ORIGINAL ARTICLE

PLACE OF RESIDENCE AND SOCIAL MARGINALIZATION AS PROGNOSTIC FACTORS FOR PROSTATE CANCER SURVIVAL IN VERACRUZ, MEXICO

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ABSTRACT

Objectives: To determine if the place of residence and the level of social marginalization are associated with prostate cancer survival. Materials and methods: All patients diagnosed with prostate cancer (PC) in the period from 2013 to 2017 in a tertiary healthcare hospital in Veracruz, Mexico were included. Patients resided in rural and urban areas. Variables were collected according to clinical-epidemiological and histopathological characteristics. The Kaplan Meier method and the Log Rank test were used to measure survival. Prognostic factors were determined by calculating the adjusted hazard ratio (HRa) in a multivariate analysis using the Cox proportional risk method. Results: A total of 186 PC cases were analyzed. Overall, after 5 years, 48.3% of the patients survived. Men living in urban areas had a higher probability of survival than those living in rural areas (HRa 1.67, 95% CI 1.16-2.41). Similarly, people living in areas classified as low- marginalization zones had a higher probability of survival than those living in areas with a high level of social marginalization (HRa 2.32, 95% CI 1.47-3.66). **Conclusions:** To reside in a rural place was identified as a negative prognostic factor for the survival of patients with PC regardless of other sociodemographic and clinical variables; patients living in high-marginalization places had an unfavorable survival prognosis

Keywords: Prostatic Neoplasms; Survival Analysis; Rural Population;Socioeconomic Factors; Mexico (Source: MeSH NLM).

INTRODUCCIÓN

Internationally, prostate cancer (PC) is the second most prevalent cancer in men (33.1 cases per 100,000 people) after lung cancer and is the fifth leading cause of death from malignant neoplasms in the male population [1]. In Mexico, the number of deaths from malignant prostate tumors has increased in the last two decades [2]. PC is caused by several factors, such as age, diet, ethnicity, skin color, exposure to tobacco or alcohol, and even some infections [3,4].

In Mexico, the PC panorama is characterized by a growing incidence, a greater frequency of advanced stages, increased management costs and an increase in mortality [5,6]. It has been documented that PC survival is related to the clinical stage at the moment of diagnosis and the type of treatment used [5]. In this sense, there is evidence of 5-year survival in different types of cancer, such as lung, liver, colorectal, breast, pancreatic, esophageal, bladder, and prostate [7]. In addition, some studies have shown longer survival of patients with PC who lived in urban areas and with a higher socioeconomic level, compared to those who came from rural areas and with a low socioeconomic level [8,9].

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The association of such characteristics with survival has been barely studied in Mexican population, and the information about Veracruz population is almost nonexistent. The aim of this study was to determine if the place of residence and the marginalization level are associated to prostate cancer survival in a hospital cohort.

KEY MESSAGES

Motivation for the study: No recent studies have been found to evaluate prostate cancer survival in Mexico, so the factors associated are unknown.

Main findings: Low prostate cancer survival rates were obtained, in addition, it was observed that living in rural areas and a high marginalization level are poor prognosis factors for survival.

Implications: More studies are necessary to identify the sociodemographic factors and implications associated with this public health problem, it is also required to strengthen health-related actions aimed at generating interventions that increase survival to prostate cancer.

MATERIALS AND METHODS

Study design and participants

A retrospective open cohort study was carried out in which all patients diagnosed with PC in the period between 2013-2017 were included from the State Cancer Center (CECan), which is a third-level hospital located in Xalapa, Veracruz, Mexico. The follow-up period was 60 months from the registration of the first PC case identified during the recruitment period. The applied inclusion criteria were patients diagnosed with PC within the study period and who received care at that hospital; the exclusion criteria were patients with a history of other types of cancer or who received previous antineoplastic treatment; and the elimination criteria were patients diagnosed with PC without contact information for follow-up.

Variables

The main response variable was the survival time of patients with PC defined as the time, in months, between the date of PC diagnosis and the patient's death. Death was verified by the death certificate provided by the hospital's social work coordination and through the records of the Epidemiological and Statistical System of Deaths of the national health system.

