Current controversies about PSA screening: Similarities and differences between the European Association of Urology (EAU) and the American Urological Association (AUA) Guidelines

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Abstract
During the last 2 decades screening with PSA has allowed detection of PCa at earlier stages, improving patient survival and the chances of cure with definitive local therapy. Thus, PSA screening has been widely used with the intention to decrease mortality and increase health-related quality of life. However, the true benefit of screening for PCa remains uncertain, as there is a substantial risk of overdiagnosis and overtreatment, when it is used with inappropriate frequency. Therefore, screening for PCa has generated considerable debate within the medical and broader community, as demonstrated by the varying recommendations made by medical organizations, such as the EAU and the AUA. In this paper, similarities and differences between the EAU and AUA guidelines are presented, and their scientific background is discussed. Despite the debate, both societies agree, that the PSA test does not have the required characteristics to be used as a widespread screening tool for PCa. Indication for PSA screening, therefore, should be individualized and screening should be offered to well-informed men, who should be aware of the benefits and harms of PSA screening.

Key words prostate cancer; PSA; PSA screening; AUA and EAU Guidelines

Introduction
Prostate cancer (PCa) is considered one of the most important medical issues regarding the male population. The global incidence of PCa has been estimated at 500,000 new cases each year. Between 230,000 to 240,000 men are diagnosed annually with PCa in both Europe and the US. In Europe, it is the most common solid neoplasm, with an incidence rate of 214 cases per...
1000 men, outnumbering lung and colorectal cancer and currently it is the second most common cause of cancer death in men\(^1\). For most men PCa is slow growing and does not result in clinical signs or symptoms during their lifetime. However, in some men PCa progresses and is a leading cause of cancer morbidity and mortality.

During the last 2 decades screening with PSA has allowed detection of PCa at earlier stages, improving patient survival and the chances of cure with definitive local therapy. In the National Prostate Cancer Detection Project Study\(^2\) involving serial screening with PSA, digital rectal examination and transrectal ultrasonography the rate of clinically advanced disease was reduced to less than <9% of all newly diagnosed cancers over a 10-year period, compared with 41% in a survey of 1982\(^3\). Thus, PSA screening has been widely used with the intention to decrease mortality and increase health-related quality of life, however the true benefit of screening for PCa remains uncertain\(^4\).

It is well known that initial diagnosis of PCa is based on PSA values, digital rectal examination (DRE) and transrectal ultrasound. Use of the DRE as a screening tool is limited due to poor reliability, sensitivity, and the inability to palpate the entire prostate gland, especially for small tumors that have not reached the prostatic capsule. On the other hand, PSA test produces high false-negative and false-positive results depending on thresholds used to define abnormality, and may detect prostate cancers that are unlikely to cause health problems in the future, even if left untreated, a phenomenon known in the literature as overdiagnosis\(^5\). Moreover, recent data suggested that the PSA test does not attain the likelihood ratios for a screening test, regardless of what threshold value for the PSA is assigned\(^6\).

Currently there is no consensus regarding the value and importance of PSA screening in daily practice, and this might explain the fact, that two of the biggest urological associations, namely the European Association of Urology (EAU) and the American Urological Association (AUA) in their guidelines have different approaches, and therefore different recommendations for the early detection of PCa.

**The AUA Guidelines**

The AUA guidelines do not make a distinction between early detection and screening for PCa; both imply detection of disease at an early, presymptomatic stage when an individual would have no reason to seek medical care\(^7\). In the US, early detection is driven by PSA-based screening followed by prostate biopsy for diagnostic confirmation. Therefore the AUA guidelines focus only on the efficacy of PSA screening with the specific intent to reduce prostate cancer mortality and not secondary tests often used after screening to determine the need for a prostate biopsy or a repeat prostate biopsy. In brief the AUA guideline\(^8\):

1. Does not recommend PSA screening in men under 40 years of age (Grade of recommendation C)
2. Does not recommend PSA screening in men between ages 40 to 54 years at average risk (Grade of recommendation C)
3. Does recommend a shared decision-making for men ages 55 to 69 years (Grade of recommendation B)
4. Does recommend a screening interval of ≥ 2 years, which may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. Additionally, intervals for rescreening can be individualized by a baseline PSA level (Grade of recommendation C).
5. Does not recommend PSA screening in men age ≥ 70 years or in men with a life expectancy of < 10 to 15 years (Grade of recommendation C).

