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Gender and Geographic Influence on Racial Disparity in Bladder Cancer Survival among Asian Groups in the US

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Bachelor of Medicine
Central South University
2006

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Master of Public Health
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Abstract

Gender and Geographic Influence on Racial Disparity in Bladder Cancer Survival among Asian Groups in the US
By Xi Wang

Objectives: The aim of this study is to compare bladder cancer survival patterns among Asian groups and to evaluate gender and geographic differences in bladder cancer survival between these populations in an effort to better understand any potential disparities that may exist.
Methods: Using data from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute between 2000 and 2008, Cox proportional hazard models and Kaplan-Meier's estimates were used to study differences in bladder cancer survival between selected Asian groups, adjusting for stage, age at diagnosis, year of diagnosis, radiation treatment and grade.
Results: There are significant differences in observed bladder cancer survival among Chinese, Filipino, Japanese, Korean, and Vietnamese patients ($p=0.033$). Chinese and Korean bladder cancer patients have lower risk of mortality than Filipino patients among Asian groups. Younger patients, who had surgery treatment, had lower risk of bladder cancer mortality. There is no gender and geographic influence on racial disparity in bladder cancer survival among Asian groups in the US.
Conclusions: Chinese and Korean bladder cancer patients have a higher 5-year survival in the Asian population. No gender or geographic differences in survival existed among the different Asian race groups.

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Introduction

The aim of this study is to compare bladder cancer survival patterns among Asian groups and to evaluate geographic differences in bladder cancer survival between these populations in an effort to better understand any potential disparities that may exist.

Background

Bladder cancer is the fourth most commonly diagnosed cancer among men and the eighth most common cancer among women in the United States (1), with an age-adjusted incidence rate per year of 20.8 per 100,000. It affects men more frequently than women. Men are 3 to 4 times more likely to get bladder cancer during their lifetime compared to women. According to the American Cancer Society, an estimated 73,510 new cases of bladder cancer will be diagnosed in United States, which includes 55,600 diagnoses in men and 17,910 in women. Between 1985 and 2000, bladder cancer incidence increased by 33% with roughly the same rate in both genders in the United States (2, 3).

Risk Factors

Cigarette smoking and occupational exposure are the two most well-proven risk factors for bladder cancer (4, 5).Half of the male population and 35% of the female population with bladder cancer are estimated to have the disease due to smoking related behavior. Cigarette smokers are proven to have at least a two-fold increased risk of bladder cancer compared to non-smokers (6). Occupational exposure to urothelial carcinogens is the second most important

risk factor, accounting for 5–20% of all bladder cancers (7, 8). Other environmental exposures that have been associated with bladder cancer include chronic urinary tract infections (9), cyclophosphamide use (10), and exposure to radiotherapy (11). Transitional cell carcinoma is the most common pathologic subtype of bladder cancer and is observed in greater than 90% of tumors (12). Squamous cell carcinoma and adenocarcinoma are less common and occur in approximately 5% and 1% of bladder cancers, respectively (13, 14). Secondary carcinomas can appear in the colon, uterus, ovaries, and prostate, as well as lymphomas. The most widely used and universally accepted staging system is the tumor-node-metastases (TNM) system. Under this system, Non-Muscle-Invasive-Bladder-Cancer includes <1> papillary tumors confined to the epithelial mucosa; <2> tumors invading the subepithelial tissue; <3> Tis (CIS). The International Society of Urological Pathology published a new grading system that employs specific cytologic and architectural criteria (15, 16).

