Received: 28 June 2022 | Revised: 25 August 2022 | Accepted: 29 August 2022

DOI: 10.1002/ijc.34295

CANCER EPIDEMIOLOGY

IJC INTERNATIONAL JOURNAL of CANCER

Adherence to a risk-adapted screening strategy for prostate cancer: First results of the PROBASE trial

Agne Krilaviciute[1] | Peter Albers[1,2] | Jale Lakes[2] | Jan Philipp Radtke[2] | Kathleen Herkommer[3] | Jürgen Gschwend[3] | Inga Peters[4,5] | Markus Kuczyk[4] | Stefan A. Koerber[6] | Jürgen Debus[6] | Glen Kristiansen[7] | Lars Schimmöller[8] | Gerald Antoch[8] | Marcus Makowski[9] | Frank Wacker[10] | Heinz Schlemmer[11] | Axel Benner[12] | Frederik Giesel[13] | Roswitha Siener[6,14] | Christian Arsov[2] | Boris Hadaschik[15] | Nikolaus Becker[1] | Rudolf Kaaks[16]

Correspondence
Peter Albers, Division of Personalized Early Detection of Prostate Cancer, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 581, 69120 Heidelberg, Germany.
Email: p.albers@dkfz.de

Present address
Christian Arsov, Elisabeth-Krankenhaus Rheydt, Klinik für Urologie und Kinderurologie, Städtische Kliniken Mönchengladbach GmbH, Mönchengladbach, Germany.

Boris Hadaschik, Department of Urology, University Hospital Essen, Essen, Germany.

Funding information
Deutsche Krebshilfe

Abstract

PROBASE is a population-based, randomized trial of 46 495 German men recruited at age 45 to compare effects of risk-adapted prostate cancer (PCa) screening starting either immediately at age 45, or at a deferred age of 50 years. Based on prostate-specific antigen (PSA) levels, men are classified into risk groups with different screening intervals: low-risk (<1.5 ng/ml, 5-yearly screening), intermediate-risk (1.5-2.99 ng/ml, 2 yearly), and high risk (>3 ng/ml, recommendation for immediate biopsy). Over the first 6 years of study participation, attendance rates to scheduled screening visits varied from 70.5% to 79.4%, depending on the study arm and risk group allocation, in addition 11.2% to 25.4% of men reported self-initiated PSA tests outside the PROBASE protocol. 38.5% of participants had a history of digital rectal examination or PSA testing prior to recruitment to PROBASE, frequently associated with family history of PCa. These men showed higher rates (33% to 57%, depending on subgroups) of self-initiated PSA testing in-between PROBASE screening rounds. In the high-risk groups (both arms), the biopsy acceptance rate was 64% overall, but was higher among men with screening PSA ≥4 ng/ml (>71%) and with PIRADS ≥3 findings upon multiparameter magnetic resonance imaging (mpMRI) (>72%), compared with men with PSA ≥3 to 4 ng/ml (57%) or PIRADS score ≤ 2 (59%). Overall, PROBASE shows good acceptance of a risk-adapted PCa screening strategy in Germany. Implementation of such a strategy should be accompanied by a well-structured communication, to explain not only the benefits but also the harms of PSA screening.

Abbreviations: DRE, digital rectal examination; ERSPC, European Randomized study of Screening for Prostate Cancer; PCa, prostate cancer; PSA, prostate-specific antigen; RCT, randomized clinical trial.

Agne Krilaviciute and Peter Albers shared first-authorship. Nikolaus Becker and Rudolf Kaaks shared senior-authorship.

For affiliation refer to page 863

KEYWORDS
compliance, contamination, prostate cancer, prostate-specific antigen, PSA, screening

What's new?

Screening for prostate-specific antigen (PSA) reduces deaths from prostate cancer, but routine PSA screening for all participants leads to overdiagnosis and overtreatment. The PROBASE study, initiated in 2014, uses a risk-adapted PSA screening strategy that adjusts the screening schedule depending on the participant's initial PSA level. Here, the authors report that adherence rates during the first 6 years of the trial were good, with attendance rates in the 70% to 80% range, and the biopsy acceptance rate was 71% among men with PSA of 4 or higher.

1 | INTRODUCTION

The European Randomized Study of Screening for Prostate Cancer (ERSPC) has provided conclusive evidence that prostate-specific antigen (PSA) screening can reduce prostate cancer (PCa) mortality.[1] However, it was also found that, relative to the number of cases with aggressive PCa that were detected early enough to reduce PCa-related mortality, routine PSA screening at regular (mostly 4-year) intervals for all screening participants entailed major risks of harms in the form of over-diagnosis (ie, the early diagnosis of PCa that would not have become symptomatic during a man's lifetime) and over-treatment (ie, treatment of tumors detected early, without tangible benefit in terms of extended life expectancy).[1]

To improve the overall balance of screening benefits (reduced PCa-related mortality) and harms, risk-adapted screening approaches are being proposed that modulate screening intervals depending on a man's estimated risk of having clinically relevant PCa in the next years.[2] Risk stratification may be based on a man's age and serum concentrations of PSA, as well as on clinical risk factors and genetic profiling.[2] For example, the diagnostic work-up of screen-positive men may be improved using magnetic resonance imaging (MRI) of the prostate.[3-5] Microsimulation models of risk-adapted screening also showed a several-fold net benefit improvement compared with conventional age-based screening strategies.[6-8] So far, however, only few studies have been started to test risk-adapted screening strategies in population-based screening cohorts.

Recently, two large population-based trials have been launched to investigate risk-adapted screening for PCa mortality reduction, both expected to deliver results by the end of this decade. In Finland, the PROSCREEN trial is a population-based randomized screening trial of 67 000 men aged 55 to 67 years at entry, which uses initial (baseline) PSA measurements to assign individually adapted screening intervals, and which combines PSA with a four-kallikrein (4 K) score test and multiparametric MRI (mpMRI) to identify men requiring prostate biopsies.[9] Other large risk-adapted screeing trials, for example, Göteborg 2[10] and STLM3,[11] will provide information on how to improve the accuracy of the detection of clinically significant PCa. In Germany, we initiated in 2014 the PROBASE study—a prospective screening trial of over 46 000 men that tests a risk-adapted screening strategy using baseline PSA measurements to assign individualized screening intervals, with baseline PSA and risk stratification starting either at age of 45 or 50 in a 1:1 randomized design.[12]

Key determinants for the effectiveness of risk-adapted screening strategies in practice are screening participation and long-term adherence of screening participants to a screening program, compliance with recommended screening intervals, and compliance with recommendations for further diagnostic work-up for those who receive a positive PSA test. Likewise, the quality of the PROBASE study as a randomized trial will also depend on the compliance of study participants with the study protocol, since initially about 90% of them were recommended 5 year intervals until the next PSA screening. To examine adherence to the recommended screening strategy in PROBASE, we here describe the response to personal screening invitations for PSA tests, response to biopsy indications, and self-initiated interventions outside the indicated study protocol during the first 8 years of the study.

