

Disparities on prostate cancer survival in Mexico: a retrospective cohort study

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Abstract

Objective. To estimate prostate cancer (PC) survival in Mexico and explore survival disparities according to the marginalization level of residence place. **Materials and methods.** A nationwide administrative claims database (4 110 men) whose PC treatment was financed by *Seguro Popular* between 2012-2016, was cross-linked to the National Mortality Registry up to December 2019. Patients were classified according to their oncological risk at diagnosis and the marginalization level of the residence municipality. Cox proportional hazards regression was used to estimate multi-variable survival functions. **Results.** Five-years PC survival (69%; 95%CI: 68,71%) ranged from 72% to 54% at very low and very high marginalization, respectively (p for trend<0.001). The lowest PC survival was observed in men with high-risk PC (47%; 95%CI: 33,66%) residents in very high marginalization municipalities. **Conclusions.** Overall, PC survival was lower than that reported in other Latin American countries. The distribution of oncologic risk and survival differences across marginalization levels suggests limited early detection and cancer health disparities.

Keywords: health status disparities; prostate cancer; survival; Mexico

Resumen

Objetivo. Estimar la supervivencia por cáncer de próstata (CP) en México y explorar diferencias por nivel de marginación del lugar de residencia. **Material y métodos.** Se vinculó la información de 4 110 hombres cuyo tratamiento para CP fue financiado por el Seguro Popular (2012-2016) con el Registro Nacional de Mortalidad disponible a 2019. La supervivencia se estimó mediante el Kaplan-Meier y riesgos proporcionales de Cox. **Resultados.** La supervivencia a cinco años por CP (69%; IC95%: 68,71%) osciló entre 72% en muy baja marginación y 54% en muy alta (p de tendencia<0.001). La supervivencia más baja (47 %; IC95%: 33,66%) se observó en hombres residentes en municipios de muy alta marginación y con CP de alto riesgo. **Conclusiones.** En general, la supervivencia por CP es una de las más bajas reportadas en la región. Las diferencias por marginación municipal sugieren una detección temprana limitada y disparidad en el acceso a la atención.

Palabras clave: cáncer de próstata; disparidades en el estado de salud; México; supervivencia

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The stage at diagnosis together with other social determinants (marital status, and socioeconomic neighborhood status) explains around 45% of disparities in prostate cancer (PC) survival.¹ The worst survival rates observed among men with advanced stage at diagnosis, unmarried, and residents of low socioeconomic neighborhoods could be a consequence of poor access to health care, differences in insurance health,^{2,3} and cultural barriers^{3,4} which reduce the opportunities for timely diagnosis and treatment.

In Mexico, PC is the leading cause of cancer (42.2 per 100 000 inhabitants) and cancer-related deaths (10.6 per 100 000 inhabitants) in men.⁵ As expected for a country where PC screening is opportunistic and there is no uniform compliance of timely detection program, a large proportion (~70%) of cases are classified as poorly differentiated at diagnosis,⁶ and the PC mortality risk has increased nationwide at a constant rate (2% annually) over the past 13 years. The highest annual increase was observed among states with very high (4.4%) and high (7.7%) marginalization rates.⁷ Nevertheless, as far as we know there is no information regarding population-based PC survival. The scarce information is limited to small hospital-based studies in relation to clinical determinants.⁸⁻¹⁰ Only one study with 186 PC patients identified in a tertiary healthcare hospital in Veracruz,¹¹ evaluated social PC survival determinants. The PC survival at five years was 48.3%, and the lowest survival was observed among those men residents in rural and high-marginated areas.

Because a high proportion of the Mexican population (57%) did not have some type of social security, from 2003 to 2019 was implemented the *Seguro Popular*. Under specific guidelines, this public insurance program financed the diagnosis and treatment of some diseases such as cancer; the goal was to reduce disparities in health and ensure the universal right to health.¹² PC treatment was incorporated in 2012, and the nationwide coverage increased over time. In the absence of a national cancer registry, information from this public insurance program permits to get an overview of PC survival for the most vulnerable group of the population.

We aimed to estimate national PC-specific survival according to the marginalization level of residence place in patients incorporated into the *Seguro Popular* from 2012 to 2016.

Materials and methods

Data

Through a collaborative agreement with the *Comisión Nacional de Protección Social en Salud*, we conducted a

retrospective cohort study with males aged between 40 and 95 years diagnosed and treated for PC under *Seguro Popular's* Fund for Catastrophic Expenses Protection (*Fondo de Protección para Gastos Catastróficos*), between January 2012 and December 2016.

