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Causes of death in men with prostate cancer: Results from the Danish Prostate Cancer Registry (DAPROCAdata)

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ABSTRACT

Background: Current knowledge of the validity of registry data on prostate cancer-specific death is limited. We aimed to determine the underlying cause of death among Danish men with prostate cancer, to estimate the level of misattribution of prostate cancer death, and to examine the risk of death from prostate cancer when accounting for competing risk of death.

Material and methods: We investigated a nationwide cohort of 15,878 prostate cancer patients diagnosed in 2010–2014; with 3343 deaths occurring through 2016. Blinded medical chart review was carried out for 670 deaths and compared to the national cause of death registry. Five death categories were defined: 1) prostate cancer-specific death, 2) other unspecified urological cancer death, 3) other cancer death 4) cardiovascular disease death, and 5) other causes of death. Competing risk analyses compared Cox cause-specific and Fine-Gray regression models.

Results: Chart review attributed 51.2% of deaths to prostate cancer, 17.0% to cardiovascular disease, and 16.7% to other causes. The Danish Register of Causes of Death attributed 71.7% of deaths to prostate cancer when including all registered contributing causes of death, and 57.0% of deaths when including only the primary registered cause of death. The probability of death by prostate cancer was 10% at 2-year survival.

Conclusions: More than half of the deceased men in our study cohort died of their prostate cancer disease within a mean of 2.4 years of follow up. Data from the death registry is prone to misclassification, potentially overestimating the proportion of deaths from prostate cancer.

1. Introduction

Data from the Unites States and Sweden have earlier suggested that prostate cancer is a disease that men live with rather than die of, such that the majority of men with prostate cancer will die from causes other than their prostate cancer [1,2]. Prostate cancer mortality rates have been reported to be higher in Denmark than in other Scandinavian countries and the United States with an age-standardized (World Standard Population) mortality rate of 16.5 per 100,000 persons per year for the period 2011–2015 [3–5]. In the same period from 2011 to 2015, approximately 4500 new cases of prostate cancer and approximately 1200 deaths were attributed to prostate cancer each year according to Nordic cancer statistics [4].

There are several plausible explanations for the reported excess of prostate cancer deaths in Denmark, including differences in national PSA screening strategies contributing to lead-time bias and underlying comorbidity in the Danish male population [3]. Misattribution in death certificates may also contribute to an over-reporting of prostate cancer deaths. Studies from other countries with similar demographics have quantified the magnitude of misattribution in both population-based and clinical trials settings with differing results [6–9].

Current data on the validity of death certificates for Danish men with prostate cancer is limited. We therefore investigated cause of death in a nationwide cohort of men diagnosed with prostate cancer in the 5-year period from 2010 to 2014. We examined the validity of death certificates in the Danish Register of Causes of Death against blinded medical records review. We aimed to determine the underlying cause of death among men with prostate cancer, to estimate the level of misattribution of prostate cancer deaths in the Danish Register of Causes of Death, and to examine the time to death from prostate cancer when

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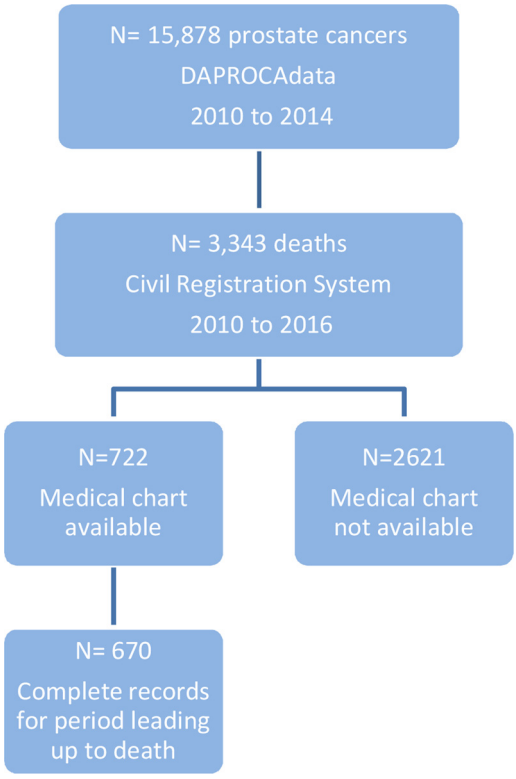

Fig. 1. Identification of deceased study subjects for blinded medical chart review.

accounting for competing risks of death.

