



ORIGINAL ARTICLE

Serum thymidine kinase 1 concentration as a predictive biomarker in prostate cancer

Per-Olof Lundgren MD, PhD¹  | Bernhard Tribukait MD, PhD²  |
Anders Kjellman MD, PhD¹ | Ulf Norming MD, PhD³ | Kiran Jagarlmudi PhD^{4,5} |
Ove Gustafsson MD, PhD¹

¹Department of Clinical Science, Intervention and Technology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden

²Department of Oncology-Pathology, Karolinska Institute and University Hospital, Stockholm, Sweden

³Department of Clinical Science and Education, Södersjukhuset, Stockholm, Sweden

⁴Department of Anatomy, Physiology, and Biochemistry, Swedish University of Agricultural Sciences, Uppsala, Sweden

⁵Research and Development Division, AroCell AB, Uppsala, Sweden

Correspondence

Per-Olof Lundgren MD, PhD, Department of Urology, Karolinska University Hospital C1:77, 141 86 Stockholm, Sweden.

Email: per-olof.lundgren@regionstockholm.se

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Abstract

Background: Thymidine kinase 1 (TK1) recycles DNA before cell division. We do not know if baseline blood concentrations of TK1 predict death in prostate cancer within 30 years.

Our objective is to determine if there is an association between baseline levels of TK1 and future prostate cancer-specific mortality.

Methods: With a “proof of concept” approach, we performed a nested case-control study among 1782 individuals screened for prostate cancer between 1988 and 1989. The concentration of TK1 was measured in frozen serum from 330 men, 36 of whom have died of prostate cancer.

The primary endpoint was prostate cancer-specific mortality and outcomes after 30 years were analyzed using logistic regression modeling odds ratios (Ors).

Results: The estimated OR (adjusted for age) for dying from prostate cancer among the men who had a TK1 value in the upper tertile was 2.39 (95% confidence interval 1.02–5.63). The corresponding OR, regardless of the cause of death, was 2.81 (1.24–6.34).

Conclusions: High levels of TK1 predicts death in prostate cancer within 30 years of follow-up.

KEYWORDS

prognosis, prostate cancer, thymidine kinase

1 | INTRODUCTION

Early on, Hippocrates emphasized in his writings that making a prognosis is an important part of the medical profession.¹ With a prognosis, early treatment can be initiated, and the patient can prepare for what is to come. Regarding prostate cancer, the expected course can to some extent be described with the help of histopathology

(Gleason score), prostate-specific antigen (PSA) concentration at diagnosis, and perhaps also genetic markers.^{2,3}

Thymidine kinase 1 (TK1) is a cytoplasmic enzyme while TK2 is exclusively detected in the mitochondria.^{4,5} TK1 facilitates the reuse of building blocks for DNA in connection with cell division.⁶ TK1 is upregulated during the synthesis phase of cell division, remains high during the G2 phase and decreases in concentration in connection

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with mitosis. As early as 1990, Lewenhaupt and coworkers demonstrated that a metric of the TK1 concentration in the blood may give a prognostic signal in prostate cancer.⁷ Murtola and coworkers have also recently presented data that support the existence of such a signal.⁸

Benefitting from the Swedish unique personal identification number for each resident, we have performed a 30-year follow-up assisted by the Swedish population-based registers. Between 1988 and 1989, 1782 men were screened for prostate cancer in the Stockholm region using concentrations of PSA, palpation, and ultrasound examination. Serum from these men has been stored frozen in minus 70°C. We have performed a 30-year follow-up assisted by the Swedish population-based registries. In a nested case-control study, we analyzed the concentration of TK1 in 330 men after 30 years of follow-up. With that information, we have studied if TK1 concentrations in blood predicts the risk of dying of prostate cancer.

2 | MATERIALS AND METHODS

2.1 | Design

The study is designed with a “proof of concept” approach. The entire cohort has not been analyzed, which is why the epidemiological design is a case-control study where both the cases and the controls have been retrieved from the same cohort, that is, a “nested” case-control study.

