ORIGINAL

Correlation of risk factors for prostate cancer with doubtful prostate antigen values

Correlación de los factores de riesgo de cáncer de próstata con valores de antígeno prostático dudosos

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ABSTRACT

Background: Prostate cancer is a disease that affects the male population especially after the age of 45. There are several risk factors, some modifiable, on which prevention strategies must be designed to avoid even doubtful prostate antigen levels. **Objective:** Determine the correlation of risk factors for prostate cancer with doubtful prostate antigen values. **Methods:** During the year 2022, a quantitative correlational study was carried out in the population of four clinics belonging to the "East Area" of the Camagüey municipality. The universe consisted of 80 patients in whom prostate antigen determination was performed. The variables were: age groups, color of the skin, family history of prostate cancer, previous history of other prostate disease and behavioral risks. The corresponding statistical analysis was performed for this type of study. **Results:** There was a predominance of patients with doubtful PSA/normal PSA in a ratio of 13/4 in the age group (>45 years). There was no relationship between doubtful PSA values and skin color (OR 0.74). Statistically significant relationship was found between a family history of prostate cancer and previous history of prostate conditions with doubtful PSA values (OR 5.57 and 2.04, respectively). The strongest influence was found when correlating behavioral risks and doubtful PSA values. **Conclusions:** Behavioral risks constitute modifiable factors on which health promotion and education actions can be designed to prevent the progression to high PSA levels and eventually prostate cancer. Active screening, when the other associated factors are present, is recommended.

Keywords: Prostate specific antigen; Risk factors; Prostate cancer

RESUMEN

Introducción: El cáncer de próstata es una enfermedad que afecta a la población masculina especialmente después de los 45 años. Existen varios factores de riesgo, algunos modificables, sobre los cuales se deben diseñar estrategias de prevención para evitar incluso niveles dudosos de antígeno prostático. **Objetivo:** Determinar la correlación de los factores de riesgo de cáncer de próstata con valores dudosos de antígeno prostático. **Métodos:** Estudio correlacional cuantitativo en la población de cuatro consultorios pertenecientes al "Área Este" del municipio Camagüey. El universo estuvo constituido por 80 pacientes a los que se les realizó determinación de antígeno prostático. Las variables fueron: grupos de edades, color de la piel, antecedentes familiares de cáncer de próstata, antecedentes de otras enfermedades prostáticas y riesgos conductuales. **Resultados:** Hubo predominio de pacientes con PSA dudoso/PSA normal en una relación de 13/4 en el grupo de edades (>45 años). No se encontró relación entre los valores dudosos de PSA y el color de la piel (OR 0,74). Se encontró una relación estadísticamente significativa entre la historia familiar de cáncer de próstata y la historia previa de enfermedades prostáticas con valores dudosos de PSA (OR 5,57 y 2,04, respectivamente). La influencia más fuerte se encontró al correlacionar los riesgos conductuales con los valores dudosos de PSA. **Conclusiones:** Los riesgos conductuales constituyen factores modificables sobre los que se pueden diseñar acciones de promoción y educación para la salud. Se recomienda la pesquisa activa cuando estén presentes los demás factores asociados.

Palabras clave: Antígeno prostático específico; Factores de riesgo; Cáncer

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INTRODUCTION

Prostate cancer, according to Linares Mesa NA, et al,[1] is the third most common neoplasm in men worldwide, and the first one in developed countries, excluding skin cancer. In 2020, the American Society of Clinical Oncology[2] reported that 1,414,259 people had been diagnosed with prostate cancer, and 375,304 had died from this cause.

Bray F [3] reported that prostate cancer was more prevalent in the male population out of 40 African countries. According to the World Health Organization,[4] Latin America has an annual incidence of 54.2, and according to data from the Health Statistical Yearbook,[5] in its 50th edition, malignant tumors occupy second place within the top ten causes of death in Cuba, whose rate is 277.9 per 100 thousand inhabitants. Camagüey province shows a high percentage of deaths from malignant tumors with 1,944 deaths in 2021, for a crude rate of 255.4 per 100 thousand inhabitants.

