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# Prostate-specific antigen levels in patients with risk factors for prostate carcinoma disorders

## *Níveis de antígeno específico da próstata em pacientes com fatores de risco para transtornos do carcinoma da próstata*

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## ABSTRACT

**Objective:** To verify the association between the prostate-specific antigen (PSA) serum concentration and the presence of risk factors for prostate diseases in adult patients with urogenital infections. **Materials and methods:** Analytical cross-sectional study of PSA in 60 patients aged 40 to 65 years, from January to December 2013. PSA quantification was performed in serum by solid-phase chemiluminescence in two label cycles: 1. mouse monoclonal antibody (mAb); and 2. goat polyclonal antibody (pAbs). After each cycle the free antigen was removed. The readings were taken on the INMULITE ONE Siemens® automated equipment. From the PSA, 0.0-2.5 ng/ml was used to calculate the antigen distribution trend, and a bivariate statistical analysis of PSA was as opposed to previous exams, and endogenous and environmental risk factors detected. **Results:** Patients between 50-60 years of age, with a family history of urogenital and sexually transmitted infections, toxic habits, and exposure to occupational risk prevailed. Sixty-two percent of patients presented normal PSA levels, and the remaining presented slightly elevated and very high PSA levels. In the statistical analysis, a significant association ($p < 0.001$) of PSA was found as opposed to previous tests. A significant association ($p = 0.001$) was also found between PSA versus age, family history, personal pathological history, toxic habits, and risk exposure. **Conclusion:** The high association rate found between PSA versus age and other risk factors could be used as a predictive value for prostate cancer (Pca) or other prostate disorders.

**Key words:** prostate-specific antigen; risk factors; prostate cancer.

## RESUMO

***Objetivo:*** *Verificar a associação entre o nível sérico do antígeno prostático específico (PSA) e a presença de fatores de risco para doenças da próstata em pacientes adultos com infecções urogenitais.* ***Materiais e métodos:*** *Estudo analítico transversal do PSA em 60 pacientes com idades entre 40 e 65 anos, de janeiro a dezembro de 2013. A quantificação do PSA foi realizada em soro por quimioluminescência em fase sólida em dois ciclos de marcadores: 1. anticorpo monoclonal de rato (mAb); e 2. anticorpo policlonal de cabra (pAbs). Depois de cada ciclo, o antígeno livre foi retirado. As leituras foram feitas no equipamento automatizado INMULITE ONE Siemmens®. Do PSA foram usados 0-2,5 ng/ml para calcular a taxa de distribuição do antígeno, e sua análise estatística bivariada foi apresentada em oposição a exames anteriores e a fatores de risco endógenos e relativos ao ambiente.* ***Resultados:*** *Prevaleceram os pacientes entre 50 e 60 anos de idade, com histórico familiar de casos de infecções urogenitais e sexualmente transmissíveis, hábitos tóxicos e exposição a riscos ocupacionais. Sessenta e dois por cento dos pacientes apresentaram níveis adequados de PSA; os demais, níveis levemente elevados e muito elevados. Na análise estatística, uma associação significativa (*p *< 0,001) de PSA foi descoberta em oposição a exames anteriores. Uma associação significativa (*p *= 0,001) de PSA também foi descoberta em oposição a idade, histórico familiar, histórico patológico pessoal, hábitos tóxicos e risco à exposição.* ***Conclusão:*** *A alta taxa de associação encontrada entre PSA em oposição à idade e a outros fatores de risco poderia ser usada como valor preditivo para câncer de próstata (Pca) ou outras doenças prostéticas.*

