Advances in Medicine and Engineering Interdisciplinary Research, 2024, Volume 2, Issue 3
DOI: 10.32629/ameir.v2i3.2609
ISSN Online: 2972-3825
ISSN Print: 2972-3833

Early Detection for Prostate Cancer: An Update

Pablo A. Rojas[1, 2], Benjamín García-Bloj[3, 4], Enrique Elias[1], Fernando Marchant[1, 5*]

1. Department of Urology, Clínica Las Condes, Santiago, Chile.
2. Urology Service, Complejo Asistencial Hospital Sótero del Río, Santiago, Chile.
3. Cancer Center, Clínica Las Condes, Santiago, Chile.
4. Center for Precision Oncology, Faculty of Medicine and Health Sciences, Universidad Mayor, Santiago, Chile.
5. Department of Urology, Hospital Clínico Universidad de Chile, Santiago, Chile.
*Corresponding author. Email address: fmarchant@clinicalascondes.cl

Abstract: Prostate cancer (PCa) is the most frequent cancer in men in Chile, ranking fourth with regards to mortality according to the latest GLOBOCAN 2022 statistics. The objective of this review is to clarify what methods exist for preventing PCa, as well as updating screening recommendations based on the latest available evidence. Numerous risk factors have been described for PCa, including modifiable factors such as age, race, and family history. In this context, the importance of PCa screening is heightened. Despite certain controversy regarding the usefulness of prostate-specific antigen (PSA), screening has demonstrated that it increases the diagnosis of PCa in early stages, reducing mortality by up to 30%. The objective of this review is to provide commentary on the known risk factors for PCa and the usefulness of PCa screening, considering the use of new tools such as magnetic resonance imaging (MRI) in the diagnosis of the disease.

Key words: prostate cancer; cancer screening; risk factors

1. Introduction

Prostate cancer (PCa) is currently the second most frequent cancer in men worldwide and ranks eighth in cancer mortality [1]. In Chile, according to the latest GLOBOCAN statistics in 2022, PCa is the most frequent cancer, with 9,678 new cases diagnosed in 2022, surpassing colorectal cancer and gastric cancer. Moreover, it is currently the fourth leading cause of cancer death in Chile, with 2,703 deaths in 2022 [2]. According to the statistics described, it is essential to identify risk factors for PCa and to propose an efficient screening method. Since the introduction of prostate-specific antigen (PSA) in the 1980s [3], its usefulness has been widely debated, despite the fact that the first statistics showed an 80% decrease in advanced PCa, with a 40% decrease in mortality [4]. The discussion regarding the usefulness of PSA screening is based on the possible overdiagnosis of less aggressive cancers, which could only be observed. The aim of the present review is to comment on the known risk factors for PCa and to clarify the usefulness of PCa screening, considering the use of new tools such as magnetic resonance imaging in the diagnosis of the disease.

2. Risk factors of Prostate Cancer

2.1 Modifiable risk factors

Historically, sedentary lifestyle and a diet with a high inflammatory index (rich in saturated fats and high in glycemic carbohydrates and red meat) [5] have been mentioned as risk factors for PCa. However, the evidence is weak and most of the associations have been found only in population-based studies [6]. In particular, obesity is not associated with an

increased risk, but if the patient is diagnosed with PCa, the risk of a more aggressive disease increases [7]. In addition, attempts have been made to establish a relationship between various diseases (such as infertility, prostatitis, autoimmune diseases, periodontitis, inflammatory bowel disease, metabolic syndrome, among others) and PCa; however, the evidence is mixed and inconclusive [5], so it is not possible to make recommendations regarding diet or lifestyle changes as prevention of PCa [8]. On the other hand, smoking has been mentioned as a risk factor for PCa. However, the only available evidence proposes that in a patient diagnosed with PCa, smoking is usually more lethal, with a relative risk of 1.42 compared to non-smokers [6]. Associations with the number of monthly ejaculations and marital status have also been described [6]. However, according to the available evidence, there is no real recommendation to prevent PCa.