The National Program for Cancer Control and Diagnosis (PNCDC) from Primary Health Care (PHC) promotes the active investigation of risk factors for prostate cancer, in which the determination of the value of the prostate antigen constitutes a cardinal marker.[4]

Prostate-specific antigen values (PSA) is the most used tumor marker in prostate cancer monitoring. It is a substance produced by both normal and cancerous cells in the prostate gland, and represents a fairly sensitive test. Its incorporation as a predictive method improves the accuracy of risk stratification and helps in the decision-making process to perform prostate biopsies.[6]

In this sense, Dellavedova T [7] highlights the usefulness of PSA for more than 30 years, as it is a characteristic biomarker both for the diagnosis of prostate cancer and for monitoring its response to several therapies. Additionally, Vachani C [8] emphasizes that the trend of PSA values throughout of time matters more than a single value above 4.0 ng/ml (upper limit).

Pathophysiological variations in PSA levels should be taken into account, according to age. For this, the same cut-off point and an average age have been established. Men who have a level above the median for their age have a higher risk of developing cancer. The median in the 30's is 0.5 ng/ml, and increases to 0.7 ng/ml, 0.9 ng/ml, 1.3 ng/ml, 1.7 ng/ml and 2.1 ng/ml for every decade of life until the 80's. Prostate cancer should also be suspected when the rate of increase is more than 0.75 ng/ml/year in patients in the range of 4-10 ng/ml or more than 0.35 ng/ml/year in patients with a range of less than 4 ng/ml.[9]

Explanations for the origin of prostate cancer use three indisputable elements in its genesis: aging; familial history of prostate cancer or other type of cancer; and dark-skinned ethnicity. It is also believed that tobacco and alcohol consumption may be involved, but it has not been conclusive.[10]

The risk factors, according to Vertosick EA, et al [11] can be grouped into non-modifiable (ethnicity, family history of hyperplasia and bladder cancer) and modifiable (metabolic syndrome and obesity, excessive coffee intake, sedentary lifestyle and alcoholism). In addition, Vietri MT, et al [12] attribute a strong hereditary component within the family history, with first-degree relatives (father or siblings) and the increase of the risk proportionally to age. Likewise, African American men have a higher incidence than those of other ethnics.

Obesity and other environmental factors such as diets rich in fat and sugar, could increase the risk. Since prostate cancer involves epidemiology and genetics, the interaction between genetics, the environment, external influences, and social determinants, rapidly increase the risk.[13]

This article aims of determining the correlation of risk factors for prostate cancer in patients with doubtful prostate antigen values.

METHODS

A quantitative correlational study was carried out in the male population of four clinics belonging to the "East Area" Polyclinic of the municipality of Camagüey, Cuba, during the year 2022. Of 98 patients in whom PSA determination was performed, 80, who met the selection criteria, were selected. Those with doubtful PSA accounted 40, equivalent to those with normal PSA values.

Inclusion criteria

Patients with PSA values determination in the period January-December 2022, who agreed to be part of the research.

Exclusion criteria

Patients for whom the data collection was incomplete.

Patients with PSA levels above the upper limit for their age group.

The variables were: age (defined by the groups of <45 years and >45 years), skin color (white or black), family history of prostate cancer (yes - Exposed and no - Not Exposed), other prostate conditions (yes - Exposed and no - Not Exposed) and behavioral risks (yes - Exposed and no - Not Exposed). Each variable obtained two denominations according to exposed and not exposed.

The PSA values were considered doubtful when they show between 4 and 10 ng/ml, so it is important to calculate the percentage of free/total PSA values. Likewise, behavioral risk refers to those voluntary or involuntary actions carried out by an individual that can cause biological, psychological or social consequences, including smoking, alcoholism, sexually transmitted disease (STD) and exposure to certain chemical substances such as cadmium.[4,7,11,13]

Data collection and processing

The data collection form was the primary record, while individual medical records constituted the secondary record. Statistical processing was carried out using the Package for the Social Sciences (SPSS) version 24.0, and numbers and percentages were obtained as summary measures. The results were presented in the form of texts and 2 x 2 contingency tables that independently analyzed the association of a risk factor with doubtful PSA values. Incidence, difference and rate ratio, cumulative incidence, difference and risk ratio, as well as the odds ratio were calculated, with 95% confidence interval using the Wald method. The Chi Square (X^2) and p values were also determined. When Chi was less than 5, Z was applied to determine whether it fits the alternate hypothesis: (P1-P2)>0 or (P1-P2)<0.

