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Platinum Priority – Prostate Cancer

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Long-term Outcomes Among Noncuratively Treated Men According to Prostate Cancer Risk Category in a Nationwide, Population-based Study

Jennifer R. Rider[a,*], *Fredrik Sandin*[b], *Ove Andrén*[c], *Peter Wiklund*[d], *Jonas Hugosson*[e], *Pär Stattin*[f]

[a] *Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; and Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA;* [b] *Regional Cancer Center, Uppsala, Sweden;* [c] *Department of Urology, Örebro University Hospital, Örebro, Sweden;* [d] *Department of Molecular Medicine and Surgery, Division of Urology, Karolinska Institute, Stockholm, Sweden;* [e] *Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Göteborg, Göteborg, Sweden;* [f] *Department of Surgical and Perioperative Sciences, Urology, and Andrology, Umeå University, Umeå, Sweden; and Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

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Abstract

Background: Limited data exist on long-term outcomes among men with prostate cancer (PCa) from population-based cohorts incorporating information on clinical risk category.
Objective: To assess 15-yr mortality for men with PCa treated with noncurative intent according to clinical stage, Gleason score (GS), serum levels of prostate specific antigen (PSA), comorbidity, and age.
Design, setting, and participants: Register-based cohort study of 76 437 cases in the National Prostate Cancer Register (NPCR) of Sweden diagnosed from 1991 through 2009 and treated with noncurative intent. Each case was placed in one of five risk categories: (1) low risk: T1–T2 tumor, PSA level <10 ng/ml, and GS ≤6; (2) intermediate risk: T1–T2 tumor and PSA level 10–<20 ng/ml or GS 7; (3) high risk: T3 tumor or PSA level 20–<50 ng/ml or GS ≥8; (4) regional metastases: N1 or T4 tumor or PSA level 50–100 ng/ml; and (5) distant metastases: M1 tumor or PSA ≥100 ng/ml.
Outcome measurements and statistical analysis: Ten- and 15-yr cumulative risk of death after diagnosis from PCa, cardiovascular disease, and other causes.
Results and limitations: Among men with a Charlson Comorbidity Index (CCI) score of 0, no differences were found in observed versus expected all-cause mortality in the low-risk group. Observed mortality was only slightly greater in the intermediate-risk group, but men with high-risk localized PCa or more advanced disease had substantially higher mortality than expected. CCI was strongly associated with cumulative 10-yr mortality from causes other than PCa, especially for men <65 yr. Limitations include potential misclassification in risk category due to GS assignment.
Conclusions: PCa mortality rates vary 10-fold according to risk category. The risk of death from causes other than PCa is most strongly related to comorbidity status in younger men.

* Corresponding author. Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave., Boston, MA, 02115, USA. Tel. +1 617 432 3040; Fax: +1 617 566 7805.
E-mail address: rider@hsph.harvard.edu (J.R. Rider).

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1. Introduction

Outcomes for men with prostate cancer (PCa) vary markedly. Men are increasingly diagnosed with low-risk disease, which may have little or no impact on life expectancy [1–3]. Therefore, a man's risk of dying of other causes is an important consideration in PCa management.

Randomized trials evaluating PCa treatment are limited [4,5], leaving questions about treatment benefits and overtreatment risks. Observational studies have made major contributions to strategies for PCa risk stratification and treatment selection, but have limitations. Analyses from single centers typically include in-depth tumor characteristics, but mostly use biochemical recurrence as the end point, a relatively poor surrogate for PCa mortality [6,7]. A landmark study in Sweden of 223 men diagnosed with highly and intermediately differentiated localized PCa who received no curative therapy demonstrated that the majority of these men do not die of PCa [8]. However, because no data on serum levels of prostate-specific antigen (PSA) and Gleason score (GS) were available, the implications on current clinical practice are unclear.

Several studies have used register-based data from the linked Surveillance Epidemiology and End Results (SEER) study and US Medicare database to estimate mortality, specifically among men with localized PCa following conservative management [9,10], and according to comorbidity status [11]. However, contemporary risk categorization cannot be applied to SEER–Medicare linked data because PSA levels were not registered until recently and GS is aggregated. Moreover, SEER–Medicare linked data include only men >65 yr. A previous analysis of a subgroup of the present study population reported a 3% risk of PCa death at 10 yr after diagnosis among men with low- and intermediate-risk PCa who received surveillance as primary treatment [12].

To provide a broad depiction of long-term outcomes and better characterize men most likely to benefit from treatment and men most at risk of overtreatment, we now provide 15-yr mortality estimates for PCa death, cardiovascular death, and other causes of death among men with PCa managed noncuratively in a nationwide population-based cohort.

