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A randomized trial of risk-adapted screening for prostate cancer in young men—Results of the first screening round of the PROBASE trial

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Abstract

There is no generally accepted screening strategy for prostate cancer (PCa). From February 2014 to December 2019 a randomized trial (PROBASE) recruited 46 642 men at age 45 to determine the efficacy of risk-adapted prostate-specific antigen-based (PSA) screening, starting at either 45 or 50 years. PSA tests are used to classify participants into a low (<1.5 ng/mL), intermediate (1.5-2.99 ng/mL) or high (≥3 ng/mL) risk group. In cases of confirmed PSA values ≥3 ng/mL participants are recommended a prostate biopsy with multiparametric magnetic resonance imaging (mpMRI). Half of

Abbreviations: DRE, digital rectal examination; ERSPC, European Randomized Study of Screening for Prostate Cancer; mpMRI, multiparametric magnetic resonance imaging; NAKO, German National Cohort Study; PCa, prostate cancer; PLCO Trial, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PSA, prostate specific antigen.

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the participants (N = 23 341) were offered PSA screening immediately at age 45; the other half (N = 23 301) were offered digital rectal examination (DRE) with delayed PSA screening at age 50. Of 23 301 participants who accepted baseline PSA testing in the immediate screening arm, 89.2% fell into the low, 9.3% into intermediate, and 1.5% (N = 344) into the high risk group. Repeat PSA measurement confirmed high-risk status for 186 men (0.8%), of whom 120 (64.5%) underwent a biopsy. A total of 48 PCas was detected (overall prevalence 0.2%), of which 15 had International Society of Uropathology (ISUP) grade 1, 29 had ISUP 2 and only 4 had ISUP ≥3 cancers. In the delayed screening arm, 23 194 participants were enrolled and 6537 underwent a DRE with 57 suspicious findings, two of which showed PCa (both ISUP 1; detection rate 0.03%). In conclusion, the prevalence of screen-detected aggressive (ISUP ≥3) PCa in 45-year-old men is very low. DRE did not turn out effective for early detection of PCa.

KEYWORDS
prostate cancer, randomized clinical trial, risk-adapted, screening

What's new?

The German Prostate Cancer Early Detection Study Based on a Baseline PSA Value in Young Men (PROBASE) is the largest risk-adapted screening trial in prostate cancer. It is based on the observation that the baseline prostate specific antigen (PSA) level at age 45-50 is strongly predictive of a man's risk of developing advanced prostate cancer years later. The results of the first screening round showed a low prevalence (0.2%) of prostate cancer in 45-year-old men when risk-stratifying with PSA levels, with only 0.02% of aggressive cancers. In comparison, digital rectal examination showed low effectiveness for early detection of prostate cancer.

1 | INTRODUCTION

Prostate cancer (PCa) is the most frequent cancer and second leading cause of cancer death in men.[1,2] Early detection is suggested to allow for more effective treatment and to inhibit progress to metastatic disease and death, but current experience with population-based screening for PCa appears still discouraging. After a follow-up of 16 years, the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a significant reduction in mortality of 20% by prostate-specific antigen (PSA) screening in 50 to 74 years old men.[3] However, the low absolute difference in mortality rate after 16 years of screening in favor of screening of 0.17% (273/162 241), and the high number of men needed to be invited for screening (NNS = 570) and diagnosed with PCa (NND = 18) per PCa death averted indicate that screening approaches should be improved before they can be recommended to the general population. One suggested strategy to improve specificity of screening is starting screening at earlier ages when PSA may have better accuracy to detect clinically relevant PCa.[4] Another is a risk-adapted screening strategy based on observations from the Malmö Preventive Project[5] and various other prospective studies[6,7] that a baseline PSA at age 45 to 50 is strongly predictive of a man's risk of developing advanced PCa up to 30 years later. The German "Prostate Cancer Early Detection Study Based on a Baseline PSA Value in Young Men (PROBASE)" aims at improving the specificity of a PSA-based screening while preserving the sensitivity to timely detect men who are destined to metastatic disease over the next 15 years in a prospective randomized controlled setting. PROBASE was designed to compare a screening strategy starting at age 45 with a deferred beginning at age 50. The starting age for PCa screening is suggested in German national guidelines in accordance with the national statutory early detection program at age 45 years. The German statutory early detection program for PCa in Germany, however, does not include a PSA value but only a digito-rectal examination (DRE). In this report, we present the results of the first screening round at complete recruitment of the trial participants.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The PROBASE study design has been reported previously and is summarized in Figure 1.[8] The study is performed at four study sites in Germany, in and around the cities of Duesseldorf, Hannover, Heidelberg and Munich. Participants were invited by mail using random samples of 45-year-old men from the local population registries and subsequently randomized in a computerized fashion. In preparation of the trial, PSA analytic tests were compared between institutions[9] (see Supporting Information). Reference radiology and pathology were established for

