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Prostate Cancer Risk Assessment in Men with an Initial PSA below 3 ng/mL: Results from the Göteborg Randomized Population-based Prostate Cancer Screening Trial

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Abstract

Objective: To evaluate the long-term outcome of men with an initial prostate-specific antigen (PSA) level below 3 ng/mL and whether the free-to-total (F/T PSA) ratio is a useful prognostic marker in this range.

Materials and methods: This study is based on 5,174 men aged 50–66 years, who in 1995–96 participated in the first round of the Göteborg randomized screening trial (initial T-PSA level <3ng/mL). These men were subsequently invited biennially for PSA and F/T PSA screening until they reached the upper age limit (on average 69 years). Biopsy was recommended if PSA ≥ 3 ng/mL.

Results: After a median follow-up of 18.9 years, 754 men (14.6%) were diagnosed with PC. The overall cumulative PC incidence was 17.2%. It increased from 7.9% among men with T-PSA of 0.99 ng/mL to 26.0% in men with T-PSA levels of 1–1.99 ng/mL and 40.3% in men between 2–2.99 ng/mL ($p < 0.001$). The initial PSA was also related to the incidence of Gleason ≥ 7 PC (3.7% vs 9.7% vs 10.9%) and PC death (0.3% vs 1.1% vs 1.5%). Adding F/T PSA did not improve PC prediction in terms of Harrell concordance index (base model 0.76 vs 0.76) nor improvement of the likelihood of the model ($p = 0.371$).

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Conflicts of interest

Hans Lilja holds patents for free PSA, hK2, and intact PSA assays, and is named on a patent application for a statistical method to detect prostate cancer. The marker assay patents and the patent application for the statistical model has been licensed and commercialized as the 4Kscore™ by OPKO Diagnostics. Dr. Lilja receives royalties from sales of this test and owns stock in OPKO.

Conclusions: Some men with initial PSA <3 ng/mL will be diagnosed too late despite participating in an organized screening program, indicating that prompt diagnosis is justified in these men. PC incidence and risk of PC death was associated with PSA but F/T PSA had no predictive value.

Introduction

The purpose of screening for any malignant disease is to lower the disease-specific mortality by finding the cancer at an earlier stage than in standard clinical practice, when treatment is more likely to be curative or at least life prolonging. Measurement of serum prostate-specific antigen (PSA) is an established method for early detection of prostate cancer (PC) (1). Several studies suggest that PSA values below the standard cut-off for biopsy (3 ng/mL) predict the long-term risk of PC, metastatic PC and death from PC (2–4). However, PSA cut-off values of 3 to 10 ng/mL have a low specificity, resulting in a high false-positive rate, many unnecessary biopsies in men with benign conditions, and overdiagnosis of indolent PC (5, 6). These limitations of using the serum PSA as the only test to select men for a prostate biopsy are one of the main reasons for that population-based screening for PC is not recommended (7). There is thus an urgent need for better diagnostic tests to identify men with asymptomatic, curable PC who are at risk of later developing metastatic PC.

The risk that a PC detected in a screening program is incurable at the time of diagnosis is insufficiently studied. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), the mortality reduction in the men who participated was not more than 27% (8), indicating that also low sensitivity and underdiagnosis are problems in screening based on PSA and systematic transrectal biopsies. There could be several explanations to this rather moderate mortality reduction; inadequate start or/and stop age (9, 10), low compliance to the screening program, incorrect screening interval or a too high PSA cut-off to trigger biopsy. Recent research has also focused on improving PC detection and risk-stratification in men with T-PSA of < 3–4 ng/mL, as many significant cancers have been detected in this range (11–13).

To improve specificity several complementary analyses have been introduced lately. The Stockholm 3 (STHLM3) test, PHI (Prostate Health Index) and the panel of four kallikrein markers (4k-panel) may better select men for prostate biopsy than PSA alone (14). All these 3 tests include total PSA combined with other serum markers. One disadvantage with these tests in the setting of population based screening is their relatively high cost.

Several studies have described that the ratio between the free (F) and total (T) serum PSA, (F/T PSA) better discriminate between benign conditions and PC. The F/T PSA test is widely available and adds marginal costs.

The present study was based on the randomized, population-based Göteborg PC screening trial (15). One aim was to assess the outcome of men with a baseline PSA below 3 ng/mL i.e. the proportion of these men that developed PC, high grade PC or died from PC. A second aim was to investigate whether T-PSA (< 3 ng/mL) combined with the F/T ratio can

identify men who die from PC despite participating in an organized screening program and thus might have benefit from an earlier PC diagnosis.

