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Original Article

Confirmation of Prostate-specific Antigen (PSA) Values Improves Prostate Cancer Screening in Early Middle-Aged Men – Data from the PROBASE Trial

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Abstract

Background and objective: To assess the effectiveness of a confirmatory prostate-specific antigen (PSA) test as a safeguard against unnecessary work-up and to improve the specificity of prostate cancer (PCa) screening.

Methods: Overall, 72,157 PSA values corresponding to screening rounds at age 45–55 yr in the PROBASE trial were analyzed. Positive PSA tests were reported as the proportion of men with an initial or confirmatory PSA ≥ 3 ng/ml. The cumulative PCa number over 6 yr was described for men with and without confirmatory PSA decrease at baseline screening (age 45 yr). Sankey diagrams were plotted to illustrate changes in PSA values over 10 yr with 2-yearly PSA screening.

Key findings and limitations: Overall, 2782 initial PSAs and 2702 (97%) confirmatory PSAs were observed. A total of 38% (95% confidence interval [CI] 36, 40) of men with initial PSA ≥ 3 ng/ml had a PSA < 3 ng/ml at confirmatory testing. Estimates differed by age and screening round: 46% (95% CI 41, 51) in 45-yr-olds and 34% (95% CI 31, 38) in 50-yr-olds. PSA was repeated at a median of 28 d (interquartile range [IQR] 20, 39). Median change was -0.5 ng/ml (IQR -1.3 , $+0.06$). PCa risk at 6 yr was 33% in those with confirmed

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Confirmatory PSA
Repeat PSA
Prostate cancer

PSA and 7.0% in those with PSA decrease at age 45 yr (risk ratio 4.68, CI 2.55, 8.59). The main limitation is incomplete biopsy information.

Conclusion: PSA elevations in early-middle-aged men are common and PSA should be confirmed before initiating diagnostic work-up in a screening setting.

Clinical implications: Repeating PSA before initiating diagnostic work-up reduces immediate further diagnostics.

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ADVANCING PRACTICE

What does this study add?

Temporary prostate-specific antigen (PSA) elevations are common. In early middle-aged men (45–55 yr), 38% of elevated PSA dropped below the biopsy threshold when PSA was repeated within a median of 28 d. Most men remained at low PSA values over 10 yr when undergoing 2-yearly PSA screening after they initially had elevated but lower confirmatory PSA at baseline screening.

Clinical Relevance

This study provides prospective evidence from the PROBASE trial that nearly 40% of initially elevated PSA values in men aged 45–55 years fall below the biopsy threshold when PSA testing is repeated after a short interval, substantially reducing unnecessary diagnostic work-up while improving the specificity of prostate cancer screening. Individuals whose PSA normalized on repeat testing had an almost five-fold lower risk of prostate cancer over six years than those with confirmed PSA elevation, supporting the oncological safety of a confirmatory PSA strategy in early middle-aged men. These findings have direct implications for the implementation of organized PSA-based screening programmes in Europe, supporting repeat PSA testing as a simple, low-cost safeguard that may decrease unnecessary MRI examinations and biopsies without jeopardizing clinically significant cancer detection. Associate Editor: Gianluca Giannarini.

Patient Summary

In this study, we examined the benefits of confirming an initially elevated prostate-specific antigen (PSA) test within a screening program before starting diagnostic work-up. We found that PSA levels fluctuate considerably in early middle-aged men, and repeating the PSA test can safely exclude a large proportion of men from immediate diagnostics. This approach could help to avoid unnecessary procedures and make screening more efficient.

1. Introduction

In 2022, the Council of the European Union recommended exploring prostate-specific antigen (PSA)-based screening in combination with magnetic resonance imaging (MRI) in an organized prostate cancer (PCa) screening setup [1]. Based on this, the European Association of Urology (EAU) has proposed an algorithm for European countries for risk-adapted PCa screening for 50–69 yr-old men [2,3]. It uses PSA as primary test with further risk stratification in those with PSA ≥ 3 ng/ml. Slightly different adaptations of this algorithm are currently being tested within the PRAISE-U consortium [4] and the Organized Prostate cancer Testing (OPT) program in Sweden [5].

