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Incidence, stage of diagnosis and survival of gastro-esophageal cancers in rural, urban and metropolitan areas of the United States: 2004-2009

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By

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

Incidence, stage of diagnosis and survival of gastro-esophageal cancers in rural, urban and metropolitan areas of the United States: 2004-2009

By Zhensheng Wang

Background: This study aimed to assess the differences of incidence, late stage diagnosis and prognosis of three malignancies – squamous cell carcinoma of the esophagus (SCCE), adenocarcinoma of the esophagus (AE) and adenocarcinoma of the gastric cardia (AGC) – in metro, urban and rural areas in the United States.

Methods: We identified 29,527 cases of SCCE, AE or AGC reported to the Surveillance, Epidemiology, and End Results program between 2004 and 2009. Incidence estimates for each malignancy were compared across metro, urban and rural areas. Multivariable logistic regression models were applied to evaluate the association between residential setting and late (distant stage) diagnosis with results expressed as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Kaplan-Meier survival curves and Cox proportional hazard models were used to examine the association between residential setting and survival.

Results: Using metropolitan population centers as reference, incidence of AE was found to be higher in urban (rate ratio [RR]=1.13, 95% CI: 1.06, 1.20) and rural (RR=1.15, 95%: 1.05, 1.25) areas, while incidence of SCCE was lower in rural areas (RR=0.80, 95%: 0.70, 0.91). Rural patients were less likely to be diagnosed with stage IV AE compared to those residing in metropolitan areas (OR=0.79, 95% CI: 0.65, 0.97). No significant differences in prognosis of either malignancy were observed among patients residing in metro, urban and rural areas.

Conclusion: These findings indicate that certain preconceptions about urban/rural disparities in the United States are either unwarranted or out-of-date at least with respect to gastroesophageal cancers.

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Table of Contents

Background: 1

Methods: 3

Results: 6

Incidence Rates 6

Predictors of advanced (AJCC stage IV) disease 7

Survival Analysis 8

Discussion: 9

Conclusion: 13

References: 14

Tables and Figures 19

Background:

At least three unique tumor types arise from the mucosal lining of the esophagus and proximal part of the stomach. These include: squamous cell cancer of the esophagus (SCCE), adenocarcinoma of the esophagus (AE) and adenocarcinoma of the gastric cardia (AGC). Even though esophageal cancer is relatively uncommon in the United States the incidence of esophageal and proximal gastric adenocarcinomas is rapidly increasing [1].

SCCE is the predominant malignancy in the cervical and upper two thirds of the thoracic esophagus. The incidence of SCCE peaked in the early 1980s and since then started to decline to the current estimate of approximately 10 per 100,000 person-years. SCCE is more common among African American men [1]. Etiologic factors associated with SCCE include alcohol consumption, smoking, diet rich in highly salted food, and eating rapidly without sufficient mastication [2-5].

AE and AGC originate in the distal third of the esophagus and below gastroesophageal junction, respectively [6-7]. The incidence rates of AE have increased by more than 300% in the past two decades [8]. The incidence for AGC has also been increasing at a rate of 400% per year. Both AE and AGC have a elevated male to female ratio and are more common in Caucasians than in African Americans [1]. Etiologic factors associated with AE and GCA include, smoking [9], obesity [4][11], gastroesophageal reflux disease, lack of physical exercises and sedentary lifestyles [11-12].

The prevalence of the above risk factors differs across populations of rural, urban

and metropolitan areas of the US [13-15]. The population of the rural or small town areas may have less access to healthcare and as such maybe diagnosed at a later stage. Moreover, as the treatment of SCCE, AE and AGC is complex and requires multimodality approach [16-17], access to tertiary healthcare centers is expected to be limited for the patients living in remote rural areas or in small towns located far from metropolitan population centers. This is expected to have a negative impact on the survival of patients living in rural or small urban areas relative to metropolitan centers. We hypothesized that the incidence, stage at diagnosis and survival for SCCE, AE and AGC will be different in non-metropolitan and metropolitan areas.

In order to test the hypothesis, the data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program were analyzed. The SEER registry covers approximately 28% of the US population [18] and includes information on the Rural-Urban Continuum Code (RUCC) that describes residential setting for each newly diagnosed cancer case. In addition, the SEER data from 1973 to 2011 were examined for secular trends in SCCE, AE and AGC incidence and survival by type of geographic setting and across main population groups.

Methods:

The research data were obtained from the SEER Program and covered the period from January 1, 2004 through December 31, 2009. To distinguish between metro, urban and rural counties, the 2003 Rural-Urban Continuum Code (RUCC) developed by the United States Department of Agriculture (USDA) was used. The RUCC scheme classifies metropolitan counties based on the population size and further subdivides the nonmetropolitan (non-metro) counties by degree of urbanization and adjacency to a metro area or areas [19].

