**BACKGROUND:**

We sought to evaluate prostate cancer (PCa) characteristics and outcomes of Hispanics living in the United States by country of origin in the Surveillance, Epidemiology and End Results (SEER) program.

**METHODS:**

Retrospective analysis of 72,134 adult Hispanics with PCa between 1995-2014. Origin was Mexican (N=16,995; 24%), South/Central American (N=6,949; 10%), Puerto Rican (N=3,582; 5%), Cuban (N=2,587; 4%), Dominican (N=725; 1%), Hispanic not specified (NOS, N=41,296; 57%), as coded by SEER. Patient and PCa characteristics were analyzed with chi-square and Kruskal-Wallis tests. Overall and PCa survival were analyzed with Kaplan-Meier and Cox models adjusting for baseline variables.

**RESULTS:**

At diagnosis, Mexicans had more advanced stage, higher prostate-specific antigen and higher Gleason score while Cubans and Dominicans had more favorable PCa at diagnosis (all P<0.05). After a median follow up of 69 months, 20,317 men died, including 6,223 PCa deaths. Compared to Mexicans, Cubans (HR=1.22, 95%CI=[1.14-1.30]) and Puerto Ricans (HR=1.15 [1.08-1.22]) had worse overall survival while Dominicans (HR=0.76 [0.64-0.91]), South/Central Americans (HR=0.68, [0.65-0.72]) and NOS (HR=0.81 [0.78-0.84]) had better overall survival. Compared to Mexicans, Cubans (HR=1.08, [0.96-1.22]) and Puerto Ricans (HR=1.03, [0.92-1.15]) had similar PCa survival while Dominicans (HR=0.72, [0.53-0.98]), South/Central Americans (HR=0.67 [0.60-0.74]) and NOS (HR=0.68 [0.64-0.73]) had significantly better PCa survival.

**CONCLUSIONS:**

Among Hispanics in the United States, disparities in PCa characteristics and survival by country of origin exist, with Dominicans, South/Central Americans and Hispanic NOS having better PCa survival compared to Mexicans, Cubans and Puerto Ricans.

**Introduction:**

Hispanics are the second largest ethnic group in the United States and are comprised of a heterogeneous group of descendants from the Spanish-speaking countries of North, Central and South Americas, the Caribbean, and Iberian Peninsula.1 Despite varying countries of origin and varying European, Native American and West African heritage2, most prostate cancer (PCa) studies place them under a general Hispanic classification. As a group, the incidence of PCa among Hispanics is comparable to non-Hispanic Whites (NHW) and almost half of blacks with similar five-year survival between Hispanics and NHWs for all stages combined.3

While Hispanics have similar incidence rates of PCa compared to NHWs, they are less likely to be diagnosed with localized disease3 and have increased rates of advanced4 and metastatic disease.5 Additionally, Hispanics have differences in clinical factors known to influence PCa outcomes including prostate-specific antigen (PSA) screening.6 Hispanics are more likely to have a discussion of the advantages and disadvantages of PSA screening and engage in shared decision making as compared to Non-Hispanics7, but are less likely to receive definitive treatment8, 9 or pelvic lymph node dissection10 and more likely to have a delay between biopsy to radical prostatectomy11 as compared to their NHW counterparts.

Prior epidemiological studies have observed differences in rates of urological malignancies such bladder, kidney and PCa 12 among Hispanic subgroups, with the lowest incidence of PCa occurring in Mexicans and the highest rates among Cubans. While a recent study13 demonstrated differences in rates of metastatic disease on presentation, definitive treatment and PCa specific mortality (PCSM) among different subgroups of Asian American men by country of origin, it remains largely unknown if there are similar presentation or treatment disparities in PCa between disaggregated Hispanic subgroups. Thus, the aim of our study was to evaluate differences in patient and disease characteristics at diagnosis, treatment and cancer outcomes based on country of origin among Hispanics diagnosed with PCa in the Surveillance Epidemiology and End Results (SEER) database, a population based dataset which collects information on cancer statistics, incidence and population data associated by age, sex, race, clinical demographics, tumor characteristics, primary treatment and cause of death from registries covering approximately 28% of the United States population and 38% of Hispanics14

**Materials and Methods:**

*Sample:*

After exemption by the Institutional Review Board, de-identified SEER data from 1973 to 2014 (April 2017 release) was obtained from <https://seer.cancer.gov>, and stored and processed using PostgreSQL 9.5.5 (The PostgreSQL Global Development Group) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). The initial query consisted of all adult (age ≥ 18) males with PCa (International Classification of Diseases version 10, code C61) from 1973-2014 (N=1,708,661). Cases diagnosed prior to 1995 were excluded due to unavailability of several covariates. Patients were included if the histological diagnosis was compatible with adenocarcinoma (adenocarcinoma, carcinoma not otherwise specified (NOS), ductal carcinoma and prostate malignancy NOS) and the North American Association of Central Cancer Registries Hispanic identification Algorithm (NHIA) was coded as derived Hispanic origin (N=88,585, 5.2%). Patients were excluded if PCa was diagnosed at autopsy/death certificate only or their Hispanic origin was based on NHIA Surname Match Only (N=16,451). This resulted in a final study sample of 72,134 subjects. A flow chart of the patient selection is shown in Figure 1.

