EUROPEAN JOURNAL OF CANCER 46 (2010) 3061–3067

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Blinded and uniform causes of death verification in cancer screening: A major influence on the outcome of a prostate cancer screening trial?

S.J. Otto [a,*], P.J. van Leeuwen [b], J.W. Hoekstra [c], J.W. Merckelbach [d], J.H.M. Blom [e], F.H. Schröder [b], M.J. Roobol [b], H.J. de Koning [a]

[a] Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[b] Department of Urology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[c] Consultant Urologist, 's-Hertogenbosch, The Netherlands
[d] Consultant Surgeon, Rotterdam, The Netherlands
[e] Department of Urology, Sint Fransicus Gasthuis, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 15 June 2010
Received in revised form 10 August 2010
Accepted 14 September 2010

Keywords:
Prostate cancer
ERSPC
Cause of death
Official statistics
Death review
Agreement
Sensitivity
Specificity

ABSTRACT

Background: To assess the agreement between the causes of death assigned by a blinded and uniform review panel of the Rotterdam section of the European Randomised Study of Screening for Prostate Cancer and the official vital statistics and to explore the possible effect of the use of either of these two sources on the outcome of the screening trial.

Methods: A total of 670 deaths amongst men with prostate cancer, reviewed by the causes of death committee (CODC) up to 31st December 2006 were included in this study. The kappa statistics with confidence intervals (CI), sensitivity and specificity of the official statistics were determined, with the CODC considered the gold standard. The rate ratio (RR) and 95% confidence intervals (95% CI) for prostate cancer mortality, official statistics relative to CODC, were calculated following the Mantel–Haenszel procedure.

Results: The overall concordance and the kappa between official statistics and the CODC were 90.6% and 0.76 (0.71–0.82), remaining comparable when only the CODC category definitely prostate cancer was applied, with the sensitivity of official statistics increasing from 88.3% to 91.3% and specificity hardly changing (91.3% and 90.5%). High specificity and lower sensitivity is observed in the screening arm, whilst the opposite was seen in the control arm in men aged 55–69 and 70–74 years at entry. Considerable lower false positive rate was seen for both age groups in the screening arm (3.9% and 4.7%) compared to the control arm (8.4% and 14.3%). A statistically significant excess of prostate cancer death was observed for the official statistics in the age group 70–74 years, 1.53 (1.07–2.19), whilst it was not significant for men aged 55–69 at entry, 1.06 (0.83–1.36).

Conclusion: In the Rotterdam ERSPC section, official statistics tended to overreport prostate cancer as an underlying cause of death, particularly in the age group 70-plus in the control arm, which would overestimate the true effect in favour of screening.

* *Corresponding author*: Address: Department of Public Health, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 7043446; fax: +31 10 7038474.
E-mail address: s.otto@erasmusmc.nl (S.J. Otto).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.09.026

1. Introduction

Prostate cancer is still the most common malignancy diagnosed amongst men in many Western countries, and the third leading cause of death from cancer in men.[1] An early result of the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial demonstrated that prostate specific antigen (PSA) based screening reduced the mortality from prostate cancer. After a median follow-up period of 9 years, a 20% reduction was observed in the screening arm relative to the control arm that was not offered screening.[2] A secondary efficacy analysis, adjusting for both non-compliance and contamination, showed a reduction of 31% in the risk of death from prostate cancer[3], confirming the outcome of the intention-to screen analysis.

As in any cancer trial with cause-specific disease as major endpoint, a clear answer on the cause of death in the ERSPC trial is crucial for assessment of the true effect of the prostate cancer mortality.[4] Sesso and colleagues[6] demonstrated in their study comparing causes of death between nosologists and review panel that committees reviewing study endpoints is the preferred strategy in studies where specific causes of death are required, otherwise causes of death determined by nosologists can be done with. In his paper, Dubben[5] illustrated that misattribution of the cause of death would lead to loss of statistical power, which jeopardises outcome of a trial. As previously reported for randomised screening trials of breast cancer[7,8], prostate cancer[9] and colorectal cancer[10], deaths in men with prostate cancer in the ERSPC trial were also ascertained by causes of death committees, for which algorithms have been developed to review the causes of death in all men diagnosed with prostate cancer in both trial arms.[4] These procedures were designed to ensure unbiased decisions on the cause of death in men with prostate cancers.