Materials and methods

The study cohort has been extensively described earlier (15) (Figure 1). The men allocated to the screening group were invited for T-PSA and concurrent F/T-PSA testing (DELFLIA Prostatus total/free PSA-assay; Perkin-Elmer, Turku, Finland). The first screening round was completed between January 1995 and December 1996. Of 9,950 men invited to the first round, 5,855 participated. Out of these, 661 men (11%) had a T-PSA above the cut-off for biopsy (≥ 3 ng/mL) and 5,194 (89%) had a T-PSA below 3 ng/mL. Of the latter men, 20 were excluded: 1 with F/T PSA $< 1\%$, 3 with missing value, 8 with F/T PSA $> 100\%$, and 8 with T-PSA < 0.1 ng/mL. The remaining 5,174 men constitute the study group. All men were invited for biennial screening until they reached the upper age-limit, median 69 (range 67–71) years. The last date of follow-up was 31st December 2014. The men who were oldest when entering the screening trial were invited 3 times, while the youngest were invited 10 times. Men who at subsequent screening rounds had a PSA ≥ 3 ng/mL were invited to a further urological examination, including prostate biopsies (sextant biopsies up to year 2009 or a 10-core biopsy from 2009). The nominal PSA threshold to invite men to further assessment was 3 ng/mL. Because of calibration to the WHO standard, the actual PSA threshold was 3.4 ng/mL between 1995 and 1998, 2.9 ng/mL between 2000 and 2005 and 2.5 ng/mL from 2006 (13). Men with benign biopsies were invited for a new PSA test after 2 years, and if their PSA was still ≥ 3 ng/mL they were recommended a repeat biopsy with the same template. The complete incidence of PC was ascertained by linkage with the Swedish Cancer Register, which has a 98% coverage (16).

For every man with PC, all available medical documentation was retrieved to establish tumour stage, Gleason score, additional treatment and disease course. An independent committee determined the cause of death for men diagnosed with PC, based on all the available clinical documentation.

Men with a T-PSA < 3 ng/mL in the first screening round were stratified into three groups; T-PSA < 0.99 ng/mL, T-PSA 1.0–1.99 ng/mL and T-PSA 2.0–2.99 ng/mL. Their cumulative incidence (CI) of PC was calculated using the Kaplan-Meier method. Differences in CI (PC, Gleason score ≥ 7 PC and death from PC) between men in the 3 PSA strata were tested by log rank test, with $p < 0.05$ considered significant. Harrell's concordance index (c-index) (17) and likelihood ratio tests were used to evaluate whether F/T PSA could add predictive value to T-PSA alone. Models including T-PSA and age were compared with models including F/T PSA, age, F/T PSA and the interaction between T-PSA and F/T PSA. The follow-up (FU) time was calculated from date of first PSA-test (first screening round) to the date of PC diagnosis, death, emigration or 31st December 2014, whichever came first. Statistical analyses were performed using SPSS® 23.0 statistical software (IBM software, IBM Corporation, 1 New Orchard Road, Armonk, New York 10504-1722, United States) and R Statistical Software (version 3.3.1; R Foundation for Statistical Computing).

Results

The median value of T-PSA was 0.89 ng/mL (interquartile range [IQR], 0.57–1.39 ng/mL) and median value of F/T PSA was 28.7% (IQR; 21.7–37.3%) at the initial screening round. During a median FU of 18.9 years (IQR; 18.1–19.3 years), 754 PC were detected resulting in a cumulative incidence of 17.2%. The median age at initial screening round was 57.2 years (IQR; 53.8–61.4 years) and at the time of the PC diagnosis 66.8 years (63.7–69.1 years). 138/754 men (18.3%) were diagnosed after 70 years of age. Altogether 224 (30%) of cancers had a Gleason score ≥ 7 at diagnosis. Twenty-eight men died from PC (Table 1). Of the total study population 74% were complete attenders and participated in all invitations.

