Brief communication

Prostate-Specific Antigen (PSA) screening for Prostate Cancer (PCa): Main recommendations

Detección de antígeno prostático específico (PSA) para el cáncer de próstata (CaP): recomendaciones principales

Laura Pérez,[1] Herney Andrés García-Perdomo.[1,2]

Abstract

Prostate cancer is the most frequent type of cancer diagnosed in men and is the second cause of cancer death in the United States. The widespread use of Prostate-Specific Antigen since the early 1990s has significantly increased its incidence. However, screening for prostate cancer remains one of the most controversial topics in the urologic literature. The latest clinical evidence suggests that screening does not affect all-cause mortality and has only a small effect on prostate-specific mortality. At the same time, there are risks associated with biopsy and prostate cancer treatment, such as urinary incontinence, infection, and erectile dysfunction. Current recommendations propose shared decision-making with the patient but differ, with respect to the appropriate ages for screening, as well as follow-up screening intervals.

Keywords: Prostate, Cancer, Prostate-specific antigen, Screening.

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Correspondence author:
* Herney García-Perdomo. Address: Cll 4B # 36-00, Cali, Colombia. Email: herney.garcia@correounivalle.edu.co

[1] UROGIV Research Group. School of Medicine. Universidad del Valle. Cali, Colombia
[2] Division of Urology. Department of Surgery. School of Medicine. Universidad del Valle. Cali, Colombia

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Resumen

El cáncer de próstata es el tipo de cáncer más frecuente diagnosticado en los hombres. Específicamente en Estados Unidos, corresponde a la segunda causa de muerte por cáncer. El uso generalizado de antígeno prostático específico desde principios de la década de 1990 ha aumentado significativamente su incidencia. Sin embargo, el cribado del cáncer de próstata sigue siendo uno de los temas más controvertidos en la literatura urológica. La evidencia científica más reciente sugiere que el cribado no afecta la mortalidad por todas las causas y solo un pequeño efecto en la mortalidad específica de la próstata. Al mismo tiempo, existen riesgos asociados con la biopsia y el tratamiento del cáncer de próstata, como incontinencia urinaria, infección y disfunción eréctil. Las recomendaciones actuales proponen la toma de decisiones compartida con los hombres, aunque existen diferencias notables, especialmente en lo que respecta a las edades adecuadas de detección y los intervalos de seguimiento.

Palabras clave:
Próstata, cáncer, antígeno prostático específico, tamizaje.

Introduction

Prostate cancer is the most frequent solid cancer in men worldwide, which imposes a significant burden on health systems. Screening is one of the most controversial topics in the urologic literature due to uncertainty as to its benefits. On the one hand, there is data that suggest that early detection implies lower cancer mortality rates. At the same time, there are discouraging texts that state it is likely to result in unnecessary biopsies because of the number of false positive results of Prostate-Specific Antigen (PSA), implying a significantly increased risk of adverse events derived from the procedure or the treatment. The present review aimed to describe the latest clinical evidence on Prostate Cancer (PCa) screening.

Epidemiology of Prostate Cancer

According to the 2018 GLOBOCAN project, prostate cancer is the most frequently diagnosed cancer in 105 countries and is the fifth leading cause of cancer death in men. Particularly in the Sub-Saharan African countries and the Caribbean, it is the leading cause of cancer death in men. Its incidence in 2018 was 1,276,106 worldwide, accounting for 13.5% of all cancers in men, with 358,989 registered deaths, representing 3.8% of total cases.[1] In the United States, the estimated cancer statistics for 2020 are 191,930 new cases of prostate cancer, accounting for more than one in five new diagnoses.

