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Estimating the sensitivity of a prostate cancer screening programme for different PSA cut-off levels: A UK case study

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ABSTRACT

Introduction: Policy decisions about prostate cancer screening require data on the natural history of histological cancers and the resulting impact of screening. However, the gold standard procedure required to identify true positive histological cancer is a full autopsy of the gland which is not possible in screening studies, leading to verification bias. We aim to estimate the sensitivity of a prostate cancer screening round (PSA result to diagnosis) relative to histological cancer.

Methods: We developed a framework combining data on UK screened and non-screened prostate cancer populations originating from a single round of population-based PSA testing among UK men aged 50–69 years, prostate cancer incidence data, and needle biopsy data from the published literature.

Results: Sensitivity of a screening round was highest at age 65–69 years at 33% (95% CI: 30%–37%) and 24% (95% CI: 21%–28%) for PSA cut-off levels of 3 ng/ml and 4 ng/ml, respectively. Sensitivity was lowest at age 50–54 at 15% (95% CI: 12%–17%) and 9% (95% CI: 8%–11%) for PSA cut-off levels of 3 ng/ml and 4 ng/ml, respectively. In contrast, the clinical detection rate in the absence of mass screening, relative to histological cancer, varied between 0.2%–0.7% at age 50–54 and 1.2%–2.7% at age 65–69 from 1995 to 2012.

Conclusions: The framework enabled the sensitivity of a prostate cancer screening round relative to histological cancer diagnosis to be estimated and provides a basis to determine the impact and cost-effectiveness of prostate cancer screening. The approach could be adapted to inform the sensitivity of other biomarkers, cancers and screening programmes.

1. Introduction

Prostate cancer represents the highest incidence of all cancers in men in Europe and the US (23% of all cancers) and is the third main cause of cancer mortality (9% of all cancer deaths) [1]. Questions remain about the scale of the contribution of early detection and treatment [2–5]. Many screen-detected cases would never have become clinically apparent within the man's lifetime, as undiagnosed histological cancer increases with age from 2% (95% CI: 1–3%) between 20 and 29 years-of-age to 69% (95% CI: 51–83%) by 90–99 years-of-age [6].

Public policy decisions for prostate cancer screening programmes rely on natural history models and model-based cost-effectiveness analyses as no conclusive data exist, even from the two largest prostate cancer screening trials [4,5]. Such models simulate the progression of prostate cancer in the absence and presence of organised screening programmes, requiring data on the sensitivity of such programmes in order to simulate the number of cases detected and managed in each PSA testing round relative to a pool of undetected histological cancers. These models need to simulate the clinical incidence of prostate cancer during and after screening, this requires data on both the sensitivity of screening and clinical detection rates relative to histological cancer.

This is challenging as the gold standard procedure required to identify histological cancer involves the removal and step section biopsies (full slicing of the prostate gland into thin sections) undertaken during a full autopsy of the gland. Application of this 'gold standard' is not possible in screening studies, leading to verification bias, as only those with a PSA level above a chosen cut-point are referred for biopsy (and not all diagnosed with cancer will receive surgery). Those below the PSA cut-off or for whom cancer was not detected at biopsy do not

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undergo any step-section biopsy of the prostate gland. Furthermore, needle biopsies cannot be viewed as an alternative gold standard procedure as their sensitivity can be as low as 30% relative to histological cancer [7,8]. New approaches to prostate cancer diagnosis include the use of high quality Magnetic Resonance Imaging (MRI), which may increase rates of detection, particularly for anteriorly situated cancers [9].

In this study, we estimate the proportion of histological cancers that were detected after a single round of population-based PSA testing (i.e. sensitivity) among UK men, stratified by PSA cut-off level; the true prevalence of histological prostate cancer in the UK and the clinical detection rate in the absence of organised screening.

2. Methods

2.1. Data and framework

Prostate 'screening programme' refers to the entire patient pathway from the initial PSA test to biopsy and diagnostic tests for those with a PSA level above a specified cut-point (e.g. 3 or 4 ng/ml). The outcome is prostate cancer detection or no cancer detection.

Expanding previous methodology [10], we used the association between true prevalence (TP) (see Box 1), based on a definitive gold standard procedure for the screen population (i.e. step-section at autopsy amongst men who died of causes other than prostate cancer), and apparent prevalence (AP) of prostate cancer, based on diagnostic testing of individuals with raised PSA levels in the screened population (i.e. prostate biopsy (initial and repeats), digital rectal examination, free-to-total PSA, magnetic resonance imaging (MRI) or computerised tomography (CT) scans) [11],

$$AP = TP \times sens + (1 - TP) \times (1 - spec) \quad (1)$$

where *sens* and *spec* represent the sensitivity and specificity of the screening programme. Eq. (1) can be arranged to inform the screening programme sensitivity relative to histological prostate cancer, i.e. proportion of all prostate cancers (TP) actually detected on screening, as,