2. Methods

2.1. Study population and data collection

The Prostate Cancer Database Sweden (PCBaSe) [13] is based on the National Prostate Cancer Register (NPCR) of Sweden, which currently covers >96% of all newly diagnosed PCa cases and includes detailed information on tumor characteristics and primary treatment [1]. We linked NPCR to other national registers through the Swedish personal identification number to obtain covariate and outcome data. The Swedish Cause of Death Register collects date and underlying cause of death coded according to the World Health Organization (WHO) International Classifications of Diseases, Injuries, and Causes of Death. The number of nonreported events is low and estimated to 0.7% of all deaths [14]. To assess the burden of concomitant disease, we used the Charlson Comorbidity Index (CCI) as previously described in detail [15–17]. Information on all inpatient episodes up to 5 yr prior to date of diagnosis was retrieved from the National Swedish Inpatient Registry, initiated in 1987.

We abstracted the following information from PCBaSe: age; PSA level; treatment delivered or planned within 6 mo after date of diagnosis; tumor grade and stage; comorbidity according to CCI; and date and cause of death. GS was used to assess tumor grade. If WHO tumor grade was reported, conversion to GS was conducted as follows: WHO grade 1 was the equivalent of Gleason 2–6, WHO grade 2 to Gleason 7, and WHO grade 3 to Gleason 8–10 [18].

We categorized men with PCa into five risk groups according to a modified version of the National Comprehensive Cancer Network (NCCN) guidelines [19]. The NCCN does not distinguish between regionally metastatic and distant metastatic disease, but we divided the category *metastatic PCa* into two categories to reflect variability in outcomes. Risk categories were defined as follows: (1) low risk: a clinically local, stage T1–T2 tumor, PSA level <10 ng/ml, and GS ≤6; (2) intermediate risk: T1–T2 tumor and PSA level 10–<20 ng/ml or GS 7; (3) high risk: T3 tumor or PSA level 20–<50 ng/ml or GS ≥8; (4) regional metastases: T4 or N1 tumor or PSA level 50–100 ng/ml; and (5) distant metastases: M1 tumor or PSA level ≥100 ng/ml.

We calculated observed versus expected all-cause mortality for men with PCa and CCI score of 0 using a comparison cohort randomly selected by Statistics Sweden from all Swedish men free of PCa at the end of the year of diagnosis of the index case. Men in the comparison cohort were randomly selected from sets of men matched to the index case on county of residence and year of birth. We selected two men for cases diagnosed with PCa from 1991 through 1995, and five men for cases diagnosed after 1995. Follow-up for both cohorts began at the time of PCa diagnosis of the index case and ended at time of death, emigration, or study closing date (December 31, 2010), whichever came first. The project was approved by the Research Ethics Board at Umeå University.

2.2. Statistical analysis

The cumulative probability of death at 10 and 15 yr among noncuratively treated men in the PCa cohort was estimated by treating death from PCa, cardiovascular diseases, and other causes as competing events. To obtain up-to-date estimates of the cumulative probability of death, a period analysis approach [20] was used. Events and person-time at risk were used to estimate the cumulative incidence functions in the 2006–2010 time window. Patients diagnosed from 1991 through 2009 potentially influence the estimates up to 15 yr of follow-up. In practice, this is done by delayed entry (or left-truncation). For instance, if a patient enters the window 3 yr after his diagnosis, then he will not influence the estimates for his first 3 yr following diagnosis, as his person-time at risk and (possible) events will only be counted in the period-analysis time window. Cumulative mortality was calculated separately for each risk category and was further stratified by age.

In addition to cumulative mortality estimates undertaken among noncuratively treated cases, observed all-cause mortality was compared to expected mortality as estimated by use of the comparison cohort defined above. Subdistribution hazard ratios were calculated using Fine and Gray competing-risk regression modeling [21]. All statistical analyses were performed with the Stata statistical software package v.11 (StataCorp LP, College Station, TX, USA).

3. Results

In total, 117 328 men with PCa were registered in NPCR from 1991 through 2009 (Table 1). Median follow-up time was 4.4 yr (range: <0.1–20.0 yr). From 1991 through 2009,

Table 1 – Characteristics of 117 328 patients with prostate cancer in the National Prostate Cancer Register of Sweden, 1991–2009