***Unitermos:*** *antígeno prostático específico; fatores de risco; neoplasia prostática.*

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## RESUMEN

***Objetivo:*** *Verificar la asociación entre el nivel sérico del antígeno prostático específico (APE) y la presencia de factores de riesgo para enfermedades de próstata en pacientes adultos con infecciones urogenitales.* ***Materiales y métodos:*** *Estudio analítico, transversal acerca del APE en 60 pacientes con edades entre 40 y 65 años, de enero a diciembre del 2013. La cuantificación del APE fue realizada en suero por quimioluminiscencia en fase sólida en dos ciclos de marcadores utilizando: 1. anticuerpo monoclonal de ratón (mAb); y 2. anticuerpo policlonal de cabra (pAbs). Después de cada ciclo, el antígeno libre se eliminó. Las lecturas se realizaron en un equipo automatizado Immulite One Siemens®. Se utilizaron 0-2,5 ng/ml del APE para determinar el nivel de distribución del antígeno, y su análisis estadístico bivariado se estableció en comparación con exámenes anteriores y factores de riesgo endógenos y relativos al entorno.* ***Resultados:*** *Prevalecieron los pacientes entre 50 y 60 años de edad, con antecedentes familiares de infecciones urogenitales y de trasmisión sexual, hábitos tóxicos y exposición a riesgos laborales. Sesenta y dos por ciento de los pacientes presentaron niveles adecuados de APE; los demás, niveles ligeramente elevados y muy elevados. En el análisis estadístico, una asociación significativa (*$p < 0,001$*) de APE fue descubierta versus exámenes previos. También se descubrió una asociación significativa (*$p = 0,001$*) de APE versus edad, antecedentes familiares, antecedentes patológicos personales, hábitos tóxicos y exposición a riesgo.* ***Conclusión:*** *El alta asociación encontrada entre APE versus edad y otros factores de riesgo podría ser usada como valor predictivo para cáncer de próstata (CaP) u otras enfermedades prostáticas.*


***Palabras clave:*** *antígeno prostático específico; factores de riesgo; neoplasia prostática.*

## INTRODUCTION

Prostate cancer (PCa) is a malignant solid tumor that is usually asymptomatic for several years and is the second cause of morbidity and mortality in male population aged 50 and above[1-6]. In Latin America, the high prevalence and increase of new cases of PCa are related to the lack of prevention programs to detect neoplasia in the early stage, so that when the patient goes to the clinic, the tumor is in an advanced state[7]. Statistics collected from Brazil, Colombia, Ecuador, and Costa Rica have shown an increase in the prevalence of PCa-associated morbidity[7-10].

The National Tumor Network (NTN) in Ecuador has available a record of cancer cases in Quito, Guayaquil, Manabí, Cuenca, Loja, and Los Ríos, which has allowed the estimation of the prevalence and incidence of PCa morbidity and mortality in male population. In Guayaquil, the estimated prevalence rate of PCa was $31.3 \times 100{,}000$ inhabitants, it is the second most common cancer among men in the city[10]. In the country, there is a certain trend towards an increase in the prevalence of this type of tumor. In 2014 from the 906 new cases of cancer in men, PCa occupied first place with 143 cases (15%)[10].

The trend of prevalence of PCa may be related to its slow progressive carcinogenic development that depends on endogenous and environmental factors, and the availability and sensitivity of diagnostic tests used in the study of the gland in asymptomatic men aged 40 years or older[11-16]. Clinical markers of prostate abnormalities include digital rectal examination (DRE) with 69% and 92% of sensitivity and specificity, respectively, and serum quantification of total prostate-specific antigen (PSA) with 84.5% and 98%[17-20]. The results of the DRE depend on the experience of the person who performes it; while PSA depends on the sensitivity and precision of the analytical technique[21], among which the most sensitive and precise is the chemiluminescence used in this study. However, the use of cut-off values of total PSA versus age, using more precise and sensitive analytical techniques such as chemiluminescence, can contribute to measurements to Individualize Screening[22] of the presence of PCa in primary health care.

The controversial criteria of using PSA as an indicator of prostatic alterations is due to the risk of overdiagnosis and excessive treatment[23] or may be due to the recommended cut-off value that does not take into account the patient's age which could explain the presence of PCa in patients with values $< 4$ ng/ml[24, 25]. Although there are new markers for PCa, the correlation between the PSA versus a positive DRE, the age and the presence of risk factors in patients raise the predictive value of proteins in the diagnosis of PCa[22, 26, 27].