2.2 | Cohort

To evaluate diagnostic methods for prostate cancer, a screening study was conducted in 1988 and 1989. In a defined part of southern Stockholm, Sweden, about 27,000 men between the ages of 55 and 70 were resided according to population registries. The defined part of Stockholm consisted of the catchment area for the South General Hospital in Stockholm. With few exceptions, the area was of a pronounced urban character with a relatively homogeneous Caucasian population. From the background population, 2400 were randomized to be invited to a screening trial for prostate cancer. A total of 1782 men accepted the invitation and were examined. The screening consisted of rectal palpation of the prostate, ultrasound examination, and testing of PSA. According to the screening algorithm, quadrant biopsies of the prostate were performed if there were abnormal findings on palpation, ultrasound or if PSA > 10 ng/ml. PSA between 7 and 10 ng/ml led to re-examination with ultrasound and palpation. In addition to determining the concentration of PSA by the Hybritech Tandem R method at the time of screening,⁹ the proportion of free PSA, prostate volume, PSA density, and (in a sample of the cohort) androgen activity in serum were recorded. The androgen activity and the isomers of PSA were analyzed on thawed serum a few years after the screening.¹⁰ In addition, another tube of blood was taken for

immediate centrifugation and storage at -70°C. The PSA cut off for biopsies (10 ng/ml) was set, without previous experience with PSA, to evaluate the, at the time, new biomarker PSAs ability to detect prostate cancer. The screening detected 65 cases of prostate cancer, almost exclusively by palpation/ultrasound findings. Detailed method description and short- and long-term outcomes regarding the screening as such are described in other publications.¹¹⁻¹³

From the total cohort's frozen serum samples, samples of frozen serum were taken from 36 men who had died of prostate cancer and from 294 randomly selected men who had not died of prostate cancer. The case-control ratio is thus about 1:8. The tubes with serum were transported from their storage site to the laboratory on carbonated ice. All tubes had been thawed once before—approximately 25 years before this analysis. In the laboratory, the serum samples were analyzed for concentration of TK1 at the Department of Anatomy, Physiology, and Biochemistry, Swedish University of Agricultural Sciences, Uppsala, Sweden, with TK210 enzyme-linked immunoassay (ELISA), produced by AroCell AB. The samples were thawed on arrival at the laboratory and aliquoted to 200 µl before restored in the biobank. The aliquoted tubes were then thawed in connection with the analysis. In total, the samples were thawed three times before analysis. Internal testing shows that up to four cycles of freezing and thawing did not have any significant effect on TK1 protein determination by AroCell TK 210 ELISA. The test is based on two monoclonal antibodies against the C-terminal region of TK1. The tests were performed according to the manufacturer's instructions (www.arocell.com). Briefly, a specific antibody binds to a first epitope on TK1, and a second specific antibody binds to a second epitope on the target molecule. The second antibody is called “the detection antibody” and allows the detection and quantification of TK1 in a sample by initiating a light-emitting reaction.¹⁴ The sample selection process was blind to all clinical data except cancer-specific death. The laboratory analysis of TK1 was blinded regarding both exposure and outcome.

The samples were analyzed along with two internal controls and one quality control sample with predetermined TK1 protein values. The serum samples, internal controls (2 and 15 ng/ml), and quality control serum samples (0.5 ng/ml) were analyzed in duplicates in each run.

The overall coefficient of variation (CV) between the runs for controls and quality control sample was in the range of 3.5%–9.6% which indicates robustness and reproducibility of the assay.