However, PSA, while typically rising in the presence of PCa, also fluctuates because of various benign factors including infections, sexual activity, medication use or physical activity such as cycling, and also because of growth of the prostate [6–8]. As a result, initiating further diagnostic procedures, such as MRI or biopsy, based on a single

elevated PSA measurement may lead to unnecessary and potentially harmful investigations. To account for these fluctuations, a strategy of repeating or confirming PSA could be used and it has been shown to be associated with a reduced risk of PCa [9–11]. However, this approach also faces a risk of missing some high-grade cancers [10]. Repeating PSA test before further investigations is listed as a weak recommendation in the EAU guidelines [12]; however, confirmatory PSA is not a part of the EAU proposed screening algorithm.

In the PROBASE trial, a strategy requiring confirmation of a PSA value ≥ 3 ng/ml before initiating further diagnostic work-up has been in place since 2014. The current analysis quantifies PSA decreases in early middle-aged men and focusses specifically on those with PSA decrease and their long-term PCa risk. The current analysis aims to assess the effectiveness of using confirmatory PSA testing step as a safeguard against premature diagnostics and its potential to improve the specificity of PCa screening program.

2. Materials and methods

2.1. PROBASE trial

PROBASE is an ongoing randomized trial comparing outcomes of risk-adapted PCa screening when screening starts at 45 yr (immediate screening arm) versus at 50 yr (deferred screening arm). Depending on the baseline PSA value at those ages, participants are classified to “low-risk” if PSA is <1.5 ng/ml and “intermediate risk” for PSA of 1.5–<3 ng/ml. PSA values of ≥ 3 ng/ml are repeated which value determines the final risk group. Men with confirmed PSA value ≥ 3 ng/ml are recommended a biopsy independent from the MRI results [13].

2.2. Data

Data on PROBASE screening PSA tests, MRI and biopsies were extracted from the electronic database Onkostar on March 30, 2026. To allow time for data entry to the database, data entries were restricted to January 1, 2026. Data on screening rounds between ages 45 and 55 yr we analyzed. Men who withdrew from the trial with complete data erasure were excluded from this analysis ($N = 66$). Among them, $N = 54$ either had not participated in any screening round or had initial PSA <3 ng/ml at age 45 yr. Among the rest, one had confirmed elevated PSA at age 45 yr and PSA values are unknown for 11 individuals.

PSA screening round was specified by the theoretical age at the time of per-protocol planned PSA screening invitation. The PROBASE screening schema by the age of 55 yr is shown in [Supplementary Fig. 1](#). The factual age of screened study participants corresponding to age at per-protocol planned screening round is shown in [Supplementary Table 1](#).

2.3. Statistical analysis

All analyses were descriptive, focusing on summary statistics such as proportions, medians with interquartile range (IQR) and 95% confidence intervals (CI), and were carried out using Stata version 18 (StataCorp, College Station, TX).

The number of having a positive PSA test in different PROBASE screening rounds was reported as proportions of initial or confirmatory PSA ≥ 3 ng/ml among the screened populations. Corresponding CIs for proportions were calculated using the Wilson method, applying the normal approximation with a 95% confidence level. Differences between the initial and confirmatory PSA values were reported as medians and percentage change relative to the initial PSA.

A Sankey diagram was used to visually illustrate changes in PSA categories between the initial and confirmatory PSA values at multiple screening rounds over 10 yr for men in the 2-yearly screening schedule. For men starting 2-yearly PSA screening at age 45 yr, screening rounds at 45, 47, 49, 51, 53 and 55 yr could be presented, and for men starting with PSA screening at age 50 yr—screening rounds at 50, 52, and 54 yr. Sankey diagrams were generated with Python.