2 | STUDY COHORT AND METHODS

2.1 | The PROBASE study

The German Statutory Early Detection Program—launched in 1971—recommends digital rectal examinations (DRE) beginning with the age of 45 years in the frame of annual self-initiated visits at office-based physicians or urologists.[13] The DRE examinations are paid by the health insurance but PSA tests are not reimbursed. Patients may order, however, an additional PSA test at their own costs.

In a randomized approach, the PROBASE study investigates the hypothesis that delaying the start of risk-adapted PSA screening to age 50 (delayed screening), as compared with screening starting at age 45 (immediate screening), will result in significantly fewer false-positive PCa tests, while PCa detection remains early enough to avoid a significant increase in distant metastases until the age of 60, as described previously in further detail.[12] The PROBASE trial uses a PSA test rather than DRE and an organized approach that is risk-based rather than rigidly annual-based self-initiated physician visits. The study is performed at four study sites in Germany, in and around the cities of Duesseldorf, Hannover, Heidelberg and Munich. Details of the study design have been reported previously.[12,14] In brief, >400 000 invitations

were sent out to 45-year-old men identified from municipal population registries, and between February 2014 and December 2019 a total of 46 495 men agreed to be randomized and take part in the trial. Of these, one random half were offered baseline PSA screening at age 45 (immediate screening arm; N = 23 301); the other half were offered DRE and were requested to return for their delayed baseline PSA screening at age 50 (deferred screening arm; N = 23 194).

In both study arms, the risk-adapted screening protocol is identical and works with three "risk" categories: (1) "low risk" in men with PSA <1.5 ng/ml leading to screening invitations every 5 years ("5-year screening rounds"), (2) "intermediate risk" in men with PSA between ≥1.5 and < 3.0 ng/ml leading to screening invitations every 2 years ("2-year screening rounds"), and (3) "high risk" in men with confirmed PSA ≥3.0 ng/ml leading to an indication for prostate biopsy. Confirmatory PSA test is done after 2 weeks for those with initial PSA ≥3 ng/ml, and based on the second PSA value participants are classified accordingly. The baseline PSA value at either age 45 (immediate screening arm) or age 50 (deferred screening arm) determines the initial personal screening schedule according to the scheme described above. Higher PSA values in the subsequent screening rounds 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.

Men with confirmed PSA ≥3 ng/ml are referred to urology clinics for further diagnostic workup and are recommended to undergo a systematic prostatic biopsy. For research purposes and according to more recent guidelines, a mpMRI examination of the prostate is also offered, however, is not intended to be used for triggering or delaying the biopsy decision. If MRI was performed, biopsies were carried out as a combination of systematic and MRI-targeted biopsies. Systematic biopsies were performed according to the Vienna nomogram[15] and suspicious lesions in MRI were double biopsied. If the biopsy is refused by the study participant or if it is negative, 3-monthly PSA testing within the first year and annual invitations for further PSA screening thereafter are recommended. Even if PSA values decreased over time, participants remained in the high-risk category and were followed by a 3-monthly PSA for at least 1 year and yearly MRIs afterwards.

After study enrollment, all participants are contacted annually either by mailed questionnaire or for a subsequent screening visit according to the risk-adapted schedule described above. At consecutive PSA screening visits, participants are interviewed by a study physician and information covering the interval since the last visit is recorded (eg, new diseases, changes in medication use, history of PSA or biopsies). Screening in the PROBASE trial ends with a PCa diagnosis, early withdrawal from the study or death, or with a final PSA screening when a participant reaches the age of 60 years. Further details about data collection in the PROBASE trial have been published previously.[12]

All data were captured centrally at the German Cancer Research Center (DKFZ) in a database (Onkostar) which is available online at the study sites, using exchange protocols in accordance with data protection regulations.

2.2 | Data analyses

Data from the database were extracted on April 1, 2022 but only records up to December 31, 2021 were considered for the present analyses to allow additional time for data entry into the central study database.

Basic data tabulations were used to describe numbers of PROBASE participants who had progressively reached their respective time points for scheduled follow-up PSA screenings and to describe compliance for each screening occasion after 2, 4 or 6 years in the immediate screening arm for men initially classified to be at intermediate risk, after 5 years in the immediate screening arm for men initially classified to be at low risk, or for first PSA screening after 5 years in the deferred screening arm. Basic tabulations were also used to describe numbers of men who in each of the screening rounds had been classified into the high-risk category, and to describe their subsequent compliance with the recommended prostate biopsy.

To estimate complete response rates at the follow-up screening occasions, we counted the cumulative screening attendance for men who had had at least 12 months' time to comply with each invitation; that is, for men who had accumulated a minimum of 3, 5, 6 and 7 years of follow-up time after baseline screening, respectively, at time of 2-, 4-, 5- or 6-year follow-up screenings (see Supplementary Figure S1). Given these minimal follow-up times, we counted men as "compliant" if their follow-up visit took place in a time frame ranging from 90 days before the scheduled visit (as the screening invitations were sent by postal letter 4 weeks prior the scheduled date and also earlier visit times could have been planned on personal request) till no later than 90 days prior to the date of the next scheduled follow-up visit. Men with the screening visit taking place later than 365 days from the scheduled date were referred to as "late-comers."

We also used basic tabulations to describe numbers of men who, at each screening occasion, reported having had a PSA testing outside the PROBASE protocol and study centers, and to examine potential factors determining PSA testing outside the protocol or other forms of noncompliance with the PROBASE study protocol.

For men who were offered a biopsy, we described 1-year biopsy acceptance, overall and stratified by screening PSA value (≥3 to <4, ≥4 to <5, ≥5 to <10, and ≥10 ng/ml), MRI findings at screening (PIRADS scores 1-2, 3, 4-5 and unknown), follow-up PSA value for men who had denied immediate biopsy (<3, ≥3 to <4, ≥4 to <5, ≥5 to <10 and ≥10 ng/ml), or history of previous PSA or DRE examination prior to enrollment in PROBASE and history of prostate cancer af the age 45.