2.3 | Registries

The Swedish cause of death register and the cancer register is maintained by the National Board of Health and Welfare. The register is virtually complete, but a defined cause of death is missing in 0.9% of the cases.¹⁵ In Sweden, it is mandatory by law that the physician in charge reports a death to the National Board of Health and Welfare within 24 h of the death and the cause of death certificate within 2 weeks. The cause of death certificate contains information about

both the primary cause of death and possible underlying causes of death. The cause of death registry has been validated for prostate cancer-specific mortality with good compliance. Prostate cancer is exaggerated as a cause of death in about 3% of cases compared to when medical records are scrutinized.^{15,16}

Each study participant's unique 10-digit personal identification number was sent in an encrypted file to the National Board of Health and Welfare together with clinical background data. The National Board of Health and Welfare then provided information on cancer diagnoses by the International Classification of Diseases 10 system with time for diagnosis as well as data from the cause of death register in, for the research group, anonymized form. The link is retained by the National Board for Health and Welfare. All participants in the study signed consent to participate in the study but also to save samples for future analyzes. Permission to carry out the study has been approved by the Ethics Review Board (D-no: 2017/1976-32). The manuscript was drafted in accordance with the REMARK guidelines.¹⁷

2.4 | Statistical analysis

Given that we lack prior cut-off levels for TK1 regarding long-term prognostics the cohort was stratified into tertiles based on its concentration of TK1 at the start of the study. Analysis of variance between strata regarding background factors: PSA, free PSA, Ratio free/total PSA, age, prostate size, and PSA density was done with chi2 test and Fischer's exact test (Table 2). The primary outcome—death from prostate cancer and the secondary outcome—death from all causes were analyzed with logistic regression and reported with odds ratios (ORs), unadjusted and adjusted for age and PSA. Due to the selection process for the cohort in question, the epidemiological integrity does not allow survival analysis or time to event analysis of the outcome. For descriptive purposes, however, data are also treated as if by time to event character, and Kaplan–Meier curves are displayed. Statistical calculations were made with either Stata 16 software, or SAS Statistical Analysis Software 14.1. Differences were considered statistically significant if $p < 0.05$.

3 | RESULTS

At the end of the follow-up period, 16% ($n = 53$) of the men were alive. Causes of death for the men in the cohort, the background cohort, and all men who died in 2018 (for reference) can be found in Supporting Information Data (Table 4). Background characteristics for both the studied cohort and for the background cohort are presented in Table 1.

One-third of all deaths in the cohort can be attributed to malignant diseases. Median concentration of TK1 was 0.25 ng/ml (interquartile range [IQR]: 0.19–0.35) for the whole cohort whereas

TABLE 1 Baseline characteristics of the study cohort ($n = 329$) and from the background cohort ($n = 1772$).

	Background cohort	Study cohort
Age, years	63.6 (54.5–71.5)	64.2 (54.6–71.5)
Total PSA, ng/ml	1.29 (0–103)	1.44 (0.1–71.5)
Free/total PSA, %	24 (1–61)	26 (4–81)
Prostate volume, cm ³	22 (18–133)	22 (18–113)
PSA density, ng/l/cm ³	0.06 (0–0.7)	0.07 (0.007–2.4)
sTK1, ng/ml		0.25 (0.04–2.58)
Follow up time, years	18.6 (0.05–30.8)	18.2 (0.3–30.7)

Note: Median values (range).

Abbreviations: PSA, prostate-specific antigen; sTK1, serum concentration of thymidine kinase. 1.

median TK1 for men who died of prostate cancer was 0.30 ng/ml (IQR: 0.21–0.41). The median follow-up time in the cohort studied was 17.9 years (range: 0.1–30.7 years). After the cohort was stratified into tertiles based on TK1 concentration at the start of the study, clinical background characteristics were checked. Small differences, if any, were found between TK1 strata regarding PSA, free PSA, the ratio free/total PSA, prostate size, PSA density, or age (Table 2).

Age-adjusted OR to die of prostate cancer in 30 years' time was 1.23 and 2.3, for TK1 tertiles two and three, respectively, as compared with tertile one (ref). The corresponding OR of dying from all causes was 1.26 and 2.74 for TK1 tertiles two and three (Table 3). The excess risk of dying from prostate cancer was statistically significant in the group with TK1 in the third tertile. Likewise, the risk of dying for any reason was statistically higher at TK1 in the third tertile.

