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Genitourinary Cancer: Prostate

What Do Prostate Cancer Patients Die Of?

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ABSTRACT

Background. **A recent rise in the incidence of prostate cancer and a more favorable outcome have increased the proportions of other causes of death in affected men. Extending the survival of prostate cancer patients thus requires knowledge of all causes of death.**

Methods. **Data on the population, cancers, and causes of death were gathered from the nationwide Swedish Family-Cancer Database. A Cox regression model, comparing prostate cancer patients with all other men, was applied. Hazard ratios (HR) were calculated both for the underlying cause and for dying with a specific cause listed among multiple causes of death.**

Findings. **Among 686,500 observed deaths, 62,500 were prostate cancer patients. For underlying causes other than prostate cancer, the highest cause-specific HRs were found for external causes (HR, 1.24; 95% confidence interval [CI], 1.16–1.31), diseases of the pulmonary circulation (HR, 1.22; 95% CI, 1.09–1.37), and heart failure (HR, 1.18; 95% CI, 1.11–1.24). For specific multiple causes, the highest HRs were found for anemia (HR, 2.28; 95% CI, 2.14–2.42), diseases of the pulmonary circulation (HR, 1.61; 95% CI, 1.55–1.68), and urinary system disease (HR, 1.90; 95% CI, 1.84–1.96).**

Interpretations. **Prostate cancer patients have a higher risk for dying from various causes other than prostate cancer, including external causes and heart failure. Mechanisms have been proposed linking these elevated risks to both cancer and treatment. More attention should be paid to comorbidities in men with prostate cancer. The present study fulfills a gap in the knowledge of death causes in prostate cancer patients.** ***The Oncologist*** 2011;16:175–181

INTRODUCTION

Approximately half of the men who receive a diagnosis of prostate cancer (PC) die from PC itself [1]. This proportion can be expected to decrease, considering the recent increase in the incidence of PC and the fact that mortality from PC has stabilized or even started to decline [2]. More efficient treatment and earlier diagnosis resulting from the introduction of prostate-specific antigen tests are thought to explain these epidemiologic changes [2, 3]. As a consequence, fewer patients are dying from PC whereas other conditions

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are playing a greater role. Improvements in survival of PC patients will increasingly require consideration of comorbidities.

Although we are not aware of any studies extensively covering causes of death in PC patients, some studies have reported higher risks for cardiovascular disease [1, 4] and suicide [4, 5] following a PC diagnosis. PC patients with heart failure have been shown to have a higher risk for death than PC patients without heart failure [6]. Also, PC is less frequently mentioned as the underlying cause of death in older patients [7] or patients with lower stage disease [6]. In the present study, we used the nationwide Swedish Family-Cancer Database to analyze causes of death in PC patients compared with all other men in the database. The aim of our study was to investigate whether a diagnosis of PC was associated with a greater risk for dying from any specific condition. We analyzed both the underlying cause and multiple causes of death, and furthermore made a distinction depending on the number of death causes. The findings may motivate a greater attention by physicians to their PC patients regarding other diseases.

Materials and Methods

The 2006 update of the Swedish Family-Cancer Database includes all individuals born after 1931 who are residing in Sweden, together with their biological parents, totaling around 11.8 million individuals [8]. The first version of the database was created in 1996 by combining the Swedish Cancer Registry and the Swedish Multigenerational Register. The database has been regularly updated and now includes more than one million cancer cases diagnosed up to the end of 2006 [8]. The database includes information about cancers, socioeconomic data, and death causes. Death causes (up to 10 multiple causes plus the one underlying cause) are coded according to different versions of the International Classification of Diseases (ICD-7 to ICD-10), depending on the year of death. The underlying cause of death is, as defined by the World Health Organization, "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury," whereas the listed multiple causes are complications and other contributing causes [9].

