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Screening for Prostate Cancer Starting at Age 50–54 Years. A Population-based Cohort Study

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Abstract

Background: Current prostate cancer screening guidelines conflict with respect to the age at which to initiate screening.
Objective: To evaluate the effect of prostate-specific antigen (PSA) screening versus zero screening, starting at age 50–54 yr, on prostate cancer mortality.
Design, setting, and participants: This is a population-based cohort study comparing 3479 men aged 50 yr through 54 yr randomized to PSA-screening in the Göteborg population-based prostate cancer screening trial, initiated in 1995, versus 4060 unscreened men aged 51–55 yr providing cryopreserved blood in the population-based Malmö Preventive Project in the pre-PSA era, during 1982–1985.
Outcome measurements and statistical analysis: Cumulative incidence and incidence rate ratios of prostate cancer diagnosis, metastasis, and prostate cancer death.
Results and limitations: At 17 yr, regular PSA-screening in Göteborg of men in their early 50s carried a more than two-fold higher risk of prostate cancer diagnosis compared with the unscreened men in Malmö (incidence rate ratio [IRR] 2.56, 95% confidence interval [CI] 2.18, 3.02), but resulted in a substantial decrease in the risk of metastases (IRR 0.43, 95% CI 0.22, 0.79) and prostate cancer death (IRR 0.29, 95% CI 0.11, 0.67). There were 57 fewer prostate cancer deaths per 10 000 men (95% CI 22, 92) in the screened group. At 17 yr, the number needed to invite to PSA-screening and the number needed to diagnose to prevent one prostate cancer death was 176 and 16, respectively. The study is limited by lack of treatment information and the comparison of the two different birth cohorts.
Conclusions: PSA screening for prostate cancer can decrease prostate cancer mortality among men aged 50–54 yr, with the number needed to invite and number needed to detect to prevent one prostate cancer death comparable to those previously reported from the European Randomized Study of Screening for Prostate Cancer for men aged 55–69 yr, at a similar follow-up. Guideline groups could consider whether guidelines for PSA screening should recommend starting no later than at ages 50–54 yr.
Patient summary: Guideline recommendations about the age to start prostate-specific antigen screening could be discussed.
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1. Introduction

Guidelines conflict regarding the age to start prostate-specific antigen (PSA) screening [1–6]. The European Association of Urology recommends obtaining a baseline PSA at age 40–45 yr [2], whereas the American Urological Association recommends starting at age 55 yr for most men [3].

There is little evidence on the effects of screening men in their early 50s. The Swedish Göteborg randomized population-based prostate cancer screening trial [7] is unique starting at ages 50–64 yr and provides a critically important opportunity to determine the impact of starting screening at ages 50–55 yr on prostate cancer incidence and mortality. While the rate of PSA-testing was low when the trial was initiated [7], a substantial proportion of men in the control arm of the trial has likely been exposed to PSA-testing during recent years [8,9]. Such contamination may dilute the relative difference in prostate cancer incidence and mortality in the conventional intention-to-screen analysis, comparing the randomized arms.

Therefore, an ideal comparison group would be an age-matched pre-PSA era cohort of men with similar background risk and similar follow-up time as the screening group. The Swedish Malmö Preventive Medicine Project is one such cohort, in which men gave blood in the early 80s as part of a cardiovascular risk factor study [10,11]. Because the PSA test was not widely disseminated until the mid-to-late 1990s in Sweden [12], this cohort has been followed without much PSA screening at all, as widely accepted and described in previous reports [10,11,13].

Our goal was to evaluate the effect of regular PSA screening starting before age 55 yr, on prostate cancer incidence, metastasis, and prostate cancer mortality, compared with an unscreened population. We hypothesized that starting screening at age 50 yr would be associated with a larger relative risk reduction than screening starting at 55–69 yr, on the grounds that, for at least some men, cancer would progress from curable to incurable after the age of 50 yr. We also hypothesized that the absolute risk reduction would be lower, because the risk of lethal prostate cancer is lower among younger than older men, given similar follow-ups.

