

Assessment of the effectiveness of clinical PSA concentration measurements in early prostate cancer detection

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Introduction. Prostate cancer is a malignant neoplasm originating primarily in the peripheral zone of the prostate gland. A patient's survival depends largely on the stage of the disease and the treatment method used, which is why early detection of the tumour plays an important role. One of the methods used for screening for prostate cancer is the measurement of prostate specific antigen (PSA) concentration.

Material and methods. The analysis was based on the results of the research found in the systematic review. The following sources of medical information were searched for secondary research: Medline (via PubMed), Embase (via Ovid), The Cochrane Library. The time range has been set to articles published between July 2011 and July 2021.

Results. The inclusion criteria for a systematic review of the clinical effectiveness of PSA measurements in the early detection of prostate cancer were met by 5 secondary scientific evidence articles. Most of the evidence found showed an increase in the detection of prostate cancer after PSA testing. In case of stage III or IV tumours and the metastatic prostate cancer (CaP) variant, a statistically significant reduction in tumour detection was demonstrated. Most of the scientific evidence indicates a statistically insignificant effect of PSA screening on the risk of death due to CaP (with a diagnostic threshold of ≥ 4 ng/ml).

Conclusions. Screening in the opportunistic variant aimed at prostate cancer with the use of PSA concentration is justified in men between 50 and 69 years of age, and in men <50 years of age should they have additional risk factors. Conversely, it seems unjustified to conduct population-based screening for prostate cancer.

Key words: prostate cancer, prostate-specific antigen, early detection of cancer

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Introduction

Prostate cancer (CaP) is a malignant neoplasm originating in the peripheral zone of the prostate gland. Almost 95% of CaP cases are adenocarcinomas, with changes occurring within the apical part of the peripheral zone of the prostate which are often of a multifocal nature [1]. It is also important that at an early stage of development CaP may cause no symptoms, or manifest symptoms specific to benign prostatic hyperplasia. As a result, early detection and application of preventive measures may be difficult. At a later stage of local development, this neoplasm may affect surrounding organs, such as seminal vesicles, bladder neck or ureteral openings, leading to erectile dysfunction, hydronephrosis and far-reaching renal failure. This neoplasm often exhibits metastatic features, involving the obturator lymph nodes and those located below the bifurcation of the common iliac vessels. In the final stage of development, CaP may also affect distant organs, such as the brain, lungs, or liver [2].

According to the literature, there are 3 main risk factors for prostate cancer [3]:

- age – this applies especially to men over 50,
- race/ethnicity – this applies especially to representatives of the Negroid race,
- genetic factors – that is, the presence of CaP cases in the family history, especially first-degree relatives (grandfather, father, brother). The risk in such case is often two or three times greater than in cases without familial history of CaP.

Some publications suggest that other risk factors are obesity, previous urinary tract infections and high consumption of saturated fatty acids, although the data is not conclusive [4].

Prostate cancer is the second most common cancer in the male population and the third in terms of all cancers in the world (1.41 million new cases in 2020; age-standardized incidence rate (world) – 30.7/100 000) [5]. In Europe, the incidence is approximately 148.1/100 000 [6], while the frequency of CaP in Poland is at the level of 117.9/100 000 people (standardization by revised European Standard Population ESP2013) [7]. According to the data stored in the Institute for Health Metrics and Evaluation database, the highest incidence values are observed in the age group of 70–74 (2,517.68/100 000), with a gradual increase visible already in the age group 50–54 (547.9/100 000) [8]. Prostate cancer was the fifth leading cause of cancer death among men in the world in 2020 (375 000 deaths; age-standardized mortality rate (world) – 7.7/100 000). However, it should be emphasized that mortality rates for CaP have decreased in many high-income countries since the mid-1990s, including those in Northern and Western Europe, but during the same period, rates increased in most countries in Central and Eastern Europe (also in Poland) [5]. This neoplasm accounts for 13.14% of malignant neoplasm incidence in the male population [9].

