# Causes of death in men with localized prostate cancer: a nationwide, population-based study 

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## Objective

To detail the distribution of causes of death from localized prostate cancer (PCa).

## Patients and Methods

The database PCBase Sweden links the Swedish National Prostate Cancer Register with other nationwide populationbased healthcare registers. We selected all 57187 men diagnosed with localized PCa between 1997 and 2009 and their 114374 PCa-free control subjects, matched according to age and county of residence. Mortality was calculated using competing risk regression analyses, taking into account PCa risk category, age and Charlson comorbidity index (CCI).

## Results

In men with low-risk PCa, all-cause mortality was lower compared with that in corresponding PCa-free men: 10-year all-cause mortality was $18 \%$ for men diagnosed at age 70 years, with a CCI score of 0 , and $21 \%$ among corresponding control subjects. Of these cases, $31 \%$ died from
cardiovascular disease (CVD) compared with $37 \%$ of the corresponding control subjects. For men with low-risk PCa, 10 -year PCa-mortality was $0.4,1$ and $3 \%$ when diagnosed at age 50, 60 and 70 years, respectively. PCa was the third most common cause of death (18\%), after CVD (31\%) and other cancers (30\%). By contrast, PCa was the most common cause of death in men with intermediate- and high-risk localized PCa.

## Conclusions

Men with low-risk PCa had lower all-cause mortality than PCa-free men because of lower CVD mortality, driven by early detection selection; however, for men with intermediateor high-risk disease, the rate of PCa death was substantial, irrespective of CCI score, and this was even more pronounced for those diagnosed at age 50 or 60 years.

## Keywords

comorbidities, prostate cancer death, curative treatment, localized disease

## Introduction

The advent of PSA testing has led to a rapid rise in the incidence of low-risk and intermediate-risk prostate cancer (PCa) in Sweden and elsewhere [1,2]. Men with low-risk PCa have a low risk of death from PCa for up to 15 years after the date of diagnosis [3-4]. In the National Prostate Cancer Register (NPCR) of Sweden, men with conservatively treated low-risk PCa (clinical local stage T1-2, Gleason score 2-6, PSA $<10 \mathrm{ng} / \mathrm{mL}$ ) had a $9 \%$ risk of PCa death and a $50 \%$ risk of death from other causes after 15 years of follow-up [5]. Despite the $9 \%$ PCa mortality, all-cause mortality for men with low-risk PCa, who were otherwise healthy, as indicated by a Charlson comorbidity index (CCI) score of 0 , was identical to that of matched PCa-free men. To further
investigate causes of death among men with localized PCa and PCa-free men, we used data in PCBaSe Sweden that originated from nationwide, population-based healthcare registers and demographic databases for 57187 men with localized PCa diagnosed between 1997 and 2009 and 114374 matched PCa-free men.