Since the early 1990s, incidence has significantly increased. Accordingly, there has been a surge in the detection of asymptomatic disease

due to widespread PSA testing, but it has stabilized in recent years. In the US, prostate cancer remains the second cause of cancer death, only after lung cancer. Nevertheless, it has the highest 5-year survival rate of all cancers, for all stages combined.[2]

African Americans have the highest incidence and mortality rates. The risk of prostate cancer is 60% higher in that population than in Whites, and the mortality rate is twice as high, most likely due to social aspects, such as limited access to healthcare, and to genetic characteristics. Different genes with SNPs are implicated in increasing susceptibility to prostate cancer in African American men.[3]

Regionally, according to the 2012-2016 population cancer register in the city of Cali, Colombia, the annual incidence rate was 53.4 per 100,000 inhabitants. For 2014-2018, deaths were estimated at 17.5 per 100,000. The 5-year survival rate improved during the period of 2000-2004. However, rates stagnated in the 2005-2009 period. In addition, 5-year survival rates are 20 to 30 points below those observed in North America and Europe.[4]

Natural History of Prostate Cancer

In many cases, prostate cancer does not become clinically evident, and men with the disease have died of other causes. A systematic review published in 2015, included 29 studies that reported the incidental finding of prostate cancer in autopsies performed in men that died of other causes and found that the prevalence of prostate cancer increased with age, from 5% at <30 years of age, to 59% at >79 years of age.[5]

Surveillance also depends on the stage at diagnosis. The 5-year relative survival rate for localized and regional stages, calculated for men diagnosed with prostate cancer between 2000-2015, is nearly 100%, whereas it is calculated at 30-50% for distant disease.[6]

History of Prostate-Specific Antigen

PSA is a protease belonging to the kallikrein family. It is secreted by epithelial cells and is also present in prostate cancer cells. Its function is to digest the gel formed by semenogelins after ejaculation, which explains why PSA serum levels are higher in prostate cancer.[7]

It was first discovered in 1966 in semen, when Mitsuwo Hara, a Japanese forensic scientist, described the protein and suggested it could be used as a forensic tool in rape cases. Later, a study in 1979 by Ming C. Wang et al. characterized PSA, suggesting it had potential clinical applications in the detection of prostate cancer. However, not until the 1990s, was it used to follow patients already known to have the disease. That concept was based on the presence of elevated PSA in patients with benign prostate hyperplasia, prostatitis, and in some cases, low or normal PSA in patients with prostate cancer.[8]

The PSA blood test as the first-line screening tool was approved by the Food and Drug Administration (FDA) in the early 1990s. PSA derivatives (PSA velocity, PSA density, and the free-to-total PSA ratio) were also approved.

The 4.0 ng/ml limit for normal PSA levels, was first proposed in a 1986 study on a small population. Later, in 1991, a more extensive study led to FDA approval, when the efficacy of the cutoff for the 50-54 age group was assessed. Consequently, the limit of > 4.0 ng/ml was settled on for recommending biopsy.[9]

The FDA also approved other PSA derivatives, such as PSA velocity, with a cutoff of ~0.35–0.40 ng/ml/year, associated with a higher risk of PCa and aggressiveness; PSA density (PSA/total prostate volume), which evaluates the risk of clinically significant PCa with a result >0.10–0.15 ng/ml/cc; and free-to-total PSA <10%, signifying a 50% higher chance of the presence of PCa in biopsy results.[10]

Prostate-Specific Antigen Screening: benefits and harms

Screening is defined as the presumptive identification of an unrecognized disease in an asymptomatic population, using tests, examinations, or procedures than can be easily applied.[11] For a prostate cancer screening test to be valuable, it must reduce morbidity and mortality, by identifying cases in an early stage, when treatment can be more effective. It should also identify risk factors that increase the probability of developing the disease.[12]

As mentioned before, due to the widespread use of PSA screening, the incidence of prostate cancer has increased sharply. At the same time, mortality has declined, and incidence related to metastatic stage has significantly decreased in the past three decades. However, in some cases, increasing the detection of the disease can lead to subjecting the patient to the risks associated with treatment, and may not prolong life.

According to the ERSCP study, employing a PSA threshold of 3.0 ng/ml, for every 1000 men screened between 55 to 69 years of age, 720 will have a negative test.