Survival depends largely on the stage of the disease and the applied treatment method; hence early tumour detection is crucial [10]. One of the methods used to screen for CaP is the measurement of the concentration of the prostate specific antigen (PSA) [11]. This test involves taking a venous blood sample from which the serum PSA concentration is then calculated. Depending on the result obtained, it is possible to identify men who are likely to develop prostate cancer. However, this tool is not a CaP-specific measurement. An increase in PSA concentration may occur with age (higher PSA values in men >40 years of age), in case of benign prostatic hyperplasia, due to physical activity, or because of a history of urinary tract infections [12]. It is possible to measure free PSA (fPSA), total PSA (tPSA) or intact PSA (iPSA) or using specific measurement protocols such as Prostate Health Index (PHI) or 4KScore, which include more than one PSA variant [13].

Objective

The clinical effectiveness of PSA concentration measurement in the early detection of prostate cancer.

Material and method

The clinical analysis was based on the research results found in the systematic review performed according to the following protocol:

- defining the inclusion criteria for publications to be included in the analysis,
- development/verification of a search strategy for scientific reports,
- searching medical information sources/updating results from medical information sources,
- acquiring full texts of scientific reports potentially useful in clinical analysis,
- selection of studies based on the criteria of inclusion in the analysis,
- analysis of the research data,
- statistical and clinical significance analysis of the results obtained from studies included in the analysis.

Searching for clinical trials was based on a detailed systematic review protocol developed in accordance with the Cochrane Collaboration guidelines before starting this research [14]. The protocol consisted of criteria for including studies in the review, the search strategy, the method of selecting studies, and the planned methodology for conducting data analysis and synthesis.

The analysis was performed on clinical trials that met the criteria for:

- population: general male population,
- interventions: measuring PSA concentration,
- alternative technologies (comparators): not limited,
- methodologies: meta-analyses of randomized trials; systematic reviews of randomized trials; meta-analysis of observational studies; systematic reviews of observational studies,

- endpoints: evaluation of the clinical effectiveness of PSA testing.

The following sources of medical information were searched for secondary research: Medline (*via* PubMed), Embase (*via* Ovid), The Cochrane Library. The last search of the databases was performed on July 27, 2021.

At all stages of the systematic review, the selection of studies was completed by two analysts working independently (MJ and AM). Inconsistencies were resolved by consensus with the participation of a third independent analyst (WM).

The quality of the secondary studies included in the analysis was assessed by verifying the key domains of the AMSTAR2 tool for critical evaluation of systematic reviews. This tool enables selection. To obtain the highest rating, the published research must score positively on every assessed aspect. Even single negative score in a critical domain results in lowering article value to low, and two or more negative scores lower the evaluation value to critically low.

Secondary research presented the results of the statistical analysis carried out by the authors of the studies (they are based on primary data and therefore constitute a reliable source of information). No meta-analysis was performed, and the results of each publication were presented separately.

Results

The inclusion criteria for a systematic review of the clinical effectiveness of PSA measurement in the early detection of prostate cancer were met by the following scientific evidence ($n = 5$; Paschen 2021, Fenton 2018, Ilic 2018, Rahal 2016, Lumen 2012):

- Paschen 2021 – meta-analysis based on 11 randomized controlled trials (RCTs), which systematically assessed the benefits and harms of population-based screening using the measurement of PSA concentration (quality: low) [15],
- Fenton 2018 – meta-analysis based on 3 RCTs and 5 observational (cohort) studies presenting systematic review of the screening evidence using PSA measurement performed; the results related to prophylaxis were not meta-analysed (quality: high) [16],
- Ilic 2018 – meta-analysis based on 5 RCTs, determining the effectiveness and safety of PSA concentration measurement as a screening test for CaP (quality: low) [17],
- Rahal 2016 – meta-analysis based on 11 RCTs, in which a quantitative review of the available screening studies using PSA concentration measurement (quality: low) was performed [18],
- Lumen 2012 – meta-analysis based on 8 RCTs, assessing the impact of population screening using PSA concentration measurement on CaP detection, stage and severity, and mortality (quality: critically low) [19].

The results of the included studies are presented below.