2. Material and methods

2.1. Subjects

Men diagnosed with prostate cancer were identified from the Danish Prostate Cancer Registry (DAPROCAdata), a nationwide prospective clinical database [10]. Data on vital status and time to death were obtained by linking patient data at the individual person level with the Danish Civil Registration System [11]. A total of 15,878 Danish men were registered with newly diagnosed prostate cancer within the period February 1, 2010 to December 31, 2014. A total of 3343 deaths occurred during follow-up from 2010 through 2016.

2.2. Determination of the underlying cause of death

A nurse abstractor collected 722 hospital medical charts and among these, 670 had complete medical documentation for the period leading up to death (Fig. 1). Due to restrictive changes in data legislation limiting access to nationwide electronic medical chart data during the course of our data collection period, we able to collect complete medical charts on 670 out of the 3343 deceased men with prostate cancer corresponding to 20% of the deceased cohort. Also, data from the primary sector was not available, except when indirectly noted in the hospital chart as an appendix or supplementary note sent from the general practitioner to the secondary hospital sector. Data on the 3343 deceased men were linked to the Danish Register of Causes of Death ('Death Registry'), which registers information from the original death certificates [12]. We tested the validity of cause of death determined by the Death Registry against the gold standard of blinded medical chart review. Cause of death was categorized into five groups: 1) prostate cancer-specific death, 2) other unspecified urological cancer death, 3) other cancer death 4) cardiovascular disease death, and 5) other causes of death, e.g. infection and trauma.

For consistency in the evaluation process, a single physician (MD, PhD background) carried out blinded medical chart review for all 670 cases. Prostate cancer-specific death was defined as death that was definitely or highly likely due to prostate cancer or a direct consequence of prostate cancer treatment. Borderline cases were evaluated based on the patient's overall disease trajectory, with weight on the prostate cancer in the rare event of multiple but equally contributing causes of death. We used the International Classification of Diseases code 'ICD-10 C61.9 prostate cancer' to identify prostate cancer-specific deaths in the Death Registry by two different algorithms: i) all contributing causes of death (primary or contributing) and ii) restricted to coding for the primary cause of death. See Appendix C for the corresponding ICD-10 codes and diseases used to define the five death categories.

2.3. Covariates

Data were linked to other national health and administrative registries for key clinical and socioeconomic variables. These included the National Pathology Registry (Gleason score), the Danish National Register of Patients (Charlson Comorbidity Index score with a look-back window of 10 years of medical history prior to prostate cancer diagnosis), and Statistics Denmark (education level, disposable income, and urbanization).

2.4. Statistical analysis

We reported summary statistics for cause of death by the five death categories and computed the positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity of the Death Registry against medical chart review. We tested two coding algorithms for determining cause of death based on registry data: i) an upper-bound estimate where registrations of all contributing causes of death were queried in registry data and ii) a lower-bound estimate where we restricted to querying only for registrations of the primary cause of death in the Death Registry. We performed competing risk analyses, including a comparison of estimates from the Cox cause-specific hazards model and the Fine and Gray subdistribution hazards model [13–15]. We estimated cumulative incidence functions (CIF) by death category to describe the incidence of the occurrence of prostate cancer deaths while taking competing risks into account. The premise of the CIF allows for modelling the effects of covariates on the probability of events occurring over time [14]. We adjusted for age, PSA value, Gleason score, clinical TNM cancer stage, Charlson Comorbidity Index score, education level, income, and urbanization. All covariates were defined at time of prostate cancer diagnosis. Follow-up time was calculated from the date of prostate cancer diagnosis until registered death, emigration, or end of follow-up (December 31, 2016); whichever occurred first. Data linkage, data management, and summary statistics were programmed using SAS software, version 9.3, and competing risks analyses were programmed using SAS version 9.4 (SAS Institute Inc.).

2.5. Ethics and data access

The release and use of data for scientific research was approved by the Danish Data Protection Agency (2013-58-0026). Data linkage and analyses were carried out on a secured server hosted at Statistics Denmark.

