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ARTICLE

Evidence of overestimating prostate cancer mortality in Estonia: a population-based study

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ABSTRACT

Background: Prostate cancer (PC) mortality statistics in Estonia has shown inconsistencies with incidence and survival trends. The aim of this population-based study was to assess the accuracy of reporting PC as the underlying cause of death and estimate the effect of misattribution in assigning cause of death on PC mortality rates.

Material and methods: The Estonian Causes of Death Registry (CoDR) and Cancer Registry provided data on all men in Estonia who died in 2017 and had a mention of PC on any field of the death certificate or had a lifetime diagnosis of PC. A blinded review of medical records was conducted by an expert panel to ascertain whether the underlying cause was PC or other death. We estimated the agreement between the underlying causes of death registered at the CoDR and those ascertained by medical review and calculated corrected mortality rates.

Results: The study population included 655 deaths. Among 277 PC deaths registered at CoDR, 164 (59%) were verified by medical review. Among 378 other deaths registered at CoDR, 17 (5%) were ascertained as PC deaths by medical review. In total, the number of PC deaths decreased from 277 to 181 and the corrected age standardized (world) mortality rate decreased from 20 to 13 per 100 000 (1.5-fold overestimation, 95% confidence interval 1.2–1.9).

Conclusions: PC mortality statistics in Estonia should be interpreted with caution and possible overestimation considered when making policy decisions. Quality assurance mechanisms should be reinforced in the whole death certification process.

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Prostate cancer; prostate cancer mortality; cause of death; death certificates

Introduction

Prostate cancer (PC) mortality in Estonia is among the highest in the world [1]. In 2015, the estimated PC mortality rate in Estonia was 22/100 000, while in most European countries, it was in the range of 10–15/100 000 [2]. A rapid rise in PC incidence in Estonia was observed in the 2000s, but the increase was limited to localized PC [3]. A similar trend has been seen in Lithuania, where a national early detection program has been in place since 2006, bringing along a very rapid rise in the number of new cases and the highest incidence rate in Europe [4]. These trends are likely due to intensive use of PSA-testing, accompanied by over-diagnosis – the diagnosis of latent cases that would not have become clinically relevant during the man's lifetime [5]. The five-year relative survival for PC in Estonia has increased rapidly and is over 90% according to the most recent estimates; in stages I and II, five-year relative survival is 100% [3,6].

The PC mortality trends observed in Estonia are not consistent with the accompanying incidence and survival trends and suggest the possibility of misattribution of PC as the underlying cause of death in men dying from other causes [3]. Evidence of over-reporting PC mortality has come forward from several countries [7,8].

The aim of this population-based study was to estimate the accuracy of reporting PC as the underlying cause of death in official mortality statistics and to estimate the effect of misattribution of PC as the cause of death on population-based mortality rates.

Material and methods

Data collection

The study population included all men in Estonia who died in 2017 and had a record of PC in either the Estonian Causes of Death Registry (CoDR) or the Estonian Cancer Registry. Among male deaths in Estonia in 2017, the CoDR first identified deaths with PC as the underlying cause of death or PC reported on other fields of the death certificate. All male

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deaths in 2017 were subsequently linked to the cancer registry to identify men who died in 2017 and had a lifetime diagnosis of PC at the cancer registry. The Estonian Cancer Registry collects information on all cancer cases diagnosed in Estonia, including cases diagnosed at autopsy and death certificate only cases. The completeness of case reporting is high as shown by data quality indicators [6].

The formation of the final study population is illustrated in Figure 1. Data obtained from the CoDR included date of birth, date of death, issuer of death certificate, basis of determining cause of death, and all causes of death reported to the registry. Data provided by the cancer registry included data on PC diagnosis (date, stage, notifying hospital) and information on other cancers diagnosed during lifetime.