Effectiveness

Prostate cancer detectability and PSA diagnostic precision

As part of the Ilic 2018 meta-analysis, based on 4 RCTs, a statistically significant effect of screening utilising PSA concentration measurement on a 23% increase in CaP detection, regardless of the stage of cancer advancement had been shown (incidence risk ratio [IRR], 1.23; 95% confidence interval [CI]: 1.03–1.48). Moreover, a meta-analysis based on 3 RCTs showed that the PSA screening test had a statistically significant influence on the increase in the detection of stage I and II prostate cancer by 39% (relative risk [RR], 1.39; 95% CI: 1.09–1.79). In the case of stage III or IV neoplasms, a statistically significant reduction in detection had been demonstrated (RR, 0.85; 95% CI: 0.72–0.99). Individual results included the PSA diagnostic threshold of ≥ 3 ng/ml [17].

As part of the Fenton 2018 meta-analysis, the authors summarized data on the effectiveness of PSA concentration measurement in detecting CaP. The conclusions of the analysis were based on 3 large primary studies (CAP 2018 [20], PLCO 2017 [21, 22], ERSCP 2014 [23, 24]). The British CAP 2018 (The Cluster Randomized Trial of PSA Testing for Prostate Cancer) showed a statistically significant effect of screening with PSA concentration measurement on an increase in CaP detection by 19% (RR, 1.19; 95% CI: 1.14–1.25). Similar results were obtained in the American study PLCO 2017 (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial), which showed a statistically significant increase in CaP detection by 12% (RR, 1.12; 95% CI: 1.07–1.17), while the European Randomized Study of Screening for Prostate Cancer (ERSPC 2014) showed the highest effectiveness of population screening using PSA – a 59% increase in CaP detection in the population of European men was observed (RR, 1.57; 95% CI: 1.51–1.62). In case of the metastatic CaP variant – a statistically significant reduction in the detection of this type of cancer was demonstrated (RR, 0.70; 95% CI: 0.60–0.82) [16].

In Lumen 2012, the authors referred to 7 large studies taking into account population screening using PSA measurements. A meta-analysis based on 7 RCTs showed a statistically significant effect of population screening compared to non-screened subjects on increasing CaP detection by 55% (RR, 1.55; 95% CI: 1.17–2.06). The diagnostic threshold of PSA concentration in the studies included in the meta-analysis ranged between 2.5 and 10 ng/ml [19].

The characteristics and results of individual studies included in the review are presented in table I.

Death due to CaP

As part of the Paschen 2021 meta-analysis based on 4 RCTs, a statistically significant reduction in the risk of death due to CaP was demonstrated when participating in the screening using PSA concentration measurement with a diagnostic threshold < 4 ng/ml (IRR, 0.68; 95% CI: 0.51–0.89) and a statistically insignificant reduction of said risk when establishing

Table I. Characteristics and individual test results concerning CaP detection

Author/ year	N research	Population, n	PSA diagnostic threshold (ng/ml)	End point	RR/IRR result (95% CI)
Ilic 2018 (MA)	4 RCT	males aged 50–74, 675 232	≥3.0	CaP incidence rate	IRR = 1.23 (1.03–1.48)
	3 RCT	men aged 50–74, 647 751		detectability of CaP in stage I or II	RR = 1.39 (1.09–1.79)
	3 RCT	men aged 50–74, 647 751		detectability of CaP in stage III or VI	RR = 0.85 (0.72–0.99)
Fenton 2018 (MA)	1 RCT (CAP 2018)	men aged 50–69, 408 825	3.0	CaP detectability	RR = 1.19 (1.14–1.25)
	1 RCT (PLCO 2017)	men aged 55–74, 76 683	4.0		RR = 1.12 (1.07–1.17)
	1 RCT (ERSPC 2014)	men aged 50–74, 181 999	2.5–4.0	detectability of the metastatic variant of the CaP	RR = 1.57 (1.51–1.62)
Lumen 2012 (MA)	7 RCT	men aged 45–74, 525 108	2.5–10.0	CaP detectability	RR = 1.55 (1.17–2.06)

MA – meta-analysis; CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio; IRR – incidence risk ratio

a PSA test threshold of ≥ 4 ng/ml (IRR, 0.95; 95% CI: 0.86–1.05). In addition, a meta-analysis based on 11 RCTs showed that screening using PSA concentration measurement statistically significantly reduces the number of deaths due to CaP over a 16-year perspective by 3 deaths/1000 people (3; 95% CI: 1–5/1000) and reduces the number of CaP progressions to the metastatic variant in the next 12 years by 3/1000 people (3; 95% CI: 2–4/1000) [15].

