Racial/Ethnic Disparities in Prostate Cancer 5-Year Survival: The Role of Health-Care Access and Disease Severity

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Posted Date: 18 April 2023

doi: 10.20944/preprints202304.0485.v1

Keywords: Prostate Cancer, Survival, Disparities, Geographic, Multilevel, Healthcare Access

Article

Racial/Ethnic Disparities in Prostate Cancer 5-Year Survival: The Role of Health-Care Access and Disease Severity

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Abstract: Introduction Prostate Cancer (PCa) exhibits one of the widest racial and socioeconomic disparities. PCa disparities have also been widely linked to location as living in more deprived regions was associated with lower healthcare access and worse outcomes. This study aims to examine PCa survival across various US counties in function of different socioeconomic profiles and discuss the role of potential intermediary factors. **Methods** The SEER database linked to county-level SES was utilized. Five-year PCa-specific survival using the Kaplan Meier method was performed for 5 racial/ethnic categories in function of SES quintiles. Multilevel Cox proportional hazards regression was performed to assess the relationship between county-level SES and PCa survival. Multivariate regression analysis was performed to examine the role of healthcare utilization and severity. **Results** 279,000 PCa records were extracted, 5-year PCa-specific survival was 94%. Overall, living in counties with worst poverty/income quintile and highest proportions of foreign-born/language-isolated increased PCa mortality by 23% each. No association was observed with county-level High-School education, while Bachelor's-level education decreased mortality risk by 23%. Associations varied considerably upon racial/ethnic stratification. Multilevel analyses showed varying contributions of individual and area-level factors to survival within minorities. The relationship between SES and PCa survival appeared to be influenced by healthcare utilization and disease stage/grade. **Discussion** Racial/ethnic categories responded differently under similar county-level SES and individual-level factors to the point where disparities reversed in Hispanics. The inclusion of Healthcare utilization and severity factors may provide partial early support for their role as intermediaries. Healthcare access (insurance) might not necessarily be associated with better PCa survival, through performing biopsy and or/surgery. County-level education plays an important role in PCa decision-making as it might elucidate discussions of other non-invasive management options. **Conclusion** Findings of this study demonstrate that interventions need to be tailored according to each group's needs. This potentially informs the focus of public health efforts in terms of planning and prioritizing. This study could also direct further research delving into pathways between area-level characteristics with PCa survival.

Keywords: prostate cancer; survival; disparities; geographic; multilevel; healthcare access

Introduction

Prostate cancer (PCa) is the second leading cause of death and the most common cancer in men residing in the U.S. (1). Although survival from PCa is relatively very high to other malignancies, remarkable disparities in PCa outcomes have been reported across multiple settings and series. For example, Non-Hispanic Blacks (NHB), on average, have a 78% higher incidence of PCa as compared

to Non-Hispanic Whites (NHW) in their lifetimes (1-4). Furthermore, PCa is more aggressive and occurs at a younger age in AA men resulting in a 2.3-fold increase in mortality rate (Vs. NHW) (3-5). Additionally, Hispanics and some populations of individuals of Asian descent have lower PCa incidence, however, suffer from more advanced disease at diagnosis (4-6).

PCa outcomes are sensitive to geographic locations (7), as disparities vary based on area-level characteristics at multiple geographic scales (7-9). Hispanics living in Mexico have a lower incidence than Hispanics living in the Caribbean (10) while Puerto Ricans living in Puerto Rico have a lower incidence than Puerto Ricans living in the mainland U.S. (11) suggesting that geographical elements may help to explain PCa disparities.

Existing literature supports the view that disparities emerge, in part, due to inequalities in access to adequate healthcare (HC) that vary across race and socioeconomic status (12,13). As an example, NHBs with PCa experienced delays in care and were less likely to undergo definitive management such as surgery (2,14). Most importantly, advances in imaging and procedures, and surgical access are critical in PCa (15) as they appear to interfere with disparities in outcomes. For example, NHBs, lower socioeconomic status, and older age were found to be associated with underutilization of PCa diagnostic imaging (Deville). More importantly, Multiparametric Magnetic Resonance Imaging (mpMRI) fusion-guided biopsy, a revolutionary technique in accurately diagnosing and staging PCa was less likely to be performed by NHBs even though it has been found to possess better performance indicators in that group as compared to NHW (16,17). Disparities in PCa outcomes after treatment were noted as worse bowel and urinary functions were reported by men from racial/ethnic minorities suggesting receipt of lower-quality treatment (18). Additionally, disparities decreased in magnitude in equal-access samples like the Veterans Health Administration, indicating non-clinical causal pathways for PCa disparities (19).

To date, area-level PCa disparities in survival have been mostly studied across NHW and NHB and in relatively smaller geographical scales such as neighborhoods or zip codes (20-22). Some evidence suggests that associations between area-level SES and PCa measure highly rely on the geographical scale chosen (23-25). The goal of the present study was to describe differences in PCa outcomes across an expanded category of racial/ethnic groups, to examine whether county-level SES helped to explain disparities in PCa survival, and understand how potential factors influence any established association between county-level SES and PCa survival.

Methods

Data sources and study population

Disparities in five-year PCa survival were estimated by race/ethnicity and SES. The study cohort was derived from the SEER cancer database. The SEER (NCI) program provides valuable information on various cancer statistics as it's a population-based cohort that covers around one-third of the US population and contains a larger proportion of foreign-born, thereby facilitating studies of racial and ethnic disparities (26).

