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Platinum Priority – Prostate Cancer
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Risk-adjusted Screening for Prostate Cancer—Defining the Low-risk Group by Data from the PROBASE Trial

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Abstract

Background: Risk-adjusted screening for prostate cancer (PCa) aims to reduce harms by less frequent retesting, especially in men at a low risk of PCa. Definitions of low risk are based mainly on studies in men starting screening at age 55–60 yr.
Objective: To identify men at age 45 yr with a low risk of PCa.
Design, setting, and participants: A population-based, risk-adjusted PCa screening trial was conducted in Germany using baseline prostate-specific antigen (PSA) starting in young men (PROBASE).
Intervention: PSA measurements starting at the age of 45 yr.

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Screening

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Outcome measurements and statistical analysis: The incidence of PCa within 5 yr was assessed in men with screen-negative baseline PSA <1.5 ng/ml compared with those with PSA 1.5–≤3.0 ng/ml.

Results and limitations: Of 23 301 men who received a first PSA test at age 45 yr, 0.79% had a screen-positive PSA value of ≥3 ng/ml. Among the 89% of men who had a screen-negative baseline PSA value of <1.5 ng/ml, only 0.45% received a positive PSA test ≥3 ng/ml upon retesting after 5 yr. By contrast, for those with a screen-negative baseline PSA value of 1.5–3 ng/ml, 13% surpassed 3 ng/ml upon biennial testing within the next 4 yr. The incidence of PCa in subsequent screening rounds increased with increasing baseline PSA levels, from 0.13 per 1000 person-years for men with initial PSA level of <1.5 ng/ml to 8.0 per 1000 person-years for those with PSA levels of 1.5–3.0 ng/ml. A limitation is a follow-up time of only 5 yr, so far.

Conclusions: Men with baseline PSA <1.5 ng/ml at age 45 yr are at a very low risk of PCa over the next 5 yr.

Patient summary: The PROBASE study showed that men with baseline prostate-specific antigen (PSA) <1.5 ng/ml at age 45 yr have a very low prostate cancer detection rate over 5 yr and do not need PSA retesting during this time.

ADVANCING PRACTICE BOX

What does this study add?

early nine out of ten men (89%) have a low PSA level at age 45. When re-tested after five years, only a very small percentage (0.45%) had a positive PSA test (3 ng/ml or higher). By contrast, men with a higher baseline PSA (between 1.5 and 3 ng/ml) were more likely to have a PSA above 3 ng/ml in future tests. When screened biennially, about 13% had elevated PSA within the next four years. Prostate cancer incidence in subsequent screening rounds increased with increasing baseline PSA levels, but only 9 prostate cancers were detected after five years among >14,000 men with low baseline PSA (<1.5 ng/ml).

Clinical Relevance

We analyzed results from PSA screening within the first 5 years in population-based, risk-adjusted prostate cancer screening trial in Germany (PROBASE). PROBASE trial uses baseline PSA to classify men into different risk groups at young age. The main outcome was prostate cancer incidence in five years in men with screen-negative baseline PSA <1.5 ng/ml compared to 1.5-<3.0 ng/ml measured at 45 years of age. Associate Editor: Gianluca Giannarini, M.D.

Patient Summary

The PROBASE study showed that men with baseline PSA <1.5 ng/ml at age 45 have a very low prostate cancer detection rate over five years and do not need PSA re-testing duringthis time.

1. Introduction

Population-based screening for prostate cancer (PCa) based on prostate-specific antigen (PSA) alone reduces PCa-specific mortality significantly [1–3]. However, this comes with a high rate of overdetection of cancers that may not ultimately cause major harms to men during their lifetime.

Based on a retrospective analysis, early baseline PSA measurements can predict long-term PCa risk [4]. Corroborated by the findings from European screening trials regarding the lower limit of a PSA test to define a low-risk group [5–7], risk-adapted screening strategies are being proposed that aim to reduce the number of men who are screened unnecessarily often, so as to potentially reduce overdetection and subsequent overtreatment that may cause more harms than benefits [8]. Especially for men at a low risk of PCa, screening frequency may be reduced to avoid PSA testing that largely results in negative findings and to avoid clinical workup of false-positive PSA tests (“overscreening”), thus optimizing the number needed to screen to identify a PCa case and saving costs.