To assess the effect of confirmatory PSA, cumulative PCa cases were analyzed across subgroups defined by initial and confirmatory PSA levels at age 45 yr. As such, the cumulative number of PCa cases was reported for men with confirmed PSA ≥ 3 ng/ml and those with an elevated initial PSA followed by a lower confirmatory value. Lower PSA category was reported as follows: <1.5, 1.5–<2; 2–<2.5; and 2.5–<3 ng/ml. PCa cases were further stratified by International Society of Urological Pathology (ISUP) Grade Group (GG). PCa numbers within 6 yr from the study enrollment were reported to capture screening round 5 yr later for men in the low-risk group. An additional 1 yr was considered to capture the biopsy outcome. By the time of this analysis, all study participants at low risk or in the deferred screening arm have received the invitation to PSA screening 5 yr from the study enrollment. The individual theoretical study follow-up time for each study participant varied from 6 yr (for those recruited in 2019) to 11 yr (for those recruited in 2014).

A sensitivity analysis was performed to compare various rules of classifying men at “high risk” at age 45 yr and numbers of men undergoing biopsy, detected or missed PCa, and the positive predictive value (PPV) of each rule.

3. Results

A total of 72 157 screening PSA values were observed, corresponding to screening rounds between the screening ages of 45 and 55 yr. PSA ≥ 3 ng/ml was observed 2782 times, of which 2702 (97%) were retested within the median time of 28 d (IQR: 20, 39).

3.1. Number of positive PSA result per screening round

[Table 1](#) shows the number of positive (≥ 3 ng/ml) initial or confirmed PSA test at different screening rounds. Of the 2782 initially elevated screening tests, 59% remained above 3 ng/ml and were recommended a biopsy, 38% decreased below it and returned to PSA screening schedule and 2.9% ($N = 80$) were assigned to a high-risk group and recommended a biopsy based on the initially elevated PSA value (<5.3% per screening round, [Supplementary Table 2](#)). Among men screened for the first time within the PROBASE trial (ages 45 and 50 yr), PSA values ≥ 3 ng/ml were observed in 1.5% and 3.7%, respectively, and PSA remained above ≥ 3 ng/ml in 0.76% and 2.3% after PSA was repeated. Among 45-yr-olds, 46% of participants, and among 50-yr-olds, one-third (34%) were not offered immediate biopsy because their PSA decreased below 3 ng/ml threshold.

The median values of initial elevated PSAs and confirmatory PSAs were 3.69 (IQR, 3.28, 4.54) and 3.22 ng/ml (IQR, 2.61, 3.98), respectively. PSA levels declined at repeated measurement by a median of -0.5 ng/ml (IQR: -1.3, +0.06) ([Supplementary Fig. 2](#)). Levels of confirmatory PSA by screening round are shown in [Supplementary Fig. 3](#). Between 15% and 25% of men at the time of confirmatory PSA had a PSA of 2.5–<3 ng/ml, that is, just below the biopsy threshold.

Table 1 – Number of positive (≥ 3 ng/ml) prostate specific antigen (PSA) findings at initial or confirmed PSA measurement in different PROBASE screening rounds