**The EAU Guidelines**

Based on the current evidence in the literature the EAU has a different recommendation for the early detection of PCa. The updated EAU guidelines do not recommend widespread mass screening for PCa and early detection in well-informed men is strongly recommended. A baseline PSA determination at age 40 to 45 years has been suggested upon which the subsequent screening interval may then be based. Furthermore, the EAU guidelines do not use a specific chronological age as a threshold for screening, but screening in men with a life expectancy > 10 years is recommended independent on chronological age. More specifically, the EAU has come to following statements\(^9\):

1. Early detection of PCa reduces prostate cancer-related mortality.
2. Early detection of PCa reduces the risk of being diagnosed and developing advanced and metastatic prostate cancer.
3. A baseline serum PSA level should be obtained at 40 - 45 years of age.
4. Intervals for early detection of PCa should be adapted to the baseline PSA serum concentration.
5. PSA screening should be offered to men with a life expectancy of > 10 years.
6. In the future, multivariable clinical risk - prediction tools need to be integrated into the decision making process.

Scientific background
Population based recommendations for cancer screening should ideally be based on high quality evidence derived from systematic reviews of randomized controlled trials (RCT) that document a positive impact of screening on outcomes that are the most important to patients. Currently five prospective RCT’s on PCa screening are available, and these include a total of 341,342 participants. All involved PSA testing, with or without DRE, though the interval and threshold for further evaluation varied across trials. The age of participants ranged from 45 to 80 years and duration of follow - up from 7 to 20 years. These five RCT’s are:
- European Randomized Study of Screening for Prostate Cancer (ERSPC)
- Norrkoping
- Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)
- Quebec and
- Göteborg

The most important data provided from these RCT’s was related to prostate cancer specific mortality. Additional reported outcomes included PCa diagnosis, all cause mortality, stage at diagnosis, and treatment follow - up. The ERSPC and PLCO studies provided data on number of biopsies performed and harms associated with screening (e.g. biopsy - associated complications such as infection or bleeding). Besides these five RCT’s there is a significant number of systematic reviews and meta - analyses in the literature, which are providing evaluation and interpretation of the data.

Prostate cancer specific mortality
Most of the RCT’s showed that PCa screening did not result in a statistically significant reduction in PCa specific mortality between men randomized to screening or control. Meta - analysis of these 5 RCT’s showed that the Relative Risk (RR) was 0.95 (95% CI 0.85 - 1.07). However, the ERSPC study reported a 21% significant benefit for screening in PCa specific mortality in a pre - specified group of men aged 55 to 69 years ( RR 0.80, 95% CI 0.65 - 0.98). Moreover, the ERSPC study concluded, that the benefit of screening becomes more evident as follow - up increases, with a RR reduction of 38% in men with a follow - up of 10 - 11 years. This conclusion was also confirmed by the Göteborg study, according to which most of the benefit from screening occurs after 10 years of follow - up.

All cause mortality
PCa screening did not result in a statistically significant reduction in all cause mortality. Meta - analysis of four studies investigating all cause mortality did not determine any significant differences between men randomized to screen or control (RR 1.00, 95% CI, 0.96 - 1.03).

Prostate cancer diagnosis
PCa screening increased the number of men diagnosed with PCa. A meta - analysis of four of the five RCT’s (ERSPC, PLCO, Norrcoping, Göteborg), which investigated PCa diagnosis across both screening and control groups, indicates that screening is associated with a 35% increase in the number of men diagnosed with prostate cancer. (RR 1.30, 95% CI, 1.02 - 1.65). Localized PCa was more commonly diagnosed in men randomized to screening, whilst the proportion of men diagnosed with advanced PCa was significantly lower in the screening group compared to the men serving as controls (RR 0.80, 95% CI, 0.73 - 0.87).

Harms of screening
Generally, PCa screening resulted in a range of harms that can be considered minor to major in severity and transient in duration. Common minor harms from screening include bleeding, bruising and short - term anxiety. Common major harms include overtreatment and overdiagnosis, false - positive results for the PSA test, as well as medical complications, such as infection,
blood loss requiring transfusion, pneumonia, erectile dysfunction, and incontinence. The RCT’s failed to report complications rates in the screening and control group, so data could not be quantitatively pooled. The ERSPC trial did not include updates on the adverse events it reported in 2002. The PLCO trial reported that DRE led to bleeding or pain at a rate of 0.3 per 10,000 screenings and the PSA test included 3 episodes of fainting per 10,000 screenings. Complications, such as infections, bleeding and urinary difficulties, occurred in 68 per 10,000 diagnostic evaluations. No other studies reported data in either a qualitative or quantitative format.

Nevertheless, the main harm of screening is overdiagnosis, that results in unnecessary treatment and harms, which are frequent, often persist and are at least moderate in severity. The ERSPC trial reported that the overdiagnosis rate was estimated to be up to 50%. In the same trial the false-positive rate for men who had an elevated PSA value (different PSA thresholds were used to define elevated, but typically was defined as > 3.0 ng/mL) and subsequently underwent a biopsy was 75.9%. Therefore, the known harms associated with screening suggest that any small mortality benefit of screening at 10 years would be challenged by the occurrence of these harms that occur early and may persist.