The cumulative incidence of PC in relation to the initial T-PSA is presented in Figure 2A-B. The 20-year cumulative PC incidence was higher in men with a higher initial PSA value ($p<0.001$): it was 7.9% in men with T-PSA <0.99 ng/mL, 26.0% in men with T-PSA 1–1.99 ng/mL, and 40.3 % in men with T-PSA 2–2.99 ng/mL. Figure 3 shows the distribution of F/T PSA versus T-PSA in all men, in men with later diagnosis of PC and in men who died from PC. Of those dying from PC, 17 had a F/T PSA below and 11 a F/T PSA above the median T-PSA (calculated per PSA group). Adding F/T PSA did not improve PC prediction neither as assessed by Harrell concordance index (base model 0.76 versus 0.76), nor by the likelihood of the model ($p=0.371$). For men with Gleason score ≥ 7 PC, the corresponding figures were 0.68 versus 0.67 and $p=0.079$.

Discussion

The present study confirms previous reports of that the PSA level within “the normal range” (<3 ng/mL) is strongly predictive of the future risk of being diagnosed with PC. Both the time from the first PSA test to a PC diagnosis, and the cumulative incidence of PC co-varied with the initial T-PSA level. Men with an initial PSA between 2 and 2.99 ng/mL had a cumulative PC incidence as high as 40%, approximately 5 times higher than men with a T-PSA below 1 ng/mL. Men with PSA levels between 1 and 1.99 ng/mL more resembled men with values between 2 and 2.99 ng/mL, regarding cumulative incidence of PC, Gleason score ≥ 7 PC and PC death. Men with T-PSA <1 ng/mL had a much lower risk profile (Table 1).

These findings are in accordance with several other studies reporting that men with a PSA of <1 ng/mL have a very low risk of developing advanced PC and of PC death within 25 years (18–20). In a study from the Swiss section of the ERSPC by Randazzo et al (12), men with initial PSA values of <3 ng/mL were stratified into the same PSA groups as in our study. They found that the cumulative incidence of PC was 23.6% in men with an initial PSA of 2–2.99 ng/mL. Their study was based on 4,350 men, aged 55–70 years, and after a median FU time of 11.6 years, 3.2% of the men were diagnosed with Gleason score ≥ 7 cancer, which is similar to our result (4.3%). The Swiss study also found a very low 8-year incidence (0.2%) of Gleason score ≥ 7 PC in men with an initial T-PSA of <1 ng/mL.

A screening program primarily aims at detecting potentially lethal cancer, while it is still curable. We found that relatively many men ($n=28$) in the Göteborg screening study died

from PC, despite entering the screening program with a PSA level below 3 ng/mL. This suggests that the diagnostic methods used in our screening program did not have a “perfect sensitivity” despite being to be the most intensive screening program within the ERSPC (8). Improving sensitivity means earlier diagnosis in men with potentially fatal PC. Previous studies have reported that potentially significant cancers are present in men with low PSA values (11, 12, 21). Findings from the STHLM3 study, where additional tests were used in the PSA range of 1–3 ng/mL, showed that out of the 603 high-risk cancers found in the study, 124 (21%) were identified in the PSA range below 3 ng/mL (11). Lowering the PSA threshold for biopsy to detect more potentially fatal PC without increasing overdiagnosis would be a challenge. It has been suggested that men with PSA < 3 ng/mL should have a biopsy if their PSA velocity is high or their F/T PSA ratio low (17, 24).

The high risk of detecting insignificant PC is also exemplified in the present study, in which cancers detected during subsequent screening were mainly in the low risk category (73% were Gleason score 6 cancers). The proportion of PC that would be found if the PSA cut-off were lowered to 1 or 2 ng/mL is unknown, but data from the Prostate Cancer Prevention Trial (PCPT) give some hints (13): sextant biopsies in men with a PSA between 1 and 1.99 ng/mL detected PC in 17% of men, which can be compared to the cumulative PC incidence of 26% in our study. In the PCPT study, cancers were detected in 24% of the men with a PSA between 2 and 2.99 ng/mL; the cumulative PC incidence in our study, based on 19 years of follow-up, was 40%. These comparisons give no estimate of how much the risk of overdiagnosis would increase with lowering the PSA cut-off for biopsy, but such a strategy would definitely lead to an earlier diagnosis in many men. Prospective studies are needed to better understand the balance between harms and benefits in programs with a lower PSA cut-off.

T-PSA is still the best biomarker available for finding PC, but overdiagnosis of insignificant cancers is the major disadvantage with PSA based screening as evaluated in the randomized trials and the main argument against introduction of mass-screening with PSA (22). Complementary screening tests such as serum markers or imaging (23) that could help differentiate between high-risk and low-risk PC are clearly needed. Many of the new biomarkers are costly, so mass-testing with these consume large healthcare resources.

