

Age-Specific Reference Ranges for Serum Prostate-Specific Antigen in Puerto Rican Men with Proven Prostate Cancer

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Objectives: The purpose of this research was to carry out a statistical study (the first such) of prostate-specific antigen (PSA) levels in Puerto Rican men (including residents of Puerto Rico not born on the island) with proven prostate cancer (PC). We also sought to propose new age-specific PSA reference ranges to improve the diagnosis and prognosis of PC.

Methods: In order to address our objectives, a PSA statistical analysis of 16,305 Puerto Rican men (from 2004–2012) with proven PC was carried out.

Results: For all Puerto Rican PC patients, PSA statistical central measures and variability were determined. For instance, the mean, median, mode, index of dispersion (ID), and interquartile range (IQR) had the values 16.9 ng/mL, 7.2 ng/mL, 4.5 ng/mL, 3.1 ng/mL, and 11.3 ng/mL, respectively. The ID values suggest significant PSA data variability, and the IQR values show that the PSA data are over-dispersed. We found the median age-specific PSA reference ranges and confidence interval (CI) for all Puerto Rican men with proven PC. Also, we obtained the median PSA level and CI of Puerto Rican men with proven PC in 2 ranges ($0 < \text{PSA} \leq 4$ ng/mL) and ($4 \text{ ng/mL} < \text{PSA} < 98$ ng/mL).

Conclusion: The main objectives of this research were achieved. First, a statistical study of PSA levels in Puerto Rican men with proven PC was conducted. Second, 2 new age-specific PSA reference ranges were obtained in order to improve decision making and medical treatment in PC. [*P R Health Sci J* 2019;38:87-91]

Key words: Prostate cancer, PSA, Puerto Rico

In Puerto Rico, prostate cancer (PC) has the highest incidence and level of mortality than any other type of cancer (1). Compared with that of the United States (US), the overall PC incidence in Puerto Rico is higher (2). It is higher than the overall incidence of the populations of US non-Hispanic whites and US Hispanics and lower than that of US non-Hispanic blacks (2). In 2012, at the global level, Puerto Rico ranked within the top 20 countries with the highest incidence of PC (3).

Although a biopsy is the standard definitive medical procedure to detect PC, a less invasive approach is to measure the PSA level in the blood. In 1986, a PSA clinical test was developed, and since then, it has been used in screening for PC. To obtain a clinically relevant PSA cut-off value, a study was commissioned, which found that 99% of 472 healthy Anglo-Saxon men had a total PSA level below 4.0 ng/mL. As a result of this study, the standard cut-off value for PSA throughout a large part of the world, including Puerto Rico has been determined to be 4.00 ng/mL. Currently, the PSA test is quite controversial (4-6), due to the possible presence of false negatives and false positives and, unfortunately, because it is not entirely prostate-cancer specific. However, the PSA test is still widely used due to its availability, inexpensive cost, ease of administration, and non-invasive nature, and also because it is

prostate specific. To add to the complexity of this issue, several studies (7–16) have concluded that men of different ethnic groups may have different PSA cut-off levels. Moreover, it has been suggested that using different age-specific PSA reference ranges for different ethnic groups may improve the diagnosis and prognosis of PC in the members of those groups. The current age-specific PSA reference ranges are obtained using the 95th percentile values of PSA in healthy men of different ethnicities. In fact, a review of the literature shows that authors have always used healthy male populations to establish PSA cut-off values and age-specific reference ranges. However, actual age-specific PSA reference ranges do not discriminate between slow- and fast-growing (aggressive) tumors. In this paper, we show new age-specific PSA reference ranges related to small and fast-growing tumors. This new information is

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crucial for the successful diagnosis and determination of the prognosis of PC.

Patients and Methods

In Puerto Rico, it is mandatory to report any cancer diagnosis to the Puerto Rico Central Cancer Registry (PRCCR). We have used this registry for our research, specifically, a PSA database provided by the PRCCR of Puerto Rican men with proven PC, in the period spanning from 2004 to 2012. We should mention that the extracted data do not distinguish between Puerto Rico-born and non-Puerto Rico born men living in Puerto Rico. However, using data provided by the Instituto de Estadísticas de Puerto Rico, we have estimated that the percentage of non-Puerto Rico men is very small (3.56%, with those being, on average, from 45 to 85 years old and over) compared to the population of Puerto Rico-born men.

