Association between one-time prostate-specific antigen (PSA) test with free/total PSA ratio and prostate cancer mortality: A 30-year prospective cohort study

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Objectives
To explore if there is a long-term association between baseline prostate-specific antigen (PSA), including free/total PSA ratio and long-term (30-year) risk for prostate cancer death.

Subjects and methods
In all, 1782 men were screened for prostate cancer through PSA analysis. Some years later, frozen plasma samples were used to calculate the ratio of free to total PSA (f/t PSA). At 30-year follow-up, baseline PSA and f/t PSA were compared with recent data extracts from the Swedish Cause of Death Registry and Swedish Cancer Registry. PSA values and f/t PSA values were treated as continuous variables in a multivariable analysis and also stratified according to their distribution and useful clinical thresholds.

Results
Risk of death from prostate cancer after 30 years of follow-up was significantly increased with a higher baseline PSA level, with the hazard ratio being 1.04 (95% confidence interval 1.03–1.09) per increase of one unit of PSA. Adding f/t PSA increased the model’s ability to discriminate (concordance index 0.84–0.88). Men with PSA levels <1.0 ng/mL had a very low long-term risk of prostate cancer death (1.2% risk). An f/t PSA ≥ 0.25 extended the low-risk range to PSA < 2.0 ng/mL (1.5% risk).

Conclusion
Prostate-specific antigen testing can be carried out less frequently or can be discontinued in men aged 55–70 years if their PSA levels are <2.0 ng/mL and the f/t PSA is ≥0.25.

Keywords
prostate-specific antigen, prognosis, prostate cancer, screening, mortality, #PCSM, #ProstateCancer, #uroonc

Introduction
Since the late 1980s and early 1990s, analysis of PSA has been the basis of all attempts at early detection of prostate cancer. Several systematic studies on population-based screening programmes were published. Simultaneously, widespread opportunistic screening for prostate cancer emerged. This raised the issue of overdiagnosis and consequent overtreatment of indolent prostate cancer. The total number of PSA tests performed varies globally and is difficult to estimate. In Sweden Jonsson et al. [1] reported in 2011 that 56% of all men aged between 55 and 69 years had had their PSA level tested. Around the same time, the 10-year risk of undergoing PSA testing at least once for men aged 45–69 years was 39% in the UK [2].

A majority of circulating PSA is bound to proteins (mostly α1-antichymotrypsin), whereas a smaller fraction is free. Most commercial PSA kits measure the total PSA. However, the diagnostic precision of PSA can be enhanced by analysing the ratio of free to total PSA (f/t PSA) because a low percentage of free PSA (i.e. a low f/t PSA) suggests significant prostate cancer – a correlation established not long after the arrival of the PSA test itself [3]. Two meta-analyses published in 2005 and 2006 found that the f/t PSA was mostly useful in the ‘PSA grey zone’, i.e. 4–10 ng/mL [4] or 2–10 ng/mL [5].
Most Swedish laboratories today have set the normal f/t PSA value to >0.18.

The possibility of using one single PSA test to assess the future risk of prostate cancer has been discussed. Several studies have concluded that a low baseline PSA indicates a low risk of significant future prostate cancer. For example, Lilja et al. [6] and Preston et al. [7] established that a low midlife PSA value indicated low to negligible future risk for significant or lethal prostate cancer. When reviewing the Prostate, Lung, Colorectal, and Ovarian Cancer screening study (PLCO) cohort of approximately 13 000 men aged 55–60 years after 13 years, Kovac et al. [8] found that the incidence of significant prostate cancer was only 0.4% for men with a baseline PSA of ≤0.49 ng/mL. Significant prostate cancer was defined as clinical stage cT2b or greater, Gleason grade ≥7, or prostate cancer death. The authors argued that further PSA screening of men with low PSA levels at baseline should be performed with a low frequency and possibly ceased if PSA is <1.0 ng/mL at the age of 55–60 years (1.5% risk of significant prostate cancer for men with PSA 0.50–0.99 ng/mL and 0.40% risk for men with PSA <0.49 ng/mL) [8].