When PSA is included in the model (besides age) for men in the highest TK1 tertile, the OR for prostate cancer-specific death was 1.84 (95% CI: 0.75–4.5) and the OR for death regardless of the cause was 2.65 (1.10–6.4).

When the prostate volume and other malignant causes of death were added to the model the estimates did not change.

Kaplan–Meier's analysis of data for descriptive purposes shows a reduced cancer-specific survival and an increased incidence of prostate cancer depending on whether the baseline value of TK1 was above or below the median (Figures 1 and 2).

When TK1 is analyzed as a continuous variable, each increase in TK1 by 0.1 ng/ml gives an age-adjusted OR = 1.32 (95% confidence interval [CI]: 1.04–1.68) for total mortality and OR = 1.03 for prostate cancer-specific mortality (95% CI: 0.89–1.19), also adjusted for age.

A total of 96 men were diagnosed with prostate cancer. Of these, 61 men were diagnosed during the follow-up period, the median time from sampling to diagnosis was 8.9 years (range: 1–27 years). The time between sampling and diagnosis is demonstrated in Figure 3.

TABLE 2 Baseline clinical evaluation stratified by TK1 tertiles: 0–0.20, 0.21–0.31, and ≥ 0.32 ng/ml.

	Tertile 1 (n = 118)	Tertile 2 (n = 109)	Tertile 3 (n = 103)	χ^2
Age, years, median, (range)	63 (55–70)	63 (55–72)	64 (55–71)	0.07
Total PSA, ng/ml, median, (range)	1.9 (0.3–35)	2.0 (0.3–27)	1.9 (0.4–73)	0.052
Free PSA, ng/ml, median, (range)	0.32 (0.1–2.6)	0.36 (0.02–5.36)	0.36 (0.07–4.57)	0.51
Free/total PSA, median, (range)	0.27 (0.04–0.71)	0.25 (0.05–0.65)	0.23 (0.04–0.81)	0.49
Ellipsoid volume, ml, median, (range)	22 (7.5–99)	21 (9.8–113)	24 (11–84)	0.29
PSA density, ng/ml/cm ³ , median, (range)	0.097 (0.0093–2.36)	0.11 (0.014–1.1)	0.098 (0.018–2.7)	0.4
Prostate cancer, n (%)	25 (21)	40 (37)	31 (30)	0.036

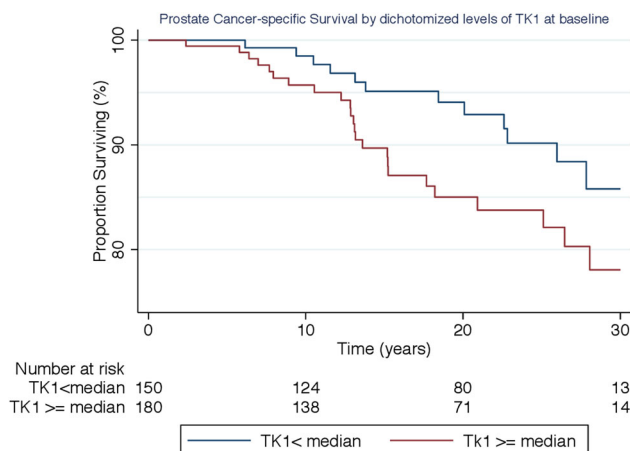
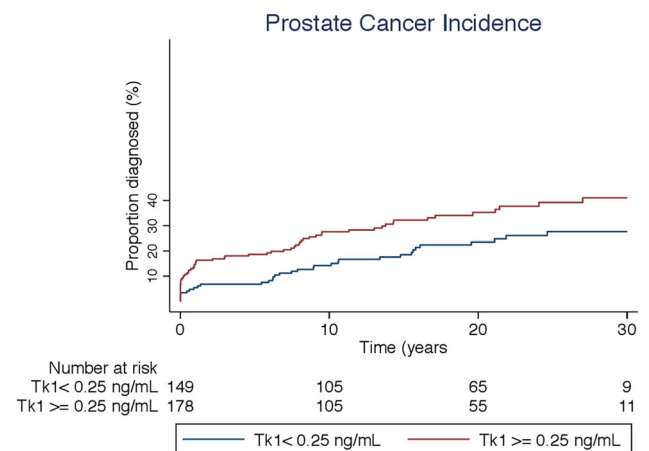
Abbreviations: PSA, prostate-specific antigen; TK1, thymidine kinase. 1

TABLE 3 ORs for prostate cancer-specific and overall mortality by TK1 tertiles.