During the period of 2004 to 2012, PRCCR recorded 26,898 reported PC cases. This database does not include data from men that were identified by a death certificate. For the present study, some of the provided PSA data were discarded, for several reasons. For example, data were discarded when the PSA test was ordered but its results were not documented in the chart. Furthermore, in this database, PSA values of 98 ng/mL and greater were given by PRCCR a unique value of 98 ng/mL. Thus, for our research purposes we discarded 10,593 records, and kept the PSA data for 16,305 Puerto Rican men diagnosed with PC. We should point out that all the clinical PSA data provided to us by the PRCCR were confirmed histologically (via biopsy). However, it certainly may be possible that some of the 16,305 Puerto Rican PC patients may concurrently have had benign prostatic hyperplasia (BPH). It is well known that BPH can also elevate PSA level values, and such values could impact the results presented in this paper, in particular, those of patients aged over 60 years. Prostatitis, the most common prostate-related problem for men younger than 50, can also raise PSA levels. A recent study of 1,772 men revealed that only 13 of them had both a PC diagnosis and prostatitis symptoms (17). Thus, although there was a lack of information about the number of PC patients with prostatitis in the data provided by PRCCR, this fact may affect only slightly the results of this research.

To carry out the statistical analysis, Puerto Rican PC patients were grouped into age groups consisting of 5-year spans. Further, in order to make a comparison of PSA levels between men of different ethnicities (Puerto Rican and Irish) with proven PC, the statistical analysis was redone using 10-year intervals. Finally, in order to establish age-specific PSA reference ranges for small slow-growing

tumors, we calculated the median PSA of all Puerto Rican men with proven PC and a PSA level of less than 4 ng/mL. For aggressive tumors, age-specific PSA reference ranges were obtained by calculating the median PSA of Puerto Rican men with proven PC and a PSA level greater than 4 ng/mL but less than 98 ng/mL.

This research was exempt from IRB review (under category 4).

Results

Figure 1 shows the PSA values of 16,305 Puerto Rican men with proven PC. The histogram in Figure 1 is right skewed, with an outlier which strongly affects the value of the mean and standard deviation. For that reason, we used the median rather than the mean PSA level in our analysis. Figure 2, illustrates the comparison between the number of cases of Puerto Rican men with PC and the different ranges of PSA values namely, those with PSA lower than or equal to 4 ng/mL (light gray), those with PSA lower than or equal to 4 ng/mL (intermediate gray), and those with PSA greater than or equal to 98 ng/mL (dark gray), respectively. Interestingly, the

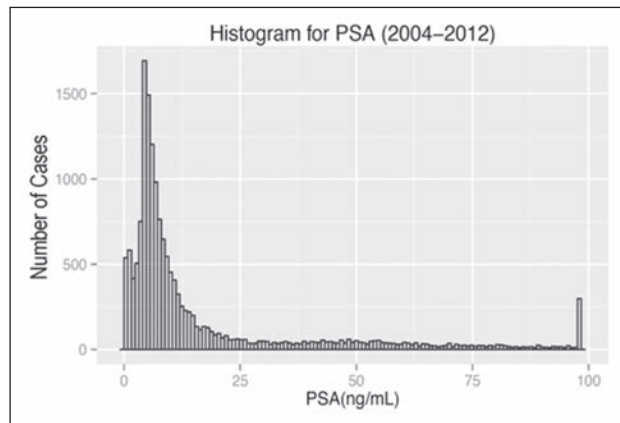


Figure 1. PSA histogram for PC patients in Puerto Rico.

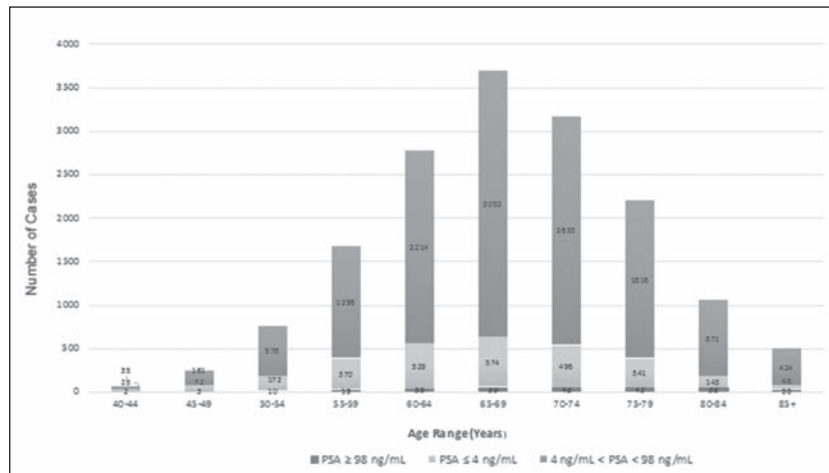


Figure 2. In dark, intermediate, and light gray: histograms for the PSA levels of PC patients in Puerto Rico with PSA levels from 4 ng/mL to 98 ng/mL, PSA levels ≤ 4 ng/mL, and PSA levels ≥ 98 ng/mL, respectively.

