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Chong Ye Date

Racial and Ethnic Differences in Clinical Characteristics and Prognosis of Gallbladder Cancer in United States: Analysis of Population Based Data

By

Chong Ye
Master of Public Health

Epidemiology

_____

Michael Goodman
Committee Chair

Racial and Ethnic Differences in Clinical Characteristics and Prognosis of Gallbladder Cancer in United States: Analysis of Population Based Data

By

Chong Ye
Bachelor of Medicine
Southern Medical University
2016

Faculty Thesis Advisor: 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 Public Health
in Epidemiology
2018

Abstract

Racial and Ethnic Differences in Clinical Characteristics and Prognosis of Gallbladder Cancer in United States: Analysis of Population Based Data
By Chong Ye

Background: While racial/ethnic differences in gallbladder cancer (GBC) incidence are well known, few studies investigated how clinical characteristics and prognosis may differ in GBC patients of various races and ethnicities. **Methods:** The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program was used to identify GBC patients diagnosed from 2000 through 2014. Multivariate logistic regression was used to estimate the association between race/ethnicity and cancer stage at diagnosis. Comparison of overall survival by race/ethnicity was done using Cox proportional hazard model. **Results:** 7,857 GBC patients reported to SEER during the study period, 4,414 patients (56.2%) were non-Hispanic Whites, 891 (11.3%) were non-Hispanic Blacks, 1,797 (22.9%) were Hispanics, 755 patients (9.6%) were Asians/ Pacific Islanders. Compared to non-Hispanic White GBC patients, both Asians/ Pacific Islanders (Odds ratio [OR]= 0.83, 95% confidence interval [CI] 0.70, 0.99) and Hispanics (OR= 0.86, 95% CI 0.76, 0.98) had significantly lower likelihood of being diagnosed with more advanced (regional or distant) stage of the disease. Statistically significant difference was also found in post-diagnosis survival between non-Hispanic Black and non-Hispanic White GBC patients (HR: 1.10, 95% CI 1.01-1.19). **Conclusion:** While Asian/Pacific Islander and Hispanic GBC patients were more likely to be diagnosed at an earlier disease stage, survival appears to be less influenced by race/ethnicity once disease stage is taken into consideration.

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Introduction

Gallbladder Anatomy and Function

Gallbladder is a pear-shaped organ situated in a fossa on the liver undersurface; it is variable in shape and volume and is divided into a fundus, a body and a neck or infundibulum (1). Gallbladder is adherent to the undersurface of the liver along liver segments IV and V (2). The free surface of gallbladder is covered by serosa that continues over the hepatic surface. Blood is supplied by cystic artery that branches from superficial channels over the serosa of the gallbladder and deep channels that travel between the organ and its hepatic bed. The venous drainage consists in part of small venous channels on the hepatic side of the gallbladder that lead to the liver directly (3) .The hepatic biliary tract is made up of hepatic ducts that follow a modal disposition identical to that of the portal vein. The common hepatic duct (CHD) is formed from union of the proximal ducts (4).

The layers of the gallbladder include the surface epithelium, lamina propria, smooth muscle, perimuscular subserosal connective tissue and serosa. The gallbladder lacks a muscularis mucosae and submucosa. The folds surrounding the lumen are lined by columnar epithelium with a core of lamina propria, an apical brush border of microvilli, very similar to intestinal absorptive cells (5, 6).

The basic functions of the gallbladder in humans are to concentrate, store and release bile produced by liver as an accessory organ of the digestive system. Bile is a dark green to yellowish brown fluid produced by the liver of most vertebrates. It aids the digestion of lipids in the small intestines. In humans, bile is produced continuously by the liver, and stored and concentrated in the gallbladder. After food consumption, the stored

bile is discharged to duodenum. The composition of bile is 97% water, 0.7% bile salts, 0.2% bilirubin, 0.51% fats (7, 8). The accumulation of the primary bile acids (cholic acid and chenodeoxycholic acid) in the gallbladder reduces the formation of the secondary bile acids (deoxycholic acid and lithocholic acid) and diminishes their concentration in the gallbladder-independent enterohepatic circulation and protects the liver (9).