## MATERIALS AND METHODS

A cross-sectional analytical study of PSA serum concentration was carried out on 60 patients aged 40-60 years hospitalized for urological alterations at the Hospital Ángel Felicísimo Roja,

Guayaquil, Ecuador, from January to December 2013; those who consented to participate voluntarily were included.

Variables included age, family history (FH) and past medical history (PH), toxic habits and occupational exposure, DRE and transrectal ultrasound (TU) results. The PSA was quantified in the serum obtained by centrifugation of 5 ml of blood from each patient by automated solid-phase sequential chemiluminescence in the INMULITE ONE Siemens® equipment and Siemens reagents using the cut-off value ≤ 4 ng/ml for readings.

In the solid-phase chemiluminescence technique (beads), the beads are coated with mouse monoclonal antibodies to PSA (anti-PSA mAb) and incubated: in the first reaction cycle the mAb-PSA complex is formed, then the sample is washed and centrifuged to remove free PSA. In the second cycle, the goat polyclonal antibody is conjugated with alkaline phosphatase (goat intestine) that is added to form the mAb-PSA complex.

Although the cut-off value ≥ 4 ng/ml was used for the readings, having considered the calculated median of PSA in the patient sample, the results were categorized as baseline (0-2 ng/ml), slightly elevated (2.1-4 ng/ml), high-moderate (4.1-10 ng/ml), and considerably high (≥ 10.1 ng/ml).

### Statistical analysis

For the interpretation of the results, the statistical package SPSS v. 21 was used. For the interpretation of the diagnostic methods for PCa, nonparametric tests and statistics were applied. Exploratory analysis was used only for the distribution of PSA values at the level of the patient sample. The results showed that this biomarker did not meet the requirements of randomness and homoscedasticity, so the Kruskal-Wallis nonparametric test of independent samples was used to compare the variation of the PSA in the groups subjected to other tests and, the Mann-Whitney *U* test with Bonferroni Correction was used to determine the differences between groups. For the PSA versus age correlation, the Spearman correlation coefficient was used; whereas for the bivariate comparison of the PSA versus non-continuous variables: PH, FH, habits of toxic consumption and occupational exposure, the Chi-square independence test for contingency tables was used.

## RESULTS

### Presence of risk factors in the study sample

In the study sample ($n$ = 60), patients aged 40-65 years, a predominance of 50 to 60 years was observed, for a calculated median of 54 ± 7 years of age. From the total number of patients, 38 (63%) had a family history: 27 (45%) of urogenital tract infections (UTIs) and 11 (18%) of sexually transmitted infections (STIs), eight (13%) of cancer, and six (10%) of obesity.

On the other hand, 24 (40%) of the patients had PH of UTIs, 10 (17%) of cancer, five (13%) of STIs, and five (13%) of obesity. Among other risk factors, 18 (30%) consume alcohol, 14 (23%) tobacco, and 10 (17%) coffee. Furthermore, the risk of occupational exposure was found in 31 (52%) cases: nine (15%) to radiation, nine (15%) to toxic gases, five (8%) to chemicals, and eight (13%) to biological agents.

### Concentration levels of total PSA in the study sample

It is noteworthy that before quantifying PSA serum levels, patients were subjected to other types of laboratory tests including biopsy. From the 60 inpatients, 23 (38%) underwent DRE, 33 (55%) TU and four (6%) biopsies. This demonstrates nonconformity with the protocol to be followed in the diagnosis of prostate carcinoma, in which the quantification of PSA and DRE must be performed prior to TU and biopsy.

In **Figure 1**, the highest number of these cases presented a mean PSA > 4 ng/ml for a calculated mean of 5.77 ± 13.92 ng/ml, where the standard deviation (SD) value indicates high individual variability, so a median of 1.75 ng/ml was taken as the central trend measure (Figure 1). Using a cut-off value of 1.75 ng/ml for PSA, 37 (62%) patients were classified with baseline levels (0.0-2.5 ng/ml), 19 (32%) slightly elevated (2.6-10 ng/ml), four (6%) moderate to considerably high (19.9 ng/ml and 20 ng/ml, respectively) (**Figure 2**).