The PROBASE trial was designed to test prospectively a risk-adjusted screening strategy in 45-yr-old men, starting with baseline PSA measurement at either 45 or 50 yr of age to define different screening intervals [9]. The age of 45 yr is also a starting age for the Early Detection Program currently in use in Germany [10]. The PROBASE trial uses baseline PSA to classify men into low- (PSA <1.5 ng/ml), intermediate- (PSA 1.5–<3.0 ng/ml), and high-risk (PSA ≥3.0 ng/ml) groups with different screening intervals. The PSA cut point of 1.5 ng/ml was based on the findings from the Malmö Preventive Cohort and the UK screening cohort, both of which indicated that an initial PSA level of <1.5 ng/ml predicted a very low risk of being found with metastatic PCa over the next 25 yr [4,11].

Here, we present the findings from the PROBASE trial for men whose initial PSA measurements at age 45 yr were

below 3 ng/ml. Our aim was to describe their risk of receiving a positive PSA test (≥3 ng/ml) or PCa diagnosis over the next 5 yr and, thus, define a group of men at a low risk in whom screening intervals may be reduced safely.

2. Patients and methods

2.1. The PROBASE trial

Detailed description of PROBASE can be found in the studies of Arsov et al [9,12]. In brief, 46 495 men at age 45 yr were recruited between 2014 and 2019, and randomized (1:1) to start with PSA screening immediately at age 45 yr (N = 23 301) or delay the start of PSA screening for 5 yr and start at age 50 yr (N = 23 194). Difference in PCa metastasis between the two study arms is the primary endpoint of the trial; however, one of the exploratory objectives was identification of groups at a low risk for PCa by their baseline PSA value. These analyses addressed this exploratory objective of the PROBASE trial.

Depending on the screening PSA value at baseline, participants at low (0 ≤ PSA < 1.5 ng/ml) or intermediate (1.5 ≤ PSA < 3.0 ng/ml) risk were reinvited for subsequent screening after 5 or 2 yr, respectively. For men with confirmed PSA ≥3 ng/ml 2 wk later, magnetic resonance imaging (MRI) and biopsy were recommended. Higher PSA values in the subsequent screening round lead to an upgrade into the respective higher risk category; by contrast, subsequent lower PSA values do not lead to the downgrading of a man's risk category.

PCa was defined by positive histological findings at biopsy. For men identified in annual questionnaires as having had a prostate biopsy outside the study centers, the information on biopsy, including biopsy materials, were requested from the urologist/clinic that performed the biopsy. These biopsies were also recorded in the PROBASE database.

2.2. Data material

Men who were randomized to the immediate screening arm and had their PSA measured at age 45 yr were included in this analysis. For the present analysis, we evaluated the results of PSA screening after 5 yr for men at a low risk at baseline (PSA <1.5 ng/ml), and after 2 and 4 yr time points since study enrollment for men at an intermediate risk at baseline (PSA 1.5–<3.0 ng/ml). Since the time of study enrollment, 13 men in the immediate screening arm of the PROBASE trial have retracted their consent and asked for data deletion (baseline risk was "low" for eight men, "intermediate" for four men, and "high" for one man). They were excluded from the analysis. The study protocol was approved by the Institutional Review Board and Ethics Committee of the Medical Faculty at Heinrich-Heine University Duesseldorf and subsequently by each participating institution's (Munich, Hannover, Heidelberg, and Duesseldorf) local ethics committee in 2013, and has been registered at https://doi.org/10.1186/ISRCTN37591328. All participants provided written informed consent. For the current analysis, data were extracted on February 1, 2024, but only data entries up until December 31, 2023 were used. All calculations were performed with Stata, version 17/MP (StataCorp. 2021, Stata Statistical Software: Release 17; StataCorp LLC, College Station, TX, USA).

2.3. Statistical evaluation

We reported frequencies of men screened and tested positive (PSA ≥3 ng/ml), and the outcome of the first biopsy from the screening round at 5 yr (for those initially at a low risk) or at 2 and 4 yr (for those initially at an intermediate risk).

Person-years (PY) accumulated in each screening round were calculated by multiplying the per-protocol-specified screening interval length by the number of screened individuals in the corresponding screening round. For those who skipped the screening round at 2 yr but complied to screening at 4 yr, the screening interval length was considered to be 4 yr.