Bladder Cancer Mortality and Survival

Approximately 14,880 deaths due to bladder cancer will occur in 2012: 10,510 deaths among men and 4370 deaths among women. As the seventh most common cause of cancer death in American men, bladder cancer contributes 3% of all cancer deaths in men (3). Between 1973 and 1999, there was a 33% decline in bladder cancer mortality, which was primarily observed seen in men (17). The overall five-year relative survival for bladder cancer during 2002 to 2008 from 18 SEER geographic areas was 77.7% (18). Men have a higher 5-year survival rate than women (17) with the gender breakdown of White males, African American males, White females and African American

females being 79.8%, 69.7%, 73.1%, and 54.3%, respectively (18). While a more advanced stage distribution among female bladder cancer patients may lead to the lower observed survival rate (18), this may not entirely explain the observed differences. In a study conducted by University Medical Center St. Radboud using data from nine population-based Surveillance, Epidemiology, and End Results (SEER) cancer registries in the United States between 1973 and 1996, researchers compared gender differences in stage-adjusted bladder cancer survival and found that survival differences remained. The male versus female 5-year survival rate among stage groups I, II, III, and IV was 96.5% versus 93.7%, 65.5% versus 59.6%, 58.8% versus 49.6%, and 27.1% versus 15.2%, respectively (19). Another possible explanation may include delayed diagnosis among women due to presenting symptoms. Significantly worse outcomes have been shown to be associated with delay of more than 3 months to treatment (20, 21). Anatomic factors influence not only medical decisions but also disease progression among middle aged and elderly populations. Thicker bladder muscles and the presence of the prostate may block metastases development or direct extension of the tumor among male bladder cancer patients resulting in improved survival among males (22). Cultural factors may also affect patients' attitude toward disease acceptance, readiness to healthcare services, and treatment decisions, which could in part influence poorer prognosis in selected individuals (23, 24).

Racial differences in Survival

A substantial body of research has explored racial and ethnic differences in bladder cancer survival. Researchers noted that five-year disease-specific survival was consistently worse for American Africans than for other ethnic

groups, even when stratified by stage and grade. Five-year disease-specific survival was 70.2% in blacks and 82.8% in whites compared with 80.7% in Hispanics, and 81.9% in Asian/Pacific Islanders (25). A number of mechanisms have been proposed to explain the association between racial and ethnic differences and overall bladder cancer survival. Recent epidemiological evidence showed that a predominance of urothelial carcinoma among African Americans may result in more severe outcomes and more advanced stages at diagnoses thus leading to lower survival (26). Genetic differences, between blacks and white may also affect the host response to different carcinogens and occupational exposures and could result in lower survival among African American populations (27-29). Other non-biologic factors, such as time from symptoms to onset of treatment, socioeconomic status, occupational exposures, cigarette smoking, dietary factors, and differences in metabolism of toxic substances are also possible factors that could explain racial differences in survival, but have not been intensively studied. A few papers have assessed the survival experience of bladder cancer patients among the Asian and Pacific Islander ethnic groups in the United States. The most recent study , conducted by Mia Hashibe and his colleagues, found Japanese and Chinese bladder cancer patients had higher overall survival rates than Caucasians, while Filipino and Hawaiian patients had lower survival using data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute between 1973 and 1998 (30).

Geographic Differences in Survival

Geographic regional variations in bladder cancer incidence and survival have been observed for decades in the United States[18]. In 1978, William (40) found

that a substantial Northeastern excess was seen in both sexes even after controlling for urbanization and socioeconomic status. These findings were consistent with work done by Michaud (31) who conducted a cohort study among male health professionals in 2001 and found that an elevated risk of bladder cancer was observed in the Northeast compared with the West. A recent contribution by Rakesh Mandal and his team reaffirmed this geographic difference among Caucasian men and was published in the 2012 Genitourinary Cancers Symposium. In this report, Caucasian men (<60 years old) with stage IV bladder cancer had lower 1- and 5-year relative survival rates in the South compared to the North. Willie (32) and his colleagues reported that African Americans diagnosed in Atlanta have significant lower survival by testing race-geographic interaction terms in their model. Pre-eminent explanations for these findings focus on smoking status (33) and occupational exposures (34, 35). While these two risk factors are generally accepted, Dominique contended that smoking patterns alone could not account for all of the increased bladder cancer observed in the Northeast (36). In terms of occupational and environmental exposures, a great deal is known about bladder cancer's associations to various industrial exposures among male workers (37), but much less is known about the actual gender of employees which may affect bladder cancer survival as well. For example, African American women may be more likely to have jobs exposed to more carcinogens of bladder cancer which could in turn explain in part their lower bladder cancer survival.