3. Results

Table 1 summarizes the baseline characteristics of the prostate cancer cohort (n = 15,878), the entire deceased cohort (n = 3343), and the subset of deceased with chart data (n = 670). Mean follow-up time was 2.4 years. As expected, the deceased men were older (median age

Table 1
Characteristics of the prostate cancer cohort at time of diagnosis (n = 15,878).

Characteristic	All prostate cancers	%	All deaths	%	Subset of deaths with medical chart review	%
Total – no.	15878		3343		670	
Median age at diagnosis, years (IQR)	69 (64-75)		75 (68-81)		74 (68-81)	
Median time from diagnosis to death, days (IQR)	800 (433-1283)		800 (433-1282)		485 (250-795)	
TNM stage - no.						
I	722	5%	174	5%	31	5%
II	7244	46%	709	21%	133	20%
III	5566	35%	1492	45%	320	48%
IV	1447	9%	715	21%	166	25%
Missing	899	6%	253	8%	20	3%
Gleason Score - no.						
≤6	3943	25%	265	8%	53	8%
7	5740	36%	699	21%	123	18%
≥8	4296	27%	1606	48%	321	48%
Missing	1899	12%	773	23%	173	26%
PSA (total ng/mL)						
Median PSA (IQR)	12.5 (7.2-34.9)		45.5 (15.0-188.0)		51.0 (16.0-226.5)	
< 4.0	544	3%	70	2%	10	1%
≥4 to 10	5843	37%	444	13%	93	14%
≥10.0	9279	58%	2717	81%	565	84%
Missing	212	1%	112	3%	2	0%
Charlson Comorbidity Index[a] - no.						
0 None	7770	49%	519	16%	83	12%
1 Low	2639	17%	439	13%	85	13%
2 Medium	1916	12%	486	15%	93	14%
3 High	3553	22%	1899	57%	409	61%
Education[b] - no.						
0 No formal education	495	3%	122	4%	31	5%
1 Primary school	4792	30%	1285	38%	249	37%
2 Secondary or trade-vocational	370	2%	65	2%	12	2%
3 Bachelors level or equivalent	9169	58%	1699	51%	331	49%
4 Masters level or above	825	5%	148	4%	40	6%
Missing	227	1%	24	1%	7	1%
Income[c] - no.		0%		0%		0%
Median income, DK (IQR)	186,479 (138936-268752)		158,098 (125307-221287)		155,818 (119047-223623)	
1 Low (0-125,000)	2520	16%	802	24%	192	29%
2 Middle (125,000-175,000)	4493	28%	1130	34%	195	29%
3 Upper-middle (175,000-250,000)	3916	25%	777	23%	137	20%
4 High (> 250,000)	4710	30%	610	18%	137	20%
Missing	239	2%	24	1%	9	1%
Urbanization[d] - no.						
1 Rural	2724	17%	588	18%	117	17%
2 Provinces	6977	44%	1402	42%	271	40%
3 Other big cities	1657	10%	366	11%	96	14%
4 Suburbs	2712	17%	580	17%	127	19%
5 Capital (Copenhagen)	1044	7%	182	5%	31	5%
Missing	764	5%	225	7%	28	4%

Abbreviation: IQR interquartile range; TNM Tumor, node, metastases; PSA prostate-specific antigen; DKK currency in Danish crowns.[a]Charlson Comorbidity Index: None = 0 comorbid diseases Low = 1 comorbidity, Medium = 2 comorbidities, High = ≥3 comorbidities as registered in the national patient (hospital) registry with a look-back window of 10 years prior to cancer diagnosis. [b]Education was defined as highest degree achieved at time of prostate cancer diagnosis. [c]Income was defined as disposable income at time of prostate cancer diagnosis. [d]Urbanization was defined by the registered address and grouped by postal code at time of prostate cancer diagnosis.

at prostate cancer diagnosis 74–75 years vs. 69 years) and had more advanced disease at diagnosis with higher proportions of men with Gleason score ≥ 8 (48% vs. 27%), clinical TNM stage III, (45–48% versus 35%), and TNM stage IV (21–25% versus 9%). A higher proportion of the deceased men had history of high comorbidity (57–61% versus 22% with high Charlson scores ≥ 3). There were no notable differences in education, income, and urbanization among the deceased men across the groups.