The residential setting, the main independent variable of interest in this study, was categorized as metro, urban or rural based on county RUCC values of 1 to 3, 4 to 6 and 7 to 9, respectively. Race was dichotomized as 'African American' and 'white'; since other race categories had insufficient number of observations. Persons categorized as neither white nor African American were excluded from the analyses. For the purpose of our study, the American Joint Committee on Cancer (AJCC) staging, 6th edition [20] was used. The primary site and morphology for esophagus and gastric cardia applied in the study were coded according to the International Classification of Diseases for Oncology, third edition (ICD-O-3) [21]. The codes for esophagus and gastric cardia were C15.0-C15.9 and C16.0, respectively. Esophageal carcinoma was further categorized into two histological groups: squamous cell carcinoma (M8058-8082) and adenocarcinoma (M8140-8573). All gastric cardia cancers in this analysis were adenocarcinomas.

Using data from 18 SEER registries dating from 2004 to 2009, the incidence rates

of SCCE, AE and AGC (age adjusted to 2000 US-Standard population) were calculated separately for metro, urban and rural areas. These comparisons were carried out for all cases combined, and stratified on race and gender. Results were expressed as rate ratios (RR) accompanied by the corresponding 95% confidence intervals (CI).

Since population in rural areas or small towns may be diagnosed at a later stage due to differences in access to care, the association between residential setting and late (distant stage) diagnosis was evaluated using multivariable logistic regression models. Data were derived from 18 SEER registries for the years 2004-2009. The covariates in all models included age of diagnosis, gender, race, marital status and region. The results of these multivariable logistic regression analyses were expressed as adjusted odds ratios (ORs) accompanied by 95% CIs.

The differences in survival for SCCE, AE and AGC across different residential settings were then studied by constructing Kaplan-Meier curves accompanied by log-rank tests for statistical significance. Multivariable Cox proportional hazard models were then used to further examine the association between residential setting and survival with results expressed as adjusted hazard ratios (HRs) and 95% CIs. The models adjusted for potential confounders including gender, age, race, marital status, surgery and radiotherapy and AJCC stage. Proportional hazard (PH) assumptions were tested for each model by examining the log-log survival curves for all independent variables under study. If the PH assumption was violated extended Cox models were used.

All analyses were performed using SAS 9.2 (SAS Institute Inc. NC, USA), and SEER*Stat version 7.1.0 (National Cancer Institute, Bethesda, Md. USA) statistical software packages.

Results:

A total of 29,527 gastroesophageal cases were reported to SEER from 2004 through 2009, among which 7,456 (25.3%) were SCCE, 12,814 (43.4%) AE and 9,257 (31.3%) AGC. As shown in Table 1, 86.8% (N=25,598) of the total cases were from metro areas while 9.2% (N=2,707) and 4.0% (N=1,169) of cases were from urban and rural areas, respectively. Among all cases 72.7% (N=21,451) were over 60 years of age at the time of diagnosis. The total study group consisted of 77.5% (N=22,894) male patients, the majority of cases (84.9%, N=25,062) were observed among whites and more than half (57.4%, N=16,958) of the patients were married. Advanced (AJCC stage IV) disease was found at diagnosis in 25.5%, 34.7% and in 36.1% of SCCE, AE and AGC cases; respectively.

Incidence Rates

Compared to metro areas the overall incidence rates of SCCE in urban areas (RR=1.12, 95% CI: 1.03, 1.21), AE in urban areas (RR=1.13, 95% CI: 1.06, 1.20) and AE in rural areas (RR=1.15, 95% CI: 1.06, 1.25) were significantly higher (Table 2). On the other hand, incidence of SCCE (RR=0.80, 95% CI: 0.70, 0.91) was lower in rural than in metro areas. African Americans had a pronounced increase in incidence of SCCE in urban (RR=1.49, 95% CI: 1.29, 1.72) and rural (RR=1.60, 95% CI: 1.24, 2.04) areas compared to African American populations of metro areas, while among whites rural areas experienced lower incidence of SCCE relative to metro areas (RR=0.76, 95% CI: 0.64, 0.88). Female residents of rural areas had a lower

incidence of SCCE, AE and AGC than their counterparts in metro area. For male patients, incidence of AE was significantly higher in rural (RR=1.12, 95% CI: 1.05, 1.19) and urban areas (RR=1.20, 95% CI: 1.10, 1.31) while incidence of SCCE was also elevated among urban males compared to men living metro areas (RR=1.17, 95% CI: 1.06, 1.29) .