While racial and geographic variations in bladder cancer have been separately demonstrated, very little is known about the interactions between race-gender

and race-regional variations among Asian groups. In short, consensus has grown for the need to fill the gap in Asian group studies. Thus the aim of this study is to compare bladder cancer survival patterns among Asian groups and also to evaluate the gender and geographic differences in bladder cancer survival between these populations in an effort to better understand potential disparities that may exist.

Methods

Study Population

Data were obtained from the SEER program of the National Cancer Institute which is the main source for cancer statistics in the United States and includes information on incidence, prevalence, and survival from specific geographic areas representing 28% of the US population. For this analysis, aimed to investigate in disparities of bladder cancer survival among Asian groups, the study population was subset to include cases:

- Greater than 0 years of age
- With the following race classifications: Chinese (768 cases), Filipino (511 cases), Japanese (659 cases), Korean (315 cases), and Vietnamese (210 cases),
- Diagnosed with a first and only primary invasive bladder cancer
- Diagnosed between 2000 and 2008 in one of the 18 SEER Registries

Due to limited sample size, subjects with other Asian race classifications are not included. Cases identified by death certificate only were also excluded due to no contribution to survival.

Survival time

Survival time was calculated as the time in months from the date of date of diagnosis until one of the following: date of death, date last known to be alive, or study endpoint (December 31, 2008 for these data). Survival time was censored at a maximum of 5 years of all subjects. The endpoint of death was defined as death from bladder cancer. Cause of death was available using ICD-10 codes in the SEER data. Among 1391 Asians, included in the analyses, 670 deaths occurred with 394 deaths due to bladder cancer. Among these cause-specific deaths, 111 cases were Chinese, 81 cases were Filipino, 109 cases were Japanese, 57 cases were Korean, and 36 cases were Vietnamese.

Covariate Definitions

Besides race and SEER registry, other covariates of interest included gender, age at diagnosis, year at diagnosis, stage, grade, surgery status, and radiation therapy. Gender was classified as male or female. Age was categorized into 10 year intervals: <60, 60-69, 70-79, and ≥80 years. Year of diagnosis was divided into two groups, 2000-2004 and 2005-2008. Stage was classified as localized, regional, distant and unknown. For the variable surgery, no surgery of the primary site or unknown if surgery was performed were grouped into no surgery, otherwise we defined surgery as conducted. Radiation therapy was dichotomizes as yes or no. 18 registries were grouped to into four regions according to geographic characteristics. In this study, the registries coded as 'Alaska Natives - 1992+', 'California excluding SF/SJM/LA - 2000+', 'Los Angeles - 1992+', 'San Francisco-Oakland SMSA - 1973+', 'San Jose-Monterey - 1992+', 'Hawaii - 1973+', 'New Mexico - 1973+' , 'Seattle (Puget Sound) - 1974+', and 'Utah - 1973+' were grouped as the West region.

Registries coded as 'Atlanta (Metropolitan) - 1975+', 'Greater Georgia - 2000+', 'Kentucky - 2000+', 'Louisiana - 2000+', and 'Rural Georgia - 1992+' were grouped as the South region; 'Connecticut - 1973+' and 'New Jersey - 2000+' were classified as the Northeast region; and 'Detroit (Metropolitan) - 1973+', and 'Iowa - 1973+' were classified as the Midwest region.

Statistical Analyses

All analyses were performed using SAS statistical software. Five Asian groups were compared with regards to demographic and clinical variables to assess whether there were statistically significant differences in the baseline characteristics of the groups. Categorical variables were presented as counts and frequencies and examined by Pearson's chi-square testing. Continuous variables were analyzed by using ANOVA. All tests were2-sided with a p-value of 0.05.

Univariate survival comparisons were made using Kaplan-Meier's plots and log-rank test is used to compare survival among different racial groups. Proportional hazard assumptions were assessed both by log-log rank survival functions and Goodness of Fit Tests. If variables did not satisfy the proportional hazard assumptions, stratified Cox regression models were used to control for those variables. Multivariable survival analyses was conducted using Cox regression modeling to adjust for race, age, stage, grade, gender, geographic region, surgical treatment, year of diagnosis and radiation treatment. Interaction terms were assessed between our main exposure (race) and each of the other covariates. The significance level for dropping variables was 0.1 and 0.05. The 5% significance level was applied to all models. The

study was approved by the institutional review board at Emory University.

