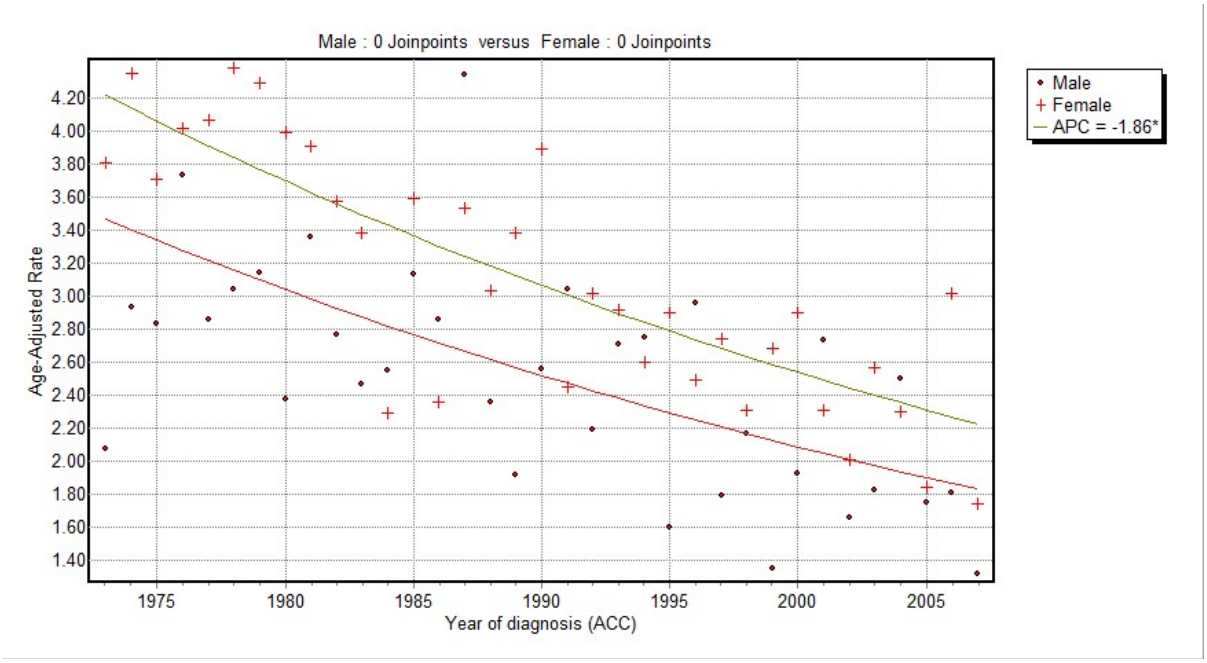

Figure 2: Joinpoint analysis of ACCHN incidence by sex: Localized stage SEER 1973-2007