Using data from both registries, the hospital or other medical service provider where the patient died or had been treated in recent years was identified. A medical chart review was conducted for all subjects by experts – urologists and oncologists, experienced in treating PC patients (IA, PB, MK, MK, RO, HP, OR, AR, MS, EV and MŽ). The cases were divided between participating experts according to the identified medical service providers. Each expert reviewed available hospital records and the central electronic patient record that includes summaries of all diagnostic and treatment activities conducted by all medical service providers in Estonia, including outpatient services and general practitioners. Available records were reviewed covering the period from PC diagnosis until death. The information used included level of PSA throughout the disease course, timing of and response to PC treatment, information on relapse and progression, adverse effects or complications of PC treatment, and severe comorbidities. For each case, the expert decided whether the underlying cause of death was PC or not, according to criteria summarized in Figure 2. These criteria were established based on literature review, clinical experience and a pilot study reviewing a small sample of cases. The review was blinded, i.e. the reviewers were unaware of the underlying cause of death assigned at the CoDR. The reviewers were instructed to refer the case to a panel review if a decision could not be made based on the criteria. The second round of review was conducted by a panel including all experts participating in the study. If necessary, special efforts were undertaken to collect additional data and queries were made to other medical service providers to obtain information not submitted to the central electronic patient record. The final decision in the panel was reached based on consensus. In general, it was enough if at least one criterion for confirming or excluding PC as the underlying cause of death was met. Conflicting information may have occurred if the patient met a criterion for confirming PC death, but also had other clinically relevant cancer with distant metastasis. In these cases, death was attributed to PC. If the information was too sparse, no decision was made regarding PC as the underlying cause of death.

For all study subjects, the final decision regarding the underlying cause of death was (1) PC death; (2) other death; (3) not able to determine due to lack of data or competing serious diseases. For patients in the latter category, the initial registered cause of death was accepted in data analysis.

Statistical analysis

We compared the underlying causes of death registered at the CoDR and ascertained by medical review and calculated positive predictive value (PPV) by dividing the number of PC deaths verified by medical review by the total number of PC deaths at the CoDR. Negative predictive value (NPV) was calculated by dividing the number of other deaths verified by medical review by the total number of other deaths at the CoDR. PPV and NPV were presented with 95% confidence intervals (CI). PPV and NPV were calculated by age at death and age at diagnosis (40–64, 65–74, 75–84, $\geq$85 years), time interval from PC diagnosis to death ($<$1 year, 1–4 years, 5–9 years, $\geq$10 years), extent of PC at diagnosis (localized, local/regional spread, distant metastasis, unknown) and the institution issuing the death certificate (regional/central hospital, local hospital, general practitioner).

The mortality rate was calculated by dividing the number of deaths by the number of Estonian male population and expressed per 100,000. The CoDR rate was calculated using the number of deaths from CoDR data; corrected mortality rate was calculated using the number of deaths verified by medical review. Absolute difference between these two rates was obtained as CoDR rate minus corrected rate; relative difference was obtained by dividing the CoDR rate by the corrected rate; the latter is presented with 95% CI. For age-standardization of mortality rates, world standard population was used.

Statistical analyses were conducted with STATA 17 (Stata, College Station, TX, USA).

The study protocol was approved by the Research Ethics Committee of the National Institute for Health Development (Decision no 196, 2 February 2020). Informed consent to participate was not required, as data were collected from existing data sources and no subjects were contacted in person.

Results

Characteristics of the study population and medical review process

A total of 655 deaths that met the inclusion criteria were included in the study population (Figure 1). For three deaths with PC reported on the death certificate (0.5%), there was no record of PC at the cancer registry since 1968.

The characteristics of the study population are shown in Table 1. Over 66% of the deaths occurred at the age of $\geq$75 years (mean age at death 78, range 40–96 years). Half of the patients had received their PC diagnosis within five years before dying. Over half of the cases (53%) had localized PC at the time of diagnosis. Nearly 40% of the death certificates had been issued by general practitioners.