Assigned risk group at baseline ^a	Evaluable screening round ^{a,b}	Screened men	Initial PSA ≥ 3 ng/ml, N (%; 95% CI)	Confirmed PSA ≥ 3 ng/ml, N (%; 95% CI) ^c	Proportion of elevated initial PSA that decreased below 3 ng/ml
Immediate screening arm					
n/a	45 (baseline)	23,281 ^d	343 (1.5%, CI: 1.3, 1.6) ^d	178 (0.76%, CI: 0.66, 0.88) ^d	46%, CI: 41, 51
Intermediate risk at 45	47	1995	198 (9.9%, CI: 8.7, 11)	129 (6.5%, CI: 5.5, 7.6)	34%, CI: 28, 41
	49	1618	202 (12%, CI: 11, 14)	128 (7.9%, CI: 6.7, 9.3)	35%, CI: 29, 42
	51	1324	223 (17%, CI: 15, 19)	138 (10%, CI: 8.9, 12)	35%, CI: 29, 41
	53	747	141 (19%, CI: 16, 22)	88 (12%, CI: 9.7, 14)	34%, CI: 27, 42
	55	265	47 (18%, CI: 14, 23)	31 (12%, CI: 8.4, 16)	32%, CI: 21, 45
Low risk at 45	50	16,124	196 (1.2%, CI: 1.1, 1.4)	66 (0.41%, CI: 0.32, 0.52)	63%, CI: 56, 70
	52	1220	127 (10%, CI: 8.8, 12)	81 (6.6%, CI: 5.4, 8.2)	36%, CI: 28, 45
	54	535	95 (18%, CI: 15, 21)	62 (12%, CI: 9.2, 15)	29%, CI: 21, 39
	55	2801	45 (1.6%, CI: 1.2, 2.1)	23 (0.82%, CI: 0.55, 1.2)	47%, CI: 33, 61
Deferred screening arm					
n/a	50 (baseline)	17,141	641 (3.7%, CI: 3.5, 4.0)	395 (2.3%, CI: 2.1, 2.5)	34%, CI: 31, 38
Intermediate risk at 50	52	1727	290 (17%, CI: 15, 19)	170 (9.8%, CI: 8.5, 11)	38%, CI: 33, 44
	54	765	169 (22%, CI: 19, 25)	114 (15%, CI: 13, 18)	29%, CI: 23, 36
Low risk at 50	55	2614	65 (2.5%, CI: 2.0, 3.2)	36 (1.4%, CI: 1.0, 1.9)	42%, CI: 31, 53
Total		72,157	2,782 (3.9%, CI: 3.7, 4.0)	1639 (2.3%, CI: 2.2, 2.4)	38%, CI: 36, 40

CI = confidence intervals.

^a PSA screening round was specified by the theoretical age at the time of per-protocol planned PSA screening invitation. PROBASE screening schema by the age of 55 is shown in Supplementary Fig. 1.^b Screening rounds at age 50 yr and older are still ongoing, as not all eligible men have yet been invited to PSA screening in their corresponding screening round, and among those who have been invited, some may not yet have responded to the invitation.^c Includes only men with known confirmatory PSA values. A total of 80 men were assigned to a “high risk” based on initial PSA value as they did not comply with invitation to repeat PSA.^d Differences from previously published data: a total of 23,301 men had their PSA measured at age 45 yr; so far N = 20 of them had asked for a complete data erasure making their PSA values unknown anymore, thus, excluded from this analysis.

3.2. PCa cases in men with elevated initial PSA at age 45 yr

Median follow-up time for men in the immediate screening arm from the study enrollment to the last available contact was 7.9 yr (IQR 5.3, 9.0). PCa values detected over time in the immediate screening arm by ISUP GG are graphically shown in Supplementary Fig. 4 and the cumulative number of PCa cases detected in the first 6 yr of the study among men with elevated initial screening PSA (minimum time in the study for all participants) are shown in Table 2. Within this time, 33% of men with confirmed PSA ≥ 3 ng/ml at baseline were diagnosed with PCa, either directly at age 45 yr (48 out of 58 tumors) or in later years for men who refused immediate biopsy. In comparison, only 7.0% of those who were reclassified to the intermediate or low risk based on confirmatory PSA were diagnosed with PCa (risk ratio [RR] 4.68, CI 2.55, 8.59), with most cases (9 out of 11) occurring in those whose confirmatory PSA decreased just below 3 ng/ml (2.5–<3). No PCa cases have been observed within 6 yr in men with a PSA decrease below 1.5 ng/ml. The overall number of ISUP GG 3–5 cancers was low and increased from 4/58 cases (6.9%) within the first 6 yr to 7/63 (11%) within the 10 yr in men with confirmed PSA above 3 ng/ml (Supplementary Fig. 4). Of note, 2/11 cancers (18%) were ISUP GG 3–5 in those with PSA decrease at 6 yr. Similar proportion of ISUP GG 3–5 cancers (22%) was observed in men directly classified to intermediate risk based on their initial PSA value (Supplementary Table 3).

Outcomes of potentially different rules for classifying men to high risk at age 45 yr are shown in Table 3. PPV varied between 20% for a single elevated PSA to 33% for the rule used in the PROBASE protocol.