The sociodemographic covariables were schooling (with or without studies), marginalization level of the place of residence (very high, high, medium, low or very low) according to the Consejo Nacional de Población, which takes into account eight socioeconomic indicators (percentage of illiterate population 15 years or older, without complete primary education, homes without tap water services, electricity, refrigerator, or toilet, with dirt floor and average number of inhabitants per room) [10]; the area of habitual residence in rural areas, if it was a place with less than 2,500 inhabitants, or in urban areas, if they habitually lived in places with more than 2,500 inhabitants, according to the classification of the Instituto Nacional de Estadística y Geografía (INEGI) [11]; and occupation (agricultural and related activities vs. other activities).

The clinical-histopathological variables were comorbidity (presence or absence of diabetes mellitus or arterial hypertension), prostate specific antigen (PSA); <10 ng/dL; 10 to 20 ng/dL; >20 ng/dL, histologic differentiation (well-differentiated, moderately-differentiated, and poorly-differentiated), Gleason Scale score (≤6, 7, or ≥8), metastasis (present or absent), clinical stage (I, II, III, or IV, according to the criteria of the American Joint Committee on Cancer, AJCC). Depending on tumor extension, there are two stages: early stage (localized tumor), and advanced stage (tumor extends through the prostatic capsule or invades adjacent structures), and two types of treatment: neoadjuvant hormone therapy (before prostatectomy) and adjuvant (after prostatectomy) [12].

Specific survival was calculated considering the period between the date of the histopathological diagnosis and the date of death or the end of the follow-up, whichever occurred first.

Data collection instrument

A data collection card was designed and validated by three specialized doctors, both from the hospital where the study was carried out and from the National Institute of Oncology and Radiobiology of Havana, Cuba. The information source was the patients' clinical file. The date and cause of death were obtained from the death certificate or from the records of the Epidemiological and Statistical System of Deceases (SEED).

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Statistical analysis

The Fisher's chi-square or exact test on categorical variables was used to compare the demographic and clinical characteristics between rural and urban strata, and the Student's t-test was used to compare age groups. Survival analysis was calculated with the Kaplan-Meier method; patients who were still alive at the end of follow-up or whose current status was unknown were considered as censored data. Survival probabilities for each possible prognostic factor were compared by means of the Log Rank test, initially specifying a crude model for each variable to be analyzed. Subsequently, proportional risk models were adjusted by Cox regression. Adjustment variables were included in the model, according to the background review on the most important prognostic variables related to prostate cancer survival [9,13,14]. During the multivariate analysis, the covariables were dichotomized, including the total sample: age at the time of diagnosis, place of habitual residence, social marginalization level, clinical stage, histological differentiation grade and type of treatment. Raw and adjusted hazard ratios (HR) and their respective 95% confidence intervals were calculated. The analyses were carried out through the statistical software SPSS 23.0 (IBM Inc., NY, USA).

Ethical aspects

The research protocol was submitted and approved by the Technical Council of the Public Health Institute of the Universidad Veracruzana and by the Committee of Research Ethics of the National Center of Cancerology "Dr. Miguel Dorantes Mesa", with registration number C.E.I.-2018-044.

RESULTS

General characteristics

We identified 198 patients with PC, 12 of whom did not meet the inclusion criteria and were excluded. Finally, the files of 186 patients were analyzed. The lethality was 28.5% (n = 53). Follow-up was not completed in 8.6% (n = 16) of the cases. The mean age at diagnosis was 69.2 ± 8.96 years, and the mean age at death was 76.3.

Differences between urban and rural groups

Regarding the place of residence, 62.4% of the patients lived in rural areas. Differences were statistically significant when comparing the proportions of the rural and urban groups by schooling, marginalization level, occupation, and presence of metastasis (Table 1).

When comparing the clinical pathological characteristics, stage III was the most frequent in both areas. In contrast, stage IV was found 3.25 times less in patients with habitual urban residence compared to those in rural areas. In the same way, bone metastases were 3 times more frequent in those of urban zone than from rural zone (Table 1).