Medical chart review showed that prostate cancer accounted for 51.2% of deaths, cardiovascular disease for 17.0%, other causes for 16.7%, other cancers for 13.9%, and lastly, other unspecified urological cancer death accounted for 1.2% of deaths (Table 2). The Danish Death Registry overestimated the proportion of deaths attributed to prostate cancer at 71.7% (70.0% for the subset of 670) when including all contributing causes of death, i.e. including cases where prostate cancer was registered as either the primary or a contributing cause of death.

We calculated measures of validity from the 670 men with complete medical records (Fig. 2), comparing to registry data where all contributing causes of death were included. The positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of the Danish Death Registry were 66.7%, 85.1%, 91.3% and 52.3%, respectively. Overall, there was a 73.1% (343/469) agreement between registry data and medical chart data for prostate cancer-specific death, and a 66.0% agreement for all five categories of death (442/670).

We restricted our analysis to prostate cancer-specific deaths defined as deaths registered with prostate cancer as the primary cause of death on death certificates, and excluded cases where prostate cancer was registered as a contributing cause of death. When restricting to registrations of prostate cancer as the primary cause of death, the proportion of deaths attributed to prostate cancer declined to 57.0% (55.5% for the

Table 2
Causes of death in Danish men with prostate cancer by data source (n = 3343 deaths).

Death groups - no. (%)	Death registry (PC as any contributing cause)[a]	Death registry (PC as primary cause)[b]	Death registry (PC as any contributing cause in subset with medical chart review)[c]	Death registry (PC as primary cause in subset with medical chart review)[d]	Medical chart review
Total deaths investigated - no. (%)	3343 (100.0)	3343 (100.0)	670 (100.0)	670 (100.0)	670 (100.0)
1 Prostate cancer-specific death	2397 (71.7)	1905 (57.0)	469 (70.0)	372 (55.5)	343 (51.2)
2 Other unspecified urological cancer death	15 (0.5)	18(0.54)	6 (0.9)	7 (1.0)	8 (1.2)
3 Other cancer death	285 (8.5)	436 (13.0)	58 (8.7)	93 (13.9)	93 (13.9)
4 Cardiovascular disease death	312 (9.3)	385 (11.5)	74 (11.0)	78 (11.6)	114 (17.0)
5 Other causes (e.g. infection, trauma)	334 (10.0)	599 (17.9)	63 (9.4)	120 (17.9)	112 (16.7)

Abbreviation: Death registry; Danish Register of Causes of Death. [a]Death as registered in Danish Register of Causes of Death for all deceased and where prostate cancer was registered as any contributing cause of death. [b]Death as registered in Danish Register of Causes of Death for all deceased and where prostate cancer was registered as the primary cause of death. [c]Death as registered in Danish Register of Causes of Death for the subset with medical chart review and where prostate cancer was registered as any contributing cause of death. [d]Death as registered in Danish Register of Causes of Death for the subset with medical chart review and where prostate cancer was registered as the primary cause of death.

Fig. 2. Measures of validity for the chart review cohort (n = 670).

subset of 670 cases). See Table 2.

Fig. 3 plots the cumulative incidence functions (CIF) when accounting for competing causes of death in men with prostate cancer. At 2 years of survival time (approximately 750 days, the probability of death by prostate cancer was 10%; other unspecified urological death was 0.1%; other cancer death was 1.3%; cardiovascular disease death was 1%; and death by other causes was 1.7%. At 11-years of survival time, the probability of death by prostate cancer was 50%, compared to 9% for cardiovascular disease death, and 8% for death by other causes. At 10-years of survival, the probability of death by other cancers was 6%. At 4-years of survival, the probability of death by other unspecified urological death was 0.2%.