## Patients and Methods <br> Study Population and Data Collection

In 2010, the NPCR of Sweden was linked to a number of other population-based registers via the use of the Swedish personal identity number [6]. The resulting database, PCBaSe Sweden 2.0, also includes a control series of men free of PCa
at the time of sampling. The controls were randomly selected from men who matched an index case by county of residence and birth year [6]. We included men who were diagnosed with localized PCa between 1997 and 2009, who had not received androgen deprivation therapy as primary treatment ( $n=57$ 187), and their matched controls $(n=114374)$. Men on androgen deprivation therapy ( $n=17$ 537) were excluded because we had no additional information available on why these men with localized PCa were being treated with this therapy. Our focus was on men with localized disease treated with the standard treatment options available: surveillance, radical prostatectomy or radiotherapy. PCa-free men who were diagnosed with PCa during the follow-up were kept in the control group as we aimed to compare risk and cause of death for men with similar baseline characteristics to a background population in which PCa risk was not excluded. Follow-up was available until 31 December 2011.
The main outcome of interest was death as registered in the National Cause of Death Register [7]. We specifically studied death from PCa (International Classification of Diseases [ICD]-10: C61), other cancers (ICD-10: C00-99, apart from C61), cardiovascular disease (CVD; ICD-10: I00-I99), chronic obstructive pulmonary disease (ICD-10: J40-44), and collapsed other causes into one category. We included information on the following potential confounders: age at diagnosis, PCa risk category, delivered or planned primary treatment $<6$ months after date of diagnosis, household, level of education and comorbidity. The variable 'household' reflects a man's partnership status and was defined as not single, single with children, or single with no children. From the NPCR, which started in 1996 and captures $98 \%$ of all newly diagnosed, biopsy-confirmed PCa cases as compared with the Swedish Cancer Registry [8], we had detailed information about tumour characteristics and primary treatment [8,9]. Prostate cancer risk categories were defined according to a modification of the National Comprehensive Cancer Network Guidelines [6,10]. More specifically, low-risk localized PCa was defined as T1-2, Gleason score $2-6$, and PSA $<10 \mathrm{ng} / \mathrm{mL}$, whereas intermediate risk localized PCa was defined as T1-2, Gleason score 7 and/or $10<$ PSA $<20 \mathrm{ng} / \mathrm{mL}$, and high-risk localized PCa was defined as T3 and/or Gleason score 8-10 and/or $20<$ PSA $<50 \mathrm{ng} / \mathrm{mL}$. Information on household and level of education was taken from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (or LISA by its Swedish acronym), a database that integrates existing data from the labour market and educational and social sectors [11]. The CCI was calculated to assess the burden of concomitant disease and we used 17 groups of diseases with a specific weight ( $1,2,3$ and 6 ) assigned to each disease category based on discharge diagnoses in the National Patient Register [12,13]. The sum of these weights resulted in three levels of CCI score: 0 for no comorbidity, 1 for mild, and $2+$ for severe comorbidity [14].

## Statistical Analysis

Because PCa risk category at time of diagnosis is associated with socio-economic factors and comorbidity [15], we first performed univariate and multivariate conditional logistic regression to analyse how education, household and CCI were associated with low-, intermediate- and high-risk localized PCa , respectively. Fine and Gray competing risk regression analyses were then used to estimate 10 -year cause-specific mortality [16]. We first ran a multivariate Cox proportional hazards model for death from all causes. All variables were statistically significantly associated with outcome: age, CCI, education level, household and PCa risk category (results not shown). Year of PCa diagnosis did not have a strong effect on death from all causes, and, after inclusion in the models specified below, the results did not alter. Year of diagnosis was therefore not taken into account in our predictive models. We decided to predict mortality by age category (50, 60 and 70 years), CCI ( 0 and $2+$ ), and PCa risk category (PCa-free control subjects and men with low-, intermediateand high-risk localized PCa). Furthermore, to account for the strong association between age and death, all models included age as a second-degree polynomial. To facilitate the interpretation of the results we kept education level and household constant at their intermediate category for all prediction models: intermediate education level (10-12 years of school) and men who were married or in a civil partnership. A distinction between single men with and without children was made because fatherhood and civil status affect healthcare-seeking behaviour [17]. Thus, the different prediction parameters used in our models were based on age (50, 60 and 70 years at time of diagnosis), household (married or in civil partnership), education level (10-12 years of school), and CCI ( 0 and 2+). Household and education level were kept constant, whereas results were shown for different levels of age, CCI and PCa risk categories. As mortality may be different for curatively treated men compared with all men diagnosed with localized PCa as a result of the effect of treatment, but also as a result of selection of otherwise healthy men for curative treatments, competing risk regression analyses were also performed for this subgroup.
All data management was performed using sas release 9.2 (SAS Institute, Cary, NC, USA) and all statistical analysis were performed with R version 2.15.1 ( R Foundation for Statistical Computing, Vienna, Austria). The Research Ethics Board at Umeå University approved the project.

## Results

Of the 57187 men diagnosed with localized PCa between 1997 and 2009, 23460 (41\%) had low-risk disease, 20124 (35\%) intermediate-risk and 13603 (24\%) high-risk disease.