A low F/T PSA ratio has been shown to indicate increased risk of PC in men with a T-PSA of > 3 ng/mL, but also in men with a PSA between 2 and 4 ng/mL (24, 25). As the F/T PSA is a cheap and widely available test, and could potentially be a useful complimentary test for screening, we evaluated its predictive value in men with an initial PSA below 3 ng/mL. Unfortunately, we found no additional value of adding F/T PSA to T-PSA for predicting future Gleason score ≥ 7 PC or death from PC. Figure 3 shows that men who develop and/or die from PC have a F/T PSA spread around the median value and that F/T PSA and T-PSA co-vary.

Few other studies have investigated the clinical use of F/T PSA for the prediction of later PC in screened men with a PSA of < 3 ng/mL. Sasaki et al (21) also analysed the detection of PC at subsequent screening rounds. Data was analysed in 6,368 men with a T-PSA < 4 ng/mL at initial screening, and they reported that F/T PSA was a strong predictor of a

subsequent diagnosis of PC. Of concern is that only men with PSA >4 ng/mL and men with a PSA of 2–4 ng/mL and a F/T ratio <12% were biopsied. This means that the overall value of F/T PSA in the PSA range of 2–4 ng/mL could not be evaluated. Moreover, they did not stratify the outcome by PSA levels. A similar study from the Finnish section of ERSPC was published by Finne et al (26). In their study men with a PSA of > 4 ng/mL or a PSA between 3 and 4 plus a F/T ratio <16% were biopsied. Both these studies found a higher risk of PC in men with low F/T ratio, possibly as these men were selected for biopsy.

Results supporting the present study come from the Dutch section of ERSPC where they analysed the risk of PC in subsequent screening visits and the predictive capabilities of F/T ratio, PCA3, 4k-panel and the ERSPC risk calculator. They found no additional value of F/T ratio but both PCA3 and the 4k-panel contributed (27).

We therefore conclude that F/T PSA does not provide any additional prognostic information apart from what T-PSA give and thus do not help in identifying men in the PSA range below 3 ng/mL who might need further urological work-up.

The optimal screening algorithm is still to be defined. From our study, we cannot conclude the best screening strategy, nor the time for re-testing. However, when PSA <1 ng/mL it is questionable to use additional biomarkers as these men have a very low risk and thus PSA alone is sufficient. A total number of 7 men with an initial T-PSA <1 ng/mL died from PC in this study. Many of them would probably have been curable if detected in the range between 1 and 3 ng/mL. Apart from evaluating new serum markers in screening situations another promising strategy is to incorporate MRI in this context and only perform targeted biopsies on MRI positive men. Such approach seems to dramatically decrease the risk of overdiagnosis (23). In 2016, we published our experience with offering men with a T-PSA between 1.8 and 2.99 ng/mL a pre-biopsy MRI which confirmed that MRI also seem to work as a screening tool in this range, and that several significant cancers were detected (28). However, MRI is costly and savings could be made using a biomarker with better specificity compared to T-PSA to select men for MRI.

Our study has some strengths and limitations. This is a rather large cohort of men who participated in a long-term screening program with high attendance rate. The FU-time was long and few men were “lost to follow-up” due to the high coverage in the Swedish Cancer Registry. However, this is a report on a cross-sectional test result and the outcome might not reflect other populations with different ages or underlying PC prevalence. In this cohort, a 6-core biopsy was the standard until 2009, whereas 10 or 12-cores are performed today.

We are rapidly approaching a paradigm shift in PC diagnosis where new biomarkers and imaging will play an important role in order to enhance diagnostic procedure. Future research should focus upon establishing appropriate PSA cut-offs but also investigate whether incorporation of other biomarkers such as PCA3 and 4k-panel are cost-effective in selecting men for imaging.

Conclusions

Total PSA within the PSA range below 3 ng/mL is strongly related to the risk of being diagnosed with PC and also to the risk of dying from PC. Some men in the PSA range between 1 and 3 ng/mL would benefit from an earlier diagnosis, but F/T PSA ratio does not seem helpful to select these men. Better markers and/or imaging should be evaluated in this range.

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Consort diagram

PSA = prostate specific antigen
DRE = digital rectal examination
TRUS= trans-rectal ultra-sound examination

* 20 men excluded

Figure 1.
Consort diagram showing study design

Figure 2A.