The multivariable-adjusted hazard ratios for the cause-specific and subdistribution hazard models are shown in Table 3. Overall, the hazard ratios for both the Cox model and the Fine-Gray model were similar in magnitude and direction. Notably, cancer stage, Gleason score, and the Charlson Comorbidity Index score were associated with an increased risk of prostate cancer-specific death. Charlson Comorbidity Index scores more strongly affected the hazards ratio for deaths by other cancers (four to five- fold increased risk) compared to deaths by prostate cancer (one and a half-fold increased risk). Data for the multivariable-adjusted analyses were based on the Death Registry, including all contributing causes of death.

Table 4 compares the two regression models for prostate cancer-specific deaths using the following data algorithms from the Death Registry: i) inclusion of all contributing causes of death; and ii) restriction to only coding for the primary causes of death. Similar to our findings in Table 3, we observed that the hazard ratios for both the Cox and Fine and Gray models were again very similar in magnitude and direction, where cancer stage, Gleason score and the Charlson Comorbidity Index score were associated with an increased risk of prostate cancer-specific death.

4. Discussion

In this nationwide cohort study, prostate cancer accounted for at least half of all deaths, followed by cardiovascular disease, and thereafter death by other causes, e.g. infection and trauma. Given the short follow-up period of mean 2.4 years, the 3343 death cases in this study represent the most clinically aggressive tumors, in contrast to the majority group of survivors with clinically nonaggressive tumors. This is reflected in the relatively low overall probability of death by prostate cancer after 2 years of survival time (10%).

Overall, data from the Danish Causes of Death Registry

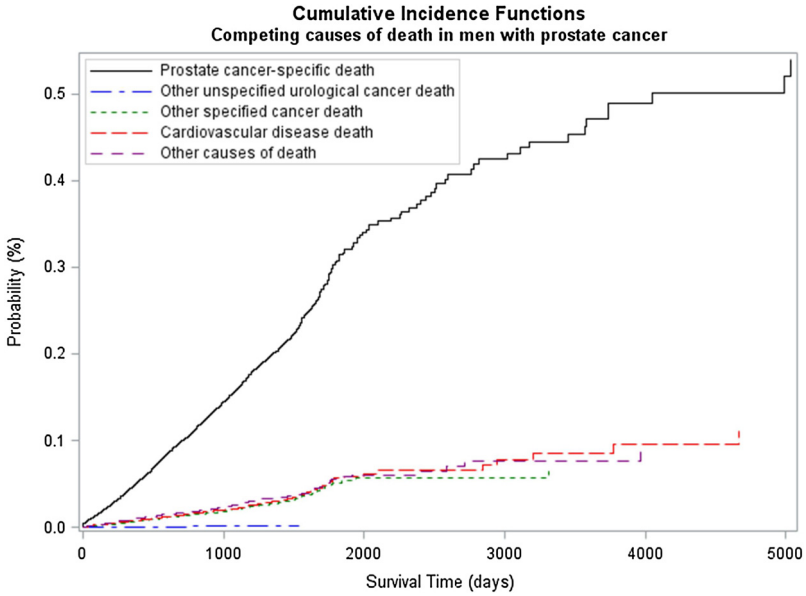

Fig. 3. Cumulative incidence functions for competing causes of death in Danish men with prostate cancer (n = 15,878).

overestimated the proportion of deaths attributable to prostate cancer. Compared to medical chart data, the proportion of misattribution ranged from 5% (lower bound estimate) to 21% (upper bound estimate). With respect to data validity, there was a 73% agreement between registry data and data from chart review when using the broad algorithm for all contributing causes of death. Using a more narrow definition of cause of death (restricted to only registrations of prostate cancer as the primary cause of death) yielded results that were more in alignment with medical chart data. When examining the subset of 670 men for whom we had both chart data and registry data, we found that prostate cancer-specific death accounted for 55.5% in registry data compared to 51.2% in medical chart data. However, using registrations of prostate cancer as the primary cause of death may selectively underestimate prostate cancer deaths masked by hospital-acquired pneumonia or urosepsis. In these cases, the infection prevails as the primary cause of death, despite the fact that prostate cancer was the reason for hospital admission and the true underlying cause of death.

Although this was a nationwide study, it was limited by missing data with a limited sample size for chart review. Complete medical records were available in only 20% of the deceased cohort (670/3343), and data from general practitioners for deaths occurring outside of the hospital and ambulance setting was not available. However, the distribution of death categories for the subset with chart review was relatively similar to the distribution of death categories when comparing to data from the Death Registry restricted to primary causes of death (Table 2).