Predictors of advanced (AJCC stage IV) disease

As shown in Table 3 patients in rural areas were less likely to be diagnosed with stage IV AE compared to those residing in metropolitan areas (adjusted OR=0.79, 95% CI: 0.65, 0.97). No statistically significant results were found in any other analyses of the association between type of residence (metro, urban or rural) and advanced diagnosis stage for any other cancer sites. A comparison of the likelihood of stage IV diagnosis among black patients compared to whites produced ORs (95% CIs) of 1.06 (0.92-1.22) for SCCE, 1.03 (0.80-1.32) for AE, and 1.32 (1.08-1.62) for GCA. The frequency of stage IV diagnosis decreased as the age of diagnosis increased for all three cancer types. Another strong predictor for stage IV disease was marital status; using married patients as the reference category the adjusted ORs for single patients were significantly elevated in all analyses with a range between 1.16 and 1.22. The corresponding associations comparing married patients to those categorized as widowed, separated or divorced were less pronounced (Table 3).

Survival Analysis

As shown in figure 1, no significant differences in survival of metro urban and rural patients were observed for any of the three malignancies. The results of survival analyses are shown in Table 4. For all three cancer types there were no significant differences in survival between patients living in urban and rural areas compared to their metro counterparts. Black patients experienced higher mortality than white patients with HR (95 % CI) estimates of 1.12 (1.05, 1.20), 1.19 (1.04, 1.36) and 1.16 (1.04, 1.30) for SCCE, AE, and AGC, respectively. Surgery of primary site significantly reduced mortality for all three malignancies by approximately 60%. The corresponding reduction in mortality attributable to radiation therapy was in the 32-55% range. Not married patients had a modest but statistically significant decrease in survival compared to patients who were married at the time of diagnosis. For all three malignancies, there was a clear inverse relation between AJCC stage and survival. .

Discussion:

Although SCCE, AE and AGC arise in the same organ, they represent three distinct disease entities. The risk factors for these malignancies include race [22], gender [23], and lifestyle characteristics such as obesity [4, 11], predominance of sedentary activities [12, 24], and consumption of tobacco and alcohol [5, 9]. Previous literature showed that race [25], gender [25], age [25], surgery [26] and neoadjuvant therapy (chemotherapy or chemoradiotherapy) [27, 28] are potential determinants for the prognosis of gastro-esophageal cancers including SCCE, AE and AGC.

Our hypothesis was that incidence and outcomes of SCCE, AE and AGC vary across populations in the metro, urban and rural areas. We postulated *a priori* that differences in lifestyles would result in lower incidence of AE and CA in the rural populations and that decreased access to specialized care in rural areas would adversely affect timeliness of diagnosis and survival.

Contrary to expectations, the analysis of the observed overall incidence of SCCE and AGC across metro, urban and rural areas demonstrated that the incidence is similar in all three groups of patients. This observation suggests that the overall prevalence of obesity, sedentary lifestyle, reflux disease, tobacco and alcohol consumption may not be significantly different in residents of rural regions, small towns or metropolitan population centers. The only exception from this pattern was the somewhat pronounced increase in incidence of SCCE among rural and urban blacks compared to blacks residing in metropolitan population centers.

With respect to outcome, the results of the analysis did not reveal any significant

differences in the stage distribution between the rural and metro populations. Similarly, no significant difference in overall survival was observed. These observations suggest that the access to healthcare and quality of therapy may not be that different in large cities compared to small towns or rural areas. Our findings are consistent with a recent study of breast cancer patients in Southwest Georgia, which reported that metro and non-metro patients experienced no significant differences in receiving or completing chemotherapy [29]. In a study comparing in-hospital mortality among recipients of cancer surgery between urban and rural hospitals, Martin et al. found that receiving treatment at a rural hospital did not confer a worse prognosis. [30]. Another recent study also found that rural residence was not associated with late stage diagnosis or receipt of treatment among colorectal cancer patients in Georgia [31].

Married SCCE, AE and AGC patients were more likely to have earlier stage disease compared with those who were reported to be single, widowed, divorced or separated. Similar observations have been reported in studies of colon [32], breast [33] and prostate cancer [34]. Moreover, married SCCE, AE and AGC patients had better prognosis compared to patients who at the time of diagnosis were not married. This finding was in accordance with the previously reported results indicating that married AE and Barrett's esophagus patients r had a higher quality of life compared to single patients [35]. Possible explanation is that support provided by a spouse could have a beneficial effect on health care through seeking care early in the course of the disease. On the other hand, several studies [36, 37] suggested that health

affects marital status, which means people in robust health tended to get and stay married.

Young age was a strong risk factor for late stage diagnosis of SCCE, AE and AGC and our data supported a dose-response relation between age and the likelihood of being diagnosed with a more advanced disease. In this respect our study is in agreement with at least one previous report that indicated a moderate association between higher stage of breast cancer and young age [38].

The link of younger age to higher stage of SCCE, AE and GCA cannot be readily explained and that will need further evaluation. It is possible that non-specific early symptoms of cancer in younger population are more likely to be attributed to benign disease, which in turn may delay the correct diagnosis. On the other hand, malignancies in younger patients may be more aggressive and characterized by the early presence of metastasis.