The predictive value of f/t PSA is somewhat controversial. The Rotterdam section of the European Randomized Screening for Prostate Cancer (ERSPC) trial detected an increased ability to detect minimal prostate cancer using free PSA in combination with human glandular kallikrein 2 (hK2) [9]. A nested case–control study based on a Swedish cohort of more than 40 000 men similarly detected an increased association with lethal prostate cancer when PSA was combined with hK2 and f/t PSA [10].

By contrast, Frånland et al. [11] recently published data from the Swedish arm of the ERSPC trial almost 19 years after inclusion where baseline PSA was predictive of both prostate cancer incidence and mortality, but f/t PSA was not. The data were in this case based on men with PSA <3.0 ng/mL in the original screening round, and they were rescreened biennially and recommended biopsies if PSA was >3.0 ng/mL.

In the present study, we evaluated the association between prostate cancer death and a one-time PSA and f/t PSA screening at 30-year follow-up.

### Subjects and Methods

In 1988 and 1989, 2400 men aged 55–70 years were randomly selected from a background population of nearly 27 000 men. They were invited to participate in a screening trial for prostate cancer and 1782 accepted. The background population consisted of all Swedish men aged 55–70 years, who lived in a defined part of southern Stockholm (the catchment area of Stockholm South General Hospital) according to Swedish census records. The area was predominantly urban and predominantly White. The not-invited population constituted a control group in later evaluations of the screening effort itself [12,13]. All men were examined with a DRE, prostate ultrasonography, and PSA analysis. The PSA threshold for biopsies was arbitrarily set to 10 and 7 ng/mL for reexamination with TRUS and DRE. After PSA was measured (using the Hybritech Tandem-R method), the blood samples were centrifuged, and sera of all participants were stored at −70 °C. The original screening study yielded 65 cases of prostate cancer [14]. A total of 41 were treated with curative intent: 11 were treated with radical prostatectomy, 26 were treated with radiation therapy, and four were included in a therapeutic study with Nd-YAG laser ablation preceded by TURP [15]. Furthermore, 18 men were followed up with active surveillance, five were surgically castrated, and one received androgen deprivation therapy. Determination of f/t PSA was performed on thawed samples 6 years later using immunofluorometric assays thoroughly described elsewhere [16]. All patients were followed up for up to 30 years by extracting information from the Swedish Cancer Registry and the Swedish Cause of Death Registry. PSA values were retrieved for all men except in four cases, and f/t PSA values were missing in 25 cases. The baseline characteristics of the study population are outlined in Table 1.

The Swedish Cause of Death Registry is maintained by the Swedish National Board for Health and Welfare. A death is reported to the tax authorities within 24 h, and the cause of death is then reported within 3 weeks. If a person dies abroad, he or she is still included in the registry but usually with the code for ‘unknown cause of death’. All deaths are included in the registry, but the underlying cause of death is missing in 0.9% of cases. In our cohort, only 3/1469 deaths or 0.2% did not have an underlying cause of death registered.

### Table 1 Clinical and demographic characteristics of the cohort stratified by outcome.

| Age at blood draw, years | Entire cohort (n = 1778) | Prostate cancer diagnoses during follow-up (n = 262) | Lethal prostate cancer during follow-up (n = 86) |
|--------------------------|-------------------------|---------------------------------|---------------------------------|
|                          | 64 (60–67)              | 63 (60–66)                      | 64 (61–67)                      |
| Baseline PSA, ng/mL      | 1.8 (1.6–3.0)           | 3.3 (1.9–6.6)                   | 4.2 (1.9–7.4)                   |
| Baseline f/t PSA         | 0.25 (0.18–0.33)        | 0.18 (0.11–0.26)                | 0.15 (0.10–0.23)                |

Data are presented as median (interquartile range). f/t PSA, free to total PSA ratio.
Prostate cancer was regarded as the cause of death if registered as the primary cause of death or as the underlying cause of death by the responsible physician. The Swedish Cause of Death Registry has been validated regarding prostate cancer mortality in a previous study and has been found to have high accuracy, with approximately 3% more deaths attributed to prostate cancer in official records than in reviewed cases [17,18]. The data were extracted by submitting study participants’ unique 10-digit personal number followed by clinical data, e.g. PSA and f/t PSA values, to the Swedish National Board for Health and Welfare. Extracts were then returned anonymized with data regarding causes and dates of death and complete extracts from the cancer registry regarding all neoplastic diagnoses.