*Variables:*

Variables evaluated included NHIA-derived Hispanic origin by country (Mexican, Puerto Rican, Cuban, Dominican, South or Central American excluding Brazilian, and Spanish/Hispanic/Latino NOS), age at diagnosis, year of diagnosis, PSA, tumor stage, best available Gleason score (2-6, 7, or 8-10), primary treatment, marital status (married, single/never married, divorced, widowed, separated, domestic partner or unknown), insurance status (privately insured, insured [no specifics], Medicaid and uninsured) and socioeconomic status (SES). SES was examined with 4 county-attributed census variables available in SEER: median family income, percentage of adults in poverty, unemployment percentage and percent of adults not attaining high school education. PSA was categorized into values of 0-3.9, 4-9.9, 10-19.9, >20 ng/ml and missing. Covariates were determined at the time of diagnosis or shortly thereafter (in the case of treatment choice). Year of diagnosis was categorized into 1995-1999, 2000-2004, 2005-2009 and 2010-2014. Stage of disease at diagnosis was determined using TNM classification of malignant tumors. Definitive treatments were classified as radical prostatectomy (RP), radiation treatment (XRT), a combination of RP and XRT (RP/XRT), or neither RP nor XRT. Age at diagnosis and SES variables were considered continuous variables, while all others were treated as categorical. Missing values were treated as a separate category.The primary outcomes were overall and PCa-specific survival after diagnosis.

*Statistical Analysis:*

Descriptive statistics are presented as median and interquartile range (IQR) for continuous data or count and percentage for categorical variables. Baseline patient and disease characteristics across Hispanic subgroups were compared with Kruskal-Wallis tests for continuous data and chi-squared tests for categorical variables. Survival was estimated and plotted using the Kaplan-Meier method. The association between Hispanic subgroups and overall and PCa specific survival was analyzed using log-ranked test and Cox proportional hazards in uni- and multivariable analysis adjusting for *a priori* selected variables: age, year of diagnosis, PSA, treatment, tumor stage, Gleason score, educational attainment, poverty, unemployment, income, insurance, and marital status. PCa specific survival was defined as time from diagnosis to death by PCa. The Mexican group was chosen as the referent group from multivariable models as the largest identified subgroup. All analyses were two-tailed and performed using Stata 12.0 (StataCorp, College Station, TX). P < 0.05 was considered statistically significant.

**Results:**

Baseline characteristics for Hispanic men are shown in Table 1. The median (IQR) age and PSA at diagnosis were 67 (60-74) and 7.2 (5.0-12.8), respectively. Tumor stage was mainly localized (41.5% T1 and 45.8% T2 versus 11.2% T3 and 1.5% T4). Gleason score was predominantly 2-6 (44.1%). Treatment was XRT only in 32.0%, RP only 31.1%, both RP/XRT 1.8% and no RP/XRT in 35.1%. Only a minority of men undergoing RP had lymph node dissection (24.3%). Most subjects had health insurance (80.4%) or Medicaid (15.5%) and were married (74.2%). The median (IQR) family income was US $62,290 (59,630-74,230), adults in poverty was 14.6% (9.2-14.7), unemployment was 11.0% (8.8-12.1) and adults not attaining high school education was 18.0% (13.2-23.2).

A total of 16,995 (23.6%) men were Mexican, 6,949 (9.6%) were South or Central American, 3,582 (5.0%) were Puerto Rican, 2,587 (3.6%) Cuban, 725 (1.0%) Dominican Republic, and 41,296 (57.3%) were Spanish/Hispanic/Latino NOS. There were several significant differences in baseline patient and disease characteristics across groups (Table 1). Cubans were older (median age of 70 years) while South/Central Americans and Dominicans were the youngest (median age of 65 years). Median PSA at the time of diagnosis was lowest among Dominicans and Puerto Ricans at 6.8 ng/ml while highest in Mexicans at 7.8 ng/ml (5.3-15.0). Dominicans presented with the most favorable stage at diagnosis with only 6.5% T3/T4 disease, while 14.0% and 13.0% of Mexicans and South/Central Americans had T3/T4 disease, respectively. Overall N1-3 presentations were low varying between 0% among Dominicans to 1.7% among South/Central Americans (P=0.02). While Gleason 2-6 was the most common score for each subgroup, 20.6% of Mexicans had Gleason scores 8-10 compared to only 16.4% of Cubans. RP only was most frequently used treatment among South/Central Americans (35.3%), compared to only 20.6% in Cubans. Conversely, Cubans underwent XRT only in 46.2% compared to 29.6% of Mexicans.

