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The relationship between prostate-specific antigen and prostate cancer risk: the Prostate Biopsy Collaborative Group

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Abstract

PURPOSE—The relationship between prostate specific antigen (PSA) level and prostate cancer risk remains subject to fundamental disagreements. We hypothesize that the risk of prostate cancer on biopsy for a given PSA level is affected by identifiable characteristics of the cohort under study.

EXPERIMENTAL DESIGN—We used data from 5 European and 3 US cohorts of men undergoing biopsy for prostate cancer; six were population-based studies and two were clinical cohorts. The association between PSA and prostate cancer was calculated separately for each cohort using locally-weighted scatterplot smoothing.

RESULTS—The final data set included 25,772 biopsies and 8,503 cancers. There were gross disparities between cohorts with respect to both the prostate cancer risk at a given PSA level and the shape of the risk curve. These disparities were associated with identifiable differences between cohorts: for a given PSA level, a greater number of biopsy cores increased risk of cancer (odds ratio for >6 vs. 6 core biopsy 1.35; 95% C.I. 1.18, 1.54; $p<0.0005$); recent screening led to a smaller increase in risk per unit change in PSA ($p=0.001$ for interaction term) and US cohorts had higher risk than the European cohorts (2.14; 95% C.I. 1.99, 2.30; $p<0.0005$).

CONCLUSIONS—Our results suggest that the relationship between PSA and risk of a positive prostate biopsy varies, both in terms of the probability of prostate cancer at a given PSA value and the shape of the risk curve. This poses challenges to the use of PSA-driven algorithms to determine whether biopsy is indicated.

Keywords

prostate cancer; PSA; prediction; multicenter studies; screening

introduction

Prostate specific antigen (PSA) is the only molecular marker used for screening a common cancer. Yet more than 30 years after its discovery, the relationship between PSA level and prostate cancer risk has not been fully characterized.

Indeed, there remain disagreements even on such fundamental issues as whether risk rises with PSA and whether a low PSA level can rule out prostate cancer. For example, whereas Stamey et al have claimed that PSA does not predict prostate cancer in contemporary cohorts1, the Prostate Cancer Prevention Trial (PCPT) investigators reported a very strong association between PSA and the risk of a positive biopsy[2]. Similarly, while the results of the PCPT suggest

that prostate cancer is common in men with very low PSA levels, an analysis of data from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer Screening (ERSPC) found that very few men with low baseline PSA were diagnosed with prostate cancer after 12 years of follow-up3.

Such differences have been expressed quantitatively in prediction models that calculate an individual's probability of having biopsy-detectable prostate cancer on the basis of PSA level and other risk factors, such as age and family history. These models, generally known as "risk calculators" have been shown to provide very different estimates of risk for a given PSA level[4]. There are two possible reasons for these differences. First, investigators use different statistical methods to develop their models, including adjustment for different covariates. Second, each prediction model is based on a single cohort of men undergoing biopsy and these cohorts differ in a variety of ways, such as participants' history of PSA screening, whether or not PSA was used as a sole criterion for biopsy and the number of cores taken during biopsy.

We hypothesize that the relationship between PSA and the risk of prostate cancer on biopsy depends on these identifiable characteristics of the cohort under study. To test this hypothesis, we obtained raw data from a heterogeneous set of prostate biopsy cohorts. We then analyzed these data sets using standardized statistical methods.

Material and methods

Biopsy cohorts

We utilized data sets from eight biopsy cohorts, 5 from Europe and 3 from the US. Description of the study cohorts, including biopsy algorithm and biopsy scheme, are given in Table 1. The data sets were restricted to subjects age 50 to 75 when biopsied and for ongoing studies, to data made available in 2009, and hence may differ from prior or future publications on the same cohort. Data sets were obtained under waivers from local ethical review committees.

Four of the data sets were from studies of PSA screening for prostate cancer (the Göteborg, Rotterdam and Tarn, sections of the ERSPC 5 and SABOR6) while two were from clinical cohorts (Cleveland Clinic, Durham VA). The Tyrol cohort was not expressly established as a screening trial, but involved extensive attempts to encourage men to attend free-of-charge PSA testing, with the result that approximately 80% of the target population attended screening7. Similarly, the ProtecT study8 is not a screening study, but used population-based invitations to PSA testing to accrue patients to a treatment trial.

The Göteborg and Rotterdam cohorts consisted of data from the first biopsy. The cohorts were divided depending on whether biopsy occurred after a first or later PSA test (i.e. recently screened vs. previously unscreened). The Tarn cohort consisted of men biopsied during the first round of ERSPC. Although some participants had prior PSA screening, this was not well characterized and so we did not split into two separate cohorts with and without previous screening. For the SABOR cohort, if a participant had multiple biopsies, then only the last biopsy was included.

In total, we obtained raw data from 8 centers in 6 countries, comprising 25,772 biopsies in 23,070 men with 8,503 cancer cases. All patients in the data set underwent biopsy, so there is no issue of verification bias. As a comparator for our raw data cohorts, the risk curve for the PCPT was obtained using the formula for the PCPT risk calculator.

PSA measurements

Measurements of PSA were performed in accordance with procedures in place at the respective institutions. The type of assay used at each institution during each year was documented. PSA

measures were then recalibrated to the World Health Organization standard (PSA-WHO 96/670) using an appropriate correction factor.

Statistical methods

The predicted probability of biopsy-detected prostate cancer for a given PSA was calculated using locally weighted scatterplot ("lowess") smoothing[9]. All PSA values < 100 ng/mL were used in the calculation of the risk curve, even though risk curves only for PSA values ≤ 10 ng/mL are displayed.