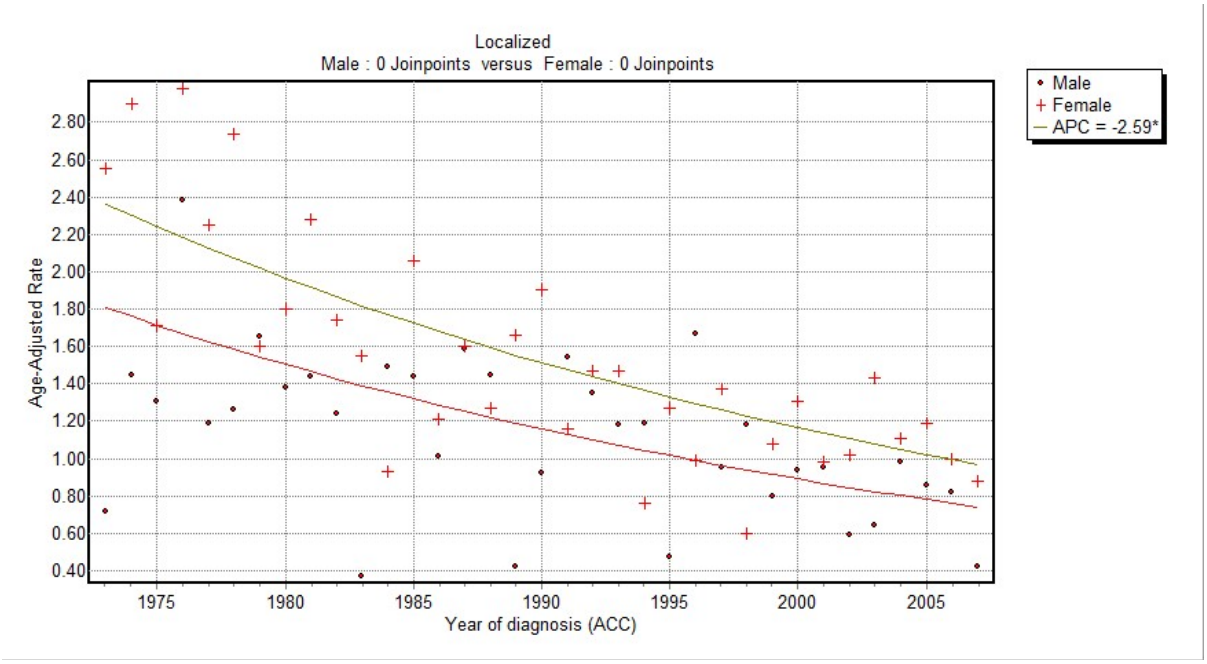

Figure 3: Joinpoint analysis of ACCHN incidence by sex: Regional stage SEER 1973-2007

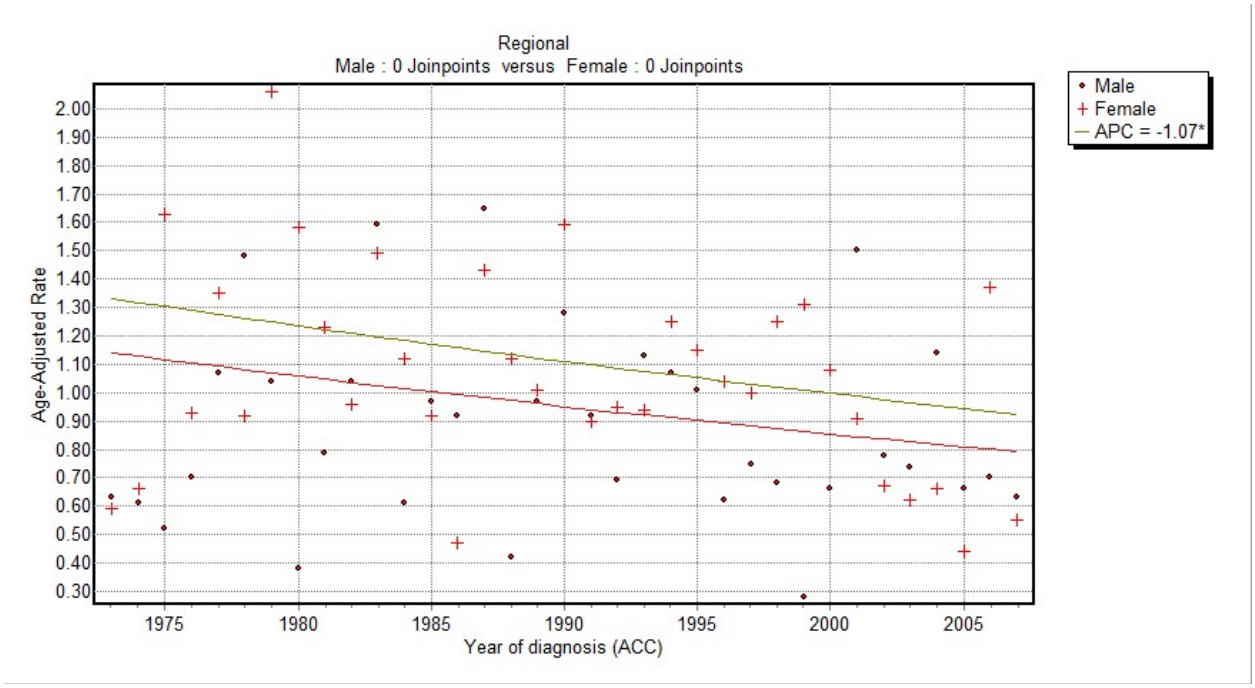

Figure 4: Joinpoint analysis of ACCHN incidence by sex: Distant stage SEER 1973-2007