Outcome definition

The primary outcome of this study is 5-year PCa survival. Cancer-specific mortality was utilized to ascertain net survival and; probability of surviving PCa in the absence of other causes of death. We included biopsy-confirmed diagnoses among men aged 18 years and older. Analyses focused on diagnoses initiated from January 1st, 2007, to December 31st, 2011, followed up for at least five years through December 31st, 2016. Participants who had missing information on survival follow-up were excluded (11.4%), however, this did not result in a selection bias as no significant differences in racial composition and SES status were found in the excluded sample. Disease severity was also described through a later SEER summary stage at diagnosis (distant) and a more aggressive Gleason Score (GS=8-10).

 doi:10.20944/preprints202304.0485.v1

Race/Ethnicity and Risk Factors

Groups included all five races/ethnicities within the SEER registry: NHW, NHB, Non-Hispanic Asian or Pacific Islander (NHAPI), Non-Hispanic American Indian or Alaska Native (NHAI/AN), and Hispanics (HISP). Individual characteristics selected were factors that are known to be associated with PCa survival such as age, marital status, stage at diagnosis, and GS (27,28). Healthcare (HC) access was ascertained through individual-level insurance status, while HC utilization was through having a GS done and PCa-directed surgery.

Socioeconomic Status (SES)

Area-based SES was derived from the SEER linkage with the American Community Survey (ACS). County-level 5-year ACS were collected for each case enclosed in its corresponding county. The 2007-2011 5-year ACS linkage was selected as it would reflect the SES of the selected PCa cohort diagnosed between 2007-2011. County-level SES represented income (median household income), material deprivation (percentage of individuals 150% below poverty level, percentage of family below poverty level, unemployment rates), social class levels (percentage of individuals with less than high-school education, percentage of individuals with at least a bachelor-level education) and population composition (percentage of foreign-born, percentage of language isolation). Such variables are often included in health outcomes research relating poorer SES status with poorer health outcomes such as higher mortality (29,30). SES characteristics were classified into quintiles, ranging from worse to best. Because some variables tend to explain very similar constructs, composite indices have been created. “Percentage of individuals 150% below poverty level”, “percentage of family below poverty level”, and “median household income” have been grouped into a single index named “Poverty/Income”. “Percentage of foreign-born”, “percentage of language isolation” have also been grouped into a single index called “Foreign-born/language-isolation”.

Statistical Analysis

Overall baseline characteristics were examined for significance using the chi-square test. 5-year prostate cancer-specific survival was determined using the official software for the SEER database, SEERStat. The end of follow-up status was either "dead" or "alive" and intervals were in months, totaling 60 months. Kaplan-Meier curves were used to examine 5-year survival for racial/ethnic groups in the lowest and highest SES quintiles and log-rank test to examine equality for survival functions.

Cox-proportional hazard models assessed relationships between county-level SES and PCa survival (31). The model was adjusted for established and independent risk factors for poorer PCa survival; age, and marital status, and stratified by races/ethnicities to assess in-between groups disparities. We used the variance inflation factor (VIF) to verify the absence of multicollinearity (32). Because worse PCa can often be predicted by poorer access to care and more severe disease (12), individual-level factors measuring those were also included in subsequent modeling to compare results with and without them.

Because observations are located within the county of residence, geographical clustering was plausible and a multilevel survival cox proportional hazards model with mixed effects incorporating cluster-specific random effects that could potentially modify the baseline hazard function was performed and an exponential distribution was specified. A multivariate logistic regression examining the relationship between SES and advanced disease (i.e.: Distant stage and GS 8-10) and healthcare utilization (having a GS and undergoing PCa-directed surgery) was performed. Stata v.16 was utilized for statistical analyses and a p-value of less than 0.05 was considered statistically significant.

Results

Table 1 represents the baseline characteristics of participants stratified by race/ethnicity. The total number of participants was 279,000. NHB expectedly exhibited the youngest age at diagnosis at

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63.6 years. Five-year PCa survival ranged between 93% and 94% in all groups except NHAI/AN which had the lowest survival (88%). NHB, NHAPI, and Hispanics had the most advanced stage at diagnosis and were also found to have the highest proportion of GS≥8. Although PCa-directed surgery was present in slightly less than half of the patients, NHAI/AN and NHB were the least to undergo one. More than half of the groups had medical insurance at diagnosis while NHAI/AN, HISP, and NHAPI had the highest percentage of Medicaid-insured patients. NHW had the lowest rates of uninsured while NHB had the highest (Table 1).

Hispanics resided in counties with the worst education where almost half (42.2%) had the highest percentage of less than high school education (<HS) and only 12.6% achieved at least a bachelor's-level education (≥BL). More than one-third of NHAPI and NHB resided in counties with the highest poverty/income. Almost half of NHAPIs (45%) and HISP (41%) resided in counties with the highest concentrations of foreign-born/language isolated (Table 1).

Figure 1 provided Kaplan Meier survival curves for individuals in the lowest and highest quintiles of SES variables stratified by racial/ethnic groups throughout the five-year follow-up. Log-rank test was statistically significant for all the plots included. For each graph, observations were restricted to the most and the least deprived quintiles to illustrate racial/ethnic comparisons in survival throughout extreme SES variations. Lowest survival was observed within the worst quintiles of "Poverty/Income" as well as "<HS" education. NHAI/AN exhibited the poorest survival rates within all five most deprived SES quintiles. NHW kept having the highest survival even in counties with the worst unemployment and poverty/income rates. NHAPI had the highest survival in counties with the lowest foreign/born-language isolation rates while HISP had the highest survival in counties with the best HS education (Q1 of <HS) (Figure 1).