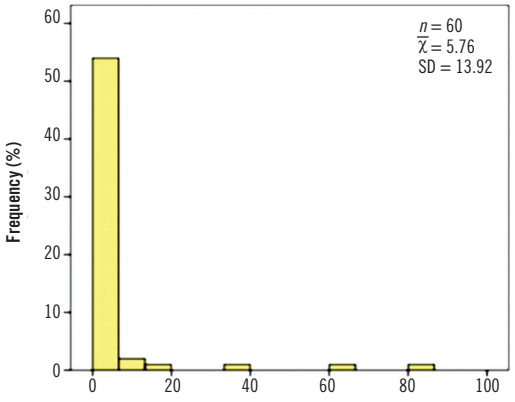


FIGURE 1 – *Patient distribution histogram according to PSA for a cut-off value of 4 ng/ml*

*Source: Chemiluminometric quantifications of PSA.*

*PSA: prostate-specific antigen; SD: standard deviation.*

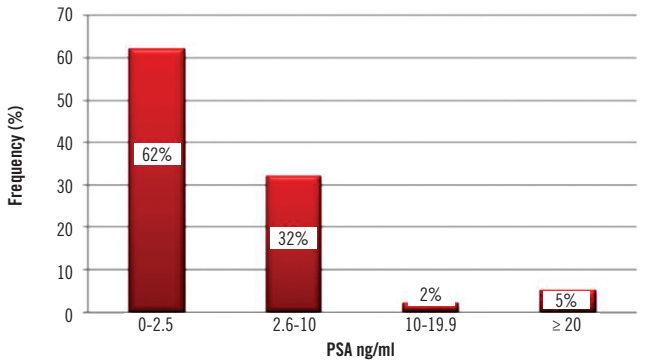


**FIGURE 2 –** *Distribution of patients according to the stratification of serum levels of the PSA categorized as basal, slightly moderate and considerably high*

*PSA: prostate-specific antigen; SD: standard deviation.*

In **Figure 3**, we present diagram box and whisker plot of the comparison of PSA versus DRE, TU, and biopsy, with a very significant Kruskal-Wallis hypothesis test ($p < 0.001$), which indicates that, at least in one of the groups of previous examinations, the antigen presents a different distribution. Therefore, it is observed that the highest values of PSA were located in the "Biopsy" group; although, it was precisely in this group that the greatest dispersion of the antigen values was found (Figure 3).

On the other hand, the Mann-Whitney *U* test with the Bonferroni correction was significant ($p < 0.017$). A similar result was found in the bivariate comparisons of previous and post-quantification tests of the PSA, the differences were very significant ($p = 0.001$) for TU versus DRE; TU versus biopsies ($p = 0.001$).

## Relationship between levels of PSA and risk factors for PCa

### *Distribution of patients by age and [PSA]*

In 25 (42%) patients the PSA was above the cut-off values by age group. It is noteworthy that four (13%) cases in the 50-63-year-old age group presented PSA > 10 ng/ml (19.5 ng/ml, 63.6 ng/ml, 36.6 ng/ml; 84.4 ng/ml) indicating that there is an association between the increase of antigen levels with tumor volume and age of patients.

### *Statistical analysis of the association between PSA and FH*

In the evaluation of the association between PSA versus FH, the Independence Test by Chi-square of contingency tables was used, to contrast the null hypothesis that supports: "two qualitative variables are not associated", applying the categorization of PSA values: 0.0-2.5 ng/ml; 2.6-10 ng/ml; 10.1 ng/ml, and 20 ng/ml.

Low values of PSA were observed in 26 (43%) patients with FH of STIs and slightly elevated in 12 (20%) with FH of UTIs (**Figure 4**).

