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INVITED OPINION

Prostate Cancer

Prostate cancer: screening and early detection

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Prostate cancer is the second most common cancer in men; therefore, the development of adequate programs of prevention is essential to achieve an early detection of the disease and to reduce the mortality. Over the years, many screening studies were conducted, but their results were conflicting. They did not report a significant reduction of cancer mortality with a high rate of overdiagnosis and overtreatment. We analyzed the main risk factors for prostate cancer, especially genetic ones, not only leading to relevant changes in the treatment of metastatic disease but also being able to guide the management of the screening. Updated data of the main screening programs were reported. Although prostate-specific antigen (PSA) resulted to be the most commonly used serum marker for diagnosis of prostate cancer, it has to be integrated with imaging tools such as magnetic resonance that also support the decision of performing a targeted biopsy. The international guidelines on screening and detection of prostate cancer are presented. They state that the individual screening should not be proposed to all men just based on age, but it should also consider comorbidities, life expectancy, individual's preferences, and risk factors. The planning of an individual screening program should always be guided by a risk-adapted approach: the starting age of screening should be anticipated in men at higher risk, as those with African descent, germline breast cancer susceptibility gene (*BRCA*) mutations, and strong family history. In the future, clinical studies should include new laboratory and imaging biomarkers to better customize the screening.

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Prostate cancer is the second most frequent cancer and the fifth cause of death in males, with higher incidence rates in more industrialized countries, Southern Africa and the Caribbean.[1] The risk of developing prostate cancer depends on several factors. Age, family history, and genetic predisposition are the main nonmodifiable risk factors. Although family history is a well-recognized risk factor, one case of prostate cancer may be considered hereditary when he is in a family presented with ≥3 cases of prostate cancer, members of three successive generations are affected by prostate cancer, or ≥2 men are diagnosed before 55 years old. About 9% of prostate cancers are truly hereditary and are usually diagnosed 6–7 years earlier compared to nonhereditary ones. Advances in genomic profiling allowed to identify different genes associated with risk of developing aggressive prostate cancer. They include both DNA repair genes (such as breast cancer 2, early onset [*BRCA2*], breast cancer 1, early onset [*BRCA1*], ATM serine/threonine kinase [*ATM*], or checkpoint kinase 2 [*CHEK2*], expressed up to 8% or 23% if mutation is germinal or somatic, respectively), and genes involved in Lynch syndrome (MutL homolog 1 [*MLH1*], mutS homolog 2 [*MSH2*], MSH6, and PMS1 homolog 2, mismatch repair system component [*PMS2*]), with a higher prevalence in metastatic diseases compared to localized disease. Moreover, modifiable risk factors show to be associated with prostate cancer development, in particular metabolic syndrome, obesity, and cigarette smoking.[2,3]

The prognosis of prostate cancer may range from indolent tumors, that are often associated with overdiagnosis and overtreatment, to clinically aggressive tumors. Thus, the screening programs, able to early detect prostate cancers regardless of their prognostic features, remain controversial.

PSA is the most commonly used serum marker for the diagnosis of prostate cancer, but it is not cancer-specific and may also be elevated in nonmalignant conditions, such as benign prostatic hypertrophy and prostatitis; moreover, it could be at normal levels even if in the presence of prostate cancer.[4] Radiological examinations, such as prostatic magnetic resonance imaging (MRI), have already shown to be useful in this diagnostic process, but an accurate evaluation of risk factors and the implementation of biomolecular analyses are essential to identify the patients that need to be screened by MRI.

International guidelines and several meta-analyses[3,5] did not support the PSA-based screening programs, since they did not show survival advantages and were associated with overdiagnosis and overtreatment.

In the present work, we describe the evidence concerning the selection of men to whom screening should be proposed, report the recommendations of the international guidelines, and focus on the essential role of genetic biomarkers and the development of a risk-adapted strategy to better define the patients who benefit most from the screening.