Table 2 represents the cox-proportional hazard model in function of SES for the overall population and then stratified into racial/ethnic groups. For every SES variable, worst SES quintile is compared to the best SES quintile. Overall, living in a county with the worst poverty/income rates and highest proportions of foreign-born/language-isolated had a significant 23% increase in the risk of PCa mortality (P<0.01). On the contrary, living in a county with the highest rates of ≥BL education and unemployment had a significant protective effect on PCa survival (HR 0.77, 95%CI 0.70-0.85) and HR 0.89, 95%CI 0.83-0.95 respectively). County-level HS education did not have a significant effect on PCa survival except in HISP where <HS education doubled the risk of PCa mortality. Upon stratification, same statistically significant directions remained in NHW while they almost completely disappeared in the remaining groups, however, the higher mortality risk associated with worst poverty/income remained. Highest rates of "≥BL" had a considerate and significant protective effect in NHAI/AN (HR 0.17, 0.05-0.97, P<0.05), however, their survival was extensively affected by highest proportions of foreign-born/language-isolated (HR 6.6, 1.17-35.76, P<0.05). PCa survival in NHAPI men was not statistically affected by any SES factor included.

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Table 1: Baseline characteristics and 5-year survival of PCa cancer patients stratified into racial/ethnic groups

	Overall 239,613	NHW (186,596)	NHB (40,130)	HISP (24,348)	NHAPI (12,654)	NHAIAN (931)	P-value
Mean age at diagnosis +/-SD	65.40 +/-9.4	66.4 +/- 9.4	63.6 +/- 9.4	66.1 +/- 9.6	68.1 +/- 9.3	66.3 +/- 9.2	<0.01
5-year PCa survival	0.94	0.94	0.93	0.93	0.94	0.88	<0.01
Year of diagnosis							
2007	50,641	39,970	7,922	4,678	2,601	179	
%	21.13	21.4	19.7	19.2	20.6	19.2	
2008	47,879	37,302	7,840	4,763	2,455	180	
%	19.98	19.9	19.5	19.6	19.4	19.3	
2009	48,485	37,050	8,168	5,018	2,514	182	
%	20.23	19.9	20.4	20.6	19.9	19.6	
2010	46,690	35,998	8,056	4,881	2,466	203	
%	19.49	19.3	20.1	20.1	19.5	21.8	
2011	45,918	36,276	8,144	5,008	2,618	187	<0.01
%	19.16	19.4	20.3	20.6	20.7	20.1	
Marital Status							
Divorced/Separated	17,243	11,007	4,089	1,472	396	110	
%	7.20	6.59	11.8	7.06	3.6	13.79	
Married	157,828	115,628	18,481	13,425	8,152	446	
%	65.87	69.21	53.33	64.34	74.20	55.89	
Single	22,835	13,504	6,301	1,968	691	69	
%	9.53	8.08	18.18	9.43	6.29	8.65	
Unknown/missing	35,674	24,601	5,784	3,368	1,748	173	
%	14.89	16.12	16.69	19.17	15.91	21.67	<0.01
Insurance Status							
Any Medicaid	10,204	3637	2504	2510	1300	121	
%	4.26	2.18	7.23	12.03	11.83	15.16	
Insured	202,120	146063	28151	15719	8663	602	
%	84.35	87.42	81.23	75.34	78.85	75.44	
Uninsured	3,215	1562	963	511	139	12	
%	1.34	0.93	2.78	2.45	1.27	1.50	
Unknown/missing	24,080	15814	3036	2125	885	63	
%	10.06	9.47	8.76	10.18	8.05	7.89	<0.01
Stage							
Localized	191,882	150,306	32,705	18,445	9,634	695	
%	80.08	80.6	81.5	75.8	76.1	74.7	
Regional	29,868	23,180	4,075	3,025	1,748	108	
%	12.46	12.4	10.2	12.4	13.8	11.6	
Distant	9,554	7,232	2,093	1,264	633	72	
	3.99	3.9	5.2	5.2	5.0	7.7	
Unknown/unstaged	8,309	5,878	1,257	1,614	639	56	<0.01
%	3.47	3.2	3.1	6.6	5.1	6.0	
Gleason Score							
GS 6	56,158	43,560	8,376	5,410	2,470	175	
%	23.44	23.3	20.9	22.2	19.5	18.8	
GS 7	52,076	40,308	8,853	4,663	2,654	181	
%	21.73	21.6	22.0	19.2	21.0	19.4	
GS 8	9,600	7,426	1,811	1,068	723	42	
%	4.01	4.0	4.5	4.4	5.7	4.5	
GS 9	7,516	6,001	1,296	812	576	34	
%	3.14	3.2	3.2	3.3	4.6	3.7	
GS 10	913	742	166	115	63	2	
%	0.38	0.4	0.4	0.5	0.5	0.2	
Not done	1126	726	175	132	70	10	
%	0.47	0.43	0.5	0.63	0.64	1.25	
Unknown	113,350	88559	19628	12280	6168	497	
%	47.30	47.5	48.9	50.5	48.8	53.4	<0.01
Surgery							
Yes	100,558	79,443	13,661	9,731	4,885	312	
%	41.97	42.6	34.0	40.0	38.6	33.5	
No	136,794	105,350	26,184	14,455	7,571	614	
%	57.09	56.5	65.3	59.4	59.8	66.0	
Unknown	2,267	1,803	285	162	198	5	<0.01
%	0.95	1.0	0.7	0.7	1.6	0.5	
Less than high school education							
Q1 (best)	49,326	44,997	4,996	1,504	1,624	254	
%	20.59	24.1	12.5	6.2	12.8	27.3	