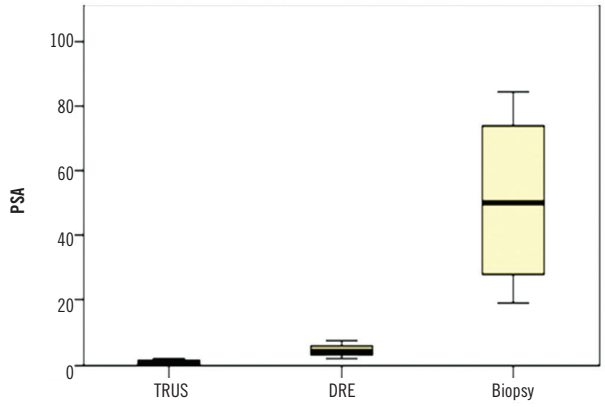


**FIGURE 3 –** *Box and whiskers diagram of the distribution of the serum variable PSA in each group of patients undergoing previous examinations*

*PSA: prostate-specific antigen; TRUS: trans-rectal ultrasound guided; DRE: digital rectal examination.*

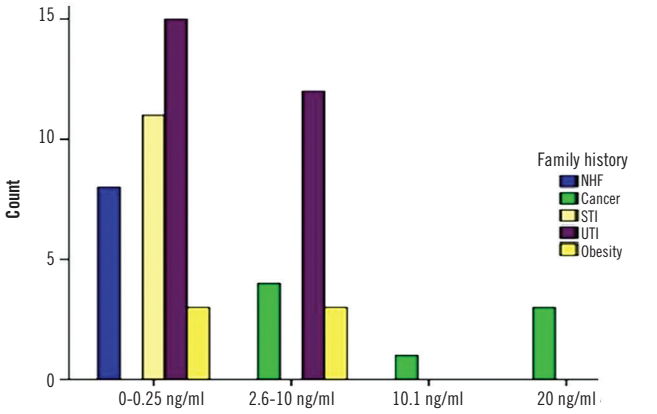


**FIGURE 4 –** *Histogram of distribution of concentration levels of the PSA according to the family's pathological history*

*PSA: prostate-specific antigen; STI: sexually transmitted infections; UTI: urogenital tract infections.*

According to the results of the Chi-square test, there is a significant association ($p < 0.05$) between the PSA serum concentration and patient's FH ($p = 0.001$), suggesting the influence of the family history in the distribution of PSA values. A similar result was found in the analysis of PSA versus PH, in which the Pearson Chi-square test was markedly significant ($p = 0.001$), confirming that there is a significant association between PSA and PH in the sample of patients studied.

### Association between PSA and toxic habits

In the comparison of PSA versus toxic habits, the Chi-square Pearson test was very significant ($p = 0.001$), so it can be assured that there are association between an increase of PSA serum levels and toxic habits.

### Association between PSA and occupational risk exposure

In the analysis of the association between PSA serum versus working exposure to risk factors, the Pearson Chi-square test was significant ($p = 0.001$), which suggests that there is a significant association of PSA with occupational exposure.

It is noteworthy that in five (50%) of the 10 radiation-exposed patients, the PSA was > 4 ng/ml (5.9 ng/ml, 5.3 ng/ml, 63.6 ng/ml, 6.9 ng/ml, and 19.3 ng/ml), and out of the five (8%) exposed to chemical agents, only two had very high PSA value (84.4 ng/ml and 36.6 ng/ml). On the other hand, from the nine (15%) cases exposed to toxic gases, in five the PSA was 4.1-6.3 ng/ml, classified as slightly elevated.

## DISCUSSION

PCa is the most frequent neoplasm and the second cause of death of the male population in the United States[1, 3]. At the global level, the incidence and mortality rate shows great variability among countries[2, 4-7]. The United States in 2014 recorded 172,258 new cases and 28,343 deaths from PCa[3]. On the other hand, it has been estimated for 2018 around 1735,350 new cases and 609,640 cancer deaths in the United States. It draws attention as 19% (164,690) of new cases and 9% (29,430) of deaths is due to PCa[28].