Detection rates of PCa were calculated as follows: (number of screen-detected cancers)/PY × 1000. Similarly, rates of positive screen test were calculated as follows: (number of screen-positive tests)/PY × 1000. This approach provides annual rates allowing the comparison between men with one 5-yr screening round and men with screening rounds every 2 yr.

PCa aggressiveness was defined by the International Society of Urological Pathology (ISUP) grade group (GG) for screen-detected PCa for analyzed screening rounds, cancers detected at later time points, as well as cancers detected outside of the protocol. Screening PSA tests as well as PSA tests taken outside of the protocol, which were reported to the study centers, were separated in the database. Cancers after screen-positive PSA test were considered to be screen-detected PCa. For those who did not have a biopsy after an elevated screening PSA test, we reported the number of men who had unsuspicious/negative MRI (Prostate Imaging Reporting and Data System [PI-RADS] 1–2) or controlled PSA <3 ng/ml after screening PSA.

All results are shown separately for men with baseline PSA split into the following strata: 0–<0.5, 0.5–<1.0, and 1.0–<1.5 ng/ml for the PROBASE initial low-risk group, and 1.5–<2.0, 2.0–<2.5, and 2.5–3.0 ng/ml for those initially at an intermediate risk.

3. Results

3.1. Distribution of PSA values at ages 45 and 50 yr

The median PSA at age 45 yr was 0.74 ng/ml (interquartile range 0.5–1.07) among the evaluable 23 288 men in the PROBASE immediate screening arm (Fig. 1A). Of the PSA values, 71% were below 1.0 ng/ml, and another 18% were in the interval 1.0–<1.5 ng/ml (together 89%). Among those who participated in follow-up screening at age 50 yr, the median PSA value was only marginally higher (0.76 ng/ml; Fig. 1B–D).

3.2. Results at subsequent screening rounds

3.2.1. Screen-positive tests

Of the 23 301 men randomized to immediate PSA-based screening at age 45 yr, 0.79% had a screen-positive PSA value of ≥3 ng/ml. Of the 89% of men who had a screen-negative baseline PSA value of <1.5 ng/ml, only 0.45% (N = 64) had a