In the first round of medical review, a decision whether the underlying cause was PC or other death was made for 584 men (89%). The remaining 71 men were subjected to

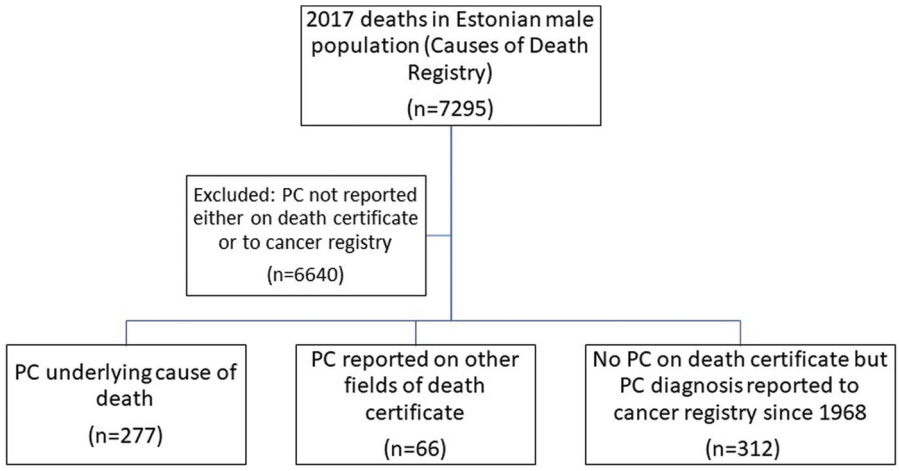

Figure 1. Formation of the final study population ($n = 655$) for the verification of prostate cancer (PC) as the underlying cause of death.

Criteria used to confirm prostate cancer as the underlying cause of death	Criteria used to exclude prostate cancer as the underlying cause of death
•Prostate cancer with distant metastasis where treatment options have been exhausted, patient on best supportive care •Prostate cancer with distant metastasis, progression of disease during treatment •Patient died during active prostate cancer treatment due to treatment complications •Prostate cancer with distant metastasis diagnosed at autopsy	•No prostate cancer diagnosis during lifetime •Patient on „watchful waiting“ after initial diagnosis with no clinical disease activity •Previous radical treatment with no recurrence and immediate cause of death not related to cancer treatment •Hormone therapy with complete response to treatment and immediate cause of death not related to cancer treatment •Other clinically relevant cancer with distant metastasis

Figure 2. Criteria for confirming or excluding prostate cancer as the underlying cause of death.

panel review. Compared to the 584 men for whom the decision was made in the first round, these 71 men were older (age ≥85 years 45% *vs* 25%) and the death certificate had been issued more often by general practitioners (59% *vs* 37%), both $p < 0.01$. The panel review resulted in a decision for 66 men. For the remaining five men, the decision could not be made due to lack of medical data during the last few years of their lives and CoDR cause of death was accepted in further analysis (three PC and two other deaths).

Comparison of CoDR and medical review data

The total number of deaths in Estonia in 2017 with PC as the underlying cause of death was 277 according to the CoDR and 181 according to the medical review, indicating a 1.5-fold overestimation (Table 2). Of the 277 PC deaths registered at the CoDR, 164 (59%) were verified by medical review. Among 378 deaths registered as other deaths at the CoDR, 17 (5%) were ascertained as PC deaths by medical review.

The overall PPV and NPV were 59% and 95%, respectively (Table 3). The PPV decreased with age at death and was 38% in the oldest age group, an estimate significantly lower than in age groups 65–74 and 75–84 (67% and 65%, respectively). A similar trend was seen for age at diagnosis, but no distinct association was apparent with time from diagnosis to death. The PPV was 43% for men with localized PC at diagnosis, which was significantly lower than the 87% seen for men who had distant metastases at diagnosis. The PPV was slightly lower for death certificates issued by general practitioners compared to those issued at hospitals. The differences across subgroups were smaller for NPV, but a low NPV was seen for men with distant PC at diagnosis (61%), which was significantly below the estimates seen for localized and unknown categories. The PPV and NPV were higher for deaths with a decision made in the first round (96% and 61%, respectively) than for those requiring a panel review (87% and 44%, respectively).