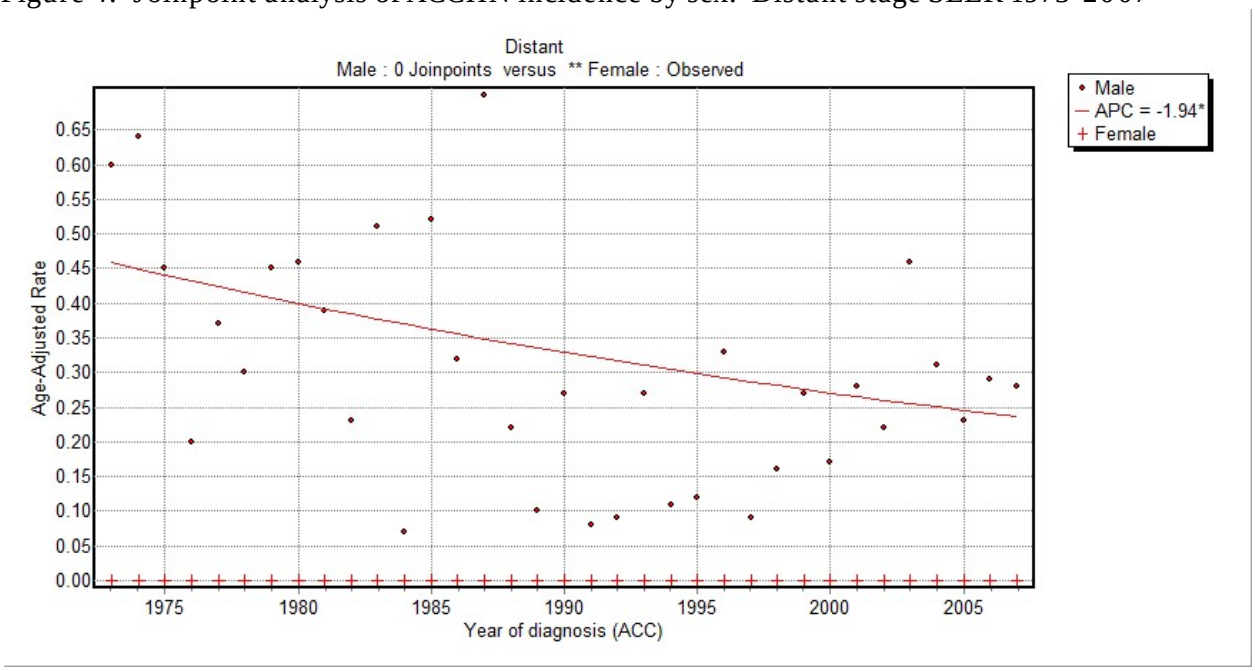

Figure 5: Joinpoint analysis of ACCHN incidence by Stage: Localized vs. Regional SEER 1973-2007