No racial differences in stage distribution were found for SCCE, AE; however black AGC patients were more likely to be diagnosed with advanced disease compared to whites. There was also a modest but statistically significant racial disparity in survival with black patients showing worse prognosis for all three malignancies. This observation is agreement with other studies showing that black race is associated with lower likelihood of receiving surgery [39] and worse survival among esophageal cancer patients [40].

Among patients with all three malignancies, those who received surgery of primary site had a better prognosis than those who did not. In another SEER study

focusing on the temporal trends of esophageal cancer from 1970s, the median survival of local, regional and metastatic esophageal cancer improved from 11, 10 and 4 months in 1970s to 35, 15 and 6 months after 2000. Meanwhile, percentages of patients undergoing surgery increased from 55% in the 1970s to 64% between 2000 and 2007. In that study, the authors concluded that complete cure of non-metastatic esophageal cancer was possible based on early diagnosis and treatment [25]. Our findings further confirm the protective effect of surgery on gastroesophageal cancer outcomes. Previous literature pointed out that radiation therapy along with surgery could improve survival of esophageal cancer compared with radiation therapy alone [41, 42]. However, in our study radiation therapy significantly improved the prognosis of all three malignancies independently of surgery.

The interpretation of these findings requires understanding of the strengths and limitations of the SEER data. As previously noted elsewhere [43, 44], the large sample size enables SEER-based studies to have sufficient power of detecting relatively moderate associations and permits a variety of multivariable analyses. The population based, as opposed to institution-based, identification of cases increases the generalizability of findings and the active follow-up of cases improves the accuracy of survival analyses. While institutional studies often have more detailed information about each patient, those studies usually are confined to major referral centers and may not be representative of the SCCE, AE and AGC cases treated in community hospitals and clinics.

The main limitations of this study pertain to the lack of data on certain important

clinical and demographic variables. While SEER data on surgery and radiation are reasonably complete, the information pertaining to systemic treatment such as chemotherapy is usually missing and is not included the public use files. In addition, SEER data do not contain information on such important predictors of survival as lifestyle characteristics, health insurance and socioeconomic status all of which may determine incidence and outcomes of cancers including SCCE, AE and AGC. Another important data item that may need to be considered is the effect of provider- and facility-related characteristics, which cannot be addressed in the context of SEER-based research. For all of the above reasons, both cancer registry-based and institution-based studies provide useful non-overlapping information that contributes to the evidence despite their strengths and limitations [45, 46].

Conclusion:

No significant differences in incidence, late stage diagnosis or survival of SCCE, AE and AGC were found across metro, urban and rural populations. These findings add to the growing evidence that certain preconceptions about urban/rural disparities in the United States are either unwarranted or out-of-date.

References:

[1] Ries I., Melbert D, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2004. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/css/1975-2004, based on November 2006 SEER data submission, posted to SEER website, 2007

[2] Brown LM, Hoover R, Silverman D, Baris D, Hayes R, Swanson GM, et al. Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors. Am J Epidemiol. 2001; 153(2): 114-22.

[3] Brown LM, Silverman DT, Pottern LM, Schoenberg JB, Greenberg RS, Swanson GM, et al. Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States: alcohol, tobacco, and socioeconomic factors. Cancer Causes Control. 1994; 5(4): 333-40.

[4] Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med. 1999; 130(11): 883-90.

[5] Yu MC, Garabrant DH, Peters JM, Mack TM. Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. Cancer Res. 1988; 48(13): 3843-8.

[6] DeVita, Hellman, Rosenberg. Cancer Principles & Practice of Oncology, 8th ed. Vol. 1 Philadelphia: Lippincott Williams & Wilkins Inc., 2008.

[7] Siewert JR, Feith M. Werner, M.Stein HJ. Adenocarcinoma of the esophagogastric junction. Results of surgical therapy based on anatomic-topographic classification in 1,002 consecutive patients. Ann Surg 2000; 232:353

[8] Jermal A, Seiegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin, 2006; 56(2); 106

[9] Figueroa JD, Terry MB, Gammon MD, Vaughan TL, Risch HA, Zhang FF, et al. Cigarette smoking, body mass index, gastro-esophageal reflux disease, and non-steroidal anti-inflammatory drug use and risk of subtypes of esophageal and gastric cancers by P53 overexpression. Cancer Causes Control. 2009; 20(3): 361-8.

[10] Mayne ST, Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. J Nutr. 2002; 132(11 Suppl): 3467S-70S.

[11] Etemadi A, Golozar A, Kamangar F, Freedman ND, Shakeri R, Matthews C, et al. Large body size and sedentary lifestyle during childhood and early adulthood and esophageal squamous cell carcinoma in a high-risk population. Ann Oncol. 2012; 23(6): 1593-600.

