Policy Paper on

PSA SCREENING FOR PROSTATE CANCER

Has the time come to reconsider structured population-based PSA screening for prostate cancer?

European Association of Urology

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1. Executive Summary

INTRODUCTION: WHY THIS PAPER NOW?

Prostate cancer (PCa) is the most commonly diagnosed cancer in men, with more than 417,000 new cases and 92,000 deaths in Europe recorded each year. Last year, registry data have shown that death from prostate cancer has overruled death from colorectal cancer being the second most cause of cancer-related death in men behind lung cancer. Despite this significant public health burden, relatively little is performed on prostate cancer screening at EU level, particularly in comparison to breast, cervical and colorectal cancers.

- **Recent evidence demonstrates the efficacy of prostate cancer screening**

The European Randomised Study of Screening for Prostate Cancer (ERSPC) demonstrates that PSA screening **reduces disease-specific mortality by 21%, which is equivalent to one death prevented per 781 men invited for screening or one per 27 prostate cancer detected**. The evidence shows that after 20 yrs of follow-up the number of patients needed to screen and diagnose prostate cancer decreased to 101 and 13, respectively, to prevent one prostate cancer death [8, 10]. As such, PSA screening results in mortality reduction are obviously better than in breast or colon cancer screening.

- **Worrying statistics on prostate cancer mortality where prostate cancer screening has been cut back**

Key evidence has emerged from two independent studies in 2017 and 2018 to demonstrate that a lack of prostate cancer screening is reversing the trends of declining death rates. Since practitioners in both the UK, and the USA have been advised not to perform PSA for early detection, worrying statistics are emerging to demonstrate that cancer mortality is increasing. [17, 28]

- **Quality of Life**

Where mortality rate is always considered in screening options, the quality of life of a patient is seldom taken into account. Early treatment for prostate cancer lowers the risk of incontinence and impotence significantly, while treatment at metastatic phase has a negative effect on the quality of life. Hence, there is a big opportunity to improve the quality of life if early detection is achieved in combination with avoidance of overtreatment.

- **The availability of gold standard good practice and emerging new technologies**

Since PSA screening ultimately reduces the rate of men with metastatic PCa at diagnosis and, in turn, mortality, different organisations have reconsidered their views on screening. The European Association of Urology (EAU) released its recommendations on early detection in the year 2013 [33].

At the same time, individualised risk-adapted screening strategies, as well as mpMRI and biomarkers to select candidates for prostate biopsy will reduce the risk of overdiagnosis which has been a concern in the past. Moreover, the adoption of active surveillance as an option in patients with low-risk decreases overtreatment.

WHAT SHOULD THE EU DO?

The European Union can no longer continue to overlook the most common cause of cancer and the second most common cause of death from cancer in men in Europe. Urgent action is required to ensure the new Commission is mandated to support EU Member States in prostate cancer screening in their national cancer plans.

- The 2003 Council Recommendations on population-based screening need to be urgently reviewed, with prostate cancer added to the list of cancers to be addressed.
- Member States should already support a policy update on prostate cancer screening through their work on the EU Joint Action, the Innovative Partnership for Action Against Cancer (IPAAC)
- MEPs should ensure that European action on Prostate Cancer screening is included in the group manifestos as they prepare for European elections
- The new college of Commissioners mandated in 2019 should be empowered by the European Parliament and Member States to support Member States with European guidelines on prostate cancer screening.
- Member States should also bring good practice on prostate cancer screening to the Steering Group on Health Promotion, Disease Prevention and Management of non-communicable diseases, where the European Commission can assist in channelling necessary support and funding at EU level.

2. Introduction

Prostate cancer is the first most frequently diagnosed solid cancer and the second most common cause of cancer death among European men with more than 450,000 new cases and 107,000 deaths expected in 2018 in Europe [1, 2]. Prostate cancer is characterised by slow development when diagnosed at an early stage [3]. Conversely, it is almost always too advanced to be cured when diagnosed late. The need for more extensive surgical approaches and/or hormonal or chemotherapies is associated with a negative impact on quality of life in men with advanced disease as compared to those men diagnosed at an early stage.