2.2 Non-modifiable risk factors

Age is the main risk factor for PCa. The probability of cancer increases from approximately 2% after the age of sixty years to 9% in men over 70 years [9]. Autopsy studies of men who have died of other causes show that up to 70% of men over 70 years of age have PCa [10].

Black race is a known factor in PCa. African-American men have 1.7 times the risk of developing PCa than white men, and if they are diagnosed with cancer, they have 2.1 times the risk of dying from PCa [9]. According to a recent review, the differences in PCa between white and black men can be explained by different biological mechanisms (both genetic differences and differences in the tumor microenvironment, among others) in addition to socioeconomic factors (such as access to education) [11]. Currently, in Chile, demographic changes secondary to immigration make early screening essential to avoid the presentation of more aggressive PCa.

The third proven risk factor is family history [12]. The risk of siblings and children of patients diagnosed with PCa is 2.5 times that of the former [13]. Specifically, the relative risk of cancer for first-degree relatives with PCa is 1.8. In the case of a father and brother history, this risk increases to 5.5, and in the case of two brothers with PCa, this risk increases to 7.7.

2.3 Hereditary prostate cancer

Hereditary PCa, i.e. associated with genetic mutations, is becoming increasingly common, as advances in science and knowledge of the disease allow us to diagnose these patients to a greater extent. Precision medicine, which promotes a personalized approach to cancer treatment, has amplified the clinical relevance of genetic sequencing technologies in prostate cancer, both at the germline and somatic levels. In patients with metastatic disease, pathogenic germline mutations can be identified in up to 15% of cases [15]. In the non-metastatic setting, this figure ranges from 5-7% [12, 16]. Identifying these variants can lead to therapeutic adjustments and provide a more accurate prognosis of disease progression, in addition to assessing oncologic risk in family members for timely prevention.

Germline genetic evaluation provides guidance on the mechanisms and etiology of the carcinogenic process, especially in young patients, and points to a predisposition to the early development of neoplasms in healthy relatives [17]. The genes most frequently associated with hereditary PCa are linked to DNA repair. BRCA2 and HOXB13 stand out for their direct association; in particular, HOXB13 is associated with a significantly elevated risk of up to 8 times higher than the general population for early manifestation of this pathology [18]. On the other hand, BRCA2, together with BRCA1, ATM, PALB2, RAD51C and RAD51D, have an evident correlation with favorable responses to targeted therapies, such as PARP inhibitors [19]. In addition, genes linked to Lynch syndrome (MLH1, MSH2, MSH6, PMS2 and deletions in EPCAM) play critical roles in mismatch DNA repair [20]. Importantly, these mutations not only increase the risk of PCa, but also predispose to other cancers, such as those associated with BRCA1 and BRCA2, and high-risk tumors in Lynch syndrome patients [21].

Before proceeding with genetic testing, it is imperative to discuss with the patient the goals, benefits, risks, and family implications of the test [22]. Legal protections against genetic discrimination should also be addressed. This evaluation, ideally, should be facilitated by genetic counselors, who can provide detailed patient education, support in the genetic screening process, and assist in identifying carriers among family members [23].

Particularly, germline genetic testing is recommended for patients with metastatic prostate cancer, for those with localized high-risk cancer with a Gleason score ≥7, and for individuals with a family history of associated cancers or who have been diagnosed at a young age [24].

Finally, it is pertinent to note that the overall lifetime risk of developing prostate cancer is approximately 12.9%, according to the SEER program of the US National Cancer Institute [25]. This risk increases significantly in carriers of germline mutations, depending on the gene affected [26]. Identification and appropriate genetic counseling of these individuals is essential for early detection and more effective clinical management [27]. For this reason, international guidelines make some special screening recommendations in patients at risk of hereditary PCa that we will review later.