Table 1 Baseline characteristics for men with localized prostate cancer (PCa) and matched PCa-free control subjects.

|  | Low-risk PCa ( $n=23$ 460) | Intermediate-risk PCa $(n=20124)$ | High-risk PCa $(n=13603)$ | $\begin{gathered} \text { No PCa } \\ (n=114374) \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: |
| Mean (sD) follow-up time, years | 6.4 (3.2) | 6.2 (3.3) | 6.3 (3.4) | 6.3 (3.3) |
| Age group |  |  |  |  |
| $<65$ years | 10741 (45.8) | 6682 (33.2) | 3369 (24.8) | 41584 (36.4) |
| 65-74 years | 9578 (40.8) | 9109 (45.3) | 5817 (42.8) | 49008 (42.8) |
| 75-84 years | 2876 (12.3) | 3858 (19.2) | 3659 (26.9) | 20786 (18.2) |
| $\geq 85$ years | 265 (1.1) | 475 (2.4) | 758 (5.6) | 2996 (2.6) |
| Time period, $n(\%)$ |  |  |  |  |
| 1997-2000 | 3445 (14.7) | 3658 (18.2) | 3706 (27.2) | 209 (4.9) |
| 2001-2003 | 5015 (21.4) | 4175 (20.7) | 3051 (22.4) | 690 (16.2) |
| 2004-2006 | 7479 (31.9) | 5682 (28.2) | 3444 (25.3) | 1483 (34.8) |
| 2007-2009 | 7521 (32.1) | 6609 (32.8) | 3402 (25.0) | 1877 (44.1) |
| Treatment, $n$ (\%) |  |  |  |  |
| No PCa |  |  |  |  |
| Surveillance | 10907 (46.5) | 7726 (38.4) | 5753 (42.3) | 114374 (100.0) |
| Radical prostatectomy | 9515 (40.6) | 8218 (40.8) | 2695 (19.8) |  |
| Radiotherapy | 3038 (12.9) | 4180 (20.8) | 5155 (37.9) |  |
| Household, $\boldsymbol{n}$ (\%) |  |  |  |  |
| Not single | 17638 (75.2) | 14753 (73.3) | 9710 (71.4) | 77494 (67.8) |
| Single with children | 4079 (17.4) | 3767 (18.7) | 2655 (19.5) | 23455 (20.5) |
| Single, no children | 1743 (7.4) | 1604 (8.0) | 1238 (9.1) | 13425 (11.7) |
| Education, $\boldsymbol{n}$ (\%) |  |  |  |  |
| Low: $<10$ years | 7984 (34.0) | 7632 (37.9) | 5871 (43.2) | 48540 (42.4) |
| Intermediate: 10-12 years | 9248 (39.4) | 7613 (37.8) | 4792 (35.2) | 41024 (35.9) |
| High: >12 years | 6077 (25.9) | 4699 (23.4) | 2713 (19.9) | 22643 (19.8) |
| Missing | 151 (0.6) | 180 (0.9) | 227 (1.7) | 2167 (1.9) |
| CCI score, $n(\%)$ |  |  |  |  |
| 0 | 17572 (74.9) | 14541 (72.3) | 9192 (67.6) | 79592 (69.6) |
| 1 | 3448 (14.7) | 3212 (16.0) | 2381 (17.5) | 18597 (16.3) |
| 2+ | 2440 (10.4) | 2371 (11.8) | 2030 (14.9) | 16185 (14.2) |
| Death |  |  |  |  |
| PCa-related | 866 (3.7) | 925 (4.6) | 718 (5.3) | 5164 (4.5) |
| From other causes | 2314 (9.9) | 3307 (16.4) | 4033 (29.6) | 19260 (16.8) |

PCa, prostate cancer; CCI, Charlson comorbidity index. All men were diagnosed/selected between 1997 and 2009 in PCBaSe Sweden 2.0.

The baseline characteristics of these men and their 114374 PCa-free matched control subjects are shown in Table 1. The proportion of PCa deaths in the PCa-free control group was $\sim 4.5 \%$, which reflects the lifetime risk of PCa and known incidence:death rate of $3: 1$ to $4: 1$. The proportion of PCa deaths was not much higher compared with the PCa group in this study as all men had localized PCa.
Table 2 shows the risk of PCa according to educational level, household and comorbidity. Men who were married or in partnership and men with a high educational level had a higher risk of PCa in all three risk categories and men with no comorbidity had an elevated risk of intermediate-risk PCa and a non-statistically significant elevated risk of low- and high-risk PCa.