number of cases that fall in the range of $0 < \text{PSA} < 4 \text{ ng/mL}$ is about 17% of the total population, while those with a PSA of 98 ng/mL or greater comprised only 1.8%. Thus, based on this information, we estimated the proportion of false negatives to be 17%, using a PSA cut-off value of 4.0 ng/mL. Figure 2 shows that the PC incidence was greater in the population of men aged 65 to 69 years, regardless of PSA value. The median PSA level vs. age for the entire population is plotted in Figure 3. The median PSA evolution over time can be modeled by a cubic equation in time ($-49.9277 + 2.7750 t - 0.0469 t^2 + 0.0003 t^3$), where t is given in years, and PSA in ng/mL. There is an inflexion point at 52.11 years. PSA velocity (PSAV) and

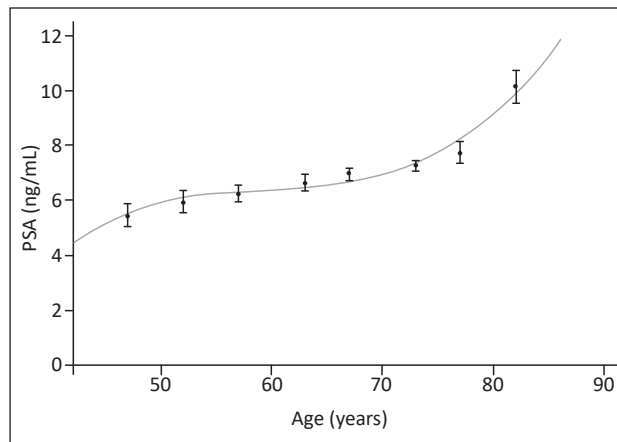


Figure 3. The median PSA values follow a cubic equation in time (light gray). Dots show median PSA levels from clinical data, and the error bars are 95% CIs.

acceleration (PSAA) can be easily derived. PSAV is determined using the following quadratic equation ($2.7775 - 0.0938 t + 0.0009 t^2$). PSAA is determined with the following linear equation ($-0.0938 + 0.0018 t$). PSAV and PSAA suggest that before the inflexion point, PSA values increase slowly, compared to the rate of increase of PSA values after the inflexion point.

In Table 1, measures of central tendencies including means, medians, modes, percentiles (5th, 95th), and quartiles were calculated for each of the 2 age groups that composed of 5-year age ranges (1-A) and that composed of 10-year age ranges (1-B). On Table 1-A, it can be seen that the PSA is bimodal, with a value of 5 ng/mL for the age group including 50- to 54-year-olds as well as that made up of 70- to 74-year-olds.

Table 1-B is also helpful in comparing the PSA levels of the 5th percentile of Anglo Saxon men diagnosed with PC (18) with the PSAs of the 5th percentile of Puerto Rican PC patients. In fact, the groups of Anglo Saxon men aged 50 to 59 years and those aged 60 to 69 years diagnosed with PC and in the 5th percentile had PSA levels of 1.2 ng/mL and 1.7 ng/mL, respectively. These results must be compared with the respective PSA level values for the same age groups (50–59 years: 1.0 ng/mL; 60–69 years: 1.1 ng/mL) of Puerto Rican men diagnosed with PC.

Discussion

As is very well established, currently, PSA cut-off values are estimated by using the PSA values of the 95th percentile of a healthy male population. Thus, to obtain PSA cut-off values from a population of men with proven PC, a 5th percentile analysis should be considered. However, we are aware that this proposal favors sensitivity over specificity. To obtain a balance between sensitivity and specificity, we propose, instead, to use for cut-off values the median PSA of men with proven cancer and PSA values less than or equal to 4 ng/mL. These new age-specific PSA reference ranges (second column in Table 2 and in Figure 4 dark broken dashed line) will be useful to the understanding of PSA evolution with respect to time in Puerto Rican patients with small slow-growing tumors in their prostates. Further, in Table 2 (third column) are listed the median PSAs for Puerto Rican PC patients with PSAs in the range of 4 ng/mL to 98.0 ng/mL. The purpose of this undertaking was to obtain age-specific PSA reference ranges for the diagnosis and prognosis of aggressive tumors. In Figure 4, we have plotted the second

Table 1. PSA levels of men in Puerto Rico with proven PC, grouped by age, in 5- (1-A) and 10-year (1-B) intervals.