Information on sociodemographic factors, medical history and behavioral patterns towards screening recommendations, including a history of previous PSA or DRE examination prior to enrollment in PROBASE, reasons for PSA and time of last PSA and DRE was collected at the time of enrollment in the study at age 45. We describe medical history (cancer and other underlying diseases), extended family history of PCa (among father, brother[s], uncle[s] and grandfather[s]), as well as PSA and DRE use and reason for PSA testing before age 45 for all study participants together as well as stratified by family history of PCa before age 45.

All calculations were performed with Stata, version 14/IC (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

3 | RESULTS

3.1 | Numbers of participants at enrollment (immediate and deferred screening arms)

A total of 46 495 men accepted to take part in the PROBASE study and attended a first study visit. Of these, 17.1% (N = 7944) reported a family history of PCa (ie, PCa diagnosis for a grandfather, father, uncle[s] or brother[s], see Table 1). About one third of participants (34.3%) had a DRE prior to enrollment in the PROBASE trial and 15.8% (N = 7335) reported having had a prior history of PSA testing. Men with a family history of PCa had undergone both DRE and PSA testing before age 45 more often (43.1% and 27.5%, respectively) than men without a family history (33.8% and 13.9%, respectively). Among men without a family history, prior PSA testing was more often reported to be motivated by symptoms (11.1%) than among those who did report a family history (6.8%). More than half of the prior PSA tests (4080 out of 7335 = 55.6%) were done in the context of a routine check-up. Irrespective of family history, men who reported PSA testing prior to PROBASE enrollment were more likely to have a history of urological disorders, previous cancer diagnosis (other than cancer of the prostate), endocrine diseases, gastrointestinal disorders or cardiovascular diseases (Supplementary Table S1).

TABLE 1 Basic characteristics of the PROBASE study population at age 45 at the study enrollment

Characteristics (column percentage)		Family history of prostate cancer			
		Yes (*N* = 7944; 17.1%)	No (*N* = 35 967; 77.4%)	Unknown (*N* = 2584; 5.6%)	Total (*N* = 46 495; 100%)[a]
PSA before age 45	No	5515 (69.4%)	29 455 (81.9%)	1044 (40.4%)	36 014 (77.5%)
	Unknown	245 (3.1%)	1516 (4.2%)	1385 (53.6%)	3146 (6.8%)
	Yes	2184 (27.5%)	4996 (13.9%)	155 (6.0%)	7335 (15.8%)
	Reasons for PSA testing[b,c]				
	Routine check-up	759 (34.8%)	3223 (64.5%)	98 (63.2%)	4080 (55.6%)
	Due to family history	1464 (67.0%)	n/a	n/a	1464 (20.0%)
	Symptom-related	149 (6.8%)	556 (11.1%)	8 (5.2%)	713 (9.7%)
	Search for prostate cancer	7 (0.3%)	35 (0.7%)	2 (1.3%)	44 (0.6%)
	Unknown	206 (9.4%)	1224 (24.5%)	44 (28.4%)	1474 (20.1%)
	Time of last PSA[c]				
	In the last 12 months	862 (39.5%)	1878 (37.6%)	52 (33.5%)	2792 (38.1%)
	1-2 yr. ago	601 (27.5%)	1247 (25.0%)	39 (25.2%)	1887 (25.7%)
	3-5 yr. ago	371 (17.0%)	857 (17.2%)	25 (16.1%)	1253 (17.1%)
	More than 5 yr. ago	147 (6.7%)	322 (6.4%)	8 (5.2%)	477 (6.5%)
	Unknown	203 (9.3%)	692 (13.9%)	31 (20.0%)	926 (12.6%)
DRE before age 45	No	4219 (53.1%)	22 432 (62.4%)	852 (33.0%)	27 503 (59.2%)
	Unknown	302 (3.8%)	1389 (3.9%)	1330 (51.5%)	3021 (6.5%)
	Yes	3423 (43.1%)	12 146 (33.8%)	402 (15.6%)	15 971 (34.3%)
	DRE by urologist[c]	2221 (64.9%)	7573 (62.3%)	249 (61.9%)	10 043 (62.9%)
	Time of last DRE[c]				
	In the last 12 months	1082 (31.6%)	3473 (28.6%)	113 (28.1%)	4668 (29.2%)
	1-2 yr. ago	762 (22.3%)	2572 (21.2%)	95 (23.6%)	3429 (21.5%)
	3-5 yr. ago	747 (21.8%)	2551 (21.0%)	69 (17.2%)	3367 (21.1%)
	More than 5 yr. ago	765 (22.3%)	3158 (26.0%)	105 (26.1%)	4028 (25.2%)
	Unknown	67 (2.0%)	392 (3.2%)	20 (5.0%)	479 (3.0%)
Had PSA or DRE before age 45		3968 (49.9%)	13 458 (37.4%)	452 (17.5%)	17 878 (38.5%)

Abbreviations: DRE, digital rectal examination; PSA, prostate specific antigen.

[a]Indicated relatives among those with family history of prostate cancer: Grandfather (N = 2449, 30.8%), Father (N = 927, 11.7%), Uncle (N = 827, 10.4%), Brother (N = 66, 0.8%), and No data (N = 4141, 52.1%).

[b]Multiple reasons could have been mentioned by each participant.

[c]Percentage from those with respective positive response to PSA or DRE testing in the past.

TABLE 2 Compliance with a prostate specific antigen (PSA) screening invitation by screening round

Screening round	Follow-up time since study enrollment	Immediate screening, start at age 45 (Study arm A; N = 23 301)									Deferred screening, start at age 50 (Study arm B; N = 23 194)			
		High risk (N = 186)	Intermediate risk (N = 2291)				Low risk (N = 20 824)							
				Compliant, N				Compliant, N				Compliant, N		
			Eligible[a], N	Within 1Y[b]	"Late comers"[c]	Total	Eligible[a], N	Within 1Y[b]	"Late comers"[c]	Total	Eligible[a], N	Within 1Y[2]	"Late comers"[c]	Total
2-yr.	<2 yrs	n/a	0				n/a				n/a			
	≥2 to <3 yrs		246	157 (63.8%)	n/a									
	≥3 yrs		2045	1769 (86.5%)	31 (1.5%)	1800 (88.0%)								
	Total		2291											
4-yr.	<4 yrs	n/a	645	6 (0.9%)			n/a				n/a			
	≥4 to <5 yrs		386	246 (63.7%)										
	≥5 yrs		1130	831 (73.5%)	35 (3.1%)	866 (76.6%)								
	Total		2161[d]											
5-yr./deferred baseline	<5 yrs	n/a	n/a				10 187	70 (0.7%)			11 302	73 (0.6%)		
	≥5 to <6 yrs						4278	2257 (52.8%)			4744	2483 (52.3%)		
	≥6 yrs						6359	4979 (78.3%)	71 (1.1%)	5050 (79.4%)	7092	5064 (71.4%)	121 (1.7%)	5185 (73.1%)
	Total						20 824				23 138[e]			
6-yr.	<6 yrs	n/a	1402	7 (0.5%)			n/a				n/a			
	≥6 to <7 yrs		414	245 (59.2%)										
	≥7 yrs		224	152 (67.9%)	6 (2.7%)	158 (70.5%)								
	Total		2040[c]											

Note: Indicated in shaded areas are the numbers of men who had accumulated at least 12 months of study follow-up time after the dates of scheduled follow-up screenings, enabling estimates of compliance for sub-sets of PROBASE participants with the 2-, 4-, 5- and 6-year screening rounds. *At date of present analysis (data extraction December 31, 2021).