A total of 20,317 patients died over a median follow-up of 69 (32-116) months. The median time to all-cause death was 53 (22-96) months. Of these deaths, 6,223 (28.2%) were attributed to PCa. The median follow-up for PCSM was 68 (31-114) months with a median time to PCa death of 34 (13-72) months. Figures 2a and 2b show the overall and PCa-specific survival by country of origin. In univariate analyses, Cubans (HR=1.22, 95%CI=[1.14-1.30]) and Puerto Ricans (HR=1.15 [1.08-1.22]) had worse overall survival, while Dominicans (HR=0.76, [0.64-0.91]), South/Central Americans (HR=0.68 [0.65-0.72]) and NOS (HR=0.81, [0.78-0.84]) had better survival compared to Mexicans (Table 2). Similar results were found in multivariable analysis where Cubans (HR = 1.07, [1.00-1.14]) and Puerto Ricans (HR=1.17, [1.10-1.25]) had worse overall survival while Dominicans (HR=0.73, [0.61-0.88]), South/Central Americans (HR=0.79, [0.75-0.84]), and NOS (HR=0.82, [0.79-0.84]) had better overall survival as compared to Mexicans. Regarding PCa specific mortality, Cubans (HR=1.08, [0.96-1.22]) and Puerto Ricans (HR=1.03, [0.92-1.15]) had similar PCa survival compared to Mexicans, while Dominicans (HR=0.72, [0.53-0.98]), South/Central Americans (HR=0.67 [0.60-0.74]) and NOS (HR=0.68 [0.64-0.73]) had significantly better PCa survival (Table 3). Results were virtually unchanged in multivariable analysis where Cubans (HR = 1.06, [0.93-1.20]) and Puerto Ricans (HR=1.02, [0.91-1.15]) had similar PCa survival compared to Mexicans, while Dominicans (HR=0.69, [0.53-0.97]), South/Central Americans (HR=0.78, [0.71-0.87]), and NOS (HR=0.75, [0.71-0.80]) had better PCa survival.

**Discussion:**

Hispanics are the largest and fasting growing ethnic group in the United States.15 Despite genetic, environmental, and cultural differences, Hispanics are often reported as a single ethnic group.16 Variability between Hispanic subgroups have been noted in malignancies including breast, lung and liver cancers15 but it remains unclear whether PCa disparities exist within this population. In this study, we found significant differences in PCa among Hispanic subgroups including disease characteristics at presentation, treatment and survival which have not been previously reported. Within a large population-based sample of the United States, we found Hispanics of Mexican origin have the least favorable PCa characteristics at presentation, with the highest median PSA (7.8 ng/ml), advanced disease (14.0%) and high-grade Gleason scores (20.6%) of any Hispanic subgroup. Conversely, Cuban and Dominicans had more favorable disease at diagnosis. Regarding treatment choices, Cubans were treated with the highest proportion of XRT, while South/Central Americans were treated with the highest proportion of RP. Compared to Mexicans, Cubans and Puerto Ricans had similar PCa survival, while Dominicans, South/Central Americans and Hispanic NOS demonstrated significantly better PCa survival. Despite more favorable disease characteristics, Cubans and Puerto Ricans had worse overall survival while Dominicans, South/Central Americans and Hispanic NOS had significantly better survival compared to Mexicans. Thus, PCa disparities among Hispanics do exist. However, patient and disease characteristics and treatment data captured by SEER alone do not completely explain the disparate survival observed.

 Prior studies have demonstrated variability in PCa incidence and PCSM between and within Hispanic subgroups in the United States and their native populations. While Puerto Ricans living in Florida had similar adjusted incidence rates to their country of origin, Mexicans living in Florida had almost a 2-fold greater incidence of PCa and Cuban Hispanics living in Florida had almost a 4-fold greater incidence of PCa as compared to resident Cubans.12 We found that, as compared to Mexicans, Cubans and Puerto Ricans had similar PCSM, while Dominicans, South/Central Americans and Hispanic NOS demonstrated significantly better PCSM, which does not match the previously reported age standardized mortality rates seen in native populations demonstrating that Cubans had a higher mortality than Mexicans.17 These studies indicate that differences exist between native Hispanics and Hispanics living in the USA which suggests that adopting an American lifestyle may change their risk of PCa and cancer mortality.