Logistic regression was used to test for a difference in the biopsy detection rate based on biopsy scheme (six cores versus more than six), previous PSA screening (ever vs. never), and geographic location (US versus European cohorts). The regression analyses excluded men with prior biopsy, and therefore included only 1 biopsy per patient. The analysis of biopsy scheme was restricted to European cohorts because very few patients in the US received limited biopsy. Similarly, the analysis of previous PSA screening was restricted to European cohorts because all US cohorts included patients with previous PSA screening; the Tyrol cohort was also excluded from this analysis, since it was unknown who had previous screening. Covariates for these analyses were PSA, DRE and family history; the analysis of prior screening also included biopsy scheme as a covariate and vice versa. Patients with PSA values ≥ 100 ng/mL (n=104, 0.4%) were excluded from the logistic regression analyses. All analyses were conducted using Stata 10.1 (Stata Corp., College Station, TX).

Results

Clinical characteristics and biopsy results of each cohort are given in Table 2. The cohorts are highly comparable in terms of age and prostate volume. Cancer prevalence varies from 26% (ERSPC cohorts) to 47% (Durham VA) although 7 of the 10 cohorts had prevalence less than 35%. PSA levels vary systematically with cancer grade: cohorts with a lower median PSA, such as ERSPC and SABOR, had a lower proportion of high grade cancers than cohorts with high median PSA, such as Durham VA and Cleveland Clinic. There are large, unexplained differences in DRE findings between cohorts. For example, the rate of positive DRE was three times higher in the SABOR cohort compared to Tyrol (29% versus 10%), despite a lower incidence of high-grade tumors (8% vs 21%). This may reflect the subjective nature of DRE.

Our principal results are given in Figure 1, which shows the probability of a positive prostate biopsy by PSA level for each cohort. Panel A shows gross disparities between cohorts with respect to both the prostate cancer risk at a given PSA level and the shape of the curve. As race and DRE affect risk and are commonly included in prostate cancer risk calculators, panel B of figure 1 shows results when men with positive DRE and those of African origin are excluded. Large differences between cohorts remain. For example, at the commonly used PSA threshold of 4 ng/mL, risk varies from 15% (Göteborg round 1) to 40% (SABOR). Panel C repeats this analysis for high grade cancer, that is, patients with Gleason 6 or below were categorized as disease-free. There are similar large differences in risk by PSA level, with similar patterns between cohorts as for the analysis of all cancers.

One obvious difference between cohorts is that some include men with very low PSAs whereas, such as ERSPC, only include men with PSA of 3 ng/mL and above. However, there were no important differences in the risk curves when analysis was conducted restricting the sample to men with PSA ≥ 3 ng/mL (data not shown).

We then examined whether identifiable aspects of the cohorts might explain the different relationships between PSA level and prostate cancer risk. Figure 2 compares ProtecT with the first round of the two ERSPC cohorts. All three cohorts were European, population-based trials

of men without a history of PSA screening; ProtecT, however, used 10-core biopsy in contrast to the ERSPC six-core scheme. It is apparent that use of more biopsy cores finds more cancers at a given PSA level. In an analysis including only European cohorts, the number of cores was significantly associated with cancer risk after adjustment for PSA level and prior screening (odds ratio for more than six versus six-core biopsy of 1.35; 95% C.I. 1.18, 1.54; p<0.0005).

In figure 3, we compare round 1 of ERSPC, which includes only unscreened men, with subsequent rounds of ERSPC, which include only men with prior PSA screening. Prior PSA screening clearly leads to a flattening of the relationship between PSA level and the likelihood of a positive biopsy. As PSA doubles from 4 to 8 ng/mL, risk increases by about 50% in previously unscreened ERSPC participants, with no large increases in risk for ERSPC participants with prior screening. We tested for an interaction between PSA level and prior screening, which would indicate a different relationship between PSA and cancer in participants with and without prior screening. The interaction term was statistically significant (p=0.001) and negative (i.e. odds ratio less than 1), confirming the hypothesis that PSA has a smaller effect on the risk of prostate cancer for participants with prior screening. It can also be seen in figure 3 that the curve for ERSPC Göteborg participants with prior screening is flatter than the respective curve for ERSPC Rotterdam participants. This could be due to the shorter screening interval in Göteborg (2 years) compared to Rotterdam (4 years).

One unexplained characteristic of our findings is that the US cohorts generally have higher risk than the European cohorts for a given PSA level. For example, risk at a PSA of 4 ng/mL is approximately 20% for ERSPC Rotterdam but approximately 40% for Cleveland Clinic. The effect of geographical location was statistically significant when controlling for PSA level (odds ratio for US versus European cohorts of 2.14; 95% C.I. 1.99, 2.30; p<0.0005).

Discussion

We have combined data from 8 prostate biopsy cohorts to create a single data set of 25,772 biopsies with 8,503 cancers. Our results suggest that the relationship between PSA and prostate cancer risk varies, both in terms of the probability of a detectable prostate cancer at a given PSA and the shape of the risk curve. These differences are not trivial, with a 2.5 fold difference in risk between cohorts at the commonly used PSA threshold of 4 ng/mL.

We have been able to identify characteristics of cohorts that affect the relationship between PSA level and prostate cancer risk: use of a greater number of biopsy cores increases risk; the relationship between PSA and risk is flatter if men have had prior PSA tests. Both of these findings are well in keeping with prior literature and make clear clinical sense. With respect to biopsy scheme, prostate tumors are often small and may be missed if only a limited number of biopsy samples are taken. As regards previous screening, most clinicians would agree that in an unscreened man, a PSA of 8 ng/mL constitutes higher risk than a PSA of 6 ng/mL. However, if the man had been screened two years previously, and had a PSA below current biopsy thresholds, many would consider the difference between 8 and 6 ng/mL to be clinically irrelevant “noise”, most likely associated with benign prostate disease.