3.3. Changes in PSA categories over time

Changes in PSA levels over time among men who had an elevated initial PSA at baseline screening (age 45 or 50 yr) but confirmatory PSA of 1.5–3 ng/ml (PROBASE intermediate risk, 2-yr screening) are shown in Fig. 1. At age 45 yr, we observed 119 such men, and cumulatively over the 10 yr, 48 (40%) crossed the threshold for biopsy in later rounds and 14 (12%) had been diagnosed with PCa (N = 2 ISUP GG 3–5 cases) (Supplementary Fig. 4). Although follow-up is less mature for men with a PSA decrease at age 50 yr, a similar pattern is seen, with most remaining below 3 ng/ml over the next 4 yr. Worth noting, a substantial proportion of men in both screening arms remained with PSA <1.5 ng/ml over time (15–50% in each subsequent round). Sankey diagrams for men with initial PSA levels of 1.5–<2, 2–<2.5, and 2.5–<3 at baseline screening are shown in Supplementary Fig. 5.

4. Discussion

The current analysis of the PROBASE trial evaluated the impact of incorporating a confirmatory PSA test to reduce clinical work-up and potential overdiagnosis after a single

Table 2 – Cumulative number of prostate cancers detected within the first 6 yr of the study in men with various baseline prostate specific antigen (PSA) values at age 45 yr

Baseline screening at age 45 yr		Prostate cancers (cumulative incidence, %) ^a				Proportion of	
PSA (ng/ml)	N	ISUP GG 1	ISUP GG 2	ISUP GG 3–5	Total	ISUP GG 1–2	ISUP GG 3–5
≥3 _{init} → ≥3 _{conf}	178	18 (10%, CI: 6.6, 15)	36 (20%, CI: 15, 27)	4 (2.2%, CI: 1.1, 5.4)	58 (33%, CI: 26, 40)	93% CI: 84, 97	6.9% CI: 3.4, 16
≥3 _{init} → no conf. PSA	7	0	0	0	0	n/a	n/a
≥3 _{init} → <3 _{conf}	158	4 (2.5%, CI: 1.3, 6.1)	5 (3.2%, CI: 1.6, 6.9)	2 (1.3%, CI: 0.72, 4.1)	11 (7.0%, CI: 4.1, 12)	82% CI: 53, 94	18% CI: 9.0, 44
Total (≥3 _{init})	343 ^b	22 (6.4%, CI: 4.3, 9.5)	41 (12%, CI: 9.0, 16)	6 (1.7%, CI: 0.91, 3.7)	69 (20%, CI: 16, 25)	91% CI: 82, 96	8.7% CI: 4.5, 17
Smaller confirmatory PSA categories							
≥3 _{init} → 2.5–<3 _{conf}	50	3 (6.0%, CI: 3.0, 15)	5 (10%, CI: 5.0, 21)	1 (2.0%, CI: 1.8, 9.1)	9 (18%, CI: 10, 30)	89% CI: 57, 93	11% CI: 7.5, 38
≥3 _{init} → 2–<2.5 _{conf}	35	1 (2.9%, CI: 2.0, 13)	0 (0%, CI: 0, 10)	1 (2.9%, CI: 2.5, 13)	2 (5.7%, CI: 3.1, 17)	50% CI: 17, 83	50% CI: 17, 83
≥3 _{init} → 1.5–<2 _{conf}	34	0	0	0	0	n/a	n/a
≥3 _{init} → <1.5 _{conf}	39	0	0	0	0	n/a	n/a

Label definitions—conf: confirmatory PSA value after an initial PSA ≥3 ng/ml; init: initial PSA value.

^a Prostate cancer at the initial or repeated biopsy. Time restricted to first 6 yr since study enrollment that is the minimum study time for all men in the trial (last participant was enrolled in December 2019).

^b As reported by Arsov et al, 344 individuals had initial PSA above 3 ng/ml, however, one individual was excluded from this analysis as exact PSA levels at initial or confirmatory PSA measurements are unknown. When comparing the current database records with the already published information, we can define that this person had initial and confirmed PSA ≥3 ng/ml. At the time of his withdrawal, cancer linkage was not yet available and therefore, there is no information whether this person had been diagnosed with prostate cancer or not.