Figure 1 shows the predicted 10-year mortality after PCa diagnosis by categories of age, comorbidity, and PCa risk category, showing that mortality increased with each of these factors. For men with low-risk PCa, all-cause mortality was lower than for corresponding PCa-free men. All-cause mortality at 10 years was estimated to be $18 \%$ in men with lowrisk PCa diagnosed at age 70 years and with a CCI score of 0 , and $21 \%$ among their controls. Of these cases, $31 \%$ died from

CVD whereas $37 \%$ of their controls died from CVD (Fig. 1 and Table 3). The 10 -year PCa mortality rate was estimated to be $0.4 \%$ for men diagnosed at age 50 years with low-risk PCa, $1 \%$ for those diagnosed at age 60 years, and $3 \%$ for those diagnosed at age 70 years. PCa was the third most common cause of death (18\%), after CVD (31\%) and other cancers (30\%), in lowrisk PCa at 10 years after diagnosis (Table 3).
By contrast, men with intermediate- and high-risk localized PCa had a higher all-cause mortality than PCa-free-men. In men with high-risk PCa,10-year PCa mortality was estimated to be $10 \%$ among men diagnosed at age 50 years, $12 \%$ for those diagnosed at age 60 years, and $15 \%$ for those diagnosed at age 70 years. Prostate cancer was by far the most common cause of death: $80 \%$ of high-risk men diagnosed at age 50 years who died, died from PCa and corresponding proportions were $62 \%$ for men diagnosed at age 60 years and $46 \%$ for those diagnosed at age 70 years (Table 3). A small proportion of control subjects were subsequently diagnosed with PCa during the follow-up and PCa mortality was estimated to be $0.1 \%$ for men included as control subjects at age 50 years, $0.4 \%$ for men included at age 60 years and $1 \%$ at age 70 years (Fig. 1).

Table 2 Univariate and multivariate odds ratios and 95\% Cls for risk of low-, intermediate-, or high-risk localized prostate cancer.

|  | Univariate model |  | Multivariate model |  |
| :---: | :---: | :---: | :---: | :---: |
|  | OR | 95\% Cl | OR | 95\% Cl |
| Low-risk prostate cancer |  |  |  |  |
| Education |  |  |  |  |
| High | 1.00 | Ref. | 1.00 | Ref. |
| Intermediate | 0.90 | 0.87-0.93 | 0.91 | 0.88-0.94 |
| Low | 0.73 | 0.70-0.75 | 0.75 | 0.73-0.78 |
| Household |  |  |  |  |
| Not single | 1.00 | Ref. | 1.00 | Ref. |
| Single with children | 0.83 | 0.80-0.86 | 0.84 | 0.82-0.87 |
| Single, no children | 0.63 | 0.60-0.66 | 0.65 | 0.62-0.69 |
| CCI |  |  |  |  |
| 0 | 1.00 | Ref. | 1.00 | Ref. |
| 1 | 0.94 | 0.91-0.98 | 0.96 | 0.92-1.00 |
| $2+$ | 0.85 | 0.82-0.89 | 0.97 | 0.92-1.02 |
| Intermediate-risk prostate cancer |  |  |  |  |
| Education |  |  |  |  |
| High | 1.00 | Ref. | 1.00 | Ref. |
| Intermediate | 0.91 | 0.87-0.94 | 0.92 | 0.89-0.96 |
| Low | 0.75 | 0.72-0.78 | 0.78 | 0.75-0.81 |
| Household |  |  |  |  |
| Not single | 1.00 | Ref. | 1.00 | Ref. |
| Single with children | 0.87 | 0.84-0.90 | 0.88 | 0.85-0.91 |
| Single, no children | 0.67 | 0.64-0.71 | 0.70 | 0.66-0.73 |
| CCI |  |  |  |  |
| 0 | 1.00 | Ref. | 1.00 | Ref. |
| 1 | 0.94 | 0.90-0.97 | 0.95 | 0.91-0.99 |
| $2+$ | 0.79 | 0.76-0.83 | 0.88 | 0.84-0.93 |
| High-risk prostate cancer |  |  |  |  |
| Education |  |  |  |  |
| High | 1.00 | Ref. | 1.00 | Ref. |
| Intermediate | 0.91 | 0.87-0.96 | 0.92 | 0.88-0.97 |
| Low | 0.83 | 0.79-0.87 | 0.85 | 0.81-0.89 |
| Household |  |  |  |  |
| Not single | 1.00 | Ref. | 1.00 | Ref. |
| Single with children | 0.87 | 0.84-0.91 | 0.88 | 0.85-0.92 |
| Single, no children | 0.76 | 0.72-0.81 | 0.78 | 0.74-0.83 |
| CCI |  |  |  |  |
| 0 | 1.00 | Ref. | 1.00 | Ref. |
| 1 | 0.95 | 0.91-1.00 | 0.96 | 0.92-1.01 |
| $2+$ | 0.87 | 0.83-0.91 | 0.95 | 0.90-1.01 |

OR, odds ratio; PCa, prostate cancer; CCI, Charlson comorbidity index.