3. Prostate Cancer Screening Method Recommendation

3.1 PSA screening

Since the beginning of the use of PSA as a screening method, there has been debate regarding its usefulness in preventing mortality from PCa, because there is a risk of overdiagnosis of non-lethal cancers. In general, PCa is classified according to Gleason Grading Groups (GGG) ranging from 1 (previously known as Gleason 3 + 3) to 5 [28]. According to the available literature, GGG = 1 corresponds to a clinically non-significant PCa, as it has no metastatic potential and would explain less than 1% of PCa deaths [29]. It is for this reason that the current goal of screening is to diagnose clinically significant PCa (PCaCS), i.e. with GGG ≥ 2 [30], since treatment of GGG = 1 leads to unnecessary morbidity (impotence, incontinence, among others) [31].

Several studies have explored the usefulness of PSA screening. One of the most important is the multicenter randomized European Randomized Study of Screening for Prostate Cancer (ERSPC), where 162,243 men aged 50-69 years were enrolled, with a median follow-up of 12 years [32] and an update in 2019, with 16 years of follow-up [33]. The study shows an absolute risk decrease of metastatic PCa of 3.1 per 100 thousand randomized men. Thus, with 16 years of follow-up, there is a decrease in the number of cases needed to screen to prevent one death (18 men). On the other hand, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial of 2009 [34], did not demonstrate mortality benefits of PSA screening, recruiting 76,693 men aged 55-74 years.

Given this disparity in the results, a recent systematic review analyzed the most important studies on PCa screening [35], with a total of more than 721,000 patients. The results highlight that PSA screening reduces PCa-specific mortality, but has no effect on overall mortality. In addition, screening increases the diagnosis of early stage PCa (with a relative risk RR of 1.39) and decreases diagnosis in advanced stages (RR 0.85).

Finally, we can analyze the statistics of PCa in the light of the recommendations carried out. The first reports on the usefulness of screening following its emergence in the 1980s showed a decrease in PCa mortality between the years 1992 and 2017, with a drop from 39 to 19 per 100 thousand inhabitants [36] to be attributable attributable 45-70% to PSA according to simulation models [4]. On the other hand, in 2012, the United States Preventive Services Taskforce issued a recommendation against using PSA as screening and doing so only according to patient risk [37]. Subsequently, a 2020 study evaluated the effect of this measure [38]. Thus, according to the US SEER (Surveillance, Epidemiology, and End Results), a decrease in the incidence of PCa, mainly GGG = 1, was demonstrated; however, an increase in the incidence of metastatic PCa was observed, both in men under 74 years of age (increase from 6.2 to 7.1 men per 100,000 population) and

in men over 75 years of age (from 16.8 to 22.6 men per 100,000 population).

According to this evidence, we can conclude that PSA screening for early detection of PCa has been shown to decrease cancer mortality should continue to be performed. This is why the main urological and cancer societies of the world provide their screening recommendations for timely and effective screening.

3.2 International guideline recommendations

3.2.1 European Association of Urology/European Association of Nuclear Medicine/European Association for Radiotherapy and Oncology/European Association of Urogenital Radiology/International Society of Oncological Geriatrics (EUA-EAU-EANM-ESTRO-ESUR-SIOG guidelines) [39].

According to the latest update of the year 2023 of the European guidelines, the first factor to consider is the patient's opinion regarding screening, taking into account the risks and benefits of performing it. Once in agreement with the patient, the indication for screening in patients at risk of PCa considers the performance of PSA in:

- Men over 50 years of age.
- Men over 45 years of age with a family history of PCa.
- Men over 45 years of age with African ancestry.
- Men over 40 years of age who are carriers of BRCA2 mutations.

Screening should be performed with PSA and later with digital rectal examination (DRE) in patients with a life expectancy of more than 15 years, so comorbidities play a preponderant role more than age alone. On the other hand, digital rectal examination alone is not a useful screening tool, due to its low sensitivity (less than 60%).