Results

Cohort demographics

1391 patients were identified in SEER data by one of the Asian race categories: 410 were Chinese, 284 were Filipino, 364 were Japanese, 200 were Korean, and 133 were Vietnamese (Table 1). The majority of individuals were diagnosed at or above age 70 years, whereas Vietnamese had the highest percentage of patients diagnosed under 60 years old. Chinese, Japanese and Vietnamese were more likely to be diagnosed between 2000 and 2004. The male to female ratio was 2.5 for Chinese, 2.5 for Filipino, 2.8 for Japanese, 3.0 for Korean, and 2.25 for Vietnamese. There were no statistically significant associations between race and gender across the Asian groups. The majority of the Asian groups in SEER data were likely to live in the West region of the country (87.1%, 94.0%, 96.4%, 83.0%, 90.0%). Significant differences were observed across the race groups with a larger percentage of Chinese and Korean bladder cancer patients residing in the Northeast at diagnosis relative to the other Asian race groups.

Tumor characteristics

The distribution of related clinical factors for bladder cancer patients by ethnicity are shown in the Table 1. The distribution of bladder cancer stage is significantly different among Asian racial groups, although all groups were most commonly diagnosed at localized stage. Korean and Chinese tended to be diagnosed at an earlier stage of disease. Korean cases had the largest percentage of localized stage diagnosis (69%) with lower distant stage

diagnosis (6.5%) compared with other Asian groups. A similar pattern was found in Chinese cases that a lower percentage of distant diagnosis (6.3%) and higher localized stage diagnosis (65.9%). Filipino, Japanese and Vietnamese cases, on the other hand, had a larger percentage of late stage diagnoses. The majority of patients did not receive Radiation therapy. There were no statistically significant associations between surgery and race, grade and race, radiation and race respectively.

Survival time

The Kaplan-Meier survival plot for cause-specific bladder cancer survival for the 5 Asian ethnic groups is shown in the figure1. The log-rank test shows that there is a statistically significant difference in 5-year bladder cancer survival among Asian groups (p=0.033). Filipino have a lower 5 year survival than other four groups of Asian patients. In table 2, the median survival time was the highest for Chinese patients at 19 months, followed by Vietnamese patients at 18.0, Korean patients at 16.5 months, Japanese patients at 16.0 months, Filipino patients at 11.5 months. Statistically significant differences in bladder cancer survival during univariate analyses were also observed for age and surgery with younger patients and those treated with surgery having better survival. There was no significant difference between survival time and grade, gender, stage, radiation treatment, or geography.

Predictors of Bladder Cancer mortality

The result of a multivariate Cox proportional hazard model for the risk of bladder cancer mortality is shown in Table 3. Due to several variables that failed the proportional hazards assumption, the cox proportional model was further stratified by stage, grade, and radiation. To conduct Cox proportional

hazards modeling, interaction variables were created between each variable and race. None of these interactions were statistically significant. Finally race, surgery, gender, geography and age were kept in the model.

Within our cohort, Filipino which has the lowest survival months was regarded as the referent group. Compared with Filipino, Chinese and Korean cases have significant differences in the risk of bladder cancer mortality adjusted by other variables. Chinese patients have lower risk of bladder cancer mortality with a hazard ratio of 0.79 [(0.65, 0.95)95%C.I.]. Korean patients also have lower risk of bladder cancer mortality with a hazard ratio of 0.80[(0.64, 0.99)95%C.I.]. Patients who had surgery [HR=0.63, (0.47,0.84)], were younger also had lower risk of bladder cancer mortality.

Among Asian groups, there was no significant difference in the risk of bladder cancer mortality between males and females (p=0.977). There was also no significant difference among the four SEER regions of the USA.