Correction of mortality rate

The age-standardized mortality rate for PC decreased from 20.0 to 13.1 per 100,000 after correcting the number of PC deaths, indicating a statistically significant 1.5-fold overestimation (95% CI 1.2–1.9) (Table 4). In age group ≥85 years, the CoDR mortality rate was 2.3 (95% CI 1.5–3.7) times higher than the corrected rate (951.6 *vs* 413.7).

Table 1. Characteristics of the study population for the verification of prostate cancer as the underlying cause of death, Estonia 2017.

	No	%
Total	655	100
Age at death		
40–64	63	9.6
65–74	158	24.1
75–84	258	39.4
≥85	176	26.9
Age at prostate cancer diagnosis[a]		
40–64	133	20.4
65–74	263	40.3
75–84	215	33.0
85+	41	6.3
Time from diagnosis to death[a]		
<1 year	107	16.4
1–4 years	225	34.5
5–9 years	191	29.3
≥10 years	129	19.8
Extent of prostate cancer at diagnosis[a]		
Localized	348	53.1
Local or regional spread	66	10.1
Distant metastasis	86	13.1
Unknown	152	23.2
Issuer of death certificate		
Regional/central hospitals	241	36.8
Local hospitals	156	23.8
General practitioners	258	39.4

[a]three men did not have a record of prostate cancer at cancer registry.

Table 2. Results of the medical review verifying prostate cancer as the underlying cause of death, Estonia 2017.

	Medical review			
	Prostate cancer death $n = 181$		Other death $n = 474$	
	No	% (95% CI)	No	% (95% CI)
Causes of Death Registry				
Prostate cancer death $n = 277$	164	59 (53–65)	113	41 (35–47)
Other death $n = 378$	17	5 (3–8)	361	95 (93–97)

CI: confidence interval.

Discussion

In this population-based study aimed at estimating the accuracy of reporting PC as the underlying cause of death in Estonia, a 1.5-fold overestimation of PC mortality in Estonia was found in 2017. The overestimation was more than two-fold in men age ≥85 years but was also present and ranged from 1.3 to 1.4 in other age groups. Medical review verified less than half of PC deaths attributed to men with localized PC at diagnosis, while the verification rate was close to 90% in men who had distant metastases at the time of diagnosis.

PC mortality in Estonia, reported as the highest in Europe in 2015 [2], has remained stable in Estonia over the past decades [3], while a clear decline has been apparent in European Union as a whole, but also in most countries individually [2]. The corrected estimate obtained in this study would be closer to those seen in the countries of Northern and Central Europe [1] and more in line with the observed incidence increase limited to localized PC [3] and overall five-year relative survival of 92% [6].

In Norway and Denmark, population-based studies have also shown overestimation of PC mortality, albeit of a smaller magnitude than in our study [7,9]. The overall agreement between CoDR data and medical review in Estonia was 65% for PC-specific death (277 *vs* 181 deaths), which is lower than the 73% observed in Denmark [9] and the 78% in Norway [7]. The PPV in our data (59%) was lower than seen in the Danish study (67%), while the NPV in Estonia was as high as 96%, compared to 85% in Denmark [9]. Owing to the high NPV, the overall agreement between the CoDR data and medical review in our data was 80%, while it was 86% in a Swedish register-based study [10] and 87% in a Canadian study [11]. In the settings of clinical trials, studies have reported over 90% agreement between official death certificates and medical review in Sweden (96%), Finland (95%) and the UK (92%) [12–14].

Misattribution of the cause of death to PC is dependent on the pool of prevalent cases in the population [8]. From 1995 to 2011, PC incidence in Estonia increased at a rate of 9% per year, most likely because of widespread PSA testing [3]. With the increasing number of prevalent PC cases, it can be expected that misattribution of the underlying cause of death to PC also increased. In New Mexico, misattribution was suggested to explain about half of the PC mortality rise from 1985 to 1995 [15]. The lowest PPV was seen in the oldest age group, which is consistent with the notion that misattribution is dependent on the proportion of prevalent cases who die of other causes [8]. The age pattern is in line with previous reports [7]. At ages where concurrent diseases are common or for cases where recent clinical data are lacking, it may be unclear if the patient has died from cancer, comorbidities or complications related to the cancer treatment, making it challenging to identify the cause of death correctly.