The 2018 Ilic meta-analysis based on 4 RCTs did not show a statistically significant effect of screening with PSA concentration measurement on CaP mortality (IRR, 0.96; 95% CI: 0.85–1.08) [17].

The 2018 Fenton meta-analysis considered the conclusions of the 3 RCT evaluation. Two studies (CAP 2018, PLCO 2017) showed no statistically significant effect of PSA screening on

the risk of death due to CaP (RR, 0.96; 95% CI: 0.85–1.08; RR, 1.04; 95% CI: 0.87–1.24). In turn, the third study (ERSPC 2014) showed a statistically significant effect of PSA screening on the risk of death from CaP (RR, 0.79; 95% CI: 0.69–0.91) [16].

As part of the Rahal 2016 meta-analysis, the authors took into account 11 RCTs, finding no statistically significant effect of screening using PSA concentration measurement on CaP mortality (RR, 0.89; 95% CI: 0.76–1.04) [18].

The Lumen 2012 meta-analysis based on 7 RCTs did not show a statistically significant effect of population screening using PSA concentration measurement on the reduction of the risk of death due to CaP (RR, 0.88; 95% CI: 0.72–1.06). However, based on 4 RCTs, using the adjusted analysis (studies with: follow-up >8 years; PSA test in the control group <33.3%; compliance in the screening group >75%), a statistically significant effect of

Table II. Characteristics and individual test results concerning death due to CaP

Author/ year	N research	Population, n	PSA diagnostic threshold (ng/ml)	End point	RR/IRR result (95% CI)
Paschen 2021 (MA)	4 RCT	men aged 55–70, 66 832	<4	death due to CaP	IRR = 0.68 (0.51–0.89)*
	4 RCT	men aged 55–70, 199 085	≥4		IRR = 0.95 (0.86–1.05)
Ilic 2018 (MA)	4 RCT	men over 18 years of age with or without lower urinary tract symptoms that would suggest the presence of prostate cancer, 718 258	≥3.0		IRR = 0.96 (0.85–1.08)
Fenton 2018 (MA)	1 RCT (CAP 2018)	men aged 55–74, 418 732	3.0		RR = 0.96 (0.85–1.08)
	1 RCT (PLCO 2017)	men aged 55–74, 84 748	4.0		RR = 1.04 (0.87–1.24)
	1 RCT (ERSPC 2014)	men aged 55–74, 175 758	2.5–4.0		RR = 0.79 (0.69–0.91)*
Rahal 2016 (MA)	11 RCT	men aged 55–69, 302 497	–		RR = 0.89 (0.76–1.04)
Lumen 2012 (MA)	7 RCT	men aged 45–74, 571 594	–		RR = 0.88 (0.72–1.06)

* a statistically significant results

MA – meta-analysis; CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio; IRR – incidence risk ratio

population screening using PSA concentration measurement on reduction of the risk of death due to CaP by 24% (RR, 0.76; 95% CI: 0.58–0.98) [19]. The characteristics and results of individual studies included in the review are presented in table II.

Overall mortality

As part of the Ilic 2018 meta-analysis based on 4 RCTs, no statistically significant effect of screening using PSA concentration measurements on overall mortality was demonstrated (IRR, 0.99; 95% CI: 0.98–1.01) [17].

In the Fenton 2018 meta-analysis, none of the 3 RCTs included (CAP 2018, PLCO 2017, ERSPC 2014) showed a statistically significant effect of PSA screening on overall mortality (RR, 0.99; 95% CI: 0.94–1.03; RR, 0.98; 95% CI: 0.95–1.00; RR, 1.00; 95% CI: 0.98–1.02) [16]. The characteristics and results of individual studies included in the review are presented in table III.