Discussion

5-year survival from bladder cancer differed among Chinese, Filipino, Japanese, Korean, and Vietnamese ethnicities in this study, which is consistent with previous research (30). In this study, 5-year survival of bladder cancer patients was associated with race, age at diagnosis, and surgery treatment, stratifying on cancer stage. For bladder cancer deaths, patents with younger age of diagnosis and those undergoing surgery had lower risk of death.

Previous studies of SEER data for the period 1973-1979 (38) and the period

1973-1998 showed that Chinese patients have higher survival than Filipinos, which is confirmed by this study using data from 2000-2008. One explanation for the higher survival of Chinese may be better income and access to medical care relative to Filipino patients. However, Japanese patients, who were reported as having the highest 5-year relative survival rate in prior studies(38), had no statistically significant difference in survival compared with Filipino patients in this study. Interestingly, Chinese and Korean patients have same pattern of bladder cancer survival in this study. The mean age at diagnosis was very similar among Korean patients (70.6years) and Chinese patients (73.0 years). The median survival months were also very similar between Korean patients (16.5 months) and Chinese patients (19.0 months). Closeness in cultural background and dietary may explain this similarity.

Gender differences were reported in previous studies and male patients had higher survival than female patients, after adjustment for age, grade, stage, and surgery (30,39). However gender was not a risk factor for bladder cancer deaths in this study.

Geographic differences in bladder cancer survival have been reported among African-Americans and Caucasians, but very little is known among Asian groups. This study investigated associations between race and regions, but found no association between bladder survival and region among the Asian cohort after controlling for other variables, we nevertheless hope this study will facilitate more research on race-region interactions among Asian group of bladder cancer survival pattern as the majority of bladder cancer occurs in the

West region.

Surgical treatment is a strong risk factor of bladder cancer mortality for cause-specific bladder cancer patients in our study. After adjusting other variables in the model, the hazards ratio of patients who did receive surgery is 0.63 times than those did not receive surgical treatment.

Strengths and Weakness

Strengths of this study are our comparisons among Asian groups, rather than comparisons with Caucasians, to find bladder cancer survival pattern specific to Asian groups. Additionally, along with demographical changes of the American population, this is the first study to our knowledge to report Korean bladder cancer survival pattern.

Weaknesses include the lack of information on socioeconomic status, genotypes , environmental factors and smoking status , which are all important risk factors of bladder cancer survival. Additionally, this study divided the country into four major regions which may not be able to explain the racial differences within specific geographic parts of USA. Access to healthcare, willingness to obtain health care, or delay in obtaining healthcare should also be taken into consideration to further explain disparities among Asians groups.

Future directions

As smokers have been demonstrated in previous studies to have a worse prognosis than nonsmokers, future studies should take smoking status into consideration to fully explain racial and geographic differences among bladder

cancer patients.

Previous studies have also shown that ethnic survival differences are influenced by socioeconomic status delayed diagnosis. Future studies should explore the role of socioeconomic status and healthcare use among Asian groups compared with Caucasians. By understanding these factors, public health professionals can provide better interventions and surveillance in bladder cancer.

Table 1. Comparison of Clinical factors for Chinese, Japanese, Filipino, Korean, and Vietnamese Patients with Bladder Cancer