[a]Men who had accumulated the indicated follow-up time since study enrollment.

[b]Had a PSA screening test registered by the study physician later than +365 days from the screening invitation but no later than −90 days to the invitation to the next screening, that is, so-called "late-comers."

[c]Men who upgraded to a high risk in the previous round were excluded as were those who withdrew, died or were diagnosed with prostate cancer earlier than 90 days to the screening invitation for the previous screening round (N = 130 for the 4-year round, N = 251 for the 6-year round).

[d]Men with suspicious digital rectal examination findings at the time of recruitment (N = 56) were not analyzed in this sub-analyses as they were offered a biopsy at age 45.

[e]Had a PSA screening test registered by the study physician between −90 and +365 days from the screening invitation.

3.2 | Response to PSA screening invitations

Of the 46 495 study participants, 23 301 were randomized to the immediate screening arm, and 23 194 to the deferred screening arm. In the immediate screening arm, 20 824 (89.4%) and 2291 (9.8%) were rated as low-risk and intermediate-risk, respectively, and 186 (0.8%) were rated at high risk. The median follow-up time in the study from the enrollment to the date of data extraction for this analysis (December 31, 2021) for all study participants was 5.1 years (interquartile range: 3.7-6.3 years).

Table 2 shows the numbers of PROBASE participants in the low- and intermediate-risk groups of the immediate screening arm, and in the deferred screening arm, respectively. Grouping by follow-up time since study enrollment indicates the numbers of men that at the time of data extraction for the present analyses (December 31, 2021) had reached (or not yet reached) their scheduled dates for screenings 2, 4, 5 or 6 years after enrollment. Based on the numbers of men who had accumulated at least 12 months of study follow-up time after the dates of scheduled follow-up screenings (shaded areas in Table 2), we estimated the compliance for PROBASE participants with the 2-, 4-, 5- and 6-year screening rounds. In the immediate screening arm, men assigned to the low-risk group showed an overall screening attendance rate of 79.4% 5 years after enrollment and baseline testing, whereas in the deferred screening arm the attendance rate to the first PSA screening at age 50 was 73.1%. Stratified analyses showed a difference in absolute participation rates of up to 3% to 4% comparing men with or without a family history of PCa (Supplementary Tables S2a and 2b), or comparing men with or without a history of PSA testing (Supplementary Tables S3a, 3b) or history of DRE testing (Supplementary Tables S4a and 4b) prior to PROBASE study enrollment. In the intermediate-risk group, a total of 88.0% of men had attended the 2-year screening, either within 12 months of their scheduled screening date (86.5%) or as "late comers" (1.5%), and likewise, a total of 76.6% and 70.5% attended the 4-year and the 6-year screening rounds, respectively (Table 1). Further analyses showed that participation in a next screening round was higher among those who had complied with the previous round invitation (Supplementary Figure S2): In the intermediate risk group, the rate of response to the 4-year screening was 83.6% for among men who had responded to the 2-year screening invitation (N = 1800), but only 8.6% among those (N = 245) who had skipped the 2-year round. Likewise, the participation in the 6-year round was 86.5% among men who had attended the 4-year screening, compared with 50.7% among those who had skipped the 4-year round.

3.3 | Self-initiated PSA tests between PSA screening rounds

At the time of each screening PSA visit, study participants were asked by the study physician to report whether they had self-initiated PSA tests outside of the PROBASE protocol. Table 3 describes the percentages of PROBASE participants who reported having had a self-initiated PSA test between two consecutive screening rounds, or between study enrollment and deferred screening for participants in

TABLE 3 Prostate specific antigen (PSA) testing before entering the study at age 45 and between consecutive screening rounds

	Immediate Screening, start at age 45 (Study arm A)									Deferred Screening, start at age 50 (Study arm B)		
	High risk			Intermediate risk			Low risk			Had PSA testing, N (%)		
Time of PSA testing	Had PSA testing, N (%)			Had PSA testing, N (%)			Had PSA testing, N (%)			Yes	No/unknown	Total
	Yes	No/unknown	Total	Yes	No/unknown	Total	Yes	No/unknown	Total			
Before age 45	39 (21.0%)	147 (79.0%)	186	435 (19.0%)	1856 (81.0%)	2291	3179 (15.3%)	17 645 (84.7%)	20 824	3682 (15.9%)	19 512 (84.1%)	23 194
Between baseline and 2 yr. round	n/a			218 (11.2%)	1739 (88.8%)	1957	n/a			n/a		
Between the 2 yr. and 4 yr. rounds	n/a			152 (13.6%)	966 (86.4%)	1118	n/a			n/a		
Between baseline and 5 yr. round	n/a			n/a			1376 (18.7%)	6001 (81.3%)	7377	1965 (25.4%)	5776 (74.6%)	7741
Between the 4 yr. and 6 yr. rounds	n/a			61 (14.9%)	349 (85.1%)	410	n/a			n/a		

Note: PSA testing after the enrollment was available only among men who complied with PSA screening invitations in the trial. *At date of present analysis (data extraction December 31, 2021). For few individuals who skipped the 2-yr. round but participated in the 4-yr. round (N = 10), who skipped the 4-yr. round but participated in the 6-yr. round (N = 35) it is unclear whether reported PSA testing since the last study visit happened in between the screening rounds or whether that PSA was done at the time of scheduled PSA screening that was not recorded in the study.