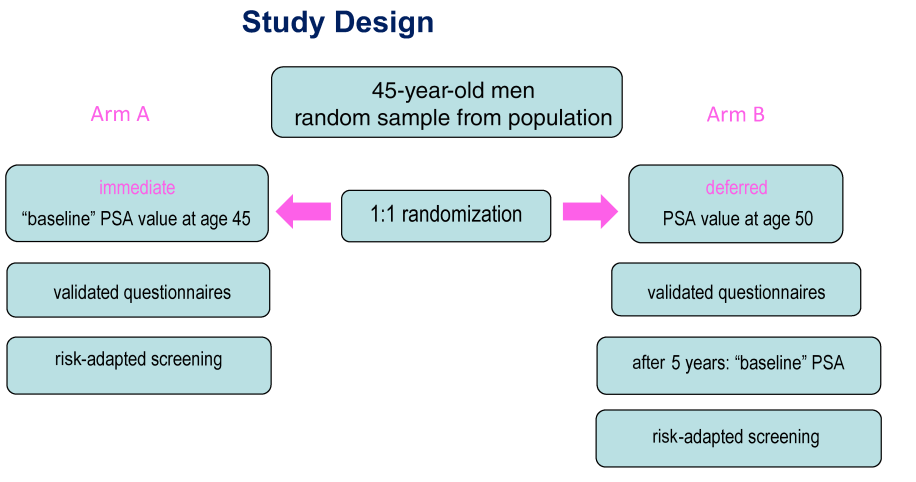
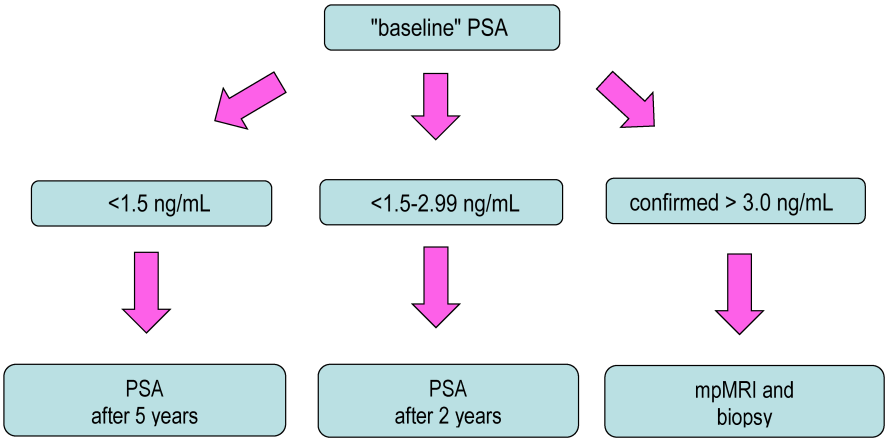


FIGURE 1 Study design [Color figure can be viewed at wileyonlinelibrary.com]