[12] Vigen C, Bernstein L, Wu AH. Occupational physical activity and risk of adenocarcinomas of the esophagus and stomach. Int J Cancer. 2006; 118(4): 1004-9.

[13] Parks SE, Housemann RA, Brownson RC. Differential correlates of physical activity in urban and rural adults of various socioeconomic backgrounds in the United States. J Epidemiol Community Health. 2003; 57(1): 29-35.

[14] Befort CA, Nazir N, Perri MG. Prevalence of obesity among adults from rural and urban areas of the United States: findings from NHANES (2005-2008). J Rural Health. 2012; 28(4): 392-7.

[15] Borders TF, Booth BM. Rural, suburban, and urban variations in alcohol consumption in the United States: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. J Rural Health. 2007; 23(4): 314-21.

[16] Chang DT, Chapman C, Shen J, Su Z, Koong AC. Treatment of esophageal cancer based on histology: a surveillance epidemiology and end results analysis. Am J Clin Oncol. 2009; 32(4): 405-10.

[17] Schreiber D, Rineer J, Vongtama D, Wortham A, Han P, Schwartz D, et al. Impact of postoperative radiation after esophagectomy for esophageal cancer. J Thorac Oncol. 2010; 5(2): 244-50.

[18] Surveillance, Epidemiology and End Results (SEER) Overview, National Cancer Institute http://seer.cancer.gov/about/overview

[19] Surveillance, Epidemiology and End Results (SEER) Rural Urban Continuum Code, National Cancer Institute.
http://seer.cancer.gov/seerstat/variables/countyattribs/ruralurban.html

[20] Greene, F. L. , D. L. Page , and I. D. Fleming . et al, eds, for the American Joint Committee on Cancer. AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer-Verlag; 2002

[21] Fritz A, Percy C, Jack A, Sobin L, Parkin DM, Whelan S: International Classification of Diseases for Oncology, ed 3. Geneva, World Health Organization, 2000.

[22] Wu X, Chen VW, Ruiz B, Andrews P, Su LJ, Correa P. Incidence of esophageal and gastric carcinomas among American Asians/Pacific Islanders, whites, and blacks: subsite and histology differences. Cancer. 2006; 106(3): 683-92.

[23] Devesa SS, Blot WJ, Fraumeni JF, Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer. 1998; **83**(10): 2049-53.

[24] Huerta JM, Navarro C, Chirlaque MD, Tormo MJ, Steindorf K, Buckland G, et al.

Prospective study of physical activity and risk of primary adenocarcinomas of the oesophagus and stomach in the EPIC (European Prospective Investigation into Cancer and nutrition) cohort. Cancer Causes Control. 2010; **21**(5): 657-69.

[25] Dubecz A, Gall I, Solymosi N, Schweigert M, Peters JH, Feith M, et al. Temporal trends in long-term survival and cure rates in esophageal cancer: a SEER database analysis. J Thorac Oncol. 2012; 7(2): 443-7.

[26] Wu PC, Posner MC. The role of surgery in the management of oesophageal cancer. Lancet Oncol. 2003; 4(8): 481-8.

[27] Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998; 339(27): 1979-84.

[28] Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol. 2007; 25(24): 3719-25.

[29] Lipscomb J, Gillespie TW, Goodman M, Richardson LC, Pollack LA, Ryerson AB, et al. Black-white differences in receipt and completion of adjuvant chemotherapy among breast cancer patients in a rural region of the US. Breast Cancer Res Treat. 2012; 133(1): 285-96.

[30] Markin A, Habermann EB, Chow CJ, Zhu Y, Vickers SM, Al-Refaie WB. Rurality and cancer surgery in the United States. Am J Surg. 2012; 204(5): 569-73.

[31] Hines RB, Markossian TW. Differences in late-stage diagnosis, treatment, and colorectal cancer-related death between rural and urban African Americans and whites in Georgia. J Rural Health. 2012; 28(3): 296-305.

[32] Wang L, Wilson SE, Stewart 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; 35(5): 417-22.

[33] Osborne C, Ostir GV, Du X, Peek MK, Goodwin JS. The influence of marital status on the stage at diagnosis, treatment, and survival of older women with breast cancer. Breast Cancer Res Treat. 2005; 93(1): 41-7.

[34] Abdollah F, Sun M, Thuret R, Abdo A, Morgan M, Jeldres C, et al. The effect of marital status on stage and survival of prostate cancer patients treated with radical prostatectomy: a population-based study. Cancer Causes Control. 2011; 22(8): 1085-95.