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Q2	48,547	41,508	5,971	2,512	3,108	124	
%	20.26	22.3	14.9	10.3	24.6	13.3	
Q3	48,134	35,487	8,789	4,901	3,488	186	
%	20.09	19.0	21.9	20.2	27.6	20.0	
Q4	47,575	33,965	12,293	5,105	1,329	166	
%	19.85	18.2	30.6	21.0	10.5	17.8	
Q5 (worst)	45,944	30,571	8,073	10,304	3,102	201	<0.01
%	19.17	16.4	20.1	42.4	24.5	21.6	
At last bachelor-level education							
Q1 (worst)	52,040	42,573	9,116	5,788	930	328	
%	21.72	22.8	22.7	23.8	7.4	35.2	
Q2	43,561	35,285	9,285	2,442	1,304	263	
%	18.18	18.9	23.1	10.0	10.3	28.3	
Q3	47,261	33,043	6,476	8,076	4,733	147	
%	19.72	17.7	16.1	33.20	37.4	15.8	
Q4	49,600	39,272	7,179	4,968	2,157	104	
%	20.70	21.1	17.9	20.4	17.0	11.2	
Q5 (best)	47,064	36,355	8,066	3,052	3,527	89	<0.01
%	19.64	19.5	20.1	12.6	27.9	9.6	
Unemployment							
Q1 (best)	49,084	43,406	4,232	2,431	3,288	165	
%	20.48	23.3	10.6	10.0	26.00	17.7	
Q2	50,958	42,207	5,681	4,258	3,045	251	
%	21.27	22.6	14.2	17.5	24.1	27.0	
Q3	46,533	38,053	7,147	3,631	2,086	122	
%	19.42	20.4	17.8	14.9	16.5	13.1	
Q4	47,391	31,011	11,153	8,303	2,968	184	
%	19.78	16.6	27.8	34.1	23.5	19.8	
Q5 (worst)	45,560	31,851	11,909	5,703	1,264	209	
%	19.01	17.1	29.7	23.4	10.0	22.5	<0.01
Foreign-born/language-isolated							
Q1 (lowest)	48,022	37666	9148	607	144	98	
%	20.04	22.55	26.40	2.91	1.31	12.28	
Q2	49,454	38637	7329	1672	708	291	
%	20.64	23.13	21.15	8.02	6.45	36.47	
Q3	48,130	33885	7332	2856	3099	204	
%	20.09	20.29	21.16	13.70	28.21	25.56	
Q4	47,392	31473	5066	7166	2126	134	
%	19.78	18.84	14.62	34.37	19.36	16.79	
Q5 (highest)	46,528	25357	5777	8547	4907	71	
	19.42	15.18	16.67	41.00	44.67	8.90	
Poverty/income							
Q1 (best)	48,402	3147	79	4110	3508	36551	
%	20.20	15.09	9.90	37.42	10.12	21.88	
Q2	48,853	2924	206	2514	5554	36349	
%	20.39	14.03	25.81	22.89	16.03	21.76	
Q3	46,533	3693	153	1461	4541	35697	
%	19.42	17.71	19.17	13.30	13.10	21.37	
Q4	48,737	7980	98	2500	9124	27589	
%	20.34	38.28	12.28	22.76	26.33	16.52	
Q5 (worst)	47,001	3104	262	399	11925	30832	<0.01
%	19.61	14.80	32.84	3.63	34.42	18.47	

HISP=Hispanics, NHAPI= Non-Hispanic Asian Pacific Islanders, NHAI/AN=Non-Hispanic American Indian/Alaska Natives, NHB=Non-Hispanic Blacks, NHW=Non-Hispanic Whites.

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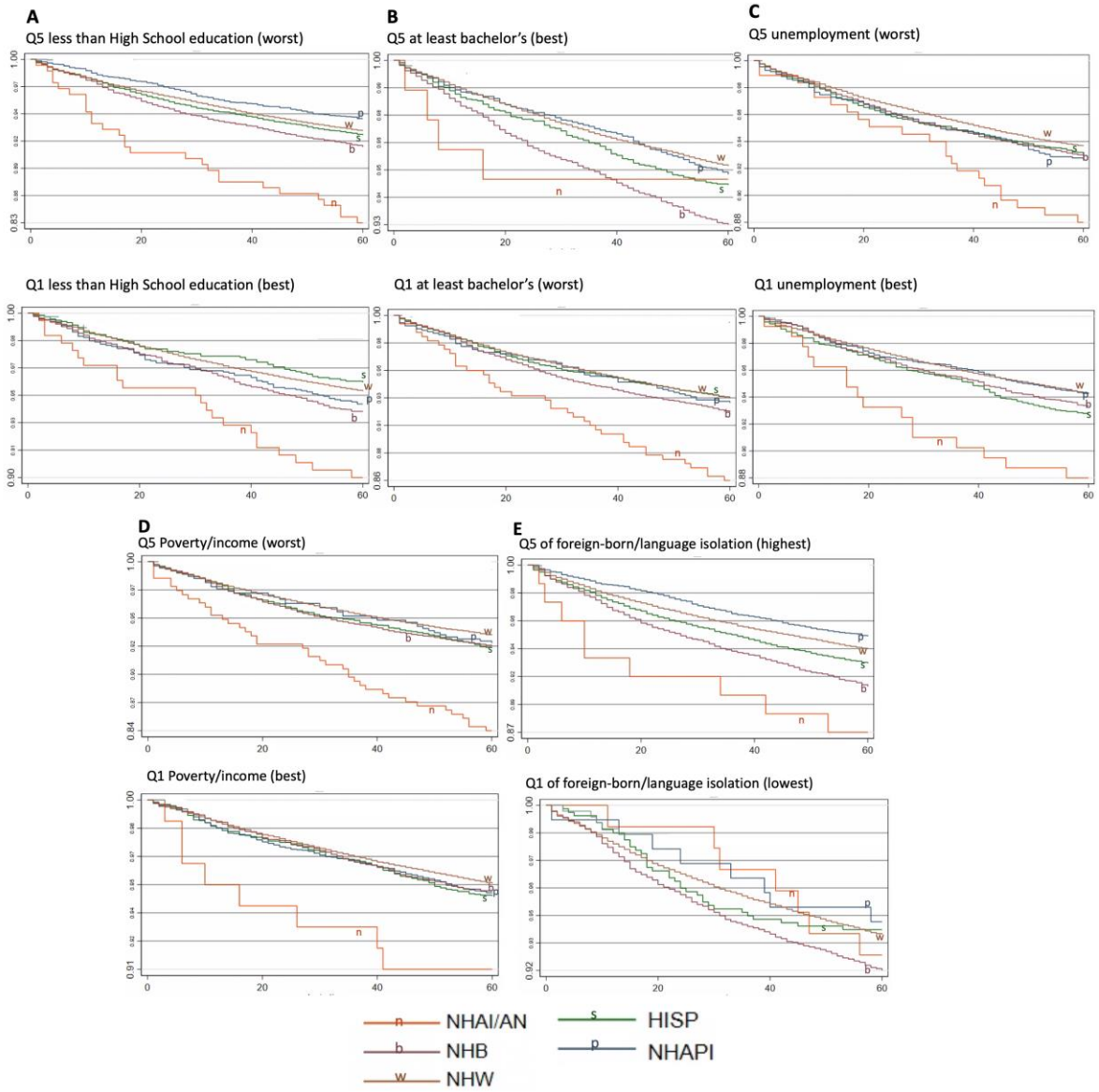
Figure 1: Cumulative survival of PCa from diagnosis stratified by racial/ethnic groups for each county-level SES, Q5 Vs. Q1 for: Less than high-school level education, (A), At least Bachelor-level (B), Unemployment (C), Poverty/Income (D) and, Foreign-born/language isolated (E). Follow-up in all figures is 60 months = 5 years, x axis is time in weeks