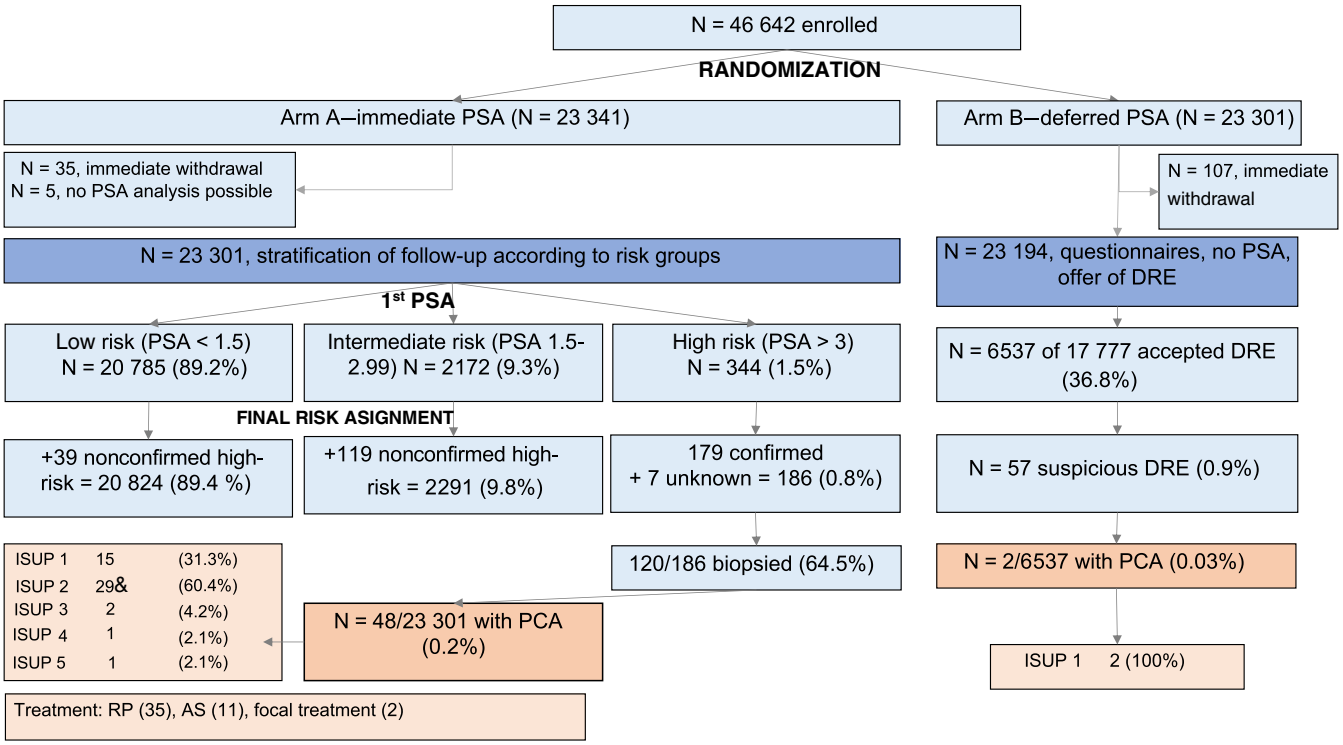


FIGURE 2 Consort flowsheet of the PROBASE trial [Color figure can be viewed at wileyonlinelibrary.com]

reproducible quality measurements by specialists with proven expertise in quality control.[10,11] Baseline questionnaires were adapted to the German National Cohort Study (NAKO)[12] and supplemented by validated questionnaires regarding quality of life (Short Form Health Survey, SF12, International Prostate Symptom Score, IPSS), voiding and sexual function (International Index of Erectily Funktion, IIEF-6, Expanded Prostate Cancer Index Composite, EPIC-26), and psychooncology (Patient Health Questionnaire, PHQ-2; Generalized Anxiety Disorder, GAD-2). All data were captured centrally at the German Cancer Research Center (DKFZ) in a database (Onkostar) which is available online at the study sites according to data protection regulations.

2.2 | Procedures

Between February 2014 and December 2019 (71 months), >400 000 invitations were sent out and 46 642 participants agreed to be randomized (Figure 2). A field study at all sites was performed to evaluate reasons for nonparticipation. At the study sites, participants were seen by a physician for informed consent, registration of medical history and questionnaires, and blood was drawn for biobanking in both arms and immediate PSA measurements in Arm A (immediate screening).

Participants in Arm B (delayed screening) consented to the trial and agreed to be followed yearly by mailed questionnaires until their PSA value was determined at age 50. At enrolment, they were offered to undergo digital rectal examination (DRE) as part of the German statutory early detection program for men age 45 and older in three of four study centers.