[35] Miller RC, Atherton PJ, Kabat BF, Fredericksen MB, Geno DM, Deschamps C, et

al. Marital status and quality of life in patients with esophageal cancer or Barrett's esophagus: the mayo clinic esophageal adenocarcinoma and Barrett's esophagus registry study. Dig Dis Sci. 2010; 55(10): 2860-8.

[36] Lillard LA, Panis CWA. Marital status and mortality: the role of health. Demography 1996;33:313-27.

[37] Joung IM, van de Mheen HD, Stronks K, van Poppel FW, Mackenbach JP. A longitudinal study of health selection in marital transitions. Soc Sci Med 1998;46(February (3)):425-35

[38] Partridge AH, Hughes ME, Ottesen RA, Wong YN, Edge SB, Theriault RL, et al. The effect of age on delay in diagnosis and stage of breast cancer. Oncologist. 2012; 17(6): 775-82.

[39] Revels SL, Banerjee M, Yin H, Sonnenday CJ, Birkmeyer JD. Racial Disparities in Surgical Resection and Survival among Elderly Patients with Poor Prognosis Cancer. J Am Coll Surg. 2013; 216(2): 312-9.

[40] Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, McGinn TG, et al. Racial disparities in esophageal cancer treatment and outcomes. Ann Surg Oncol. 2008; 15(3): 881-8.

[41] Suntharalingam M, Moughan J, Coia LR, Krasna MJ, Kachnic L, Haller DG, et al. Outcome results of the 1996-1999 patterns of care survey of the national practice for patients receiving radiation therapy for carcinoma of the esophagus. J Clin Oncol. 2005; 23(10): 2325-31.

[42] Gomi K, Oguchi M, Hirokawa Y, Kenjo M, Ogata T, Takahashi Y, et al. Process and preliminary outcome of a patterns-of-care study of esophageal cancer in Japan: patients treated with surgery and radiotherapy. Int J Radiat Oncol Biol Phys. 2003; 56(3): 813-22.

[43] Ellington CL, G.M., Kono SA, Grist W, Wadsworth T, Chen AY, Owonikoko T, Ramalingam S, Shin DM, Khuri FR, Beitler JJ, Saba NF. , Adenoid cystic carcinoma of the head and neck: Incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data. Cancer 2012. 118(18): p. 4444-51.

[44] Saba NF, G.M., Ward K, Flowers C, Ramalingam S, Owonikoko T, Chen A, Grist W, Wadsworth T, Beitler JJ, Khuri FR, Shin DM. , Gender and ethnic disparities in incidence and survival of squamous cell carcinoma of the oral tongue, base of tongue, and tonsils: a Surveillance, Epidemiology and End Results program-based analysis. . Oncology, 2011. 81(1): p. 12-20

[45] Ludwig MS, G.M., Miller DL, Johnstone PA. , Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer. . Chest 2005. 128: p. 1545-50.

[46] Esiashvili N, G.M., Marcus RB Jr. , Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End Results data. . J Pediatr Hematol Oncol 2008. 30(425-30)

Tables and Figures

Table 1: Characteristics of Gastroesophageal Carcinoma Cases by Histology Types: SEER 2004-2009

Case Characteristics	All Cases (n=29,527)		Histology Types SCCE (n=7,456)		AE (n=12,814)		AGC (n=9,257)	
	N	%	N	%	N	%	N	%
RUCC[1]								
Metro	25,598	86.8%	6,478	87.1%	10,989	85.9%	8,131	88.0%
Urban	2,707	9.2%	715	9.6%	1,216	9.5%	776	8.4%
Rural	1,169	4.0%	244	3.3%	592	4.6%	333	3.6%
Age of Diagnosis								
<50	2,275	7.7%	434	5.8%	1,002	7.8%	839	9.1%
50-59	5,801	19.6%	1,434	19.2%	2,616	20.4%	1,751	18.9%
60-69	8,261	28.0%	2,165	29.1%	3,685	28.8%	2,411	26.0%
70+	13,190	44.7%	3,423	45.9%	5,511	43.0%	4,256	46.0%
Gender								
Male	22,894	77.5%	4,771	64.0%	10,942	85.4%	7,181	77.6%
Female	6,633	22.5%	2,685	36.0%	1,872	14.6%	2,076	22.4%
Race								
White	25,062	84.9%	4,781	64.1%	12,145	94.8%	8,136	87.9%
Black	2,814	9.5%	1,966	26.4%	330	2.6%	518	5.6%
Other[2]	1,651	5.6%	709	9.5%	339	2.6%	603	6.5%
Marital Status								
Married	16,958	57.4%	3,328	44.6%	7,880	61.5%	5,750	62.1%
Single	4,065	13.8%	1,453	19.5%	1,548	12.1%	1,064	11.5%
Div/Sep/Wid[3]	7,229	24.5%	2,346	31.5%	2,805	21.9%	2,078	22.4%
Unknown	1,275	4.3%	329	4.4%	581	4.5%	365	4.0%
SEER Historic Stage								
Localized/Regional	16,048	54.4%	4,164	55.9%	6,783	52.9%%	5,101	55.1%
Distant	10,481	35.5%	2,314	31.0%	4,815	37.6%	3,352	36.2%
Unstaged	2,998	10.1%	978	13.1%	1,216	9.5%	804	8.7%
AJCC Stage[4]								
I/II/III	15,377	52.1%	4,095	54.9%	6,604	51.5%	4,678	50.5%
IV	9,683	32.8%	1,898	25.5%	4,442	34.7%	3,343	36.1%
Unknown Stage	4,464	15.1%	1,463	19.6%	1,765	13.8%	1,236	13.4%