In this paper, we compared the causes of death amongst deceased men with prostate cancer coded from death certificates and registered at Statistics Netherlands with those assigned by the causes of death committee (CODC) of the Rotterdam ERSPC section, based on the review of medical records and additional medical information, and explored the possible effect of the use of either of these two sources on the outcome of the screening trial.

2. Methods

2.1. Rotterdam section of ERSPC

The details of the Rotterdam section of ERSPC have been described in detail in Ref. 11. Briefly, men aged 55–74 years living in the city of Rotterdam and 12 neighbouring municipalities selected from population registries of the respective municipalities were personally invited to participate in the screening trial. Men who responded by returning the intake questionnaire and who provided written informed consent were randomised (participation rate, i.e. the proportion of men invited and actually randomised, was 49%). A total of 42,376 men in the target population were randomised to the screening arm (n = 21,210) and the control arm (n = 21,166) between June 1994 and March 2000. A re-screening interval of 4 years was used after the prevalence screening round and after the protocol change in February 1997[12], the initial and follow-up screenings in this centre were solely based on PSA testing with a cut-off level of 3.0 ng/ml as referral for biopsy.

The written informed consent also granted permission for exchange of information with the participant's general practitioner, and retrieval of relevant follow-up data from the Causes of Death Registry, General Practitioner laboratories[13,14], cancer registry and from the Nationwide Network and Registry of histo- and cytopathology. Up to 31st December 2006, there were a total of 3120 men with a prostate cancer diagnosis (screening and control arms combined) and 679 deaths amongst these men.

2.2. Reviewed causes of death

As described previously by De Koning and colleagues[4], data on prostate cancer other than those screen-detected, i.e. interval cancer in the screening arm, prostate cancer diagnoses amongst non-participants in the screening arm and men in the control arm, were obtained from linkages with the regional Comprehensive Cancer Registry, Rotterdam. For each deceased man with prostate cancer, all available information of medical records from either primary or secondary care (including outpatient visit letters, letters from specialists, laboratory results, radiology and pathology reports) was collected. The anonymous and for trial arm blinded information was reviewed by the CODC using the flow charts as reported in reference.[4] The CODC was also blinded to the causes of death registered at Statistics Netherlands.

The final cause of death of the cases reviewed that resulted from the flowchart was classified as definitely intervention-related, probably or possibly prostate cancer or other intercurrent causes (with or without prostate cancer as a contributory factor). For the final analyses of the ERSPC trial,[2] it was proposed to apply the categories, definitely prostate cancer death, probable prostate cancer death and intervention-related deaths as primary outcome measures for disease-specific mortality.

2.3. Official causes of death

Data on vital status of the participants were ascertained through linkages of the trial database to those of the Central Bureau of Genealogy (CBG) and Causes of Death Registry of Statistics Netherlands.[15] Record linkage with the CBG was necessary for men recruited in one municipality that did not provide a personal administrative number, which was required for linkage with the Causes of Death Registry of Statistics Netherlands. Through CBG, the death certificate number, date and place of death and birth date were obtained which were then applied as a key linkage to obtain the cause of death (underlying and contributory) from the Causes of Death Registry of Statistics Netherlands. Causes of death were reported according to coding system of the International Classification of Diseases Ninth Revision (ICD-9, 1994–1995; n = 3 deaths), and Tenth Revision (ICD-10, from 1996 onwards).

The outcome of these linkages was analysed by SJO, who is not a member of the CODC. The official causes of death were not disclosed to the CODC. Men coded at Statistics Netherlands as died from prostate cancer as underlying or contributory cause of death and for whom no prostate cancer diagnosis was reported by the cancer registry, were notified to the CODC, using the trial number, for inclusion in the review process, without disclosing the official cause of death.

2.4. *Statistical analysis*

All deaths amongst men with prostate cancer up to the cut-off date 31st December 2006 and having been reviewed were included in this study. Analyses were restricted to the causes of death amongst the deceased men in whom prostate cancer was diagnosed after the randomisation (incident cases) either by detection at screening or otherwise diagnosed as reported by the cancer registry. As it is not yet allowed to analyse the data by study arm before publication of the final analysis of the ERSPC trial, no absolute numbers of prostate cancer deaths by study arms are disclosed.