Similar to other countries, autopsy rates are low in Denmark. Only 10% of all deaths and 20% of deaths occurring in-hospital in Denmark are autopsied compared to the autopsy rate of 75% in the 1970s [12]. These trends are unfortunate since autopsy is the highest clinical standard for ascertaining the cause of death. Medical records review of the 670 cases was performed by the same physician for a consistent, albeit person-specific, evaluation of the cause of death. Also, particular attention was paid to the assessment of deaths with complicating events such as acute myocardial infarction, urosepsis, and pneumonia to discriminate whether or not prostate cancer was the underlying cause of death.

There are several underlying reasons, taken alone or in combination, that may cause incorrect labelling of death from other causes as death from prostate cancer [16]. The general perception of cancer as a severe diagnosis can, in and of itself, lead to registering prostate cancer as a contributing cause to death. Also, there may be a general misunderstanding as to how to code for causes of death by physicians. Since the death certificates allow for one primary cause of death and up to three contributing causes of death, cancer may likely be added as a secondary or tertiary cause of death to fill in the available lines with the best intention of detailed registration. Finally, in cause-specific mortality analyses, the methodological practice of using the primary cause of death or all contributing causes of death when defining cause of death varies in the literature, which complicates comparison across studies.

Our findings are consistent with previous results from Great Britain, showing that in countries with low rates of asymptomatic PSA screening, prostate cancer remains a leading cause of death among men with prostate cancer. In 2013, an analysis of data from the Thames Cancer Registry showed that 50% of the deaths occurring in men with prostate cancer were due to prostate cancer itself [17]. A 2016 study investigated 1236 U.K. death certificates in men from a prostate cancer trial cohort and attributed prostate cancer death to 42%; and reported high sensitivity (91%) and specificity (92%) of the U.K. death certificates [18].

Other Scandinavian countries have investigated causes of death and the validity of death registrations among men with prostate cancer [9,19,20]. In a large validation study of 5675 deaths and the reliability of the Swedish Cause of Death Register, investigators reported an 86% agreement between Swedish registry data and medical records review, in contrast to our findings of 73% agreement for prostate cancer-specific deaths in the Danish death registry [8]. They also found that misattribution of prostate cancer death increased with increasing age and comorbidity. The Swedish validation study defined prostate cancer death strictly as the primary cause of death registered in the Swedish Death Registry. A Norwegian study from 2018 of 764 deaths concluded that prostate cancer deaths were over-reported and misattribution of cause of death was particularly associated with increasing age (> 75 years old) [9]. The Finnish Randomized Study of Screening for Prostate Cancer reported a 95% agreement after comparing 442 medical records with the Finnish cause of death registry [19]. All of the above studies classified death as binary categories, i.e. prostate cancer-specific death and non-prostate cancer death. We extended the knowledge by differentiating between five death categories and by performing a comparative competing risks analysis of two regression models.

Misclassification of the cause of death in national death registries and death certificates can have implications for cause-specific mortality analysis as demonstrated by Hoffmann et al. [7].This study validated

Table 3
Hazard ratios (95% CI) from Fine & Gray subdistribution and Cox cause-specific hazard models for competing causes of death in Danish men with prostate cancer (n = 15,878).