The chosen study time was 1987–2006, because during this time all death causes were coded according to either the ICD-9 (used in 1987–1996) or the ICD-10 (used since 1997), which are easy to compare. All men born before 1957 residing in Sweden were defined as the study population, totaling 2.27 million men, of which 117,000 were PC patients. PC patients were defined as those who were diagnosed with PC (ICD-7 code 177) as the first invasive cancer. The rest of the men were part of the nonprostate group, which was the reference group. The underlying cause and multiple causes of death were allocated into several distinguishable disease categories (see below). Hazard ratios (HRs) for death from a specific cause for PC patients compared with men without PC were calculated using a Cox regression model with age as the underlying time scale. All calculations were made with SAS software (PROC PHREG; SAS Version 9.2; SAS Institute, Cary, NC). Subjects entered the study at the time of immigration, presence at census, or January 1987, whichever occurred most recently. Men initially in the reference group were assigned to the PC group at the time of their PC diagnosis. Censoring events were death from a cause other than the cause of interest, emigration, absence at census, or December 2006. First, HRs were calculated for the underlying cause of death, wherein the event of interest was having a specific condition as the underlying cause. Then, analyses were made on multiple causes of death, wherein the event of interest was having a specific cause listed among multiple causes. Finally, a distinction was made depending on the number of death causes. Here, the event of interest was having a specific death cause listed among multiple causes, as well as having a certain number of death causes: two, three, and four or more. Thus, it could be determined whether some death causes were more frequent in either PC patients with few death causes or PC patients with many contributing conditions causing death. The underlying cause was always included in the calculations on multiple causes. The socioeconomic index and the geographical region of residence were included as covariates, with individuals grouped according to last known entry in a census.

Definitions of Disease Categories

ICD codes used in the disease categories were the following (ICD-10; ICD-9): myocardial infarction (I21-I22; 410), other coronary heart disease (I20, I23-I25; 411–414), cerebrovascular accident (I60-I69; 430–438), arterial disease (I70-I79; 440–448), heart failure (I50; 428), pneumonia (J10-J18; 480–487), chronic lower respiratory disease (J40-J49; 490–496), external causes (S00-T98, V01-Y98; 800–900, e800-e999), complications of diagnostic or surgical procedures (Y60-Y84; e870-e879), complications of therapeutic drug or vaccine usage (Y40-Y59; e930-e949), suicide (X60-X84; e950-e959), traffic accident (V01-V99; e800-e848), falls (W00-W19; e880-e888), other heart disease (I30-I49, I52; 420–427), gastrointestinal disease (K00-K93; 520–579), dementia (F00-F03, G30; 290, 331.0), diabetes (E10-E14; 250), complications of heart disease (I51; 429), urinary system disease (N00-N39; 580–599), symptoms (R00-R99; 780–799), pulmonary circula-

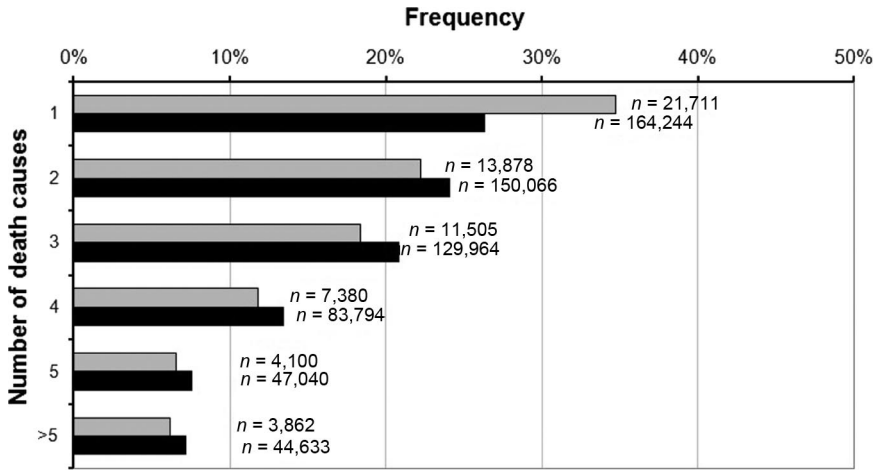

Figure 1. Number of death causes in deceased men with (gray) and without (black) prostate cancer.

tion (I26-I28, J81; 415–417, 514), nervous system disease (G00-G99, except G30; 320–359, except 331.0), hypertensive disease (I10-I19; 401–405), other bacterial disease (A30-A49; 030–041), psychic disease (F04-F99; 291–319), anemia (D50-D64; 280–285), tumors other than prostate cancer (C00-D48, excluding C61, C77-C80, and C97; 140–239, excluding 185, 196–199), and prostate cancer (C61; 185).