Abbreviations

HISP=Hispanics, NHAPI= Non-Hispanic Asian Pacific Islanders, NHAI/AN=Non-Hispanic American Indian/Alaska Natives, NHB=Non-Hispanic Blacks, NHW=Non-Hispanic Whites. Scale of the graph was adjusted according to the survival values to allow easier visual comparison.

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Table 2: SES model adjusted for age at diagnosis and marital status, stratified by race/ethnicity

	Coef.	p-value	[95% Conf	Interval]	Sig
Overall					
Less than High School education	1.056	0.343	0.943	1.183	
At least Bachelors-level education	0.771	**<0.01**	0.699	0.851	***
Unemployment	0.889	**0.001**	0.829	0.953	***
Poverty/income	1.227	**<0.01**	1.118	1.348	***
Foreign born/Language isolated	1.233	**<0.01**	1.122	1.354	***
NHW					
Less than High School education	1.130	0.083	0.980	1.290	
At least Bachelors-level education	0.680	**0.000**	0.610	0.770	***
Unemployment	0.850	**0.000**	0.790	0.930	***
Poverty/income	1.140	**0.029**	1.010	1.270	**
Foreign born/ Language isolated	1.260	**0.000**	1.120	1.410	***
NHB					
Less than High School education	1.120	0.429	0.840	1.500	
At least Bachelors-level education	1.090	0.489	0.860	1.380	
Unemployment	0.990	0.930	0.840	1.180	
Poverty/income	1.380	**0.011**	1.080	1.780	**
Foreign born/ Language isolated	1.210	0.118	0.950	1.530	
HISP					
HS	2.030	**0.019**	1.120	3.670	**
Bachelors	1.510	0.060	0.980	2.330	
Unemployment	0.970	0.837	0.730	1.300	
Poverty/income	1.230	0.283	0.850	1.780	
Foreign born/ Language isolated	1.010	0.963	0.660	1.550	
NHAPI					
Less than High School education	1.340	0.599	0.450	3.980	
At least Bachelors-level education	1.320	0.532	0.560	3.120	
Unemployment	1.450	0.272	0.750	2.810	
Poverty/income	1.220	0.606	0.570	2.590	
Foreign born/Language isolated	1.010	0.982	0.410	2.510	
NHAI/AN					
Less than High School education	0.300	0.193	0.050	1.820	
At least Bachelors-level education	0.170	**0.046**	0.030	0.970	**
Unemployment	0.920	0.838	0.440	1.960	
Poverty/income	0.860	0.832	0.210	3.500	
Foreign born/ Language isolated	6.460	**0.033**	1.170	35.760	**

*Model is adjusted for age and marital status
** p-value <0.05
*** p-value <0.01

HISP=Hispanics, NHAPI= Non-Hispanic Asian Pacific Islanders, NHAI/AN=Non-Hispanic American Indian/Alaska Natives, NHB=Non-Hispanic Blacks, NHW=Non-Hispanic Whites.

Table 3 illustrates our multilevel analysis, which accounts for county-level clustering effects. Model 1 represents group-level cox proportional HR with NHW as the reference, adjusted for marital status and age. Model 2: adjusted for model 1 covariates and county-level SES covariates. Model 3: adjusted for model 2 covariates and individual-level covariates. HISP men were at higher risk of PCa mortality in models 1 and 2, however, upon adjusting for county-and individual-level covariates, HISP exhibited lower mortality than NHW (0.89, 95%CI 0.85-0.95, P<0.01). NHAI/AN had twice the mortality of NHW in both models 1 and 2. This disparity was attenuated in model 3 when accounting for individual-level factors such as insurance and cancer severity and treatment (surgery). NHB (Vs. NHW) were 1.6 times more likely to die from PCa in models 1 and 2, however, such disparity decreased to 1.2 (95%CI 1.07-1.6, p=0.01) in model 3. The protective effect in NHAPIs was further increased in model 3 (0.68, 95%CI 0.62-0.74).