Men with PSA less than 1 ng/ml at 40 years of age or less than 2 ng/ml at 60 years of age have a very low risk of dying from PCa, so that in patients with no family history, their follow-up could be every 8 years. On the contrary, patients with PSA greater than these cut-off points (greater than 1 ng/ml at 40 years of age or greater than 2 ng/ml at 60 years of age), should be followed up every 2 years. Finally, in patients with PSA between 3 and 10 ng/ml, it is always recommended to repeat the PSA before performing new studies, being recommended to use a risk calculator in patients with PSA outside the normal range or to perform an MRI in the same case.

3.2.2 Guide of the American Urological Association/Society of Urologic Oncology (AUA-SUO guidelines) [30].

The AUA recently published its update on screening and early detection of PCa. Regarding the age at which screening should begin, it is proposed that all men should undergo a PSA test between 45 and 50 years of age. This screening should be started earlier at 40-45 years in men at increased risk, i.e. patients with black ancestry, germline mutations or a family history of PCa.

In addition, it is proposed that screening should be performed only with PSA in the first instance, and in the case of levels greater than 2 ng/ml, digital rectal examination should be performed. Like the European guidelines, they do not recommend digital rectal examination as a screening method. On the other hand, the American guidelines recommend screening every 2 to 4 years in men between 50 and 69 years of age. Like the European guidelines, the recommendation in the event of a suspicious PSA is to repeat the examination before performing new studies. Finally, the guidelines do not recommend considering PSA velocity alone as a useful tool in PCa screening.

3.2.3 National Comprehensive Cancer Network (NCCN) [24]

The NCCN screening guideline is updated annually. In its latest available version, it clarifies that PCa screening increases the detection of all cancers, both indolent and clinically significant prostate cancer (CSCC), and therefore the greatest importance is not to overtreat non-significant tumors. Likewise, it is key to educate the patient to accept screening in an informed manner.

Regarding the age at which screening should begin, the NCCN guidelines recommend starting at 45 years of age. Regarding the screening interval, in men between 45 and 75 years of age, it recommends PSA every 1 to 2 years in patients with PSA between 1 and 3 ng/ml or even every 4 years in patients with PSA less than 1 ng/ml. On the other hand, patients at high risk of PCa (black race, family history and genetic predisposition) should begin screening at 40 years of age with annual follow-up. Even in patients with a family history (several first-degree members with PCa before the age of 60), screening could begin 10 years before the age of diagnosis of the family member with PCa. Like the previously mentioned guidelines, the NCCN recommends repeating the PSA if it is altered before continuing with the study. In addition, it recommends performing digital rectal examination only in patients with elevated PSA and not using it as the sole screening method. Regarding the cut-off point, a PSA greater than 3 ng/ml should trigger further study (or 4 ng/ml in patients older than 75 years). Finally, regarding the age of completion of the screening, it suggests 75 years as a limit; however, in patients older than this age and in very good condition, the test could be performed according to the patient and the medical criteria.

3.3 Digital rectal examination as a screening method

As mentioned, no guidelines currently recommend digital rectal examination as the only screening method. This recommendation finds further justification in a recent systematic review and meta-analysis that includes 8 studies, with more than 85,000 patients in total. The study shows that digital rectal examination in addition to PSA does not improve cancer detection compared to PSA. Thus, PSA is a sufficient screening method on its own, so digital rectal examination should be avoided, as it causes discomfort to the patient, and could be an excuse to avoid screening, delaying early diagnosis [40].