		Risk category at diagnosis					
	Total cohort (*N* = 117 328)	Low risk (*n* = 26 410, 22.5%)	Intermediate risk (*n* = 26 611, 22.7%)	High risk (*n* = 30 159, 25.7%)	Regionally metastatic (*n* = 10 315, 8.8%)	Distant metastases (*n* = 20 391, 17.4%)	Missing (*n* = 3442, 2.9%)
Year of diagnosis, no. (%)							
1991–1993	5384 (4.6)	476 (1.8)	918 (3.4)	1413 (4.7)	520 (5.0)	1563 (7.7)	494 (14.4)
1994–1996	6208 (5.3)	629 (2.4)	1001 (3.8)	1760 (5.8)	815 (7.9)	1816 (8.9)	187 (5.4)
1997–1999	18 162 (15.5)	2509 (9.5)	3225 (12.1)	5286 (17.5)	2115 (20.5)	4480 (22.0)	547 (15.9)
2000–2002	22 305 (19.0)	4617 (17.5)	4590 (17.2)	6096 (20.2)	2185 (21.2)	4238 (20.8)	579 (16.8)
2003–2005	28 304 (24.1)	7625 (28.9)	6800 (25.6)	7137 (23.7)	2228 (21.6)	3902 (19.1)	612 (17.8)
2006–2009	36 965 (31.5)	10 554 (40.0)	10 077 (37.9)	8467 (28.1)	2452 (23.8)	4392 (21.5)	1023 (29.7)
Age at diagnosis, yr, no. (%)							
≤55	4923 (4.2)	2270 (8.6)	1194 (4.5)	598 (2.0)	270 (2.6)	475 (2.3)	116 (3.4)
56–65	28 671 (24.4)	10 994 (41.6)	7763 (29.2)	4818 (16.0)	1602 (15.5)	2778 (13.6)	716 (20.8)
66–75	43 771 (37.3)	9870 (37.4)	11 156 (41.9)	11 229 (37.2)	3478 (33.7)	6785 (33.3)	1253 (36.4)
76–85	33 768 (28.8)	3049 (11.5)	5893 (22.1)	11 456 (38.0)	3979 (38.6)	8219 (40.3)	1172 (34.0)
>85	6195 (5.3)	227 (0.9)	605 (2.3)	2058 (6.8)	986 (9.6)	2134 (10.5)	185 (5.4)
Age at diagnosis, yr							
Median (IQR)	71 (64–78)	65 (60–71)	69 (63–75)	74 (68–80)	75 (68–81)	76 (69–81)	73 (66–79)
Serum PSA level, ng/ml							
Median (IQR)	14.0 (7.0–41.0)	5.8 (4.2–7.4)	11.0 (7.3–14.0)	22.0 (12.0–31.0)	60.4 (50.0–76.0)	192.0 (100.0–500.0)	7.5 (4.7–11.0)
Missing, no. (%)	4272 (3.6)	0 (0.0)	690 (2.6)	929 (3.1)	160 (1.6)	391 (1.9)	2102 (61.1)
Gleason score, no. (%)							
Grade 2–6	51 187 (43.6)	26 410 (100.0)	9929 (37.3)	8021 (26.6)	2051 (19.9)	2344 (11.5)	2432 (70.7)
Grade 7	39 608 (33.8)	0 (0.0)	16 480 (61.9)	10 867 (36.0)	4352 (42.2)	7549 (37.0)	360 (10.5)
Grade 8–10	23 842 (20.3)	0 (0.0)	0 (0.0)	10 773 (35.7)	3642 (35.3)	9427 (46.2)	0 (0.0)
Missing	2691 (2.3)	0 (0.0)	202 (0.8)	498 (1.7)	270 (2.6)	1071 (5.3)	650 (18.9)
Charlson comorbidity index, no. (%)							
0	92 163 (78.6)	22 687 (85.9)	21 785 (81.9)	22 957 (76.1)	7729 (74.9)	14 856 (72.9)	2149 (62.4)
1	13 419 (11.4)	2063 (7.8)	2766 (10.4)	3945 (13.1)	1348 (13.1)	2845 (14.0)	452 (13.1)
2+	11 746 (10.0)	1660 (6.3)	2060 (7.7)	3257 (10.8)	1238 (12.0)	2690 (13.2)	841 (24.4)
Socioeconomic index, no. (%)							
Low	31 300 (26.7)	5449 (20.6)	6195 (23.3)	8633 (28.6)	3164 (30.7)	6888 (33.8)	971 (28.2)
Middle	47 325 (40.3)	12 186 (46.1)	11 499 (43.2)	11 523 (38.2)	3809 (36.9)	6987 (34.3)	1321 (38.4)
High	37 025 (31.6)	8437 (31.9)	8572 (32.2)	9555 (31.7)	3189 (30.9)	6180 (30.3)	1092 (31.7)
Missing	1678 (1.4)	338 (1.3)	345 (1.3)	448 (1.5)	153 (1.5)	336 (1.6)	58 (1.7)
Planned treatment, no. (%)							
Surveillance	31 115 (26.5)	11 553 (43.7)	8668 (32.6)	6786 (22.5)	1276 (12.4)	884 (4.3)	1948 (56.6)
Curative therapy	35 662 (30.4)	12 676 (48.0)	12 659 (47.6)	8170 (27.1)	1092 (10.6)	266 (1.3)	799 (23.2)
Palliative therapy	45 322 (38.6)	1241 (4.7)	4148 (15.6)	13 865 (46.0)	7529 (73.0)	18 168 (89.1)	371 (10.8)
Missing	5229 (4.5)	940 (3.6)	1136 (4.3)	1338 (4.4)	418 (4.1)	1073 (5.3)	324 (9.4)

IQR = interquartile range; PSA = prostate-specific antigen.