The records contained the following information: patient's national identification number (*clave única de registro de población*, CURP), date of birth, age, state and municipality of residence, date of diagnosis, and place of medical attention. At diagnosis, each patient was classified according to oncological risk based on the concentration of prostate-specific antigen (PSA), Gleason score, and clinical stage of the tumor.¹³ Low-risk (PSA < 10 ng/mL, Gleason < 6, tumor clinical stage T1 or T2a), intermediate-risk (PSA = 10-20 ng/mL, Gleason = 7, or T2b), and high-risk (PSA > 20 ng/mL, Gleason = 8-10, or ≥T2c). The treatment received was in accordance with the risk-based treatment guidelines defined by an expert group of urologist oncologists and validated by national health authorities.¹⁴

We classified the municipality of residence into five categories: very low, low, intermediate, high, and very high, according to the marginalization index developed by the National Population Council.¹⁵ This widely used index considers four dimensions: education, housing, monetary income, and affectation due to spatial location.

The deaths of patients with PC between 2012 and 2019 were identified by linking the information from the *Seguro Popular* administrative records with that of the epidemiological and statistical death record subsystem (*Subsistema Epidemiológico y Estadístico de Defunciones*, SEED). Records were linked using a modified version of the Fellegi-Sunter model and an algorithm designed at the *Instituto Nacional de Salud Pública* (INSP).¹⁶ Briefly, the CURP, first and last names, and date of birth were used for cross-linking. Using these names as the initial blocking variables, we identified pairs with high similarity. We compared them using CURP and date of birth to identify those with a high similarity score (≥0.9) and classified pairs as matching, potentially matching, or non-matching records. Matching pairs were retained, potentially matching pairs were manually reviewed, and nonmatching pairs were discarded.

Three members of our group examined the cause of death for all identified cases (LTS, JGHP, and FRC). PC deaths were defined as those for which the underlying or associated cause of death corresponded to code C-61X of the International Classification of Diseases (ICD) 10th edition. Underlying causes of death codes unrelated to PC were classified as "other causes".

In an exploratory analysis, we observed that patients residing and treated in the state of Guerrero had an unusual pattern in the distribution of oncological risk

and PC-lethality. This may be the result of coding errors, selective migration, or underreporting of deaths. Thus, from 5 559 identified cases, we excluded 38 due to lack of information regarding the oncological risk or diagnosis date, 982 due to lack of information about the municipality of residence, and 429 patients residing and treated in Guerrero. The final sample included 4 110 men. This project was approved by the INSP Institutional Review Board (Project ID: 1695).

Statistical analysis

Sociodemographic and clinical characteristics were described using measures of central tendency or proportion depending on the variable. Differences according to the municipality marginalization level of residence were evaluated using chi-squared or Kruskal-Wallis tests.

To estimate overall survival probabilities, the follow-up period consisted in the time elapsed from diagnosis until death for any cause or the end of the follow-up period (December 31, 2019), whichever occurred first. For PC-specific survival analysis, subjects were followed from date of diagnosis until death due to PC or censoring for death due to another cause than PC, or end of follow-up. For a simple visual display of crude overall and PC survival, we used the Kaplan-Meier method. To estimate adjusted PC survival according to the marginalization level of place of residence, oncological risk, and medical attention at the residence state, we used independent multivariate Cox proportional

hazards models based on Directed Acyclic Graphs. The marginalization level and medical attention in the residence-state models were adjusted by age. The oncological risk model was adjusted by age at diagnosis and marginalization levels. To explore a possible difference in the PC survival rate at each marginalization stratum according to oncological PC risk, we conducted a stratified analysis adjusted for age at diagnosis and estimated PC-specific survival curves.

The effects of atypical values and linearity were assessed from the graphs using the Martingale and score residuals. Because censoring under Cox's proportional hazards regression does not eliminate the possibility of competing events, we verified our results using a competing risk model described by Fine and Gray.¹⁷ Data was analyzed using the statistical software R, version 1.3.1093, using the *survival*, *surminer*, *pec* and *cmprsk* packages.