3.4 Usefulness of magnetic resonance imaging in early diagnosis

During the past decades, when faced with clinical suspicion of PCa due to elevated PSA or altered digital rectal examination, systematic prostate biopsy (SPB) was the standard for diagnosis [41]. However, since it is a random sampling of the prostate [42], it achieves a PCa detection rate of only 50% [43]. It is in this context where prostate MRI followed by biopsy targeting suspicious lesions (BpT) emerges as an alternative for the diagnosis of PCaCS, avoiding overdiagnosis and consequent overtreatment of patients with less aggressive tumors. According to the latest evidence, MRI would potentially reduce the number of biopsy procedures by 33% [44]. Despite this, one of the major shortcomings of the previously mentioned screening studies is that none of them includes in the diagnostic flowchart the role of MRI as an adjunct after PSA [35].

MRI categorizes patients with suspected PCa according to the Prostate Imaging Reporting and Data System (PIRADS, categorizing lesions from 1 to 5) reporting that patients with PIRADS 4 and 5 lesions present PCa in 60% and 83%, respectively [45].

When BpT is performed, 38% of patients present PCaCS, compared to BpS, which shows a detection of 26% ($p < 0.05$) [44]. At the same time, a recent study by Ecklund et al. shows that BpT diagnoses less non-significant PCa (4% in this work) compared to BpS (12% of patients) [46]. Tu et al [47], in a meta-analysis of more than 30 publications, showed that the overall detection rates between BpS and BpT are equal (RR 0.98, 95% CI 0.92-1.05). However, BpT detects more PCaCS than BpS alone (RR 1.19, 95% CI 1.10-1.30). In addition, several meta-analyses show that BpT improves PCaCS detection by more than 50% compared to BpS alone [47, 48]. This superiority (of BpT over BpS) occurs both in patients who have never had a biopsy and in patients with a history of previous negative biopsy [49].

At present, most international guidelines (NCCN [24], EUA [39], AUA [49]) recommend performing MRI examinations on patients and newborns with previous biopsies before biopsy, if available. In addition, they also

recommend performing BpT based on the availability of the technology, whether it is transrectal or perineal.

Finally, one of the aspects still under discussion regarding MRI and consequent biopsy is whether we should simply sample the suspicious lesion or perform BpT plus BpS, increasing the number of samples. The PAIREDCAP study [50] demonstrated that BpT plus BpS achieves detection rates above 70%, and that up to 33% of PCaCS could be missed by not using both techniques together [38]. Tu et al. [47] recommend performing BpT and BpS, since omitting BpS would mean missing 11% of PCaCS. In the same line, Adhoot et al. [51] published that the sum of BpS and BpT achieves 10% more PCa diagnosis, of which 28% is ISUP 3 PCa. The EUA guideline strongly recommends performing BpT + BpS [39], while the AUA guideline leaves open the possibility of performing BpS or not [49].

3.5 Biomarkers in the early detection of PCa

A number of biomarkers have now been developed to help establish the need for prostate biopsy in patients with PSA less than 10 ng/ml [52]. The major utility of these markers is that they could reduce the number of prostate biopsies by approximately 35% [53]. However, the use of these markers does not yet achieve sufficient evidence to be categorically recommended as part of the diagnostic algorithm for PCa [24, 30, 39].

The available biomarkers can be divided into markers in blood or urine. In blood, the Prostate Health Index (PHI), IsoPSA and the four-kallikrein (4K) score, among others, stand out. All these blood biomarkers are based on PSA and its isoforms, and are approved by the FDA [39]. In Chile, only the 4K score is available. In urine, the markers prostate cancer antigen 3 (PCA3) and SelectMDx, both based on RNA expression, have been described [39]. In Chile, only SelectMDx is available.