We have also seen that US cohorts generally have higher risk than European cohorts. Given that a genetic difference seems unlikely, on the grounds that large differences persisted after exclusion of patients with African origins (OR 2.02;95% C.I. 1.86, 2.19; p<0.0005), we see several possible explanations for this observation. First, US biopsies in our data set almost exclusively involved 8 or more cores, whereas many of the European biopsies were 6 core. That said, the odds ratio for biopsy scheme (OR = 1.35) is much lower than that for geographic region when European patients with more than 6 cores were excluded (OR = 2.11).Second, there may be differences in biopsy technique[10] or pathologic analysis, for example, if US

urologists were less likely to miss cancer. There is no direct evidence of such an effect. Third, the European cohorts tend to be representative of the population as a whole, whereas the US cohorts include selected groups. The fourth explanation, and to us the most plausible one, is that in the US cohorts, prostate biopsy was more usually at the discretion of the attending urologist. Such a decision might be influenced by considerations such as a work up for benign disease or longitudinal monitoring over time to see whether PSA falls11. Our data set includes only the final PSA at the time of biopsy, not the initial PSA prompting consideration of biopsy. Take the case of two patients with an initial PSA of 4 ng/mL: in the US it may be that only one would proceed to biopsy, because elevated PSA in the other patient is ascribed to a benign prostatic condition discovered during clinical workup; in the ERSPC, both patients would proceed to biopsy as per the study protocol. This would lead to an overall lower proportion of patients found to have cancer on biopsy in the European cohorts.

We are aware that "prostate cancer risk" can refer not only to the probability that a man currently has prostate cancer – the sense in which it is used in this paper - but also to the likelihood that he will develop it subsequently. There is excellent evidence that PSA has a clear and consistent association with subsequent risk of clinically-detected cancer, especially advanced cancers likely to prove life-threatening[12–14]. These findings are unaffected by the results presented here.

However, our findings have do several implications prostate cancer detection. First, our work casts doubt on the simplistic use of PSA cut-offs to determine biopsy. A common approach has been to call men with a PSA < 4 ng/mL "negative", where as a PSA of 4 ng/mL would indicate biopsy. Here we show that this threshold is associated with risks of prostate cancer ranging from 15 to 40%. It is unsound to give the same recommendation to patients across such a wide spectrum of risk. The alternative to the use of cut-points is to accept that risk varies continuously, such that a PSA of 3.9 ng/mL constitutes a different risk to 0.5 ng/mL[15]. Combined with the insight that factors other than PSA can affect risk - such as age, race, family history and prior negative biopsy – this has led investigators to develop multivariable prediction models that provide a patient with a percentage probability of cancer. These risk calculators are easily accessible via web applications and appear to have become widely used in clinical practice.

Yet our work poses comparable challenges to risk calculators as to PSA thresholds. The underlying statistical models were typically created by analysis of a single cohort, for example, the control arm of the PCPT for the PCPT risk calculator[15] and the Rotterdam section of the ERSPC for the ERSPC risk calculator[16,17]. Although these models include several predictors, they are typically strongly dependent on PSA: the discriminative accuracy of the PCPT calculator, for example, is 0.702 compared to 0.678 for PSA alone[15].

Given that the relationship between PSA level and risk of cancer at biopsy is highly dependent on identifiable cohort characteristics, we do not believe it sound for investigators to analyze a single cohort and develop a risk prediction model unless they either restrict to specific types of patients, such as men without prior screening, or separately evaluate their tool in a wide range of settings.

The obvious corollary is that care should be taken with respect to clinical use of prediction models. It is far from clear that the PCPT risk calculator, developed on US men subject to intense screening, is applicable to unscreened European men. Indeed, the PCPT risk calculator has been applied retrospectively to the ERSPC and been found to be miscalibrated, giving a higher risk than was found[3,17]. By the same token, it is questionable whether the risk calculator based on European men[16] can be applied to a US clinical population. It may be that risk calculators based on a panel of markers may overcome the limitations of PSA alone[18].

Regardless, the value of any model would need to be demonstrated by validating the risk calculator on a variety of different types of cohort, particular those in clinical settings.

Investigators should be cautious about drawing general conclusions about PSA and cancer risk on the basis of a single cohort. For example, Schwartz and colleagues analyzed data from biopsies "performed at our institution", a hospital in the US, and concluded that, in recent years, there was essentially no correlation between PSA and biopsy outcome in DRE negative men with a PSA above 2 ng/mL[19]. Such a conclusion is well in keeping with our findings for cohorts with recent screening, but not our findings for cohorts consisting of men without a recent PSA test.

This observation has profound consequences for research methodology. Prostate cancer research has hitherto been based almost exclusively on studies of individual cohorts. The result has been a plethora of conflicting findings as to the most basic questions in the field, such as whether risk rises as PSA increases above biopsy thresholds or whether there is a substantive risk of cancer at low PSAs. We have found that sharing data as a collaboration between multiple centers provides robust insights into PSA, and helps explain the discrepancies between previously published findings. We would encourage other researchers to go beyond the culture of competing publications and work together on shared data sets.

In conclusion, by analyzing data from multiple cohorts, we have shown that the relationship between PSA and the risk of biopsy-detectable prostate cancer systematically depending on the type of cohort studied. This poses challenges to the use of PSA to determine biopsy, whether in the form of a PSA threshold, such as 4 ng/mL, or in statistical risk calculators where risk is driven primarily by PSA level.

Statement of Translational Relevance

Prostate cancer research has hitherto been based almost exclusively on studies of individual cohorts. The result has been a plethora of conflicting findings as to the most basic questions in the field, such as whether risk rises as prostate-specific antigen (PSA) increases above biopsy thresholds or whether there is a substantive risk of cancer at low PSAs. We analyzed pre-biopsy levels of (PSA) on 25,772 prostate biopsies and 8,503 cancers from 8 different cohorts in 6 different countries. There were gross disparities between cohorts with respect to both the prostate cancer risk at a given PSA level and the shape of the risk curve. This poses challenges to the use of PSA-driven algorithms to determine whether biopsy is indicated: neither PSA cut-points for biopsy, such as 4 ng / ml, nor the use of "risk calculators" based on PSA, appear likely to give results that are generalizable across different cohorts.