Similarly to all-cause mortality, risk of PCa mortality increased with age and PCa risk category, regardless of comorbidity status. The 10-year PCa mortality for men with intermediate-risk disease was estimated to be very similar for men with a CCI score of 0 and a CCI score of $2+$ : 10-year PCa mortality was 2,4 and $8 \%$ at age 50,60 and 70 years, respectively, for men with a CCI score of 0 and 2,3 and $6 \%$ at age 50, 60 and 70 years, respectively, for men with a CCI score of $2+$. In relative terms, the proportion of PCa death for men with a CCI score of $2+$ was half of that of men with a CCI score of 0 (15 vs $32 \%$; Table 3).

Data for chronic obstructive pulmonary disease are not shown in Fig. 1 and Table 3 as this was a very rare cause of death in all groups. The highest proportion (3\%) of deaths from this disease was observed for PCa-free men aged

70 years at baseline, with a CCI score of $2+$. Consequently, death from chronic obstructive pulmonary disease was incorporated in the group including death from other causes.

Finally, we also estimated mortality for the subgroup of curatively treated men (Fig. S1). All-cause mortality was slightly lower in these men compared with the total group of men with localized PCa. For instance, 10-year all-cause mortality was estimated to be $20 \%$ for curatively treated men diagnosed with intermediate-risk disease at age 70 years and with a CCI score of 0 , compared with $25 \%$ for corresponding men in the total group. The 10-year PCa mortality, however, was slightly different in the curatively treated group. For instance, for men with intermediate-risk disease and a CCI score of 0 this was estimated to be 4, 5 and $7 \%$ diagnosed at age 50,60 and 70 years in the curatively treated group compared with 2, 4 and $8 \%$ in the total group. In relative terms, the proportion of PCa death was higher in those with a CCI score of 0 than those with a CCI score of $2+$ (Table S1). The distribution of all other causes of death in curatively treated men was otherwise quite similar to that observed in the total group.

## Discussion

In this nationwide, population-based study, men with lowrisk PCa had a lower 10-year all-cause mortality compared with PCa-free control subjects, irrespective of comorbidity levels, which was mainly attributable to a lower cardiovascular mortality. The 10-year PCa mortality for men with low-risk disease varied between 0.3 and $4 \%$, and PCa was the third most common cause of death among these men, after CVD and other cancers. By contrast, men with intermediate- and high-risk PCa had higher all-cause mortality than their comparison cohort, mainly driven by death from PCa, which was the most common cause of death among these men.

The uptake of PSA testing has gradually increased in Sweden since the late 1990s [18]. This increase in opportunistic screening has caused a drastic rise in the incidence of PCa , as well as a stage migration at time of diagnosis: a twofold increase in the proportion of low-risk disease (14-28\%) and a twofold decrease in the proportion of metastatic disease (25$11 \%$ ) between 1998 and 2011 in Sweden [19]. In a study that modelled PSA screening based on incidence patterns, $56 \%$ of Swedish men were estimated to have undergone at least one PSA test in 2007 [20]. In a study in the Stockholm area in 2011, a direct assessment showed that, at age 50-59 years, $46 \%$ of men had undergone PSA testing during the previous 5 years, $68 \%$ at age $60-69$ years, and $77 \%$ at age $70-79$ years [21]; however, the intensity of PSA testing is still lower in many parts of Sweden in comparison with the USA, where it is estimated that $75 \%$ of men aged $\geq 50$ years have had a PSA test [22].

Fig. 1 Predicted risk of death 10 years after prostate cancer (PCa) diagnosis for men aged 50, 60, and 70 years at date of diagnosis, by PCa risk category and Charlson comorbidity index (CCl). The risk of death from all causes is represented by the size of the pie charts. Each section of the pies represents the proportion of men who died from a specific cause estimated with Fine and Gray analyses.