	Fine & Gray Subdistribution Hazard Model				
Covariate	1 Prostate cancer-specific death	2 Other unspecified urological cancer death	3 Other cancer death	4 Cardiovascular disease death	5 Other causes
Age (years)	1.02 (1.01-1.03)	0.98 (0.92-1.04)	1.00 (0.98-1.01)	1.07 (1.04-1.09)	1.06 (1.03-1.08)
PSA (total μg/l)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Gleason Score	1.77 (1.68-1.86)	0.62 (0.35-1.09)	0.74 (0.64-0.84)	0.86 (0.75-0.98)	1.13 (0.99-1.29)
Clinical TNM Stage	1.12 (1.09-1.15)	0.92 (0.74-1.15)	0.95 (0.90-1.00)	0.96 (0.91-1.01)	0.97 (0.93-1.03
Charlson Comorbidity Index[a]	1.48 (1.42-1.54)	4.96 (1.31-18.79)	4.47 (3.65-5.48)	1.52 (1.36-1.70)	1.39 (1.25-1.55)
Education[b]	0.92 (0.88-0.96)	1.19 (0.70-2.03)	1.20 (1.06-1.36)	0.97 (0.85-1.10)	0.90 (0.80-1.02)
Income[c]	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Urbanization[d]	0.97 (0.94-1.01)	1.31 (0.82-2.09)	0.89 (0.79-1.00)	1.04 (0.93-1.16)	1.00 (0.89-1.11)
Trend *p*- value	< 0.0001	0.04	< 0.0001	< 0.0001	< 0.0001
	Cox Cause-Specific Hazard Model				
Covariate	1 Prostate cancer-specific death	2 Other unspecified urological cancer death	3 Other cancer death	4 Cardiovascular disease death	5 Other causes
Age (years)	1.03 (1.21-1.03)	0.98 (0.92-1.05)	1.00 (0.98-1.02)	1.07 (1.05-1.09)	1.06 (1.04-1.08)
PSA (total μg/l)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)
Gleason Score	1.80 (1.71-1.89)	0.64 (0.34-1.19)	0.77 (0.67-0.88)	0.90 (0.79-1.02)	1.18 (1.04-1.33)
Clinical TNM Stage	1.13 (1.11-1.16)	0.92 (0.73-1.16)	0.95 (0.90-1.00)	0.97 (0.92-1.02)	0.98 (0.93-1.03)
Charlson Comorbidity Index[a]	1.54 (1.47-1.60)	5.06 (2.00-12.85)	4.61 (3.67-5.79)	1.57 (1.40-1.76)	1.44 (1.29-1.60)
Education[b]	0.92 (0.88-0.96)	1.18 (0.68-2.05)	1.19 (1.04-1.36)	0.96 (0.85-1.08)	0.90 (0.80-1.01)
Income[c]	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Urbanization[d]	0.96 (0.92-1.00)	1.30 (0.84-1.99)	0.87 (0.77-0.98)	1.02 (0.91-1.13)	0.98 (0.88-1.09)
Trend *p*- value	< 0.0001	0.0002	< 0.0001	< 0.0001	< 0.0001

Each cell contains multivariable-adjusted HR (95% confidence intervals), adjusted for age, cancer stage, PSA value, Gleason score, Charlson Comorbidity Index Score (CCI), education, income, and urbanization at time of PC diagnosis. Data based on the Danish Death registry including all contributing causes of death. [a]Charlson Comorbidity Index: None = 0 comorbid diseases, Low = 1 comorbidity, Medium = 2 comorbidities, High = ≥ 3 comorbidities as registered in the national patient (hospital) registry with a look-back window of 10 years prior to cancer diagnosis. [b]Education was defined as highest degree achieved at time of prostate cancer diagnosis. [c]Income was defined as disposable income at time of prostate cancer diagnosis. [d]Urbanization was defined by the registered address and grouped by postal code at time of prostate cancer diagnosis.

Table 4
Comparison of data from Danish Register of Causes of Death with inclusion of all contributing causes of death versus restriction to only coding for the primary causes of death (n = 15,878).

	Fine & Gray Subdistribution Hazard Model for prostate cancer-specific death	
Covariate	All contributing causes of death	Primary cause of death
Age (years)	1.02 (1.01-1.03)	1.01 (1.00-1.02)
PSA (total μg/l)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Gleason Score	1.77 (1.68-1.86)	1.99 (1.87-2.11)
Clinical TNM Stage	1.12 (1.09-1.15)	1.15(1.11 - 1.19)
Charlson Comorbidity Index[a]	1.48 (1.42-1.54)	1.39 (1.32-1.45)
Education[b]	0.92 (0.88-0.96)	0.89 (0.85-0.94)
Income[c]	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Urbanization[d]	0.97 (0.94-1.01)	0.97 (0.93-1.02)
Trend *p*- value	< 0.0001	
	Cox Cause-Specific Hazard Model for prostate cancer-specific death	
Covariate	All contributing causes of death	Primary cause of death
Age (years)	1.03 (1.21-1.03)	1.02 (1.01-1.02)
PSA (total μg/l)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Gleason Score	1.80 (1.71-1.89)	2.02 (1.90-2.14)
Clinical TNM Stage	1.13 (1.11-1.16)	1.17 (1.14-1.20)
Charlson Comorbidity Index[a]	1.54 (1.47-1.60)	1.44 (1.38-1.51)
Education[b]	0.92 (0.88-0.96)	0.89 (0.85-0.94)
Income[c]	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Urbanization[d]	0.96 (0.92-1.00)	0.96 (0.91-1.00)
Trend *p*- value	< 0.0001	< 0.0001