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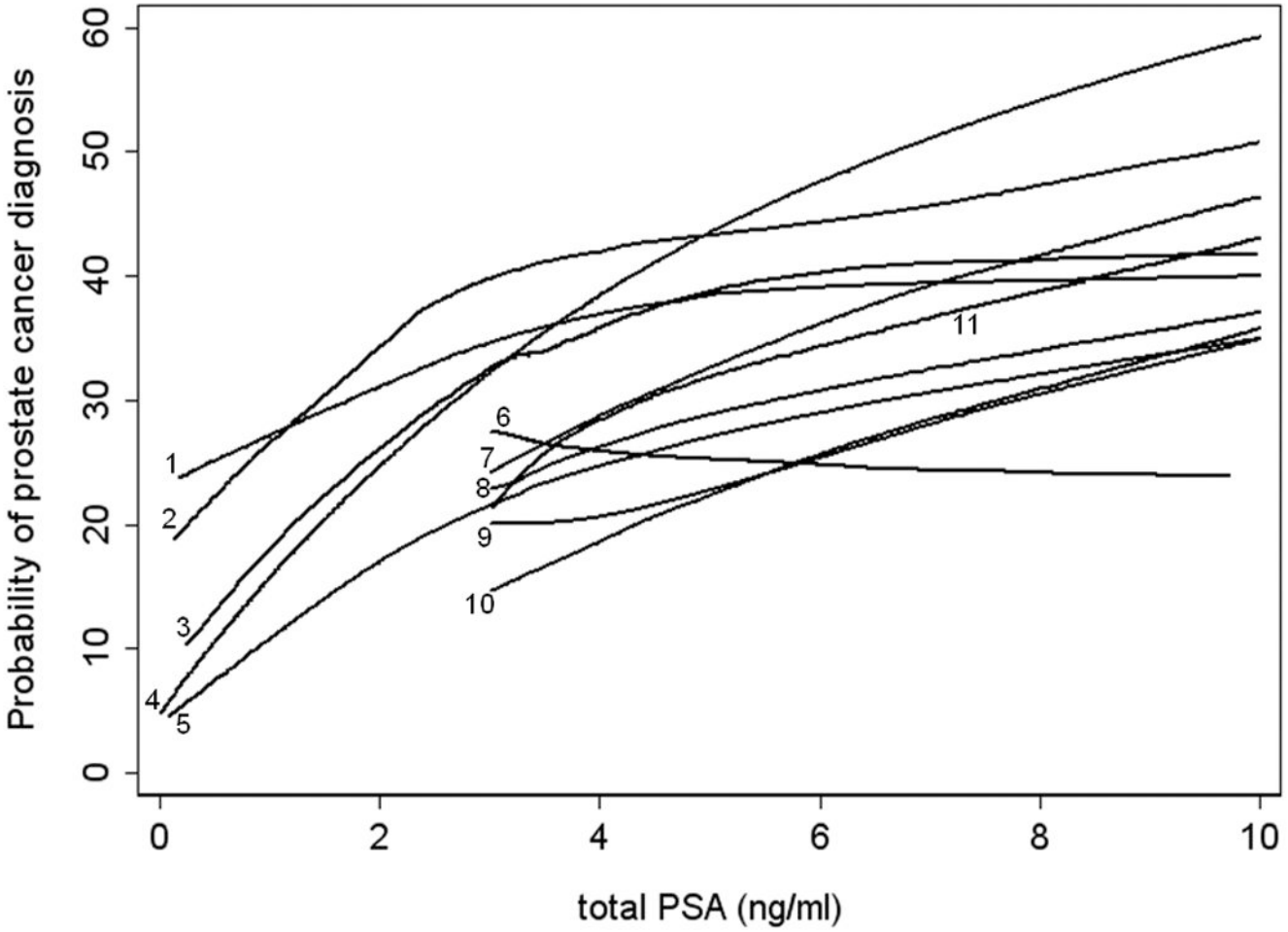