Outcomes of clinically localized PCa managed without primary curative therapy were also investigated in a study based on the Surveillance, Epidemiology and End Results programme. Men aged 78 years at the time of diagnosis had a PCa-specific mortality of $8 \%$ if they had a welldifferentiated cancer, whereas this was $9 \%$ for men with a moderately differentiated cancer and $26 \%$ for men with a poorly differentiated cancer [23]. The present study showed lower numbers, but focused on all treatment groups combined.

Even in a comparison with a matched group of men with no comorbidities, we showed that men with low-risk PCa had a lower 10-year all-cause mortality, which was most likely driven by the lower CVD mortality caused by a self-selection of health-conscious men who chose to undergo PSA testing and who are subsequently diagnosed with PCa .
Apart from an early detection selection, differences in PCa stage distribution can also influence mortality from PCa as well as other diseases. This was illustrated in a recent study from the UK, in which $36 \%$ of men with localized PCa died from PCa [24]. This figure is substantially higher than in all groups in the present study, except for men diagnosed with high-risk PCa at age 70 years and with high comorbidity (PCa mortality at 10 years: $47 \%$ ).

The present results for curatively treated men are in accordance with a study of 18209 men who underwent radical prostatectomy at a US tertial referral centre [25] in which all-cause mortality was half of that in the general US population, with particularly low death rates for heart disease, chronic respiratory conditions, and diabetes. The proportion of men with CCI $=0$ in the US radical prostatectomy cohort was $86 \%$ compared with $75 \%$ in our low-risk group, supporting the hypothesis that men who undergo radical prostatectomy are an even more selected group of healthy men. Mortality from other cancers was higher in men with low-risk PCa than in the comparison cohort and an even higher proportion of death from other cancers was seen in curatively treated men. We have previously shown that men with PCa who are curatively treated have a lower incidence of other primary cancers than men in the general population [26]. Thus, the higher mortality from other cancers seems to be driven by the lower competing risk from CVD mortality and not by an increased risk of cancer.
Because the category of low-risk PCa now constitutes a large proportion of PCa in the Western world and in particular in the USA, all-cause mortality is a poor outcome measure if the aim is to study the effects of different interventions on the course of PCa; however,

Table 3 Distribution of causes of death 10 years after prostate cancer ( PCa ) diagnosis for men aged 50,60 and 70 years at date of diagnosis, by PCa risk category and Charlson comorbidity index score.

| Cause of death, \% | cCl score 0 |  |  | CCl score 2+ |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Age 50 years | Age 60 years | Age 70 years | Age 50 years | Age 60 years | Age 70 years |
| Control subjects |  |  |  |  |  |  |
| PCa | 2.2 | 4.1 | 5.8 | 0.8 | 1.5 | 2.1 |
| Other cancers | 37.8 | 38.3 | 30.1 | 36.2 | 36.3 | 28.6 |
| CVD | 22.6 | 28.8 | 36.6 | 27.8 | 35.1 | 43.4 |
| Other specified causes | 37.4 | 28.8 | 27.5 | 35.2 | 27.1 | 25.8 |
| Overall mortality | 2.7 | 8.5 | 21.0 | 5.8 | 18.0 | 44.0 |
| Low risk PCa |  |  |  |  |  |  |
| $\mathrm{PCa}$ | 15.2 | 16.9 | 18.2 | 5.4 | 6.2 | 6.9 |
| Other cancers | 48.7 | 40.2 | 29.5 | 56.3 | 47.1 | 35.3 |
| CVD | 15.5 | 22.1 | 30.6 | 16.8 | 24.5 | 34.3 |
| Other specified causes | 20.6 | 20.8 | 21.6 | 21.5 | 22.2 | 23.5 |
| Overall mortality | 2.7 | 7.5 | 18.3 | 6.1 | 16.2 | 38.2 |
| Intermediate risk PCa |  |  |  |  |  |  |
| PCa | 48.5 | 37.5 | 31.7 | 25.5 | 17.9 | 14.9 |
| Other cancers | 27.9 | 31.6 | 25.4 | 44.6 | 45.2 | 34.7 |
| CVD | 6.6 | 14.4 | 25.1 | 10.0 | 19.5 | 32.2 |
| Other specified causes | 17.0 | 16.5 | 17.8 | 19.8 | 17.4 | 18.2 |
| Overall mortality | 4.1 | 10.7 | 24.9 | 6.1 | 17.7 | 41.9 |
| High risk PCa |  |  |  |  |  |  |
| $\mathrm{PCa}$ | 80.2 | 61.9 | 46.1 | 65.0 | 43.1 | 28.9 |
| Other cancers | 13.3 | 19.1 | 18.1 | 23.7 | 28.9 | 24.3 |
| CVD | 3.4 | 9.9 | 19.8 | 6.2 | 15.6 | 27.3 |
| Other specified causes | 3.2 | 9.1 | 16.0 | 5.1 | 12.5 | 19.5 |
| Overall mortality | 12.8 | 19.4 | 33.5 | 13.7 | 24.3 | 46.8 |