Results

Table I shows the characteristics of the 4 110 males affiliated to *Seguro Popular* who were diagnosed and received treatment for PC between January 2012 and December 2016, according to marginalization level of residence place. The median follow-up was 4.0 years (IQR: 3.8-5.2), ranging from 3.7 to 4.1 years in residents of very high and very low marginalization municipalities, respectively. The proportion of patients treated in a state different from their usual residence increased

Table I
SOCIODEMOGRAPHIC CHARACTERISTICS OF MEN WITH PROSTATE CANCER DIAGNOSIS AND TREATED UNDER *SEGURO POPULAR* AFFILIATION ACCORDING TO MARGINALIZATION LEVEL OF THE RESIDENCE PLACE. MEXICO 2012-2019

Municipality marginalization level	PC cases (n)	Median follow-up (years)	Out-of-state treatment (%)	Characteristics at diagnosis						
				Median (IQR)	Age (years)			Oncological risk group* (%)		
					< 65	65 -75	> 75	Low	Intermediate	High
All	4 110	4.0		69.0 (63-75)	33.1	42.2	24.6	8.4	21.8	69.8
Very low	2 473	4.1 [‡]	22.0	68.0 (62-75) [‡]	37.4 [‡]	41.0	21.6	8.7	23.7	67.6
Low	739	4.0	34.2	71.0 (65-76)	26.9	46.5	26.5	9.2	21.0	69.8
Medium	495	3.8	33.1	71.0 (65-77)	28.1	39.8	32.1	7.1	18.0	74.9
High	358	3.9	44.7	71.0 (65-77)	25.1	43.6	31.3	7.3	15.6	77.1
Very high	45	3.7	62.2 [§]	72.0 (67-76)	22.2	51.1	26.7	2.2	20.0	77.8 [§]

* Low-risk (PSA < 10 ng/mL, Gleason < 6, tumor clinical stage T1 [cT1] or cT2a), intermediate-risk (PSA = 10-20 ng/mL, Gleason = 7, or cT2b), and high risk (PSA > 20 ng/mL, Gleason=8-10, or ≥cT2c).

[‡] Kruskal-Wallis Test p<0.01

[§] Chi-squared test p<0.05

PC: prostate cancer

according to marginalization level (62.2% in very high vs. 22.0% in very low).

Median age at diagnosis was 69 years, and 33.1% of cases were under 65 years old, and 69.8% were classified as high-risk PC. According to marginalization level, residents in very low marginalization municipalities had the lowest median age at diagnosis and the highest proportion of cases <65 years old (37.4%). Regarding the distribution by oncological risk, the proportion of high-risk PC increased as marginalization levels increased (table I) without changes throughout the study period.

We identified 1 556 deaths, from which 1 196 had PC as underlying cause of death. The five-years crude overall and PC-specific survival were 62% (95%CI: 60,63%) and 69% (95% CI: 68,71%), respectively. During the first two years, both were similar; however, after that, until the end of the follow-up, the overall survival was lower (figure 1A and 1B). After adjustment for age at diagnosis, overall and specific survival rates at five-years decrease as marginalization level increases. The lowest age-adjusted overall (46%; 95%CI: 33,62%) and PC-specific survival rate (54%; 95%CI: 41,71%) were observed among residents of very high marginalization municipalities (table II). PC-specific survival at each marginalization level varied according to oncological risk. The greatest survival was for the low-risk group (~91%) at all marginalization levels. Among patients with

high-risk PC, survival was 61% (95%CI: 59,63%), which decreased to 47% (95%CI: 33,66%) among residents in municipalities with very high marginalization (table II, figure 2).

Table III shows the factors associated with the risk of dying from PC. Regardless of age at diagnosis, the probability of dying from PC increased consistently as municipality marginalization level increased (p for trend<0.001). The highest risk was observed among males resident in the very high marginalization municipalities (HR= 1.81; 95%CI: 1.15; 2.86). As expected, the death risk increased with the increase of oncological risk at diagnosis (p for trend < 0.001). Compared to subjects with low-risk PC, the probability of dying from PC for high-risk patients was 6 times higher. Moreover, receiving the medical attention at the residence state (HR=0.83; 95%CI: 0.73; 0.94; $p = 0.002$) was associated with a significant reduction in the probability of dying from PC. Our results did not change using competing risk models.