Statistical Analysis

The primary study endpoint, the association between baseline PSA and long-term cancer-specific mortality, was estimated using multivariable Cox regression analysis. PSA was adjusted for age and f/t PSA. The ability of the model to discriminate between risk strata and the ability of the biomarkers to predict time to event was estimated with Harrell’s concordance index (C-index). The maximum value of the C-index is 1, and 0.5 represents a random prediction [19]. To evaluate the contribution of f/t PSA to the prognostic model, both univariate and multivariable regression models were set up.

To evaluate the clinical usefulness and the potential long-term discriminatory ability of the markers, the cohort was stratified both by distribution of PSA and f/t PSA, i.e. the data were categorized according to quartiles and medians of PSA and f/t PSA and also, according to clinically useful thresholds, in this case, PSA < 1 ng/mL and PSA < 2 ng/mL.

Since all clinical decision-making regarding prostate cancer (screening, treatment etc.) is highly age-dependent, we also stratified the men by age: 55–59 years, 60–64 years and 65–70 years.

To demonstrate the association between the baseline markers PSA and f/t PSA graphically, values are plotted, using the locally weighted scatterplot smoothing technique, in Fig. 1 and Fig. 2.

Differences were considered statistically significant if \( P < 0.05 \). All statistical analyses were made using Stata 16 software. Approval was obtained from the local ethical review board (No 2017/1976-32). The manuscript was drafted using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [20] and the Guidelines for reporting of statistics for clinical research in urology [21].

Results

After 30 years, 22% of the study population was still alive. The median (interquartile range [IQR]) follow-up time was 18.0 (10.8–26.6) years for non-cases. The median (IQR) PSA at baseline was 1.8 (1.6–3.0) ng/mL and the f/t PSA was 0.25 (0.18–0.75). At 30-year follow-up, the cumulative incidence of prostate cancer was 15% \((n = 262)\) and the prostate cancer-specific mortality rate was 4.9% \((n = 88)\).
The prostate cancer incidence rates were 6.8% and 25%, and the corresponding long-term cancer-specific mortality rates were 2.4% and 8.3% for men with PSA < 2.0 ng/mL and PSA ≥ 2.0 ng/mL, respectively. Absolute risks for lethal prostate cancer stratified by age and baseline biochemistry are shown in Table 2. Both PSA and f/t PSA were found to be strongly associated with future prostate cancer mortality: hazard ratio 1.04 (95% CI 1.03–1.06) per unit increase in PSA at baseline and hazard ratio 0.85 (95% CI 0.85–0.92) per unit increase in f/t PSA. The multivariable hazard ratios are outlined in Table 3. The relationship between risk of lethal prostate cancer and baseline biochemistry is graphically illustrated in Figs 1 and 2.

Addition of f/t PSA to the model increased the overall C-index from 0.84 to 0.88.

The pairwise log-rank test for prostate cancer-specific survival was significantly different depending on f/t PSA level, regardless of whether PSA was below or above 2 ng/mL ($P = 0.013$ and $P = 0.032$, respectively).

An f/t PSA ≥ 0.25 indicated a favourable risk stratification even if PSA levels were somewhat higher. When excluding men with f/t PSA < 0.25, the 30-year cumulative incidence of prostate cancer mortality was 1.5% for men with baseline PSA < 2.0 ng/mL and 3.2% for men with baseline PSA ≥ 2.0 ng/mL.