Cumulative incidence of prostate cancer in various PSA groups

Figure 2B.

Cumulative incidence of Gleason ≥ 7 tumours in various PSA groups

Scatter plot of F/T PSA versus T-PSA at baseline. Men who later developed Prostate Cancer are marked in blue and those who died from PC in red.

Figure 3. Scatter plot of F/T PSA versus T-PSA at baseline.

Men who later developed Prostate Cancer are marked in blue and those who died from PC in red.

Table 1.

Characteristics of various PSA groups (T-PSA at first screening round in 1995–1996)

	PSA group 1 PSA < 1 ng/ml	PSA group 2 PSA 1–1.99 ng/ml	PSA group 3 PSA 2–2.99 ng/ml	All men in study population
No of men at baseline / initial screening (%)	2931 (56.6)	1708 (33.0)	535 (10.3)	5174 (100)
Age at initial PSA screening, Md (IQR) yr	56.5 (53.4, 60.6)	57.9 (54.3, 61.8)	59.3 (55.4, 63.1)	57.2 (53.8, 61.4)
Age at diagnosis, Md (IQR) yr	68.0 (65.9, 70.2)	66.6 (64.0, 68.9)	65.5 (61.6, 68.4)	66.8 (63.7, 69.1)
No of PC detected (%)	189 (6.4)	370 (21.7)	195 (36.4)	754 (14.6)
No of PC diagnosed within study* (%)	120/189 (63)	290/370 (78)	157/195 (81)	567/754 (75)
Cumulative incidence of PC (95 % CI) %	7.9 (6.9, 9.1)	26.0 (23.6, 28.6)	40.3 (35.9, 45.0)	17.2 (16.1, 18.5)
No of PC deaths (%)	7 (0.2)	15 (0.9)	6 (1.1)	28 (0.5)
No of PC deaths within study* (%)	2/7 (29)	5/15 (33)	3/6 (50)	10/28 (36)
Cumulative Incidence PC death (95 % CI) %	0.3 (0.1, 0.6)	1.1 (0.7, 1.8)	1.5 (0.7, 3.4)	0.7 (0.5, 1.0)
PSA at initial screening, Md (IQR)	0.6 (0.4, 0.8)	1.3 (1.2, 1.6)	2.4 (2.2, 2.7)	0.9 (0.6, 1.4)
PSA at diagnosis, Md (IQR)	4.0 (3.3, 6.0)	4.1 (3.4, 5.8)	4.5 (3.7, 5.8)	4.2 (3.4, 5.8)
Time from first PSA to diagnosis, Md (IQR) yr	13.4 (10.1, 16.0)	10.0 (6.2, 13.0)	6.0 (4.1, 9.5)	10.0 (6.1, 13.9)
Time from first PSA to PC death, Md (IQR) yr	15.1 (9.7, 15.9)	14.5 (9.6, 15.4)	15.9 (15.3, 16.1)	15.1 (9.7, 16.0)
F/T PSA ratio at initial screening (%)	33.2 (26.2, 41.7)	24.8 (19.4, 31.5)	20.7 (16.6, 25.7)	28.7 (21.7, 37.3)
F/T PSA ratio in Gleason score < 7 at diagnosis	31.0 (25.6, 41.2)	24.5 (19.1, 30.8)	20.3 (16.9, 24.7)	24.3 (19.0, 30.8)
F/T PSA ratio in Gleason score ≥ 7 at diagnosis	28.9 (23.2, 36.0)	24.5 (18.9, 31.3)	21.1 (15.9, 25.7)	25.7 (20.2, 32.9)
No of PC – Gleason score ≥ 7 (%)	82 (2.8)	107 (6.3)	35 (6.5)	224 (4.3)
No of PC – Gleason score ≥ 7 within study* (%)	45/82 (54.9)	53/107 (49.5)	18/35 (51 %)	116/224 (51.4)
Cumulative Incidence Gleason ≥ 7 (95 % CI) %	3.7 (2.9, 4.5)	9.7 (7.8, 12.0)	10.9 (7.7, 15.4)	6.2 (5.4, 7.1)

Md = median, IQR= interquartile range, CI= confidence interval, PC= prostate cancer, PSA= prostate-specific antigen, F/T PSA ratio = free-to-total PSA ratio

* Screen-detected cancers