Ethical aspects

The study was approved by the Scientific Council and the Ethics Committee of the Polyclinic, and the information obtained was not used for purposes other than the research. The principles of the Declaration of Helsinki were taken into account.

RESULTS

Table 1 analyzes the association of doubtful PSA values with the age groups over 45 years (Exposed) and under 45 years (Unexposed). The first group (over 45 years (Exposed)) had 69 patients, and a doubtful/normal PSA ratio of 38/31 was obtained; while in the second group (under 45 years (Not Exposed)) containing 11 patients, the ratio was 2/9. The speed of onset (IT) of this event in the population is 1.00 and the risk of developing the disease (AI) during the period studied was 50.00. The odds ratio (OR), showing values greater than 1, indicates that patients over 45 years of age have a greater risk of getting sick. Similarly, when calculating p in Wald's Chi Square as it is less than 0.05, the null hypothesis is rejected, and there is a relationship between the variables.

Table 1. Association of PSA values with age groups.

	Doubtful PSA	TP*/PSA normal
Exposed	38	31
Not Exposed	2	9

Frequency and association	Measure○	IC 95 %●
Incidence rate (IR)	1.00	0.73;1.36
Exposed IR	1.23	0.89;1.69
Unexposed IR	0.22	0.06;0.88
Rate Differences (RD)	1.01	0.51;1.51
Rate Ratio (RR)	5.59	1.35;23.17
Cumulative Incidence (CI)	50.00	12.06;207.26
CI Exposed	55.07	40.07;75.68
CI Not Exposed	18.18	4.55;72.69
Risk Differences (RD)	36.89	10.22;63.56
Risk Ratio (RR)	3.03	0.85;10.80
Odds Ratio (OR)	5.52	1.11;27.43

Chi Square (X2) = 5.16 p = <0.025
Note: *Time-Person, ○IT and DT can be multiplied by a number multiple of 10, ○AI and RD are expressed in percentages and are mathematically analogous to the prevalence, ●95% confidence intervals by the Wald method.
Source: Data collection form.

Those who did and did not present doubtful PSA values in relation to black (Exposed) and white (Not Exposed) skin color are associated in Table 2. A ratio of 18/21 was obtained for the first group (Exposed) and it was 22/19 for the second (Not Exposed). The frequency of suffering from this condition is 0.86 (RR) times higher in patients with black skin than in patients with white skin. Obtaining a negative value in the risk difference (RD) indicates that this factor does not favor the disease. In relation to pin Wald's Chi Square, being greater than 0.05 shows that there is no relationship between the

variables.

Table 2. Association of PSA values with skin color.

	Doubtful PSA	TP*/PSA normal
Exposed	18	21
Not Exposed	22	19

Frequency and association	Measure○	IC 95 %●
Incidence rate (IR)	1.00	0.73;1.36
Exposed IR	0.86	0.54;1.36
Unexposed IR	1.16	0.76;1.76
Rate Differences (RD)	-0.30	-0.93;0.33
Rate Ratio (RR)	0.74	0.40;1.38
Cumulative Incidence (CI)	50.00	26.82;93.22
CI Exposed	46.15	29.08;73.25
CI Not Exposed	53.66	35.33;81.49
Risk Differences (RD)	-7.51	-29.65;14.63
Risk Ratio (RR)	0.86	0.55;1.34
Odds Ratio (OR)	0.74	0.31;1.78

Chi Square (X2) = 5.16 p = <0.025
Note: *Time-Person, ○TI and DT can be multiplied by a number multiple of 10, ○AI and RD are expressed in percentages and are mathematically analogous to the prevalence, ●95% confidence intervals by the Wald method.
Source: Data collection form.

Table 3 represents the risk of presenting doubtful PSA values in relation to a family history of prostate disease. Of the 40 exposed, 30 had a doubtful PSA values and 2 had a normal PSA values, while of the 40 not exposed, 5 had a doubtful PSA values and 16 had a normal PSA values. The incidence rate of the disease was 1.00 (95% CI = 0.58;1.51). The cumulative incidence of exposed people reached 68.18, as there was a close relationship between the history family of prostate disease and presenting doubtful PSA. The odds ratio (OR) showed values greater than 1 denoting that those in whom the history was collected had a higher risk. By calculating p in Wald's Chi Square as less than 0.05, the null hypothesis is rejected, and the relationship between the variables examined is accepted.