In the study arm with immediate PSA screening (Arm A) participants were distributed to risk groups according to their initial PSA value; in cases of initial PSA ≥3 ng/mL this was repeated for confirmation after 2 weeks and based on the second value, participants were grouped accordingly (Figure 2). Participants in the low-risk (ie, PSA <1.5 ng/mL) and the intermediate-risk group (PSA 1.5-2.99 ng/mL) were reinvited for the second screening round after 5 and 2 years, respectively. All participants assigned to the high-risk group (confirmatory PSA ≥3 ng/mL) were offered multiparametric magnetic resonance imaging (mpMRI) of the prostate before biopsy as part of a research project investigating the value of mpMRI in this setting. Since the trial was started before mpMRI was recommended for primary diagnosis of PCa in the European Association of Urology (EAU) guidelines in 2019, the indication for biopsy was only based on the confirmed PSA value ≥3 ng/mL. Thus, mpMRI is not part of the screening strategy of PROBASE. In patients with concurrent mpMRI, prostate biopsy was conducted as mpMRI/ultrasound fusion biopsy of target lesions (maximum of 3 with 2 cores per target) followed by 12 to 18 systematic biopsies depending on the volume of the prostate. Participants who did not accept the offer of a mpMRI examination underwent a systematic 12 to 18 core biopsy only. Subjects assigned to the high-risk group with negative biopsies were then recommended 3-monthly PSA testing within the first year. Treatment decisions were based on reference pathology only.

Detection rates of PCa were calculated with a cut-off of 12 months after confirmation of an elevated PSA ≥3 ng/mL in Arm A (immediate screening) or suspicious DRE in Arm B (delayed screening).

The study will be finished at the time when participants have reached the age of 60 with an evaluation of metastasis from PCa. In addition, requests to the cancer registries will be performed for those not longer participating in the study.

TABLE 1 Baseline characteristics

	Arm A	Arm B
Evaluable participants	23 301	23 194
Mean age (min-max)	45.47 (44.14-46.95)	45.47 (44.21-47.10)
Ethnicity		
Caucasian (%)	97.06	97.13
Asian (%)	1.05	0.94
African (%)	0.96	0.97
Other (%)	0.94	0.96
PSA before age 45 (%)	3682 (15.9)	3652 (15.7)
DRE before age 45 (%)	8145 (35.1)	8030 (34.5)
Family history (%)		
Yes	3985 (17.1)	3919 (16.9)
No	18 063 (77.5)	17 936 (77.3)
Unknown	1253 (5.4)	1339 (5.8)

2.3 | Primary and secondary endpoints, and study hypothesis

The primary endpoint of the study is the cumulative incidence of distant metastatic PCa, defined as radiographically and histologically proven bone metastases and/or radiographically and histologically proven nonregional lymph node or visceral metastases up to the age of 60 years. The central aim of the study is to test the hypothesis that delaying the start of risk-adapted PSA screening to age 50 (study Arm B, delayed screening), as compared to age 45 (study Arm A, immediate screening), will result in significantly fewer false-positive PCa tests, while PCa detection remains early enough to avoid an increase in distant metastasis (until the age of 60).

Secondary objectives of the study include, among others, to evaluate the distribution of PSA values in a screening population of young men at age 45 and 50, to assess the prevalence of PCa in these age groups, and to compare patient outcomes after curative treatment of screen-detected cancer and quality of life in both study arms. Details on statistical (composite) null hypotheses and sample size calculations are in the Supporting Information.

3 | STATISTICAL METHODS

The basic profile of the study cohort is presented descriptively as absolute numbers and proportions. Screening outcomes were computed with number of confirmed cancers in relation to (a) all recalls

TABLE 2 Results of the first screening round

(A) Risk groups according to baseline PSA value in Arm A (immediate PSA)				
			PSA levels (ng/mL)	
Group	Number	Percent	Mean SD	Median IQR
Risk groups according to first baseline PSA (n = 23 301, February 2020)				
High	344	1.48	4.67	3.69
Intermediate	2172	9.32	1.94	1.84
Low	20 785	89.21	0.72	0.68
Total	23 301	100	0.89	0.74
Confirmed PSA at 2 weeks (n = 344 high risk participants, February 2020)				
High	179	53.12	5.03	3.86
Intermediate	119	35.31	2.33	2.37
Low	39	11.57	1.03	1.08
Total	337	100	3.61	2.04
Not done	7	–	–	–
Risk groups according to confirmed PSA (n = 23 301 participants, February 2020)				
High[a]	186	0.80	5.27	4.13
Intermediate[b]	2291	9.83	2.05	1.86
Low[c]	20 824	89.37	0.73	0.68
Total	23 301	100	0.89	0.74

(B) Results of MRI and prostate biopsies			
	MRI performed	MRI not performed	Total
Biopsy performed	114	6	120
Biopsy not performed	33	33	66
Total (%)	147 (79.0)	39 (21.0)	186 (100.0)

(C) Results of histopathological analysis of biopsies	
ISUP 1	15
ISUP 2	29
ISUP 3	2
ISUP 4	1
ISUP 5	1
Total	48
	100%

(D) Treatment of patients with prostate cancer				
	Total	RP	AS	FT
ISUP 1	15	6	8	1
ISUP 2	29	25	3	1
ISUP 3	2	2	0	0
ISUP 4	1	1	0	0
ISUP 5	1	1	0	0
Total	48	35	11	2

Abbreviations: AS, active surveillance; FT, focal treatment; ISUP, grade group according to International Society of Urological Pathology; RP, radical prostatectomy; Tx, treatment.