Table 3 – Outcome of different rules of assigning men to “high risk” at age 45 yr with the outcome within the first 6 yr since study enrollment

Measured parameters:	Different rules to recommend a biopsy at age 45 yr						
	PROBASE protocol: ≥3.0 + ≥3.0	Single PSA ≥3.0	Single PSA ≥3.5	Single PSA ≥4.0	“Nordström”: ≥3.0 + decrease less than 20% or ≥3.0	Adapted PROBASE: ≥3.0 + ≥2.5	Average of two PSAs ≥3.0
Observed number of participants in category	178 0.76%	343 1.5%	210 0.90%	145 0.62%	308 1.3%	228 0.98%	223 1.0%
1st biopsy							
N	131	154	110	80	144	148	141
N, positive	55 (45%)	65 (42%)	49 (45%)	33 (41%)	61 (42%)	64 (43%)	61 (43%)
All biopsies							
N	159	189	131	95	175	179	171
N, positive	58 (44%)	68 (36%)	51 (39%)	35 (37%)	64 (36%)	67 (37%)	64 (37%)
Cancers in men <u>assigned</u> to a “high risk” (at “45” + later in time):							
Total	58	69	51	35	65	67	64
ISUP GG 1	18	22	16	11	20	21	20
ISUP GG 2	36	41	31	20	39	41	39
ISUP GG 3	2	4	2	2	4	3	3
ISUP GG 4	1	1	1	1	1	1	1
ISUP GG 5	1	1	1	1	1	1	1
Cancers in men <u>not assigned</u> to a “high risk” (at “45” + later in time):							
Total	82	71	89	105	75	73	76
ISUP GG 1	29	25	31	36	27	26	27
ISUP GG 2	34	29	39	50	31	29	31
ISUP GG 3	11	9	11	11	9	10	10
ISUP GG 4	4	4	4	4	4	4	4
ISUP GG 5	4	4	4	4	4	4	4
ISUP GG 2–5 cancers detected within the rule / outside the rule	40/53 43%/57%	47/46 51%/49%	35/58 38%/62%	24/69 26%/74%	45/48 48%/52%	46/47 49%/51%	44/49 47%/53%
Presumed positivity rate, PPV	58/178 33%	69/343 20%	51/210 24%	35/145 24%	65/308 21%	67/228 29%	64/223 29%
Presumed detection rate	58/23,301 0.25%	69/23,301 0.30%	51/23,301 0.22%	35/23,301 0.15%	65/23,301 0.28%	67/23,301 0.29%	64/23,301 0.27%

ISUP GG = International Society of Urological Pathology Group Grade.