No distinct association of PPV was apparent with time from diagnosis to death, while previous studies have shown higher rate of misclassification in men with a recent diagnosis of PC [11–13]. The overall agreement between CoDR and medical review was slightly over 80% both for localized and advanced disease. In a Swedish study, the agreement rates were higher, particularly for localized PC (88%) [10]. The PPV values in our data were the lowest among men with localized and highest among men with distant PC at diagnosis, while the opposite was seen for NPV. The low NPV among men with distant metastasis suggests that the criteria for determining the condition that led to the immediate cause of death may not be clear in practice, particularly for conditions that may result from cancer treatment.

The accuracy of the death certificates is heavily dependent on the knowledge, skills and experience of physicians filling in the death certificates. Misattribution may result from errors in completing the correct sequence of events leading to death in Part I of the death certificate as well as a misconception that any cancer mentioned in the medical records should be included in the death certificate. Both PPV and NPV were the lowest for death certificates issued by general practitioners, who may lack information on recent treatment outcomes or the latest malignancy related health status, particularly practitioners servicing nursing homes. Surprisingly, the PPV was also low for regional and central hospitals. It has been suggested that hospital deaths usually mean that the death certificate has been issued by the

Table 3. Overall agreement between the Causes of Death Registry (CoDR) and medical review, positive predictive value (PPV) and negative predictive value (NPV) for prostate cancer (PC) cause of death validity, Estonia 2017.

Characteristic	Total no	Agreement % (95% CI)	No of PC deaths at CoDR	PPV % (95% CI)	No of other deaths at CoDR	NPV % (95% CI)
Total	655	80 (77–83)	277	59 (53–65)	378	95 (93–97)
Age at death						
40–64	63	89 (78–95)	20	70 (46–88)	43	98 (88–100)
65–74	158	83 (76–88)	76	67 (55–77)	82	98 (91–100)
75–84	258	81 (76–86)	112	65 (56–74)	146	93 (88–97)
≥85	176	73 (66–80)	69	38 (26–50)	107	96 (91–99)
Age at diagnosis[a]						
40–64	133	87 (80–92)	48	69 (54–81)	85	98 (92–100)
65–74	263	84 (79–88)	106	64 (54–73)	157	97 (94–99)
75–84	215	73 (67–79)	99	51 (40–61)	116	92 (86–96)
≥85	41	68 (52–82)	22	50 (28–72)	19	89 (67–99)
Time from diagnosis to death[a]						
<1 year	107	76 (66–83)	51	55 (40–69)	56	95 (85–99)
1–4 years	225	79 (73–84)	108	63 (53–72)	117	93 (87–97)
5–9 years	191	79 (73–85)	79	56 (44–69)	112	96 (90–99)
≥10 years	129	88 (81–93)	37	59 (42–75)	92	99 (94–100)
Extent of PC at diagnosis[a]						
Localized	348	83 (78–87)	98	43 (33–53)	250	98 (96–100)
Local or regional spread	66	77 (65–87)	42	67 (50–80)	24	96 (79–100)
Distant metastasis	86	81 (72–89)	68	87 (76–94)	18	61 (36–83)
Unknown	152	74 (67–81)	67	49 (37–62)	85	94 (87–98)
Issuer of death certificate						
Regional/central hospitals	241	87 (82–91)	77	61 (49–72)	164	99 (96–100)
Local hospitals	156	81 (74–87)	76	64 (53–75)	80	96 (89–99)
General practitioners	258	74 (68–79)	124	55 (46–64)	134	91 (85–95)
Decision made						
First round of review	584	82 (79–85)	236	61 (55–68)	348	96 (94–98)
Panel review	71	62 (50–73)	41	44 (28–60)	30	87 (69–96)

PPV: PC deaths verified by medical review/PC deaths at CoDR; NPV: other deaths verified by medical review/other deaths at CoDR; CI: confidence interval.
[a]Three men did not have a record of prostate cancer at the cancer registry.