SCREENING

At the beginning of the 1990s, several clinical studies were planned to assess the role of PSA as a screening tool. The European Randomized Study of Screening for Prostate Cancer (ERSPC), a multicenter population-based trial including more than 162 000 men aged 55–69 years, randomized to perform a PSA blood test (intervention group) or not (control group). The primary endpoint was to assess whether PSA screening decreased prostate cancer mortality. At the 16-year follow-up, the incidence of prostate cancer was 13.3% in screening arm versus 10.3% in control arm, with a rate ratio (RR) between two arms of 0.80 (95% confidence interval [CI]: 0.72–0.89, $P < 0.001$) and a difference in

Table 1: Recommendations from the European Association of Urology and American Urology Association guidelines on screening and early detection of prostate cancer

Guideline	*Recommendation*	*Strong rating*
EAU guidelines[3]	Do not subject men to PSA testing without counseling them on the potential risks and benefits	Strong
	Offer an individualized risk-adapted strategy for early detection to a well-informed man with a life expectancy of at least 10–15 years	Weak
	Offer early PSA testing to well-informed men at elevated risk of having PCa Men from 50 years of age Men from 45 years of age and a family history of PCa Men of African descent from 45 years of age Men carrying *BRCA2* mutations from 40 years of age	Strong
	Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk Men with a PSA level of >1 ng ml^{-1} at 40 years of age Men with a PSA level of >2 ng ml^{-1} at 60 years of age Postpone follow-up up to 8 years in those not at risk	Weak
	In asymptomatic men with a PSA level of 3–10 ng ml^{-1} and a normal DRE, repeat the PSA test prior to further investigations	Weak
	In asymptomatic men with a PSA level of 3–10 ng ml^{-1} and a normal DRE, use one of the following tools for biopsy indication Risk calculator, provided it is correctly calibrated to the population prevalence Magnetic resonance imaging of the prostate	Strong
	An additional serum, urine biomarker test	Weak
	Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life expectancy of <15 years are unlikely to benefit	Strong
AUA guidelines[5]	Clinicians should engage in SDM with people for whom prostate cancer screening would be appropriate and proceed based on a person's values and preferences	Clinical principle
	When screening for prostate cancer, clinicians should use PSA as the first screening test	Strong recommendation; evidence level: grade A
	Clinicians should offer prostate cancer screening beginning at age 40–45 years for people at increased risk of developing prostate cancer based on the following factors: African descent, germline mutations, and strong family history of prostate cancer	Strong recommendation; evidence level: grade B
	Clinicians may begin prostate cancer screening and offer a baseline PSA test to people between ages 45 years and 50 years	Conditional recommendation; evidence level: grade B
	Clinicians should offer regular prostate cancer screening every 2–4 years to people aged 50–69 years	Strong recommendation; evidence level: grade A
	Clinicians may personalize the re-screening interval, or decide to discontinue screening, based on patient preference, age, PSA, prostate cancer risk, life expectancy, and general health following SDM	Conditional recommendation; evidence level: grade B
	Clinicians may use DRE alongside PSA to establish risk of clinically significant prostate cancer	Conditional recommendation; evidence level: grade C
	For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy	Expert opinion
	For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy	Strong recommendation; evidence level: grade B
	Clinicians and patients may use validated risk calculators to inform the SDM process regarding prostate biopsy	Conditional recommendation; evidence level: grade B
	When the risk of clinically significant prostate cancer is sufficiently low based on available clinical, laboratory, and imaging data, clinicians and patients may forgo near-term prostate biopsy	Clinical principle

EAU: European Association of Urology; AUA: American Urology Association; PCa: prostate cancer; PSA: prostate-specific antigen; DRE: digital rectal examination; SDM: shared decision-making; *BRCA2*: breast cancer 2, early onset

absolute prostate cancer mortality of 0.18%.[6] This study was limited by the heterogeneity in terms of stopping age for screening invitations, interval of PSA assessment, duration of screening, and additional screening tools employed in some centers.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was a multicenter study conducted in the USA on more than 76 000 men aged 55–74 years. The enrolled participants were randomized 1:1 to an intervention arm (with annual PSA tests for 6 years and digital rectal examinations for 4 years) and a control arm, from 1993 to 2001. After a median follow-up of 15 years, no statistically significant difference in prostate cancer mortality was reported between intervention arm (255 deaths) and control arm (244 deaths), with a RR of 1.04 (95% CI: 0.87–1.24).[7]

A Cochrane review suggested that PSA screening is associated with an increased diagnosis rate and less advanced disease, without benefits in terms of overall survival (RR: 1.00; 95% CI: 0.96–1.03) and cancer-specific survival (RR: 1.00; 95% CI: 0.86–1.17).[8]