The causes of death as assigned by the CODC were considered the gold standard. The sensitivity and the specificity of the official statistics were calculated defined as the proportion of deaths assigned by both sources as due to prostate cancer (sensitivity) and as due to other causes (specificity) and the proportion of false positive as the prostate cancer deaths registered at Statistics Netherlands for men coded dead from other cause by the CODC. The observed proportion of concordant causes of death between the two sources and the agreement were estimated by means of the kappa statistics with 95% confidence intervals (95% CI). A kappa of 1 indicates perfect agreement, whilst a kappa of 0 or less indicates no agreement.

The rate ratio (RR) and 95% confidence interval (CI) for prostate cancer mortality, Statistics Netherlands relative to CODC, were calculated following the Mantel–Haenszel procedure to adjust for the 5-year age groups[16] to detect excess prostate cancer deaths in one of the sources. The cumulative prostate cancer mortality rate by year since randomisation according to data from the two sources is presented graphically. The RR of the combined arms was chosen in order not to disclose the rate per study arm.

3. Results

From the start of the screening trial in the Rotterdam section until the cut-off date of 31st December 2006, with a mean follow-up duration of 9 years, a total of 8204 men (19.4%) aged 54–75 years at entry died in the trial cohort, the study arms combined, excluding all men with a prostate cancer diagnosis prior to randomisation. The mean age at death was 72.3 (55–86) and no statistically significant difference was observed between the screening and the control arm for all cause mortality, relative risk = 1.03 (95% CI 0.98–1.07, $P = 0.230$).

Table 1A shows the distribution of the number of deaths according to official statistics (Statistics Netherlands) by age group at entry and by prostate cancer as either underlying cause or contributory factor. According to the official statistics, 212 deaths out of 8204 were from prostate cancer as underlying cause of death.

Table 1B shows the causes of death as assigned by the CODC of the Rotterdam section. A total of 670 deaths amongst men with incident prostate cancer who died up to and including 31st December 2006, in both study arms, were reviewed and $n = 173$ deaths were attributed to prostate cancer as definite or probable prostate cancer death or death related to prostate cancer intervention based on review of the medical records of the deceased men.

Table 1 – Number[a] of men randomised, with prostate cancer and deceased from prostate cancer and other causes as assigned by Statistics Netherlands and the causes of death committee (cut-off date December 2006).

	Age group at entry (years)						
	54	55–59	60–64	65–69	70–74	75	Total
(A) No. of randomised men	345	13,494	11,252	10,072	7037	118	42,310
No. of deaths	38	1259	1700	2528	2620	59	8204
Prostate cancer as cause of death							
Underlying cause[b]	1	32	37	66	75	1	212
Contributory	0	7	22	36	24	0	89
(B) No. of incident prostate cancer	14	702	792	932	607	14	3061
No. of reviewed deaths among prostate cancer patients	2	76	116	245	226	5	670
Prostate cancer as cause of death							
Definitely	0	31	28	54	47	1	161
Intervention related	0	3	3	2	0	0	8
Probable	0	0	1	1	2	0	4
Other causes	2	42	84	188	177	4	497
Prostate cancer contributory	0	1	1	2	2	0	6
Prostate cancer possible	0	0	1	3	1	0	5

[a] Trial arms combined, excluding all men with prevalent prostate cancer (diagnosis before randomisation; $n = 59$) and men who died before randomisation ($n = 8$).

[b] Causes of death as assigned by Statistics Netherlands.

3.1. Causes of death committee versus Statistics Netherlands

Table 2 shows the outcome of the review of the $n = 670$ prostate cancer patients by the CODC cross-tabulated against the cause of death registered as official at Statistics Netherlands. Amongst the men reviewed, the vital status of three men ($n = 2$ definitely prostate cancer death and $n = 1$ non-prostate cancer cause of death) could be ascertained in neither the registry of the CBG nor the Causes of Death Registry of Statistics Netherlands. These men were further excluded from the comparison of the agreement between the two sources.