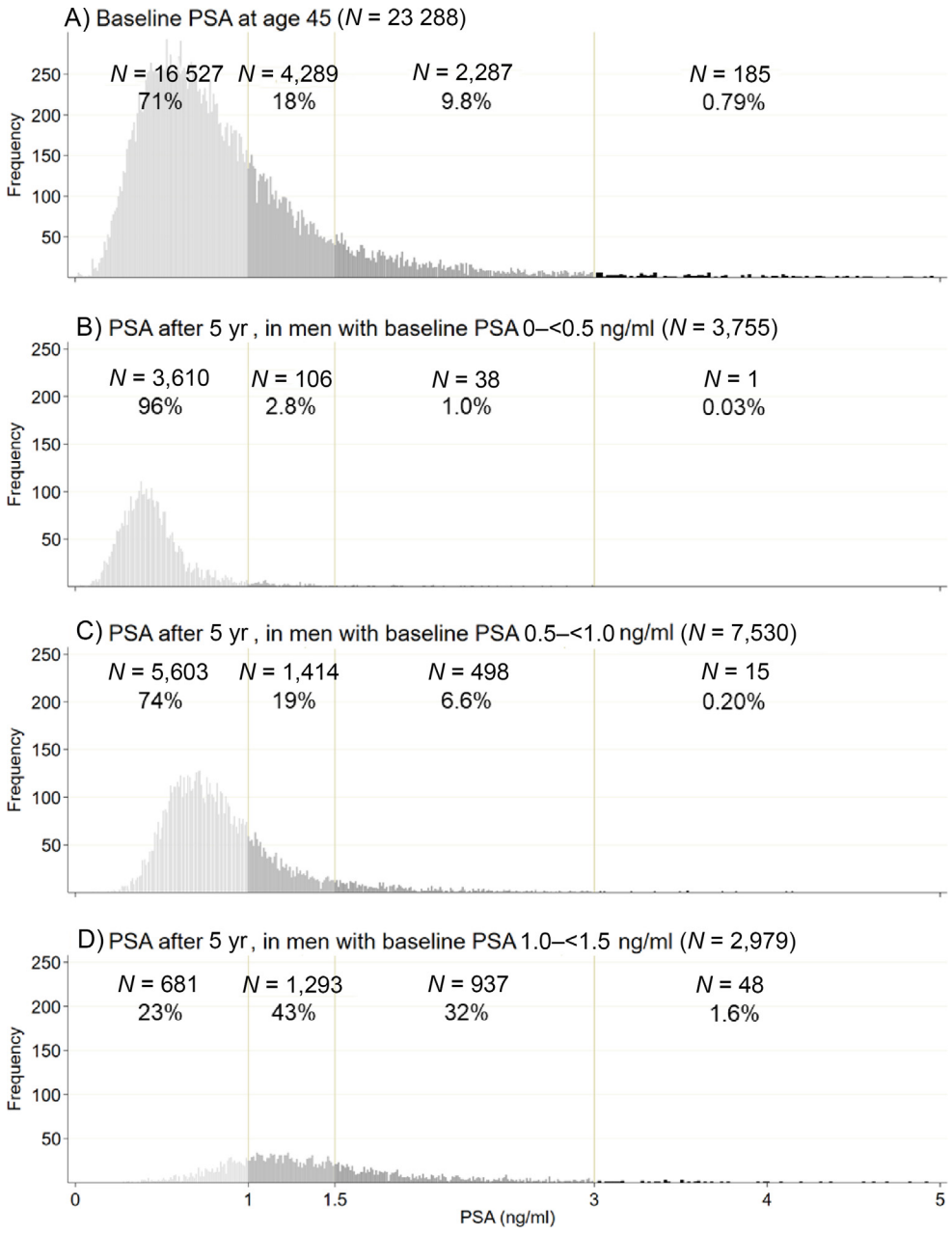

Fig. 1 – Histograms of the distribution of prostate-specific antigen (PSA) values at (A) baseline screening at age 45 yr, and (B–D) screening 5 yr after study enrollment among men who had baseline PSA of 0–<0.5, 0.5–<1, and 1–<1.5 ng/ml, respectively. PSA values >5 were not displayed in the graph: *N* = 45 (Fig. 1A), *N* = 1 (Fig. 1B), *N* = 4 (Fig. 1C), and *N* = 7 (Fig. 1D). The median PSA at age 45 yr was 0.74 ng/ml and the overall median PSA 5 yr later was 0.76 ng/ml. By the time of this analysis, *N* = 13 men retracted their consent and asked for data deletion, leaving with 23 288 out of 23 301 initially recruited in the immediate screening arm (histogram in Fig. 1A).

PSA test value of ≥3 ng/ml upon retesting after 5 yr. By contrast, of men with a with a screen-negative baseline PSA value of 1.5–<3.0 ng/ml, 13% (*N* = 261) were tested positive within 4 yr (Table 1). Examining baseline PSA strata by more refined incremental steps of 0.5 ng/ml, the number of men having PSA ≥3 ng/ml at subsequent screening rounds increased from 0.05 per 1000 PY for those with baseline PSA <0.5 ng/ml to 123.2 per 1000 PY for those with baseline PSA of 2.5–<3.0 ng/ml.

3.2.2. *Prostate cancer*

For those with screen-negative PSA tests at baseline, the incidence of PCa cases detected in subsequent screening rounds increased strongly with increasing baseline PSA levels (Table 1 and Fig. 2). Among men with baseline PSA <1.0 ng/ml, only two cases of PCa were found by PSA testing 5 yr later (0.04 PCa cases per 1000 PY), whereas seven more cases of PCa were observed among men with baseline PSA of 1.0–<1.5 ng/ml (0.47 per 1000 PY; Table 1). Overall, this corresponds to 0.13 PCa cases per 1000 PY (*N* = 9) in the PROBASE low-risk group defined by baseline PSA <1.5 ng/ml. By contrast, among men with a baseline PSA value of 1.5–<3.0 ng/ml (intermediate-risk group), 58 PCa cases were found in subsequent, biennial screening rounds, corresponding to 8.0 PCa cases per 1000 PY.