Accordingly, international guidelines[3,5] did not support the PSA-based screening programs, and usually, national health prevention programs did not include PSA-based screening. Therefore, when PSA is used as the main screening test, additional screening tools are needed to reduce the risk of overdiagnosis. The PSA density (PSA divided by prostate volume in grams) was introduced for a differential diagnosis between cancer and benign prostatic diseases.[3,5]

Furthermore, multiparametric MRI (mpMRI) demonstrated to have a central role in driving prostate biopsy in the case of persistent suspect of cancer after negative biopsies.[3,5] To improve the diagnostic efficacy of mpMRI, the European Society of Urogenital Radiology developed the Prostate Imaging Reporting and Data System

(PI-RADS), a score from 1 to 5 indicating the likelihood that a prostate lesion identified on mpMRI is a clinically significant prostate cancer.[3,5]

Over the years, several studies tried to optimize the combined use of PSA and mpMRI as screening tool, as the GÖTEBORG-2 trial, that confirmed the role of MRI-guided biopsy in avoiding overdiagnosis of prostate cancer.[9]

EARLY DETECTION

The early detection of significant prostate cancer may reduce the number of men diagnosed with advanced/metastatic disease and, consequently, the prostate cancer-specific mortality rates.

Considering the limits of the data provided by previously reported literature, the decision of starting a PSA screening should be adequately shared between clinicians and patients, as recommended by the international guidelines (**Table 1**).[3,5,10] The patient should be informed on the risk/benefit ratio, mainly on the risk of overdiagnosis.

The first screening tool is the evaluation of PSA levels, whose threshold is changed over time, and nowadays, the most commonly accepted is 4 ng ml^{-1}. Literature data suggest that it may return within the normal range in 25% to 40% of cases, and this parameter is influenced by several factors (sexual activity, cycling activity, *etc*.).[4]

Prostate cancer may be also suspected based on digital rectal examination (DRE).[3,5]

A general principle is that an individualized risk-adapted strategy for early detection of prostate cancer should always be offered to a well-informed man with a life expectancy of at least 10 years to 15 years.

Both the European Association of Urology (EAU) and the American Urological Association (AUA) guidelines strongly recommend offering prostate cancer screening every 2 years to 4 years to men aged 50–69 years.

It should be anticipated in men at high risk, as those from 45 years of age and a family history of prostate cancer, those of African descent from 45 years of age, and those carrying *BRCA2* mutations from 40 years of age.[3,5]

The indication to perform a prostate biopsy does not just depend on PSA level or PSA density, but it must also consider clinical data from DRE and radiological information from MRI. Therefore, nowadays, the standard biopsy is ultrasound guided and/or MRI targeted.

CONCLUSION

Prostate cancer screening could impact on the diagnosis and management of this disease. The incidence of prostate cancer is progressively increased over the years, making it the second most common tumor in men. PSA is a noninvasive, cheap, and easy performed test, but evidence on its role as a screening tool are conflicting. In fact, some studies, although well designed and based on a large population, did not report a statistically significant reduction of cancer mortality, while revealed high rates of overdiagnosis and overtreatment. This means that the screening should not be proposed to all men just based on age, but also considering other factors such as comorbidities, life expectancy, and individual preferences. In particular, the identification of the men with risk factors as African descent, germline mutations, and strong family cancer history is essential, because these subjects have an amplified risk to develop prostate cancer.

As part of a risk-adapted approach, the male candidates for prostate cancer screening should be well informed and addressed to a personalized screening program. In other words, a population-based screening program should not only be based on PSA, but it should be flexible, taking into account the regional/national variations in prostate cancer risk and health-care resources, in order to produce an individually tailored screening program. About that, genetics has also demonstrated to play an important role. Extensive molecular screening in patients affected by prostate cancer allowed the identification of several genes that are associated with the development of the tumor. Moreover, the detection of these genes may increase the number of men at risk who would benefit from a screening program. Besides, the introduction in clinical practice of MRI and targeted biopsy has notably reduced the rates of overdiagnosis: they allow to better identify the men who really benefit from an early diagnosis and to reduce the number of men who would never die from prostate cancer. Finally, new laboratory and imaging biomarkers are awaited, and future clinical studies should consider this unmet need.

AUTHOR CONTRIBUTIONS

Both authors equally contributed to the study, and read and approved the final manuscript.

COMPETING INTERESTS

Both authors declared no competing interests.

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