Table 3: Multilevel survival modeling accounting for county-level grouping

	Model 1				Model 2				Model 3			
	HR	P-value	Upper 95%CI	Lower 95%CI	HR	p-value	Upper 95%CI	Lower 95%CI	HR	p-value	Upper 95%CI	Lower 95%CI
Race/ethnicity												
HISP	1.21	**0.034**	1.14	1.28	1.11	**0.01**	1.04	1.17	0.90	**<0.01**	0.85	0.95
NHAI/AN	2.04	0.211	1.67	2.50	1.85	**<0.01**	1.50	2.28	1.32	**<0.01**	1.07	1.62
NHAPI	0.84	**0.035**	0.78	0.91	0.80	**<0.01**	0.73	0.87	0.68	**<0.01**	0.62	0.74
NHB	1.61	**0.036**	1.54	1.68	1.63	**<0.01**	1.16	1.71	1.20	**<0.01**	1.14	1.26
County-level SES (Q5 Vs Q1)												
Less than high school					0.99	0.921	0.85	1.15	1.04	0.57	0.91	1.18
At least bachelor-level					0.74	**<0.01**	0.64	0.86	0.88	**0.029**	0.78	0.99
Unemployment					0.88	**0.01**	0.80	0.97	0.93	0.072	0.86	1.01
Poverty/Income					1.31	**<0.01**	1.13	1.51	1.21	**0.01**	1.08	1.36
Foreign-born/Language isolated					1.22	**<0.01**	1.05	1.43	1.03	0.610	0.92	1.16
Individual-level characteristics												
Stage at diagnosis (ref=local)												
Regional									2.74	**<0.01**	2.56	2.93
Distant									24.77	**<0.01**	23.76	25.83
Gleason Score (ref=GS6)												
GS7									1.96	**<0.01**	9.23	11.88
GS8									4.27	**<0.01**	1.77	2.17
GS9									6.88	**<0.01**	3.85	4.75
GS10									10.47	**<0.01**	6.24	7.60
Not Done/unknown									6.88	**<0.01**	6.11	7.76
Surgery (ref=no)												
Yes									0.54	**<0.01**	0.51	0.57
Year of diagnosis												
2011 Vs 2007									0.91	**<0.01**	0.90	0.93
Insurance status at diagnosis (Vs no insurance)												
Any Medicaid									0.69	**<0.01**	0.62	0.77
Insured									0.44	**<0.01**	0.40	0.49

- Model 1: adjusted for marital status and age.
- Model 2: adjusted for model 1 covariates and SES.
- Model 3: adjusted for model 2 covariates and individual-level characteristics.

HISP=Hispanics, NHAPI= Non-Hispanic Asian Pacific Islanders, NHAI/AN=Non-Hispanic American Indian/Alaska Natives, NHB=Non-Hispanic Blacks, NHW=Non-Hispanic Whites.

All county-level SES (except "<HS") were significantly associated with 5-year PCa survival in all races/ethnic groups in model 2. Upon adjusting for disease severity and surgery in model 3, the significant association only remained for ≥BL and poverty/income. Having a distant stage and advanced GS was significantly associated with the worst survival while undergoing a PCa-directed surgery and having insurance were the most protective covariates. As "diagnosis year" advanced, risk of PCa-specific mortality decreased (0.72, 95%CI 0.68-0.77).

Table 4 examines the relationship between SES and disease severity ("Stage" and "GS") and HC access/utilization ("GS not done" and "surgery"). The risk of having a distant stage significantly increased by around 30% and 20% with worst "<HS" (RR 1.27 95%CI 1.19-1.36) and poverty/income (RR 1.2 95%CI 1.13-1.23). The risk of having a worse GS (GS=8-10) significantly decreased with highest proportion of "≥BL" (RR 0.9 95%CI 0.86-0.95). Highest rates of foreign-born/language-isolated rates significantly protected against the highest GS (RR 0.91 95%CI 0.86-0.95).

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Table 4: Relative Risk of late-stage diagnosis (Distant stage and advanced GS) and Surgery in relation to SES