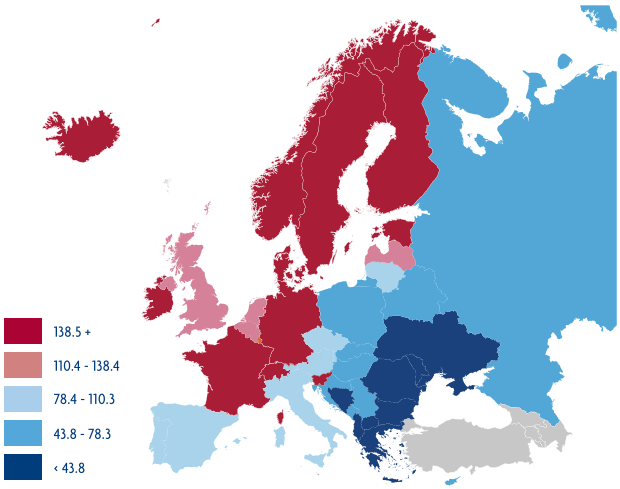


Figure 1: Estimated incidence prostate cancer in men, 2012

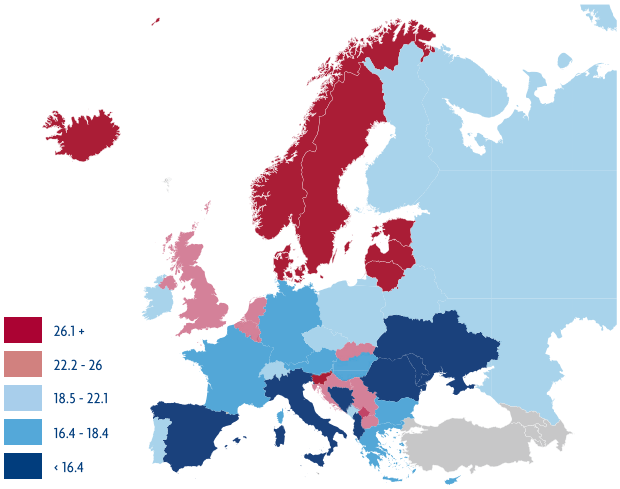


Figure 2: Estimated mortality from prostate cancer in men, 2012

The treatment of advanced and metastatic disease is very costly and only marginally improves survival [4]. While the costs of robot-assisted radical prostatectomy, which is one of the most used treatments for early prostate cancer, does not exceed €15,000 per patient [5], the costs for the management of patients with castration-resistant, non-curable PCa can be estimated in approximately €140,000 per patient per year up to €300,000 during a patient's lifetime in Western countries [6].

PSA stands for Prostate Specific Antigen, which is a protein that can be measured in the blood of men. Elevated PSA levels might be detected in men with prostate cancer and PSA has been proposed as a biomarker or indicator [7]. Screening based on PSA allows for the detection of PCa at an early stage, reducing cancer-specific mortality at long-term follow-up [7-11]. Nonetheless, many of the tumours detected by PSA develop slowly and men would not have experienced any symptoms during their lifetime [12, 13].

Given the risk of overdiagnosis (and overtreatment) associated with screening, in the year 2012 the US Preventive Services Task Force released a recommendation against its use [14]. The consequence of the release of these recommendations was a reduction in PSA-based screening [15]. This led to more men with advanced PCa and a tendency towards higher prostate cancer death rates [16-18].

Member States have so far mandated the European Commission to support population-based screening programmes for breast, colon and cervical cancer, while prostate cancer screening has been overlooked.

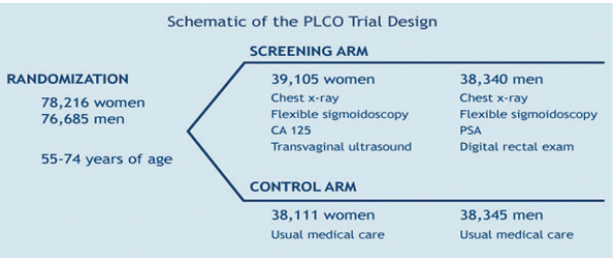
Due to recent developments, the Commission has proposed the EU's Joint Action on Innovation Partnership in Action Against Cancer as the best place to start the policy work on a possible inclusion of prostate cancer screening programmes in the National Cancer plans http://www.europarl.europa.eu/doceo/document/E-8-2017-007165-ASW_EN.html.

3. Is PSA-based screening reducing mortality? New evidence proves it is.

The implementation of structured screening programmes based on repeated measurements of PSA leads to the detection of prostate cancer at an early stage, improving our ability to cure the disease [19]. This reduces the risk of metastases during follow-up and of dying from the disease itself. The evidence assessing the role of screening based on multiple PSA testing rounds is dominated by two randomised trials [7, 20, 21].