In the official statistics, there were $n = 18$ men in whom prostate cancer was present at death as underlying cause ($n = 18$, mean age at death 77.0, range 62–84) although no diagnosis of prostate cancer is known for these men. These cases are currently under review and are considered as false positives in the official statistics in additional analyses. The observed agreement between Statistics Netherlands and the CODC was 90.6% (604/667) and kappa 0.76 (95% CI 0.71–0.82), and a sensitivity of 88.3% (151/171) and a specificity of 91.3% (453/496). Including the $n = 18$ prostate cancer deaths in official statistics without diagnosis affected the specificity, which declined to 88.2% and the false positive rate increased from 6.4% to 8.9%.

The sensitivity, specificity and the false positive rate of the official statistics versus the CODC for the control and the screening arm are presented in Table 3 for the reviewed cases by age group 55–69 and 70–74 years at entry and year of follow-up (2002 and 2006). For men aged 55–69 years at entry, analysis of the deaths from prostate cancer in the two study arms revealed that the sensitivity of official statistics slightly declined in the screening arm, from 85.7% in 2002 to 84.6% in 2006, whereas the sensitivity remained unaltered in the control arm, i.e. 89.3% in 2002 and 89.9% in 2006. The specificity in the screening arm remained high and unchanged at 95.2% in 2006 against a specificity of 84.9% in the control arm, which increased from 73.9% in 2002. The proportion of false positive prostate cancer deaths (i.e. attribution to prostate cancer by the official statistics for men coded death from other cause by the CODC) also differed amongst the two study arms. In the screening arm, this proportion was comparable between 2002 and 2006, 3.6% in 2002 and 3.9% in 2006, whilst in the control arm higher figures were noticed, 11.8% in 2002 and 8.4% in 2006. In the older age group 70–74 years at entry, the sensitivity declined in both arm, although more pronounced in the screening arm. The specificity (slightly) increased in both study arms. Similar to the age group 55–69, the false positive rates were higher in the control arm compared to the screening arm, 14.3% and 4.7% in 2006, respectively.

3.2. Cumulative prostate cancer death and rate ratio Statistics Netherlands relative to CODC

Fig. 1 shows the cumulative prostate cancer mortality for the age group 55–69 and 70–74 years at entry, calculated on the basis of the prostate cancer deaths assigned by the CODC (definite, probable and intervention related), and those registered as underlying cause at Statistics Netherlands, including on the one hand only prostate cancer deaths amongst men with confirmed diagnosis and on the other hand including the 18 prostate cancer deaths without diagnosis. In the age group 55–69 years, a divergence in mortality rates of the prostate cancer deaths according to the CODC and Statistics Netherlands occurred after 10 years follow-up. In the age group 70–74, the two curves based on data of Statistics Netherlands followed the same course in the first 7 years and started to diverge thereafter. A divergence from the rates calculated on the basis of data of the CODC occurred already after year 3 in trial.

At the cut-off date 31st December 2006, median follow-up 9.2 years, the rate ratio Statistics Netherlands relative to the CODC indicated an excess of prostate cancer death registered

Table 2 – Attribution of causes of death according to the CODC and official statistics.[a]

CODC	Statistics Netherlands			Sensitivity[b] (95% CI)	Specificity[b] (95% CI)	Observed concordance	Kappa statistics (95% CI)
	Prostate cancer	Other	Total				
Prostate cancer[c]	151	20	173	88.3% (82.3–92.5)	91.3% (88.4–93.6)	90.6%	0.76 (0.71–0.82)
Other	43	453	497		88.2% (84.9–90.7)[d]	88.2%	0.71 (0.65–0.77)
Under review[e]	18	–	18				
Total	212	473	685				
Definitely prostate cancer	146	14	161	91.3% (85.5–95.0)	90.5% (87.6–92.9)	90.7%	0.76 (0.71–0.82)
Other	48	459	509		87.4% (84.2–90.1)[d]	88.3%	0.71 (0.65–0.77)
Under review	18	–	18				
Total	212	473	685				

[a] *Abbreviations:* CODC, causes of death committee and CI, confidence interval.
[b] Excluding the cases under review and those unknown to Statistics Netherlands.
[c] Coded by the CODC as definitely and probably prostate cancer deaths and deaths related to prostate cancer intervention.
[d] Calculated assuming the cases with no prostate cancer diagnosis under review false positives in official statistics.
[e] No prostate cancer diagnosis registered at the cancer registry for the $n = 18$ who died of prostate cancer as underlying according to official statistics; cases are under review.

Table 3 – Sensitivity and specificity of official statistics versus the CODC by age group at entry and year of follow-up[a].