Discussion

In this Mexican cohort of patients with no social security, significant disparities in overall and PC-specific survival emerged according to the marginalization level of the residence's municipality. The lowest 5-year

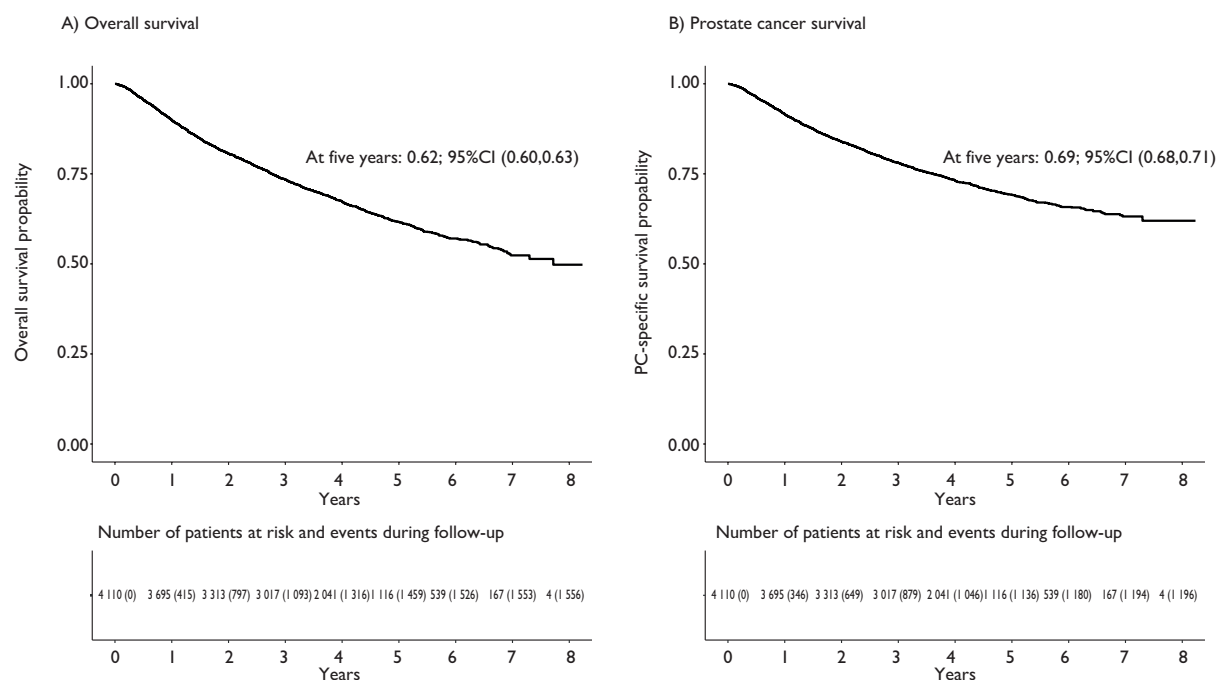


FIGURE 1. FIVE-YEAR CRUDE OVERALL AND PROSTATE CANCER-SPECIFIC SURVIVAL AMONG MEN AFFILIATED TO SEGURO POPULAR, MEXICO 2012-2019

Table II
ADJUSTED OVERALL AND PC-SPECIFIC SURVIVAL (95%CI) AT 5-YEAR FOLLOW-UP
ACCORDING TO MUNICIPALITY MARGINALIZATION OF THE RESIDENCE PLACE AND ONCOLOGICAL RISK.
SEGURO POPULAR, MEXICO 2012-2019