	RR of Distant Stage (Vs. localized)				GS 8-10 (Vs. GS 6-7)				GS Not Done (GS Done)				Surgery (vs. No Surgery)			
SES	RR	95%CI		P	RR	95%CI		P	RR	95%CI		P	RR	95%CI		P
Less than High School education (Vs. Q1)																
Q2	0.994	0.928	1.065	0.866	0.984	0.937	1.033	0.514	1.228	0.992	1.522	0.060	1.094	1.068	1.128	<0.001
Q3	1.185	1.109	1.266	<0.001	0.896	0.855	0.940	<0.001	2.064	1.703	2.502	<0.001	0.865	0.842	0.889	<0.001
Q4	1.099	1.028	1.176	0.006	0.958	0.914	1.004	0.076	1.425	1.159	1.752	0.001	1.111	1.081	1.142	<0.001
Q5 (worst)	1.271	1.188	1.360	<0.001	0.947	0.903	0.993	0.025	1.382	1.120	1.705	0.003	1.171	1.138	1.204	<0.001
At least Bachelor's-level education(Vs. Q1)																
Q2	0.886	0.029	0.830	0.946	0.960	0.915	1.009	0.105	0.785	0.647	0.954	0.015	0.982	0.955	1.010	0.205
Q3	1.012	0.033	0.950	1.078	0.973	0.928	1.020	0.259	0.798	0.663	0.960	0.017	1.383	1.346	1.422	<0.001
Q4	0.940	0.030	0.883	1.000	0.976	0.932	1.022	0.305	1.170	0.988	1.386	0.069	1.076	1.048	1.105	<0.001
Q5 (best)	0.861	0.028	0.807	0.918	0.902	0.860	0.945	<0.001	0.888	0.740	1.065	0.201	0.824	0.802	0.847	<0.001
Unemployment (Vs. Q1)																
Q2	0.989	0.749	0.927	1.056	0.909	0.867	0.954	<0.001	1.274	1.048	1.547	0.015	0.958	0.932	0.984	0.002
Q3	1.051	0.142	0.984	1.122	0.912	0.867	0.958	<0.001	1.463	1.208	1.772	<0.001	0.820	0.798	0.843	<0.001
Q4	1.055	0.115	0.987	1.127	0.901	0.857	0.946	<0.001	1.038	0.846	1.274	0.720	0.960	0.934	0.987	0.004
Q5 (worst)	1.044	0.201	0.977	1.115	0.915	0.872	0.962	<0.001	1.399	1.152	1.699	0.001	0.825	0.802	0.848	<0.001
Poverty/income (Vs. Q1)																
Q2	1.118	1.045	1.196	0.001	1.054	1.006	1.104	0.027	1.176	0.974	1.419	0.092	1.062	1.033	1.091	<0.001
Q3	1.121	1.048	1.200	0.001	1.027	0.979	1.078	0.269	1.437	1.198	1.724	<0.001	1.155	1.123	1.187	<0.001
Q4	1.224	1.146	1.309	0.001	0.992	0.945	1.041	0.741	0.923	0.759	1.123	0.423	1.202	1.169	1.236	<0.001
Q5 (worst)	1.205	1.127	1.287	0.001	1.010	0.961	1.061	0.706	0.922	0.755	1.127	0.430	0.991	0.964	1.019	0.537
Foreign/ Language isolated (Vs. Q1)																
Q2	0.855	0.799	0.914	<0.001	0.956	0.910	1.005	0.080	0.842	0.677	1.047	0.122	1.090	1.060	1.120	<0.001
Q3	0.975	0.913	1.041	0.451	0.920	0.875	0.968	0.001	1.299	1.068	1.580	0.009	0.838	0.815	0.862	<0.001
Q4	0.976	0.917	1.046	0.538	0.935	0.890	0.982	0.008	1.570	1.297	1.900	<0.001	1.034	1.005	1.063	0.020
Q5 (highest)	1.070	1.000	1.142	0.048	0.908	0.864	0.955	<0.001	1.495	1.232	1.814	<0.001	1.084	1.053	1.115	<0.001

*Adjusting for insurance status did not change the results

HISP=Hispanics, NHAPI= Non-Hispanic Asian Pacific Islanders, NHAI/AN=Non-Hispanic American Indian/Alaska Natives, NHB=Non-Hispanic Blacks, NHW=Non-Hispanic Whites.

The risk of "GS not done" significantly decreased with better education (both "<HS" and "≥BL"). Residing in a county with the highest unemployment rate significantly increased the risk of having a "GS not done" by 40% (1.40 95%CI 1.52-1.69). The highest percentage of foreign-born/language-isolated increased the risk of not doing a GS by half (RR 1.50 95%CI 1.23-184). The risk of having surgery varied according to education level; where it increased with lower HS and decreased with higher "≥BL" education rates. Finally, residing in a county with the worst unemployment and poverty rates significantly decreased the risk of surgery while foreign-born/language-isolation significantly increased it (Table 4).

Discussion

The goal of the present study was to describe the degree to which county-level SES explained PCa survival in U.S. residents across a wide group of races and ethnicities. To our knowledge, this is the first study to examine the association between county-level SES and PCa-specific survival across five different racial/ethnic categories. In addition to other studies in the literature, our study included five racial/ethnic categories and examined how survival changes specifically in response to county-level SES profile in each racial/ethnic category included. Additionally, this study examined the

potential pathway leading to worse PCa survival by demonstrating the influence of late-stage diagnosis and poorer healthcare utilization. Such analysis highlights how PCa survival behaves in the function of race/ethnicity under different SES profiles and informs public health policies on potential county-level interventions to decrease the disparity gaps in PCa.

Overall, lower area-level SES was associated with reduced PCa survival, which was in agreement with the literature examining a similar relationship, however, on a neighborhood level (20-22). For example, a systematic review of 169 international publications established that men living in disadvantaged and/or rural areas face a greater PCa burden (33). They also had consistently lower prostate-specific antigen (PSA) testing and PCa incidence, poorer survival, more advanced disease, and higher mortality (33). DeRouen et.al. also established a relationship between poorer neighborhood SES and poor PCa survival. Similarly, to our study, they found that although NHB had worse survival than NHW, the relationship was attenuated when accounting for neighborhood-level SES (21). Our positive associations between county-level education and PCa stage/grade were also similarly found on the neighborhood level (22). When adjusting for county-level SES (model 2, Table 3), PCa survival disparities between groups only slightly attenuated, suggesting other factors may have contributed to survival disparities between groups. Those could have been related to rural/urban status, commuting and traffic patterns, residential mobility, and/or food environment (21,22).

Racially stratified findings illustrated within-group disparities in 5-year prostate-specific survival suggesting varying county-level SES associations across race/ethnicity. NHW were more sensitive to changes in county-level SES while remaining minorities were not. In fact, education (≥BL), unemployment, and foreign-born/language-isolation did not impact PCa survival in NHB, suggesting that interventions on those factors might not turn out as beneficial on minorities as when applied to NHW. Such findings could also support the diminishing returns hypothesis where minorities might not achieve the same health gains at higher SES as do their nonminority counterparts (NHW) at the same SES levels (34-36). For example, Kish et al identified that mortality risk for NHB increased with higher neighborhood SES compared with NHW in the same SES quintile (20). Further, higher education was also found to be protective for advanced PCa among men residing in low SES, but not for men residing in high SES California neighborhoods (21) which suggests a varying effect on PCa survival even under similar area-level characteristics.