(1-A) PSA levels for PC patients in Puerto Rico, grouped by age (in 5-year intervals)

Age range	N	Mean ± SD	Median	5 th percentile	95 th percentile	Lower quartile	Upper quartile	Mode
40–44	63	10.22 ± 18.88	4.60	1.04	31.30	3.30	6.95	3.60
45–49	244	13.84 ± 20.60	5.50	0.92	65.12	3.80	12.73	3.90
50–54	772	14.66 ± 20.57	6.00	1.10	59.65	4.10	12.53	5.00
55–59	1711	15.21 ± 20.85	6.30	1.00	65.20	4.20	13.80	4.20
60–64	2812	16.04 ± 21.71	6.70	0.90	69.19	4.40	14.70	4.40
65–69	3726	16.29 ± 21.99	7.00	1.30	71.50	4.60	14.70	4.80
70–74	3208	16.88 ± 22.65	7.30	1.20	73.77	4.70	15.00	5.00
75–79	2213	17.67 ± 23.16	7.80	1.10	76.02	4.80	17.00	98.00
80–84	1056	20.51 ± 25.06	10.20	1.28	84.18	5.50	21.12	98.00
85+	500	24.97 ± 27.15	13.60	2.10	98.00	7.20	30.47	98.00

(1-B) PSA levels for PC patients in Puerto Rico, grouped by age (in 10-year intervals)

Age range	N	Mean ± SD	Median	5 th percentile	95 th percentile	Lower quartile	Upper quartile	Mode
40–49	307	13.20 ± 20.28	5.20	0.93	64.53	3.70	10.95	3.90
50–59	2483	15.04 ± 20.76	6.20	1.00	65.00	4.10	13.35	4.20
60–69	6538	16.19 ± 21.86	6.90	1.10	70.12	4.50	14.70	4.50
70–79	5421	17.20 ± 22.86	7.50	1.20	75.00	4.80	15.90	98.00

(intermediate gray) and third columns (in dark gray) of Table 2. This provides a new PSA interpretation. In dark broken dashed lines (Fig. 4), Puerto Rican patients' tumors should be small and a recommendation of "watchful waiting" may be suggested by the physician. Age-specific PSA reference ranges for patients with aggressive tumors are plotted in a broken line (Fig. 4)

Table 2. The table shows the median PSA levels and CIs for 3 populations of men in Puerto Rico with proven PC. The first column is for all patients, the second column is for patients with PSAs ≤ 4 ng/mL, and the third column is for patients with PSA levels from 4 ng/mL to 98 ng/mL.

Age-specific PSA reference ranges for patients in Puerto Rico with proven PC.

Age range (years)	Median PSA (ng/mL) for all population (95% CI)	Median PSA ≤ 4 ng/mL (95% CI)	4 ng/mL < Median PSA < 98 ng/mL (95% CI)
40-44	4.60 (3.80 – 5.40)	3.10 (2.30 – 3.60)	6.20 (5.20 – 7.80)
45-49	5.50 (4.80 – 5.90)	2.75 (2.40 – 3.50)	8.00 (6.50 – 10.40)
50-54	6.00 (5.60 – 6.40)	2.70 (2.40 – 3.00)	7.90 (7.20 – 8.60)
55-59	6.30 (6.00 – 6.60)	2.50 (2.30 – 2.70)	8.00 (7.60 – 8.50)
60-64	6.70 (6.40 – 7.00)	2.20 (1.90 – 2.50)	8.30 (8.10 – 8.70)
65-69	7.00 (6.70 – 7.20)	2.20 (2.00 – 2.50)	8.10 (7.90 – 8.50)
70-74	7.30 (7.00 – 7.50)	2.10 (1.80 – 2.30)	8.50 (8.20 – 8.80)
75-79	7.80 (7.50 – 8.20)	1.80 (1.50 – 2.10)	9.10 (8.70 – 9.50)
80-84	10.20 (9.60 – 10.80)	1.90 (1.50 – 2.20)	11.40 (10.70 – 12.10)

Conclusions

In Puerto Rico, PC is an endemic disease. Concerning PC, there are 2 important and urgent needs. The first, is to find a reliable PSA cut-off value to improve the diagnosis and subsequent prognosis (of a given individual) of PC. The second is to accurately identify aggressive tumors without an invasive procedure, such as a biopsy. In this paper, we have attempted to shed some light on these needs.