Follow-up testing will not identify prostate cancer, and of the patients that undergo biopsy, four will have complications that require hospitalization. Out of 1000 men, 102 will be diagnosed with prostate cancer, but 33 of them will not become ill or die from the disease. Five men will die from prostate cancer, despite the screening.[13]

The rate of complications associated with biopsy is about 2%, of which 0.8% are infectious complications.[14] Other complications include pain, bleeding, and urinary obstruction but it does not increase mortality. Additionally, no PSA threshold completely excludes prostate cancer, as shown in Table 1.[15]

Table 1. Risk of prostate cancer based on PSA value

PSA levels	Risk of prostate cancer
0-0.5 ng/ml	6.6%
0.6-1 ng/ml	10.1%
1.1-2 ng/ml	17.0%
2.1-3 ng/ml	23.9%
3.1-4 ng/ml	26.9%

A recent meta-analysis that included five randomized controlled trials, comparing PSA screening with usual care in men not diagnosed with prostate cancer, showed that prostate cancer screening does not decrease all-cause mortality. It may have only a small effect on prostate-specific mortality, signifying one less death from prostate cancer per 1000 men screened over ten years.[16]

Current recommendations about prostate cancer screening

We now describe the latest guideline recommendations, which still differ in many aspects, although they all emphasize shared decision-making and screening in well-informed men.

The final recommendations of the United States Preventive Services Task Force (USPSTF), published in May of 2018, are that men 55 to 69 years of age should make their own decisions about whether to be screened or not (a level C recommendation) and men 70 years of age and older should not undergo routine screening.[17]

In addition to discussing the risks and benefits of prostate cancer screening, the European Association of Urology (EAU) recommends no screening in men with a life expectancy below 10-15 years. Individual risk considerations are included, such as a family history of PCa and being African American. For those cases, the recommendation is to screen at >45 years of age, whereas screening in other men would be at 50 years of age. For the follow-up, the cutoff value for PSA established by the EAU is > 1 ng/ml at 40 years of age and 2 ng/ml at 60 years of age, with intervals of two years for those initially at risk, and eight years for those at no risk.[18]

The American Urological Association (AUA) recommends that screening in men at average risk of PCa be carried out at between 55 and 69 years of age but recommends no routine PSA screening in men over 70 years of age or in men with a life expectancy below 10-15 years. However, men over 70 years of age, that are in excellent health, may benefit from screening. Follow-up screening intervals are preferred every two years or more, rather than annually, to reduce the harms of screening.[19]

Finally, the National Comprehensive Cancer Network (NCCN) proposes shared decision-making at age 40 for men with known BRCA1-2 mutations and for African American men, with annual follow-up. For men at average risk, the recommendation is to start testing at age 45 and stop at age 75, unless there is little or no comorbidity in very healthy men, in whom testing should be repeated every 1-4 years, if the PSA level is <4ng/ml. Follow-up intervals are different in men between 45-75 years of age. For those with a PSA result <1ng/ml, the interval is 2-4 years, whereas in men with a PSA level of 1-3ng/ml, testing should be repeated in 1-2 years (Table 2).[20]

Table 2. International guideline recommendations for prostate cancer screening

Guideline	Screening ages for men at average risk	Screening ages for men at increased risk	Follow-up
USPSTF	55-69 years of age	No specific age	-
EAU	>50 years of age - patients with life expectancy >10-15 years	>45 years	If PSA <1ng/ml and 2ng/ml at the ages of 40 and 60, respectively: 8 years. If PSA > 1ng/ml and 2ng/ml at the ages of 40 and 60, respectively: 2 years.
AUA	55-69 years of age or >70 years of age, who are in excellent health	No specific recommendations	Two years or more. Should be individualized by a baseline PSA level.
NCCN	45-75 years of age and >75 years of age, only in men in excellent health, with little or no comorbidity	>40 years	Men with increased risk: annual Men with average risk, 45-75 years of age: If PSA is <1ng/ml: 2-4 years If PSA is 1-3ng/ml: 1-2 years Men at average risk >75 years of age: 1-4 years.

Conclusions

Prostate cancer screening continues to be a very controversial issue due to the lack of evidence supporting a decrease in morbidity and mortality. However, it is a public health problem, as it is the second cause of cancer death in the United States, and the most common cancer diagnosed in men worldwide.

There are still many differences between current guideline recommendations, especially with respect to patient ages for screening and whether risk factors should be taken into account for earlier screening. However, what the guidelines all have in common is that men undergoing screening must be well-informed, which means physicians must have sufficient knowledge about screening risks and benefits, to be able to discuss those issues with their patients.