4. Conclusions

PCa is an increasingly frequent pathology with a rising mortality rate in our country. According to the literature, there is insufficient evidence to identify modifiable risk factors. PSA screening reduces cancer mortality, so it should continue to be performed according to the patient's risk, avoiding overtreatment of indolent tumors. Currently, prostate MRI plays a key role in diagnosing clinically significant PCa and its use is recommended prior to prostate biopsy.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] WHO. World Health Organization. International Agency for Research on Cancer. Global Cancer Observatory. Cancer Today. GLOBOCAN 2024. Population fact sheets: World. https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf

[2] WHO. World Health Organization. International Agency for Research on Cancer. Global Cancer Observatory. Cancer Today. GLOBOCAN 2024. Population fact sheets: Chile. https://gco.iarc.who.int/media/globocan/factsheets/populations/152-chile-fact-sheet.pdf

[3] Catalona WJ. History of the discovery and clinical translation of prostate-specific antigen. *Asian J Urol*. 2014;1(1):12-14. doi: 10.1016/j.ajur.2014.09.008

[4] Etzioni R, Tsodikov A, Mariotto A, Szabo A, Falcon S, Wegelin J, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control*. 2008;19(2):175-181. doi: 10.1007/s10552-007-9083-8

[5] Moradi S, Issah A, Mohammadi H, Mirzaei K. Associations between dietary inflammatory index and incidence of breast and prostate cancer: a systematic review and meta-analysis. *Nutrition*. 2018;55-56:168-178. doi: 10.1016/j.nut.2018.04.018

[6] Bergengren O, Pekala KR, Matsoukas K, Fainberg J, Mungovan SF, Bratt O, et al. 2022 update on prostate cancer

epidemiology and risk factors-a systematic review. *Eur Urol*. 2023;84(2):191-206. doi: 10.1016/j.eururo.2023.04.021

[7] Fang X, Wei J, He X, Lian J, Han D, An P, et al. Quantitative association between body mass index and the risk of cancer: a global Meta-analysis of prospective cohort studies. *Int J Cancer*. 2018;143(7):1595-1603. doi: 10.1002/ijc.31553

[8] Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*. 2021;79(2):243-262. doi: 10.1016/j.eururo.2020.09.042

[9] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33. doi: 10.3322/caac.21708

[10] Bell KJ, 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):1749-1757. doi: 10.1002/ijc.29538.

[11] Gong J, Kim DM, Freeman MR, Kim H, Ellis L, Smith B, et al. Genetic and biological drivers of prostate cancer disparities in Black men. *Nat Rev Urol*. 2023. doi: 10.1038/s41585-023-00828-w.

[12] Giri VN, Obeid E, Gross L, Bealin L, Hyatt C, Hegarty SE, et al. Inherited mutations in men undergoing multigene panel testing for prostate cancer: emerging implications for personalized prostate cancer genetic evaluation. *JCO Precis Oncol*. 2017;1:PO.16.00039. doi: 10.1200/PO.16.00039

[13] Johns LE, Houlston RS. A systematic review and meta-analysis of familial prostate cancer risk. *BJU Int*. 2003;91(9):789-794. doi: 10.1046/j.1464-410x.2003.04232.x

[14] Albright F, Stephenson RA, Agarwal N, Teerlink CC, Lowrance WT, Farnham JM, et al. Prostate cancer risk prediction based on complete prostate cancer family history. *Prostate*. 2015;75(4):390-398. doi: 10.1002/pros.22925

[15] Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016; 375(5):443-453. doi: 10.1056/NEJMoa1603144

[16] Nicolosi P, Ledet E, Yang S, Michalski S, Freschi B, O'Leary E, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol*. 2019;5(4):523-528. doi: 10.1001/jamaoncol.2018.6760

[17] Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. *J Natl Compr Canc Netw*. 2019;17(5):515-21. doi: 10.6004/jnccn.2019.7307

[18] Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, et al. Germline mutations in HOXB13 and prostate-cancer risk. *N Engl J Med.* 2012;366(2):141-149. doi: 10.1056/NEJMoa1110000

[19] de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-2102. doi: 10.1056/NEJMoa1911440

[20] Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, et al. Cancer risks by gene, age, and gender in 6,350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med*. 2020;22(1):15-25. doi: 10.1038/s41436-019-0596-9

[21] LaDuca H, Polley EC, Yussuf A, Hoang L, Gutierrez S, Hart SN, et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet Med*. 2020;22(2):407-415. doi: 10.1038/s41436-019-0633-8

[22] Russo J, Giri VN. Germline testing and genetic counselling in prostate cancer. *Nat Rev Urol*. 2022;19(6):331-343. doi: 10.1038/s41585- 022-00580-7

[23] Giri VN, Gross L, Gomella LG, Hyatt C. How I do it: genetic counseling and genetic testing for inherited prostate cancer. *Can J Urol*. 2016;23(2):8247-8253.