Men with PSA < 1.0 ng/mL had a very low long-term risk for prostate cancer death (1.2%) based on just one case of lethal prostate cancer in this group.

### Discussion

A low baseline PSA in combination with a high percentage of free PSA was strongly associated with a low risk of future lethal prostate cancer. These data support earlier findings that a single PSA test can risk-stratify for significant prostate cancer, or as was the case in the present study, the risk for prostate cancer death. We also found that f/t PSA strengthened the association between a single PSA test and prostate cancer mortality.

Current recommendations regarding PSA screening vary. Most reservations regarding PSA screening for prostate cancer are concerned with the risk of harms from the screening, i.e. overdiagnosing and overtreatment, rather than disputing the ability to detect prostate cancer at an early, curable stage. The US Preventive Services Task Force recommends shared decision-making between patient and physician regarding PSA screening once the patient is informed about the risk of overdiagnosing and overtreatment [22].

In our cohort, 57% of the men had a PSA level < 2.0 ng/mL at baseline and 691 men (39%) had an f/t PSA ≥ 0.25 in addition to PSA < 2.0 ng/mL. On the basis of this result, if 40% of all men can be excluded from PSA screening after one single midlife test, perhaps the balance between benefits and harms of PSA screening can be shifted and the benefits can outweigh the harms for the remaining men with less favourable baseline characteristics.

The men included in this study were not offered repeat testing or examinations, and outcomes were probably less
Table 2 Absolute 30-year risk of lethal prostate cancer stratified by age and levels of PSA and free/total PSA ratio.

| PSA stratification | 55-59 years | 60-64 years | 65-70 years | All ages |
|--------------------|-------------|-------------|-------------|----------|
| Number of events   | Absolute risk (95% CI) | Number of events | Absolute risk (95% CI) | Number of events | Absolute risk (95% CI) | Number of events | Absolute risk (95% CI) |
| 1st quartile PSA 0-1.5 ng/mL | 2 | 1.5 (0.18, 5.3) | 2 | 1.8 (0.21, 6.3) | 2 | 1.54 (0.19, 5.5) | 6 | 1.6 (0.59, 3.4) |
| f/t PSA < 0.18 | 0 | 0 (n.e) | 0 | 0 (n.e) | 0 | 0 (n.e) | 14 | 3.6 (1.7, 6.8) |
| f/t PSA < 0.25 | 3 | 8.3 (10, 27) | 1 | 4.8 (12, 24) | 2 | 11 (1.4, 35) | 5 | 7.9 (2.6, 18) |
| f/t PSA > 0.25 | 0 | 0 (n.e) | 1 | 1.09 (0.028, 5.9) | 1 | 0 (n.e) | 1 | 0.33 (0.085, 1.9) |
| 2nd quartile PSA 1.6-1.8 ng/mL | 2 | 2.2 (0.26, 7.6) | 1 | 0.93 (0.023, 5.1) | 5 | 3.5 (1.1, 7.9) | 8 | 2.38 (1.03, 4.64) |
| 3rd quartile PSA 1.9-3.0 ng/mL | 2 | 1.2 (0.15, 4.4) | 3 | 5.26 (1.1, 15) | 2 | 3.03 (0.37, 11) | 5 | 2.91 (0.98, 6.65) |
| 4th quartile PSA > 3.0 ng/mL | 3 | 4.6 (0.96, 13) | 12 | 8.6 (4.5, 14) | 4 | 2.2 (0.59, 5.5) | 19 | 4.6 (2.8, 7.1) |
| <1 ng/mL | 4 | 11 (4.4, 21) | 16 | 11 (6.5, 17) | 27 | 11 (7.2, 15) | 50 | 11 (8.1, 14) |
| f/t PSA < 0.18 | 5 | 12 (4.1, 26) | 13 | 18 (9.7, 28) | 21 | 19 (12.27) | 37 | 19 (12.22) |
| f/t PSA < 0.25 | 7 | 13 (5.3, 24) | 15 | 12 (6.8, 19) | 24 | 13 (8.2, 18) | 46 | 12 (9.1, 16) |
| f/t PSA > 0.25 | 0 | 0 (n.e) | 3 | 6.3 (1.3, 19) | 2 | 2.6 (0.31, 8.9) | 5 | 3.33 (1.09, 7.61) |
| <2 ng/mL | 2 | 1.0 (0.12, 3.7) | 4 | 1.9 (0.51, 4.7) | 5 | 1.9 (0.61, 4.3) | 11 | 1.6 (0.82, 2.9) |
| f/t PSA < 0.18 | 0 | 0 (n.e) | 0 | 0 (n.e) | 0 | 0 (n.e) | 0 | 0 (n.e) |
| f/t PSA < 0.25 | 0 | 0 (n.e) | 0 | 0 (n.e) | 0 | 0 (n.e) | 0 | 0 (n.e) |
| f/t PSA > 0.25 | 0 | 0 (n.e) | 5 | 5.9 (0.15, 29) | 0 | 0 (n.e) | 1 | 1.8 (0.045, 9.6) |
| f/t PSA > 0.25 | 2 | 2.2 (0.26, 7.6) | 1 | 0.93 (0.023, 5.1) | 5 | 3.5 (1.1, 7.9) | 8 | 2.38 (1.03, 4.64) |
| f/t PSA > 0.25 | 2 | 2.2 (0.26, 7.6) | 1 | 0.93 (0.023, 5.1) | 5 | 3.5 (1.1, 7.9) | 8 | 2.38 (1.03, 4.64) |