Age group at entry (years)	Follow-up year	Reviewed men (cumulative N)	Obs. concordance (%)	Sens. (%)	Spec. (%)	FP (%)	Control arm			Screening arm		
							Sens. (%)	Spec. (%)	FP (%)	Sens. (%)	Spec. (%)	FP (%)
55–69	2002	161	90.1	87.8	91.1	6.2	89.3	73.9	11.8	85.7	95.5	3.6
	2006	434	91.0	87.6	92.3	5.5	89.9	84.9	8.4	84.6	95.2	3.9
70–74	2002	84	91.7	100.0	89.2	8.3	100.0	76.5	15.4	100.0	93.8	5.2
	2006	226	89.8	89.8	89.8	8.0	95.5	80.0	14.3	85.2	94.3	4.7

[a] *Abbreviations:* CODC, causes of death committee, Obs., observed, Sens., sensitivity, Spec., specificity, and FP, false positive.

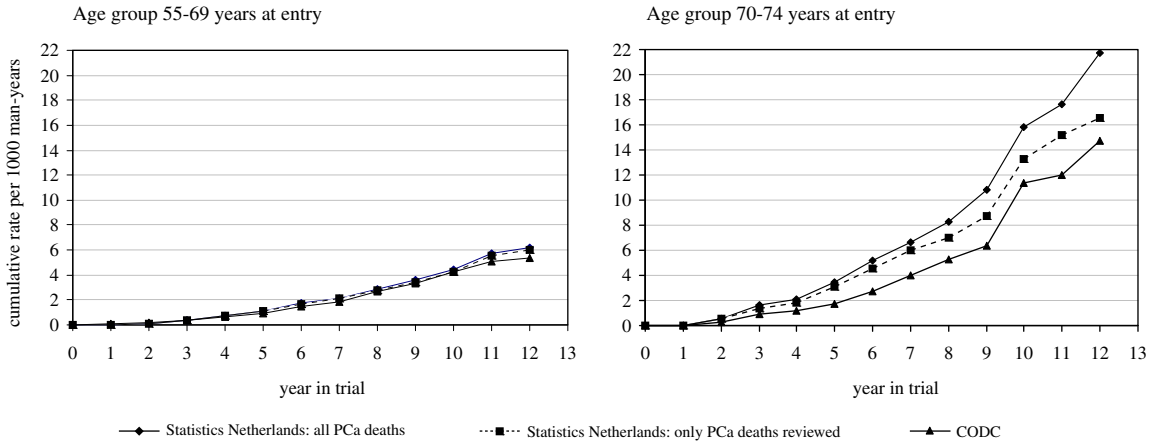

Fig. 1 – Cumulative prostate cancer mortality in the age groups 55–69 and 70–74 years at entry. Legend: PCa, prostate cancer and CODC, causes of death committee.

at Statistics Netherlands for the age group 70–74 years at entry, 1.27 (95% CI 0.87–1.84), which became higher and statistically significant when the rate of all prostate cancer death (including the $n = 18$ cases under review) is compared to those reviewed, 1.53 (95% CI 1.07–2.19). For the age group 55–69 at entry, no differences are observed in the rates of Statistics Netherlands for this age group, with a non-significant rate ratio of 1.06 (95% CI 0.83–1.35). A non-significant higher mortality of prostate cancer death as seen from the official statistics, disregard the status of prostate cancer diagnosis, 1.10 (95% CI 0.86–1.40).

4. Discussion

In the current study, we assessed the agreement between the Statistics Netherlands and CODC, considered the gold standard, for the prostate cancer death and death from other causes in the Rotterdam section of the ERSPC and explored the possible effect of the use of either of these two sources on the outcome of the screening trial. The results indicated substantial agreement between the CODC and Statistics Netherlands as determined by the kappa statistics. The high proportion of concordance, even when only the CODC category definitely prostate cancer was considered, is in line with those previously reported in studies comparing official causes of death or death certificate causes with reviewed medical records.[15–19]

In the Finnish section of ERSPC, the agreement of the causes of death had been assessed before and showed higher overall concordance between official causes of death and the review panel, 97.4% (kappa 0.95)[18], than that observed in current study, 90.6% (kappa 0.76). Possible explanations for this discrepancy might lie in different systems of coding at Statistics Finland compared to The Netherlands, as the Finnish review panel used the same algorithm as in Rotterdam, high autopsy rate in the Finnish sample (32.7%). The number of cases of the Finnish review committee included in the analysis was fewer than in our current study, $n = 315$ versus $n = 670$. Furthermore the age groups invited for participation in the trial are different, in that, in the Finnish section were randomised men aged 55, 59, 63 and 67 years versus 55–74 years in the Rotterdam section.