Number needed to invite

The Fenton 2018 meta-analysis showed that it was necessary to invite 154 men to the CAP 2018 study (95% CI: 128–192), 84 men to the PLCO 2017 study (95% CI: 59–144) and 26 men to the ERSPC 2014 study (95% CI: 24–29) to diagnose one additional case of CAP in men [16]. The characteristics and results of the Fenton 2018 study regarding number needed to invite (NNI) are presented in table IV.

Safety

Some of the found scientific publications (n = 4) refer to the results of the ERSCP, PLCO and/or CAP studies, which analysed

the effectiveness of population screening for CaP and the side effects resulting from this type of screening (Paschen 2021, Fenton 2018, Ilic 2018, Lumen 2012). Based on the above-mentioned study, the authors analysed: the frequency of false-positive results, the rate of over-detection, as well as the percentage and consequences of prostate biopsies based on the PSA result [15–17, 19].

False Positive Results

In PLCO 2017, 10.4% of men had at least 1 false positive PSA test result of all participants who underwent at least 1 PSA test in the first 4 (out of 6 cycles) screening tests (n/N = 3387/32 567). In turn, in the ERSPC 2014 study, 17.8% of men received at least 1 false positive PSA test result among all participants who were tested at least once in one of the 5 centres (n/N = 10 965/61 604).

Over-detection

Depending on the method of measuring over-detection, the percentage of over-detection ranged from 16.4 to 20.7% in the PLCO 2017 study and from 33.2 to 50.4% in the ERSPC 2014 study. In the CaP 2018 study, the over-detection rate was 40.7%

Biopsy based on PSA result

In the PLCO 2017 study, 12.6% of men underwent at least 1 biopsy (6295 biopsies in total) in all PLCO screening cycles (16.4 biopsies/ 100 men assigned to screening). Of the men subjected to biopsy, 2% experienced complications such as infection, bleeding, or difficulty urinating (n/N = 97/4861).

Table III. Characteristics and individual test results concerning all-cause mortality

Author/ year	N research	Population, n	End point	RR/IRR result (95% CI)
Ilic 2018 (MA)	4 RCT	men over 18 years of age with or without lower urinary tract symptoms that would suggest the presence of prostate cancer, 718 258	general mortality	IRR = 0.99 (0.98–1.01)
Fenton 2018 (MA)	1 RCT (CAP 2018)	men aged 55–74, 418 732		RR = 0.99 (0.94–1.03)
	1 RCT (PLCO 2017)	men aged 55–74, 84 748		RR = 0.98 (0.95–1.00)
	1 RCT (ERSPC 2014)	men aged 55–74, 175 758		RR = 1.00 (0.98–1.02)

MA – meta-analysis; CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio; IRR – incidence risk ratio

Table IV. Fenton 2018 results for number needed to invite (NNI)

Author/year	N research	Population, n	End point	NNI score (95% CI)
Fenton 2018 (MA)	1 RCT (CAP 2018)	men aged 55–74, 418 732	NNI	NNI = 154 (128–192)
	1 RCT (PLCO 2017)	men aged 55–74, 84 748		NNI = 84 (59–144)
	1 RCT (ERSPC 2014)	men aged 55–74, 175 758		NNI = 26 (24–29)

MA – meta-analysis; CI – confidence interval; RCT – randomized controlled trial; NNI – number needed to invite

In the ERSPC 2014 study, the biopsy rate among men randomized for screening was 27.7 biopsies/100 men. In CaP 2018, 7.3% of participants (n/N = 71/977) and 5.5% of participants (n/N = 54/981) experienced moderate or severe pain and moderate or severe fever within one month of biopsy, respectively.

In the PLCO 2017, ERSPC 2014 and CaP 2018 studies, prostate cancer, based on the performed biopsy, was not confirmed in 67.7%, 75.8% and 60.6% of the participants of the respective studies. Moreover, there was no statistically significant relationship between the biopsy performed and the reduction of the risk of death (ERSPC 2014, PLCO 2017).