Table 3 Hazard ratio for prostate cancer-specific death and prostate cancer diagnosis by PSA.

| Prostate cancer mortality | Hazard ratio (95% CI) (multivariable) | P |
|---------------------------|--------------------------------------|---|
| Age                       |                                       |   |
| 55-59 years               | 1.14 (0.87-1.49)                     | 0.3 |
| 60-64 years               | 1.07 (1.03-1.11)                     | <0.001 |
| 65-70 years               | 1.04 (1.02-1.06)                     | <0.001 |
| All                       | 1.04 (1.03-1.06)                     | <0.001 |

| Prostate cancer diagnosis | Hazard ratio (95% CI) (multivariable) | P |
|---------------------------|--------------------------------------|---|
| Age                       |                                       |   |
| 55-59 years               | 1.16 (1.09-1.24)                     | <0.001 |
| 60-64 years               | 1.07 (1.04-1.09)                     | <0.001 |
| 65-70 years               | 1.04 (1.02-1.04)                     | <0.001 |
| All                       | 1.05 (1.04-1.05)                     | <0.001 |

It is generally perceived that f/t PSA is not as diagnostically or prognostically meaningful in lower PSA ranges [5]. In the present study, f/t PSA did affect the model’s ability to discriminate between cases and non-cases also in men with PSA < 2.0 ng/mL (Harrell’s C-index 0.62–0.79). A combination of both PSA and f/t PSA thus seems to be more helpful in risk stratification.

The men invited to participate in this study were aged between 55 and 70 years at the time of the PSA test (median age 64 years). Compared with the long-term PSA follow-up of the PLCO and the Swedish arm of the ERSPC [8,11] (55–60 and 50–66 years, respectively), our cohort was slightly older at the start of follow-up. When Lilja et al. [6] evaluated

affected by intensive screening and treatment compared to other trials. For example, Fränlund et al. [11] evaluated the predictability of f/t PSA in men with PSA <3.0 ng/ mL in the first round of screening in the Swedish arm of the ERSPC. In later rounds of the screening, 14.6% were diagnosed with (and treated for) prostate cancer, probably affecting the outcome and the ability to detect improved prognostics with f/t PSA [11]. Given the time in which this study was conducted and the one-time design, these data represent the ‘natural history’ of the disease and possibly the true prognostic efficacy of baseline PSA and f/t PSA.

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the prognostic value of a midlife PSA, the participants were aged 44–50 years at the time of testing. Arguably, higher long-term risks should be accepted for older men.