Cancer of the Gallbladder: Clinical Presentation and Prognosis

Gallbladder cancer (GBC) was first described in 1777 (10). It is one of the biliary tract cancers, which include intrahepatic- cholangiocarcinoma, extrahepatic-cholangiocarcinoma and certain forms of ampullary cancer (11). GBC is the most common biliary tract malignancy with the worst overall prognosis (12). It is considered the most aggressive carcinoma of the biliary tract (13). Over 90 percent of GBC are adenocarcinomas. About 60% of tumors originate in the fundus of the organ while the remaining 30% and 10% arise in the gallbladder body and the neck, respectively (14). At clinical presentation, GBC is similar to biliary colic or chronic cholecystitis. Right upper quadrant or epigastric pain is the most common symptom (54-83%), followed by jaundice (10-46%), nausea and vomiting (15-43%), anorexia (4-41%), and weight loss (10-39%) (15). Most cases of GBC become symptomatic when the disease is in the advanced stage, and 75% of patients are diagnosed when the disease is beyond the limits of resection (16). GBC is staged based on TNM classification, which is the most widely used system for classifying the anatomic extent of cancer spread (17). The T component describes the relative invasion of tumor through the layers of the gallbladder wall and into adjacent structures. It is a primary factor dictating appropriate treatment and in

determining outcome (16). The N component describes involvement of the nearby (regional) lymph nodes, and the M stage categories describe distant metastatic status of GBC (18, 19). The summary stage takes into consideration all TNM stages and is assigned as follows: Stage 0 ($T_{is}N_0M_0$), Stage I ($T_1N_0M_0$), Stage II ($T_2N_0M_0$), Stage IIIA ($T_3N_0M_0$), Stage IIIB ($T_{1-3}N_1M_0$), Stage IVA ($T_4N_{0-1}M_0$), and Stage IVB ($T_{any}N_{any}M_1$ / $T_{any}N_2M_0$) (20).

Surgery is the only curative treatment for patients with GBC. Most of the GBC cases are diagnosed incidentally. The probability of finding GBC after cholecystectomy for presumed benign disease (mainly cholelithiasis) ranges from less than 1% to 3% (21). For tumors invading beyond the muscularis layer (T>1) in addition to cholecystectomy, limited hepatic resection and portal lymphadenectomy are considered the optimal surgical approach (21). T3 tumors perforate the serosa and directly invade adjacent organs such as liver, duodenum or stomach, colon, pancreas, omentum as well as extrahepatic bile ducts. These tumors are suitable for radical resection but the post-operative morbidity may be substantial. T4 tumors are usually not amenable to surgical resection (22). Patients with stage IV GBC have dismal prognosis, even after attempted curative resection (23). There are currently no recommendations for neoadjuvant treatment in patients with locally advanced gallbladder malignancy. By contrast, adjuvant treatment is recommended; and includes a combination of chemotherapy and radiation (12).

GBC carries a poor prognosis; and the only chance for cure lies in early detection and complete surgical resection and the extent of resection for each stage remains controversial (24). The dismal prognosis is related to rapid hepatic invasion and subsequent metastatic progression due to the gallbladder lacking serosal layer adjacent to

the liver (25). Less than 10% of patients have tumors that are resectable at the time of surgery, and around 50% have lymph node metastasis (26).

The 5-year survival for all stages of GBC is about 5% while the incidentally detected tumors carry a better prognosis because they are often diagnosed without clinical signs (27). Whereas median survival for GBC is 9.2 months, it is substantially higher (26.5 months) for cancers diagnosed incidentally at the time of cholecystectomy (28). The data from the international medical literature indicates that among patients with T1 tumors, 5-year survival ranges from 60% to nearly 100% after a simple and extended cholecystectomy, respectively. The corresponding 5-year survival estimates for T2 tumors ranges depending on a number of factors, which include lymph node involvement, postoperative margin status and depth of subserosal invasion. The survival of patients with $T_2N_0M_0$ without a second radical operation varies from 10% to 22% while those with a radical resection the survival rates is from 60% to 80%. The 5-year survival is further decreased for T3 GBC (15%), particularly for T4 disease (5%) (27, 29).

Epidemiology of GBC

Geographic variability of GBC is remarkable, and appears to correspond to the worldwide prevalence of gallstones. Populations of Asia are considered at high risk continent for GBC while the United States and most western and Mediterranean European countries (like UK, France, Norway) are considered areas of relatively low risk (30). Additional populations with the high GBC incidence are Chileans, Bolivians, North American Indians, Mexican-Americans and Central Europeans. All of these populations also appear to have high prevalence of cholelithiasis (14).