	Chinese N(%)	Filipino N(%)	Japanese N(%)	Korean N(%)	Vietnamese N(%)	χ^2 P-value
Total	410	284	364	200	133	
Mean age	73.0	71.0	74.3	70.6	69.5	<0.01*
Age at diagnosis						
<60	61(14.9)	58(20.4)	51(14.0)	31(15.5)	32(24.0)	
60-69	62(15.1)	55(19.4)	58(16.0)	57(28.5)	30(22.6)	<0.01+
70-79	140(34.2)	95(33.5)	133(36.6)	67(33.5)	42(31.6)	
≥80	147(35.9)	76(26.8)	122(33.5)	45(22.5)	29(21.8)	
Gender						
Male	294(71.8)	203(71.5)	269(73.9)	150(75.0)	93(70.0)	0.86
Female	116(28.3)	81(28.5)	95(26.1)	50(25.0)	40(30.0)	
Male:Female Ratio	2.5	2.5	2.8	3.0	2.25	
Year of diagnosis						
2000-2004	216(52.7)	139(48.9)	195(53.6)	90(45.0)	69(51.9)	0.03+
2005-2008	194(47.3)	145(51.1)	169 (46.4)	110(55.0)	64(48.1)	
Grade						
Well differentiated	13(3.2)	5(1.8)	11(3.0)	4(2.0)	6(4.5)	
Moderately differentiated	84(20.5)	49(17.3)	41(11.3)	30(15.0)	23(17.3)	0.07+
Poorly differentiated	127(31.0)	90(31.7)	135(37.1)	72(36.0)	41(30.8)	
Undifferentiated	140(34.2)	92(32.4)	139(38.2)	71(35.5)	47(35.3)	
missing	46	48	38	23	16	
Stage						
Localized	270(65.9)	170(59.9)	236(64.8)	138(69.0)	85(63.9)	
Regional	65(15.9)	48(16.9)	52(14.3)	27(13.5)	15(11.3)	<0.01+
Distant	26(6.3)	33(11.6)	43(11.8)	13(6.5)	16(12.0)	
Unknown	41(10.0)	20(7.0)	21(5.8)	14(7.0)	7(7.5)	
Surgery						
No	55(13.4)	43(15.1)	41(11.3)	22(11.0)	17(12.8)	0.57
Yes	355(86.6)	241(84.9)	323(88.7)	178(89.0)	116(87.2)	
Radiation					114(85.7)	
No	368(89.8)	247(87.0)	307(84.3)	171(85.5)	18(13.5)	
Yes	39(9.5)	33(11.6)	54(14.8)	24(12.0)	1	0.26
missing	3	4	3	5		
Region						
West	357(87.1)	267(94.0)	351(96.4)	165(83.0)	120(90.0)	
South	9(2.2)	3(1.1)	6(1.7)	8(4.0)	9(8.0)	<0.01
Northeast	40(9.8)	12(4.2)	5(1.4)	25(12.5)	4(0.1)	
Midwest	4(1.0)	2(1.0)	2(1.0)	2(1.0)	0(0.0)	