low-risk PCa increased and metastatic disease decreased substantially (Supplemental Fig. 1). The majority of men with PCa (78.6%) had no comorbidity according to CCI at diagnosis; the proportion of men having CCI score 0 was highest in the low-risk category and lowest in the metastases category (85.9% vs 72.9%; $p < 0.001$). To determine if variation in CCI score was due to PCa disease or confounded by age (median age between cases with low-risk disease and metastatic disease differed by 8 yr), we compared the proportions of CCI score 0 among PCa cases and matched PCa-free comparison men within risk categories. The proportions of comparison men with no comorbidities (84.2% of in the

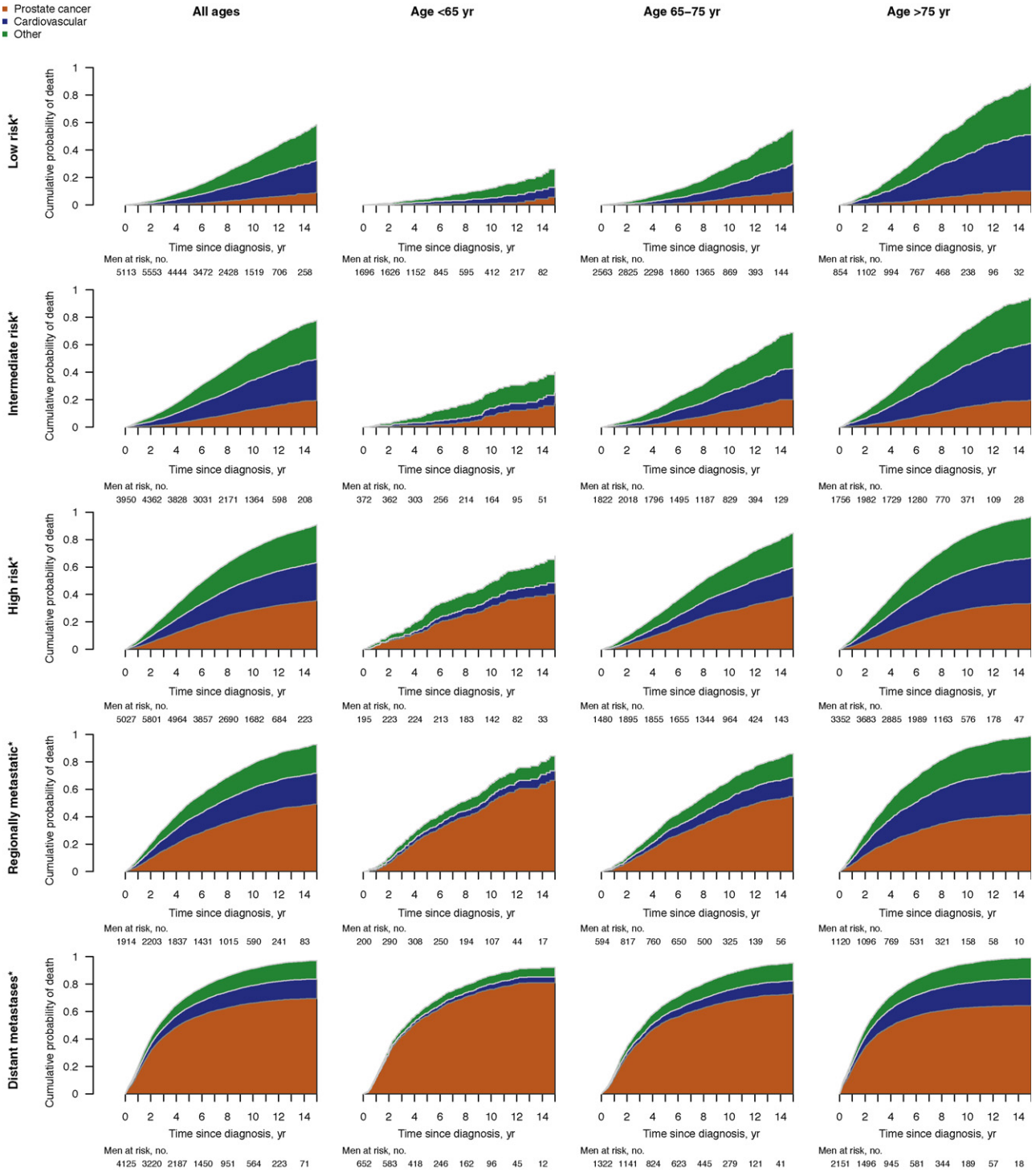

Fig. 1 – Cumulative mortality from prostate cancer, cardiovascular disease, and other causes according to age and risk category. Estimates are based on men in the National Prostate Cancer Register from 1991 through 2009. Included mortality events occurred from 2006 through 2010. A modified version of risk categories according to the National Comprehensive Cancer Network was used: low risk = T1–T2 tumor, prostate-specific antigen (PSA) level <10 ng/ml and Gleason score (GS) ≤6; intermediate risk = T1–T2 tumor and PSA level 10–<20 ng/ml or GS 7; high risk = T3 tumor or PSA level 20–<50 ng/ml or GS ≥8; regional metastases = T4 or N1 tumor or PSA level 50–100 ng/ml; and distant metastases = M1 tumor or PSA level ≥ 100 ng/ml.

low-risk group and 75.1% of in the distant metastases group) were similar to cases within each risk category, indicating that the variability was likely age related.

More than half of the cohort was treated with noncurative intent. In general, noncuratively treated men were older and had higher CCI score. The proportion of men with localized disease treated with curative intent was similar among low- and intermediate-risk patients (48.0% and 47.6%, respectively), but lower among men with high-risk disease (27.1%). Overall, management with curative intent increased markedly over time (7.0% in 1991 vs 43.7% in 2009).

3.1. Cumulative mortality by risk and age category among noncuratively treated men

We restricted subsequent analyses to noncuratively treated men (N = 76 437). Mortality rates from PCa, cardiovascular disease, and other diseases varied almost 10-fold according to risk category and age (Fig. 1). We observed continuous increases in PCa mortality rates beyond 10 yr of follow up among men with localized PCa (Table 2). At 15 yr after diagnosis, the cumulative risk of PCa death was 8.9% (95% confidence interval [CI], 7.4–10.5) for low-risk disease; 19.6% (95% CI, 18.0–21.2) for intermediate-risk disease; 35.5% (95% CI, 34.2.2–36.8) for high-risk disease; 49.1% (95% CI, 47.1–51.2) for regionally metastatic disease; and 69.5% (95% CI, 68.2–70.7) for distant metastatic PCa.

The cumulative risk of death from other causes at 10 and 15 yr increased strongly with age (Table 2). Competing causes of death were distributed equally among cardiovascular deaths and all other causes of death regardless of risk group. Considerable increases in death from other causes occurred between 10 and 15 yr after PCa diagnosis except among those with distant metastases. The risk of dying of other causes for men with low-risk PCa was 29.0% (95% CI, 27.5–30.5) at 10 yr and 49.5% (95% CI, 46.5–52.4) at 15 yr. These relative increases attenuated with increases in risk category and age at diagnosis.

3.2. Cumulative mortality, competing causes of death, and comorbidity among noncuratively treated men

PCa mortality rates among noncuratively treated men with low- and intermediate-risk disease were similar regardless of comorbidity (Fig. 2). Comorbidity was a strong predictor of death from causes other than PCa, especially for the youngest men. Among men aged <65 yr, the subhazard ratios for other causes of death comparing CCI score ≥2 versus CCI score 0 were 6.1 (95% CI, 3.7–9.9) in the low-risk group, 9.3 (95% CI, 4.9–17.6) in the intermediate-risk group, and 5.1 (95% CI, 2.6–10.1) in the high-risk group. Mortality from other causes comparing CCI score ≥2 versus CCI score 0 were approximately three-fold greater for men aged 65–75 yr and approximately two-fold greater for men aged ≥75 yr, regardless of designation in the low-, intermediate-, or high-risk category (Supplemental Table 1).

Given that comorbidities influence all-cause mortality, we restricted our investigation of observed versus expected mortality to PCa cases and the matched comparison cohort with CCI score 0 (Fig. 3). For men with low-risk PCa, the expected and observed all-cause mortality plots were superimposed during the entire 15-yr follow-up. Some difference was observed for intermediate-risk PCa

Table 2 – Percent cumulative 10- and 15-yr mortality (95% confidence interval) by age and prostate cancer stage

Disease-risk category by age group	10-yr mortality		15-yr mortality		p value[1]	
	Prostate cancer	Other	Prostate cancer	Other	Prostate cancer	Other
All ages						
Low risk	4.5 (3.8–5.2)	29.0 (27.5–30.5)	8.9 (7.4–10.5)	49.5 (46.5–52.4)		
Intermediate risk	13.0 (11.9–14.0)	42.4 (40.9–43.9)	19.6 (18.0–21.2)	58.1 (56.0–60.2)		
High risk	28.8 (27.7–29.8)	44.9 (43.7–46.0)	35.5 (34.2–36.8)	55.4 (53.9–56.8)	<0.001	<0.001
Regionally metastatic	41.3 (39.5–43.1)	37.5 (35.7–39.3)	49.1 (47.1–51.2)	43.5 (41.5–45.5)		
Distant metastases	66.1 (64.9–67.3)	25.1 (24.0–26.3)	69.5 (68.2–70.7)	27.7 (26.5–28.9)		
Age <65 yr						
Low risk	1.2 (0.6–2.1)	11.0 (9.0–13.3)	5.5 (2.7–9.8)	20.6 (15.7–26.0)		
Intermediate risk	8.3 (5.4–12.1)	17.0 (12.9–21.5)	17.4 (11.4–24.4)	22.6 (17.0–28.8)		
High risk	30.8 (25.6–36.3)	17.6 (13.4–22.3)	40.2 (33.6–46.6)	27.7 (20.6–35.3)	<0.001	<0.001
Regionally metastatic	50.9 (45.6–55.9)	13.2 (9.8–17.0)	66.5 (59.5–72.7)	17.8 (13.1–23.1)		
Distant metastases	76.1 (73.0–78.9)	9.9 (8.0–12.1)	81.0 (78.0–83.7)	11.1 (8.9–13.6)		
Age 65–75 yr						
Low risk	4.5 (3.6–5.5)	23.2 (21.3–25.2)	9.6 (7.4–12.1)	45.1 (41.0–49.2)		
Intermediate risk	11.7 (10.3–13.2)	31.6 (29.5–33.8)	19.9 (17.6–22.4)	48.8 (45.4–52.0)		
High risk	27.8 (26.0–29.6)	33.2 (31.3–35.1)	38.7 (36.3–41.0)	46.0 (43.5–48.5)	<0.001	<0.001
Regionally metastatic	42.1 (39.1–45.1)	23.9 (21.3–26.6)	54.7 (51.0–58.1)	31.2 (27.9–34.5)		
Distant metastases	67.3 (65.2–69.4)	20.1 (18.3–22.0)	72.7 (70.6–74.8)	22.6 (20.7–24.5)		
Age >75 yr						
Low risk	7.2 (5.7–8.9)	55.5 (52.3–58.6)	10.1 (7.9–12.5)	78.0 (73.5–81.9)		
Intermediate risk	14.9 (13.3–16.5)	56.3 (54.1–58.5)	19.6 (17.4–21.9)	74.4 (71.4–77.1)		
High risk	29.4 (28.0–30.7)	53.4 (51.9–54.9)	33.4 (31.9–35.0)	63.4 (61.6–65.1)	<0.001	<0.001
Regionally metastatic	38.5 (36.1–40.9)	51.6 (49.1–54.1)	41.8 (39.2–44.4)	56.8 (54.1–59.3)		
Distant metastases	62.7 (60.9–64.4)	32.2 (30.5–33.9)	64.3 (62.5–66.0)	34.9 (33.1–36.6)		

[1] p value for the null hypothesis of no difference between risk groups was calculated using Fine and Gray [20] competing-risk regression models.

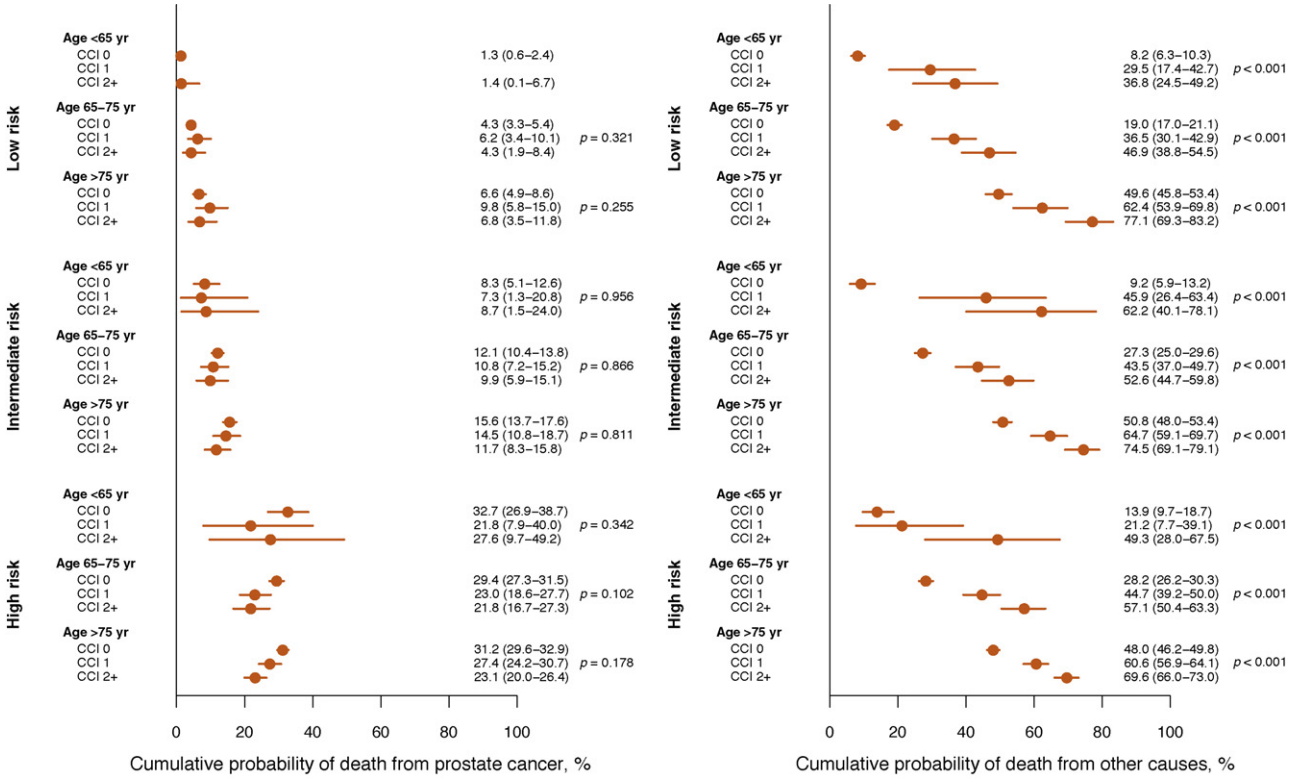

Fig. 2 – Cumulative 10-yr mortality from prostate cancer and other causes (95% confidence interval) by risk category, age, and Charlson Comorbidity Index (CCI). Estimates are based on men in the National Prostate Cancer Register from 1991 through 2009.

after approximately 5 yr of follow up, and for men with high-risk PCa and metastatic PCa, the curves clearly diverged soon after diagnosis.