The official vital statistics had both high sensitivity (88.3%) and high specificity (91.3) at the cut-off date of December 2006. In the core age group, 55–69 years at entry, there was a tendency of unaltered specificity in the screening arm and increasing specificity in the control arm over time, whilst the opposite was observed for the sensitivity. It might be argued that this change might be due to coding procedures over time, but a recent report of Statistics Netherlands demonstrated high agreement in the coding of prostate cancer as underlying cause (breast cancer being higher).[20] Consequently, this finding says something about the completion of death certificates, as this reflects the accuracy of the physician concerned[6], who was more or less aware of the screening status of the deceased and the outcome of treatment. The latter is illustrated by the observed excess prostate cancer mortality (not statistically significant) of 27% in the age group 70–

74 years (6% in the age groups 55–69), amongst cases for whom the prostate cancer had been ascertained and of 53% when the false positives are included. This has been referred to by Black and colleagues[21] as sticky-diagnosis bias, an overestimation of the cause-specific mortality in the screening arm, because the disease is more likely to be diagnosed in the screening than in the control arm and consequently negatively affects the true effect of screening, i.e. no effect of screening. As the data were not analysed by study arm, we cannot report the direction of the effect of the excess prostate cancer deaths reported by the official statistics. However, this finding implies that blinded review of the causes of death amongst older prostate cancer patients in a trial is of vital importance to detect the true reduction. This is underlined in the decrease in the sensitivity in this age group over time from 100% in 2002 to 89.9% in 2006, which can be attributed to the well-known misclassification of underlying cause of death in older individuals due to (multiple) co-morbidities.[15,22]

Misclassification of the underlying cause-of-death would be detrimental for intervention studies in which changes (i.e. reduction) in the disease-specific death rate is the study endpoint. Lloyd-Jones and colleagues[23] stated, after assessment of the accuracy of death certificates for coding coronary heart disease as the underlying cause of death, that the sole use of death certificates might cause an underestimation of the true effect of the intervention, with a bias towards the null, although the latter is likely to be more pronounced in studies on cardiovascular disease than in cancer studies, for which the death certificate has a higher sensitivity and specificity. In the analysis of four of the Swedish breast cancer screening trials, Nystrom and colleagues[8] demonstrated that only marginal differences were present in the RR of breast cancer death when calculated based on causes assigned by the review panel (End point Committee) and causes of death from Statistics Sweden. Similarly, Doria-Rose and colleagues[19] found that RRs using mortality review data tended to provide a slightly higher impact of screening on mortality of specific cancer sites (lung, breast and colon cancer). However, this remained uncertain in the current study as no analysis disclosing the prostate cancer mortality rate in the two study arm was performed. Nevertheless, prostate cancer as a cause of death was slightly higher in both study arms according to the official statistics and judging by the proportion of false positive attribution of death to prostate cancer in the control arm of about 8% in the age group 55–69 and 14% in the age group 70–74 years, and twice as low in the screening arm, more deaths were misattributed to prostate cancer in the control arm than in the screening arm in the official statistics. This implies that calculation of the estimate of the risk of prostate cancer death in the screening arm relative to the control group using official statistics might yield an overestimation of the true effect of screening, suggesting a higher reduction in the prostate cancer mortality than expected based on reviewed data.

In conclusion, the agreement of official causes of death with the CODC in the Rotterdam section of ERSPC is high for men in whom prostate cancer has been confirmed, although, official statistics tended to overreport prostate cancer as underlying death, particularly in the age group 70-plus in the control arm, which would overestimate the true effect on cancer specific mortality in favour of PSA based screening.

Financial sources of support

This work was supported by grants from Europe against Cancer and the fifth and sixth framework programme of the European Union, by grants from agencies or health authorities in the participating countries, and by unconditional grants from Beckman Coulter. The studies in each national centre were funded by numerous local grants.

Conflict of interest statement

None declared.

Acknowledgements

We gratefully acknowledge Statistics Netherlands (Causes of Death Registry) for supply of the mortality data.

REFERENCES

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010;**46**:765–81.
2. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;**360**:1320–8.
3. Roobol MJ, Kerkhof M, Schroder FH, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol* 2009;**56**:584–91.
4. de Koning HJ, Blom J, Merkelbach JW, et al. Determining the cause of death in randomized screening trial(s) for prostate cancer. *BJU Int Suppl* 2003;**92**:71–8.
5. Dubben HH. Trials of prostate-cancer screening are not worthwhile. *Lancet Oncol* 2009;**10**:294–8.
6. Sesso HD, Gaziano JM, Glynn RJ, Buring JE. Value of an endpoints committee versus the use of nosologists for validating cause of death. *Contemp Clin Trials* 2006;**27**:333–9.
7. Chamberlain J, Coleman D, Ellman R, Moss S. Verification of the cause of death in the trial of early detection of breast cancer. UK trial of early detection of breast cancer group. Trial co-ordinating centre. *Br J Cancer* 1991;**64**:1151–6.
8. Nystrom L, Larsson LG, Rutqvist LE, et al. Determination of cause of death among breast cancer cases in the Swedish randomized mammography screening trials. A comparison between official statistics and validation by an endpoint committee. *Acta Oncol* 1995;**34**:145–52.
9. Miller AB, Yurgalevitch S, Weissfeld JL, Prostate LColorectal and Ovarian Cancer Screening Trial Project Team. Death review process in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. *Control Clin Trials* 2000;**S21**:400S–6S.
10. Robinson MH, Rodrigues VC, Hardcastle JD, et al. Faecal occult blood screening for colorectal cancer at Nottingham: details of the verification process. *J Med Screen* 2000;**7**:97–8.

11. Roobol MJ, Kirkels WJ, Schroder FH. Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, The Netherlands). *BJU Int* 2003;**92**(Suppl. 2):48–54.
12. Beemsterboer PM, Kranse R, de Koning HJ, Habbema JD, Schröder FH. Changing role of 3 screening modalities in the European randomized study of screening for prostate cancer (Rotterdam). *Int J Cancer* 1999;**84**:437–41.
13. Beemsterboer PM, de Koning HJ, Kranse R, et al. Prostate specific antigen testing and digital rectal examination before and during a randomized trial of screening for prostate cancer: European randomized study of screening for prostate cancer, Rotterdam. *J Urol* 2000;**164**:1216–20.
14. Otto SJ, van der Cruijsen IW, Liem MK, et al. Effective PSA contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. *Int J Cancer* 2003;**105**:394–9.
15. Albertsen PC, Walters S, Hanley JA. A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. *J Urol* 2000;**163**:519–23.
16. Hoffman RM, Stone SN, Hunt WC, Key CR, Gilliland FD. Effects of misattribution in assigning cause of death on prostate cancer mortality rates. *Ann Epidemiol* 2003;**13**:450–4.
17. Fall K, Stromberg F, Rosell J, Andren O, Varenhorst E. Reliability of death certificates in prostate cancer patients. *Scand J Urol Nephrol* 2008;**42**:352–7.
18. Makinen T, Karhunen P, Aro J, et al. Assessment of causes of death in a prostate cancer screening trial. *Int J Cancer* 2008;**122**:413–7.
19. Doria-Rose VP, Marcus PM, Miller AB, et al. Does the source of death information affect cancer screening efficacy results? A study of the use of mortality review versus death certificates in four randomized trials. *Clin Trials* 2010;**7**:69–77.
20. Harteloh P, de Bruin K, Kardaun J. The reliability of cause-of-death coding in The Netherlands. *Eur J Epidemiol* 2010. doi:10.1007/s10654-010-9445-.
21. Black WC, Haggstrom DA, Welch HG. All-cause mortality in randomized trials of cancer screening. *J Natl Cancer Inst* 2002;**94**:167–73.
22. Newschaffer CJ, Otani K, McDonald MK, Penberthy LT. Causes of death in elderly prostate cancer patients and in a comparison nonprostate cancer cohort. *J Natl Cancer Inst* 2000;**92**:613–21.
23. Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann Intern Med* 1998;**129**:1020–6.