Each cell contains multivariable-adjusted HR (95% confidence intervals), adjusted for age, cancer stage, PSA value, Gleason score, Charlson Comorbidity Index Score (CCI), education, income, and urbanization at time of PC diagnosis. [a]Charlson Comorbidity Index: None = 0 comorbid diseases, Low = 1 comorbidity, Medium = 2 comorbidities, High = ≥ 3 comorbidities as registered in the national patient (hospital) registry with a look-back window of 10 years prior to cancer diagnosis. [b]Education was defined as highest degree achieved at time of prostate cancer diagnosis. [c]Income was defined as disposable income at time of prostate cancer diagnosis. [d]Urbanization was defined by the registered address and grouped by postal code at time of prostate cancer diagnosis.

death certificates in New Mexico, USA and demonstrated that attribution bias overestimated mortality estimates by 53% of the observed increase in prostate cancer mortality [7]. It is important that competing risks of death are accounted for when estimating the cumulative death rates, as failing to do so can result in overestimation of the risks as previously demonstrated in the literature [15,21–23].

In this study, the Cox cause-specific hazard model and the Fine and Gray subdistribution hazard model yielded similar estimates, both with respect to magnitude and direction, and across death categories. This was also the case when comparing the two different data algorithms from the Danish Register of Causes of Death: 1) inclusion of all contributing causes of death and 2) restriction to only coding for the primary cause of death. In the setting where death by other causes is very frequent, the Fine and Gray subdistribution hazard model has been suggested as an alternative since it directly models the effect of covariates on the subdistribution hazard (cumulative incidence function) for all competing events [15]. In our study, the data algorithm using all contributing causes of death, resulted in a relatively low frequency of competing causes of death (less than 30% of the registry-based causes of deaths were non-prostate cancer deaths), whereas the data algorithm based on coding for primary causes of death resulted in a 50/50 distribution of prostate cancer deaths and non-prostate cancer deaths. However, even in the scenario with competing causes of death accounting for about 50% of deaths, we observed no notable differences in the magnitude or direction of the hazard ratios when comparing the Fine and Gray subdistributional hazard model to the Cox cause-specific hazard model.

4.1. Conclusions

Approximately half to two-thirds of the deceased men in our study cohort died of their prostate cancer disease within the mean 2.4 years of follow up time. However, the probability of dying of prostate cancer among the entire prostate cancer cohort was only 10% at 2 years of survival, and first reached 50% at 11 years of survival. Our findings suggest that data from the Danish Death Registry overestimates prostate cancer-specific death, and this misclassification can contribute to bias in registry-based analyses of cause-specific mortality.

Conflict of interest

The authors declare no conflicts of interest.

Authorship contribution

All authors contributed substantially to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; and the final approval of the version to be published. MNN was the lead investigator in the conception and design, data acquisition and analysis, and drafting of the manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.02.017.

Appendix A. ICD Classification of causes of death identified in Danish Death Registry

Death category	ICD-10 code
Prostate Cancer	C61
Other unspecified urological cancer	C63 Malignant neoplasm of other and unspecified male genital organs C68 Malignant neoplasm of other and unspecified urinary organs C80 Unspecified malignant neoplasm D40 Neoplasm of uncertain or unknown behavior of male genital organs D41 Neoplasm of uncertain or unknown behavior of urinary organs
Other cancers	C00-C96, excluding C61, C63, and C68
Cardiovascular disease	I00-I15; I20-I99
Other causes	All other codes than those listed above

Abbreviations: ICD-10, International Classification of Diseases defined by the World Health Organization (WHO), 10th revision.

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