2. Methods

2.1. Participants, measurements, and outcomes

The study populations, measurements, and outcome ascertainment have been described in detail elsewhere [7,10,11,13–16]. The Göteborg trial (International Standard Randomized Controlled Trial Number 54449243) randomized 20 000 men to biennial PSA screening or to a control group (1:1 ratio) in 1995. Men with a PSA level above the cut-off (initially 3.0 ng/ml and 2.5 ng/ml since 2005) were recommended further urological work-up including prostate biopsy. The upper age limit for screening was 70 yr [7]. In the present study, men in the screened cohort in Göteborg consisted of 3479 men randomized to screening aged 50 yr through 54 yr at their first PSA-invitation date in 1995–1997 and men in the unscreened cohort in Malmö consisted of 4060 men who provided blood samples at age 51–55 yr in 1982–1985.

2.2. Statistics

Our primary aim was to compare the number of cancers diagnosed, documented distant metastases, and prostate cancer deaths between the screened and unscreened participants. We calculated cumulative incidence for the outcomes of prostate cancer, prostate cancer metastases, overall mortality, and prostate cancer death based on 17 yr of follow-up from the time of blood draw. For Göteborg men randomized to screening who never had a PSA test, we used the median date of the blood draw among those attending. Of patients who were not diagnosed with prostate cancer, 81% in Malmö and 62% in Göteborg had 17 yr of follow-up. At 13 yr, the corresponding proportions were 85% and 88%, respectively.

Incidence rate ratios and incidence rate differences for the effect of screening on prostate cancer diagnosis, metastasis, and death were calculated based on 17 yr of follow-up. The primary analysis was made on the basis of the intention-to-screen principle. Thus, our approach was biased towards the null, because we compared everyone in Göteborg (whether they attended or not) with only attendees in Malmö. Screening attendees tend to be healthier and more health conscious than the average population invited (“healthy worker bias” or “healthy screenee bias”) [17]. Secondary analyses were performed restricted to attendees only in Göteborg, that is, men randomized to screening who participated and had a PSA test at least once.

Several hypotheses can explain any observed difference in prostate cancer mortality between the two noncontemporaneous cohorts. The first is if more men die of other causes in one cohort, their risk of dying from prostate cancer would be lower. Overall mortality is close to death from other causes and so we calculated the incidence rate difference of overall mortality between Göteborg and Malmö. A second hypothesis would be improvements in treatment over time. If, for instance, an effective drug for prostate cancer was developed between the end of the Malmö cohort and the beginning of the Göteborg cohort, this would lead to a survival advantage for the latter. To assess whether differences in treatment would affect our findings, we investigated the age-standardized prostate cancer mortality in Sweden over the time frame of both cohorts [18]. If prostate cancer mortality rates remained constant, then there would be no evidence that any mortality differences between these two cohorts were related to differences in treatment. The third hypothesis would be that differences in prostate cancer mortality between cohorts were related to an effect of PSA screening.

To quantify the benefits of regular PSA screening, we calculated the number of men needed to invite to screening (NNI) and the number of men needed to be diagnosed (NND) to prevent one man from dying from prostate cancer. We calculated the NNI to screening as the inverse of the absolute risk reduction between the screened and unscreened groups based on 17 yr of follow-up. We calculated the NND as the inverse absolute risk reduction multiplied by the excess incidence of prostate cancer diagnosis in the screened group based on 17 yr of follow-up. As a sensitivity analysis, we calculated cumulative incidences adjusted for the competing risk of death from other causes.

We believe that prostate cancer metastasis were followed more closely in Göteborg, since these patients were attendees of a screening trial in regular contact with the urology clinic and had access to tests such as bone scintigraphy. We therefore performed a sensitivity analysis where we defined Malmö participants without previous documented evidence of distant metastasis but who died of prostate cancer between 17 yr and 19 yr of follow-up as developing distant metastasis at 17 yr of follow-up. All analyses were performed using Stata, version 12.0 (StataCorp, College Station, TX, USA).

3. Results

Over 17-yr follow-up, 463 men were diagnosed out of 3479 men in Göteborg (15.0% cumulative incidence)

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