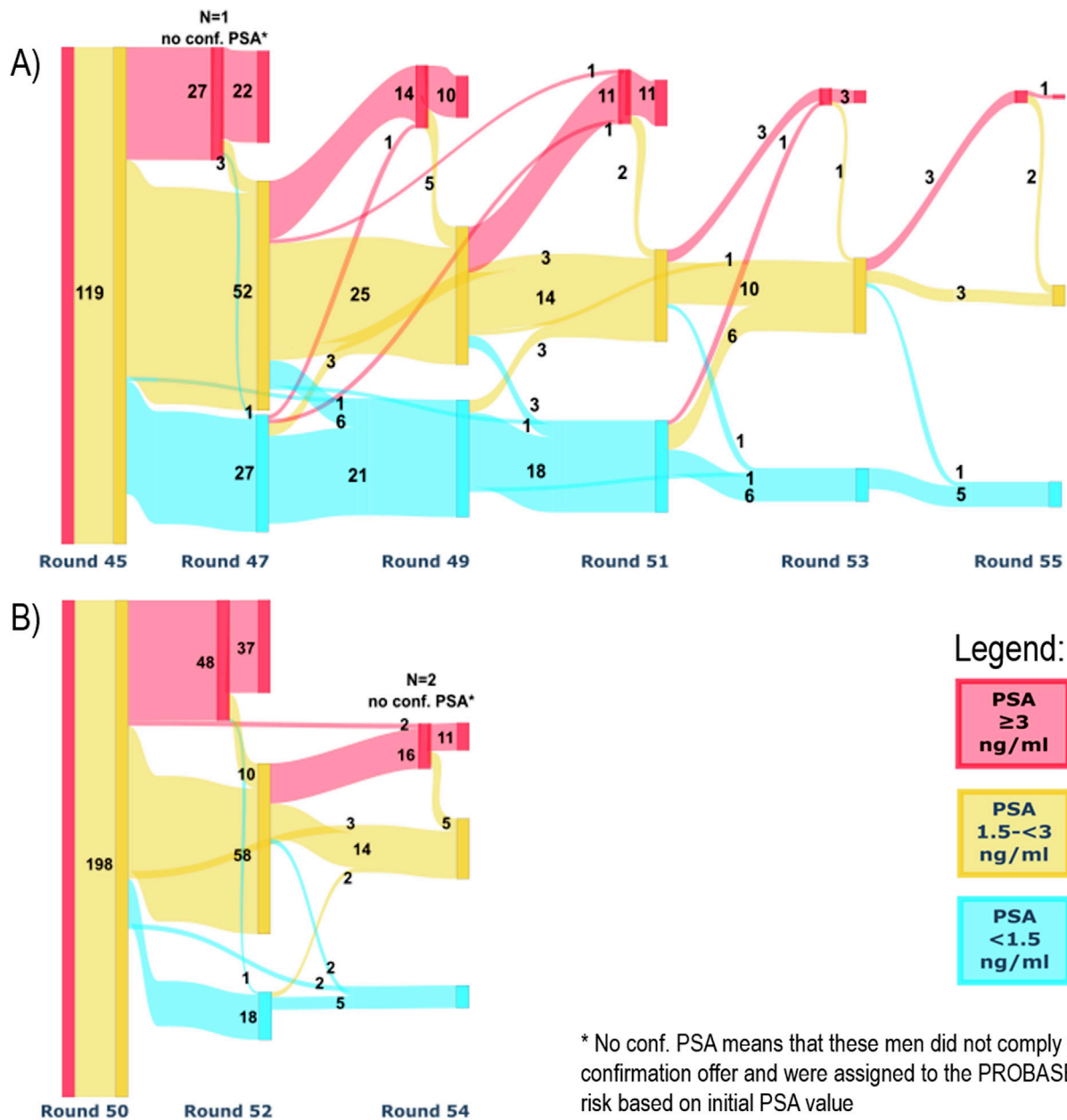


Fig. 1 – Sankey graph demonstrating PSA changes over 2-yearly screening rounds in men who experienced a PSA decrease at age 45 yr (upper panel) or at age 50 yr (lower panel). Note: Numbers within branches represent men with that particular PSA value.

suspicious PSA value ≥ 3 ng/ml. PROBASE demonstrated that a PSA decrease was a common occurrence when retested after a short time with 38% of initially positive PSA tests falling below 3 ng/ml. PROBASE demonstrates that men with a PSA decrease below 3 ng/ml at age 45 yr had a remarkably nearly 5-fold lower PCa risk within 6 yr than those with confirmed PSA ≥ 3 ng/ml.

Differences in PSA values upon retesting can result from natural biological causes, such as subclinical infections or changes in day-to-day activities, and technical factors, such as differences in assays or laboratory methods that may yield varying results [14]. Confirming an elevated PSA can potentially clear up some of these falsely-positive test results, by accounting for regression to the mean, for

instance [15]. PSA reduction because of biological variation could be expected in cases of cleared out infections or because of physician-provided guidance to avoid activities such as cycling, sexual activity, or vigorous exercise in the days leading up to the test. It was shown that prostatitis is the most common finding at the time of negative biopsy in young middle-aged men [16] and, overall, around half of the negative biopsies in PROBASE so far were associated with prostatitis (data not shown). Another reason for temporary PSA increase could be because of sexually transmitted infections as positive associations were shown for infections of chlamydia or gonorrhea and PSA rise [17,18]; however, no such associations could be confirmed in PROBASE [19].