[24] Moses KA, Sprenkle PC, Bahler C, Box G, Carlsson SV, Catalona WJ, et al. NCCN Guidelines® Insights: Prostate Cancer Early Detection, Version 1. 2023. *J Natl Compr Canc Netw*. 2023;21(3):236-246. doi: 10.6004/jnccn.2023.0014

[25] National Cancer Institute. 2020. SEER Cancer Stat Facts: Prostate Cancer. Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/prost.html

[26] Doan DK, Schmidt KT, Chau CH, Figg WD. Germline genetics of prostate cancer: prevalence of risk variants and clinical implications for disease management. *Cancers (Basel)*. 2021;13(9):2154. doi: 10.3390/cancers13092154

[27] Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS, et al. Implementation of germline testing for prostate cancer: philadelphia prostate cancer consensus conference 2019. *J Clin Oncol*. 2020;38(24):2798-2811. doi: 10.1200/JCO.20.00046

[28] Erickson A, Sandeman K, Lahdensuo K, Nordling S, Kallajoki M, Seikkula H, et al. New prostate cancer grade grouping system predicts survival after radical prostatectomy. *Hum Pathol*. 2018;5:159-166. doi: 10.1016/j.humpath.2018.01.027

[29] Tosoian JJ, Mamawala M, Epstein JI, Landis P, Macura KJ, Simopoulos DN, et al. Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort. *Eur Urol*. 2020;77(6):675-682. doi: 10.1016/j.eururo.2019.12.017

[30] Wei JT, Barocas D, Carlsson S, Coakley F, Eggener S, Etzioni R, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part I: Prostate Cancer Screening. *J Urol*. 2023;210(1):46-53. doi: 10.1097/JU.0000000000003491

[31] Preston MA. Screening for prostate cancer. In: UpToDate, Elmore JG, (Ed). (Accessed on August 7, 2023.)

[32] Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, et al.; ERSPC Investigators. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014;384(9959):2027-2035. doi: 10.1016/S0140-6736(14)60525-0

[33] Hugosson J, Roobol MJ, Månsson M, Tammela TLJ, Zappa M, Nelen V, et al.; ERSPC investigators. A 16-yr follow-up of the European randomized study of screening for prostate cancer. *Eur Urol*. 2019;76(1):43-51. doi: 10.1016/j.eururo.2019.02.009

[34] Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al.; PLCO Project Team. Mortality results from a randomized prostate cancer screening trial. *N Engl J Med*. 2009;360(13):1310-1319. doi: 10.1056/NEJMoa0810696. Erratum in: N Engl J Med. 2009;360(17):1797.

[35] 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;362:k3519. doi: 10.1136/bmj.k3519

[36] SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance Research Program, National Cancer Institute; 2023 Apr 19. https://seer.cancer.gov/statistics-network/explorer

[37] Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157(2):120-134. doi: 10.7326/0003-4819-157-2-201207170-00459

[38] Butler SS, Muralidhar V, Zhao SG, Sanford NN, Franco I, Fullerton ZH, et al. Prostate cancer incidence across stage, NCCN risk groups, and age before and after USPSTF Grade D recommendations against prostate specific antigen screening in 2012. *Cancer*. 2020;126(4):717-724. doi: 10.1002/cncr.32604

[39] EAU Guidelines. Edn. Presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6