Table 1 – Screen-positive men (PSA ≥3 ng/ml) and number of prostate cancer at screening round 5 yr after enrollment among men who had low (<1.5 ng/ml) baseline PSA, and at screening rounds 2 or 4 yr after enrollment for men with intermediate risk (1.5–<3.0 ng/ml) at baseline

Baseline PSA at study enrollment (ng/ml)	Number at study enrollment [a]	Eligible for screening	Attended screening (% from eligible participants)	Person-years [b]	PSA ≥3.0 ng/ml at screening		Prostate cancer	
					N (% from screened)	*N* per 1000 person-years	*N*	*N* per 1000 person-years
PROBASE low-risk group: second screening after 5 yr								
0–<0.5	5604	4864 [c]	3750 (77)	18 750	1 (0.03)	0.05	0	NA
0.5–<1.0	10 923	9574 [c]	7522 (79)	37 610	15 (0.19)	0.40	2	0.05
1.0–<1.5	4289	3833 [c]	2976 (78)	14 880	48 (1.6)	3.2	7	0.47
0–<1.0 (cumulative)	16 527	14 438	11 272 (78)	56 360	16 (0.14)	0.28	2	0.04
0–<1.5 (cumulative)	20 816	18 271	14 248 (78)	71 240	64 (0.45)	0.89	9	0.13
PROBASE intermediate-risk group: second and third screening after 2 and 4 yr, respectively								
1.5–<2.0	1421	1421 [d]	1262 (89) [e]	4590	73 (5.8)	15.9	9	2.0
2.0–<2.5	579	579 [d]	515 (89) [e]	1842	86 (17)	46.7	21	11.4
2.5–<3.0	287	287 [d]	255 (89) [e]	828	102 (40)	123.2	28	33.8
1.5–<3.0 (cumulative)	2287	2287 [d]	2032 (89) [e]	7260	261 (13)	36.0	58	8.0

PSA = prostate-specific antigen.
[a] *N* = 23 301 men were randomized to immediate screening arm. By the time of this analysis, *N* = 13 men retracted their consent and asked for data deletion, leaving with 23 288 men in the immediate screening arm. Baseline PSA was <1.5 ng/ml for *N* = 20 816 (89.4%), 1.5–<3 ng/ml for *N* = 2287 (9.8%), and ≥3 ng/ml for *N* = 185 (0.8%) men.
[b] Person-years approximated by multiplying the per-protocol-specified screening interval length by the number of screened individuals in the corresponding screening round.
[c] PSA screening is scheduled no later than the data cut used in this manuscript, that is, December 31, 2023 (for men with baseline PSA <1.5 ng/ml). A total of *N* = 740 (baseline PSA 0–<0.5), *N* = 1349 (baseline PSA 0.5–<1.0), and *N* = 456 (baseline PSA 1.0–<1.5) men have not been invited to PSA screening 5 yr later by the time of this publication.
[d] Detailed screening round–specific information is listed in Supplementary Figures 1A–C. Participants who have already been tested positive in 2-yr screening round or withdrew/died between study enrollment and the 2-yr screening round were not eligible for screening at 4-yr screening round.
[e] Attended at least one out of two subsequent screening rounds. Detailed screening round–specific information is listed in Supplementary Figures 1A–C.

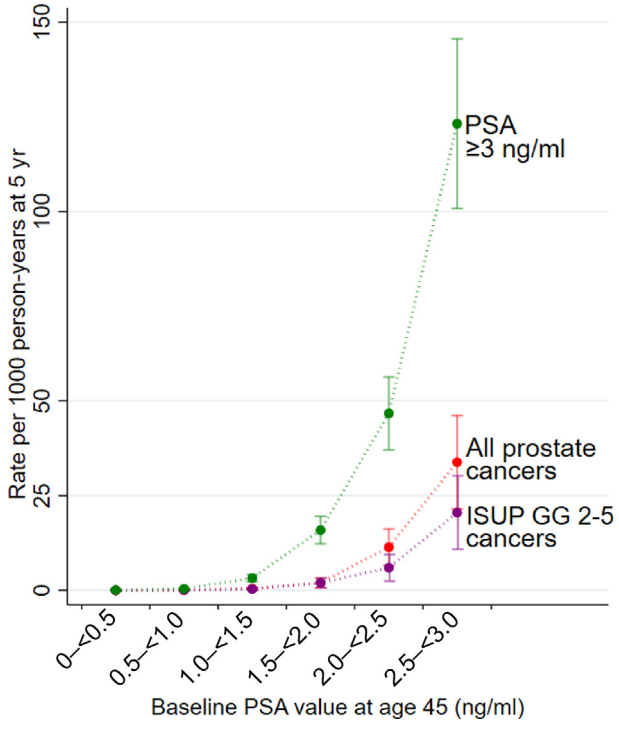

Fig. 2 – Number of men with a screen-positive PSA test result and with a prostate cancer diagnosis according to the baseline PSA value. For men with baseline PSA <1.5, the screening round 5 yr later was analyzed, and for men with a baseline PSA value of 1.5–<3, screening rounds 2 and 4 yr later were considered. GG = grade group; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen.