The European Randomised Study of Screening for Prostate Cancer (ERSPC) randomised 182,000 men aged 50 to 74 years to PSA screening every 4 years vs. control [7]. At 13-year follow-up, PSA screening reduced disease-specific mortality by 21%, which is equivalent to one death prevented per 781 men invited for screening or one per 27 prostate cancer detected. After almost 20 years of follow-up the number of patients needed to screen and diagnose decreased to 101 and 13, respectively, to prevent one prostate cancer death [8, 10]. In comparison, for diagnosing breast cancer the numbers needed to screen vary between 111 and 235, while for diagnosing colon cancer is 850. Therefore, PSA screening with comparable follow-up is even more effective compared to breast or colon cancer screening.

The second trial was the prostate arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), which randomised more than 76,000 men to annual PSA testing for 6 years vs. usual care [20]. After 17 years of follow-up, no differences in mortality were detected between the two arms [21]. However, one out of two men had undergone at least 1 PSA test before randomisation [20]. Moreover, up to 80% of men in the control group reported having undergone at least 1 PSA test during the trial [22]. As such, this study should be considered as the comparison between organised vs. opportunistic screening rather than an assessment of PSA screening. Recent analyses accounting for differences in the two studies suggest that the efficacy of screening in the PLCO setting might be consistent with what was observed in the ERSPC trial [9].



4. Concerns on Overdiagnosis and Overtreatment

Despite this compelling evidence on the efficiency of PCa screening, the medical community has historically been divided because of the risk of overdiagnosis and overtreatment.

Overdiagnosis is defined as the detection of a disease in men who don't experience any symptoms at the moment of detection and would not develop any symptoms during their lifetime if not identified by early detection activities [23]. The risk of overdiagnosis has been estimated to be as high as 40% in screen-detected prostate cancer [24] and is particularly important given the slow development of the disease itself [25]. Overdiagnosis applies particularly to older men or those with lower PSA values, where the beneficial effect of treatment is limited [12, 13].

Although PSA screening reduces the risk of mortality, its main drawback is a substantial number of unnecessary biopsies and detection of insignificant cancers, which could lead to overtreatment [26, 27].

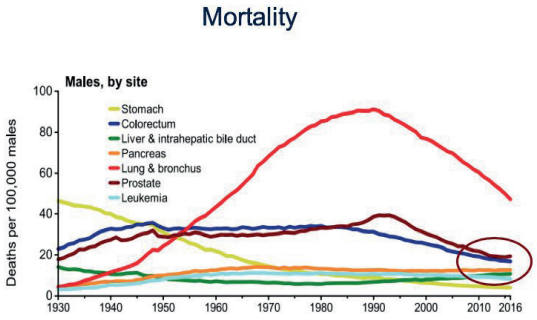
The issues related to overdiagnosis and overtreatment were the main drivers for the strong recommendations against PSA screening released by the United States Preventive Services Task Force in the year 2012 [14].

Do these concerns remain valid? The EAU believes there are reasons why these concerns need to be readdressed and reviewed:

4.1 THE CONSEQUENCES OF NOT PERFORMING PSA SCREENING

Recent studies demonstrate that cutting back on PSA screening has a direct correlation with a rise in mortality rates from Prostate Cancer:

1. In many European countries general practitioners and patients were informed not to perform PSA for early detection. In the United Kingdom, 4 out of 10 prostate cancer diagnoses are currently diagnosed at a locally advanced or metastatic stage [28].
2. In the United States, after a documented long decline of death rates of prostate cancer, prostate cancer mortality is increasing for the 1st time since early 1990 [17]. This has happened in parallel with PSA screening decline, where a decrease by 10-18% of screening rates has been observed in recent years [30, 31]. Moreover, an increase in the number of patients with metastatic and advanced disease has been observed at the same time [30, 32].



4.2 EARLY DETECTION OF PROSTATE CANCER: RECOMMENDATIONS ARE AVAILABLE

Since PSA screening ultimately reduces the rate of men with metastatic PCa at diagnosis and, in turn, mortality, different organisations have reconsidered their views on screening. The European Association of Urology (EAU) released its recommendations on early detection in the year 2013 [33]. The panel recommended that a baseline PSA level should be obtained at the age of 40-45 years to initiate a risk-adapted follow-up with the purpose of reducing metastatic prostate cancer and mortality. Screening should then be offered to well-informed men with a life expectancy ≥10 years and the intervals for screening should be adapted according to the baseline PSA obtained at the age of 40-45 years [34].

The American Urological Association (AUA) guidelines on screening recognise that the decision to undergo PSA screening involves weighing the potential benefits and harms and strongly recommends shared decision-making for well-informed men aged 55 to 69 years. An interval of two years or more may be preferred over annual screening to reduce the risk of overdiagnosis and overtreatment [35].