[a]Confirmed + not done.

[b]Intermediate first PSA + nonconfirmed high risk/intermediate second PSA.

[c]Low first PSA + nonconfirmed high risk/low second PS.

(positive predictive value, PPV-1), (b) all biopsies (PPV-2), and (c) all performed screens (detection rate, DR). Data were managed in and extracted from the Onkostar-based central database of PROBASE. All calculations were performed with SAS.[13]

4 | RESULTS

By December 31, 2019, 5.9 years of accrual provided 46 642 participants who were randomized to either immediate or delayed risk-adapted screening according to Figure 2. Just at time of randomization, 142 subjects withdrew their consent (35 in the immediate screening arm, 107 in the delayed screening arm). Since they did not contribute screening test results, they were excluded from the study. The present report focuses on the initial screening experiences in the immediate screening arm, including a 12 months workup period for the high-risk group. During this first year of running the study, further 62 participants (21 in the immediate screening arm, 41 in the delayed screening arm) withdrew from the study (data not shown).

Participants in the deferred screening arm have started to be seen again for PSA testing only since February 2019, and are not included in the present report.

Baseline characteristics of participants in both arms of the trial were balanced. (Table 1).

Of 23 301 participants who accepted PSA testing in the immediate screening arm, 20 785 (89.2%) and 2172 (9.3%) were rated as low-risk and intermediate-risk, respectively. Three hundred and forty-four participants (1.5%) had an initial PSA value ≥3 ng/mL, of whom 179 (52.0%) had a second and confirmatory PSA measurement of ≥3 ng/mL 2 weeks later and were directed in the high-risk group. In seven participants, the second PSA value could not be measured, they were counted as high-risk based on the initial value. The high-risk group thus consisted of 186 participants (179 participants with confirmation, 7 without) representing 0.8% of all study participants with baseline PSA-testing (Table 2A). The distribution of PSA values at age 45 shows mean and median PSA values of 0.89 ng/mL and 0.74 ng/mL, respectively, for the full cohort of participants in the immediate screening arm. The 186 participants at high-risk had mean and median PSA values of 5.27 ng/mL and 4.13 ng/mL, respectively.

Data on MRI are available from 147 of 186 (79.0%) participants in the high-risk group (Table 2B). One hundred and twenty men (64.5%) accepted to undergo a biopsy. In 114 of those an MRI/ultrasound fusion biopsy with an additional systematic biopsy was performed, the remaining 6 participants underwent a systematic biopsy only.

Overall, 48 PCas were detected. Forty-four of 48 (91.7%) had International Society of Uropathology grade group (ISUP) ≤2, only 4 (8.3%) had aggressive cancers with ISUP ≥3 (Table 2C).

Most men with PCa (n = 35/48, 72.9%) underwent radical prostatectomy, eight (16.7%) elected for active surveillance and one selected a focal treatment (Table 2D).

Of 23 194 participants in the delayed screening arm (Arm B), 17 777 were offered DRE, and among the 6537 (36.8%) who accepted there were 57 suspicious findings (0.9%), and 37 biopsies were performed. Two of the participants with positive DRE were found with PCa, both with ISUP 1 cancers (overall prevalence 0.03%).