The high prevalence and mortality rate of PCa in the male population in Latin America and the Caribbean is attributed to the irregularity of screening policies and the absence of indicative symptoms during the early stages of tumor development[7]. Conditions influence the progressive evolution of tumor cells so that when the patient comes for medical examination with a urological problem, the tumor is at an advanced stage that limits the options of effective therapy and increases the risk of mortality.

In the multicenter study of 63,926 men with no symptoms of prostate alterations, by Gelpi *et al*. in 2010[24], PSA cut-off values were established by age group, which demonstrated the effect of the age factor on the variations of the circulating levels of the protein. In the study sample, patients older than 50 years were predominant, as well as FH, consumption of toxic substances and occupational exposure to physical, chemical and biological agents, are risk factors for prostate pathological changes[1].

Although DRE and PSA have been shown to be effective in the diagnosis of prostatitis and PCa, there are controversial criteria for the semiological value of the protein, which is attributed to the cut-off value (≤ 4 ng/ml) of clinical laboratories. As the value of ≤ 4 ng/ml does not allow, to assure the absence of pathological alteration of the prostate, as has been demonstrated by other studies[26-28], for the comparison of the variations of PSA versus other risk indicators for PCa, the median calculated by age group was used.

In the statistical processing of the PSA values versus the qualitative variables (age, FH, PH, toxic consumption, and occupational exposure) by the non-parametric Chi-square test for contingency tables, a very significant association was found ($p < 0.001$) of PSA with FH, PH, toxic habits and occupational risk exposure, which allows us to assure, with 99% confidence, that there are association relationships between these pairs of variables. In the comparison of the PSA quantitative variable against the results of DRE, TU and biopsy, the Kruskal-Wallis test was significant ($p < 0.05$), indicating that the antigen levels are different in at least one of the groups; while the results of the Mann-Whitney *U* test do not differ from that observed by other investigators since it confirmed that there is an influence of FH and exogenous risk factors on the development of PCa.

## CONCLUSION

The high association ratio found between PSA versus age and other risk factors could be used as a predictive value for Pca or other prostate disorders.

## REFERENCES

1. Cancer Statistics Working Group. United States Cancer Statistics: 1999-2014 incidence and mortality web-based report. CDC and Prevention, and NCI. 2017. Available at: http://www.cdc.gov/uscs.

2. Jemal A, Bray F, Center MM, et al. Cancer statistics. CA Cancer J Clin. 2011 Mar-Apr; 61(2): 134.

3. Centros para el Control y la Prevención de Enfermedades e Instituto Nacional del Cáncer; 2017. Available at: http://www.cdc.gov/uscs.

4. Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol. 2012; 61: 1079-92.

5. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v 1.0. Cancer incidence and mortality worldwide. IARC Cancer Base, no. 11 Franc. Available at: http://globocan.iarc.fr.

6. Wong MC, Goggins WB, Wang HH, et al. Global incidence and mortality for prostate cancer: analysis of temporal patterns and trends in 36 countries. Eur Urol. 2016 Nov; 70(5): 862-74. doi: 10.1016/j.eururo.2016.05.043. Epub 2016.

7. Pow-Sang M, Destefano V, Astigueta JC, et al. Cáncer de próstata en Latinoamérica. Actas Urol Esp. 2009; 33(10): 1057-61. Available at: www.elsevier.es/actasuro.

8. Organización Panamericana de la Salud. PAO/WHO. Salud en las Américas 2007. Available at: http://www.paho.org/spanish/dd/ais/coredata.htm.

9. Ministerio de Salud de Costa Rica. Estadística de Cáncer. Registro Nacional de Tumores; 2014.

10. Sociedad de Lucha Contra el Cáncer (SOLCA) Ecuador. Registro de tumores en hombres; 2010. SOLCA 2014.

11. Steinberg GD, Carter BS, Beaty TH, et al. Family history and the risk of prostate cancer. Prostate 1990; 17(4): 337-47.