Table 1. Sociodemographic and clinical-pathological characteristics of the cohort according to the place of residence.

Variable	Place of residence		p value
	Urban	Rural	
	n = 70 (%)	n = 116 (%)	
Age			
Mean (SD)	68 (±8.4)	70 (±9,2)	0.100 [b]
Schooling			
Without studies	19 (27.1)	52 (44,8)	0.016 [a]
With studies	51 (72.9)	64 (55,2)	
Socio-economic marginalization level			
Very low - low	25 (35.7)	18 (20,5)	
Medium	31 (44.3)	53 (60,2)	0.002 [a]
High - very high	14 (20.0)	17 (19,3)	
Occupation			
Agricultural and related	47 (67.1)	104 (89.7)	<0.00 [a]
Other	23 (32.9)	12 (10.3)	
Comorbidity (diabetes or hypertension)			
Yes	16 (22.9)	34 (29.3)	0.336 [a]
No	54 (77.1)	82 (70.7)	
Gleason Scale Score			
≤6	29 (41.4)	60 (51.7)	
7	19 (27.1)	16 (13.8)	0.073 [a]
≥8	22 (31.4)	40 (34.5)	
Clinical stage			
I	3 (4.3)	7 (6.0)	
II	19 (27.1)	30 (25.9)	0.057 [c]
III	36 (51.4)	40 (34.5)	
IV	12 (17.1)	39 (33.6)	
Histologic grade			
Well differentiated	7 (10.0)	8 (6.9)	
Moderately differentiated	27 (38.6)	44 (32.9)	0.726 [a]
Poorly differentiated	36 (51.4)	64 (55.2)	
Presence of metastasis			
Positive	12 (17.1)	39 (33.6)	0.023 [a]
Negative	58 (82.9)	77 (66.4)	
Location of metastasis			
Bone	8 (75.0)	28 (71.8)	0.054 [a]
Other	4 (25.0)	11 (28.2)	

[a] Chi-square test, [b] Student's t-test, [c] Fisher exact test

Survival analysis

Overall survival for subjects in the 2013 cohort was 70.6% (95% CI: 62.1 to 77.5) at 1 year; 70.6% (95% CI: 62.1 to 77.5) at 3 years, and 47.7% (95% CI: 31.7 to 63.0) at 5 years.

Statistically significant differences were observed in survival by level of marginalization, where patients with high/very high marginalization level presented lower survival than those coming from areas of very low or low marginalization. Likewise, the survival of patients coming from areas of medium marginalization was even greater than those of low/exceptionally low marginalization (Table 2).

Depending on the clinical stage, lower survival was observed in stage IV subjects compared to stages I and II. According to the degree of histological differentiation (Figure 1), the cumulative proportion that survived at the end of the 60-month interval was 73% in the well-differentiated group, 70% in the moderately differentiated group, and 30% in the poorly differentiated group (p = 0.035).

Table 2. Cohort subjects' survival at 1, 3 and 5 years of follow-up.

Variable	Patients alive	Survival [a]			p value [b]
		1 years	3 years	5 years	
		n (%)	n (%)	n (%)	
Age (years)					
≤60	35	27 (76)	16 (60)	4 (25)	0.051
>60	151	131 (87)	96 (73)	54 (56)	
Place of residence					
Rural	116	93 (80)	56 (60)	54 (28)	<0.001
Urban	70	64 (91)	49 (77)	35 (71)	
Schooling					
Without studies	71	58 (81)	35 (61)	16 (45)	0.118
With studies	115	100 (87)	76 (76)	37 (49)	
Occupation					
Agricultural and related	151	124 (82)	88 (71)	45 (51)	0.289
Other	35	33 (94)	22 (68)	7 (32)	
Socio-economic marginalization level					
Very low - low	43	38 (89)	26 (69)	18 (69)	
Medium	84	80 (95)	73 (91)	59 (81)	<0.001
High - very high	59	41 (69)	20 (48)	4 (18)	
Clinical stage					
I	10	10 (100)	10 (100)	9 (86)	<0.001
II	49	46 (94)	39 (85)	30 (77)	
III	76	67 (88)	47 (71)	20 (43)	
IV	51	34 (66)	15 (46)	4 (29)	
Gleason Scale					
Low risk	15	15 (100)	14 (92)	10 (76)	0.152
Moderate risk	75	63 (84)	47 (74)	31 (67)	
High risk	96	79 (82)	50 (64)	7 (13)	
Metastasis					
Present	51	34 (66)	15 (46)	4 (29)	<0.001
Absent	135	123 (91)	97 (79)	52 (54)	
Metastasis location					
Bone	40	27 (68)	12 (44)	3 (28)	0.955
Other	11	6 (58)	4 (58)	1 (29)	
Type of treatment					
Adjuvant	93	83 (89)	64 (77)	28 (44)	0.031
Neoadjuvant	93	73 (79)	46 (63)	21 (46)	