the deferred screening arm. One out of four men (25.4%) who complied with the PSA screening invitation at the 5-year screening round in the deferred screening arm confirmed having additional PSA tests since PROBASE enrollment vs one out of five men (18.7%) for the low-risk group in the immediate screening arm (*P* value <.001, X^2 test). In the immediate screening arm, 11.2% to 14.9% of men participating in the 2-, 4-, and 6-year screening rounds reported additional, out-of-protocol PSA testing after their previous PROBASE screening visit. Depending on the screening round, 33% to 57% of men reported additional, out-of-protocol PSA testing in between PROBASE screening rounds (Supplementary Table S5a), and out-of-protocol testing was reported more frequently among men with a prior history of PSA testing before entry into the PROBASE study (Supplementary Table S5a) relative to men without such prior history. The association between out-of-protocol testing and prior history of PSA testing was strongest among men in the intermediate risk group attending the 2-year screening round (OR = 8.1 [95% CI 6.0-11.0]), somewhat weaker for men attending the 4- or −5 year rounds (odds ratios

TABLE 4 Biopsy acceptance among men with PSA ≥3 ng/ml[a]

Characteristics	1-year biopsy compliance		Total	*p* value of Chi^2
	Yes, *N*. (%)	No, *N*. (%)		
Total, men[b]	320 (63.6%)	183 (36.4%)	503	
Screening round:			Total = 503	0.050
Baseline	120 (64.5%)	66 (35.5%)	186	
2-year (immediate screening arm)	81 (73.6%)	29 (26.4%)	110	
4-year (immediate screening arm)	33 (50.0%)	33 (50.0%)	66	
6-year (immediate screening arm)	6 (66.7%)	3 (33.3%)	9	
5-year (immediate screening arm)	12 (54.5%)	10 (45.5%)	22	
5-year (deferred screening arm)	68 (61.8%)	52 (38.2%)	110	
PSA level at the screening:			Total = 503	0.003
≥3 to <4 ng/ml	164 (56.7%)	125 (43.3%)	289	
≥4 to <5 ng/ml	72 (71.3%)	29 (28.7%)	101	
≥5 to <10 ng/ml	69 (74.2%)	24 (25.8%)	93	
≥10 ng/ml	15 (75.0%)	5 (25.0%)	20	
MRI score:			Total = 410	<0.001
PIRADS 1–2	58 (59.2%)	40 (40.8%)	98	("Unknown" excluded)
PIRADS 3	145 (72.9%)	54 (27.1%)	199	
PIRADS 4–5	105 (92.9%)	8 (0.7%)	113	
Unknown	4 (40.0%)	6 (60.0%)	10	
Follow-up PSA tests in men who did not undergo immediate biopsy:			Total = 141	<0.001
<3 ng/ml	2 (4.4%)	43 (95.6%)	45	
≥3 to <4 ng/ml	19 (41.3%)	27 (58.7%)	46	
≥4–<5 ng/ml	10 (40.0%)	15 (60.0%)	25	
≥5 to <10 ng/ml	9 (47.4%)	10 (52.6%)	19	
≥10 ng/ml	5 (83.3%)	1 (16.7%)	6	
Family history of prostate cancer:			Total = 503	0.084
Yes	79 (70.5%)	33 (29.5%)	112	
No/unknown	241 (61.6%)	150 (56.5%)	391	
PSA before age 45:			Total = 503	0.386
Yes	68 (67.3%)	33 (32.7%)	101	
No/unknown	252 (62.7%)	150 (38.4%)	402	
DRE before age 45:			Total = 503	0.059
Yes	111 (58.4%)	79 (41.6%)	190	
No/unknown	209 (66.8%)	104 (33.2%)	282	

[a]At date of present analysis (data extraction December 31, 2021).
[b]All men had at least 1 year of follow-up time after screening PSA test to comply with the biopsy recommendation.

between 5.6 [3.9-8.1] and 6.0 [5.3-6.8]), and still somewhat weaker for men attending the 6-year screening round (OR = 4.2 [2.3-7.5]). Increased out-of-protocol PSA testing was also observed for men with prior history of DRE (Supplementary Table S5b), or (less strongly) with a family history of PCa (Supplementary Table S5c) relative to men without such histories.

3.4 | Response to biopsy indication

All men with a confirmatory screening PSA ≥3 ng/ml were recommended to undergo a diagnostic workup by prostate biopsy. At the reference date for the present data analyses (December 31, 2021), this group included a total of 649 men (shown in Supplementary Table S6), and 503 of them have had at least 1 year of follow-up time to comply with the biopsy indication. Table 4 shows 1-year biopsy acceptance rate among these men. The overall biopsy acceptance rate was 63.6% but this rate varied between 50.0% and 73.6% for the different screening rounds. Among men who tested PSA-positive at their first baseline screening, either at age 45 (immediate screening arm) or at age 50 (deferred arm), the 1-year biopsy acceptance rates were 64.5% and 61.8%, respectively. Biopsy acceptance gradually increased to 69.9% with additional follow-up time for men who were offered a biopsy at the age of 45 (additional 10 men have had biopsy later than 1 year after being recommended to undergo prostate biopsy; shown in Supplementary Table S6). Biopsy acceptance was higher (>71%) in men who had a screening PSA value ≥4 ng/ml, which is the PSA-threshold level at which prostatic biopsy is recommended according to standard urological practice in Germany,[16] as compared with biopsy acceptance among men with PSA between 3 and 4 ng/ml (56.7%). In line with this, biopsy acceptance tended to decrease in further screening rounds, in which the proportion of men having PSA levels between 3 and 4 ng/ml increased (Supplementary Figure S3).

In addition, as shown in Tables 4, 141 out of 503 men (28.0%) had a further PSA test before taking a biopsy decision. Of these, 45 had a follow-up PSA <3 ng/ml, and 43 of those (95.6%) declined biopsy in the first year, including many with PIRADS score ≥ 3 (Supplementary Figure S4). MRI findings influenced biopsy decision, where biopsy acceptance rose from 59.2% in those with PIRADS 1 to 2 findings to 72.9% (PIRADS 3) and reached 92.9% for men with PIRADS 4 to 5 findings. Response to biopsy indication showed no association with prior history of DRE or PSA testing, or family history of PCa, at the time of study entry.

4 | DISCUSSION

While quantitative modeling studies indicate that risk-adapted strategies may improve the overall harm-to-benefit ratio for PCa screening programs, only few studies so far have started to examine such strategies in practice. We here report estimates from the German PROBASE trial—a study of 46 495 men 45 years of age who started PSA screening either immediately (immediate screening arm), or 5 years after study enrollment at age 50 (deferred screening arm)—of attendance rates to scheduled screening rounds, rates of self-initiated PSA testing in addition to the PROBASE protocol, compliance with the recommendation to undergo prostate biopsy in case of a positive PSA test, and potential determinants that may affect adherence.