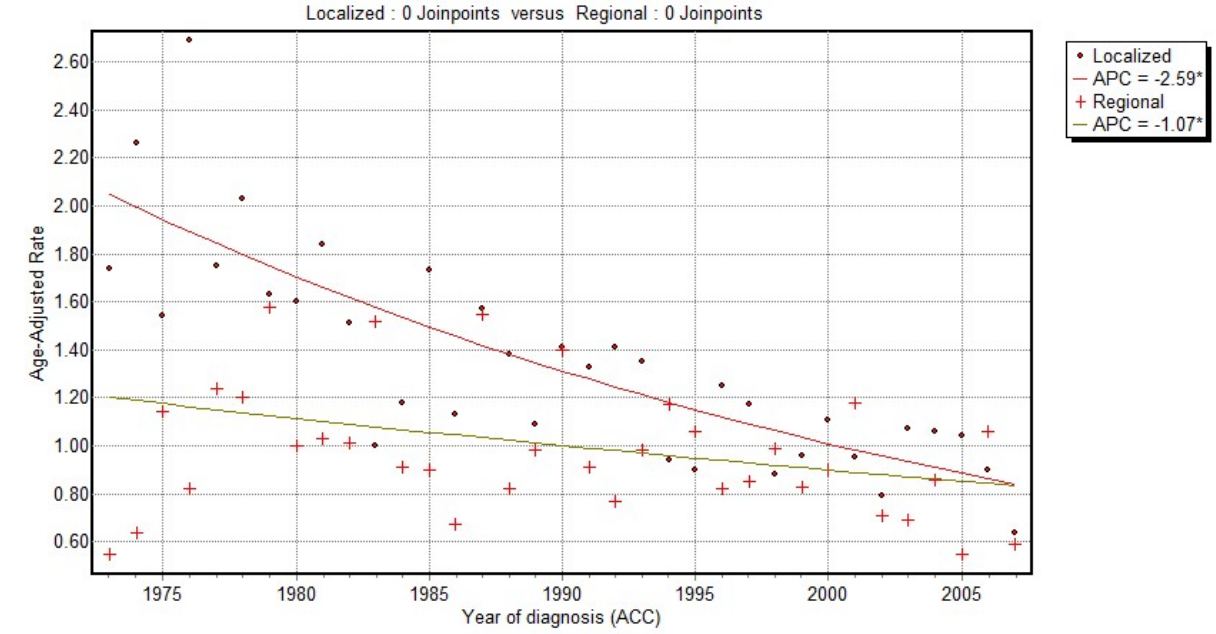

Figure 6: Joinpoint analysis of ACCHN incidence by Stage: Localized vs. Distant SEER 1973-2007

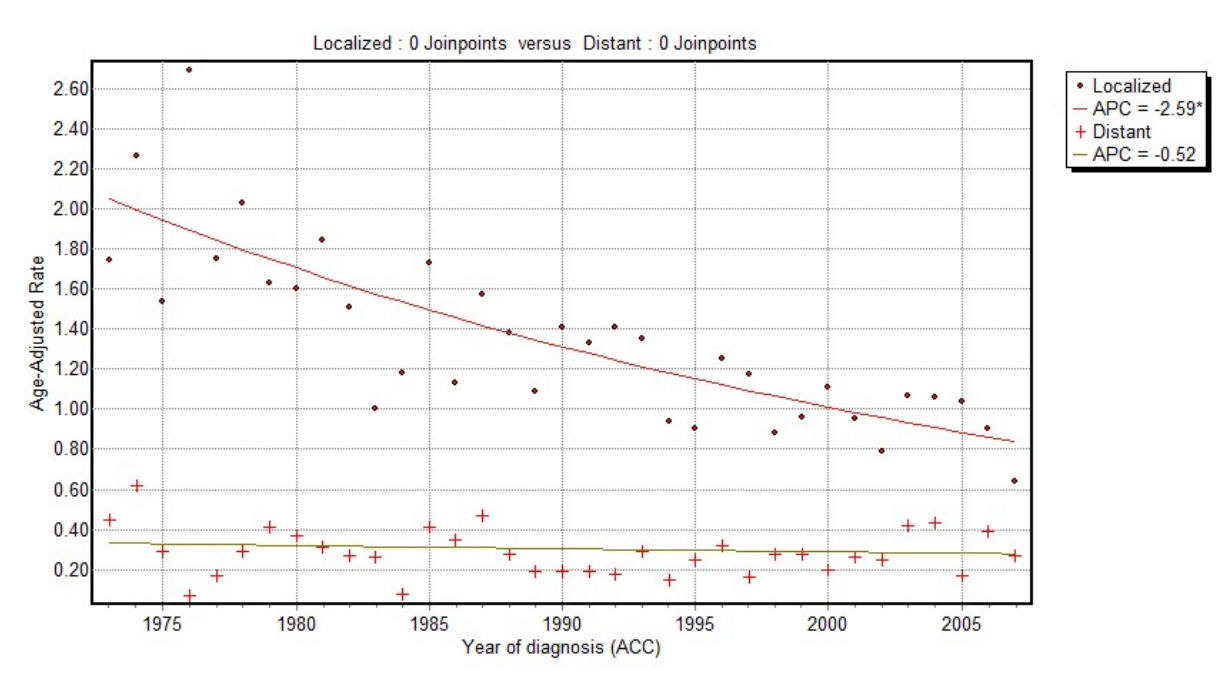

Figure 7: Joinpoint analysis of ACCHN incidence by Stage: Regional vs. Distant stages SEER 1973-2007

