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Prostate cancer specific mortality in the Florence screening pilot study cohort 1992–1993

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ABSTRACT

The impact of screening on prostate cancer mortality is still unknown. A favourable impact is suggested by uncontrolled and possibly biased studies. Mortality from all causes and from prostate cancer was assessed in a cohort of 6861 males aged 60–74 years, participants to a pilot screening study during 1991–1994. Observed/expected mortality was determined by linkage with cancer and mortality registries. Prostate cancer standardised mortality rate (SMR) in the overall series (751 subjects excluded by GPs for disabling illness or prostate cancer; 3448 refusers, 2662 attenders; 67,321.2 men-year) was 0.96 (95% confidence interval (CI) = 0.74–1.22) when deaths from prevalent cancers diagnosed before screening were considered. Reduced prostate cancer mortality (SMR = 0.48; 95% CI = 0.26–0.83), persisting beyond five years after study entry (SMR = 0.48; 95% CI = 0.22–0.90), was observed in attenders and not in refusers (SMR = 0.99; 95% CI = 0.69–1.37). This finding might suggest a screening effect, but might also be ascribed to an healthy screening effect, and cannot be assumed as a reliable evidence of screening efficacy.

1. Introduction

Screening for prostate cancer (PC) has been the object of several studies, but existing evidence of its efficacy in reducing PC mortality is still inconclusive.[1–9] A recent paper on a randomised trial[10] suggests a strong effect of prostate specific antigen (PSA) screening in reducing mortality from PC, although the result are based on small numbers. Two large randomised trials are ongoing in the US (PCLO) and in Europe (ERSPC),[11] but mortality data are not yet available. In spite of such a lack in evidence, the observed large diagnostic anticipation and favourable stage shift in screen detected subjects,[12] which might be simply explained with a large overdiagnosis effect,[13–15] has been arbitrarily assumed as a reliable indicator of efficacy and opportunistic screening by PSA is increasingly performed in western countries, particularly in the US.[16,17] Most likely as a consequence of such opportunistic screening, a sharp rise in PC incidence has been observed in the US,[18] which has not been followed by a decrease in mortality for several years, and a recent drop in mortality rates, observed in both countries with low and high PSA use, may be simply ascribed to improved therapy.[9]

Two pilot studies of prostate cancer screening have been performed at the Centro per lo Studio e la Prevenzione Oncologica (CSPO) of Florence[19] during 1991–1994, selecting a random sample of the resident population for screening invitation. The present study analyses mortality rates from prostate cancer in the pilot study cohort, for which a considerably long follow-up is now available, by comparing observed to expected deaths. Possible implication on screening impact on mortality are discussed.

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2. Materials and methods

Two pilot studies of the feasibility of two different PC screening approaches by (a) digital rectal examination (DRE) + transrectal ultrasonography (TRUS) or (b) by PSA only were performed at the CSPO during 1991–1994, completing two biennial screening rounds (only first screening responders were invited to second screening). Detailed features of these studies have already been reported.[19,20] All National Health Service registered general practitioners (GPs) from two rural and one urban area of Florence District were invited to join the study: as over 98% (130 of 132) 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 practices were considered for the pilot study purpose. GPs were asked to exclude subjects with major, disabling illness, unlikely to attend invitation, or with prevalent PC (22 subjects were excluded for prevalent PC): based on such a selection, subjects were excluded from or received invitation to screening. The adopted screening protocol was not particularly aggressive, as random sextant biopsy was limited to subjects with PSA values of 10 ng/ml or above, and directed biopsy was prompted by suspicious findings at DRE or TRUS (biopsy rate was 2.7% in the DRE–TRUS screening or 2.8% in the PSA screening pilot study). As both screening studies showed a comparable PC detection rate (1.82% and 1.67%) and prevalence/incidence ratio,[19] with a comparable diagnostic anticipation, pooled analysis of both cohorts was done for the study purpose.

Linkage of all study subjects (excluded and not invited, invited and non-responders, invited and examined) with population based Cancer Registry[21] (most recent official update to December 2002), and to Regional Mortality Registry (most recent official update to December 2003) was performed (deterministic linkage based on name and date of birth) to identify incident PC, deaths and their cause. Information on emigration from the screening area was available, showing that migration outside the region in the study cohort age group and in the study period was negligible (less than 1 per 1000 per year in subjects of <50 years of age). Separate analyses were carried on, alternatively considering or excluding PC occurring before the date of invitation. Mortality trends from PC and other causes were determined for the whole cohort, for time periods, and for single subgroups of subjects excluded from invitation (henceforth referred to as 'not invited'), not responding to invitation (henceforth referred to as 'refusers'), and attending screening invitation (henceforth referred to as 'attenders'). For the study purpose, a total of 6861 subjects, accounting for 5.6% of the total district population in that age group, was considered (not invited = 751, responders = 2662, refusers = 3448). Figures as slightly different from those recently reported in a study of overdiagnosis concerning the same cohort,[20] as a minority of subjects for whom mortality registry follow-up was not available (e.g. migration) was excluded from the analysis. Overall, a total of 67,321.2 men-years was considered, accounting for an average follow-up of 9.79 years.

The expected number of deaths (from PC and other causes) was calculated by multiplying the age-, period- and site-specific mortality rates of the Province of Florence provided by the Regional Mortality Registry by person-years in the whole cohort and single subgroups. PC mortality analysis was performed (a) in the whole cohort considering the whole study period, (b) alternatively including or excluding deaths from prevalent PC, and (c) separately for the first and subsequent five-year observation period. The ratio of observed to expected deaths standardised mortality ratio (SMR) and its 95% confidence interval (95% CI) were computed assuming a Poisson distribution for observed cases. Furthermore, an internal analysis comparing mortality rates from PC in attenders versus refusers was performed using a Poisson regression.

3. Results

Mortality from all causes in the whole cohort was as expected (SMR = 1.00; 95% CI = 0.96–1.04), which confirms that the study cohort is a representative sample of the general population. Significant SMR excess was evident among not invited subjects (SMR = 1.80; 95% CI = 1.64–1.99), but not among refusers (SMR = 1.04; 95% CI = 0.98–1.10), whereas it was significantly lower for attenders (SMR = 0.73; 95% CI = 0.67–0.79). Data are presented in Table 1.

Mortality from PC in the overall series, without exclusion of deaths from prevalent PC, did not differ significantly from that expected (SMR = 0.96; 95% CI = 0.74–1.22). Mortality from PC was significantly lower in attenders (SMR = 0.48; 95% CI = 0.26–0.83) but not among refusers (SMR = 0.99; 95% CI = 0.69–1.37), and was significantly higher in not invited subjects (SMR = 2.50; 95% CI 1.51–3.90). A similar mortality reduction was evident in attenders during the first 5 years after invitation (SMR = 0.50; 95% CI = 0.14–1.28) but persisted beyond that date (SMR = 0.48; 95% CI = 0.22–0.90). Data are presented in Table 2.

Table 1 – Observed (Obs) and expected (Exp) deaths, standardised mortality ratio (SMR), and 95% confidence intervals (95% CI) from all causes in the study cohort by period (⩽ or >5 years after the invitation date to the screening)

	Overall mortality											
	⩽5 years				>5 years				Total			
	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
Not invited	240	95.1	2.52	2.21–2.86	184	139.9	1.32	1.13–1.52	424	234.9	1.80	1.64–1.99
Refusers	427	430.2	0.99	0.89–1.08	778	727.1	1.07	1.00–1.15	1205	1157.3	1.04	0.98–1.10
Attenders	179	326.0	0.55	0.47–0.64	472	568.8	0.83	0.76–0.91	651	894.8	0.73	0.67–0.79
Total	846	851.3	0.99	0.93–1.06	1434	1435.9	1.00	0.95–1.05	2280	2296.7	1.00	0.96–1.04

Table 2 – Observed (Obs) and expected (Exp) deaths, standardised mortality ratio (SMR), and 95% confidence intervals (95% CI) for prostate cancer in the study cohort by period (⩽ or >5 years after the invitation date to the screening)

	Prostate cancer mortality											
	⩽5 years				>5 years				Total (no. 6890 records)			
	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
Not invited	12	2.7	4.44	2.30–7.76	7	5.0	1.40	0.56–2.88	19	7.6	2.50	1.51–3.90
Refusers	8	10.8	0.74	0.32–1.46	27	24.5	1.10	0.73–1.60	35	35.3	0.99	0.69–1.37
Attenders	4	8	0.50	0.14–1.28	9	18.9	0.48	0.22–0.90	13	26.9	0.48	0.26–0.83
Total	24	21.5	1.12	0.72–1.66	43	48.5	0.89	0.64–1.19	67	69.8	0.96	0.74–1.22

Deaths from prevalent prostate cancer diagnosed prior to screening are not excluded.

Table 3 – Observed (Obs) and expected (Exp) deaths, standardised mortality ratio (SMR), and 95% confidence intervals (95% CI) for prostate cancer in the study cohort by period (⩽ or >5 years after the invitation date to the screening)

	Prostate cancer mortality											
	⩽5 years				>5 years				Total			
	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
Not invited	3	2.6	1.17	0.24–3.37	5	4.8	1.03	0.34–2.43	8	7.4	1.08	0.47–2.13
Refusers	5	10.8	0.46	0.15–1.08	25	24.4	1.02	0.66–1.51	30	35.2	0.85	0.58–1.22
Attenders	3	8.0	0.37	0.08–1.10	9	18.9	0.48	0.22–0.90	12	26.9	0.45	0.23–0.78
Total	11	21.4	0.52	0.26–0.92	39	48.2	0.81	0.58–1.11	50	69.5	0.72	0.53–0.95

Deaths from prevalent prostate cancer diagnosed prior to screening are excluded.

Mortality from PC in the overall series, after exclusion of deaths from prevalent PC, differed significantly from that expected (SMR = 0.72; 95% CI = 0.53–0.95). Mortality from PC was significantly lower in attenders (SMR = 0.45; 95% CI = 0.23–0.78) but not among refusers (SMR = 0.85; 95% CI = 0.58–1.22) or in not invited subjects (SMR = 1.08; 95% CI 0.47–2.13). A greater mortality reduction was evident in attenders during the first 5 years after invitation (SMR = 0.37; 95% CI = 0.08–1.10), but it persisted also beyond that date (SMR = 0.48; 95% CI = 0.22–0.90). Data are presented in Table 3.