$$sens = \frac{AP}{TP} \quad (2)$$

where the specificity of the 'screening programme' is assumed to be 100% following diagnostic testing as it is very unlikely that men will be wrongly confirmed as having prostate cancer following all diagnostic tests post initial PSA and biopsy testing. Hence, this conceptualisation of specificity is different from the specificity of the initial prostate biopsy test which is high but not perfect [7]. Furthermore, by focusing on screen attenders, we explicitly excluded the screening attendance rate so that it can be added subsequently as an independent input. In sensitivity analysis, we used Eq. (1) to model apparent prevalence where the specificity of the screening programme is not assumed to be 100% based on data of pT0 findings in radical prostatectomy specimens (0.2%, see Online Appendix) [12].

Likewise, cancer detection data in non-screen populations represents the apparent prevalence (AP) in Eq. (2) but the *sens* component now refers to the proportion of histological cancers detected clinically in areas without formal screening, i.e. sensitivity of clinical detection or clinical detection rate.

Bibliographic databases were systematically searched for studies reporting on the sensitivity of PSA screening and biopsy testing relative to histological cancer (see Online Appendix) [7,8,13]. UK cancer registries and national databases were interrogated for data on the clinical incidence of cancer. Data on a single round of population-based PSA testing among UK men came from the ongoing UK-based Prostate testing for cancer and Treatment trial (ProtecT) (personal communication from ProtecT). Table 1 reports the identified evidence.

2.2. True prevalence of prostate cancer

We used 25 autopsy studies from a systematic review [6] to estimate the association between histological cancer and age as a continuous variable (odds ratio (OR) of 1.06 per year increase in age in predominantly white populations) using a Bayesian logistic meta-regression (see Online Appendix). This provided informed prior distributions of the parameters of true prevalence of $P_{0,i}$ histological cancer in age *i*,

2.3. UK-specific data on screening prevalence

We obtained screening prevalence data by age-group and PSA cut-off level (3 and 4 ng/ml) from the diagnostic phase of the ongoing UK-based ProtecT trial examining treatment options for screen detected men (Table 1, i = 1,…,8) [14]. In this trial, men aged 50–69 years old in general practices in and around nine cities in the UK were invited to attend an appointment for a PSA test between 2001 and 2009. Those with a PSA level above the 3 ng/ml cut-off were recommended to receive a standardised protocol of digital rectal examination and transrectal ultrasound-guided needle biopsy. Men diagnosed with clinically localised prostate cancer were invited to participate in the trial of treatments [14].

Using Eq. (2), the sensitivity of the single round of the 'screening programme', $\theta_{i,j}$, was estimated by dividing the screening prevalence at age *i* and PSA cutoff level *j* (3 and 4 ng/ml), $prev_{i,j}^{SCR}$, by the respective histological prevalence of prostate cancer, $P_{0,i}$,

$$\theta_{i,j} = \frac{prev_{i,j}^{SCR}}{P_{0,i}} \quad \text{for i} = 1,\ldots,4 \text{ j} = 1, 2$$

The sensitivity of the 'screening programme' was further assumed to be a function of the proportion of histological cancers at age *i* with PSA levels above the screening cut-off level *j* ($psa_{i,j}^{PCa}$); biopsy acceptance rate at age *i* ($bupt_i$) and the sensitivity of the biopsy procedure to detect histological cancer ($bsens^{PSA}$),

$$\theta_{i,j} = psa_{i,j}^{PCa} \times bupt_i \times bsens^{PSA} \quad \text{for i} = 1,\ldots,4 \text{ j} = 1, 2$$

The biopsy acceptance rate, $bupt_i$, was informed by the diagnostic phase of the ProtecT trial (Table 1, i = 20,…,24). An autopsy study [13] provided data on the sensitivity of 12-core needle biopsy, $bsens^{PSA}$, relative to histological cancers with PSA values equal or above 4 ng/ml (Table 1, i = 17). The authors reported the sensitivity of needle biopsy to be similar for histological cancers with PSA values below and above 4 ng/ml (53% and 59%, respectively) and we assumed the sensitivity of needle biopsy for cancers above PSA 3 and 4 ng/ml to be the same.

The proportion of histological cancers with PSA levels above the 3 ng/ml and 4 ng/ml cutoff ($psa_{i,j}^{PCa}$) was estimated using data from the ProtecT trial and from the autopsy study [13]. The proportion of men screened with PSA levels above cut-off level *j* ($psa_{i,j}^{ALL}$) is a weighted

Box 1
Apparent and true prevalence of disease.

- Apparent prevalence: number of men testing positive by a diagnostic test (conditional on the initial PSA being above a specified cut-off level) divided by the total number of men screened in the population;
- True prevalence: actual number of men with histological prostate cancer divided by the number of men in the population.