The present study also differs from the aforementioned studies with regard to endpoints: the more contemporary prospective trials with a shorter follow-up have designated prostate cancer diagnosis (overall and/or significant prostate cancer) as the endpoint. In the present study with a longer follow-up duration, the more significant and meaningful endpoint prostate cancer death was used.

Our findings suggest that future PSA screening can be less intense for at-risk men aged between 55 and 70 years with PSA < 2 ng/mL along with f/t PSA ≥ 0.2, as their long-term risk for prostate cancer-specific mortality is very low.

The youngest cohort of men (aged 55–59 years at time of blood draw) are also seemingly at low risk of future lethal prostate cancer, but the association does not reach statistical significance, most likely because there were few events. The 30-year risk of being diagnosed with prostate cancer was strongly associated with baseline PSA for all age groups.

Because the subgroup with the most beneficial combination of biochemistry, constitutes a large part (39%) of the total population, there are possible implications for healthcare professionals and for decision-makers regarding population-based screening.

Earlier observations [6-8,23] that men with a baseline PSA <1.0 ng/mL are at a very low lifetime risk were also confirmed in this study.

There is, however, a discrepancy. Vickers et al. [23] report a 25-year risk for metastasized disease of 0.5% for men with PSA <0.65 ng/mL and a risk of death from prostate cancer of 0.9 for men with PSA <1.06 ng/mL. Preston et al. [7] report a risk of 0.59% for men with PSA <0.96 ng/mL in a 30-year evaluation of male US physicians. The corresponding risk in the present study is much higher at 1.2% (95% CI 0.3–6.5).

This discrepancy can possibly be attributed to methodological differences. Both Vickers et al and Preston et al. reviewed the patient records of the men diagnosed with prostate cancer, whereas cause of death in the present study was determined by the physician responsible for reporting the death to the national board for health and welfare. Prostate cancer is exaggerated (3%) as the primary or underlying cause of death, possibly affecting the data [17,18].

Also, there were very few cancer-specific deaths in the population with very low PSA levels; there was only one case of lethal prostate cancer with PSA ≤ 1.0 ng/mL in our cohort. Hence confidence intervals regarding risk in the very low PSA segment were very wide and conclusions, other than that the lifetime risk for prostate cancer-specific death is low, should be drawn with caution.

This study has several limitations. Even though cancer-specific death is a solid endpoint, further clinical information, such as distant metastases, would be of value. Because the cohort comprised men participating in a one-time screening trial, we lacked data on PSA and f/t PSA at the time of diagnosis (if diagnosed during follow-up and not at inclusion). Such data could provide details on the increase in PSA level over time and further aid in risk stratification. Furthermore, additional data during follow-up could enable more sophisticated estimation of the ability of PSA and f/t PSA to discriminate between outcomes.

Since cause of death was extracted from registries one must interpret the exact risks with that in mind. The internal validity, by contrast, is unaffected since physicians responsible for determining the cause of death were unaware of the blood tests taken during the screening trial.

Several thresholds were tested; those chosen for their clinical relevance, i.e. PSA < 2.0 ng/mL and f/t PSA > 0.25, were selected so as to be as useful as possible in clinical decision-making and to add to preexisting evidence regarding PSA-stratified screening regimens. There is little controversy that a PSA level < 1.0 ng/mL indicates a very low risk of future significant prostate cancer. The objective with this evaluation was to explore whether the PSA threshold could be elevated to 2.0 ng/mL if combined with f/T PSA. The fraction of free PSA in this case simply dichotomized to above or below 0.25 (above or below median value) and also dichotomized to above or below 0.18 the current threshold used in most Swedish laboratories. Nonetheless, it is possible that other combinations of the two markers could perform statistically better in discriminating between cases and non-cases in the long-term setting.

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Disclosure of Interests
None declared.

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Abbreviations: ERSPC, European Randomized Screening for Prostate Cancer; f/t PSA, free-to-total PSA ratio; hK2, human glandular kallikrein 2; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer.