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Determining overdiagnosis by screening with DRE/TRUS or PSA (Florence pilot studies, 1991–1994)

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Abstract

The rate of overdiagnosis of prostate carcinoma was assessed by following 6890 participants in pilot screening studies from 1991 to 1994. Observed/expected incidence and mortality were determined using data from the Cancer and Mortality Registry. The cancer detection rate (1.75%) and observed/expected ratio (12.5:1) were high at the first screening, and substantially lower at the second screening (0.65% or 4.10:1). According to the registry follow-up, prostate cancer occurred in 225 subjects in the whole study cohort, while 178.2 were expected with 50 652 men/years at risk. The standardised incidence rate was 1.66 in the screened (95%CI = 1.4–2.0), 0.97 in the non-responders (95%CI = 0.8–1.2) and 1.23 in subjects excluded from invitation due to previous cancer or major illness (95%CI = 0.8–1.5). A 66% excess incidence rate was observed in the screened subjects over a 9-year period, confirming previous estimates of overdiagnosis.
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Keywords: Prostate cancer; Screening; Overdiagnosis

1. Introduction

Screening for prostate cancer is presently under evaluation in two large prospective randomised trials in the United States (US) (PCLO) and Europe (ERSPC) [1], both aim to assess the impact of screening on prostate cancer mortality. Thus far, no mortality data are available from these studies and only first screening round cancer detection rates are known from the ERSPC study [2], showing a high observed/detected ratio suggesting there is substantial overdiagnosis.

Although the efficacy of screening in reducing prostate cancer mortality is yet to be proven, opportunistic screening using prostate-specific antigen (PSA) levels is increasingly performed in Western countries, particularly in the US [3,4]. A sharp rise in prostate cancer incidence has been observed in the US as a consequence of such opportunistic screening [5]. This has not been followed by a decrease in mortality for several years, suggesting there may be diagnostic anticipation and overdiagnosis.

Detection of "latent" non-aggressive cancers that will not to become clinically evident (overdiagnosis) is an unavoidable consequence of screening, but its magnitude and the side-effects of overtreatment can be a major drawback, where screening might ultimately be more harmful than beneficial. This might be the case for screening for prostate cancer, for which the amount of overdiagnosis has been estimated to be high [6,7] and where radical treatment has major side-effects [8]. Thus, continuous monitoring and evaluation of the overdiagnosis rate using current data from existing screening programmes is necessary.

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A preliminary estimate of the overdiagnosis rate was published in 1998, based on the follow-up of two pilot studies of prostate cancer screening performed at the Centro per lo Studio e la Prevenzione Oncologica (CSPO) in Florence [9,10]. The present study analyses prostate cancer incidence in the same cohort after longer follow-up. The aim of the present study was to estimate the magnitude of overdiagnosis associated with screening.

2. Patients and methods

Two pilot studies assessing the feasibility of prostate cancer screening by digital rectal examination (DRE) + transrectal ultrasonography (TRUS) or by PSA were performed at the CSPO from 1991 to 1994, completing two biennial screening rounds (only first screening responders were invited to the second screening). Detailed features of these studies have already been reported in [11]. The screening protocol was not aggressive, as random sextant biopsy was limited to subjects with PSA values of 10 ng/ml or above, whereas directed biopsy was prompted by suspicious findings at DRE or TRUS. A random sample of National Health Service general practices (GP) were invited to join the study: as over 98% GPs accepted, the study population was assumed to be representative of the whole population in the District. Resident men aged 60–74 years registered at GPs and volunteering to be part of the studies were invited to screening. GPs were asked to exclude subjects with major, disabling illness, those unlikely to attend invitation, or those with known prostate cancer. As both screening studies showed almost the same prevalence/incidence ratio [11], with a comparable diagnostic anticipation, a pooled analysis of both cohorts was done with the purpose of estimating the overdiagnosis rate in a larger sample.

Linkage of all study subjects (excluded, non-responders, examined) with regional registries was performed (deterministic linkage based on name and date of birth), and incident prostate cancers (population-based Tuscany Tumour Registry [12], updated to December 2000), as well as deaths (from all causes) (population based Regional Mortality Registry, updated to December 2001) were identified. Information on emigration from the screening area was available, showing that the emigration rate in the study cohort age group and in the study period was negligible. Prostate cancers occurring before the date of invitation or of exclusion were not considered. Trends of prostate cancer incidence were determined for the whole cohort, for different time periods, and for single subgroups (invited and screened, non-responders to invitation, excluded and not invited).

Overdiagnosis was determined as the ratio (standardised incidence ratio: SIR) of prostate cancers observed in the study period and the number of cancers expected according to age-specific incidence rates provided by the Tuscany Cancer registry and to men/years at risk. Standardised mortality ratio (SMR) and 95% confidence intervals (95%CI) were computed to compare the observed and expected mortality from all causes. The expected number of prostate cancer cases (and deaths) was calculated by multiplying the age-, period- and site-specific incidence (and mortality) rates by the Tuscany Cancer Registry (and Regional Mortality Registry) by corresponding person-years. Observed prostate cancers were compared with those expected according to SIR, through the observed/expected ratio. 95%CI were computed assuming a Poisson distribution for the observed cases.

3. Results

Table 1 shows the detection rates of the two pilot study screening rounds. The detection rates at first or second screening rounds were 1.75% and 0.65%, respectively. Corresponding values of observed to expected incidence were 12.5 or 4.10:1, respectively. The clinical stage of the screen-detected cancers was T1c in 3, T2a in 23, T2b in 14, T3 in 7 and Tx in one case at the first screening, whereas it was T2a in all cases at the second screening. The Gleason score was <7, 7, >7 or unknown in 52%, 25%, 20% or 2% of cases at the first screening, and in 61%, 23%, 0% or 15% at the second screening, respectively.

Table 2 reports incident prostate cancers observed in the study cohort. Overall, 225 cases were observed, while 178.2 were expected for 50 652 men/years at risk. SIR was 1.66 in the screened (95%CI = 1.4–2.0), 0.97 in the non-responders (95%CI = 0.8–1.2) and 1.23 in the excluded subjects (95%CI = 0.8–1.5), respectively. In the whole study cohort, a SIR of 1.26 (95%CI = 1.1–1.4) was observed.

Table 3 shows the observed SIR according to the different time periods (less than 5 years/more than 5 years after the invitation date): the only significant difference in observed compared with expected incidence occurred in invited and examined subjects in the first 5 years after the invitation (SIR = 2.11, 95%CI = 1.2–2.6).

Table 4 shows mortality from all causes in the study cohort. Mortality in the whole cohort was as expected (SMR = 0.72, 95%CI = 0.7–0.8). A significant excess in the SMR was evident for subjects excluded from invitation by their GP (SMR = 1.67, 95%CI = 1.5–1.9), and, to a much lower extent, and non-statistically significant, for invited, but not examined subjects (SMR = 1.05, 95%CI = 0.98–1.1), whereas it was significantly lower for the screened subjects (SMR = 0.72, 95%CI = 0.7–0.8).

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