Results

The total number of deaths was 686,500. Of these, 62,500 were PC patients. PC patients had fewer death causes than all other men (Fig. 1). In the initial calculations, underlying causes were investigated (Table 1). Apart from PC, which was the underlying cause in 50% of decedents in the PC group, the most common underlying causes in PC patients were various cardiovascular diseases, other tumors, and respiratory diseases. The highest HRs were found for external causes (1.24), pulmonary circulation (1.22), and heart failure (1.18). Anemia, dementia, and urinary system disease featured low HRs as underlying causes. Separate HRs (not shown) were computed for two follow-up times: <5 years and >5 years following diagnosis. Differences between these follow-up times were minor. Nevertheless, the HR for heart failure was higher >5 years after diagnosis of PC (HR, 1.27; 95% confidence interval [CI], 1.18–1.36) than <5 years after diagnosis (HR, 1.07; 95% CI, 0.99–1.16), whereas the HR for pulmonary circulation was lower—1.13 (95% CI, 0.95–1.35) versus 1.30; (95% CI, 1.11–1.51). In analyses on multiple causes of death, the number of death causes was not considered (Table 1). The highest HRs were attributed to anemia (2.28), urinary system disease (1.90), and pulmonary circulation (1.61). In further analyses on multiple causes, the number of death causes was accounted for (Table 2). Urinary tract disease (3.10), anemia (2.74), and pulmonary circulation (1.93) showed the highest HRs when they were one of the two listed death causes.

Discussion

We investigated causes of death in PC patients, with a group of men without PC as the comparison group. Having access to a large database, we used a Cox regression model with death from a specific cause as the event of interest. We found that PC patients had a higher risk for dying from external causes, heart failure, and diseases of the pulmonary circulation. Moreover, we discovered PC patients to have a greater risk for dying with anemia and urinary system disease among the listed multiple causes. The highest HRs for these two causes were seen among decedents with only two listed death causes. There were also some lower risks, most notably a substantially lower risk for dying from dementia. A previous Swedish study found that neoplastic conditions were infrequently mentioned as the underlying cause of death in dementia patients, compared with patients without dementia [10]. Our results might be a result of fewer cancer diagnoses in dementia patients. We also suspect a possible overrepresentation of PC as the underlying cause, especially in deaths occurring shortly after diagnosis and in older men. This possible overrepresentation of PC was our motivation for also comparing death cause–specific risks <5 years and >5 years after diagnosis. More benign conditions, such as anemia, are possibly more seldom chosen as the underlying cause of death if the physician issuing the death certificate is aware of a previous PC diagnosis. This could explain the lower risks.

Our study compared 27 non-PC death causes among both the underlying cause and multiple causes of death. The reliability of the underlying cause is probably higher than that of multiple causes, but these may be used complemen-

Table 1. HRs for dying from selected conditions when individuals were diagnosed with PC as their first cancer (n = 116,945) compared with all other men (n = 2,152,094)

	Underlying cause of death				One of multiple causes of death			
Death cause	**Death with PC**	**Death without PC**	**HR**	**95% CI**	**Death with PC**	**Death without PC**	**HR**	**95% CI**
Myocardial infarction	5,693	110,945	1.01	0.98–1.04	6,902	126,381	**1.06**	1.04–1.09
Other coronary heart disease	3,909	65,615	**1.04**	1.01–1.08	9,284	144,697	**1.18**	1.15–1.20
Cerebrovascular accident	3,457	56,340	0.99	0.96–1.03	6,664	93,601	**1.14**	1.11–1.17
Arterial disease	1,453	24,752	0.97	0.92–1.02	5,059	82,634	1.02	0.99–1.05
Heart failure	1,421	15,393	**1.18**	1.11–1.24	10,422	113,598	**1.36**	1.34–1.39
Pneumonia	1,359	21,554	**0.89**	0.84–0.94	6,197	76,878	**1.25**	1.22–1.28
Chronic lower respiratory disease	1,205	18,391	**1.10**	1.04–1.17	3,186	42,974	**1.24**	1.20–1.29
External causes	1,198	34,513	**1.24**	1.16–1.31	5,011	80,864	**1.55**	1.50–1.59
Complications of diagnostic or surgical procedures	27	416	0.93	0.63–1.37	2,846	35,864	**1.64**	1.58–1.70
Complications of therapeutic drug or vaccine use	3	38	1.74	0.53–5.79	362	5,276	**1.45**	1.30–1.61
Suicide	287	10,699	**1.74**	1.54–1.97	290	10,740	**1.75**	1.55–1.97
Traffic accident	98	4,614	1.05	0.85–1.28	106	4,818	1.05	0.86–1.27
Falls	347	5,767	**1.16**	1.04–1.30	780	9,399	**1.45**	1.35–1.56
Other heart disease	1,076	16,946	**1.07**	1.01–1.14	5,789	76,509	**1.27**	1.24–1.31
Gastrointestinal disease	996	20,910	**1.09**	1.02–1.16	3,222	48,287	**1.45**	1.40–1.50
Dementia	776	14,790	**0.67**	0.63–0.72	2,667	37,058	**0.92**	0.88–0.96
Diabetes	515	11,210	0.92	0.84–1.00	3,675	53,903	**1.26**	1.22–1.31
Complications of heart disease	400	6,168	**1.16**	1.05–1.28	2,528	37,245	**1.29**	1.24–1.34
Urinary system disease	395	8,151	**0.69**	0.62–0.77	5,019	41,908	**1.90**	1.84–1.96
Symptoms	356	8,284	**0.77**	0.70–0.86	9,264	109,429	**1.43**	1.40–1.46
Pulmonary circulation	311	4,884	**1.22**	1.09–1.37	2,778	32,474	**1.61**	1.55–1.68
Nervous system disease	307	8,293	**0.89**	0.79–0.99	2,061	32,185	**1.27**	1.22–1.33
Hypertensive disease	254	3,814	1.06	0.94–1.21	2,274	33,434	**1.22**	1.17–1.27
Other bacterial disease	209	2,808	**1.25**	1.08–1.44	958	12,749	**1.44**	1.35–1.54
Psychic disease	89	6,533	**0.79**	0.64–0.98	675	30,751	0.93	0.86–1.01
Anemia	51	993	**0.74**	0.56–0.98	1,145	7,148	**2.28**	2.14–2.42
Tumor other than prostate cancer	4,512	132,112	**0.80**	0.78–0.82	6,264	151,269	**0.92**	0.90–0.94
Prostate cancer	31,226	4,962	147.9	143.2–152.8	42,719	8,316	105.5	102.9–108.2

Boldface entries indicate significant HRs.
Abbreviations: CI, confidence interval; HR, hazard ratio; PC, prostate cancer.

tary to each other. Multiple causes of death are important contributors to mortality and they show the spectrum of comorbidities. Also, because half of the dead PC patients had PC listed as the underlying cause, excluding multiple causes would yield less information. To date, most studies on mortality are restricted to using the underlying cause only, a shortcoming that was pointed out earlier [10]. Our study also differs from earlier studies in the use of cause-specific HRs. In contrast, some other studies have analyzed death causes reported on the death certificates of PC patients, compared with men without PC [1, 7]. The influence of comorbidities on survival [6] and the odds of death [7] has also been investigated.

In the interpretation of our study, the limitation that our method does not take causality into consideration has to be taken into account. Thus, we cannot conclude whether PC (or its treatment) increases the risk for a comorbidity, or vice versa. Moreover, our results rely on the validity of death certificates. Studies on the reliability of Swedish death certificates have found that reports of a malignant

Table 2. HRs for having a selected condition as one of a specific number of death causes when individuals were diagnosed with PC as their first cancer (n = 116,945) compared with all other men (n = 2,152,094)

	As one of two death causes				As one of three death causes				As one of four or more death causes			
Death cause	**Death with PC**	**Death without PC**	**HR**	**95% CI**	**Death with PC**	**Death without PC**	**HR**	**95% CI**	**Death with PC**	**Death without PC**	**HR**	**95% CI**
Myocardial infarction	1,570	34,665	**0.92**	0.87–0.97	1,735	30,723	**1.09**	1.03–1.14	2,916	41,615	**1.29**	1.24–1.34
Other coronary heart disease	1,502	33,334	**0.92**	0.88–0.97	2,325	38,022	**1.12**	1.07–1.17	5,282	66,695	**1.36**	1.32–1.39
Cerebrovascular accident	1,318	18,406	**1.17**	1.11–1.24	1,505	20,414	**1.17**	1.11–1.23	3,283	41,776	**1.23**	1.18–1.27
Arterial disease	772	15,610	**0.84**	0.78–0.90	1,184	20,369	0.97	0.92–1.03	2,928	42,954	**1.13**	1.09–1.17
Heart failure	1,784	19,210	**1.34**	1.27–1.40	2,839	29,602	**1.41**	1.35–1.46	5,603	61,287	**1.39**	1.35–1.43
Pneumonia	1,548	18,150	**1.35**	1.28–1.42	1,627	20,634	**1.22**	1.16–1.28	2,792	33,885	**1.29**	1.24–1.34
Chronic lower respiratory disease	425	6,299	**1.17**	1.06–1.29	789	11,089	**1.20**	1.11–1.29	1,921	24,423	**1.29**	1.23–1.35
External causes	557	10,997	**1.56**	1.43–1.70	1,086	14,133	**1.69**	1.59–1.80	2,959	37,012	**1.53**	1.47–1.59
Complications of diagnostic or surgical procedures	264	3,692	**1.67**	1.47–1.89	649	7,553	**1.86**	1.71–2.02	1,911	24,068	**1.58**	1.51–1.66
Complications of therapeutic drug or vaccine use	6	112	1.08	0.47–2.47	57	901	**1.37**	1.05–1.80	299	4,247	**1.48**	1.31–1.66
Suicide	45	1,389	**1.91**	1.40–2.59	33	443	**3.41**	2.34–4.95	11	204	**2.29**	1.22–4.32
Traffic accident	16	593	1.01	0.61–1.67	7	265	0.76	0.36–1.63	10	260	0.90	0.48–1.71
Falls	149	2,084	**1.43**	1.21–1.70	211	2,351	**1.47**	1.28–1.70	357	3,641	**1.49**	1.34–1.67
Other heart disease	635	11,364	1.04	0.96–1.12	1,380	19,222	**1.24**	1.18–1.31	3,723	44,813	**1.35**	1.30–1.39
Gastrointestinal disease	595	8,280	**1.69**	1.55–1.84	749	11,349	**1.51**	1.40–1.63	1,806	26,830	**1.40**	1.33–1.47
Dementia	414	7,490	**0.71**	0.65–0.79	683	9,631	**0.91**	0.84–0.98	1,492	17,919	**1.06**	1.00–1.11
Diabetes	321	5,091	**1.24**	1.10–1.39	835	12,953	**1.20**	1.12–1.29	2,510	35,595	**1.29**	1.23–1.34
Complications of heart disease	390	5,758	**1.29**	1.16–1.43	695	9,898	**1.35**	1.25–1.46	1,397	20,401	**1.28**	1.21–1.35
Urinary system disease	1,025	5,010	**3.10**	2.89–3.31	1,212	8,846	**2.07**	1.95–2.20	2,732	27,184	**1.64**	1.58–1.71
Symptoms	1,942	19,805	**1.72**	1.64–1.80	2,284	25,841	**1.48**	1.42–1.55	4,719	56,418	**1.38**	1.34–1.42
Pulmonary circulation	529	5,478	**1.93**	1.76–2.12	709	7,993	**1.65**	1.53–1.79	1,476	17,572	**1.55**	1.47–1.64
Nervous system disease	270	5,270	**1.20**	1.06–1.36	456	7,382	**1.26**	1.14–1.38	1,305	18,149	**1.32**	1.25–1.40
Hypertensive disease	137	3,426	**0.83**	0.70–0.98	435	7,281	**1.11**	1.01–1.23	1,701	22,697	**1.30**	1.24–1.37
Other bacterial disease	168	1,935	**1.68**	1.43–1.97	243	2,777	**1.69**	1.48–1.93	528	7,746	**1.31**	1.20–1.43
Psychic disease	110	8,327	0.83	0.68–1.00	149	7,429	0.85	0.72–1.00	400	12,465	1.01	0.91–1.11
Anemia	128	720	**2.74**	2.26–3.32	294	1,569	**2.66**	2.35–3.02	722	4,719	**2.14**	1.98–2.32
Tumor other than prostate cancer	1,638	31,556	**1.15**	1.10–1.21	1,221	22,252	**1.10**	1.04–1.17	1,837	27,784	**1.20**	1.14–1.25
Prostate cancer	8,819	1,785	**100.2**	94.9–105.7	7,085	1,668	**73.6**	69.6–77.8	9,968	2,770	**56.1**	53.7–58.6

Boldface entries indicate significant HRs.
Abbreviations: CI, confidence interval; HR, hazard ratio; PC, prostate cancer.

neoplasm or ischemic heart disease as the underlying cause are reliable [12]. In comparison, certificates with chronic obstructive pulmonary disease or nonischemic heart disease as the underlying cause are not as accurate. Therefore, the reliability of our results on more common death causes is most likely higher than the reliability of our results on less common causes. One study specifically examined the reliability of death certificates in PC patients, concluding that the reliability is high, especially in younger men with localized disease [13]. In Sweden, the physician who issues the death certificate may vary, depending on where the death occurred. In 1997–2003, approximately 42%–45% of Swedish men aged >65 years died in hospitals [14]. Even though very limited data are available on death locations of Swedish PC patients, one can assume that the majority of terminally ill patients are nursed in hospitals or hospices.