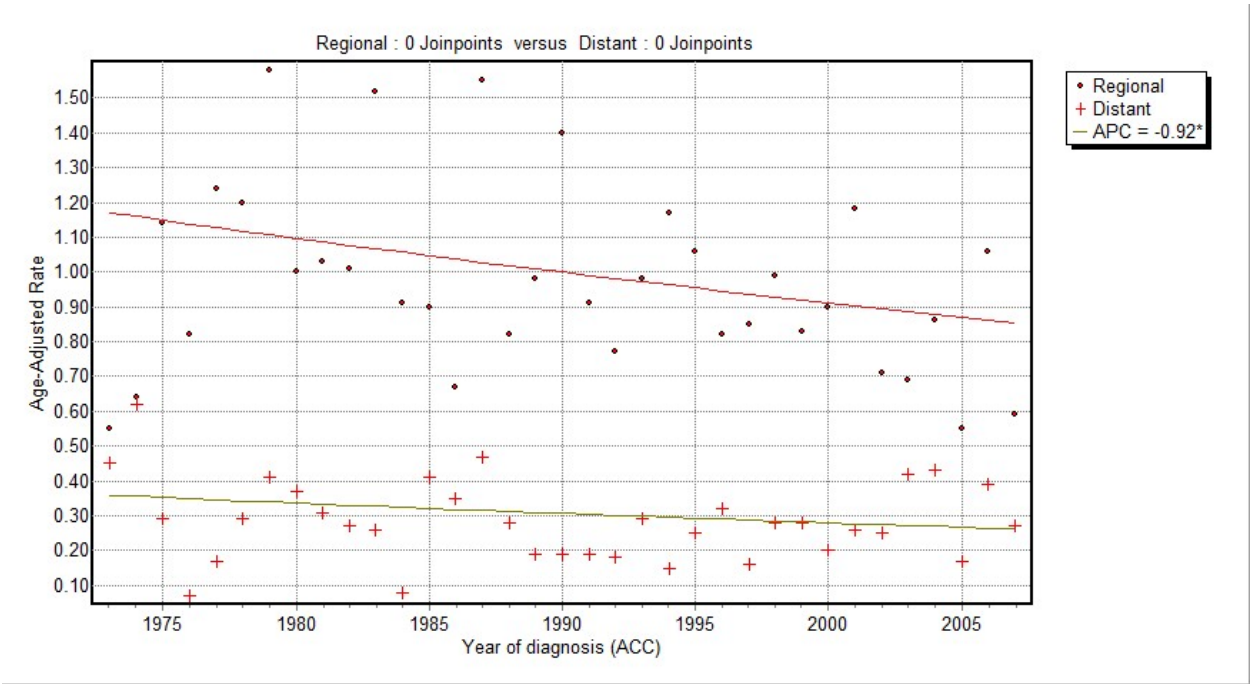

Figure 8: Joinpoint analysis of ACCHN incidence by Race: All Stages SEER 1973-2007

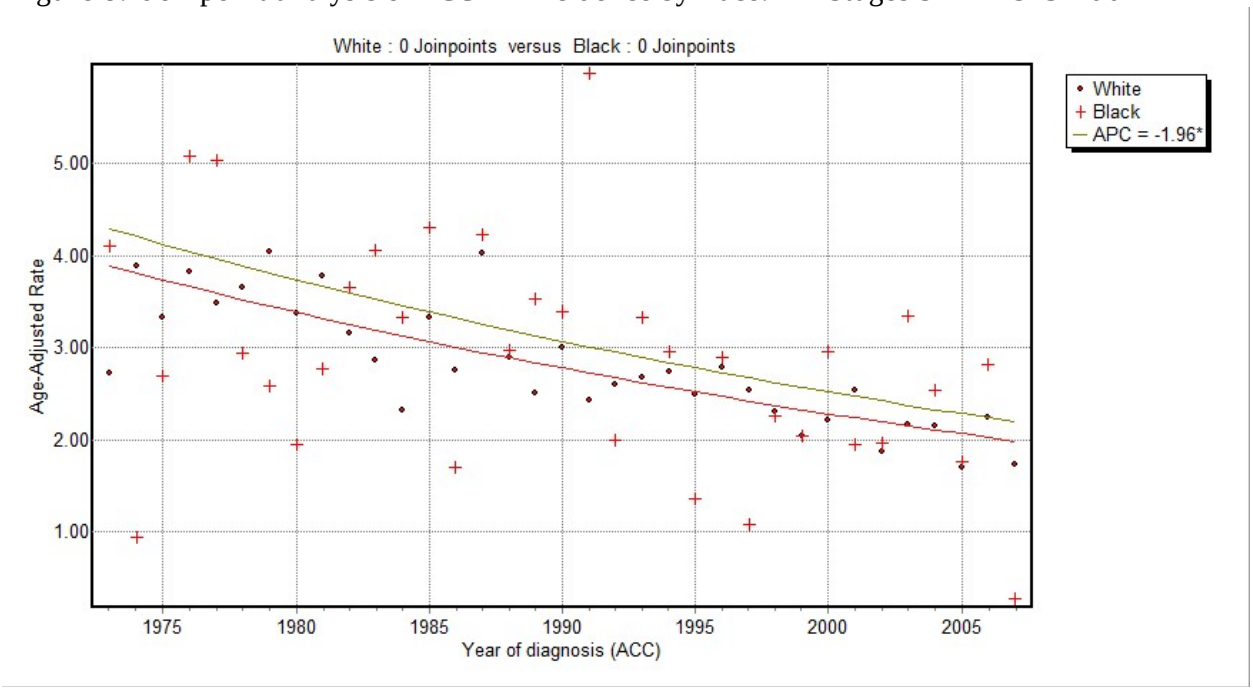

Figure 9: Kaplan-Meier Survival Curve based on Sex (0: Male, 1: Female): All Stages SEER 1973-2007