*Anova

Table 2. 5-year Survival from Bladder Cancer among Asian Ethnic Groups

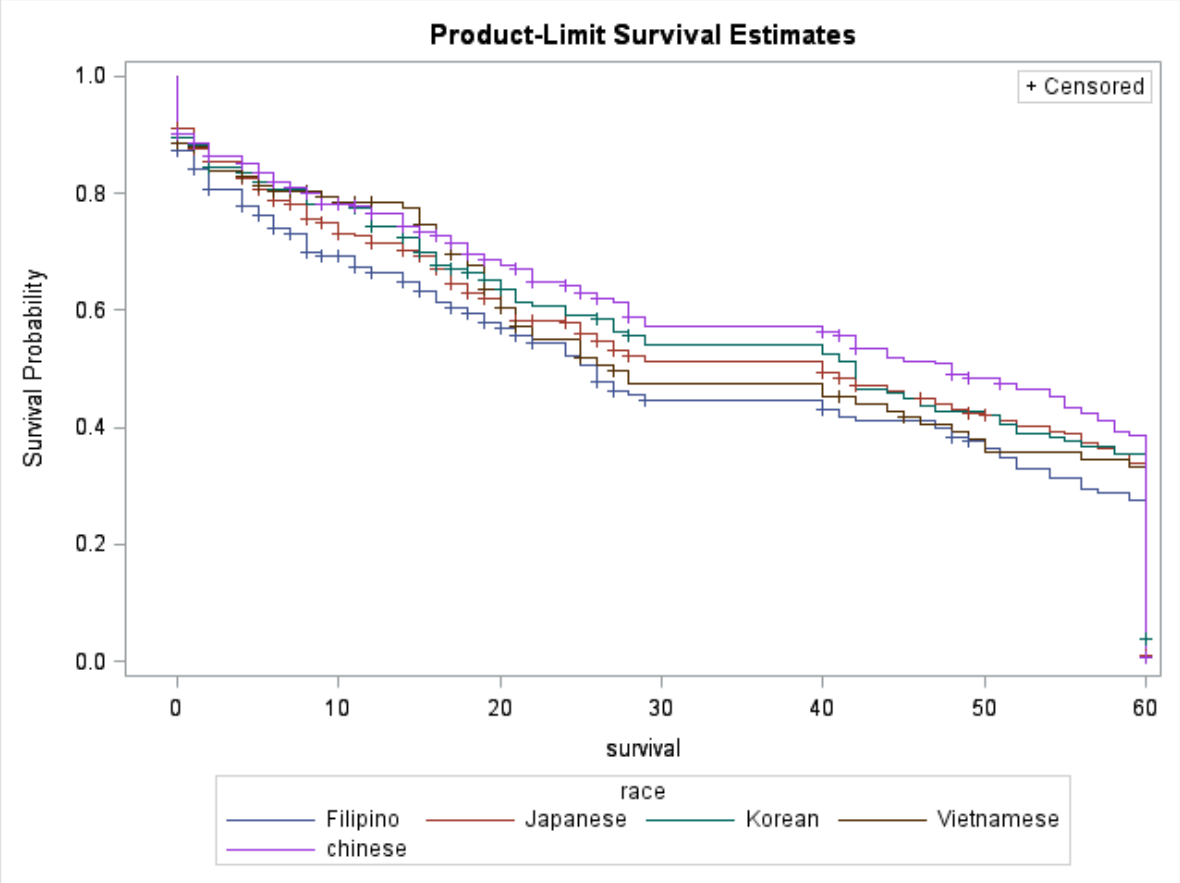
	Subjects	Deaths	Median Survival (months)	Log-rank p-value
Total	1391	394	17.0	
Asian Ethnicities				
Chinese	410	111	19.0	
Filipino	284	81	11.5	0.030
Japanese	364	109	16.0	
Korean	200	57	16.5	
Vietnamese	133	36	18.0	
Age at diagnosis				
<60	233	51	24.0	
60-69	262	52	21.5	0.017
70-79	477	132	18.0	
≥80	419	159	10.0	
Gender				
Male	1009	268	17.0	0.732
Female	382	126	14.0	
Grade				
Well differentiated	39	57	8.0	
Moderately differentiated	227	1	40.0	
Poorly differentiatedI	465	26	28.0	0.097
Undifferentiated	489	143	16.0	
Stage				
Localized	899	165	21.0	
Regional	207	91	17.0	0.211
Distant	131	89	5.0	
Unknown	103	40	12.0	
Surgery				
No	178	69	5.0	0.004
Yes	1213	325	18.0	
Radiation				
No	1207	290	18.0	0.148
Yes	168	93	12.0	
Region				
West	1260	369	17.0	
South	35	26	17.0	
Northeast	86	71	17.5	0.471
Midwest	10	9	43.5	

Table 3. Cox Proportional Hazard Model for Risk of Bladder Cancer Mortality among Asian Groups

Variables[#]	Hazard Ratio OR	95%CI		P-value
Race				
Filipino	1.00	Reference		
Chinese	0.79	0.65	0.95	<0.001[#]
Japanese	0.89	0.72	1.08	0.212
Korean	0.80	0.64	0.99	0.038
Vietnamese	0.89	0.69	1.15	0.382[#]
Surgery*	0.63	0.47	0.84	<0.001[#]
Age				
<60	1.00	Reference		
60-69	1.06	1.02	1.09	<0.001[#]
70-79	1.09	1.03	1.15	<0.001[#]
≥80	1.32	1.23	1.40	<0.001[#]
Gender	1.00	0.86	1.17	0.998
Region				
West	1.00	Reference		
South	0.98	0.65	1.47	0.977
Northeast	1.54	0.72	1.84	0.549
Midwest	1.01	0.46	2.22	0.976

*without surgery as reference group
[#]stratified stage, grade, radiation therapy, year of diagnosis
#statistically significant under $p<0.05$

Figure 1. 5-year Survival from Bladder Cancer by race



Log-rank test: p=0.033

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