5 | DISCUSSION

5.1 | Characterization of study population

After 5.9 years, this multicenter screening trial accrued 46 642 participants out of >400 000 men invited. A main reason not to participate was the expressed lack of interest in the trial (69%), whereas 10% stated that their general practitioner already took care of early detection. The invitation acceptance rate below 20% is not unexpected given the well-known low compliance of males with the German Statutory Early Detection Program launched in 1971. In general, the compliance with this program was reported to be as low as 11.7% for the age group of 40 to 49 years.[14] The critical public discussion on the PSA test may have further influenced the decision not to participate in the study.[15]

5.2 | PSA distribution and risk groups

There are only sparse data on PSA values in young men (<50 years) and a cut-off for "low-risk" therefore needed to be defined based on published evidence. The distribution of PSA values of participants in the immediate screening matched with previously reported data from cohorts of young men in the United States, Sweden, and the United Kingdom.[16-18] The PSA cut-off of 1.5 ng/mL, which was derived from the 90th percentile in the Malmö cohort to define a low-risk group, matched almost exactly the low-risk cohort in PROBASE with 89.4% and compared well to 88.6% in the Sheffield cohort.[16]

At their initial test, 344 men (1.5%) had PSA values ≥3 ng/mL. Contrary to all PSA-based screening trials so far, we performed confirmatory PSA tests 2 weeks later which rendered 119 men back to the intermediate and 39 men to the low-risk group. Thus, the high-risk group consisted of the remaining 186 men (0.80% of all men). Fluctuation of PSA values in young men seems to be frequent possibly due to indolent inflammatory reactions of the prostate.[19] This is the first study which reports on this finding and as a consequence we recommend that the indication for further diagnostic tests should only be based on two PSA values. PROBASE will give special attention to the future PCa prevalence among those who have been excluded from biopsy by this second PSA measurement.

From the public health point of view, the compliance of the 45-year-old screening participants with the recommended workup regimen appears important. Only 113 (60.8%) followed the

recommended biopsy within 12 months without further testing, and only 29 (39.7%) of the 73 refusers accepted the recommended 3-monthly PSA tests leading to seven further biopsies. It will be interesting to consider whether the compliance will increase with age of screening and could provide a further important criterion for the design of future screening modalities.

5.3 | PCa detection rate and aggressiveness

The detection rate of any PCa based on the performed biopsies in this cohort was 0.2% (48/23 301). In comparison with nonage-adapted mammography screening, the present positive predictive value to define a high-risk group (PPV-1 = 0.8%, 186/23 301) was slightly lower (mammography screening 1.1%). The positive predictive value to find cancer in the high-risk group (PPV-2 = 0.26, 48/186; mammography screening 0.52, 16 369/31 190) and the detection rate was lower as compared to mammography screening (0.2%, 48/23 301; mammography screening 0.77%).[20] In addition, PSA in this risk-adapted fashion presents a blood test as opposed to mammography which is not only more expensive but also potentially harmful.

In the ERSPC trial every fourth invitee (20 437/72 890) had elevated PSA (>3 ng/mL), whereas in PROBASE only every 125th invitee had elevated PSA including confirmation after 2 weeks.[3]

In terms of aggressiveness, 15/48 (31.0%) of detected cancers in the first screening round were found to have a favorable histology (ISUP 1) (Table 2D). Newly published data of large single center prospective active surveillance (AS) trials and one randomized trial demonstrate an up to 15 years cancer-specific survival rate of ISUP 1 cancers of 99.4 to 99.9%.[21-23] At least half of those did not need definitive treatment during the study period. Lately, data have also been released for ISUP 2 and ISUP 3 patients undergoing AS, again confirming very high cancer-specific survival rates of 94% to 100% but lower treatment-free survival rates with 39% and 49% at 8 and 10 years, respectively.[24,25] These data together with the early PROBASE results raise the question of when PCa should be detected and treated.

5.4 | Treatment of screen-detected cancers

After radical prostatectomy of 35 men, all were organ-confined. All of the significant cancers were ISUP 2 which confirmed biopsy results and supports the assumption that in this young age group PCa screening did not result in late detection of significant cancers. The reverse question, whether screening can start at age 50 instead of 45 without meaningful loss in the overall sensitivity for timely detection of tumors destined to become clinically significant, is a central research question of this trial.