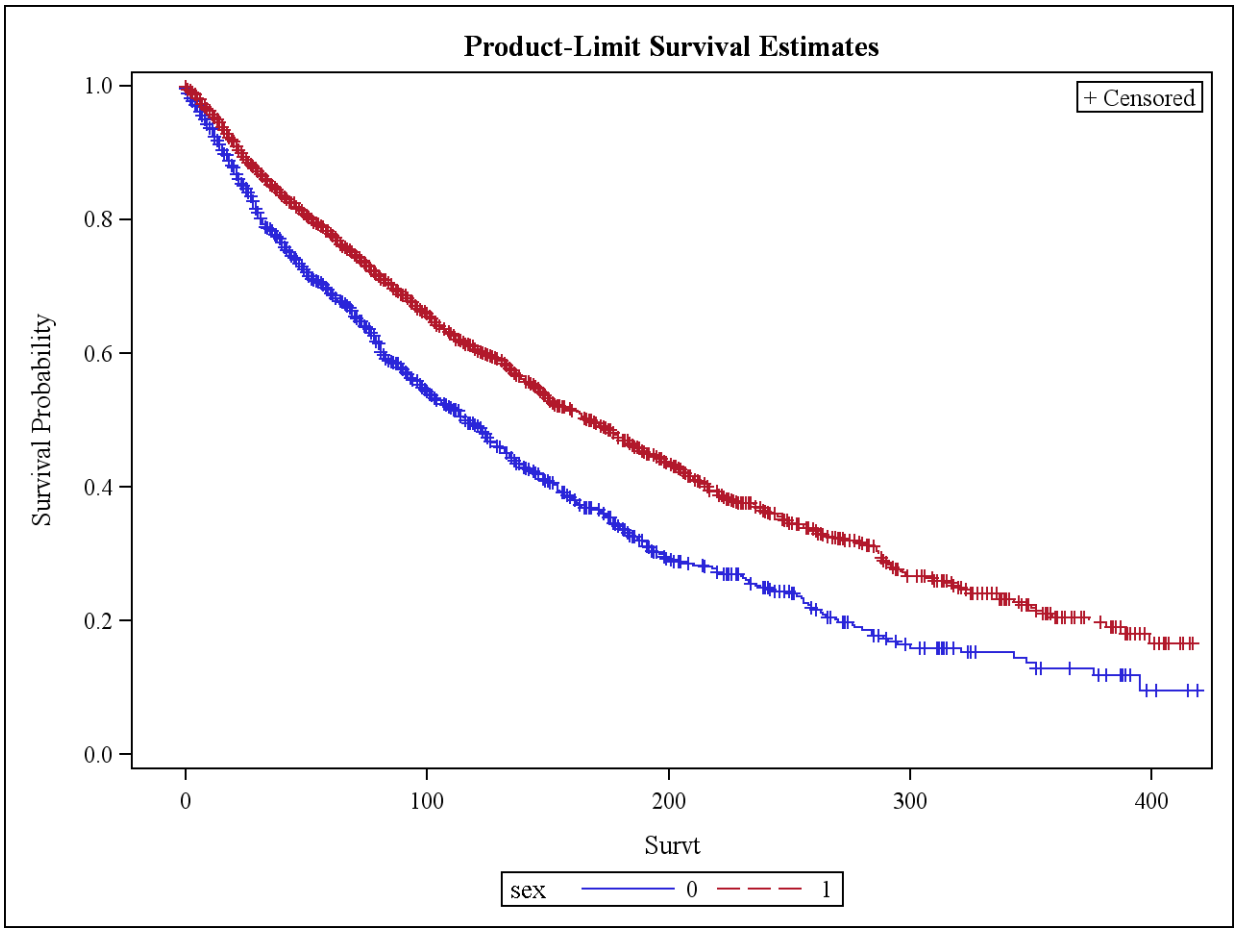

Table 1: Characteristics of adenoid carcinoma cases of head neck by time interval: SEER database, 1973-2007

Case Characteristics	All Cases (n = 3026)		Time Interval 1973-1982 (n = 613)		1983-1992 (n = 639)		1993-2002 (n = 1009)		2003+ (n = 765)	
	N	%	N	%	N	%	N	%	N	%
Male	1,240	40.98%	233	38.01%	267	41.78%	435	43.11%	305	39.87%
Female	1,786	59.02%	380	61.99%	372	58.22%	574	56.89%	460	60.13%
White	2,471	81.66%	537	87.60%	527	82.47%	811	80.38%	596	77.91%
Black	286	9.45%	45	7.34%	66	10.33%	96	9.51%	79	10.33%
Asian or Pacific Islander	235	7.77%	24	3.92%	43	6.73%	89	8.82%	79	10.33%
Other*	34	1.12%	7	1.14%	3	0.47%	13	1.29%	11	1.44%
Localized	1372	45.34%	325	53.02%	291	45.54%	440	43.61%	316	41.31%
Regional	1101	36.38%	182	29.69%	234	36.62%	411	40.73%	274	35.82%
Distant	350	11.57%	55	8.97%	55	8.61%	107	10.60%	133	17.39%
Unstaged**	203	6.71%	51	8.32%	59	9.23%	51	5.05%	42	5.49%
Salivary Gland	1,754	57.96%	345	56.28%	332	51.96%	598	59.27%	479	62.61%
Oral Cavity	1,117	36.91%	238	38.83%	268	41.94%	357	35.38%	254	33.20%
Neck/Pharynx	138	4.56%	28	4.57%	31	4.85%	48	4.76%	31	4.05%
Other***	17	0.56%	2	0.33%	8	1.25%	6	0.59%	1	0.13%

* American Indian, Alaska Native, or unspecified
** Using SEER Historic Stage A
*** Site Recode: Other Oral Cavity and Pharynx

Table 2a: Relative Survival of ACCHN by Time Interval (5yr, 10yr, 15yr): SEER database, 1973-2007

All Cases	1973-1982 (N = 566)			1983-1992 (N = 589)			1993+ (N = 1555)		
	RS	95% Cum CI		RS	95% Cum CI		RS	95% Cum CI	
60 mo	86.44%	82.05%	89.83%	85.57%#	81.32%#	88.91%#	82.48%#	79.58%#	85.01%#
120 mo	75.54%#	69.96%#	80.23%#	74.13%#	68.70%#	78.76%#	69.14%#	64.39%#	73.39%#
179 mo	66.62%	60.14%	72.29%	66.68%#	60.39%#	72.20%#	60.24%#	52.46%#	67.15%#
	1973-1982 (N = 220)			**1983-1992 (N = 242)**			**1993+ (N = 649)**		
Males	RS	95% Cum CI		RS	95% Cum CI		RS	95% Cum CI	
60 mo	79.57%	71.51%	85.57%	80.54%#	73.24%#	86.03%#	79.90%#	65.23%#	54.10%#
120 mo	65.90%#	56.35%#	73.84%#	68.30%#	59.14%#	75.83%#	75.23%#	57.70%#	42.39%#
179 mo	54.02%	43.63%	63.30%	58.93%#	49.00%#	67.57%#	83.78%#	71.75%#	64.42%#
	1973-1982 (N = 346)			**1983-1992 (N = 347)**			**1993+ (N = 906)**		
Females	RS	95% Cum CI		RS	95% Cum CI		RS	95% Cum CI	
60 mo	90.35%#	85.06%#	93.83%#	88.67%#	83.27%#	92.40%#	84.23%#	80.44%#	87.35%#
120 mo	81.26%#	74.15%#	86.59%#	77.63%#	70.76%#	83.07%#	71.67%#	65.27%#	77.10%#
179 mo	73.87%	65.46%	80.53%	71.23%#	63.11%#	77.88%#	64.26%#	53.83%#	72.93%#

