Cancer Epidemiology 45 (2016) 1–5

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

# Estimating bias in causes of death ascertainment in the Finnish Randomized Study of Screening for Prostate Cancer

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ARTICLE INFO

*Article history:*
Received 24 May 2016
Received in revised form 23 August 2016
Accepted 30 August 2016
Available online 14 September 2016

*Keywords:*
Mass screening
Prostatic neoplasms
Prostate-specific antigen
Randomized controlled trials
Mortality
Cause of death

ABSTRACT

*Background:* Precise cause of death (CoD) ascertainment is crucial in any cancer screening trial to avoid bias from misclassification due to excessive recording of diagnosed cancer as a CoD in death certificates instead of non-cancer disease that actually caused death. We estimated whether there was bias in CoD determination between screening (SA) and control arms (CA) in a population-based prostate cancer (PCa) screening trial.

*Methods:* Our trial is the largest component of the European Randomized Study of Screening for Prostate Cancer with more than 80,000 men. Randomly selected deaths in men with PCa (N = 442/2568 cases, 17.2%) were reviewed by an independent CoD committee. Median follow-up was 16.8 years in both arms.

*Results:* Overdiagnosis of PCa was present in the SA as the risk ratio for PCa incidence was 1.19 (95% confidence interval (CI) 1.14–1.24). The hazard ratio (HR) for PCa mortality was 0.94 (95%CI 0.82–1.08) in favor of the SA. Agreement with official CoD registry was 94.6% ($\kappa = 0.88$) in the SA and 95.4% ($\kappa = 0.91$) in the CA. Altogether 14 PCa deaths were estimated as false-positive in both arms and exclusion of these resulted in HR 0.92 (95% CI 0.80–1.06).

*Conclusions:* A small differential misclassification bias in ascertainment of CoD was present, most likely due to attribution bias (overdiagnosis in the SA). Maximum precision in CoD ascertainment can only be achieved with independent review of all deaths in the diseased population. However, this is cumbersome and expensive and may provide little benefit compared to random sampling.



## 1. Introduction

Population-based prostate cancer (PCa) screening remains controversial despite evidence for mortality reduction by the European Randomized Study of Screening for Prostate Cancer (ERSPC) [1]. The problem with overdiagnosis of low-risk PCas and subsequent overtreatment as well as issues of cost-effectiveness and quality of life remain to be fully evaluated [2–5].

The Finnish Randomized Study of Screening for Prostate Cancer is the largest component of the multinational ERSPC trial with over 80, 000 men. The population-based Finnish trial showed a non-significant 15% relative reduction in PCa mortality at 12 years of follow-up (HR 0.85; 95% confidence interval (CI) 0.69–1.04) [6]. In a subsequent analysis, non-participation in the screening arm (SA) was shown to have a major impact on PCa mortality in the Finnish trial, as correcting for non-participation improved the result into HR 0.78 (95% CI 0.64–0.96) [7]. A substantial diluting effect may also be caused by screening contamination (i.e. unorganized

*Abbreviations:* CoD, cause of death; SA, screening arm; CA, control arm; PCa, prostate cancer; CI, confidence interval; HR, hazard ratio; ERSPC, European Randomized Study of Screening for Prostate Cancer; PLCO, prostate, lung, colorectal and ovarian cancer screening trial; PSA, prostate-specific antigen.

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http://dx.doi.org/10.1016/j.canep.2016.08.022
1877-7821/

prostate-specific antigen (PSA) testing) in the control arm (CA), which remains to be addressed in detail.

A cornerstone in any mortality study is accuracy of data on causes of death (CoD), and therefore it is customary to establish an independent CoD review committee to validate these data. Such review committees have been used both in the ERSPC trial [8] and Prostate, Lung, Colorectal and Ovarian (PLCO) trial [9]. The Finnish trial also used a CoD committee that systematically reviewed all deaths in patients with diagnosed PCa in 1996–2003, blinded in terms of death certificate and trial arm. The agreement between official causes of death and the committee was shown to be excellent (97.7%; $\kappa = 0.95$) [10] suggesting reliability of official CoD statistics in Finland and therefore systematic review was discontinued. Official CoD data have since been used in mortality estimates, because reviewing individually all deaths in men with PCa would be far too laborious, given little improvement over registered CoD.

The purpose of this study was to analyze whether there was bias present in CoD ascertainment by trial arm, i.e. differential misclassification that could affect the mortality results. A secondary purpose was to reassess the level of agreement between official CoD registry and the random cases reviewed by the CoD committee.

## 2. Materials & methods

The Finnish Randomized Study of Screening for Prostate Cancer is the largest single center of the European Randomized Study of Screening for Prostate Cancer, with altogether 31 868 (39.8%) men in the screening arm and 48 299 (60.2%) men in the control arm. The ERSPC trial is registered (http://registered-trials.com, number ISRCTN49127736). The trial protocol has been published in detail previously [6]. To summarize, the men born in 1929–1944 (aged 55–67 years at entry) were identified from the population registry. A random sample of 8 000 men was annually allocated to the SA and the rest of the men in each age group formed the CA. The men in the CA were not contacted.