Our findings must be interpreted in the context of German policy with regard to PCa screening. The German Statutory Early Detection Program—launched in 1971—recommends DRE, starting at the age of 45 years, as part of annual self-initiated visits at office-based physicians or urologists. German health insurances reimburse DRE examinations, but not PSA testing unless it is motivated by a suspicious DRE finding; patients may, however, order PSA tests at their own costs. According to a large-scale population survey among men 45 to 79 years of age, conducted in 2013, about 20% of the age group 45 to 49 reported having undergone a DRE and 12% reported having had a PSA test within the past 12 months.[17] With increasing age groups, these percentages progressively rose to 56% and 45%, respectively, for men 70 to 79 years of age.[17] Similar observations were made in an earlier survey (2008).[18]

In PROBASE, one out of six participants (15.8%) had a history of PSA testing before enrollment to PROBASE, which is above the prevalence of PSA testing described above in the general population.[17] Likewise, one out of three men (34.4%) reporting DRE testing prior to PROBASE enrollment, again well above the DRE testing rate for men below age 45 in the general population (which is below 20%). Since the official starting age for screening with DRE in Germany is 45 years, it is unlikely that men in the PROBASE study had DRE performed in the frame of the current German PCa screening program. Rather, DRE use might reflect the percentage of men who participate in several other statutory health checkup programs in Germany. The German health insurances and the Ministry of Health encourage all residents to participate in early detection programs, for example, for diabetes or high blood pressure, and offer various tools and consultations to detect diseases as early as possible, as part of general health check-ups (eg, "Gesundheits check-up" beginning at age 35).

The higher-than-average use of DRE and PSA testing prior to PROBASE enrollment appeared to be frequently motivated by men's concerns specifically with regard to their genitourinary health, as the DREs had been performed predominantly (62.9%) in specialized urology practices, rather than by general practitioners. Analyses of PROBASE questionnaire data showed that family history of PCa, but also pre-existing urologic or other concerns or morbidities (eg, cancer, endocrine disorders), were frequent self-reported motivations associated with PSA testing before enrollment into the PROBASE study. After enrollment into the PROBASE trial, prior PSA testing, use of DRE and self-reported family history each were related to further self-initiated PSA testing additionally to the tests scheduled for PROBASE, whereas at the same time these prior behaviors were also related to a better adherence to the scheduled screening rounds. Depending on screening arm and risk group allocation, between 11% and 25% of all study participants who adhered to scheduled follow-up visits reported having had further PSA tests additionally to the recommended PROBASE protocol. The frequency of additional PSA testing in between scheduled PROBASE screening rounds, however, was

4- to 8-fold increased (odds ratios) for men who already had a history of PSA testing prior to PROBASE enrollment compared with those without prior PSA history, depending on the follow-up screening round. Additional PSA testing was also increased among men with prior history of DRE and to a lesser degree, with a self-reported family history of PCa at the time of study entry. Again, these data indicate that pre-existing concern about genitourinary health was a strong and continuing "driver" of PSA testing both within and outside the PROBASE study context.

Overall, about 80% of men in the immediate screening arm (ie, starting PSA testing at age 45) returned for scheduled screening rounds during their first 5 or more years in the study, compared with only 74% for men whose first PSA testing was deferred until the age of 50. In absolute, these adherence rates in both study arms exceed by far the usual participation rates observed in other European prostate screening trials[19,20] and long-established cancer screening programs in Germany, such as routine screening for breast cancer (52%[21]) and colorectal cancer (11-26%[22]), although it should be acknowledged that those men who agreed to participate in PROBASE (<12% from all invited) might have represented men who have higher interest in screening in general. Regarding the lower participation in the deferred screening arm, we speculate that dissatisfaction with the lack of an immediate screening offer may have motivated a proportion of men to independently seek PSA testing through medical practices, abandoning further participation in the PROBASE trial. Future analyses, after at least 5 more years of screening, will show whether after the initial drop-outs observed in the first 5 years the adherence rates will stabilize, or whether there will be continuing attrition of the PROBASE study cohort. We anticipate that increased communication with the study participants, for example, through the use of annual newsletters to remind men of the advantages of adhering to individually optimized, risk-adapted screening schedules and to keep them informed about findings from the trial, will help maintain a high level of long-term adherence.

Among men who had a confirmed PSA test ≥3 ng/ml, and who thus were classified into the high-risk group, only up to 64% accepted to undergo the recommended prostate biopsy at one of the PROBASE study centers within 1 year of the positive PSA test, although the overall biopsy compliance rates varied across risk groups and screening rounds. The 1-year biopsy compliance rates varied also according to the actual PSA level at the time of the positive test, with ~74% compliance for those with PSA values ≥4 ng/ml, compared with 57% for those with values between 3 to 4 ng/ml. In Germany, as in many other countries, 4 ng/ml is the generally accepted PSA threshold value for recommending biopsy.[16] In PROBASE, a lower threshold of 3 ng/ml was chosen for classifying men into the high-risk category (screening PSA test "positive") considering the fact that PSA levels are significantly lower among younger men below the age of 50, as compared with men of older ages. Many of the men who hesitated to have an immediate prostate biopsy may have asked for a second opinion from urologists outside the PROBASE study centers, potentially leading to contradictory advice regarding the immediate need for biopsy. This might have been particularly the case for men who had PSA screening tests with values below 4 ng/ml. In addition, some of these men may have subsequently had additional follow-up measurements with PSA declining below 3 ng/ml. Temporarily elevated PSA values are known in this young age group caused by subclinical intraprostatic inflammation.[23] Another factor that could have influenced men's decisions of having an immediate biopsy was the increasing role of mpMRI, which over recent years has now been established as a guideline recommendation as a valuable noninvasive tool for improving the specificity of an elevated PSA test.[24] Especially for men with elevated PSA, but unsuspicious mpMRI, the necessity of having an immediate biopsy is being debated, whereas men with elevated PSA and PIRADS 4 or 5 scoring on mpMRI are recommended to undergo biopsy.[2,24] Despite the lack of evidence that mpMRI in young men at age 45 yields equivalent high negative predictive values as compared with elderly men, the information of a negative mpMRI result has certainly influenced men's decision not to undergo a biopsy.

Despite encouraging results regarding the overall adherence to the study protocol, the PROBASE study has a few limitations. Information about PSA testing outside the PROBASE protocol was recorded only for men who attended the scheduled screening visits. Although nearly 50% of men who had not adhered to scheduled follow-up screening invitations completed at least three annual follow-up questionnaires (data not shown), deliberately, no questions were asked about PSA tests outside the PROBASE schedule, to avoid giving them unintended incentives to use self-initiated tests. The downside of this latter strategy is that we have no quantitative documentation of the frequency of self-initiated PSA testing among men who did not attend follow-up visits scheduled in PROBASE.