Nevertheless, these five RCT’s differed considerably in their design, screening methodologies, frequencies, thresholds and analysis thus limiting the value of strict reliance on pool estimates. For example, all but one study included measurement of PSA as a screening test in all participants; the Norrkoping study initially used only DRE but then used a combination of PSA and DRE. Three of the five studies did not consistently use DRE in all participants; in the ERSPC trial the screening method differed by participating country and was mostly based on PSA. In the Göteborg study screening was based on PSA testing alone, and participants underwent a DRE only if the test result was abnormal. Four of the five studies provided information on all cause mortality, all studies on deaths from PCa and on diagnosis of PCa. Length of follow-up ranged from about 4 to 15 years. All but the Quebec and the Göteborg study provided information on cancer stage at diagnosis. The ERSPC trial and, to a limited extend, the Göteborg trial allowed subgroup analyses for death from PCa based on age groups, but only the Göteborg study provided age specific information for all cause mortality. Furthermore, all of these RCT’s have been criticized for being too small, methodologic problems, or for being inconclusive because of a high rate of contamination.

On the other hand the evidence that the guideline panels of both the EAU and AUA were based on may be the same, the weighting of the evidence and the perspectives of each panel can be very different (eg public health vs individual perspectives) leading to different interpretations of evidence and policy implications. Thus the AUA guideline panel interpreted the evidence from the perspective of the individual with emphasis on the information, both benefits and harms, which an asymptomatic man would need to make an informed decision about PCa screening.

The EAU guideline panel relied on different strategy, which was based on the most important results of the two positive RCT’s: namely the ERSPC and the Göteborg. Thus, besides the significant reduction in PCa mortality in men aged 55-69 years, which was demonstrated only in the ERSPC study, it was also demonstrated (1) that a diagnosis of PCa was significantly greater in the screening group, (2) that localized PCa was more commonly diagnosed in the screening group, (3) that the proportion of men with locally advanced PCa, or aggressive Gleason score 8-10 PCa was significantly lower in the screening group, (4) that the benefit of screening becomes more evident as follow-up increases.

**Similarities and differences between EAU and AUA Guidelines**

The most basic principle on which both the EAU and the AUA guidelines rely is that any benefits from PCa screening must be balanced against any harms. Both urologic societies agree that at present, widespread mass screening for PCa is not appropriate, as the PSA test does not have the required characteristics to be used as a widespread screening tool, since there is not sufficient evidence that is needed to establish recognized threshold values for a “negative” and “positive” test results.

However there are also important differences be-
between both guidelines regarding the PSA screening. Thus, the AUA guideline panel does not recommend routine screening in men between 40 to 54 years of age, and for men ages 55 to 69 years the panel recommends shared decision-making after weighting the benefits and harms from screening. On the other hand the EAU guideline panel concludes that a baseline PSA level should be obtained at 40-45 years of age, according to which, PSA screening should then be individualized. This EAU recommendation is based on the results of several studies, which have indicated that a baseline PSA level above the median PSA for age group might be a better indicator of PCa development than other clinical risk factors, such as race, family history, or suspicious DRE.

Regarding the screening interval, the AUA guideline panel recommends a routine screening interval of two years or more, and this interval may be preferred over annual screening, in those men who have participated in shared decision making and decided on screening, so that the majority of the benefits can be preserved and harms, overdiagnosis, and false positive results reduced. For the EAU guideline panel, screening intervals should be adapted to the baseline PSA level. More specifically, screening intervals should be 2-4 years for men with PSA level > 1.0 mg/dL at 45-59 years of age, whereas it could be up to 8 years in men with PSA level below this threshold value, indicating that shorter intervals are preferable to avoid the risk of missing significant cancers, but, on the other hand, longer intervals might be preferable to reduce the substantial risk of overdiagnosis and reduce costs associated with frequent screening.

Another significant difference between the EAU and AUA guidelines on PCa screening regards the age limit, beyond which routine PSA screening should be discontinued. The AUA panel does not recommend routine PSA screening in men age 70 years or more, or any man with less than a 10-15 year life expectancy. The panel believes, that although a group of men over 70 years of age can have a life expectancy >10-15 years, or may are in excellent health condition, and may benefit from PSA screening, however the evidence to support the magnitude of benefit in this age group is very limited. Moreover, there is strong evidence, that the ratio of harm to benefit increases with age, and that the likelihood of overdiagnosis is extremely high, particularly among men with low-risk disease.