Table 3. Association of PSA values and family history of prostate cancer.

	Doubtful PSA	TP*/PSA normal
Exposed	30	14
Not Exposed	10	26

Frequency and association	Measure○	IC 95 %●
Incidence rate (IR)	1.00	0.73;1.36
Exposed IR	2.4	1.50;3.06
Unexposed IR	0.38	0.20;0.71
Rate Differences (RD)	1.76	0.96;2.56
Rate Ratio (RR)	5.63	2.75;11.52
Cumulative Incidence (CI)	50.00	24.44;102.28
CI Exposed	68.18	47.67;97.51
CI Not Exposed	27.78	14.95;51.63
Risk Differences (RD)	40.40	20.05;60.75
Risk Ratio (RR)	2.45	1.40;4.31
Odds Ratio (OR)	5.57	2.12;14.65

Chi Square (X2) = 5.16 p = <0.025
Note: *Time-Person, ○TI and DT can be multiplied by a number multiple of 10, ○AI and RD are expressed in percentages and are mathematically analogous to the prevalence, ●95% confidence intervals by the Wald method.
Source: Data collection form.

The ratio of behavioral risk with doubtful and normal PSA values (26/20), as well as that of unexposed people with doubtful and normal PSA values (4/20) is seen in Table 4. It also shows an incidence rate of 1.00, as well as, the rate ratio (RT) of presenting doubtful PSA values upon contact with behavioral risk factors was 9.00. The cumulative incidence rate (CI) reached values of 50.00 for presenting doubtful PSA values during the analyzed period. The frequency of having doubtful values was 3.86 (RR) times higher in those who had a history of behavioral factors than those who did not. Odds ratio showed a result greater than 1 (9.00), which means that those who had behavioral risks were at greater risk of presenting doubtful PSA values. With respect to pin Wald's Chi Square, being less than 0.05, the null hypothesis is discarded and there is a relationship between the variables.

Table 4. Association of PSA values with and without a history of behavioral risks.

	Doubtful PSA	TP*/PSA normal
Exposed	36	20
Not Exposed	4	20

Frequency and association	Measure○	IC 95 %●
Incidence rate (IR)	1.00	0.73;1.36
Exposed IR	1.80	1.30;2.50
Unexposed IR	0.20	0.08;0.53
Rate Differences (RD)	1.60	0.98;2.22
Rate Ratio (RR)	9.00	3.20;25.29
Cumulative Incidence (CI)	50.00	17.80;140.48
CI Exposed	64.29	46.37;89.13
CI Not Exposed	16.67	6.26;44.42
Risk Differences (RD)	47.62	27.81;67.43
Risk Ratio (RR)	3.86	1.54;6.64
Odds Ratio (OR)	9.00	2.70;30.02

Chi Square (X2) = 5.16 p = <0.025
Note: *Time-Person, ○TI and DT can be multiplied by a number multiple of 10, ○AI and RD are expressed in percentages and are mathematically analogous to the prevalence, ●95% confidence intervals by the Wald method.
Source: Data collection form.

Table 5 associates the risk that exists between a previous history of prostate conditions (Exposed) or not (Unexposed). Of the total of Exposed, doubtful PSA values was found in 22, while 15 remained within normal values. In the Not Exposed, 18 had doubtful PSA values and 25 had normal PSA. When calculating the OR, the result obtained was 2.04, which denotes that patients with a previous history of other prostate diseases have double the risk of presenting doubtful PSA values. In the same way, when determining p in Wald's Chi Square, it was 0.025, therefore, the null hypothesis is rejected and there is a relationship between the variables.

Table 5. Association of PSA values with and without a previous history of other prostate conditions.

	Doubtful PSA	TP*/PSA normal
Exposed	22	15
Not Exposed	18	25

Frequency and association	Measure○	IC 95 %●
Incidence rate (IR)	1.00	0.73;1.36
Exposed IR	1.47	0.97;2.23
Unexposed IR	0.72	0.45;1.14
Rate Differences (RD)	0.75	0.05;1.45
Rate Ratio (RR)	2.04	1.09;3.80
Cumulative Incidence (CI)	50.00	26.82;93.22
CI Exposed	59.46	39.15;90.30
CI Not Exposed	41.86	26.37;66.44
Risk Differences (RD)	17.60	-4.31;39.51
Risk Ratio (RR)	1.41	0.91;2.21
Odds Ratio (OR)	2.04	0.83;4.98

Chi Square (X2) = 5.16 p = <0.025
Note: *Time-Person, ○IT and DT can be multiplied by a number multiple of 10, ○AI and RD are expressed in percentages and are mathematically analogous to the prevalence, ●95% confidence intervals by the Wald method.
Source: Data collection form.