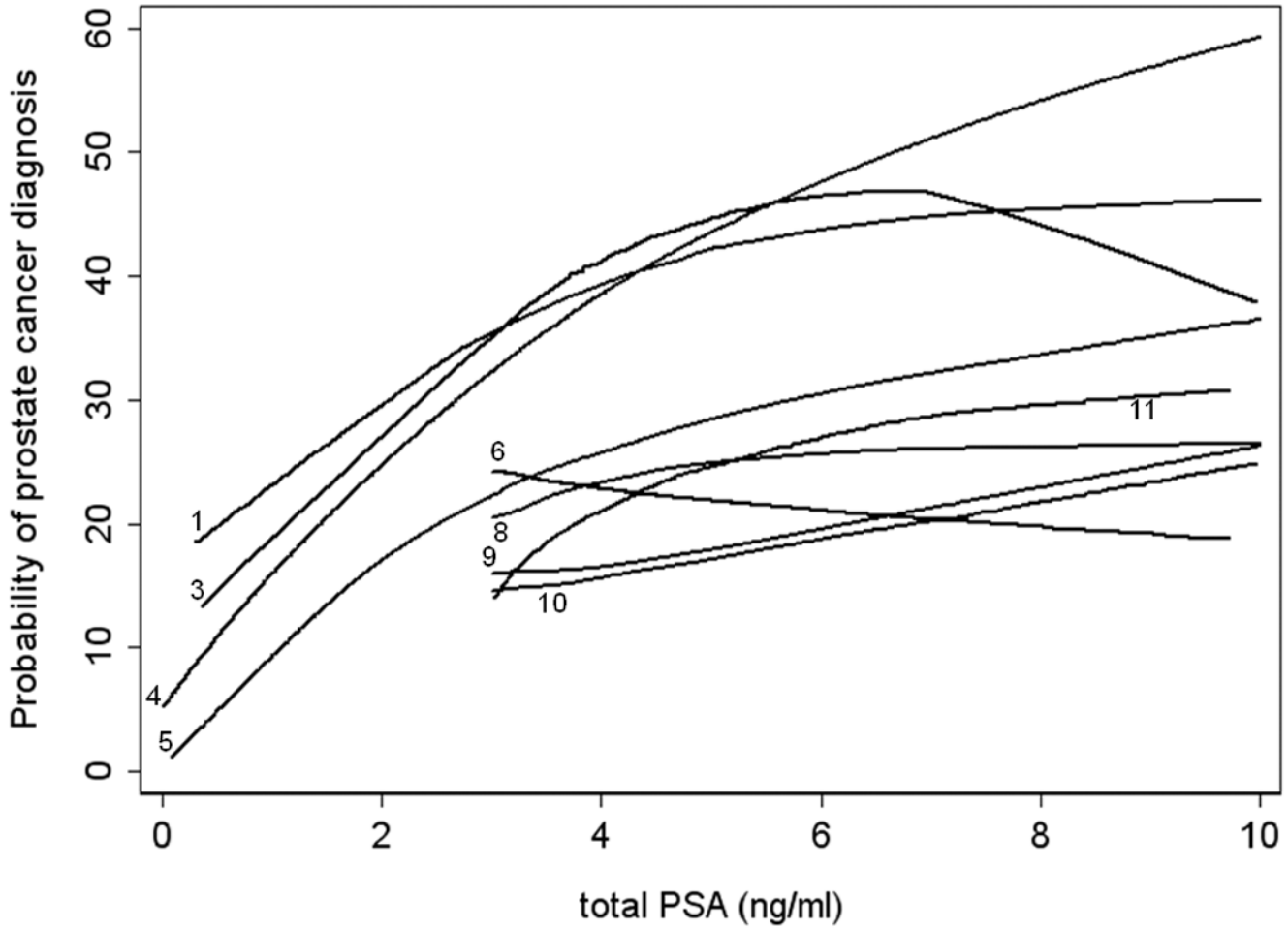

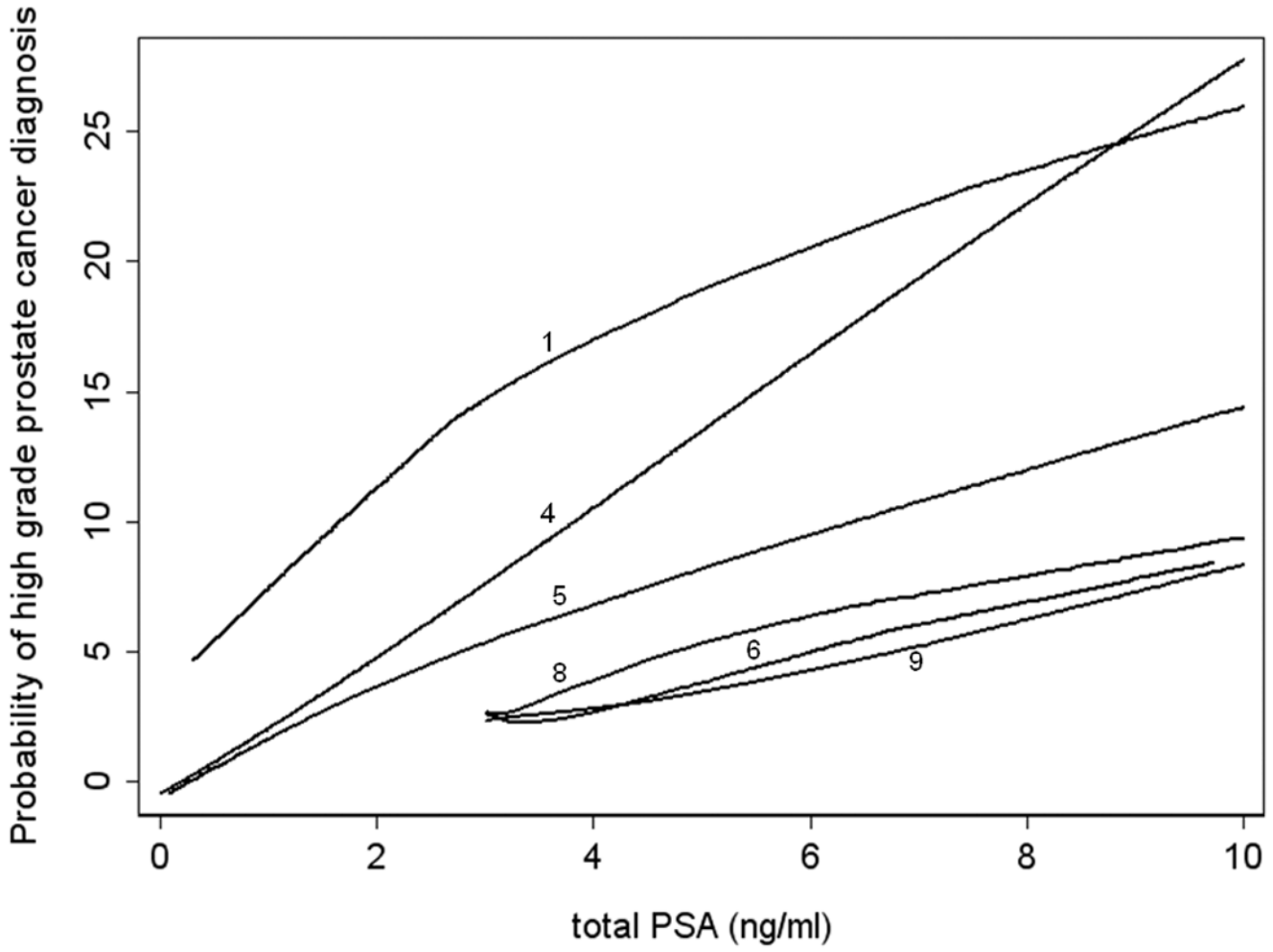

Figure 1.
Predicted probability of prostate cancer with increasing PSA, separately by cohort.
Legend:

1. Cleveland Clinic
2. Durham VA
3. SABOR
4. PCPT
5. Tyrol
6. Göteborg rounds 2 to 6
7. ProtecT
8. Rotterdam rounds 2 to 3
9. Rotterdam round 1
10. Göteborg round 1
11. Tarn

Panel A: Prediction of prostate cancer

Panel B: Prediction of prostate cancer for men with negative DRE, non-African origin, and no prior biopsy. Note that ProtecT and Durham are excluded because DRE result was not available for the majority of men biopsied in those cohorts. The SABOR cohort includes only a very small number of men with PSA > 7 (n=16), and sampling variation likely explains the apparent reduction in risk above PSA of 7.

Panel C: Prediction of high grade prostate cancer for men with negative DRE, non-African origin, and no prior biopsy. Note that ProtecT and Durham are excluded because DRE result was not available for the majority of men biopsied in those cohorts; Göteborg round 1, Tarn and SABOR are excluded due to low numbers of high grade cancers. The risk from the PCPT risk calculator was determined for a man age 65 at biopsy, which was close to the mean age of the entire cohort.

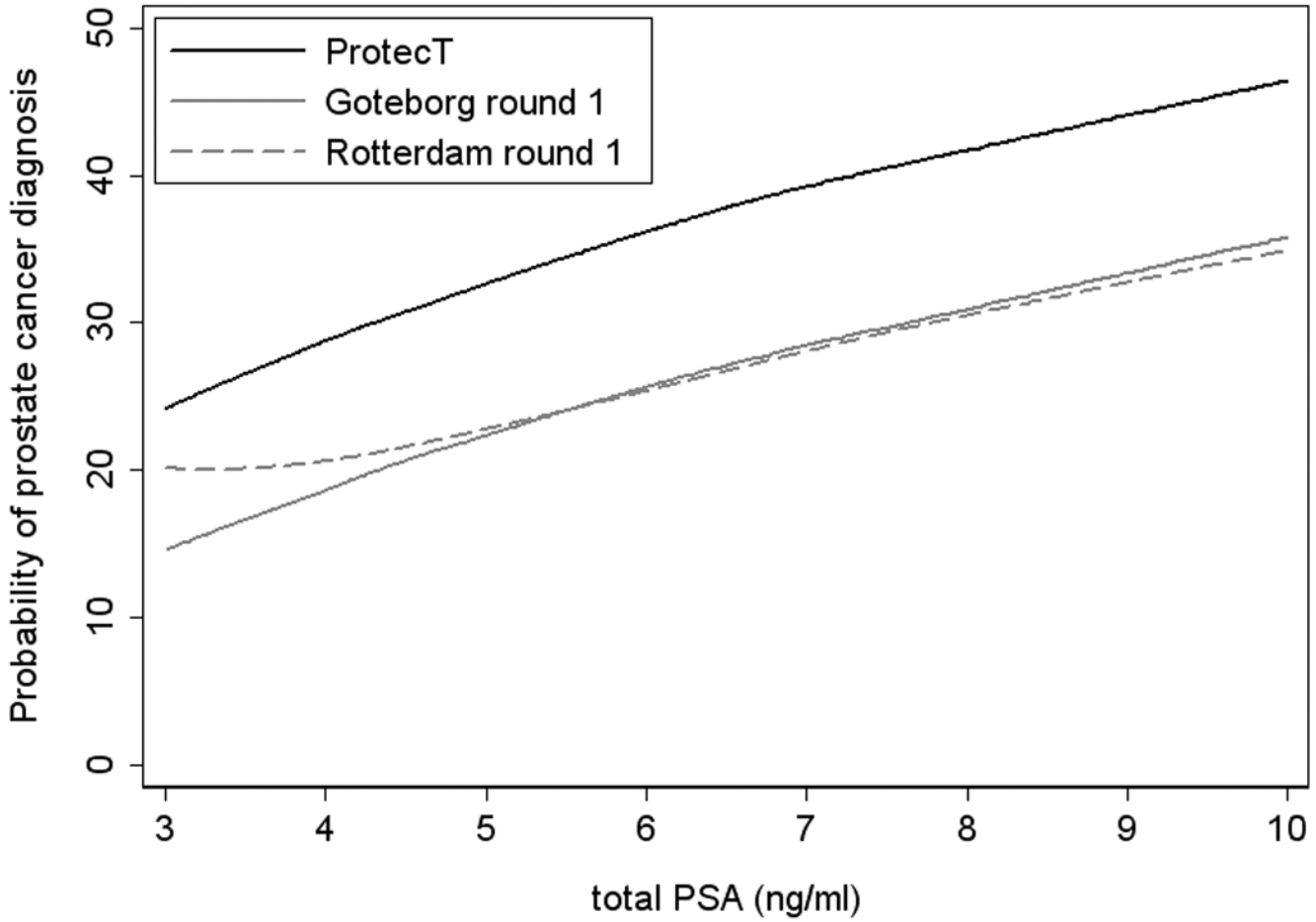

Figure 2.
Effects of biopsy scheme. ProtecT (10 cores) vs ERSPC Göteborg and Rotterdam (6 cores)