Kaplan-Meier method. No adjustment for heterogeneity.
Confidence interval: Log(-Log()) Transformation. The level is 95%.
* If the relative cumulative survival is over 100 percent, it has been adjusted.
\# If the relative cumulative survival increased from a prior interval, it has been adjusted.
\+ The statistic could not be calculated.

Table 2b: Relative Survival of ACCHN by Time Interval (5yr, 10yr, 15yr): SEER database, 1973-2007

	1973-1982 (N = 494)			**1983-1992 (N = 481)**			**1993+ (N = 1216)**		
White	RS	95% Cum CI		RS	95% Cum CI		RS	95% Cum CI	
60 mo	87.27%	82.47%	90.83%	86.17%#	81.38%#	89.80%#	82.40%	79.04%	85.27%
120 mo	76.17%#	70.08%#	81.19%#	76.17%#	70.04%#	81.22%#	70.02%#	64.64%#	74.75%#
179 mo	67.20%	60.11%	73.30%	68.86%#	61.71%#	74.95%#	60.42%#	51.32%#	68.35%#
	1973-1982 (N = 42)			**1983-1992 (N = 64)**			**1993+ (N = 159)**		
Black	RS	95% Cum CI		RS	95% Cum CI		RS	95% Cum CI	
60 mo	81.40%#	64.19%#	90.89%#	81.21%#	65.54%#	90.26%#	85.23%#	75.58%#	91.28%#
120 mo	73.42%#	50.91%#	86.82%#	66.33%#	48.09%#	79.43%#	65.23%#	49.33%#	77.24%#
179 mo	66.45%#	43.04%#	82.03%#	55.58%#	36.37%#	71.10%#	56.24%#	34.22%#	73.43%#
	1973-1982 (N = 23)			**1983-1992 (N = 41)**			**1993+ (N = 157)**		
Asian/P.I.	RS	95% Cum CI		RS	95% Cum CI		RS	95% Cum CI	
60 mo	73.41%#	47.66%#	87.90%#	84.25%#	66.17%#	93.13%#	78.47%#	68.46%#	85.63%#
120 mo	58.52%#	32.88%#	77.25%#	62.32%#	42.94%#	76.76%#	65.47%#	49.97%#	77.21%#
179 mo	41.74%#	19.06%#	63.10%#	53.24%#	34.04%#	69.17%#	65.47%#	49.97%#	77.21%#

Kaplan-Meier method. No adjustment for heterogeneity.
Confidence interval: Log(-Log()) Transformation. The level is 95%.
* If the relative cumulative survival is over 100 percent, it has been adjusted.
\# If the relative cumulative survival increased from a prior interval, it has been adjusted.
\+ The statistic could not be calculated.

*Table 3: Multivariate Analysis: Adjusted Cox Proportional Hazard Model (Stratified by Age and Stage)**

Variable	Categories	HR	95% Confidence Interval	
Sex	Male	1.0 (ref)	-	-
	Female	0.72	0.64	0.81
Marital Status	Not Married**	1.0 (ref)	-	-
	Married	0.85	0.75	0.97
Surgery of Primary Site	No	1.0 (ref)	-	-
	Yes	0.50	0.42	0.61
Race	White	1.0 (ref)	-	-
	Black	1.15	0.94	1.41
Radiation Therapy	No	1.0 (ref)	-	-
	Yes	1.03	0.91	1.17
Site of Primary Tumor	Salivary Gland	1.0 (ref)	-	-
	Oral Cavity	0.84	0.74	0.95
	Neck/Pharynx	1.46	1.13	1.89
	Other	1.47	0.69	3.13
Year of Diagnosis	1973-1982	1.0 (ref)	-	-
	1982-2007	1.01	0.94	1.09

*Model adjusted by age and stage of disease at diagnosis
**Includes: Single, Widowed, Separated, and Divorced