According to the PROBASE protocol, PSA testing should be repeated in elevated cases, and if the value decreases below 3 ng/ml, even marginally, a biopsy is not recommended. Instead, the individual is reassigned to the PSA screening schedule. An alternative approach, proposed by Nordström et al, requires a PSA decrease below 3 ng/ml to be at least 20% from the initial value before withholding a biopsy. With such an approach, 17% of biopsies would have been avoided, while 5.4% of ISUP GG 2–5 cancers were missed [10]. With this approach in PROBASE, five additional ISUP GG 1–2 and two ISUP GG 3 cases would have been found (Table 3). Similar results could have been achieved if biopsy was recommended to men whose repeat PSA remained ≥ 2.5 ng/ml. Lowering the cut-off for biopsy might detect a few aggressive cancers earlier but much more non-aggressive cancers would be detected as well and overall, more men being referred for biopsy at baseline. Whether this would have improved the positive predictive value (PPV) for detecting any cancer or clinically significant cancer remains uncertain as not all men were offered a biopsy.

We demonstrated that a large proportion of men with PSA decrease at baseline remained with low PSA levels over a 10 yr period. Elevated single PSA at age 45 yr resulted only into 14 PCa cases among 158 men so far (individual study follow-up is 6–11 yr). A decline in PSA to below 1.5 ng/ml was common. This pattern was also observed among men who began PSA screening at age 50 yr. According to the proposed EAU algorithm, men with PSA between 1–3 ng/ml are classified as intermediate risk. However, in our study, most PCa in intermediate-risk men were detected in those with baseline PSA levels between 2.5 and 3 ng/ml. These findings suggest that the currently proposed intermediate-risk category (1–3 ng/ml) may be too broad and could benefit from more precise stratification for organized screening programs. From an individual perspective, the few very aggressive cancers might be very hard to catch with an only PSA- (and/or MRI-) based screening program. Only few ISUP GG 3–5 cases have been observed in PROBASE so far in >46,000 men: 90 detected via screening and 23 cases outside the screening schedule (data not shown).

All screening studies showed that the detection of significant PCa is inevitably accompanied by a “by-catch” of low ISUP GG PCa which are thought to be clinically irrelevant. To what extent they are really irrelevant among relatively young middle-aged men with a life expectancy of about four decades is not known. According to current guidelines, all ISUP GG 1 and selected ISUP GG 2 tumors are recommended active surveillance. “Prostate cancer” is a biologically heterogeneous disease which behaves differently even within the same ISUP GG [20] and additional biomarkers are needed for an adequate specification and identification of those individuals who benefit from immediate treatment.

Our study has some limitations. Firstly, PROBASE is an ongoing trial and individual follow-up time in the study is still short (varies from 6 to 11 yr). Due to the PROBASE design, only men with confirmed PSA >3 ng/ml were offered a biopsy and so we cannot certainly estimate outcomes of other potential screening strategies as cancer status for

the other men is not truly known. However, men with a low PSA value or a negative biopsy in follow-screening rounds can be assumed to be cancer-free at previous screening rounds. In contrast, those who did not follow-up with the screening invitations could potentially harbor a PCa diagnosis. Cancer registry linkage was available only in one out of four study sites and provided no additional cancer case within the first 5 yr of the study time. At the same time, biopsy results were not available in all men with confirmed PSA ≥ 3 ng/ml. Immediate biopsy was more likely to be refused with negative MRI findings or even PSA between 3 and 4 ng/ml as common urology practice is to perform a biopsy in those with PSA ≥ 4 ng/ml. Finally, while PSA protocol specifies the same theoretical age at screening across all individuals, a small proportion of men (<5% per screening round) respond to the screening invitation with a delay of several years that could potentially lead to higher PSA levels at the time of screening because of older age.

5. Conclusion

Temporary PSA elevations in a PSA-based PCa screening program in early middle-aged men are frequent. Repeating a PSA before initiating diagnostic work-up allows for a significant reduction in diagnostics. A confirmatory PSA test reduces the harm of an organized screening program without compromising the oncologic benefits.

Author contributions: Agne Krilaviciute and Peter Albers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data sharing: Data are available for bona fide researchers who request it from the authors (p.albers@dkfz.de).

Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eururo.2026.06.016>.

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