In summary, our analysis of adherence and nonadherence to risk-adapted screening revealed a few important insights for future screening strategies for PCa. First, the suggested risk-adapted screening intervals based on a baseline PSA was accepted by a high percentage (up to 80%) of participants, especially when they were offered immediate PSA screening. Second, men accepting the offer to take part in a population-based, risk-adapted PCa screening program (such as PROBASE) will likely show an over-representation of men with heightened concern or awareness of their general health, or more specifically of their genitourinary health. These latter men may tend to seek more frequent PSA testing than is actually offered to them in the context of the screening program, based on their general PCa risk classification. Men concerned about a family history of PCa or because of prostate-related symptoms, who may have an increased motivation to seek self-initiated PSA testing, may require more specifically tailored instruments for risk stratification, as well as intensified counseling regarding the purposes and general benefits of risk-adapted screening strategies. Similarly, their primary physicians need to be involved closely. A small proportion of men may have an increased familial and/or hereditary risk, and for these men, individualized genetic counseling and analyses might be used to identify whether they need intensified (yearly) screening, similar to the counseling and intensified screening strategies for women with hereditary breast cancer. The majority of men with special concerns about genitourinary health, however, may not in reality have PCa risks high

enough to justify annual screening. Third, it was noted that many men with PSA tests ≥3 ng/ml were hesitant to have an immediate prostate biopsy. Over time, biopsy acceptance rates may increase as men in the high-risk category remain in regular annual PSA screening and MRI examinations, which may indicate changes in the prostate over time. MRI was not included in the PROBASE protocol to guide the decision to perform or not perform a biopsy because at the time of the launch of PROBASE in 2014 a mpMRI was not recommended before every biopsy. Meanwhile, this recommendation has changed and every primary biopsy should be accompanied by a prior MRI of the prostate.[2,25] Although it was not recommended by the PROBASE protocol, MRI results did appear to have influenced men's decisions to have a biopsy.

In overall conclusion, we note that the PROBASE trial itself was not compromised by a too high rate of nonadherence, neither as general adherence to the risk-adapted screening strategy nor as individual adherence to recommended biopsies. We do see clear indications, however, that deviations from the PROBASE study protocol might have been caused by an insufficient understanding of the advantages of risk-adapted time intervals. These findings underscore that, in general, sufficient counseling should be given to all men attending to a risk-adapted screening program, to create awareness that frequent PCa screening is not necessarily accompanied by benefits (ie, a gain in life years through early tumor detection) but can also generate major harms (false-positive tests and follow-up diagnostics; over-diagnosis and over-treatment), and to explain that risk-adapted strategies are designed to maintain an optimized balance between an individual's expected benefits and risk of harms.

AUTHOR CONTRIBUTIONS

Agne Krilaviciute: Formal analysis, Data Curation, Writing—Original Draft, Visualization; Peter Albers: Conceptualization, Writing—Original Draft, Supervision; Jale Lakes: Writing—Review & Editing; Jan Philipp Radtke: Writing—Review & Editing; Kathleen Herkommer: Writing—Review & Editing; Jürgen Gschwend: Writing—Review & Editing; Inga Peters: Writing—Review & Editing; Markus Kuczyk: Writing—Review & Editing; Stefan A. Koerber: Writing—Review & Editing; Jürgen Debus: Writing—Review & Editing; Glen Kristiansen: Writing—Review & Editing; Lars Schimmöller: Writing—Review & Editing; Gerald Antoch: Writing—Review & Editing; Marcus Makowski: Writing—Review & Editing; Frank Wacker: Writing—Review & Editing; Heinz Schlemmer: Writing—Review & Editing; Axel Benner: Writing—Review & Editing; Frederik Giesel: Writing—Review & Editing; Roswitha Siener: Writing—Review & Editing; Christian Arsov: Writing—Review & Editing; Boris Hadaschik: Writing—Review & Editing; Nikolaus Becker: Conceptualization, Methodology, Writing—Original Draft; Rudolf Kaaks: Conceptualization, Methodology, Writing—Original Draft, Visualization. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

AFFILIATIONS

[1]Division of Personalized Early Detection of Prostate Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany
[2]Department of Urology, University Hospital, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany
[3]Department of Urology, Technical University of Munich, School of Medicine, Klinikum rechts der Isar, Munchen, Germany
[4]Department of Urology, Medical University Hannover, Hannover, Germany
[5]Department of Urology, Krankenhaus Nordwest, Frankfurt am Main, Germany
[6]Department of Radiation Oncology, Heidelberg University Hospital, Ruprecht Karls University, Heidelberg, Germany
[7]Institute of Pathology, University Hospital Bonn, Bonn, Germany
[8]Department of Diagnostic and Interventional Radiology, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany
[9]Institute of Diagnostic and Interventional Radiology, Technical University Munich, München, Germany
[10]Institute of Diagnostic and Interventional Radiology, Medical University Hannover, Hannover, Germany
[11]Department of Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[12]Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany
[13]Department of Nuclear Medicine, Medical Faculty, Duesseldorf, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany
[14]Department of Urology, University Hospital Bonn, Bonn, Germany
[15]Department of Urology, Heidelberg University Hospital, Ruprecht Karls University, Heidelberg, Germany
[16]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

ACKNOWLEDGEMENTS

The PROBASE trial is fully funded by the Deutsche Krebshilfe (Stiftung Deutsche Krebshilfe, DKH). The authors want to thank the Deutsche Krebshilfe, namely Gerd Nettekoven and Dr. Franz Kohlhuber for their continuous and generous support of the trial. The authors also want to thank Mrs. Kerstin Pieper, Mrs. Dorothee Zoller, and Dr. Sabine Behrens, Division of Cancer Epidemiology, DKFZ for their continuous and detailed support of the data management of the trial. Furthermore, we thank all documentary personnel currently working in the study sites and having contributed to the current data, namely Nadja Bergen and Karin Thiess (Hannover), Patrick Weis, Iris Hillenbrand, Alexandra Diwo, Nicole Helker, Jennifer Fontana, Isabel Marie Onkelbach, Dr. Adriane Hommertgen, Dr. Cornelia Jäkel, (Heidelberg), Dr. Simone Wachholz, Dr. Johanna Droop, Petra Zielke, Nancy Steiner (Düsseldorf), and Helga Schulwitz, Ferdous Ara Begum (Munich) for their meticulous work on the raw data. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

Prof. Dr. Dr. J. Debus declares grants from following companies, all of them not related to the content of this paper: Viewray Inc, CRI—The Clinical Research Institute GmbH, Accuray International Sàrl, RaySearch Laboratories AB, Vision RT Limited, Merck Serono GmbH, Astellas Pharma GmbH, AstraZeneca GmbH, Siemens Healthcare GmbH, Solution Academy GmbH, Quintiles GmbH, Ergomed PLC, Surrey Research Park, Pharmaceutical Research Associates GmbH,

Boehringer Ingelheim Pharma GmbH & CoKG, PTW-Freiburg Dr.Pychlau GmbH, Nanobiotix S.A., Accuray Incorporated. All other authors declare no conflict of interest regarding this manuscript.

