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Prostate Cancer

Association Between Lead Time and Prostate Cancer Grade: Evidence of Grade Progression from Long-term Follow-up of Large Population-based Cohorts Not Subject to Prostate-specific Antigen Screening

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Abstract

Background: Lead time (LT) is of key importance in early detection of cancer, but cannot be directly measured. We have previously provided LT estimates for prostate cancer (PCa) using archived blood samples from cohorts followed for many years without screening.
Objective: To determine the association between LT and PCa grade at diagnosis to provide an insight into whether grade progresses or is stable over time.
Design, setting, and participants: The setting was three long-term epidemiologic studies in Sweden including men not subject to prostate-specific antigen (PSA) screening. The cohort included 1041 men with PSA of 3–10 ng/ml at blood draw and subsequently diagnosed with PCa with grade data available.
Outcome measurements and statistical analysis: Multivariable logistic regression was used to predict high-grade (Gleason grade group $\geq$2 or World Health Organization grade 3) versus low-grade PCa at diagnosis in terms of LT, defined as the time between the date of elevated PSA and the date of PCa diagnosis with adjustment for cohort and age.
Results and limitations: The probability that PCa would be high grade at diagnosis increased with LT. Among all men combined, the risk of high-grade disease increased with LT (odds ratio 1.13, 95% confidence interval [CI] 1.10–1.16; $p < 0.0001$), with no evidence of differences in effect by age group or cohort. Higher PSA predicted shorter LT by 0.46 yr (95% CI 0.28–0.64; $p < 0.0001$) per 1 ng/ml increase in PSA. However, there was no interaction between PSA and grade, suggesting that the longer LT for high-grade tumors is not simply related to age. Limitations include the assumption that men with elevated PSA and subsequently diagnosed with PCa would have had biopsy-detectable PCa at the time of PSA elevation.

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Conclusions: Our data support grade progression, whereby following a prostate over time would reveal transitions from benign to low-grade and then high-grade PCa.
Patient summary: Men with a longer lead time between elevated prostate-specific antigen and subsequent prostate cancer diagnosis were more likely to have high-grade cancers at diagnosis.

1. Introduction

Lead time is defined as the time between screen detection and clinical detection of a cancer, and remains a key concept for early detection of cancer. If lead time is short, it is difficult to ensure that men are screened in the short window between when a cancer is first amenable to screen detection and when it is detected clinically. Conversely, long lead times tend to lead to overdiagnosis. Despite its critical importance, lead time is not directly observable for an individual man, as this would require unethical withholding of a cancer diagnosis from a patient.

Various approaches for estimating lead time have been reported. Microsimulation models, which are calibrated against population trends and the results of large trials, can provide model-based estimates of lead time [1]. A second approach is to compare the time to a given incidence of prostate cancer between control and intervention arms of a randomized trial [2,3]. Our group has pioneered a novel approach based on measurement of prostate-specific antigen (PSA) in cryopreserved anticoagulated blood plasma samples from longitudinal epidemiological studies of large, population-based cohorts not subject to PSA screening [4]. We hypothesize that a man with elevated PSA at baseline and subsequently clinically diagnosed with prostate cancer would have had screen-detectable cancer at study entry. The time between blood draw and diagnosis is thus an estimate of lead time. Using this approach, we reported that the mean lead time is probably longer than had previously been assumed and that the distribution of lead times is normal, rather than exponential, as had often been assumed [5].

One key question in prostate cancer is whether the development of high-grade cancer is an early or late event in the disease process. One hypothesis is that prostate cancer is either low-grade or high-grade at initiation and that grade remains relatively stable over time. The alternative hypothesis is that grade progresses from low to high over time as mutations accumulate in a cancerous prostate. In this study, we explored the relationship between lead time and grade to evaluate these two competing hypotheses. If cancer grade at diagnosis is inversely associated with lead time, this would suggest that grade progression is an early event on the grounds that high-grade cancer is more aggressive and is likely to be diagnosed sooner than low-grade disease. Alternatively, if a longer lead time is associated with a higher risk of high-grade disease, this would suggest that grade changes over time. Our aim was to investigate the association between lead time (from detection of elevated PSA in blood and subsequent clinical diagnosis) and prostate cancer grade.

2. Patients and methods

We used data from the Malmö Preventive Project (MPP) [6], the Malmö Diet and Cancer study (MDC) [7], and the Västerbotten Intervention Project (VIP) [8] in Sweden. In brief, the cohorts are from long-term, epidemiological population-based projects including a representative sample of healthy men aged 33–74 yr who provided cryopreserved anticoagulated blood plasma samples at baseline. There was very low rate of opportunistic PSA testing for prostate cancer during study entry and many years of study follow-up, so the large majority of the diagnoses were the result of clinical work-up. Outcomes were ascertained from a cancer registry that is known to be highly accurate [9]. Blood samples were retrieved for cases and matched controls, and PSA was measured using techniques that provide estimates that have been shown to be equivalent to contemporaneous PSA measurement [10].

Figures 1 and 2 show flow diagrams for study inclusions. Of the 26 656 participants in the MDC and MPP cohorts, 3005 men were diagnosed with prostate cancer. After excluding autopsy cancer and men with missing PSA or grade, 1946 Malmö participants were eligible for analysis, of whom 382 (20%) had high-grade cancer according to the World Health Organization (WHO) classification. Of 40 379 participants in the VIP study, 1218 men were diagnosed with cancer, with 1159 eligible for analysis based on a known biopsy grade and PSA measured in blood obtained at baseline.

Our aim was to describe empirically the distribution of the estimated time by which a PSA screen would theoretically advance the date of diagnosis—that is, the lead time—by age, PSA, and grade at subsequent prostate cancer diagnosis. High grade was defined as Gleason grade group (ng/ml) 2 or higher or WHO grade 3. We assumed that those with elevated PSA who were later clinically diagnosed with prostate cancer already had screen-detectable prostate cancer at the time of blood sampling. For our main analysis, we defined elevated PSA as $\geq$3.0 ng/ml. Given that few men undergoing regular screening present with PSA $>$10 ng/ml, we only included men with PSA of 3.0–10 ng/ml.

We plotted the risk of high-grade cancer at diagnosis against the time from baseline collection of blood to diagnosis for various age and PSA level combinations. Some participants provided blood samples at multiple ages. In this case, the earliest PSA measurement available for each age group was used. We tested the association between lead time and the risk of a high-grade cancer diagnosis among those diagnosed with cancer using univariable logistic regression for each age and study cohort separately

As a sensitivity analysis, we changed the cutoff point for elevated PSA from 3.0 ng/ml to PSA values $\geq$2–4 ng/ml. We also repeated our analyses changing the definition of high-grade cancer to $\geq$3 ng/ml. Lastly, to account for the fact that high-grade cancers have a greater propensity for metastasis, that metastasis almost inevitably leads to clinical detection, and that metastasis is a late event—something that may lead to an apparently longer lead time for high-grade cancers—we repeated all the analyses, excluding patients with metastasis at diagnosis. All analyses were performed using Stata version 13.0 (StataCorp, College Station, TX, USA).

3. Results

Table 1 lists details for the study cohorts. Of the 1945 Malmö participants subsequently diagnosed with prostate cancer, 838 (43%) had high-grade cancer at diagnosis. For the VIP

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