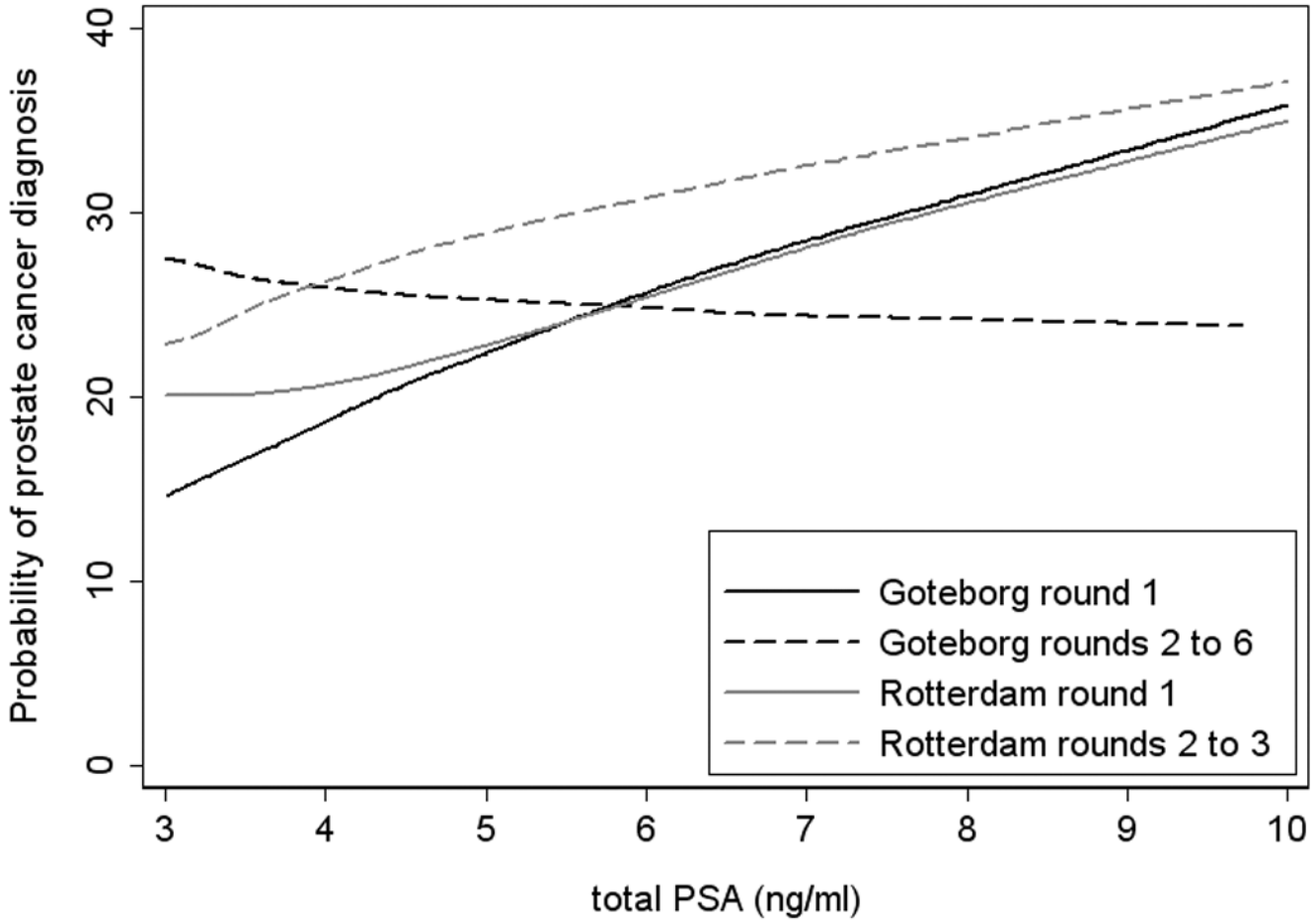

Figure 3.
Effects of previous PSA screening. Göteborg and Rotterdam round 1 (both with no previous screening) vs Göteborg rounds 2–6 and Rotterdam rounds 2–3 (all had previous screening)

Table 1

Description of study cohorts

Name of cohort	Location	Type of cohort	Biopsy algorithm		Biopsy scheme	Prior screening
			Indication for biopsy	Decision for biopsy a clinical decision?		
ERSPC Göteborg Round 1	Sweden	Screening	PSA ≥ 3 ng/mL	No	6-core †	No
ERSPC Göteborg Rounds 2–6	Sweden	Screening	PSA ≥ 3 ng/mL	No	6-core†	Yes
ERSPC Rotterdam Round 1	The Netherlands	Screening	PSA ≥ 3 ng/mL or ≥ 4 ng/mL, depending on year	No	6-core†	No
ERSPC Rotterdam Rounds 2–3	The Netherlands	Screening	PSA ≥ 3 ng/mL or ≥ 4 ng/mL*	No	6-core†	Yes
ERSPC Tarn Round 1	France	Screening	PSA ≥ 3 ng/mL	Yes	Primarily 10 to 12-core	Mixture
SABOR	San Antonio, TX	Screening	PSA ≥ 2.5 ng/mL, abnormal DRE, or family history	Yes	10–12-core	Mixture
Cleveland Clinic	Cleveland, OH	Clinical	Elevated PSA, abnormal DRE, rapid rise in PSA	Yes	Primarily >=8-core	Mixture
ProtecT	United Kingdom	Screening+	PSA ≥ 3 ng/mL	No	10-core	No
Tyrol	Austria	Screening+	PSA ≥ 1.25 ng/mL, percent free PSA, abnormal DRE	Most men with elevated PSA were biopsied	6, 10, or 10–15-core*	Mixture
Durham VA	Durham, NC	Clinical	Elevated PSA, abnormal DRE	Yes	6, 10 or 12-core *	Mixture
PCPT	US	Screening	PSA ≥ 4ng/mL or abnormal DRE for “for cause” biopsies; end of study biopsy offered to all men	In the case of “for cause” biopsies	Primarily 6 core	Yes

ERSPC: European Randomized study of Screening for Prostate Cancer; ProtecT: Prostate Testing for Cancer and Treatment; SABOR: San Antonio Center of Biomarkers of Risk for Prostate Cancer; PCPT: Prostate Cancer Prevention Trial. Data were not received from the PCPT for this study, the relationship between risk and PSA for the PCPT was obtained using the PCPT risk calculator.