Unlike the AUA approach, the EAU guideline panel suggests, that PSA screening should be offered to men with a life expectancy > 10 years, independent on chronological age. This recommendation is based on the results of several studies, which demonstrate, that local progression and death from PCa can develop even in elderly men with organ-confined disease at the time of diagnosis, so early detection and active treatment seems to be justified in men with a long life expectancy independent on chronological age. Moreover, the independent impact on age on PCa-specific survival has not been well established. Recent studies have shown that with careful patient selection, older men up to age of 75 years with Gleason score 5-7 PCa and up to age 80 years with Gleason score 8-10 PCa who undergo radical prostatectomy or radiotherapy have gains in life expectancy comparable with those of younger men. Furthermore, there is data indicating, that not age by itself but rather comorbidities are the major factor that should be considered when discussing screening or treatment of PCa. Thus, depending on age and comorbidity, men without comorbidities and with organ-confined Gleason score 5-7 PCa have 2-4% probability of dying from the disease within 5 years after diagnosis, whereas the risk increases to 12-48% in men with significant comorbidities but the same age. Therefore, for the EAU guideline panel, it seems necessary to consider patient age and comorbidities with the use of validated tools such as the Charlson Comorbidity Index (CCI), which has been validated in men with PCa, to assess life expectancy.

**Conclusion**

PSA screening results in a significant reduction in PCa related mortality, diagnosis, and development of advanced and metastatic PCa, but there is a substantial risk of overdiagnosis and overtreatment, when it is used with inappropriate frequency. Therefore, screening for PCa has generated considerable debate within the medical and broader community, as demonstrated by the varying recommendations made by medical organizations, such as the EAU and the AUA, and governed by national policies. Despite the debate, most of experts agree, that the PSA test does not have the required...
characteristics to be used as a widespread screening tool for PCA. Indication for PSA screening, therefore, should be individualized and screening should be offered to well-informed men, who should be aware of the benefits and harms of PSA screening. Furthermore, as PSA may be prostate specific, it is however not specific to PCA; therefore, continued research into alternative prostate-specific markers is required.

Κατά τη διάρκεια των δύο τελευταίων δεκαετιών ο μαζικός έλεγχος του PSA έχει συμβάλει στην πρώιμη διάγνωση του προστατικού καρκίνου και ακολούθως στην αύξηση των πιθανοτήτων ιασης μετά από τοπική θεραπεία. Έτσι ο προσυμπτωματικός έλεγχος του PSA έχει χρησιμοποιηθεί ευρέως τα τελευταία χρόνια, με σκοπό την ανίχνευση του προστατικού καρκίνου σε πρώιμο στάδιο, έτσι ώστε η αντιμετώπιση του να είναι εφικτή με στόχο την ίαση και συνεπώς τη μείωση θνητότητας και βελτίωση της ποιότητας ζωής. Ωστόσο τα πραγματικά οφέλη του προσυμπτωματικού ελέγχου παραμένουν αδιευκρίνιστα, καθώς υπάρχει σημαντικός κίνδυνος υπερδιάγνωσης, ωστόσο, εκ τούτου, γύρω από το θέμα του προσυμπτωματικού ελέγχου του PSA, έχουν δημιουργηθεί σημαντικές αντιπαραθέσεις, όχι μόνο σε ιατρικό, αλλά και σε κοινωνικό επίπεδο, γεγονός που αντικατοπτρίζεται από τις διαφορετικές συστάσεις που εκδίδονται από μεγάλες ιατρικές εταιρίες, όπως είναι η Ευρωπαϊκή Ουρολογική Εταιρία (EAU) και η Αμερικανική Ουρολογική Εταιρία (AUA). Στην παρούσα εργασία παρατίθενται οι ομοιότητες και οι διαφορές που υπάρχουν στις κατευθυντήριες οδηγίες που έχουν εκδώσει οι δύο αυτές εταιρίες σχετικά με το προσυμπτωματικό έλεγχο για τον προστατικό καρκίνο, καθώς γίνεται συζήτηση σχετικά με το επιστημονικό υπόβαθρο, πάνω στο οποίο βασίζονται. Παρά τις οποίες αντιπαραθέσεις και οι δύο εταιρίες συμφωνούν στο ότι, η εξέταση του PSA δεν διαθέτει τα απαιτούμενα χαρακτηριστικά, ώστε να μπορεί να χρησιμοποιείται ως διαγνωστικό εργαλείο για μαζικούς προσυμπτωματικούς ελέγχους. Ως έκτοτο, η ένδειξη για τη διενέργεια ελέγχου του PSA, θα πρέπει να εξατομικεύεται, ο έλεγχος δε θα πρέπει να γίνεται σε καλά πληροφορημένους άνδρες, οι οποίοι θα είναι ενήμεροι για τα οφέλη και τους πιθανούς κινδύνους που μπορεί να προκύψουν.

**Περίληψη**

Λέξεις ευρετηριασμού: καρκίνος προστάτου, PSA, προσυμπτωματικός έλεγχος, κατευθυντήριες οδηγίες AUA και EAU

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