DATA AVAILABILITY STATEMENT

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

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 consent was obtained from every trial participant before enrolment.

ORCID

Agne Krilaviciute https://orcid.org/0000-0001-8192-9759
Peter Albers https://orcid.org/0000-0002-1747-9615
Nikolaus Becker https://orcid.org/0000-0002-3230-4223
Rudolf Kaaks https://orcid.org/0000-0003-3751-3929

REFERENCES

1. Hugosson J, Roobol MJ, Mansson M, et al. A 16-yr follow-up of the European randomized study of screening for prostate cancer. *Eur Urol*. 2019;76:43-51.
2. Van Poppel H, Roobol MJ, Chapple CR, et al. Prostate-specific antigen testing as part of a risk-adapted early detection strategy for prostate cancer: European Association of Urology position and recommendations for 2021. *Eur Urol*. 2021;80:703-711.
3. Vickers AJ, Ulmert D, Sjoberg DD, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. *Brit Med J*. 2013;346. doi:10.1136/bmj.f2023
4. Alberts AR, Roobol MJ, Verbeek JFM, et al. Prediction of high-grade prostate cancer following multiparametric magnetic resonance imaging: improving the Rotterdam European randomized study of screening for prostate cancer risk calculators. *Eur Urol*. 2019;75:310-318.
5. Nordstrom T, Discacciati A, Bergman M, et al. Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. *Lancet Oncol*. 2021;22:1240-1249.
6. Carlsson SV, de Carvalho TM, Roobol MJ, et al. Estimating the harms and benefits of prostate cancer screening as used in common practice versus recommended good practice: a microsimulation screening analysis. *Cancer: Am Cancer Soc*. 2016;122:3386-3393.
7. Remmers S, Roobol MJ. Personalized strategies in population screening for prostate cancer. *Int J Cancer*. 2020;147:2977-2987.
8. Andriole GL, Grubb RL, Buys SS, et al. Mortality results from a randomized prostate-cancer screening trial. *New Engl J Med*. 2009;360:1310-1319.
9. Auvinen A, Rannikko A, Taari K, et al. A randomized trial of early detection of clinically significant prostate cancer (ProScreen): study design and rationale. *Eur J Epidemiol*. 2017;32:521-527.
10. Kohestani K, Mansson M, Godtman RA, et al. The GoTEBORG prostate cancer screening 2 trial: a prospective, randomised, population-based prostate cancer screening trial with prostate-specific antigen testing followed by magnetic resonance imaging of the prostate. *Scand J Urol*. 2021;55:116-124.
11. Gronberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol*. 2015;16:1667-1676.
12. Arsov C, Albers P, Herkommer K, et al. A randomized trial of risk-adapted screening for prostate cancer in young men: results of the first screening round of the PROBASE trial. *Int J Cancer*. 2022;150:1861-1869.
13. Richtlinien des Bundesausschusses der Ärzte und Krankenkassen über die Früherkennung von Krebserkrankungen (Krebsfrüherkennungs-Richtlinien) vom 28. April 1971 Deutsches Ärzteblatt 1971;25: 1914–6.
14. Arsov C, Becker N, Hadaschik BA, et al. Prospective randomized evaluation of risk-adapted prostate-specific antigen screening in young men: the PROBASE trial. *Eur Urol*. 2013;64:873-875.
15. Remzi M, Fong YK, Dobrovits M, et al. The Vienna nomogram: validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate volume. *J Urology*. 2005;174:1256-1260.
16. Leitlinienprogramm Onkologie, Leitlinienreport S3-Leitlinie Prostatakarzinom, 2021. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Prostatatkarzinom/Version_6/LL_Prostatakarzinom_Langversion_6.0.pdf
17. Starker A, Saß A-C. Participation in cancer screening programmes. Results of the German health interview and examination survey for adults(DEGS1) [Ger. Inanspruchnahme von Krebsfrüherkennungsuntersuchungen]. *Bundesgesundheitsblatt*. 2013;56:858-867.
18. Sieverding M, Matterne U, Ciccarello L, Luboldt H-J. Prostatakarzinomfrüherkennung in Deutschland [German language]. *Urologe*. 2008;47:1233-1238.
19. Patasius A, Smailyte G. All-cause mortality risk in National Prostate Cancer Cohort: an impact of population-based prostate cancer screening. *J Clin Med*. 2021;10:2459.
20. Alterbeck M, Jarbur E, Thimansson E, et al. Designing and implementing a population-based organised prostate cancer testing Programme. *Eur Urol Focus*. 2022;S2405-4569:00135-3.
21. Jahresbericht Evaluation, Deutsches Mammographie-Screening-Programm. https://www.mammography-screening.de/evaluation#screening-results-2013-2015, 2019.
22. Hornschuch M, Schwarz S, Haug U. 10-year prevalence of diagnostic and screening colonoscopy use in Germany: a claims data analysis. *Eur J Cancer Prev*. 2022. doi:10.1097/CEJ.0000000000000736. Online ahead of print.
23. Schatteman PHF, Hoekx L, Wyndaele JJ, Jeuris W, Van Marck E. Inflammation in prostate biopsies of men without prostatic malignancy or clinical prostatitis: correlation with total serum PSA and PSA density. *Eur Urol*. 2000;37:404-412.
24. Schoots IG, Barentsz JO, Bittencourt LK, et al. PI-RADS Committee position on MRI without contrast medium in biopsy-naive men with suspected prostate cancer: narrative review. *AJR Am J Roentgenol*. 2021;216:3-19.
25. van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ. A European model for an organised risk-stratified early detection Programme for prostate cancer. *Eur Urol Oncol*. 2021;4:731-739.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Krilaviciute A, Albers P, Lakes J, et al. Adherence to a risk-adapted screening strategy for prostate cancer: First results of the PROBASE trial. *Int J Cancer*. 2023;152(5):854-864. doi:10.1002/ijc.34295