[1] Using 2003 Rural-Urban Continuum Code

[2] American Indian/AK Native, Asian/Pacific Island, Unspecified, or Unknown

[3] Divorced/Seperated/Widowed

[4] Using Derived AJCC Stage, 6th edition, 2004

Table 2: Incidence of SCCE, AE & AGC by race and gender across different residential settings: SEER 2004-2009

		SCCE				AE				GCA			
		Incidence		95% CI		Incidence		95% CI		Incidence		95% CI	
	RUCC[1]	Rate[2]	RR	Lower	Upper	Rate	RR	Lower	Upper	Rate	RR	Lower	Upper
All Cases	Metro	1.52	1.00	Referent		2.56	1.00	Referent		1.90	1.00	Referent	
	Urban	1.70	1.12	1.03	1.21	2.89	1.13	1.06	1.20	1.87	0.98	0.91	1.06
	Rural	1.22	0.80	0.70	0.91	2.94	1.15	1.06	1.25	1.71	0.90	0.80	1.00
Black	Metro	4.01	1.00	Referent		0.71	1.00	Referent		1.14	1.00	Referent	
	Urban	5.99	1.49	1.29	1.72	0.59	0.84	0.51	1.29	1.52	1.32	0.97	1.77
	Rural	6.42	1.60	1.24	2.04	1.06	1.50	0.74	2.70	0.72	0.63	0.25	1.29
White	Metro	1.22	1.00	Referent		3.00	1.00	Referent		2.07	1.00	Referent	
	Urban	1.23	1.01	0.91	1.11	3.26	1.08	1.02	1.16	1.88	0.90	0.84	0.98
	Rural	0.92	0.76	0.64	0.88	3.08	1.03	0.94	1.12	1.79	0.87	0.77	0.97
Male	Metro	2.16	1.00	Referent		4.91	1.00	Referent		3.32	1.00	Referent	
	Urban	2.52	1.17	1.06	1.29	5.48	1.12	1.05	1.19	3.35	1.01	0.92	1.09
	Rural	1.95	0.90	0.77	1.05	5.88	1.20	1.10	1.31	3.04	0.92	0.80	1.04
Female	Metro	1.01	1.00	Referent		0.68	1.00	Referent		0.78	1.oo	Referent	
	Urban	1.00	0.99	0.86	1.14	0.72	1.05	0.89	1.23	0.63	0.82	0.68	0.97
	Rural	0.60	0.60	0.45	0.77	0.48	0.70	0.52	0.94	0.60	0.77	0.59	0.99

[1] Using 2003 Rural-Urban Continuum Code

[2] Per 100,000 and age adjusted to 2000 US-Std Population

Table 3: Logistic Regression Model Evaluating Predictors of Stage IV[1] Cases among SCCE, AE and AGC Patients: SEER 2004-2009