[a] Kaplan-Meier method, [b] Log Rank test

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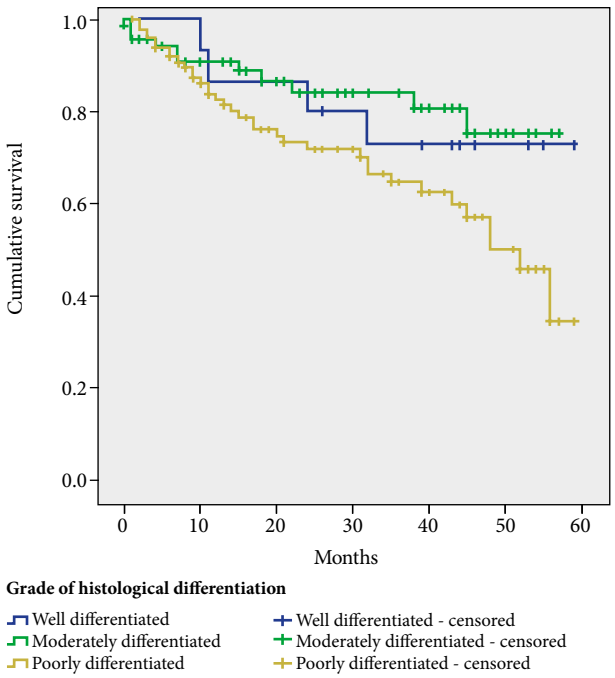

Figure 1. Prostate cancer cumulative survival curve according to histological differentiation grade.

Lower survival was observed among subjects with serum prostate-specific antigen (PSA) levels greater than 20 ng/dL prior to treatment, compared to those with levels of 10-20 and <10 ng/dL (Figure 2); the 5-year survival probabilities were 31%, 83%, and 84%, respectively (p = 0.003).

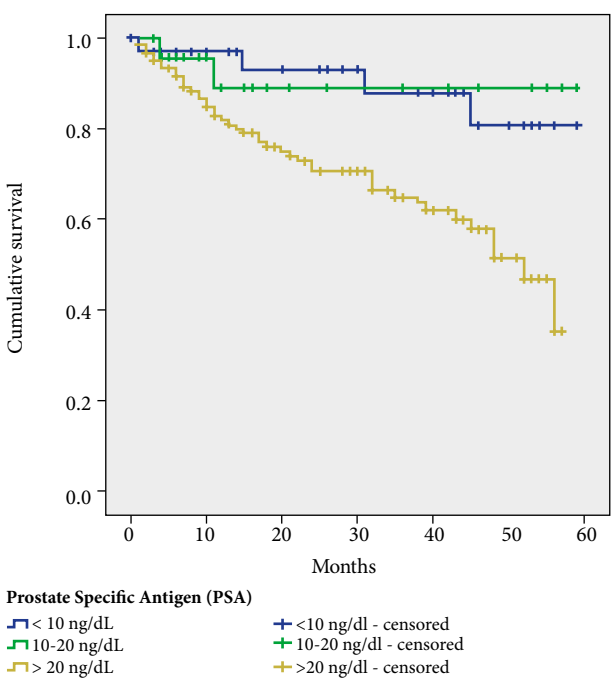

Figure 2. Prostate cancer cumulative survival curve according to prostate antigen levels.