[40] Matsukawa A, Yanagisawa T, Bekku K, Kardoust Parizi M, Laukhtina E, Klemm J, et al. Comparing the

performance of digital rectal examination and prostate-specific antigen as a screening test for prostate cancer: a systematic review and meta-analysis. *Eur Urol Oncol*. 2024:S2588-9311(23)00292-4. doi: 10.1016/j.euo.2023.12.005

[41] Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol*. 2006;175(5):1605-1612. doi: 10.1016/S0022-5347(05)00957-2

[42] Valerio M, Willis S, van der Meulen J, Emberton M, Ahmed HU. Methodological considerations in assessing the utility of imaging in early prostate cancer. *Curr Opin Urol*. 2015;25(6):536-642. doi: 10.1097/MOU.0000000000000219

[43] Shaw GL, Thomas BC, Dawson SN, Srivastava G, Vowler SL, Gnanapragasam VJ, et al. Identification of pathologically insignificant prostate cancer is not accurate in unscreened men. *Br J Cancer*. 2014;110(10):2405-2411. doi: 10.1038/bjc.2014.192

[44] Elwenspoek MMC, Sheppard AL, McInnes MDF, Merriel SWD, Rowe EWJ, Bryant RJ, et al. Comparison of multiparametric magnetic resonance imaging and targeted biopsy with systematic biopsy alone for the diagnosis of prostate cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(8):e198427. doi: 10.1001/ jamanetworkopen.2019.8427

[45] Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al.; PRECISION Study Group Collaborators. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med*. 2018; 378(19):1767-1777. doi: 10.1056/NEJMoa1801993

[46] Eklund M, Jäderling F, Discacciati A, Bergman M, Annerstedt M, Aly M, et al.; STHLM3 consortium. MRI-targeted or standard biopsy in prostate cancer screening. *N Engl J Med*. 2021;385(10):908-920. doi: 10.1056/NEJMoa2100852

[47] Tu X, Liu Z, Zhang C, Chang T, Xu H, Bao Y, et al. Diagnostic role of magnetic resonance imaging-targeted biopsy for prostate cancer in biopsy-naïve men: a meta-analysis. *Urol Int*. 2020; 104(3-4):187-198. doi: 10.1159/000504028

[48] Woo S, Suh CH, Eastham JA, Zelefsky MJ, Morris MJ, Abida W, et al. Comparison of magnetic resonance imaging-stratified clinical pathways and systematic transrectal ultrasound-guided biopsy pathway for the detection of clinically significant prostate cancer: a systematic review and meta-analysis of randomized controlled trials. *Eur Urol Oncol*. 2019;2(6):605-616. doi: 10.1016/j.euo.2019.05.004

[49] Wei JT, Barocas D, Carlsson S, Coakley F, Eggener S, Etzioni R, et al. Early Detection Of Prostate Cancer: AUA/SUO Guideline Part II: Considerations For a Prostate Biopsy. *J Urol*. 2023;210(1):54-63. doi: 10.1097/JU.0000000000003492

[50] Elkhoury FF, Felker ER, Kwan L, Sisk AE, Delfin M, Natarajan S, et al. Comparison of targeted vs systematic prostate biopsy in men who are biopsy naive: the prospective assessment of image registration in the diagnosis of prostate cancer (PAIREDCAP) study. *JAMA Surg*. 2019;154(9):811-818. doi: 10.1001/jamasurg.2019.1734

[51] Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *N Engl J Med*. 2020;382(10):917-928. doi: 10.1056/NEJMoa1910038

[52] Jain MA, Leslie SW, Sapra A. Prostate Cancer Screening. [Updated 2023 Oct 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. https://www.ncbi.nlm.nih.gov/ books/NBK556081/

[53] Abdulla A, Leslie SW. Biomarker Assays for Elevated PSA Risk Analysis. [Updated 2023 Oct 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. https://www.ncbi. nlm.nih.gov/books/NBK592381/