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References

1. **Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A.** Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.
2. **Siegel RL, Miller KD, Jemal A.** Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30. https://doi.org/10.3322/caac.21590.
3. **Shenoy D, Packianathan S, Chen AM, Vijayakumar S.** Do African-American men need separate prostate cancer screening guidelines? BMC Urol [Internet]. 2016;16(1):1–6. http://dx.doi.org/10.1186/s12894-016-0137-7
4. **Bravo LE, Muñoz N.** Epidemiology of cancer in Colombia. Colomb Med. 2018;49(1):09–12. https://dx.doi.org/10.25100%2Fcm.v49i1.3877.
5. **Bell KJL, Del Mar C, Wright G, Dickinson J, Glasziou P.** Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer. 2015;137(7):1749–57. https://doi.org/10.1002/ijc.29538.
6. **Howlader N. SEER Cancer Statistics Review 1975-2017.** Natl Cancer Inst [Internet]. 2019;2000–16. https://seer.cancer.gov/csr/1975_2016/
7. **Schröder FH.** Biomarkers and screening for prostate cancer. Ann Oncol. 2006;17(SUPPL. 10). https://doi.org/10.1093/annonc/mdl260.
8. **Catalona WJ.** History of the discovery and clinical translation of prostate-specific antigen. Asian J Urol [Internet]. 2014;1(1):12–4. http://dx.doi.org/10.1016/j.ajur.2014.09.008
9. **De Angelis G, Rittenhouse HG, Mikolajczyk SD, Blair Shamel L, Semjonow A.** Twenty Years of PSA: From Prostate Antigen to Tumor Marker. Rev Urol [Internet]. 2007;9(3):113–23.
10. **Catalona WJ.** Prostate Cancer Screening. Med Clin North Am. 2018;102(2):199–214. https://doi.org/10.1016/j.mcna.2017.11.001.
11. **Sikora K.** Cancer screening. Medicine (Baltimore). 2012;40(1):24–8.
12. **Harman LB, Flite CA, Bond K.** State of the Art and Science. Electronic Health Records: Privacy, Confidentiality, and Security. Am Med Assoc J Ethics. 2012;14(9):712–9. https://doi.org/10.1001/virtualmentor.2012.14.9.stas1-1209.

13. **Care CTF on PH.** Benefits and Harms of PSA Screening. 2014;1. Available from: https://fmf.cfpc.ca/wp-content/uploads/2016/10/S134408_Using-1000-Person-Infographics-to-Improve-Risk-Communication-with-Patients-in-Preventive-Health-Screening.pdf
14. **Pinsky PF, Parnes HL, Andriole G.** Mortality and Complications Following Prostate Biopsy in the PLCO Cancer Screening Trial. Bju. 2014;113(2):254–9. https://dx.doi.org/10.1111%2Fbju.12368.
15. **Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al.** Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004 May 27;350(22):2239–46. doi: https://doi.org/10.1056/nejmoa031918.
16. **Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, et al.** Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ. 2018 Sep 5;362:k3519. doi: https://doi.org/10.1136/bmj.k3519.
17. **Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, et al.** Screening for prostate cancer USPreventive servicestaskforcerecommendation statement. JAMA - J Am Med Assoc. 2018;319(18):1901–13. https://doi.org/10.1001/jama.2018.3710.
18. **N. Mottet van den B, E. Briers PC, J. Grummet, Henry De Santis FG, H van der Kwast, H van der Poel T Lam M, Tilki TWOR, Guidelines Associates: T. Van den Broeck MC, et al.** EAU - EANM - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer 2019. Eur Assoc Urol Guidel 2019 [Internet]. 2019;53:1–161. Available from: https://uroweb.org/guideline/prostate-cancer
19. **Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al.** Early Detection Of Prostate Cancer: AUA Guideline. Am Urol Assoc Clin Guidel. 2018;1–27. https://doi.org/10.1016/j.juro.2013.04.119.
20. **Peter R. Carroll, J. Kellog Parsons, Gerald Andriole, Robert R.** Bahnson, Sigrid Carlsson EPC. Prostate Cancer Early Detection. National Comprehensive Cancer Network; 2019.