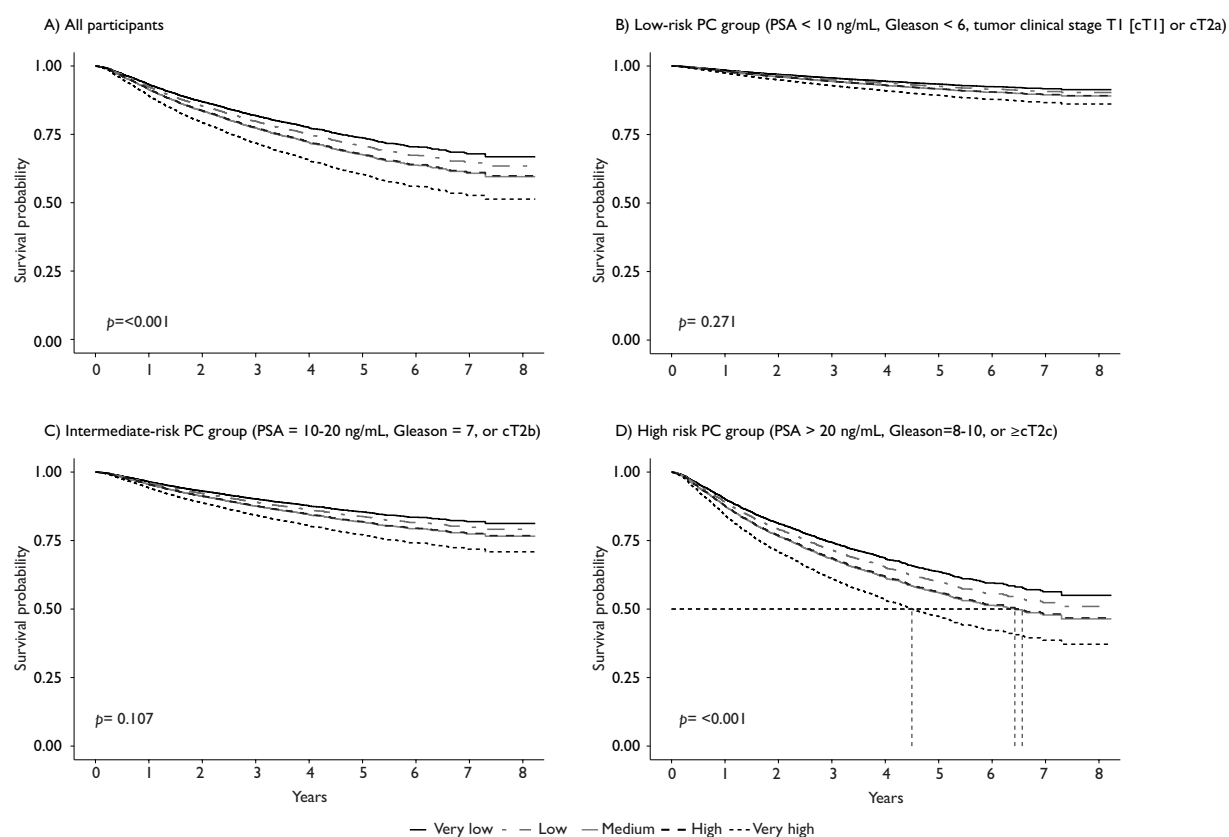
Marginalization at municipality level	Overall [‡] 5 years	PC-specific survival [‡] 5 years	Oncological risk group*		
			Low [§]	Intermediate [§]	High [§]
			5 years	5 years	5 years
All	0.62 (0.60-0.63)	0.69 (0.68-0.71)	0.93 (0.90-0.96)	0.84 (0.82-0.87)	0.61 (0.59-0.63)
Very low	0.64 (0.62-0.66)	0.72 (0.70-0.74)	0.93 (0.91-0.96)	0.86 (0.83-0.88)	0.64 (0.62-0.66)
Low	0.61 (0.58-0.65)	0.68 (0.64-0.71)	0.92 (0.89-0.96)	0.84 (0.81-0.87)	0.60 (0.56-0.64)
Medium	0.57 (0.53-0.62)	0.63 (0.59-0.67)	0.91 (0.88-0.95)	0.81 (0.78-0.85)	0.56 (0.51-0.61)
High	0.57 (0.52-0.62)	0.63 (0.58-0.69)	0.91 (0.88-0.95)	0.82 (0.78-0.86)	0.56 (0.50-0.62)
Very high	0.46 (0.33-0.62)	0.54 (0.41-0.71)	0.89 (0.83-0.95)	0.77 (0.68-0.87)	0.47 (0.33-0.66)

* Low-risk (PSA < 10 ng/mL, Gleason < 6, tumor clinical stage T1 [cT1] or cT2a), intermediate-risk (PSA = 10-20 ng/mL, Gleason = 7, or cT2b), and high risk (PSA > 20 ng/mL, Gleason=8-10, or ≥cT2c).

[‡] Adjusted by age at diagnosis.

[§] Models stratified by marginalization were adjusted by age at diagnosis.

PC: prostate cancer



P values correspond to Cox's proportional hazards model.