Table 4. Prostate cancer mortality rate per 100,000 based on the Causes of Death Registry (CoDR) data and corrected after medical review, Estonia 2017.

	No of prostate cancer deaths		Mortality rate per 100,000		Mortality rate difference	
	CoDR	Corrected after medical review	CoDR	Corrected after medical review	Absolute	Relative (95% CI)
Crude	277	181	44.7	29.2	15.5	1.5 (1.3–1.9)
Age-standardized (world)	277	181	20.0	13.1	6.9	1.5 (1.2–1.9)
Age at death						
40–64	20	15	9.5	7.2	2.3	1.3 (0.6–2.8)
65–74	76	52	148.2	103.4	44.8	1.4 (1.0–2.1)
75–84	112	83	387.0	286.8	100.2	1.3 (1.0–1.8)
≥85	69	31	951.6	413.7	537.9	2.3 (1.5–3.7)

Absolute difference = CoDR rate − corrected rate; relative difference = CoDR rate/corrected rate.

treating physician and is therefore precise [16]. Other factors to consider are the type of comorbidities and initial treatment. The presence of cardiac comorbidities was shown to affect the coding of cause of death more than other comorbid conditions [17–18], while health care providers were less likely to attribute cause of death to PC in patients known to have received more aggressive initial treatment [19]. The autopsy rate in Estonia has declined by half from 34% in 1989 to 17% in 2017, but it is still considerably higher than the European Union average of 12% [20]. Higher rate of autopsy could help minimize misattribution of cause of death.

Misattribution may also result from errors at the registry, particularly when the coding is done manually, as was the case in Estonia in 2017. Coding practices for the underlying cause of death have been shown to affect mortality estimates for hypertension, cerebrovascular disease, and alcohol-related mortality in Estonia [21,22]. Starting from July 2019, the CoDR receives electronic death certificates with ICD-10 codes mostly assigned by issuing physician. The underlying cause of death is selected automatically by IRIS software applying the WHO coding rules [23], which should ensure more accurate registration. Indeed, PC mortality rate has slightly dropped in 2020 and 2021 compared to previous years [24]. Determining the exact source of misattribution in our data will be subject to further analysis.

The main strengths of the study were the population-based study design and the ability to assess the impact of cause of death misclassification on national mortality rates owing to the inclusion of a full one-year cohort of deaths. The study year was selected as the most recent year of published cancer incidence at the start of the study. Additional strengths were the blinded review using several data sources and the availability of high-quality cancer registry data including stage. The main weakness was the possible variation in clinical decision-making due to the contribution of several experts in the first round of review; due to the study design, we were not able to assess the variability between experts. However, the resulting bias was minimized because of previously determined criteria and the second round of review in a full panel of experts which resulted in a very low

number of undecided cases ($n = 5$, 0.8%). There was no specific pattern characterizing these five cases as their age at death varied from 65 to 86 and time from diagnosis to death from 1.5 years to 20 years. The reviewers were not able to access any medical data regarding the last years of their lives. Due to the small number of these cases, the resulting bias would be marginal. The experts collected and used data on other diseases/cancers in making their decision whether PC was the underlying cause of death or not. However, due to limited resources, we were not able to systematically collect and analyze these data and the exact cause of non-PC deaths was not ascertained during medical review.

In conclusion, PC mortality statistics in Estonia should be interpreted with caution and possible overestimation should be considered when making public health policy decisions based on official statistics. The results are likely also applicable for other countries in the Eastern part of Europe showing high PC incidence and mortality that may also struggle with the quality of reporting and registration of health-related events. In addition, the results have important implications for research as our findings do not support the use of cause-specific cancer mortality as the outcome in survival studies. The overestimation of PC mortality is particularly relevant for men diagnosed with localized PC. Our results indicate that educational interventions are necessary for physicians issuing death certificates and quality assurance mechanisms should be reinforced in the whole death certification process both for hospital and non-hospital deaths.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Data can be made available upon reasonable request from the corresponding author.

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