12. Patel AR, Klein EA. Risk factors for prostate cancer. Nat Clin Pract Urol. 2009; 6: 87-95. Doi: 10.1038/ncpuro1290.

13. Fernández L, Galán Y, Jiménez R, et al. Estudio de casos y controles sobre factores de riesgo de cáncer de próstata. Rev Cub Salud Pública 2005; 31(3). ISSN 1561-3127.

14. Ferrís-i-Tortajada J, Berbel-Tornero O, García-Castell J, et al. Factores de riesgo ambientales no dietéticos en el cáncer de próstata. Actas Urol Esp Elsevier. 2011; 35(5): 289-95.

15. Ortiz-Arrazola GL, Reyes-Aguilar A, Grajales-Alonso I, et al. Identificación de factores de riesgo para cáncer de próstata. Enferm Univ. 2013; 10(1): 3-7. Available at: www.elsevier.es.

16. Fernández L, Galán Y, Jiménez R, et al. Estudio de casos y controles sobre factores de riesgo de cáncer de próstata. Rev Cub Salud Pública 2005; 31(3). Available at: http://bit.ly/XlzLUJ.

17. López Chente-Casado J, Soto-Guzmánb A, Candia-Platab MC, et al. Valor clínico del tacto rectal y el antígeno prostático específico en la detección oportuna del cáncer de próstata en Hermosillo, Sonora. Rev Mex Urol. 2013; 73(6): 299-306.

18. Halpern JA, Oromedia C, Shoag JE, et al. Digital rectal examination as an adjunct to prostate specific antigen in the detection of clinically significant prostate cancer. T J Urol. 2017. Available at: https://doi.org/10.1016/j.juro.2017.10.021.

19. Sadi MV. PSA screening for prostate cancer. Rev Assoc Med Bras. 2017; 63(8): 722-725. Doi: 10.1590/1806-9282.63.08.72.

20. Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test, a review of current evidence. JAMA. 2014; 311(11): 1143-9.

21. Navio Paredes F, Fajardo Alfaro W. Comparacion entre tacto rectal y antígeno prostático específico, con biopsia en cáncer de próstata, Hospital dos de Mayo: 2007-2016. Rev Med Carriónica. 2017; 4(1): 83-102.

22. Stacy L. Evidence-based versus personalized prostate cancer screening: using baseline prostate-specific antigen measurements to individualize screening. J Clin Oncol. 2016; 34(23): 2684-6. Doi: 10.1200/JCO.2016.68.2138.

23. Cabarkapa S, Perera M, Mc Grath S, et al. Prostate cancer screening with prostate-specific antigen: a guide to the guidelines. Prostate Int. 2016; 4: 125-9. Available at: https://doi.org/10.1016/j.prnil.2016.09.002.

24. Gelpi-Méndez JA, Gómez-Fernández E, Martín-Barallat J, et al. Valores de referencia del antígeno prostático específico (PSA) en 63 926 trabajadores sin síntomas prostáticos que participaron en el cribado de cáncer de próstata desarrollado por la Sociedad de Prevención de Ibermutuamur durante el año 2006. Acta Urol Esp. 2010; 34(8): 669-76. Available at: www.elsevier.es/acuro.

25. Shoag J, Halpern JA, Lee DJ, et al. Decline in prostate cancer screening by primary care physicians: an analysis of trends in the use of digital rectal examination and prostate specific antigen testing. J Urol 2016; 196: 1047.

26. Choi SK, Song C, Shim M, et al. Prevlence of high-grade or insignificant prostate cancer in Korean men with prostate-specific antigen levels of 3.0-4.0 ng/ml. J Urol. 2015; 85(3): 610-5. Doi: 10.1016.

27. Díaz S, Salirrosas M. Cáncer de próstata metastásico asociado a valores bajos de antígeno prostático específico. Reporte de caso. Rev Peru Med Exp Salud Públ. 2012; 29(4): 541-4.

28. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68: 7-30.

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