Tumor aggressiveness for PCa cases detected in follow-up screening rounds and outside the study protocol is shown in Table 2. Additional six PCa cases were reported outside of the study protocol. Among the 73 cases of cancer observed so far, 49 (63%) were ISUP GG 2–5 cancer.

Table 2 – International Society of Urological Pathology (ISUP) grade group (GG) score of screen-detected and outside of the trial cancers

Baseline PSA at study enrollment (ng/ml)	Screen-detected cancers [a] (+outside of the protocol cancers [b])			
	ISUP GG 1	ISUP GG 2	ISUP GG 3	ISUP GG 4/5
0–<0.5	0	0	0	0
0.5–<1.0	0	0 (+1)	1	1 (+2)
1.0–<1.5	2	3 (+1)	1	1
1.5–<2.0	0 (+1)	6 (+1)	2	1
2.0–<2.5	10	6	4	1
2.5–<3.0	11	11	3	3

PSA = prostate-specific antigen.
[a] At 5-yr screen for men with baseline PSA 0–<1.5 ng/ml and at 2- and 4-yr screen for men with baseline PSA 1.5–<3.0 ng/ml.
[b] Prostate cancer diagnoses identified by yearly questionnaires.

Of men who were recommended as per protocol to undergo a biopsy, 61% were biopsied so far (Table 3). Unsuspicious MRI examinations (PI-RADS 1–2) and/or a decrease in subsequent PSA tests below 3 ng/ml were observed in 73 of 126 (58%) men who declined an immediate biopsy. A small number of men insisted on PSA monitoring when PSA was stable; yet, PSA stayed at ≥3 ng/ml (data not shown).

4. Discussion

In view of a future risk-adjusted organized PCa screening program in Europe, data on an appropriate starting age at the time of the initial invitation, the age range to be covered by screening, frequency of PSA testing, as well as the thresholds to use risk calculators and MRI are required. Owing to scarce data, the current European Association of Urology (EAU) guidelines differ from suggestions by the EAU with regard to defining a low-risk group and retesting. According to the EAU guidelines, men at a "decreased risk of PCa metastasis or death from PCa several decades later" are

Table 3 – Biopsy acceptance and reasons of declining the immediate biopsy among men with elevated screening PSA

Baseline PSA at study enrollment (ng/ml)	Screen-positive tests (PSA ≥3 ng/ml)	Attended biopsy (%)	Did not attend biopsy		
			Low PSA or MRI (%)	Withdrew/died (%)	Pending (%)
0–<0.5	1	1 (100)	–	–	–
0.5–<1.0	15	3 (20)	12 (80)	0	0
1.0–<1.5	48	27 (56)	9 (19)	0	12 (25)
1.5–<2.0	73	41 (56)	20 (27) [a]	2 (2.7)	10 (14)
2.0–<2.5	86	57 (66)	15 (17)	4 (4.7)	10 (12)
2.5–<3.0	102	70 (69)	17 (17) [b]	2 (2.0)	13 (13)
Total	325	199 (61)	73 (22)	8 (2.5)	45 (14)

MRI = magnetic resonance imaging; PSA = prostate-specific antigen.
[a] *N* = 1 individual had a drop in PSA (<3 ng/ml) followed by withdrawal and *N* = 1 had unsuspicious MRI findings followed by withdrawal.
[b] *N* = 1 individual had a drop in PSA (<3 ng/ml) followed by withdrawal.

those with initial PSA <1 ng/ml at the age of 40 yr and <2 ng/ml at the age of 60 yr with suggested retesting at 8 yr. Men initially at risk should be retested every 2 yr [13]. In a review paper based on the EAU guideline recommendations, low risk was defined as PSA <1.0 ng/ml in men aged 50–70 yr, with the next screening in 5 yr for those aged 50–59 yr and no further screening for men aged 60–69 yr [8]. One common feature of these recommendations is the PSA cutoff between "at risk" and "decreased risk" of 1 ng/ml.