Case Characteristics	SCCE (n=5,428)					AE (n=10,775)					AGC (n=7,517)				
	Stage IV	Stage I-III	adjusted OR	95% CI		Stage IV	Stage I-III	adjusted OR	95% CI		Stage IV	Stage I-III	adjusted OR	95% CI	
				Lower	Upper				Lower	Upper				Lower	Upper
RUCC[2]															
Metro	1,502	3,200	1.00	Referent		3,732	5,512	1.00	Referent		2,751	3,847	1.00	Referent	
Urban	141	386	0.82	0.66	1.01	415	623	1.01	0.88	1.16	268	376	0.98	0.83	1.16
Rural	68	131	1.15	0.84	1.58	167	326	0.79	0.65	0.97	111	164	0.97	0.75	1.25
Age															
70+	634	1,682	1.00	Referent		1,483	2,866	1.00	Referent		1,193	2,026	1.00	Referent	
60-69	534	1,105	1.24	1.07	1.43	509	527	1.32	1.20	1.45	867	1,213	1.20	1.07	1.35
50-59	369	682	1.39	1.18	1.64	1,017	1,168	1.68	1.51	1.87	651	747	1.45	1.27	1.66
<50	174	248	1.75	1.39	2.21	1,305	1,901	1.86	1.61	2.14	419	401	1.73	1.48	2.04
Gender															
Male	1,207	2,295	1.00	Referent		3,730	5,576	1.00	Referent		2,493	3,431	1.00	Referent	
Female	504	1,422	0.67	0.59	0.76	584	886	1.02	0.90	1.15	637	956	0.94	0.83	1.06
Race															
White	1,160	2,651	1.00	Referent		4,194	6,299	1.00	Referent		2,914	4,157	1.00	Referent	
Black	551	1,066	1.06	0.92	1.22	120	163	1.03	0.80	1.32	216	230	1.32	1.08	1.62
Region															
West	693	1,475	1.00	Referent		2,116	2,936	1.00	Referent		1,569	2,137	1.00	Referent	
Northeast	356	696	1.05	0.89	1.23	787	1,187	0.91	0.81	1.01	609	930	0.90	0.79	1.01
South	497	1,145	0.83	0.70	0.97	875	1,470	0.81	0.73	0.90	546	772	0.94	0.82	1.07
Midwest	165	401	0.82	0.66	1.01	536	869	0.88	0.77	1.00	406	548	1.05	0.91	1.22
Marital status															
Married	719	1,706	1.00	Referent		2,662	4,153	1.00	Referent		1,953	2,851	1.00	Referent	
Single	413	705	1.27	1.08	1.49	590	699	1.16	1.02	1.31	419	446	1.22	1.05	1.42
Div/Sep/Wid[3]	524	1,175	1.20	1.04	1.39	925	1,376	1.10	0.99	1.21	662	965	1.07	0.95	1.20

[1] Using Derived AJCC stage, 6th edition, 2004

[2] Using 2003 Rural-Urban Continuum Code

[3] Divorced/Separated/Widowed

Table 4: Adjusted Cox Proportional Hazard Model evaluating predictors of survival in SCCE, AE & AGC Patients: SEER 2004-2009

	SCCE (n=6,582)			AE (n=12,189)			AGC (n=8,467)		
		95% CI			95% CI			95% CI	
Categories	HR	Lower	Upper	HR	Lower	Upper	HR	Lower	Upper
RUCC[1]									
Metro	1.00	Referent		1.00	Referent		1.00	Referent	
Urban	0.99	0.90	1.10	0.97	0.90	1.05	1.10	1.01	1.21
Rural	1.14	0.98	1.33	1.04	0.93	1.16	1.02	0.88	1.17
Sex									
Male	1.00	Referent		1.00	Referent		1.00	Referent	
Female	0.90	0.85	0.96	1.04	0.98	1.10	0.93	0.87	0.99
Age									
70+	1.00	Referent		1.00	Referent		1.00	Referent	
60-69	0.79	0.74	0.85	0.73	0.69	0.77	0.70	0.65	0.74
50-59	0.80	0.74	0.87	0.67	0.63	0.72	0.66	0.61	0.71
<50	0.80	0.70	0.89	0.63	0.58	0.68	0.60	0.55	0.66
Race									
White	1.00	Referent		1.00	Referent		1.00	Referent	
Black	1.12	1.05	1.20	1.19	1.04	1.36	1.16	1.04	1.30
Region									
West	1.00	Referent		1.00	Referent		1.00	Referent	
Northeast	0.87	0.80	0.94	0.91	0.86	0.97	0.83	0.77	0.89
South	1.12	1.03	1.20	1.11	1.05	1.18	1.04	0.96	1.12
Midwest	1.00	0.90	1.10	0.93	0.87	1.00	1.00	0.92	1.09
Surgery[2]									
No	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	0.39	0.35	0.43	0.37	0.35	0.40	0.38	0.36	0.41
Radiotherapy									
No	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	0.45	0.42	0.48	0.69	0.66	0.72	0.68	0.64	0.72
Marital Status									
Married	1.00	Referent		1.00	Referent		1.00	Referent	
Not Married[3]	1.22	1.15	1.30	1.22	1.16	1.28	1.23	1.16	1.30
AJCC Stage[4]									
I	1.00	Referent		1.00	Referent		1.00	Referent	
II	1.10	1.00	1.21	1.49	1.36	1.63	1.57	1.42	1.74
III	1.56	1.42	1.72	2.16	1.98	2.35	2.03	1.83	2.25
IV	2.02	1.84	2.22	3.14	2.91	3.40	2.65	2.44	2.87
Unstaged	1.50	1.36	1.65	2.04	1.87	2.23	1.71	1.55	1.89

[1] Using 2003 Rural-Urban Continuum Code

[2] Surgery of Primary Site

[3] Including single, widowed, divorced and separated

[4d] Using AJCC Derived Stage, 6th edition, 2004

Figure 1: Kaplan-Meier Survival Curves for SCCE, AE & AGC Patients by Residential Setting: SEER 2004-2009