A multivariate analysis of possible survival predictors in prostate cancer patients is presented in Table 3. In the adjusted model, the characteristics of habitual residence, such as urban type (HRa: 1.67, 95% CI: 1.16 to 2.41) and a low marginalization level (HRa: 2.32, 95% CI: 1.47 to 3.66) showed a greater probability of survival than those coming from a rural type locality or with a high marginalization level. No significant differences were found in the probability of survival with respect to clinical stage, age at diagnosis, histological differentiation, and type of treatment.

DISCUSSION

The results found show a mean age at the time of diagnosis of 69 years similar to those reported in other previous studies conducted in Mexico [15], Brazil [16], and Colombia [17], in which the mean age and standard deviation were 66.7 (±8.8), 70.5 (±8.7) and 69 (±8.6) years, respectively. Fatality was at 28%, similar to the 24% reported by Silveira *et al.* in 2013 in a Brazilian hospital [18].

Nearly 68% of the cases were diagnosed during advanced stages (stage III and IV), a figure higher than the one reported in another study carried out in the Mexican population [15], in which only 46.2% of cases were reported in stages III and IV. Differences could be explained by the fact that each of the hospitals where the research took place out serves a population with different socio-demographic characteristics, mainly regarding their usual place of residence, occupation and schooling.

It is worth mentioning that in some countries, such as the United States and New Zealand, people living in rural or less advantaged areas have a lower probability of survival, less access to health services, higher mortality, lower rates of PSA testing, and a higher risk of advanced PC [8]. This is why, it is necessary to state that geographic location provides information related to population composition and access to certain resources and services, among other aspects; while the degree of advantage reflects the probable influence of the community and social structure on the risk of developing the disease, regardless of individual socioeconomic level [8]. Regarding survival according to place of habitual residence, some studies have shown a lower survival rate in people of rural residence with prostate cancer [7,14,19].

It is essential to highlight that, among the findings of this study, a specific survival to PC at 5 years was observed near 48%, a figure equivalent to almost half of what was reported by other Latin American countries included in the largest study carried out internationally (CONCORD 3) [20]. In this

Table 3. Predictors of survival in prostate cancer patients

Variable	No ajusted model	p value	Multivariate model	p value
	HR (95% CI)		HR (95% CI)	
Usual place of residence				
Rural	1.00	0.013	1.00	0.006
Urban	1.56 (1.10-2.22)		1.67 (1.16-2.41)	
Socioeconomic marginalization level				
High	1.00	<0.001	1.00	<0.001
Low	2.29 (1.46-3.60)		2.32 (1.47-3.66)	
Clinical stage				
Advanced	1.00	0.359	1.00	0.443
Early	1.18 (0.83-1.68)		1.15 (0.80-1.66)	
Age at diagnosis (years)				
>60	1.00	0.306	1.00	0.942
≤60	1.28 (0.80-2.05)		1.02 (0.63-1.66)	
Histological differentiation grade				
Barely differentiated	1.00	0.427	1.00	0.168
Clearly differentiated	1.15 (0.82-1.62)		1.29 (0.90-1.84)	
Treatment type				
Adjuvant	1.00	0.909	1.00	0.956
Neoadjuvant	0.98 (0.70-1.39)		1.01 (0.71-1.43)	

HR: Hazard ratio; 95% CI: 95% confidence interval.

study, figures above 80% are reported in some cases such as Brazil, Costa Rica, Argentina, Ecuador and Uruguay; while in the Colombian population according to Arias and De Vries [21] this probability is around 70% (95% CI: 65.3 to 76.1).

It should be clarified that, the mentioned studies analyzed population-based data, unlike this one in which hospital-based data were collected. Also, the patients included in this study had the same insurance regime (Seguro Popular), came in greater proportion from rural areas (62.4%) and required to move from their place of residence to the CECan, located in the capital of the State of Veracruz. Then, these patients faced mainly geographical and economical barriers, as well as long waiting times for diagnosis and treatment, which may have limited or delayed their access to medical care [22,23] and, consequently, their probability of survival decreased.