	TK1 tertile 1 OR(95% CI)	TK1 tertile 2 OR(95% CI)	p	TK1 tertile 3 OR(95% CI)	p
Prostate cancer-specific mortality					
Crude	Ref	1.22 (0.48–3.1)	0.7	2.39 (1.02–5.63)	0.046
Adjusted for age	Ref	1.23 (0.48–3.15)	0.7	2.37 (1.01–5.59)	0.048
Adjusted for PSA	Ref	1.09 (0.42–2.86)	0.8	1.84 (0.75–4.53)	0.19
Adjusted for age and PSA	Ref	1.10 (0.42–2.86)	0.8	1.84 (0.75–4.52)	0.19
Overall mortality					
Crude	Ref	1.27 (0.66–2.47)	0.5	2.81 (1.24–6.34)	0.013
Adjusted for age	Ref	1.26 (0.60–2.61)	0.5	2.74 (1.14–6.54)	0.024
Adjusted for PSA	Ref	1.20 (0.62–2.35)	0.6	2.66 (1.17–6.02)	0.019
Adjusted for age and PSA	Ref	1.22 (0.58–2.54)	0.6	2.65 (1.10–6.35)	0.029

Note: 95% confidence interval. Crude and adjusted for age and PSA.

Abbreviations: OR, odds ratio; PSA, prostate-specific antigen; TK1, thymidine kinase. 1.

**FIGURE 1** Kaplan-Meier estimates of prostate cancer-specific survival by baseline level of thymidine kinase 1 [Color figure can be viewed at wileyonlinelibrary.com]**FIGURE 2** Kaplan-Meier estimates of prostate cancer incidence by baseline level of Thymidine kinase 1 [Color figure can be viewed at wileyonlinelibrary.com]

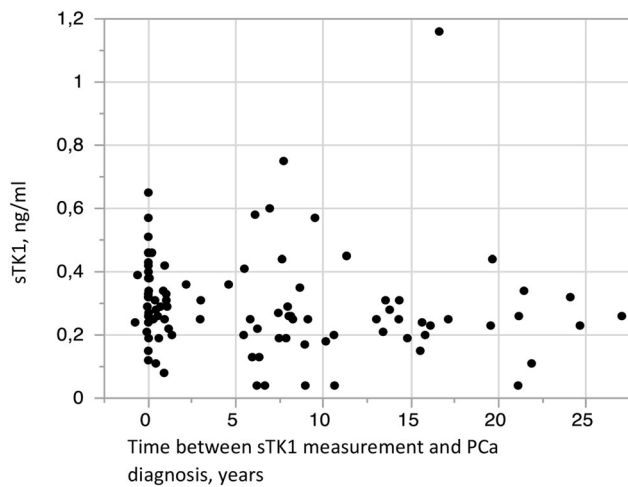


FIGURE 3 Scatterplot of baseline thymidine kinase 1 and time to diagnosis

4 | DISCUSSION

Due to Sweden's population-based registers, we have had the opportunity to follow patients without loss to follow up 30 years after the blood draw in a screening study. The clear association between long-term risk and the highest baseline values of TK1 can be explained by both properties of TK1 and properties of prostate cancer.