The men in the SA were invited to a local clinic for determination of serum PSA. Men with a PSA $\geq$4.0 ng/ml were referred to a urological clinic for diagnostic examinations including digital rectal examination, transrectal ultrasound and prostate biopsy. Men with PSA of 3.0–3.99 ng/ml were referred to an additional test, which in 1996–1998 was digital rectal examination and since 1999 determination of the free/total PSA ratio with a cut-off of 16%. Men with an abnormal additional test were referred for diagnostic examinations, similar to those with PSA $\geq$4.0 ng/ml.

The men were re-invited to the screening test four and eight years after the first screen. Information on PCas detected outside the screening protocol and in the CA were obtained from the Finnish Cancer Registry, which has a nearly complete coverage (99%) of solid cancers diagnosed in Finland [11].

The follow-up ended at death, emigration from Finland or common closing date, which in this study was December 31st, 2014. All deaths in Finland are registered by Statistics Finland, and the current 10th revision of the International Classification of Diseases (ICD-10) has been used since 1996.

To validate the quality of official CoD registry, in 1996–2003 all deaths in men with PCa diagnosis (regardless of the trial arm) were evaluated by a CoD committee with three members (specialists in the fields of urology, forensic pathology and internal medicine). The members had access to patient records, imaging studies and medical charts from both hospital records and outpatient clinics. The members evaluated the reports independently and were blinded from the official death certificate information, patient identity, trial arm and method of cancer detection. In cases of disagreement between individual reviewers, a consensus was sought in joint meetings of the committee.

A flowchart was utilized to estimate the role of underlying PCa in causing death [8]. The World Health Organization defines the underlying CoD as the disease or external injury that initiated the process that led to death. Treatment complications due to management of PCa were classified as PCa deaths according to the World Health Organization definition. Altogether 179 cases of 442 underwent autopsy.

PCa mortality and all-cause mortality were estimated using the Cox proportional hazards regression and Schoenfeld residuals were used to verify the proportionality assumption. PCa incidence between trial arms was estimated using Poisson regression with person-years (the proportionality assumption was violated with Cox regression in regard to PCa incidence).

The CoD committee was considered the gold standard. Sensitivity for identifying a PCa death was estimated as the proportion of correctly identified PCa deaths (concordance of official causes with the committee assessment) divided by all PCa deaths (according to the CoD committee). Specificity was calculated as true negatives (non-PCa deaths estimated by official registry) divided by all those that were non-PCa deaths (based on the CoD committee review). Positive predictive value was estimated as the probability that a case labeled as PCa death by the official registry was indeed correct and negative predictive value as the probability that a non-PCa death classified by the official registry was correct (Table 1). Agreement was estimated by Cohen's $\kappa$ statistic [12]. The correcting factor was calculated in both trial arms separately. The correcting factor was estimated by dividing the number of actual PCa deaths identified by the CoD committee by the number of PCa deaths identified by official CoD registry (Table 1). The number of PCa deaths in the SA and CA were multiplied by this correcting factor to estimate the amount of true number of PCa deaths in each arm.

Stata 10 (StataCorp, CollegeStation, TX, USA) was used for all analyses. 95% confidence intervals were used and all statistical tests were two-sided.

The study protocol was approved by Helsinki and Tampere University Hospital Ethics committees. Permission to use cancer registry data was obtained from Research and Development Centre for Welfare and Health (STAKES, currently National Institute for Health and Welfare).

## 3. Results

There were altogether 31 868 men in the SA and 48 299 men in the CA (Fig. 1). The median follow-up time was 16.8 years in both arms. A total of 3 587 PCas were diagnosed in the SA (cumulative incidence 11.3%) and 4 684 (9.7%) in the CA (RR 1.19 with 95% CI 1.14–1.24; $p < 0.0001$).

At the end of follow-up, 319 (1.0%) men had died of PCa in the SA and 517 (1.1%) in the CA (PCa mortality HR 0.94 with 95% CI 0.82–1.08, $p = 0.375$). Altogether 10 605 (33.3%) men had died of other causes in the SA and 15 989 (33.1%) in the CA (all-cause mortality HR 1.01 with 95% CI 0.98–1.03; $p = 0.615$).

In the SA, there were 1 115 (3.5%) men who were diagnosed with PCa and died of any cause during the follow-up and in the CA altogether 1 453 (3.0%) such men. Of these deaths, the CoD committee evaluated 205 (in the SA) and 237 (in the CA) (Table 1).

Overall, the agreement between the CoD committee and official death certificates was 95.0%. Based on the cases reviewed by the CoD committee, there were altogether 7 non-PCa deaths that were mislabeled by the official records as PCa deaths in the SA (7/68 = 10.3%) and conversely 4 incorrectly classified non-PCa deaths (4/137 = 2.9%) that turned out to be PCa deaths (Table 1). Therefore, it is estimated that with a correcting factor of 65/68 there should be