+Not formally established as a screening cohort, but involved population-based PSA testing

†In the case of an abnormality on TRUS, a seventh core was directed to the lesion.

*Varied by year of biopsy

Table 2

Clinical characteristics of each cohort: ERSPC studies

	Göteborg Round 1	Göteborg Subsequent rounds	Rotterdam Round 1	Rotterdam Subsequent rounds	Tarn
Number of patients	740	1241	2895	1494	298
Number of biopsies	740	1241	2895	1494	298
Clinical characteristics					
Age (years)	61 (58, 64)	63 (61, 67)	66 (62, 70)	67 (63, 71)	64 (60, 67)
PSA (ng/mL)	4.65 (3.68, 6.72)	3.56 (3.17, 4.26)	5.03 (3.93, 7.31)	3.45 (2.94, 4.33)	4.45 (3.53, 5.98)
Prostate volume[2] (g)	39 (30, 51)	37 (30, 47)	46 (35, 60)	44 (35, 54)	NA
DRE result					
Normal	614 (83%)	1117 (90%)	2137 (74%)	1182 (79%)	179 (60%)
Abnormal	126 (17%)	124 (10%)	758 (26%)	312 (21%)	92 (31%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	27 (9%)
Family history[3]					
No	0 (0%)	0 (0%)	1708 (59%)	875 (59%)	0 (0%)
Yes	0 (0%)	0 (0%)	328 (11%)	160 (11%)	0 (0%)
Unknown	740 (100%)	1241 (100%)	859 (30%)	459 (31%)	298 (100%)
African origin[4]					
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	740 (100%)	1241 (100%)	2895 (100%)	1494 (100%)	298 (100%)
Prior biopsy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Biopsy results					
Cancer	192 (26%)	322 (26%)	800 (28%)	388 (26%)	96 (32%)
Biopsy Gleason grade					
≤ 6	152 (79%)	269 (84%)	508 (63%)	297 (77%)	42 (44%)
7	33 (17%)	45 (14%)	234 (29%)	78 (20%)	37 (39%)
≥ 8	7 (4%)	8 (2%)	58 (7%)	13 (3%)	17 (18%)

	Göteborg Round 1	Göteborg Subsequent rounds	Rotterdam Round 1	Rotterdam Subsequent rounds	Tarn
Unknown	0 (0%)	0 (0%)	6 (1%)	0 (0%)	3 (3%)

Clinical characteristics of each cohort: Other cohorts.

	SABOR	Cleveland Clinic[1]	ProtecT	Tyrol[1]	Durham VA
Number of patients	392	2631	7324	4199	1856
Number of biopsies	392	3307	7324	5656	2425
Clinical characteristics					
Age (years)	63 (58, 68)	64 (58, 69)	63 (59, 66)	63 (57, 68)	64 (59, 69)
PSA (ng/mL)	3.42 (1.44, 5.40)	5.75 (4.31, 8.50)	4.35 (3.50, 6.20)	4.21 (2.80, 6.79)	5.17 (3.71, 8.27)
Prostate volume (g)[2]	NA	42 (30, 58)	NA	35 (27, 46)	NA
DRE result					
Normal	280 (71%)	3103 (94%)	0 (0%)	5088 (90%)	892 (37%)
Abnormal	112 (29%)	204 (6%)	0 (0%)	568 (10%)	266 (11%)
Unknown	0 (0%)	0 (0%)	7324 (100%)	0 (0%)	1267 (52%)
Family history[3]					
No	280 (71%)	1708 (52%)	5736 (78%)	0 (0%)	0 (0%)
Yes	112 (29%)	373 (11%)	454 (6%)	0 (0%)	0 (0%)
Unknown	0 (0%)	1226 (37%)	1134 (15%)	5656 (100%)	2425 (100%)
African origin[4]					
No	349 (89%)	2836 (86%)	6933 (95%)	0 (0%)	1221 (50%)
Yes	43 (11%)	425 (13%)	34 (0%)	0 (0%)	1082 (45%)
Unknown	0 (0%)	46 (1%)	357 (5%)	5656 (100%)	122 (5%)
Prior biopsy	96 (24%)	1093 (33%)	0 (0%)	1559 (28%)	574 (24%)
Biopsy results					
Cancer	133 (34%)	1292 (39%)	2570 (35%)	1562 (28%)	1148 (47%)
Biopsy Gleason grade					
≤ 6	95 (71%)	669 (52%)	1703 (66%)	911 (58%)	606 (53%)
7	28 (21%)	478 (37%)	729 (28%)	319 (20%)	387 (34%)

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Clinical characteristics of each cohort: Other cohorts.

	SABOR	Cleveland Clinic[1]	ProtecT	Tyrol[1]	Durham VA
≥ 8	10 (8%)	145 (11%)	138 (5%)	332 (21%)	155 (14%)
Unknown	3 (2%)	0 (0%)	0 (0%)	195 (12%)	14 (1%)

Data are given as median (quartiles) or frequency (proportion); NA: not available; DRE: digital rectal exam

[1] Subjects may be represented more than once if they had more than 1 negative biopsy

[2] Prostate volume was available for 733 Göteborg round 1; 967 Göteborg subsequent round; 2882 Rotterdam round 1; 1487 Rotterdam subsequent round; 2317 Cleveland Clinic; and 5178 Tyrol biopsies.

[3] Family history of prostate cancer; when unknown, subjects were assumed to have no family history of prostate cancer

[4] When unknown, subjects were assumed to be of non-African origin