Discussion

Based on the results of the research found in the systematic review, the clinical effectiveness of PSA testing in the early detection of prostate cancer was assessed.

The results of most of the evidence found indicate an increase in the detection of CaP by screening with PSA measurement [16, 17, 19]. In the case of stage III or IV tumours [17] and the metastatic CaP variant [16], a statistically significant reduction in tumour detection was demonstrated. Some of the evidence found indicates the occurrence of adverse effects resulting from screening based on the PSA test [15–17, 19]. Most of the scientific evidence indicates a statistically insignificant effect of PSA screening on the risk of death due to CaP [15, 16, 19] – at the diagnostic threshold of ≥ 4 ng/ml.

For the purposes of discussion, the current clinical practice guidelines for PSA testing were reviewed. The most important conclusions of the recommendations are presented below.

The recommendations of the Polish Society of Clinical Oncology from 2013 [25] indicate that the population screening for the diagnosis of CaP at an early stage (clinically asymptomatic) is based on the determination of serum PSA levels. The target PSA concentration values for the presence of CaP are 4.0 ng/ml. However, even in the case of lower PSA values, it is not possible to completely exclude the probable presence of this tumour. It should be noted that the Paschen 2021 meta-analysis showed a statistically significant reduction in the risk of death due to CaP with a diagnostic threshold of < 4 ng/ml.

The Polish Society of Urology in 2011 [26] indicated that despite the lower risk of death due to CaP, screening tests using the PSA measurement determine a high probability of false positive results.

The American Cancer Society (ACS 2021) [12] recommends that men should be given the opportunity to make an informed decision about undergoing screening for CaP, with the support of their physician. After being informed about the possibility of screening, adjusted to age of the patient, men who wish to undergo screening tests should have their blood tested for the presence of a prostate specific antigen.

The National Comprehensive Cancer Network (NCCN 2021) [13] emphasizes the role of patient education in recognizing

and distinguishing the symptoms of lower urinary tract diseases caused by benign prostatic hyperplasia. Measurement of the concentration of prostate-specific antigens should be offered to men aged 45–75 years who have received all the necessary information about the test and are in good health. Recommendations based on expert consensus suggest that PSA measurement should be offered to men over 75 years of age without or with a small number of comorbidities. In addition, it is not recommended to measure men who will not benefit from having prostate cancer detected (PSA testing should only be offered to men with a life expectancy ≥ 10 years).

The European Society for Medical Oncology (ESMO 2020) [27] does not recommend PSA-based screening. The organisation emphasises that measuring PSA levels contributes to the reduction of mortality, but the disadvantage is over-detection and unnecessary treatment of men with false-positive results. In addition, the recommendations indicate that an early PSA measurement may be offered to men over 50 and over 40 with a family history of CaP, African-Americans of more than 45 years of age, and carriers of the *BRCA1/2* mutation above 40 years of age.

According to the US Preventive Services Task Force Recommendation Statement (USPSTF 2018) [28], the decision to conduct PSA testing in men aged 55–69 should be made individually. Experts emphasize that the benefits of screening PSA tests are small, while the harm is significant, such as frequent over-detection, unnecessary treatment or false positive results determining the need for further diagnostics. In addition, it has been shown that screening based on PSA levels for men > 70 years is not recommended.

Limitations

In this review only publications in English are included. The search has been limited to publications from the last 10 years (July 27, 2011–July 27, 2021). The studies included in the secondary scientific evidence found covered a diverse population in terms of ethnicity and geography. Also evidence were characterized by high heterogeneity (including various methods of presenting the analysed data).

Conclusions

The authors of included studies indicated an increase in the detection of CaP during PSA screening tests, with no effect on the reduction of the risk of death due to prostate cancer. Screening in the opportunistic variant aimed at prostate cancer with the use of PSA concentration is justified in men between 50 and 69 years of age, and in men above 50 years of age with additional risk factors.

It seems unreasonable to conduct population screening based on the measurement of PSA concentration due to frequent over-detection, unnecessary treatment or false-positive results necessitating further diagnosis.

Conflict of interest: none declared

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