PCa, prostate cancer; CCI, Charlson comorbidity index; CVD, cardiovascular disease. The predictions were made based on median household status (married or in civil partnership) and intermediate educational level. Overall mortality for each category is also shown.
all-cause mortality is still used as an outcome measure for this purpose in contemporary register-based PCa studies [27]. Additionally, the lower CVD mortality in men with low-risk PCa, compared with the general population, should be taken into account when designing lifestyle interventions intended as primary CVD prevention for these men, as was recently suggested [28].

Our nationwide population-based cohort with data from several healthcare registers thus enabled us to assess risk and causes of mortality after a diagnosis of localized PCa with unprecedented precision. PCBaSe includes $98 \%$ of all new PCa cases diagnosed in Sweden as compared with the Swedish Cancer Register [6]. For these cases and for their controls we have information on tumour characteristics at time of diagnosis, primary treatment, socio-economic status and comorbidity by record linkage to healthcare registers and demographic databases. Moreover, the validity of the Cause of Death Register has been shown to be very high, in particular for men with PCa $[29,30]$.
In conclusion, in the present nationwide, population-based study, men with low-risk PCa had lower all-cause mortality than PCa-free men as a result of lower cardiovascular
mortality, probably driven by an early detection selection for PSA testing and subsequent diagnostic procedures. For men with intermediate- or high-risk disease PCa, however, the mortality rate was substantial, irrespective of CCI score, and this was even more pronounced for those diagnosed at age 50 or 60 years.

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## Conflict of Interest

None declared.

## References

1 Neppl-Huber C, Zappa M, Coebergh JW et al. Changes in incidence, survival and mortality of prostate cancer in Europe and the United States in the PSA era: additional diagnoses and avoided deaths. Ann Oncol 2012; 23: 1325-34
2 Popiolek M, Rider JR, Andren O et al. Natural history of early, localized prostate cancer: a final report from three decades of follow-up. Eur Urol 2012; 23084329
3 Rider JR, Sandin F, Andren O, Wiklund P, Hugosson J, Stattin P. Longterm outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide. Population-based Study. Eur Urol 2013; 63: 88-96
4 Holmstrom B, Holmberg E, Egevad L et al. Outcome of primary versus deferred radical prostatectomy in the National Prostate Cancer Register of Sweden Follow-Up Study. J Urol 2010; 184: 1322-7
5 Stattin P, Holmberg E, Johansson J, Holmberg L, Adolfsson J, Hugosson J. Outcomes for men with localized prostate cancer in the National Prostate Cancer Register (NPCR) of Sweden. J Natl Cancer Inst 2010; 102: 950-8
6 Van Hemelrijck M, Wigertz A, Sandin F et al. Cohort profile: The National Prostate Cancer Register (NPCR) of Sweden and Prostate Cancer data Base Sweden (PCBaSe) 2.0. Int J Epidemiol 2012; 22561842
7 Statistics in the Areas of Health and Medical Care [Internet]. 2007. Available from: http://www.socialstyrelsen.se/en/Statistics/ Statistical_databases.htm. Accessed June 2014
8 Hagel E, Garmo H, Bill-Axelson A et al. PCBaSe Sweden: a registerbased resource for prostate cancer research. Scand J Urol Nephrol 2009; 43: 342-9
9 Adolfsson J, Garmo H, Varenhorst E et al. Clinical characteristics and primary treatment of prostate cancer in Sweden between 1996 and 2005. Scand J Urol Nephrol 2007; 41: 456-77
10 Mohler J, Bahnson RR, Boston B et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw 2010; 8: 162-200
11 Statistics Sweden. Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by Swedish acronym) 2008. Available at: http://www.scb.se/Pages/List___257743.aspx. Accessed July 2011
12 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-83
13 Kastner C, Armitage J, Kimble A, Rawal J, Carter PG, Venn S. The Charlson comorbidity score: a superior comorbidity assessment tool for the prostate cancer multidisciplinary meeting. Prostate Cancer Prostatic Dis 2006; 9: 270-4
14 Berglund A, Garmo H, Tishelman C, Holmberg L, Stattin P, Lambe M. Comorbidity, treatment and mortality: a population based cohort study of prostate cancer in PCBaSe Sweden. J Urol 2011; 185: 833-9
15 Berglund A, Garmo H, Robinson D et al. Differences according to socioeconomic status in the management and mortality in men with high risk prostate cancer. Eur J Cancer 2012; 48: 75-84
16 Bakoyannis G, Touloumi G. Practical methods for competing risks data: a review. Stat Methods Med Res 2012; 21: 257-72