3.3. *Cumulative mortality among curatively treated men*

Men treated with curative intent experienced lower 10- and 15-yr cumulative mortality than men managed noncuratively, but general patterns were similar. At 15 yr, cumulative PCa mortality proportions for low-, intermediate-, and high-risk groups were 5.1% (95% CI, 2.5–8.9), 10.7% (95% CI, 8.5–13.2), and 21.7 (95% CI, 18.3–25.3).

4. Discussion

Our results from a large, contemporary, nationwide cohort in Sweden demonstrate the large variation in 15-yr PCa mortality for noncuratively treated men, ranging from 9% among men with low-risk PCa to 70% among men with distant metastases. There was a substantial impact of competing causes of death, particularly among men with localized PCa, and this was strongly related to existing comorbidities. Cardiovascular disease was responsible for approximately half of the non–PCa deaths regardless of risk group. Due to the low PCa mortality and because most noncuratively treated men with low-risk (80%) and intermediate-risk PCa (74%) had no major comorbidities, there was no difference between observed and expected cumulative all-cause mortality in low-risk disease, and only minor differences in intermediate-risk PCa. We note that men selected for noncurative treatment are generally less healthy than men pursuing curative therapy [12,22].

Two recent studies using SEER and SEER–Medicare linked databases allow us to assess generalizability in the context of US data. Our risk estimates are in the same range as in these US studies, even though risk categorization and the statistical approach were somewhat different. For instance, in a recent study by Albertsen et al. [11], PCa-specific mortality at 10 yr for men aged 66–74 yr treated conservatively with T1c/Gleason 5–7 tumors was 5% for CCI score 0, 2% for CCI score 1, and 5% for CCI score ≥2. PCa-specific mortality for men aged 65–74 yr in our low-risk category was 4% for CCI score 0, 6% for CCI score 1, and 4% for CCI score ≥2. For older men (≥75 yr) with Gleason 8–10 tumors in the Albertsen et al. study, PCa-specific mortality for T1c and T2 tumors, respectively, was 28% and 28% for CCI score 0, 24% and 20% for CCI score 1, and 19% and 16% for CCI score ≥2. For men aged >75 yr in our high-risk group, PCa-specific mortality across comorbidity categories was 31%, 27%, and 23% for CCI scores 0, 1, and ≥2, respectively. Overall cumulative mortality at 10 yr among the older high-risk men was similar in the cohorts.

Abdollah et al. [23] compared, among men of all ages with localized disease, PCa-specific mortality according to low/intermediate- versus high-risk category and management by observation, radiotherapy, or radical prostatectomy in the SEER database. Among younger men managed