DISCUSSION

The study of prostate conditions is increasingly necessary due to its high frequency and the delay in the diagnosis. Especially, the knowledge of the risk factors and prevention measures for this condition is necessary in the setting of a rapid increase in prostate cancer incidence and mortality.[5,9]

Higher frequency of patients with doubtful PSA values was found in patients aged 45 years and older, which corresponds to the report of Núñez Liza JC, et al [14] in Venezuela, who found a directly proportional relationship between age and the risk of developing prostate cancer. Also Peña Rosas GD, et al [10] reported that the average age of the volunteers was 50.4 years. In Cuba, Rodríguez Rodríguez and Pérez Moreno [15] showed a predominance of the age group of 61-70 years, which is the national average defined as prostate cancer risk in the country.

Although many consulted studies [10-12] demonstrate a higher incidence in black patients, the frequency of suffering from this condition in the present study was 0.86 times higher in white patients. A negative value in the risk difference also indicates this factor as not favoring the disease.

There is no correspondence with a review [16] that mentioned African Americans with a greater probability of presenting

abnormalities in the examination. Furthermore, another study [17] added related information on the effect of race, with a greater predisposition in black patients over others.

In Cuba, the influences of the races inherited by the ancestors make miscegenation a genetic mixture. Therefore, the predominant skin color is not accurate in determining the prevailing ethnic origin, which in the opinion of the authors does not constitute an important element to keep in mind as a risk factor.

In the opinion of Núñez Liza JC, et al,[14] men with genetic risk factors have 2 to 3 times higher risk of developing prostate cancer than the expected for their age, ethnicity and geographic location.

There are no coincidences with Peña Rosas GD, et al,[10] who failed to find any family history of prostate cancer in 26 patients out of the 30 studied.

Concerning behavioral risk factors, our results coincide with the study carried out by García Viltres M,[18] which reported 84.3% patients with sedentary lifestyle; 52.6% with average socioeconomic level and 57.8% of smoking. Nuñez Liza JC, et al [14] identified that smoking (active and passive exposure to tobacco smoke) is considered a risk factor that is 2-3 times higher in smokers of more than one pack a day, compared to non-smokers.

We agree with Sawada N,[19] when stating that obesity doubles the risk due to the overconsumption of calories contained in foods rich in carbohydrates; and excessive consumption of meat and saturated fats increase the risk up to 3.5 times.

In Cuba, an increase in prostate cancer incidence is observed, even in men under 40 years of age, and although all the risk factors influencing that have not been clarified, it has been related to biological factors (age, race), genetic factors (first-degree family history of this cancer), environmental factors, behavioral factors and dietary factors.[20] A local study,[15] found among harmful habits, daily cigarette consumption, obesity and sedentary lifestyle.

Analyzing the history of previous prostate diseases and PSA elevated, there is similarity with Vertosick EA, et al [11] and García Viltres M;[18] meanwhile, Nuñez Liza JC, et al [14] found the history of sexually transmitted disease (STD) as the main risk factor. Rodríguez Rodríguez and Pérez Moreno[15] state that patients with a high number of sexual partners constitute a subpopulation with a higher risk of suffering from prostate adenocarcinoma, as it predisposes them to prostatitis and prostatic hyperplasia.

CONCLUSIONS

Behavioral risks constitute modifiable factors on which health promotion and education actions can be designed to prevent the progression to high PSA levels, and eventually, prostate cancer. Active screening, when the other associated factors are present, is recommended.

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Conflict of interests

The authors declare no conflict of interest.

Authorship

- Rolando Rodríguez Puga: Conceptualization, data curation, formal analysis, research, methodology, supervision, validation, visualization, original draft, writing-review and editing.
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- Yoánderson Pérez Díaz: data curation, formal analysis, research, methodology, supervision, validation.
- Nirvana Vega Rodríguez: Research, methodology, original draft, writing-review and editing.
- Nurys Vásquez Rodríguez: Original draft, writing-review and editing.

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