The US Preventive Services Task Force updated their 2018 version and recommends to leave the choice of PSA-based screening in well-informed men between the age of 55 to 69 years up to an individual decision [36]. However, they discouraged the use of screening in men at the age of 70 and older, where the potential benefits of PSA screening do not outweigh the harms [36].

4.3 NEW AND EMERGING TECHNOLOGIES AND PRACTICES ARE GAME CHANGERS IN REDUCING THE RISK OF OVERDIAGNOSIS AND OVERTREATMENT

Measures aimed at minimising the risk of overdiagnoses and overtreatment while maximising the benefits of PSA screening in terms of reduction of prostate cancer mortality are urgently needed.

INDIVIDUALISED PSA-BASED SCREENING

First, PSA should be considered in the context of other clinical characteristics such as age, family history, digital rectal examination and prostate volume. Several risk calculators that take other variables into account, have been developed and their use increases the diagnostic accuracy of PSA alone [37,61].

Secondly, one single assessment of PSA values has limited value as PSA values can fluctuate. In this context, a baseline PSA obtained at the age of 40-45 years should be considered for risk-stratification of future screening intensity [38-43].

Finally, the use of PSA screening should be discouraged in men with a short life expectancy, where the risk of dying from other causes is higher than cancer mortality [12, 13, 44, 45].

MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING (mpMRI) BEFORE PROSTATE BIOPSY

The availability of mpMRI substantially changed the diagnostic paradigm of localised prostate cancer. MRI images are characterised by a high sensitivity and negative predictive value for aggressive disease [46, 47]. At the same time, it systematically overlooks insignificant prostate cancer [48]. Therefore, mpMRI has been proposed as a first test to identify men with elevated PSA levels who should be considered for a prostate biopsy [48].

The use of mpMRI before prostate biopsy would allows for the detection of a higher proportion of significant prostate cancers compared to random biopsies. This would lead to a reduction of more than 10% of diagnosing insignificant diseases and of 30% in the number of unnecessary biopsies [49]. The implementation of screening strategies that include mpMRI would avoid a substantial number of unnecessary prostate biopsies and other disease diagnoses [50, 51].

NOVEL MOLECULAR TESTS

Different molecular biomarkers have been proposed to identify men with significant prostate cancer. These tools based on algorithms including PSA or other proteins and clinical information can identify clinically significant disease with high accuracy and might further decrease the risk of overdiagnosis [52-55].

Nonetheless, they should not be considered as alternatives to PSA screening and should not be used as reflex tests. They provide complimentary information that enhance prediction of high-grade prostate cancer. Their integration with other tools such as mpMRI might ultimately reduce the number of unnecessary biopsies without increasing the risk of missing a significant disease [57, 58].

ACTIVE SURVEILLANCE FOR MEN WITH LOW RISK PROSTATE CANCER

Well-selected men with low-risk prostate cancer might be included in active surveillance programmes with the aim of reducing the risk of overtreatment without losing the window of curability [59, 60]. Patients managed with active surveillance receive periodic assessments with PSA measurements, digital rectal examination, mpMRI, and eventually prostate biopsies. Treatment starts as soon as the aggressive but still curable disease is detected in men with an adequate life expectancy.

This approach reduces treatment-related side effects like urinary incontinence and erectile dysfunction in up to 65% of patients with low- or intermediate-risk disease at 15-year follow-up [60, 61]. As a consequence, active surveillance is currently recommended by the European Association of Urology for the management of all men with low-risk prostate cancer with an adequate life expectancy [59].

5. Conclusions – urgent action required!

The European Union can no longer continue to overlook the most common cause of cancer in men in Europe which developed to be the number two cancer killer in men. Urgent action is required to ensure the new Commission is mandated to support EU Member States in prostate cancer screening in their national cancer plans.

The implementation of PSA-based screening at a European level to decrease prostate cancer mortality and improve Quality of Life should be discussed again in the light of the current evidence and should be included in the policy agenda of the European Commission. IPAAC is a possible vehicle to introduce a policy update on prostate cancer screening.

The 2003 Council Recommendations on population-based screening should be updated to include Prostate Cancer. The new European Commission should be mandated by this or other mechanisms by the European Parliament and EU Member States to produce guidelines on Prostate Cancer Screening to support EU Member States.

The EAU Guidelines could form the foundation of these recommendations as they are evidence-based and developed from a multidisciplinary point of view.

EU Member States should also bring good implementation practice on Prostate Cancer Screening to the Steering Group on Health Promotion, Disease Prevention and Management of non-communicable diseases. This in turn should encourage the European Commission to channel appropriate support and funding to Prostate Cancer screening and research.

Let's use the opportunity of new elections and a new Commission to ensure that Prostate Cancer is given the priority at EU level that is needed!

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