The purpose of screening is to advance the diagnosis of cancer into a stage in which it can efficiently be treated and a lethal progress be prevented. An early onset of screening at the age of 45 years may however cause harm by loss of quality of life due to a severe therapeutical interventions already early in life. German cancer registry data from years before widespread use of PSA testing indicate an incidence rate of 0.001% in the age group 45 to 49 years.[26] The present rate of presumably 0.2% is about 200-fold higher and raises the issue of overdiagnosis. Several authors describe a high percentage of "latent" PCa in autopsy studies even among young men which may be considered a reservoir for overdiagnosis evoked by screening. "Overdiagnosis" is mostly defined as detection of clinically indolent disease without however taking time into consideration. A cancer which appears clinically irrelevant for a 70-year-old patient might be relevant for a man in the age of 45 if it threatens life 30 years later. ISUP 1 diagnoses of the present study may comprise such cancers. No data exist about their true long-term natural history so that their specification as "overdiagnosis," rather than advancement of diagnosis for a cancer that becomes clinically relevant cancer later on, can only result from the outcome of the long-term observation of young cohorts. In addition, the diagnosis of "cancer" at young ages implies anxieties and may have influence on quality of life, also counting as harm by "overdiagnosis." In other words, the diagnosis of cancer in early detection programs should be early enough, but not too early. Future analysis of PROBASE will focus on whether the start of screening may safely be deferred to age 50 if the low prevalence of aggressive screen-detected cancers is confirmed, and it will have to take particular care on the frequency and treatment of low and favorable-risk PCa. Until final results of PROBASE are available, an algorithm of risk-adapted early detection may be useful for daily practice.[27]

5.5 | DRE in the delayed screening arm

A further important finding of this trial is the low PPV-1 = 57/6537 = 0.87% of a suspicious DRE (n = 57) in Arm B of the trial with deferred PSA testing. This is much lower as compared to the positivity of DRE in the youngest age group of 55 to 59 in the PLCO trial of 4.9%. Out of 57 participants with suspicious DRE findings, 37 agreed to be biopsied and only 2 were found to have cancer, all of them with ISUP 1. This is one of the largest evaluations of DRE among 45-year-old men as part of the statutory early detection program in Germany and convincingly shows the very low detection rate of only 0.03% (2/6537).

5.6 | Limitation of the study

The PROBASE trial was successfully enrolled in time; however, only less than 20% of men who were invited finally agreed to participate. We performed a field study to evaluate the reasons for nonparticipation and most frequently, nonparticipants did not show interest in screening. The participation rate is similar to the known low participation rate of the statutory early detection program in Germany.

A second problem relates to the refusal of a diagnostic biopsy in cases of high risk (PSA ≥3 ng/mL). First, many men needed more time for the decision to undergo a biopsy and showed up later. Second, the

MRI result influenced the decision to undergo a biopsy. Third, the level of anxiety will be analyzed and future participants will be informed about the detection rate of a biopsy based on high risk features.

Adherence to the suggested risk-adapted screening strategy will be analyzed for a subsequent publication. Currently, the data do not indicate that the rate of nonadherence may cause major violation of basic trial assumptions.

With a growing number of PCa diagnoses, future analyses will also take into account the rate of false-positive tests and numbers of indolent PCa cases diagnosed found among participants in so-called "intermediate-risk" and "high-risk" categories.

6 | CONCLUSION

Taken together, this analysis of the first screening round of the PROBASE trial shows a remarkably close matching of the suggested number of participants at different risk defined with an elevated baseline PSA value in retrospective cohorts. This confirms the feasibility to test this kind of approach in young men. The required confirmation of an elevated PSA value at a 2-weeks' distance likely improved the specificity of PSA for tumor detection. The very low positive predictive value of a DRE clearly disqualifies this screening tool in this young population.

The screen-detected cancers were mainly low or intermediate-risk (ISUP 1 and 2) and the prevalence of aggressive cancers (ISUP 3 and higher) was very low. However, patients with screen-detected cancers at age 45 have a long life-expectancy and the favorable cancer-specific survival rates reported in large AS cohorts of patients in their 60s may not apply. In the subsequent screening rounds the prevalence of PCa for men receiving their first PSA test a at age 50 in the delayed screening arm (Arm B), compared to those who received their first PSA test at age 45 (Arm A, immediate screening) and return for follow-up screening, will give more insight into the progression rate of participants with low and intermediate-risk over time and, finally, the value of mpMRI in PCa screening.

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CONFLICT OF INTEREST

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ETHICS STATEMENT

The protocol was approved by the Institutional Review and Ethics Committee of the Medical Faculty at Heinrich-Heine University Düsseldorf and subsequently by each participating institution's local ethic committee in 2013 and is registered at https://doi.org/10.1186/ISRCTN37591328. Written informed consent was obtained from every trial participant before enrolment.

DATA AVAILABILITY STATEMENT

All original data are available upon reasonable personal request to r.kaaks@dkfz.de.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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