In the following paragraphs we discuss disease-specific mechanisms as possible explanations for our findings.

Cardiovascular Diseases

Heart failure showed the highest excess risk among cardiovascular diseases in PC patients. Possible mechanisms linking cancer to cardiac disease have been proposed, although not specifically addressing PC patients. Chemotherapy is

widely known to have general cardiotoxic effects. Although no link has been shown between cardiotoxicity and radiation therapy in PC patients, it may be cardiotoxic in other cancers. A link between androgen deprivation therapy (ADT), the primary noncurative therapy for PC, and cardiovascular disease has been shown; previous studies have found that ADT-treated PC patients had a greater risk for being diagnosed with several types of cardiac disease [15]. Possible reasons for this higher risk are related to the metabolic effects of ADT: increased body fat composition, weight gain, insulin resistance, and alterations in blood lipid values [16–18]. However, the effect of ADT on cardiovascular mortality is unclear.

Anemia

Although we found that PC patients had a lower risk for dying from anemia as the underlying cause, they had a substantially higher risk for dying with it as one cause among multiple causes, especially as one of two death causes. Some mechanisms linking PC to anemia have been suggested. Treatment with ADT may cause anemia [19, 20], because testosterone is known to increase erythropoiesis [20]. Another mechanism is through bone metastasis, termed leukoerythroblastic anemia [21].

Diseases of the Pulmonary Circulation

Pulmonary embolism, often caused by a venous thromboembolus, is the major death cause in this category. Van Hemelrijck and coworkers found a higher incidence of pulmonary embolism and venous thromboembolism in PC patients receiving treatment, especially those treated with ADT, during the first 6 months after the diagnosis of PC [22]. Similarly, a substantial proportion of PC patients undergoing prostatectomy (a frequently used curative therapy for PC) have a thrombotic event shortly after the surgery [23]. Thrombotic events are well-known complications of various medical procedures, most notably after surgery in cancer patients [24, 25]. Thrombotic events may even be the first manifestations of malignancy [26]. A previous Swedish study concluded that cancer diagnoses, PC included, are frequent within 6 months after a diagnosis of deep venous embolism. Some cancer-related mechanisms have been proposed explaining the thrombotic tendency in cancer patients, sometimes referred to as Trousseau's syndrome [27]. Possible mechanisms include protease-induced activation of coagulation factors and upregulation of procoagulative enzymes by tumor hypoxia and oncogenes.

Diseases of the Urinary System

PC patients had a lower risk for dying from urinary system disease as the underlying cause, but at a higher risk for dying with it among multiple causes. End-stage renal disease patients on dialysis have a greater risk for cancer, including PC [28], and the stage of PC is also higher in these patients than in patients not on dialysis [29]. Urinary tract infections are also included in this category; men undergoing prostatectomy have a higher risk for these infections [30]. We believe that urinary tract infections and renal failure could explain our results.

External Causes

This category includes various events, such as fractures, accidents, suicide, and iatrogenic causes. Many studies have shown a decrease in bone mineral density in PC patients treated with pharmacological ADT or orchiectomy [18, 31]. The mechanism is thought to be a shortage of estrogen, which is produced through aromatization of circulating testosterone [32]. Low testosterone levels increase bone frailty, and therefore increase the risk for fractures. Another explanation for the greater prevalence of fractures in PC patients could be bone metastasis, which also causes bone frailty [22]. We also found high HRs for suicide, which is supported by a recent study by Fall and coworkers [4]. They found that the risk for suicide in PC patients was highest during the first weeks after diagnosis, suggesting that diagnosis-associated emotional stress plays a greater role than treatment- or cancer-related mechanisms. Furthermore, Bill-Axelson and coworkers described a higher suicide risk in men with advanced or metastatic PC, but not in those with localized disease [5].

In conclusion, the present study indicates that PC patients have a higher risk for dying from various causes. Most notably, heart failure and external causes were listed as the underlying cause of death, whereas urinary tract disease, diseases of the pulmonary circulation, and anemia were more frequently listed among multiple causes of death. Mechanisms have been proposed linking these conditions to both PC and its treatment. Success in fighting PC and improving the quality of life of patients requires more focus on comorbidities.

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