To gain a better understanding of those needs, we performed a statistical study of PC in Puerto Rico using the database provided by the PRCCR. Table 1 and Figures 1 and 2, summarize our

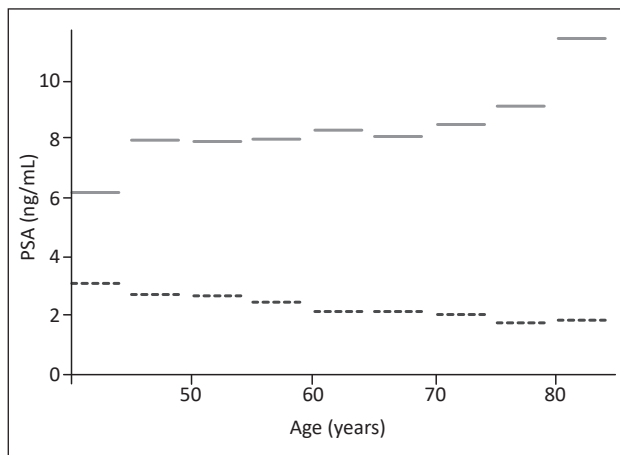


Figure 4. The median PSA levels for given age-specific reference ranges of men in Puerto Rico with proven PC; median PSA levels ≤ 4 ng/mL are in dark broken dashed line, and PSA levels of 4 ng/mL to 98 ng/mL are in a broken line.

results. In fact, we found, that as a central measure, the median is more reliable than the mean. Moreover, the incidence of PC in Puerto Rico is greatest in men who are from 65 to 69 years old. A comparison of PSA values in Puerto Rican and Anglo Saxon (from Ireland) men (18) with proven PC suggests that PSA value is dependent on a patient's ethnicity (this is the case with healthy men). Our comparison also showed that the median PSA for Puerto Rican men with proven PC followed a cubic equation in time (Fig. 3). PSAV and PSAA analytical expressions were therefore easily calculated.

Instead of the standard 4 ng/mL cut-off value, then, we propose 2 new, age-specific PSA reference ranges, which can be seen in Table 2 (columns 1 and 2) and Figure 4 (dark broken dashed lines and a broken line). Table 2 and Figure 4 provide additional information to help in the patient's decision-making process and the physician's formation of a treatment strategy. For instance, the PSA reference ranges plotted in dotted lines in Figure 4 describe the PSA values of patients with small growing tumors. In gray lines (Fig. 4), the PSA reference ranges of patients with aggressive tumors are plotted. Although, the results shown in Table 2 and Figure 4 are valid only in Puerto Rico, this research could be replicated in other places, using PC patients of different ethnicities.

Resumen

Objetivos: El propósito de esta investigación fue llevar a cabo por primera vez un estudio estadístico del antígeno prostático específico (PSA, por sus siglas en inglés) en hombres puertorriqueños (incluyendo residentes de Puerto Rico no nacidos en la isla) con cáncer de próstata clínicamente probado. También buscamos proponer para el PSA nuevos intervalos de referencia específicamente por edades, los cuales serán útiles para el diagnóstico y el pronóstico del cáncer de próstata. **Métodos:** Para alcanzar nuestros objetivos, se realizó un análisis estadístico del PSA con 16305 hombres puertorriqueños (desde 2004-2012) diagnosticados con cáncer de próstata clínicamente probado. **Resultados:** Para todos los pacientes puertorriqueños con cáncer de próstata, se encontraron las medidas de tendencia central del PSA y su variabilidad. Por ejemplo, los valores de 16.9 ng/ml, 7.2 ng/ml, 4.5 ng/ml, 3.1 ng/ml y 11.3 ng/ml indican la media, la mediana, la moda, el índice de dispersión y el rango intercuartílico, respectivamente. Los valores de índice de dispersión sugieren una gran variabilidad de los datos de PSA, y los valores de rango intercuartílico muestran que los datos de PSA están sobre dispersos. Hemos encontrado la mediana y el IC del PSA para todos los hombres puertorriqueños con cáncer de próstata en diferentes rango de edades. También se listan la

mediana del PSA y IC de hombres puertorriqueños con cáncer a la próstata en dos intervalos ($0 < \text{PSA} \leq 4 \text{ ng / mL}$) y ($4 \text{ ng / mL} < \text{PSA} < 98 \text{ ng / mL}$). Conclusión: Los principales objetivos de esta investigación han sido alcanzados. Primero, se llevó a cabo un estudio estadístico de los hombres puertorriqueños con cáncer a la próstata. En segundo lugar, nuevos rangos de referencia para el PSA se han obtenido para mejorar la toma de decisión y el tratamiento médico del cáncer a la próstata.

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