 One of the strongest known risk factors for PCa is African ancestry. Numerous studies18, 19 have linked African ancestry with increased PCa risk and worse oncologic outcomes.4, 20, 21 Hispanics inherit a mix of European, Native American and African ancestry. In one study, Dominicans and Puerto Ricans demonstrated the highest levels of African ancestry (41.8% and 23.6% African), whereas Mexicans and Ecuadorians had the lowest levels of African ancestry (5.6% and 7.3%) and the highest Native American ancestries (50.1% and 38.8%).2 The African ancestry in that study does not match the cancer characteristics and outcomes observed in our study. Although significant variation in African ancestry exists within country of origin, these discordant findings suggest that biology and genetics alone do not explain all the discrepancies observed within Hispanics.

Modifiable environmental and life style factors such as PSA screening and treatment preferences, SES, access to care, and others have been shown to influence PCa outcomes.22, 23 Within our cohort, we observed statistically significant differences in all SES variables assessed as well as insurance status and marriage percentage. In general, studies24, 25 have noted lower PSA screening rates among Hispanics, even for men with a first-degree family history of PCa.26 Variability in PSA screening has been noted among Hispanic subgroups with the highest screening rates among Cubans and the lowest rates among Dominicans.6 Variation in digital rectal examination (DRE) have also been noted with the highest proportion of men who reported having had a DRE among Cubans and the lowest rates in Mexican and Central Americans.27 In addition to PCa incidence, SES may also contribute towards oncologic outcomes. Previous SEER studies have demonstrated an independent survival benefit for married PCa patients.28 Among all men, marriage has been shown as an predictor for utilization of PSA screening.29 In our sample, Mexicans had the highest rates of marriage (76.4%) and Puerto Ricans had the lowest (64.0%), which do not match the outcomes observed. Moreover, lower socioeconomic factors have been associated with an increased risk of PCSM.30 Within our cohort, Mexicans lived in counties that had the highest rate of men without a high school degree (22.8%), the highest unemployment percentage (11.0%) and the highest percentage of families living below the poverty line (14.6%). It is possible that SES disparities, both captured and not captured in our analyses could partially explain the disparate PCa outcomes observed with worse outcomes in Mexican men. With regard to treatment, Moses *et al*8 demonstrated that Hispanics were significantly less likely to receive RP and brachytherapy and significantly more likely to receive XRT or cryotherapy as compared to NHWs. Treatment decisions for specific Hispanic subgroups have not been extensively evaluated. In our cohort, Cubans utilized XRT treatment while South/Central Americans were treated with the highest proportion of RP. Among men that received neither RP or XRT, South/Central Americans had the lowest percentage (29.9%) while Mexican and Hispanic NOS men had the highest percentage (36.1%). The higher proportion of neither RP/XRT within the Mexican cohort is somewhat surprising given the poorer disease characteristics at the time of presentation. Given the lack of a single identifiable factor explaining the differences in disease a multifactorial etiology including differences in diet31, obesity32 and PSA expression33 which have been shown to influence PCa outcomes and are not captured within this data set, are likely responsible for the disparities in PCa among Hispanics..

There are several limitations inherent to the SEER dataset. These include a lack of centralized pathology review, self-reported race, lack of intermediate outcomes such as disease progression, and missing data. Previously it has been shown that cancer survival statistics for Hispanics may overestimate survival due to incomplete data within the SEER dataset34 and it is unknown if similar discrepancies exist between Hispanics by country of origin. Moreover, 53% of patients were identified as Hispanic NOS. In addition, data on PCa risk factors (e.g. family history), screening patterns, and treatments including active surveillance, androgen deprivation therapy and chemotherapy were not available and as this study spans almost two decades and there have been significant changes regarding PCa screening, diagnosis and treatment during this time which may have affected the results obtained. Despite these limitations, our study is the first to examine PCa outcomes among Hispanic subgroups using a large population-based sample and provides important insights on PCa disparities among Hispanics.

**Conclusions:**

Among Hispanics living in the United States, disparities in PCa characteristics and survival by country of origin do exist, with Dominicans, South/Central Americans and NOS having better PCa survival compared to Mexicans, Cubans and Puerto Ricans. Understanding the potential genetic, environmental and lifestyle contributors to these differences are key to mitigate PCa disparities in Hispanics.

**Conflict of Interest:**

The authors declare no conflict of interest

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