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Prostate-specific Antigen–Based Prostate Cancer Screening: Reduction of Prostate Cancer Mortality After Correction for Nonattendance and Contamination in the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer

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Abstract

Background: Large randomized screening trials provide an estimation of the effect of screening at a population-based level. The effect of screening for individuals, however, is diluted by nonattendance and contamination in the trial arms.
Objective: To determine the prostate cancer (PCa) mortality reduction from screening after adjustment for nonattendance and contamination.
Design, setting, and participants: A total of 34 833 men in the core age group, 55–69 yr, were randomized to a screening or control arm in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Prostate-specific antigen (PSA) testing was offered to all men in the screening arm at 4-yr intervals. A prostate biopsy was offered to men with an elevated PSA. The primary end point was PCa-specific mortality.
Outcome measurements and statistical analysis: *Nonattendance* was defined as non-participation in the screening arm. *Contamination* in the control arm was defined as receiving asymptomatic PSA testing or a prostate biopsy in the absence of symptoms. Relative risks (RRs) were calculated with an intention to screen (ITS) analysis and after correction for nonattendance and contamination using a method that preserves the benefits obtained by randomization.
Results and limitations: The ITS analysis resulted in an RR of 0.68 (95% confidence interval [CI], 0.53–0.89) in favor of screening at a median follow-up of 13 yr. Correction for both nonattendance and contamination resulted in an RR of 0.49 (95% CI, 0.27–0.87) in favor of screening.
Conclusions: PCa screening as conducted in the Rotterdam section of the ERSPC can reduce the risk of dying from PCa up to 51% for an individual man choosing to be screened repeatedly compared with a man who was not screened. This benefit of screening should be balanced against the harms of overdiagnosis and subsequent overtreatment.
Trial registration: ISRCTN49127736.

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1. Introduction

The 13-yr follow-up results of the Dutch center of the European Randomized Study of Screening for Prostate Cancer (ERSPC) were published recently, showing a prostate cancer (PCa)–specific mortality reduction of 32% in favor of screening with prostate-specific antigen (PSA) [1]. Although the conventional intention to screen (ITS) analysis provides the best estimation of the PCa-specific mortality reduction on a population-based level, the potential effect of screening for an individual choosing to be screened needs to be corrected for nonattendance in the intervention arm and contamination (eg, PSA testing/prostate biopsy) in the control arm. This adjustment, however, should not influence the benefits obtained by randomization (ie, the same baseline risk of PCa mortality in both arms). A simple comparison of men who actually receive screening (attenders) and men who do not (nonattenders) could be biased, since the baseline risk of having PCa for attenders and nonattenders may be different. To correct for nonattendance and contamination without creating a difference in baseline risk in the two compared groups, a method developed by Cuzick et al. [2] was used. This method was previously applied to correct for nonattendance and contamination at the 9-yr follow-up results of the whole ERSPC [3].

The aim of this paper is to determine the PCa-specific mortality reduction from PSA-based PCa screening, adjusted for nonattendance and contamination, in the Rotterdam sections of the ERSPC, with a median follow-up of 13 yr, as well as to give detailed data on PSA and biopsy use in the control arm. Results will provide a more accurate estimation of PCa-specific mortality reduction for those men who choose to be screened compared with an ITS analysis.

2. Materials and methods

The study population and protocol have been described in detail [4,5]. In summary, in the Rotterdam section of the ERSPC, 17 443 men were randomized to the screening arm and 17 390 to the control arm in the core age group of 55–69 yr (at time of randomization). Randomization for this study started in 1993. Men in the Rotterdam section of the ERSPC were randomized after providing written informed consent. In the screening arm, men were offered PSA testing at 4-yr intervals until the age of 75 yr. Initially, a prostate biopsy was offered to men with a PSA level $\geq$4.0 ng/ml and/or an abnormal digital rectal examination (DRE). From May 1997 onward, a PSA level $\geq$3.0 ng/ml was the only indication for sextant prostate biopsy. The primary end point of the ERSPC is PCa-specific mortality.

Data on PCa for all men diagnosed outside the screening protocol (in both the screening arm and the control arm) were collected through linkage with the national cancer registry and subsequent patient chart review of all men with PCa. Cause of death for all men with PCa was assessed by an independent monitoring committee according to a predefined algorithm and blinded for the study arm [6].

Follow-up for the current analysis ended December 31, 2010. The study was approved by the medical ethical committee.

2.1. Nonattendance in the screening arm

In the screening arm, two groups were defined: nonattenders, men refusing PSA testing at the first screening round (men refusing participation were no longer invited for subsequent screening rounds), and attenders, men attending at least the first screening round.

2.2. Contamination in the control arm

Two definitions were used for *contamination* in the control arm. First, *contamination* in the control arm was defined as having at least one PSA test in the absence of symptoms (opportunistic screening). Through linkage of the ERSPC Rotterdam database to the central laboratory of the Rotterdam region in the Netherlands, PSA testing of men in the control arm could be retrieved. The central laboratory covered 77.7% of all Dutch participants [7,8]. Data were therefore extrapolated to the entire cohort. An analysis based on self-reported PSA testing of men in the screening arm showed that the 23.3% of general practitioners (GPs) not covered by the laboratory were not biased for demanding PSA tests (data not shown). To determine which men received PSA testing for clinical reasons (symptomatic testing) and which men received PSA testing for screening purposes (true contamination), a survey was conducted among GPs of a random sample of men without PCa. The reason for referral to the urologist for all men with PSA testing and PCa was known through medical records. These data could then be used to determine the true contamination rate for all Dutch participants in the control arm.

Because a screening test can be seen as such only if an abnormal test leads to an additional test to confirm the diagnosis (in the case of PCa screening, a prostate biopsy), the second definition of *contamination* was having a prostate biopsy at least once in the absence of symptoms (and thus only because of an elevated PSA test). Through linkage with the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA [Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief]), data on prostate biopsy of men in the control arm could be retrieved [8,9]. The PALGA database covers all pathology reports in the Netherlands since 1991, and correct linkage is achieved in up to 98% of cases [10]. *True contamination* was then defined in the same way as with PSA testing, using reason for referral to the urologist for all men with PCa and the reason to be tested by the GP for all men without PCa.

Data on both PSA testing and prostate biopsy were available until the end of follow-up. *Contamination*, however, was defined as a PSA test or biopsy >2 yr before the end of follow-up (before the end of 2008).

2.3. Statistical analysis

The effect of screening on the PCa-specific mortality for the ITS analysis and adjusted analysis was calculated as relative risk (RR). For the adjustment of nonattendance and contamination, the method of Cuzick et al. [2] was applied (Fig. 1). Three methods for adjustment have been described: a binary analysis; a Poisson analysis, taking into account time to PCa death, nonattendance, and contamination; and a semiparametric Cox proportional hazards analysis, assuming nonattendance and contamination occurred at randomization. In this paper, the binary analysis was used because all models gave very similar results, as described by Kerkhof et al. [11].

Although the ERSPC Section Rotterdam was not designed as a stand-alone trial, a separate power calculation was done, as described previously [1].

3. Results

The total number of men in the core age group was 34 833. At a median follow-up of 13.0 yr, 2226 men were diagnosed with PCa in the screening arm (cumulative incidence: 12.8%), and 96 men died of their disease. In the control arm, 1152 men were diagnosed with PCa (cumulative incidence: 6.6%), and 140 died of their disease at a median follow-up of