FIGURE 2. ADJUSTED PC-SPECIFIC SURVIVAL AND 95%CI ACCORDING TO MUNICIPAL MARGINALIZATION LEVEL OF THE RESIDENCE PLACE AND ONCOLOGICAL RISK GROUP AMONG MEN AFFILIATED TO SEGURO POPULAR. MEXICO 2012-2019

Table III
CHARACTERISTICS ASSOCIATED WITH PC DEATH IN MEN DIAGNOSED AND TREATED UNDER SEGURO POPULAR AFFILIATION. MEXICO 2012-2019

Characteristics	PC deaths n=1 196	Person years of follow-up	Cox's proportional hazards models			Competing risk models		
			HR	95%CI	p value	HR	95%CI	p value
Marginalization level*								
Very low	654	9 865	Ref			Ref		
Low	225	2 838	1.16	0.90 – 1.35	0.061	1.17	1.01 – 1.37	0.039
Medium	174	1 826	1.38	1.16 - 1.63	<0.001	1.40	1.18 - 1.66	<0.001
High	124	1 330	1.36	1.12 - 1.64	0.002	1.37	1.13 - 1.67	0.002
Very high	19	153	1.81	1.15 – 2.86	0.011	1.73	1.11 – 2.70	0.015
p for trend					<0.001			<0.001
Oncological risk at diagnosis ^{‡§}								
Low	24	1 660	Ref			Ref		
Intermediate	135	4 021	2.27	1.47 – 3.51	<0.001	2.29	1.49– 3.53	<0.001
High	1 037	10 331	6.52	4.35 – 9.57	<0.001	6.37	4.26 – 9.53	<0.001
p for trend					<0.001			<0.001
Medical attention at residence state [¶]								
No	375	4 444	Ref			Ref		
Yes	821	11 568	0.83	0.73 – 0.94	0.002	0.82	0.73 – 0.93	0.002

* Adjusted by age at diagnosis

‡ Adjusted by age at diagnosis and municipality marginalization

§ Low-risk (PSA < 10 ng/mL, Gleason < 6, tumor clinical stage T1 [cT1] or cT2a), intermediate-risk (PSA = 10-20 ng/mL, Gleason = 7, or cT2b), and high risk (PSA > 20 ng/mL, Gleason=8-10, or ≥cT2c).

¶ PC: prostate cancer

PC survival rate was observed among patients residing in places with a very high level of marginalization and this disparity seems to be more marked among those with high-risk PC.

Coherent with previous studies that suggest a high proportion of PC cases at diagnosis are poorly differentiated, in this study 70% of cases were classified as high-risk at diagnosis. However, in locations with very high marginalization almost four out of five patients were high-risk PC patients (77.8%). PC survival was lower than that reported for developed countries.¹⁸ Countries of the region, and those with cultural characteristics similar to Mexico, have limited information about PC survival. The 5-year specific survival observed in this study is only comparable with that reported in Colombia (69.8 to 78.6%).¹⁸⁻²⁰ Those reported for Ecuador (92.4%; 95%CI: 88.7,96.0%), Brazil (96.1%; 95%CI: 93.9,98.4%), Chile (88.7%; 95%CI: 83.5,93.8%) and Argentina (86.6%; 95%CI: 80.6,92.6%), are higher than what we found.¹⁸ In three of these countries, the percentage of gross domestic product spent on healthcare is almost twice than that of Mexico.²¹ Brazil has had great success in reaching

universal health coverage with its unified health system. They have also implemented early detection policies and improved their diagnosis and treatment.²²

Differences in PC survival based on socioeconomic conditions and place of residence have been previously reported in other settings. Socially disadvantaged neighborhoods were associated with high PC-specific mortality, mainly in African American and Hispanic patients in the United States.^{1,23} In Latin America, two studies have reported a low survival in patients with a low socioeconomic status. In Manizales, Colombia, the lowest 5-year survival (~60%), was observed for patients with the lowest socioeconomic status, according to their place of residence, and patients that were not covered by any type of insurance at diagnosis.²⁰ In Veracruz, Mexico¹¹ the lowest 5-year specific survival was for men from rural areas with a high level of marginalization.

Low PC survival rates can be attributed to delays in cancer diagnosis and treatment, which is determined by sociodemographic patient characteristics, as well as, doctor, and system characteristics. In addition to the fact that men make less use of health services²⁴ Mexican PC

screening program is opportunistic and is possible that cultural barriers may reduce the acceptance of early detection strategies. A low education level reduces the possibility to identify or awareness of symptoms that would require medical attention.³ In highly marginalized areas, medical care is provided by general practitioners and there is evidence of the proportion of primary care physicians that perform procedures related to early detection of PC is low, and many of them use concepts that do not adhere to the scientific evidence.²⁵ In addition, PC diagnosis and treatment require specialized centers, most of which are geographically far from the most marginalized areas.