The results of the PROBASE trial presented here add information on PCa outcome after 5 yr of screening in men with a baseline PSA test at age 45 yr. Among men with baseline PSA <1.5 ng/ml (PROBASE low risk), only 0.45% had PCa at the subsequent screening round at 5 yr. Defining the low-risk group with a cutoff of 1.5 ng/ml instead of 1.0 ng/ml at age 45 yr would enlarge the group of men with less frequent screening from 71% (cutoff at 1 ng/ml) to 89% (cutoff at 1.5 ng/ml), that is, by 18%. As the age group of men between 45 and 50 yr accounts for approximately 14 million men in Europe, it is of great importance where the cutoffs for defining risks at young age are settled. Avoiding "overscreening" would not only save costs for unneeded PSA tests and largely negative clinical workups, but may also increase the willingness of middle-aged men eligible for screening to comply with a screening program.

A critical issue of risk-adjusted screening strategies continues to be "overdetection" or "overdiagnosis," frequently followed by "overtreatment." Overdetection refers to the pathologically confirmed detection of PCa that would have remained clinically inapparent if not detected ("overscreening" and "overdetection" are thus different issues). Overdetection plays an undeniable role in screening among older men as disease may more likely stay inapparent during their lifetime. However, it is questionable whether this also applies to men who are screened at the age of 45 yr with life expectancy of >40 yr. The ProtecT study demonstrated that even low ISUP GG cancers can be lethal in the long term [14,15]. Thus, the clinical relevance of PCa detected by PSA screening in middle-aged men must be considered an unresolved issue, which should be explored further and should be kept in mind when determining appropriate screening intervals in risk-adjusted screening. Since overdetection refers to pathologically undisputably existing PCa, avoiding overdetection by risk adjustment only means to delay the detection of low-grade PCa by the years until the subsequent screening round. It is counterbalanced by the delay of diagnosis of potentially advanced and clinically relevant PCa. Interestingly in our analyses, the very small number of advanced PCa cases appears proportionally higher among the low-risk men than in the intermediate-risk group, and should be kept in mind for verification in future screening rounds or a detailed analysis of screen-detected PCa.

No strong evidence exists in favor of or against an earlier or a later start of a PCa screening program in Europe currently recommended to start at the age of 50 yr. If started at the age of 45 yr, a PCa screening program appears more effective with a cutoff at 1.5 ng/ml for low risk and a delayed screening interval.

The present analyses are subject to certain limitations. First, only about 78% of men with baseline PSA values <1.5 ng/ml have taken part in follow-up screening 5 yr later (the invitation for 5-yr follow-up screening is still ongoing). Second, linkage of PROBASE data with cancer registries, which is currently underway, will discover so far unrecognized cancer cases for those men who are truly lost to follow-up. Nevertheless, our present analyses clearly document the very low PSA-positive test rates and consecutively low rates for PCa diagnosis in the 5-yr follow-up of retesting using data from >14 000 men. Third, the follow-up of the low-risk group is still short at 5 yr and does not yet allow direct conclusions to be drawn about whether even longer intervals for repeat PSA testing than 5 yr could be recommended. Fourth, some participants with a screen-positive PSA test have not yet undergone a biopsy, and the reported number of cancer cases might be underestimated. Additional biopsies may increase the cancer detection rate, but even if this were to be expected and extrapolated with the same cancer detection rate of 25%, it would not change the message of our analyses. Finally, caution should be taken in drawing conclusions about tumor aggressiveness in men with low baseline PSA levels as the number of PCa cases detected so far is still quite small.

5. Conclusions

Our data contribute to better management of men who want to be screened and to enter a risk-adjusted program at the age of 45 yr. A baseline PSA level of <1.5 ng/ml at age 45 yr characterizes 89% of men with a very low risk of PCa who consecutively do not need PSA retesting for 5 yr.

***Author contributions*:** 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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Analysis and interpretation of data: Krilaviciute, Becker, Kaaks.
Drafting of the manuscript: Krilaviciute, Becker, Kaaks, Seibold, Albers.
Critical revision of the manuscript for important intellectual content: de Vrieze, Lakes, Radtke, Kuczyk, Harke, Debus, Fink, Herkommer, Gschwend, Meissner, Benner, Seibold, Kristiansen, Hadaschik, Arsov, Schimmöller, Giesel, Antoch, Makowski, Wacker, Schlemmer.
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***Data sharing statement*:** Data are available for bona fide researchers who request it from the authors (p.albers@dkfz-heidelberg.de).

Supplementary data

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