In the United States, the incidence of GBC is almost twice as high in women than in men (1.3 vs. 0.7 per 100,000 person-years). Even though this ratio varies by ethnicity, females are always at higher risk (31). Moreover, two-thirds of GBC deaths in the US occur among women (32). GBC incidence is also higher among Hispanics and American Indians/Alaska Natives (2.0 and 1.9 per 100,000 persons years, respectively) compared to US whites (1.0 per 100,000 persons years, respectively), blacks (1.7 per 100,000 persons years), and Asians/ Pacific Islanders (1.3 per 100,000 persons years) (33). GBC rates tend to increase with advancing age. It is reported that the median age at diagnosis is 67 years (34).

An important risk factor in gallbladder carcinogenesis is the presence of gallstones, which are found in 85% of GBC patients (30). GBC patients have been reported to have larger gallstones compared to cancer free subjects although the number of stones did not differ between the two groups (35). This observation probably reflects the greater duration and intensity of mucosal irritation which produces chronic inflammation (36). Chronic inflammation in turn causes DNA damage, which provokes repeated tissue proliferative attempts for restoration, releasing cytokines and growth factors and results in predisposing cells to oncogenic transformation (30). In addition, chronic inflammation will also lead to extensive calcification in the wall of gallbladder. It is reported that a calcified gallbladder cancer is associated with an increased risk of the disease (37). Bacterial degradation of bile and chronic inflammation may also play a role in the gallbladder carcinogenesis. The specific organisms that have been linked to GBC risk include *Salmonella* and *Helicobacter* (38). Other factors thought to increase GBS risk include exposures to heavy metals (e.g. nickel, cadmium and cobalt), tobacco use,

and radon, (39-42). In addition, both obese people and people with diabetes mellitus may have a higher risk of GBC (43, 44).

Racial/Ethnic Disparities in GBC Prognosis

Although data on racial/ethnic disparities in the incidence of GBC are convincing (31-33), relatively little is known if GBC patients from different racial/ethnic backgrounds experience different prognosis or have different distributions of prognostic factors. Previous data indicate that compared to GBC patients who are Non-Hispanic Whites, Asians/ Pacific Islanders and Hispanics are more likely to be diagnosed with localized stage disease. In addition the percentage of GBC cases in low grade (I or II) among Asians/ Pacific Islanders was reported to be significantly higher than that among Non-Hispanic White (45). Survival is also better Hispanics and Asians/Pacific Islanders than in other racial/ethnic groups (45) In a recent analysis of the National Cancer Database (NCDB) all-stage overall survival curves differed among racial/ethnic groups, with the greatest 5-year survival observed in Hispanics. When stratified by stage, Hispanics had greater overall survival for stage 0-3 disease (46).

While these recent data offer important insight into the racial ethnic disparities of GBC cases. It is important to point out that NCDB is not a population-based data source because it only captures 70% of newly diagnosed invasive cancers in the United States. Moreover, additional data are needed to take into consideration the association between race/ethnicity and both overall and cancer-specific survival while taking into account tumor characteristic, demographic information other than race and ethnicity, as well as treatment receipt. One previous study (45) performed these types of analyses; however,

it was based on relatively old data (through 2009) and was not able to take into consideration the effect of “immortal time bias” when adjusting for treatment receipt.

Materials and Methods

The research data were obtained from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. SEER is an authoritative source of information on cancer statistics including incidence and survival from specific geographic registries representing 28% of the US population. The analytic dataset covered the period from January 1st, 2000 to December 31st, 2014 (excluding Louisiana registry data for the second half of 2005 because of the Hurricane Katrina). The selection of GBC patients was based on primary disease site and morphology code C239 in the International Classification of Diseases for Oncology, 3rd edition(47). Patients were excluded if their cancer stage classification or race/ethnicity were unknown.