PC treatment was included in *Seguro Popular* in 2012 and not all states were included from the beginning. PC patients and authorized healthcare providers increased throughout the period; however, only 23 of 32 states had healthcare facilities authorized. Most of them had only one healthcare provider except for Mexico City (four), Jalisco, State of Mexico, and Veracruz (two each). Migration in search of medical care often means a better chance of an accurate diagnosis and treatment; nonetheless, it often leads to accessibility and economic issues that negatively affect the treatment and thus survival. To the best of our knowledge, no study has evaluated the effect of migration on PC survival. However, the lower risk of dying from PC observed for us, among those males who received treatment in the same state of their usual residence is consistent with the high risk of death observed among children with leukemia affiliated to *Seguro Popular* who migrated to a state different from their place of residence to receive treatment.²⁶

Differences in survival rates according to the oncological risk observed in this study are consistent with the results reported by Montaña JJ and colleagues in Spain.²⁷ For the low-risk group, survival was similar for all the marginalization levels. This reflects the natural course of the disease and suggests a better outcome if the health system would focus on improving early detection strategies. Survival rates could increase by improving primary prevention via education of the population, and by improving early detection through better funding and training of the medical staff.

Data for this analysis included patients from most of the states in Mexico. Adequate quality control of records²⁸ allowed us to depict the overall situation of PC in Mexico. However, our results can only be extrapolated to the population with no access to social security and less favorable socioeconomic conditions, which represent a little more than 50% of the population.¹²

When analyzing hospital discharge data from 2008, the *Secretaría de Salud*, which runs the *Seguro Popular* program, was second (37.6%) on hospital discharges related

to malignant tumor; the *Instituto Mexicano del Seguro Social* (IMSS) was at the top of the list (48.9%).²⁹ PC survival in patients with social security or that receive treatment in private institutions may be higher than that observed in this study. Based on a preliminary analysis with PC patients from Mexico City with and without social security we estimate that the proportion of poorly differentiated cancer at diagnosis (Gleason ≥ 8) was higher in patients without social security (41.1 vs. 26.4%; $p < 0.01$).

As a retrospective cohort study, there are limitations related to the quality and availability of information because, initially, it was not collected for research purposes and active follow-up had an administrative approach. Misclassification of cause of death is possible but unlikely. A previous study conducted in Mexico City and Morelos state observed that PC had a concordance of 100% between the cause of death obtained from the medical death certificate and a rigorously defined gold standard diagnosis based on medical records in hospitals.³⁰ However, we do not reject the possibility that the magnitude of these limitations could have been greater in the very high marginalization stratum. We excluded patients residing and treated in Guerrero because they had the lowest lethality and proportion of high-risk PC cases at diagnosis. As far as we know, no prevention strategy existed that would explain such results, but there are two possible explanations. First, the criteria for the classification of this type of cancer were not correctly adopted or the limited availability of resources for the treatment of PC patients during the first half of the period could generate a selective migration of high-risk patients. Second, we do not reject a possible underreporting of deaths, because this state heads the list of states with a death record of less than 90%.³¹

Municipal marginalization could be a close indicator of the individual socioeconomic status;³² however, it fails to depict the sociodemographic variability. This limitation, along with the relatively small sample, may explain why large differences in PC survival were not observed between marginalization levels. Additionally, data available for treatment type did not allow us to estimate the associated survival, and there was no information regarding comorbidities and biological prognostic factors such as the fraction of Ki67 positive cells, an immunohistochemistry marker of cellular proliferation. However, there is evidence these biological markers correlate with Gleason score³³ and this one was used to build the oncological risk.

Conclusions

This initial approach demonstrates a low survival PC rate mainly among men with high-risk PC residents in

very high marginalization municipalities and with no access to social security. Differences in the oncologic risk distribution and survival differences across marginalization levels suggest limited early detection and cancer health disparities. Follow-up on cancer survival enables the design of prevention strategies, particularly secondary and tertiary prevention, and to development of cost-effective cancer-control strategies. A nationwide cancer record and knowing the disease burden are crucial for this. A new scheme that substitutes *Seguro Popular* is being implemented³⁴ and our results could guide the implementation of this new program and could be considered a baseline to evaluate its execution.

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Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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