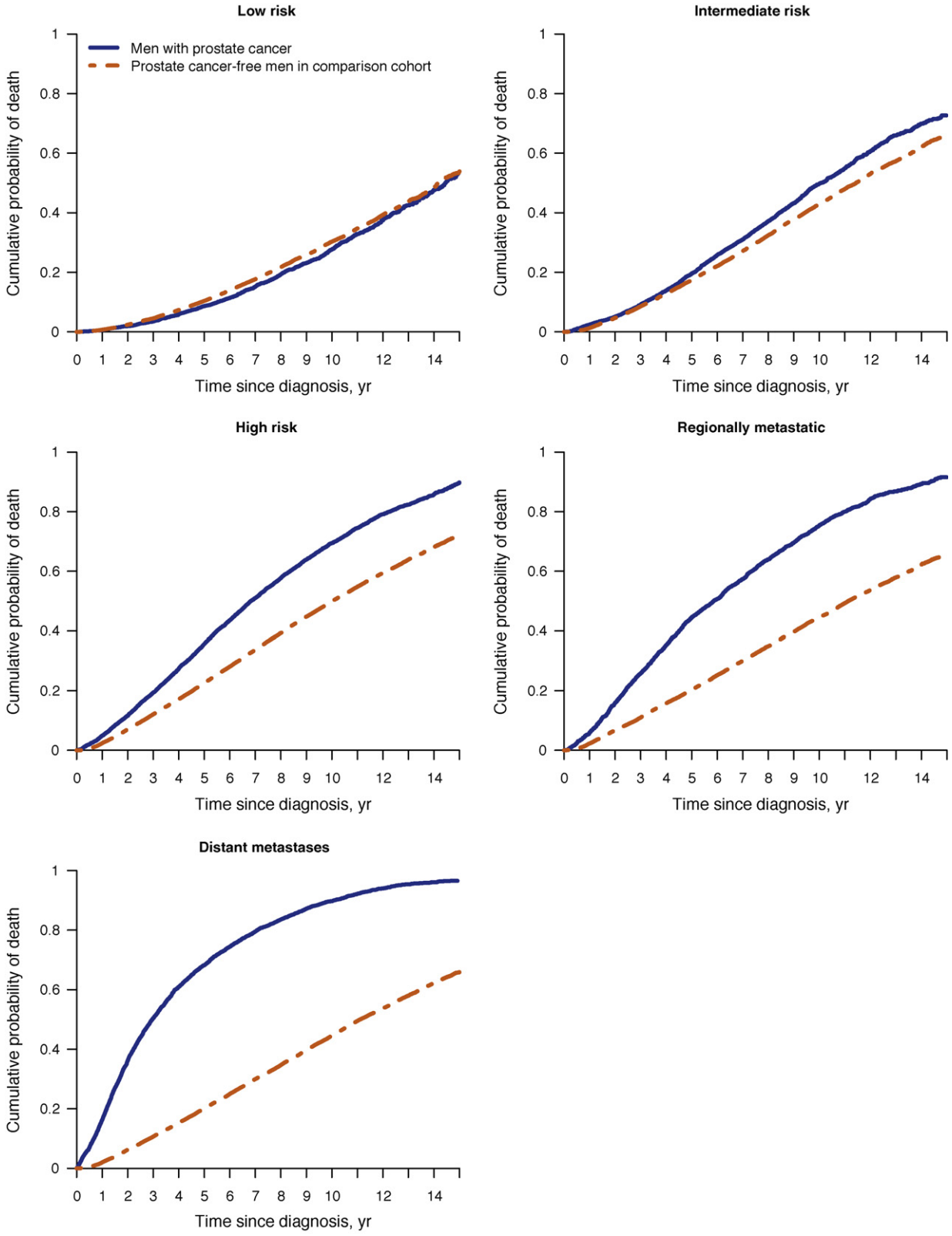

Fig. 3 – Observed versus expected all-cause mortality overall and according to risk category. Analyses were restricted to cases and men in the comparison cohort with Charlson Comorbidity Index (CCI) score of 0.

by surveillance, 10-yr PCa mortality in the Abdollah et al. study was comparable to our results in the low/intermediate-risk category (4% among men aged ≤59 yr and 5% among men aged 60–69 yr vs 3% for men <65 yr old in our cohort) and high-risk category (22% among men aged <59 yr and 60–69 yr vs 30.8% among men aged <65 yr in our cohort).

More men with localized PCa die from causes of death other than PCa, highlighting that PCa mortality cannot be interpreted in isolation. Although subgroup analyses from randomized trials should be interpreted cautiously, the benefit of surgical treatment in the Scandinavian Prostate Cancer Group 4 study of radical prostatectomy versus watchful waiting was confined to men aged <65 yr [4]. These data and our results indicate that achieving a balance between the benefits of improved survival and costs of adverse effects are especially pertinent for younger men, who have the most life-years to gain from treatment, but the most to lose in terms of quality of life.

Our study has several strengths: It was population-based and included 76 437 PCa cases treated noncuratively with data on GS, clinical stage, and serum PSA level. Follow-up was long and virtually complete for the entire cohort, and period analysis was used to base estimates on the most recent years. Limitations include the potential for bias in attribution of death following a cancer diagnosis, especially for more advanced disease. However, previous investigations have revealed the Swedish Cause of Death Register to be in good agreement with the cause of death as determined by chart reviews [24,25]. Some men had inadequate data for risk-category assignment and no data on tumor extent on biopsy were available. GS assignment was based on routine clinical evaluation in each participating hospital and the criteria for evaluating GS have changed over time. Thus, some risk-category misclassification may result from GS assignment.

5. Conclusions

There is a wide range in PCa outcomes according to risk categories. PCa mortality represents a relatively modest contributor to all-cause mortality among men diagnosed with localized low- and intermediate-risk PCa. In contrast, death rates from PCa are much higher in men with localized high-risk disease and, in particular, in with men with metastatic disease. A majority of men diagnosed with PCa do not have major comorbidity, but men who do have comorbidities have a much higher risk of death from cardiovascular disease and other causes.

Author contributions: Jennifer R. Rider had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Stattin.
Acquisition of data: Stattin, Wiklund, Andrén, Hugosson.
Analysis and interpretation of data: Rider, Sandin, Stattin.
Drafting of the manuscript: Rider.
Critical revision of the manuscript for important intellectual content: Andrén, Hugosson, Wiklund.
Statistical analysis: Sandin.
Obtaining funding: Stattin.
Administrative, technical, or material support: Stattin.
Supervision: Stattin.
Other (specify): None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2012.08.001.

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