In contrast, when the probability of survival at 1, 3, and 5 years was compared (84.6%, 70.6%, 47.7%, respectively) to other hospital-based studies, this study's findings were similar to those found in another research conducted in Iran, in which figures of 87%, 73%, and 54%, respectively, were reported [24].

In relation to 5-year survival in stage I patients (86%), our findings were similar to those reported by Migowsky *et al.* [16] in a study conducted in Brazil with a sample of 258 patients, in which the survival was of 87.8% (95% CI: 83.3 to 92.5).

Results obtained from this study provide arguments to claim that in a high proportion of advanced stage patients (68.3%), survival decreased as the stage increased. Reported survival was of 29% in stage IV, almost half of what was found in other studies (between 40% and 60%) [17,18,24]. These data show that the case identification or the search for attention are late, decreasing the probability of survival, which suggests the need to increase efforts for detection in early stages [18].

As for survival by place of habitual residence, some studies have shown a lower survival rate in persons of rural residence with PC [7,8,19]. Li et al. [7] found that 5-year survival to different types of cancer, including lung, liver, colorectal, breast, pancreatic, esophageal, bladder, and prostate was higher in patients from urban areas compared to those from rural areas (44.05 vs. 41.47%, $p < 0.001$); while, with respect to PC specifically, it was also higher in urban areas with a statistically significant difference (59.2% vs. 53.3%, $p = 0.02$).

There is evidence of variations in survival rates between different geographic areas, demonstrated mainly in studies comparing rural and urban cancer patients. Such variations may be related to exposure to risk factors, as well as to diffe-

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rential conditions for access to health services and therefore to early detection tests and timely treatment of cancer [7,25,26].

In this regard, a meta-analysis conducted in 2015 by Baade *et al* [8], which included works from different high-income countries, showed that the survival risk ratio was almost 1.7 times higher in patients living in urban areas compared to those in rural areas.

Differences found in the marginalization level were also found in this study. In the adjusted model, patients with a low marginalization level showed greater survival compared to those with a high marginalization level. Similar results in previous studies demonstrated an association between a high socioeconomic level and a greater probability of survival as can be seen in the analysis of Bravo et al [27], where men diagnosed with PC who lived in more economically advantageous areas had better survival than those living in less advantageous areas, independently of the clinical stage at the time of diagnosis (HR: 3.5, 95% CI 2.37 to 5.40).

The analyzed studies confirm the association between the degree of deprivation or socioeconomic disadvantage and survival to PC in other countries. In all of them, it has been observed that survival is lower in men with greater socioeconomic deprivation compared to those with higher or more advantageous socioeconomic levels [14,21,28-30].

In the case of Mexico, in the states with higher marginalization, there are fewer technological and human resources for the care of health problems. However, economic, geographic, educational and cultural factors, could be related to the reduction in made diagnosis and timely treatment, which may influence PC survival in people living in places with such characteristics and which support the results found in this study [23].

The main limitations for this study include its retrospective nature and the restrictions inherent to the information quality from the clinical files. From these files, a small proportion of the patients' clinical stage at the time of diagnosis was identified; thus, by determining the stage from the other clinical data, errors in classification could have been generated. In addition, the level of marginalization of each case was established by the catalogs prepared at a certain time by geographical area, so this data may not reflect the individual reality of the patients.

In conclusion, the place of rural residence was identified as a poor prognostic factor for the survival of patients with PC, regardless of other sociodemographic and clinical variables. Likewise, patients living in places with higher marginalization levels had an unfavorable survival prognosis. Differences in survival due to sociodemographic characteristics show the need to reduce the inequality gaps, especially for people living in rural areas and with higher marginalization level.

Authors' contribution: GJRR participated in the study design; data collection, analysis and interpretation; and manuscript writing. ABMT participated in the conception, design, data analysis and interpretation, and manuscript writing and revision. MRJ, OCCS, and SRCL participated in the data analysis and interpretation, and manuscript revision. All authors assume responsibility for each of the sections, and declare that they have reviewed the content and approved the final version of the article.

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