Internal analysis by means a Poisson (maximum likelihood) regression (adjusted by age) comparing the mortality rate from PC of attenders versus not attenders showed comparable results (OR = 0.48; 95% CI 0.26–0.91) to those based on SMR analysis.

4. Discussion

The pilot screening study on which the present analysis is based is characterised by a limited diagnostic aggressiveness, as compared to the currently ongoing controlled trials.[11,12] High threshold criteria adopted for random biopsy (PSA 10 ng/ml or higher in the PSA screening protocol, suspicious DRE/TRUS finding in the DRE/TRUS screening protocol) justifies a low PC detection rate, but allows for a substantial diagnostic anticipation (prevalence incidence ratio was 12.5:1 at first, 4.10:1 at second screening, lead time was estimated to be around 6–7 years).[19] This suggests a possible impact on PC mortality, and justifies the present review.

A question must be raised as to what extent the study sample was representative of the general population, and three major biases need to be discussed.

First, a major selection bias associated to the study design (GP volunteer study) may be excluded, as (a) all GPs in a given area were invited to join the study and almost all GPs volunteered and (b) the whole cohort, inclusive of not invited subjects, showed an overall mortality equal to that expected. Being a representative sample of the resident population, any reduction in whole cohort PC mortality should not be ascribed to such a selection bias.

Second, due to the exclusion from invitation of subjects with major disabling illness, or with prevalent PC, another selection bias is certainly present, and although exclusion criteria were not particularly articulated and may vary between GPs, a higher mortality (from all causes and from PC) in subjects who were excluded as compared to those who were not is expected, and in fact is quite evident from observed figures.

Third, an healthy screenee effect is also expected, with attenders being more healthy as compared to refusers. This is confirmed by observed overall mortality figures, definitely better for attenders. The healthy screenee effect might also affect PC mortality, as refusers might be less prone to (a) refer in presence of symptoms, (b) undergo diagnostic assessment, and (c) accept aggressive treatment. A difference in PC mortality between attenders and refusers might thus be ascribed to such a bias, rather than to screening.

Exclusion or inclusion of deaths from PC diagnosed before screening is another methodological point which needs to be discussed. As screening has no chance to affect mortality from such cancers, their exclusion should not affect any evidence of screening impact on mortality, whereas their inclusion would dilute any evidence of screening effect, particularly considering that the screened fraction in the present study is rather small (only 38.7% of the original cohort was screened). On the other hand, exclusion of

deaths from prevalent PC complicates mortality analysis, as it is quite difficult to disentangle the mortality reduction observed as an effect of censored deaths from that (if any) due to screening.

A separate analysis of PC mortality for the first and second five-year study period was justified by the fact that due to an estimated 6–7 years lead time, a screening effect on mortality is unlikely to surface in the first years, as it has been suggested for another population screening study for which an early evidence of mortality reduction[1] has in fact recently been denied.[22]

As previously discussed, several biases may affect the comparison between subgroups within the study, and the whole cohort should be considered instead. When deaths from prevalent PC are included in the analysis, no significant reduction of PC mortality is observed during the study period, nor in the first or second five-year study period. These findings do not necessarily deny a screening effect, which might be so small (due to low screening aggressiveness and low attendance) to disappear, when diluted by excess deaths from prevalent PC. When deaths from prevalent PC are censored, PC mortality is significantly reduced with respect to that expected, the effect being much more evident in the first five-year study period: whether such a figure is due simply to the effect of prevalent PC deaths censoring or to its combination with a screening effect it is impossible to say from whole cohort figures.

Excess PC mortality observed in not invited subjects is easily explained as prevalent PC was a reason for exclusion from invitation, and SMR is much greater in the first (4.44) as compared to the second five-year follow-up period.[1,4] This finding suggests that the effect of censoring deaths from prevalent PC on SMRs is more evident in the first five years of follow-up. In fact, when prevalent PC deaths are excluded, reduced (borderline significant) SMR is observed for both attenders and refusers during the first five years (screened = 0.37, not screened = 0.46), whereas in the second five-year period, SMR rises to normal for refusers (1.02), and reduced SMR persists and becomes statistically significant for attenders (0.48, 95% CI = 0.22–0.90). A similar time trend of SMRs among attenders and refusers is evident also when deaths from prevalent PC are not censored, but due to the previously discussed limitations of the present study, drawing any conclusion from these data on screening efficacy might be biased by the presence of an healthy screenee effect.

In conclusion, mortality figures observed in the present review of a one-arm pilot study of PC screening, associated to substantial diagnostic anticipation, cannot support nor deny screening efficacy, due to a variety of biases intrinsic to the study design. This finding stresses the need for basing any statement of screening efficacy on ongoing properly designed controlled trials, and warns about drawing conclusions from early observations of current screening practice or limited screening studies.

Conflict of interest statement

None declared.

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