When adjusting for individual-level factors representing disease severity and HC access/utilization, disparities were diminished further until they even reversed in Hispanics (model 3, Table 3). Additionally, the magnitude of change was the highest in NAHI/AN and NHB as risk of PCa-specific mortality decreased from almost 2 to 1.3 and 1.6 to 1.2 respectively from model 2 to 3 (Table 3). This could suggest that some minority groups might be more sensitive to area-level SES while others more to individual-level SES. Hence, no single method of intervention would be closing all disparity gaps, as those should be carefully crafted and tailored based on each group's needs. One could even argue that in some minority groups individual-level factors could be driving poorer PCa survival in a way that better county-level SES cannot overcome. As an example, Du Xl et al, found individual-level SES to be accounting for disparities in PCa survival (37).

Analysis demonstrating the association between poorer SES and severity (stage and grade) as well as HC utilization ("GS not done" and "surgery") may provide partial early support for the view that these factors could play an intermediary role. Since worse stage/grade and poorer HC utilization (surgery/GS not done) were associated with county-level SES and increased the risk of PCa mortality, the inclusion of those factors appeared to strengthen the relationship between SES and PCa survival. More importantly, being insured was significantly protective against PCa mortality, however, adjusting for insurance, did not change the results between SES and HC utilization and disease severity in Table 4. This could show that insurance might not necessarily affect PCa survival by performing biopsy/surgery or by having a better stage at diagnosis, contrary to some findings. Also, men residing in counties with the worst HS education rates were more likely to undergo PCa-directed surgery. Both of these findings could demonstrate how better education in PCa patients leads to more in-depth discussions with healthcare providers about additional less invasive options such as

watchful waiting (38). Other studies suggested that while guaranteeing universal adequate health insurance is important, additional measures are needed to address persisting survival disparities (39-40). Thus, interventions aiming at enhancing insurance status alone, will likely not improve healthcare utilization for men residing in SES-deprived counties.

On the other hand, protective effect of "year" could be explained by advances in PCa management or could further backup recommendations against routine screening (41) since no increase in mortality was observed. It was surprising that unemployment showed a protective effect in NHW, which became non-significant in subsequent models adjusted for individual-level covariates. Since employment is tied with health insurance in the US, we would normally expect lower HC access (and hence lower survival) caused by higher unemployment rates. However, PCa patients have a mean age between 63-64, where most of those patients would be retired. Thus, detrimental effects of unemployment might not be as pronounced in this sample of elderly patients. Still, this variable was included to test whether unemployment on a county level would show any effect on individual-level survival.

Last, NHAPI men often experienced better cancer survival than the remaining minority groups while NHAI/AN men showed to suffer from worse PCa survival disparities (Figure 1 and Table 3). Also, the six-fold mortality increase in NHAI/AN men residing in counties with the largest proportions of foreign-born/language may suggest that this group faces the strongest health burden when situated within heavily-dense foreign-born population which could be creating even more isolation for this minority group. Such findings illustrate a minority group that is relatively rarely discussed in the literature which warrants further attention and thus more public health, and clinical efforts should be focused on them. Alternatively, men residing in counties with the highest foreign-born/language-isolated proportions tend to be protected against a more aggressive GS which could be explained by the social support phenomenon where minorities exhibit better outcomes when socially surrounded and supported (42,43).

Strengths and limitations

This study has several strengths including its population-based design that covers almost one-third of the American population and its linkage to SES characteristics. To our knowledge, this study is the first study to relate county-level SES with PCa survival. Additionally, this study described how PCa survival varies across five racial/ethnic groups under different county-level SES profiles and the role of HC utilization and disease severity.

Although some suggest that census tract-level analyses might detect more accurate relationships between area-level factors and individual health outcomes (23, 25), our adoption of the county-level might have been beneficial for delving deeper into disparities pathways. Meliker et al observed disappearing survival disparities in PCa between NHBs and NHWs when moving their spatial analysis from larger scales (Federal/State Legislative Districts) to neighborhoods (44) suggesting that smaller scales often mimic "SES adjustment" as smaller entities tend to be more homogenous. This likely demonstrates the advantage of adopting relatively larger geographical boundaries to capture racial/ethnic variation of survival and the crucial importance of area-level SES in PCa survival analyses. Further, as a multilevel regression was performed within our analysis, clustering of observations has been accounted for, where findings demonstrate robustness independent of geographical cluster effects.

Despite its strengths, this study has also some limitations. Although missing data was kept at minimum in almost all covariates included (1% to 11.4%), the only exception was the large proportion of "unknown" values in GS. Despite this large percentage, "unknown" proportions remained the same across all racial/ethnic groups suggesting that missing results are not related to one group or another. Nonetheless, the absence of time-varying covariates could have also affected the estimate as, for instance, some patients could have migrated to another geographical location just after diagnosis. Furthermore, the absence of chemotherapy/radiation therapy data would have been informative in the context of individual-level variables' impact on PCa survival. Still, access to those would have been also linked to insurance status, a variable that was accounted for. Lastly, the smaller sample of

NHAI/AN as compared to remaining groups could have impacted group comparability. Due to the small NHAI/AN population, a longer period for incident cases could be adopted in the future to better represent variability within that group.

Conclusions

Overall, this study provides insight into the impact of county-level SES on 5-year PCa survival as risk of PCa-specific mortality for five ethnic/racial groups in the US. Using findings of this study could potentially inform the focus of public health efforts. As such, this study provides insight into the rising need to tailor interventions based on race/ethnicity and SES so that the benefit can be provided equitably. Future studies could benefit from performing mediation analysis for factors influencing the relationship between SES and PCa outcomes in order to more deeply understand pathways leading to PCa disparities.

Funding: Not applicable.

Disclosures: Dr. Christiane El Khoury: no disclosures exist. Dr. Sean Clouston: no disclosures exist.

Data Availability Statement: The SEER database is publicly available, with free access. In case additional information is needed regarding data analysis, we are happy to share STATA files.

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