There are no other studies with 30 years of follow-up regarding death in prostate cancer related to the concentration of TK1 in the blood. On the other hand, studies with shorter follow-up and with other endpoints are consistent with the results we obtained. Lewenhaupt and colleagues compared a panel of biomarkers on a cohort of newly diagnosed men and were able to show that TK predicted death in prostate cancer in the short-term setting, that is, within 3 years of sampling, better than, for example, PSA.^{7,18} In a poster, Murtola and coworkers report data from a cohort of 83 Finnish men, of whom 43 with newly diagnosed metastatic disease and 40 with T1/2NxM0 disease. The group with metastases had a statistically significantly higher TK1 value and in survival analysis, TK1 was a statistically significant predictor of death, cancer specific and general, adjusted hazard ratio (HR) for prostate cancer-specific death 8.33 (95% CI: 2.05–33.88) and death from all causes 5.53 (95% CI: 1.93–15.85).⁸ That TK1 concentration predicts death in prostate cancer 30 years after sampling can logically be due to malignant growth in the prostate gland long before diagnosis is made or possibly inflammatory processes in or outside the gland that are related to future tumor growth. For example, a nested case-control study by Rybicki and coworkers showed that white men with clinical prostatitis were 40% more likely to get prostate cancer.¹⁹ The median age at diagnosis in Sweden at the time was 74 years and is today 69 years. The disease has a long lead time, that is, the time from when cancer can be detected until it is diagnosed is long and was probably even longer in 1988 and 1989 when this screening study was performed.

In addition to death from prostate cancer, our study predicted that a high TK1 value, predicts the death of any cause. We have not been able

to find any specific causes of death other than prostate cancer, though. The growth of malignant cells, as well as inflammatory conditions, implies an increased cell division, which in turn can be reflected as an increased concentration of TK1 in the blood. Large screening studies with 8000 and 11,000 healthy participants, respectively, have been conducted in China, where TK1 concentration/TK1 protein levels in the blood were measured. At the time of screening, certain undiagnosed tumor diseases are captured and there are also indications that TK1 predicts not yet clinically detectable malignant diseases.^{20,21}

In our material, follow up without a loss was possible by linking register data with information about exposure. We adjusted for age and had could analyze TK1 in relation to the concentration of PSA. We do not know how large the misclassification of outcomes (prostate cancer-specific mortality) is in our material, but we do know that the magnitude of it is unaffected by the observed concentrations of TK1. Nondifferential misclassification works for a dilution of the difference in outcome between the groups predicted by the TK1 concentration. Built into this type of study are challenges in understanding the generalizability of the magnitude of the effects we documented. The intensity and technology of screening for prostate cancer are different today than it was 30 years ago, and there may be effect-modifying factors for which we do not have data. The Kaplan–Meier estimates we reported have false high estimates because we have a nested case-control study. We report them because, unlike the correct estimates with odds ratio, they give a sense of the development over time. Another possible source of error is the degradation of TK1 in samples stored for thirty years. This source of error is small if any; a study based on 264 seemingly healthy individuals found that the median concentration of TK1 was 0.24 ng/ml²² compared to 0.25 ng/ml in this material.

In addition, the obvious limitations of this study are the small sample size and the lack of additional clinical data, for example, family history, smoking, body mass index [BMI], and so forth.

Our data are consistent with the fact that TK1 can be a valuable biomarker that can aid in decision-making. A predictive long-term marker (30 years) can be valuable in a neoplasm where the clinical course usually is lengthy. A possible area of use is the evaluation of the probability of metastatic disease at the time of biochemical recurrence. Given the documented effects of androgen-receptor signaling inhibitors, taxanes, radionuclides, and immunotherapy in metastatic prostate cancer, the number of possible treatment strategies for both hormone-sensitive and castration-resistant disease has increased dramatically. In light of our and others' data, it cannot be ruled out that TK1 can assist in decisions about, when and in what order the new therapies may be introduced.

5 | CONCLUSIONS

At follow-up after 30 years, OR to die in prostate cancer was significantly higher for men with a baseline TK1 in the highest tertile. In combination with previously reported associations between TK1 and prostate cancer, we conclude that TK1 remains an interesting prognostic biomarker.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Per-Olof Lundgren  <http://orcid.org/0000-0001-7976-6962>

Bernhard Tribukait  <http://orcid.org/0000-0002-2151-3097>

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SUPPORTING INFORMATION

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

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