Race/ethnicity was grouped into 4 categories: non-Hispanic white, non-Hispanic black, Hispanic and Asian/Pacific Islander. The demographic and clinical factors considered as possible control variables included age at diagnosis, sex, SEER registry, year of diagnosis and cancer grade. Age was classified into 4 groups: <30 years, 30 to 49 years, 50 to 69 years and greater or equal to 70 years. The SEER registries were categorized into 4 different regions: North-East (New Jersey, Connecticut), South-East (Georgia registries, Louisiana), Mid-West/Mountain area (Detroit, Iowa, Kentucky, New Mexico, Utah,), and Pacific (California registries, Seattle and Hawaii, Alaska). The calendar year of diagnosis was categorized as 2000-2004, 2005-2009, and 2010-2014. The cancer grade at diagnosis was categorized based on the histologic grade of SEER as follows:

- Well differentiated: cancer cells look more like normal cells under a microscope and tend to grow and spread more slowly than poorly differentiated or undifferentiated cancer cells.
- Moderately differentiated: cancer cells look more abnormal than the well-differentiated cancer cell. They tend to spread more quickly than low-grade cancer cells.
- Poorly differentiated: cancer cells tend to grow and spread more quickly than well differentiated and moderately differentiated cells. Poorly differentiated cancers usually have a worse prognosis.
- Undifferentiated: cancer cells that do not have specialized structures or function, often grow and spread fast.

We used the "SEER historic stage A" variable, which classifies cancer cases as localized, regional, distant according to the following definitions:

- Localized cancer is a malignancy limited to the organ of origin. It has spread no further beyond the boundaries of the organ in which it started;
- Regional stage refers to tumor extension beyond the limits of the organ of original sites to the nearby lymph nodes or organs and tissues;
- Distant stage is a cancer stage that tumor cells have broken away from the primary tumor and traveled to another part of the body and begun to grow at the new location.

In this study, we excluded patients with unstaged disease and expressed stage as a binary variable (localized vs. regional/distant) because the boundary between regional and distant spread is not always clear (48).

Age-standardized incidence rates of GBC were calculated for the entire study period by race and were expressed as the number of cases per 1,000,000 person-year with 95% confidence intervals (CIs).

Multivariate logistic regression was performed to compare the likelihood of more advanced (regional/distant) stage at GBC diagnosis among different racial/ethnic groups after adjusting for age at diagnosis, sex, region, and calendar interval of diagnosis. Survival analysis was conducted using multivariate Cox models with results presented as adjusted hazard ratios (HRs) and the corresponding 95% CIs. All variables in the Cox model were examined for the proportional hazard assumption and no violation was found (49). All models were examined for collinearity and interactions. Analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC).

Results

In total, 7,857 GBC patients were selected in SEER from 2000 through 2014. Of those 4,414 patients (56.2%) were non-Hispanic Whites, 891 patients (11.3%) were non-Hispanic Blacks, 1,797 patients (22.9%) were Hispanics, 755 patients (9.6%) were Asians/ Pacific Islanders (Table 1). The study group included 5,612 females (71.4%) and 2,245 males (28.6%). As also shown in Table 1, over 40% of cases were diagnosed in the last five years of the data collection period, and most (52%) were over the age of 69 years. More than half of the GBC patients (60%) were diagnosed with regional/distant stage disease and 45% had poorly differentiated or undifferentiated tumors.

As shown in Table 2, compared to non-Hispanic Whites, the incidence rates of GBC were significantly higher among non-Hispanic Blacks (RR= 1.56; 95% CI, 1.46, 1.67), Asian/Pacific Islanders (RR= 1.37; 95% CI, 1.28, 1.48) and there was appreciable difference in incidence rates between Hispanics and Non-Hispanic Whites (RR= 2.51; 95% CI 2.38, 2.64).

In the multivariable logistic regression analyses (Table 3) both Asian/ Pacific Islanders (OR= 0.83, 95% CI 0.70, 0.99) and Hispanics (OR= 0.86, 95% CI 0.76, 0.98) had significantly lower likelihood of being diagnosed with more advanced (regional or distant) stage of disease compared to non-Hispanic Whites. The corresponding result for Non-Hispanic Blacks was not statistically significant (OR=0.97; 95% CI: 0.82-1.14). Other factors associated with more advanced GBC stage included higher tumor grade and

earlier period of diagnosis. By contrast, no associations were observed for gender and for geographic region.

Table 4 shows the results of multivariate survival analyses. The hazard ratio (HR) and 95% CI estimates of those variables that met the proportional hazards assumptions were listed in Table 4. There was evidence of statistically significant interaction ($P<0.05$) between race and both stage and geographic region for some categories. We explored this finding further by performing stratified analyses to compare associations of stage, region and age with post-diagnosis survival across racial/ethnic groups. These stratified analyses demonstrated no meaningful effect modification with all race/ethnicity-specific associations in the same direction and of similar magnitude (Supplemental Tables 1-4). For this reason, all analyses are presented for the overall no-interaction model (Table 4). Relative to here was a statistically significant difference in post-diagnosis survival between non-Hispanic Black and non-Hispanic White GBC patients (HR: 1.10, 95% CI 1.01-1.19). No significant differences in survival were observed between non-Hispanic white and two other racial/ethnic groups with HR (95% CI) estimates of 1.04 (0.97-1.12) and 1.01 (0.92-1.11) for Hispanics and Asians/Pacific Islanders, respectively. Additional factors associated with worse survival outcome included male gender, older age, more recent time period of diagnosis, advanced GBC stage, and higher tumor grade. No geographic differences in survival were observed in any of the comparisons.

Discussion

The current study evaluating racial/ethnic disparities in age-standardized GBC incidence rates, stage at diagnosis and survival offers a number of observations. First, GBC is significantly more common among non-Hispanic Blacks, Asians/Pacific Islanders and Hispanics than among non-Hispanic Whites. In addition, after controlling for sex, age, year of diagnosis, region and cancer grade, Hispanics and Asians/Pacific Islanders were significantly less likely to be diagnosed at advanced stage of GBC than non-Hispanic Whites. Whereas proportions of GBC patients diagnosed with more advanced stage of disease were similar in non-Hispanic Whites and non-Hispanic Blacks, the former group had significantly better prognosis. On the other hand no discernable difference of survival was found in Hispanics and Asians/Pacific Islanders compared to non-Hispanic Whites after controlling for disease stage and other factors. As expected, factors associated with worse GBC survival included more advanced stage, older age, higher cancer grade. Compared to men, female GBC patients had modest, but statistically significant advantage in post-diagnosis survival.

According to global cancer surveillance data (50), the age-standardized incidence rates of GBC tend to be higher in Latin America, which appears to be in agreement with our finding of the age-standardized incidence rate of Hispanics. Our results regarding racial/ethnic differences in stage at GBC diagnoses were also consistent with previous research reporting that Hispanics and Asians/Pacific Islanders had a higher proportion of cases diagnosed with localized disease (45). Additionally, the result was partially consistent with the recent analysis of the National Cancer Database (NCDB), which reported that odds of advanced GBC were 14% lower among Hispanic patients than

among non-Hispanic Whites. On the other hand, we observed no difference in stage of diagnosis between non-Hispanic Whites and Blacks and lower likelihood of advanced stage among Asian/Pacific Islander GBC patients. These results are in disagreement with the NCDB analysis, which also used non-Hispanic Whites are reference but found no difference for Asians/Pacific Islanders and elevated odds of more advanced GBC for Non-Hispanic Blacks.

It is important to keep in mind that the statistical analyses of the two studies were not exactly the same. While NCDB analyses used ordinal regression with a three-level outcome variable the outcome of interest in our study was dichotomous. Despite these differences the results for Hispanic appeared robust and consistent in both datasets.

The finding that Hispanic GBC patients are more likely to be diagnosed at early stage is plausible. One previous study reported higher prevalence of gallstones in Hispanics compared to non-Hispanics and also observed that Hispanics are more likely to report history of laparoscopic cholecystectomy (51). These observations are informative because previous literature (34, 52) indicated that early-stage GBC is typically diagnosed incidentally during laparoscopic cholecystectomy performed because of symptoms related to coexistent cholelithiasis or cholecystitis.

In contrast with previous reports (46), we observed that non-Hispanic Black GBC patients had 10% higher post-diagnosis mortality relative to their non-Hispanic White counterparts. Our result also show disagreement with another study (53) that reported a survival advantage among Non-Hispanic Blacks diagnosed with GBC. .

Perhaps the most important limitation of existing databases such as NCDB and SEER is lack of detailed information on various aspects of treatment. While SEER

collects data on surgery and radiation, information on chemotherapy is usually incomplete and is not available in the public use datasets. Moreover, SEER data are limited to first course of treatment, and for this reason does not allow assessing the full course of therapy. Previous studies reported that patients who did not receive any surgery had higher post diagnosis mortality in comparison to those who received other types treatment (25, 45, 54). It is important to keep in mind, however, that prognosis and survival of GBC patients is primarily influenced by stage of diagnosis, which in turn dictates its operability and the extent of anticancer therapy. It is also worth noting that a direct comparison of survival in surgical and non-surgical patients is difficult due to the so called "immortal time bias". The term "immortal time bias" refers to a situation when follow up of patients who received a particular treatment always includes a time interval between diagnosis and treatment initiation (55).

Another important variable missing from our study was patients' insurance/socioeconomic status, which may serve as a confounder in both stage of diagnosis and survival analysis. It was shown that residence in counties with higher levels of poverty was associated with lower likelihood of having health insurance (56). Lack of insurance has been shown as a potential reason for not receiving GBC surgery (57). In addition, individuals with better financial status and greater social support may have easier access to high-quality home and hospital care (58).

When interpreting data for the Asian/Pacific Islander and Hispanics it is important to keep in mind that these are very broad and heterogeneous groups. Individuals included in the category 'Asians/Pacific Islanders' include such diverse groups as Chinese, Korean, Filipino and South Asian(59) whereas Hispanics represent a wide range of

European, African and Native American ancestry (60). Moreover, available evidence shows that foreign-born cancer patients are diagnosed at more advanced stage or with larger tumors (61) and have worse survival than patients of the same race/ethnicity who were born in the US (62-64). It is possible that even within the same relatively homogenous racial/ethnic group GBC patients born in US may experience survival patterns that are very different from those of their foreign-born counterparts.

Conclusions

In summary, we found that geographic differences in GBC incidence reported globally are reflected in the racial/ethnic disparities observed in the United States. While Asian/Pacific Islander and Hispanic GBC patients are more likely to be diagnosed at an earlier disease stage, survival does not appear to be influenced by race/ethnicity once disease stage is taken into consideration. While non-Hispanic-Black patients had lower post-diagnosis survival in these data, a lack of consistency with other studies indicates that the observed disparity likely represents a chance finding not reflective of meaningful population differences.

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Tables

Table 1. Demographic and disease characteristics of GBC patients by racial/ethnic group; SEER 2000-2014

Patient Characteristics	Non-Hispanic Whites N (%)	Non-Hispanic Blacks N (%)	Hispanics N (%)	Asians/Pacific Islanders N (%)
Sex				
Male	1,336 (30.27)	233 (26.15)	431 (23.98)	245 (32.45)
Female	3,078 (69.73)	658 (73.85)	1,366 (76.02)	510 (67.55)
Year of Diagnosis				
2000-2004	1,472 (33.35)	242 (27.16)	511 (28.44)	232 (30.73)
2005-2009	1,145 (25.94)	230 (25.81)	465 (25.88)	192 (25.43)
2010-2014	1,797 (40.71)	419 (47.03)	821 (45.69)	331 (43.84)
Age at Diagnosis				
0-59 years	785 (17.78)	296 (33.22)	591 (32.89)	175 (23.18)
60-69 years	977 (22.13)	252 (28.28)	466 (25.93)	202 (26.75)
70-79 years	1,362 (30.86)	215 (24.13)	448 (24.93)	194 (25.70)
>= 80 years	1290 (29.23)	128 (14.37)	292 (16.25)	184 (24.37)
Region				
North East	1,003 (77.72)	175 (19.64)	185 (10.29)	74 (9.80)
South East	675 (15.29)	378 (42.42)	66 (3.67)	22 (2.91)
Mid-West Mountain	1,124 (25.46)	149 (16.72)	144 (8.01)	21 (2.78)
Pacific	1,612 (36.5)	189 (21.21)	1,402 (78.02)	638 (84.50)
Grade				
Well-Differentiated	630 (14.27)	103 (11.56)	250 (13.91)	112 (14.83)
Moderately-Differentiated	1,811 (41.03)	356 (39.96)	723 (40.23)	331 (43.84)
Poorly-Differentiated/	1,830 (41.46)	410 (46.02)	775 (43.13)	292 (38.68)
Undifferentiated	143 (3.24)	22 (2.47)	49 (2.73)	20 (2.65)
Stage[a]				
Localized	1,782 (40.37)	334 (37.49)	714 (39.73)	324 (42.91)
Regional/ Distant	2,632 (59.63)	557 (62.51)	1,083 (60.27)	431 (57.09)

[a]: Staging is according to SEER historic stage A.

Table 2. Age-standardized incidence ratea of GBC patients by racial/ethnic group 2000-2014 SEER databaseb

Race/ethnicity	Cases	Adjusted Rate (95 % CI)	Rate Ratio (95% CI)
Non-Hispanic Whites	5524	0.6 (0.6, 0.6)	1.0 (reference)
Non-Hispanic Blacks	1085	1.0 (0.9, 1.0)	1.56 (1.46, 1.67)
Hispanics	2038	1.6 (1.5, 1.6)	2.51 (2.38, 2.64)
Asians/Pacific Islanders	875	0.9 (0.8, 0.9)	1.37 (1.28, 1.48)

[a] Per 100,000 person-years; Standardized to 2000 US Population;

[b] SEER18 Registry Data

CI: Confidence interval

Table 3. Multivariable logistic regression analysis of the association between cancer stage at diagnosis and race/ethnicity of study participants

Characteristic	Regional/Distant Stage		
	OR	95% CI	
Race			
Non-Hispanic White	*ref*		
Non-Hispanic Black	0.97	0.82	1.14
Hispanic	0.86	0.76	0.98
Asian/Pacific Islander	0.83	0.70	0.99
Sex			
Male	*ref*		
Female	0.94	0.85	1.05
Age at diagnosis			
0-59 years	*ref*		
60-69 years	0.84	0.73	0.96
70-79 years	0.69	0.60	0.79
>= 80 years	0.42	0.37	0.49
Year of Diagnosis			
2000-2004	*ref*		
2005-2009	0.99	0.88	1.13
2010-2014	0.86	0.77	0.97
Region			
North East	*ref*		
South East	0.89	0.75	1.06
Mid-West Mountain	0.90	0.77	1.06
Pacific	1.04	0.91	1.19
Grade			
Well-Differentiated	*ref*		
Moderately-Differentiated	2.39	2.06	2.76
Poorly-Differentiated	5.59	4.81	6.49
Undifferentiated	6.06	4.38	8.38

Table 4. Multivariable survival analysis: Cox model results for variables that met the proportional hazards assumption

Characteristic	Hazard Ratio	95% CI		*P* value
Race				
Non-Hispanic White	*ref*			
Non-Hispanic Black	1.10	1.01	1.19	0.04
Hispanic	1.04	0.97	1.12	0.23
Asian/Pacific Islander	1.01	0.92	1.11	0.83
Sex				
Male	*ref*			
Female	0.91	0.86	0.97	0.0017
Age at diagnosis				
0-59 years	*ref*			
60-69 years	1.15	1.06	1.24	0.0005
70-79 years	1.49	1.39	1.61	<.0001
>= 80 years	2.17	2.01	2.34	<.0001
Year of Diagnosis				
2000-2004	*ref*			
2005-2009	0.85	0.80	0.91	<.0001
2010-2014	0.77	0.73	0.82	<.0001
Region				
North East	*ref*			
South East	1.07	0.98	1.17	0.16
Mid-West Mountain	1.02	0.94	1.11	0.62
Pacific	0.98	0.91	1.05	0.58
Stage				
Localized	*ref*			
Regional/Distant	2.63	2.48	2.79	<.0001
Grade				
Well-Differentiated	*ref*			
Moderately-Differentiated	1.24	1.13	1.35	<.0001
Poorly-Differentiated	1.88	1.72	2.06	<.0001
Undifferentiated	1.81	1.54	2.12	<.0001