17 Wiren SM, Drevin LI, Carlsson SV et al. Fatherhood status and risk of prostate cancer: nationwide, population-based case-control study. Int J Cancer 2013; 133: 937-43
18 National Prostate Cancer Register of S. Annual Reports. 2014
19 Ohmann EL, Loeb S, Robinson D, Bill-Axelson A, Berglund A, Stattin P. Nationwide, population-based study of prostate cancer stage migration between and within clinical risk categories. Scand J Urol 2014; 24611795
20 Jonsson H, Holmstrom B, Duffy SW, Stattin P. Uptake of prostatespecific antigen testing for early prostate cancer detection in Sweden. Int $J$ Cancer 2011; 129: 1881-8
21 Nordstrom T, Aly M, Clements MS, Weibull CE, Adolfsson J, Gronberg H. Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, despite no recommendations for PSA screening: results from a population-based study, 2003-2011. Eur Urol 2013; 63: 419-25
22 Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? JAMA 2003; 289: 1414-20
23 Lu-Yao GL, Albertsen PC, Moore DF et al. Outcomes of localized prostate cancer following conservative management. JAMA 2009; 302: 1202-9
24 Chowdhury S, Robinson D, Cahill D, Rodriguez-Vida A, Holmberg L, Moller H. Causes of death in men with prostate cancer: an analysis of 50,000 men from the Thames Cancer Registry. BJU Int 2013; 112: 1829
25 Eifler JB, Humphreys EB, Agro M, Partin AW, Trock BJ, Han M. Causes of death after radical prostatectomy at a large tertiary center. $J$ Urol 2012; 188: 798-801
26 Van Hemelrijck M, Drevin L, Holmberg L, Garmo H, Adolfsson J, Stattin P. Primary cancers before and after prostate cancer diagnosis. Cancer 2012; 118: 6207-16
27 Prasad SM, Eggener SE, Lipsitz SR, Irwin MR, Ganz PA, Hu JC. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate cancer. J Clin Oncol 2014; 32: 2471-8
28 Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst 2012; 104: 1335-42
29 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
30 Godtman R, Holmberg E, Stranne J, Hugosson J. High accuracy of Swedish death certificates in men participating in screening for prostate cancer: a comparative study of official death certificates with a cause of death committee using a standardized algorithm. Scand J Urol Nephrol 2011; 45: 226-32

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Abbreviations: PCa , prostate cancer; NPCR, Swedish National Prostate Cancer Register; CCI, Charlson comorbidity index; ICD, International Classification of Diseases.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Predicted risk of death 10 years after prostate cancer (PCa) diagnosis for men aged 50, 60 and 70 years at date of diagnosis, by PCa risk category and Charlson comorbidity index for the subgroup of men curatively treated.

Table S1 Distribution of causes of death 10 years after prostate cancer (PCa) diagnosis for men aged 50, 60 , and 70 years at date of diagnosis, by PCa risk category and Charlson comorbidity index score for the subgroup of men curatively treated.