Appendices

Supplemental Table 1. Cox model limited to non-Hispanic Whites

Characteristic	Hazard Ratio	95% CI		*P* value
Sex				
Male	*ref*			
Female	0.93	0.87	1.00	0.061
Age at diagnosis				
0- 59 years	*ref*			
60-69 years	1.11	0.99	1.24	0.07
70-79 years	1.54	1.39	1.70	<.0001
>= 80 years	2.22	2.00	2.46	<.0001
Year of Diagnosis				
2000-2004	*ref*			
2005-2009	0.85	0.78	0.92	<.0001
2010-2014	0.78	0.72	0.85	<.0001
Region				
North East	*ref*			
South East	1.09	0.98	1.22	0.12
Mid-West Mountain	1.01	0.92	1.12	0.78
Pacific	0.97	0.89	1.06	0.47
Stage				
Localized	*ref*			
Regional/Distant	2.50	2.32	2.70	<.0001
Grade				
Well-Differentiated	*ref*			
Moderately-Differentiated	1.16	1.04	1.30	0.01
Poorly-Differentiated	1.76	1.57	1.97	<.0001
Undifferentiated	1.68	1.37	2.05	<.0001

Supplemental Table 2. Cox model limited to non-Hispanic Blacks

Characteristic	Hazard Ratio	95% CI		*P* value
Sex				
Male	*ref*			
Female	1.08	0.90	1.28	0.423
Age at diagnosis				
0- 59 years	*ref*			
60-69 years	1.29	1.06	1.57	0.01
70-79 years	1.44	1.18	1.77	0.00
>= 80 years	1.87	1.48	2.37	<.0001
Year of Diagnosis				
2000-2004	*ref*			
2005-2009	0.93	0.76	1.13	0.46
2010-2014	0.75	0.63	0.91	0.00
Region				
North East	*ref*			
South East	1.12	0.91	1.39	0.30
Mid-West Mountain	1.08	0.83	1.39	0.58
Pacific	1.05	0.82	1.34	0.70
Stage				
Localized	*ref*			
Regional/Distant	2.50	2.10	2.98	<.0001
Grade				
Well-Differentiated	*ref*			
Moderately-Differentiated	1.20	0.91	1.58	0.21
Poorly-Differentiated	1.81	1.37	2.39	<.0001
Undifferentiated	2.08	1.25	3.46	0.01

Supplemental Table 3. Cox model limited to Hispanics

Characteristic	Hazard Ratio	95% CI		*P* value
Sex				
Male	*ref*			
Female	0.80	0.70	0.91	0.0007
Age at diagnosis				
0- 59 years	*ref*			
60-69 years	1.16	1.00	1.34	0.0554
70-79 years	1.40	1.20	1.62	<.0001
>= 80 years	1.94	1.65	2.29	<.0001
Year of Diagnosis				
2000-2004	*ref*			
2005-2009	0.85	0.74	0.98	0.0242
2010-2014	0.79	0.69	0.90	0.0004
Region				
North East	*ref*			
South East	0.80	0.56	1.13	0.2019
Mid-West Mountain	0.95	0.73	1.22	0.6629
Pacific	0.84	0.70	1.00	0.0510
Stage				
Localized	*ref*			
Regional/Distant	2.84	2.50	3.24	<.0001
Grade				
Well-Differentiated	*ref*			
Moderately-Differentiated	1.39	1.14	1.70	0.0011
Poorly-Differentiated	2.10	1.72	2.56	<.0001
Undifferentiated	1.64	1.13	2.40	0.0101

Supplemental Table 4. Cox model limited to Asians/ Pacific Islanders

Characteristic	Hazard Ratio	95% CI		*P* value
Sex				
Male	*ref*			
Female	0.82	0.68	0.99	0.0339
Age at diagnosis				
0- 59 years	*ref*			
60-69 years	1.07	0.82	1.39	0.6082
70-79 years	1.36	1.06	1.76	0.0162
>= 80 years	2.62	2.02	3.40	<.0001
Year of Diagnosis				
2000-2004	*ref*			
2005-2009	0.77	0.62	0.96	0.0178
2010-2014	0.71	0.58	0.87	0.0011
Region				
North East	*ref*			
South East	0.94	0.48	1.82	0.8437
Mid-West Mountain	0.94	0.50	1.77	0.8572
Pacific	1.55	1.12	2.14	0.0081
Stage				
Localized	*ref*			
Regional/Distant	3.47	2.83	4.24	<.0001
Grade				
Well-Differentiated	*ref*			
Moderately-Differentiated	1.51	1.12	2.04	0.0074
Poorly-Differentiated	2.54	1.87	3.45	<.0001
Undifferentiated	3.10	1.80	5.34	<.0001