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ORIGINAL ARTICLE

Cardiovascular, bone, and metabolic health in men with castrate-resistant prostate cancer treated with androgen deprivation: a matched cohort study

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ABSTRACT

Background: Descriptive data on late effects associated with castrate-resistant prostate cancer (CRPC) are sparse. We aimed to define the timing and incidence of cardiovascular disease (CVD), fractures, and diabetes in a patient population with CRPC.

Methods: In the population-based STHLM0 cohort 1464 men with CRPC were identified and matched with three men free from prostate cancer (PC) in the Stockholm region of Sweden. Kaplan–Meier estimates of net survival were used to describe time to CVD, fracture, and diabetes. Cox regression was used to compare incidence rates (IRRs) for the respective late effects. Cumulative incidence analyses of late effects in the presence of the competing risk of death were performed to estimate absolute risks.

Results: The Kaplan Meier estimates demonstrated a higher net probability for CVD, fracture, and diabetes among men diagnosed with CRPC compared to the matched comparators. The IRRs were 1.94 (95% CI: 1.79–2.12) for CVD, 2.08 (95% CI: 1.70–2.53) for fracture, and 2.00 (95% CI: 1.31–3.05) for diabetes, respectively, comparing men diagnosed with CRPC to men free from PC. The cumulative incidence of CVD at 12 months of follow-up was higher in men diagnosed with CRPC compared to healthy controls regardless of age with a difference in cumulative incidence being 0.20 for men aged <65 and 0.11 for men aged >84.

Conclusions: In this cohort, the incidence of CVD was significantly higher among men with CRPC compared to healthy controls. Despite having this end-stage disease this finding proves that clinicians must recognize this late effect in men diagnosed with CRPC to improve preventive actions. These men did not have a higher absolute risk of fractures and diabetes after accounting for deaths due to any cause compared to healthy controls.

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KEYWORDS
Castration-resistant prostate cancer; fracture; diabetes; comorbidity; cardiovascular disease

Introduction

Castrate-resistant prostate cancer (CRPC) has been the leading cause of prostate cancer (PC) related deaths, accounting for more than 350,000 annually worldwide [1]. Interestingly, around half of the deaths associated with PC have been due to other reasons than the disease itself, such as CVD [2]. The life expectancy of this patient population has increased with the early use of novel life-prolonging treatments, making long-term side effects of these treatments and the disease an increasingly important topic in the counseling of men with PC. Descriptive data have been sparse regarding late effects associated with CRPC and therefore needs to be investigated further in order to identify, prevent, and predict the anticipated clinical course of the disease.

Androgen deprivation therapy (ADT) has played an essential part in the management of advanced PC, and has previously been linked to numerous late effects such as cardiovascular disease (CVD), fractures, and diabetes [3–10]. Our aim with this real-world study of a Swedish CRPC cohort was to evaluate the excess risk and onset of CVD, fractures, and diabetes as compared to men free from PC, as well as the timing of these late effects from when the patients have entered the CRPC phase.

Materials and methods

Study population and data sources

Men with CRPC were identified in the STHLM0 cohort in Sweden between the years 2006 and 2014. The STHLM0 cohort is a regional population-based register for all men in Stockholm County who have undergone PSA testing or a prostate biopsy since 2003. All men with a recorded diagnosis of PC in this register were linked to the national Swedish Cancer Register for validation of the diagnosis, as reporting to this register is mandatory by Swedish law. Prescription patterns of gonadotropin-releasing hormone (GnRH)

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treatment was obtained by further linking our cohort to the national Swedish Prescribed Drug Register which includes records for all prescribed drugs since June 2005.

The cohort was also linked to the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) for information on the highest attained level of education and to the Cause of Death Register for follow-up information.

CRPC definition

The date of CRPC was based on an increase in PSA (first date of doubling of nadir PSA value with the last value being greater than 2 ng/mL, or an absolute increase of 5 ng/mL or more) despite medical or surgical castration. No information of testosterone level was available.

Matching of the CRPC cohort and the comparator cohort

For each man in our CRPC cohort, we identified all men with the same year of birth within the STHLM0 cohort. These were eligible as comparators if they had not yet been diagnosed with PC at the time of the diagnosis of the index patient. Three men matched on year of birth and free from PC at the matching date (date of CRPC diagnosis) were sampled for each individual in the CRPC cohort ($n = 4392$). The comparators were sampled at random and with replacement. This approach to identify men with the above-mentioned definition of CRPC in the STHLM0 cohort has been described in detail previously [11]. The CRPC cohort was subsequently linked to the National Prostate Cancer Register (NPCR) for detailed clinical data.

Outcomes

The incidence of the first CVD-related event, fracture, and onset of diabetes treatment after entering the CRPC phase, was obtained from the National Swedish Patient Register (CVD and fracture) and the National Swedish Prescribed Drug Register (diabetes). For CVD, all main or up to five contributing diagnoses according to the 10th revision of the International Classification of diseases (ICD-10) were classified as events. Fractures were similarly identified using ICD-10 codes and diabetic treatment was identified using the Anatomic Therapeutical Chemical Classification System (ATC) using codes, which are all presented in a table as in Supplementary Material 2. CRPC patients having diabetes before inclusion were excluded from the analysis (170 men diagnosed with CRPC and 433 comparators had a history of diabetes). All cases of diabetes in this study were thus newly diagnosed.

Statistical analysis

The matched cohort was followed from the CRPC/matching date until the date of the outcome of interest (CVD-related event, fracture, or diabetic treatment, respectively), date of death, or until the date of last follow up (31 December 2015), whichever came first.

Kaplan–Meier estimates of survival were estimated for each of the outcomes of interest, while censoring for death. The CRPC cohort was stratified into subgroups based on risk group at diagnosis (localized disease, regionally metastatic/locally advanced disease or distant metastatic disease) and the cumulative duration on ADT treatment prior to the diagnosis of CRPC. Log-rank tests were used to test for differences in survival.

Cox regression was used to estimate hazard rate ratios with 95% confidence intervals (CIs) for the respective late effects. Since the late effects of interest in this study are incidence of CVD, fracture, and diabetes the hazard ratios will be referred to as incidence rate ratios (IRRs) throughout the manuscript. The proportional hazards assumption was tested using the Schoenfeld residuals from the Cox models.

As a measure of absolute risk, cumulative incidence of CVD, fracture, and diabetes were estimated non-parametrically in the presence of competing risks. Separate analyses were performed by age group.

The Stata Software (StataCorp. 2015; *Stata Statistical Software Release 14* (StataCorp LP., College Station, TX) was used for all statistical analyses.

Results

Men in the CRPC cohort had a previous history of CVD (55.5 *vs*. 46.4% $p < 0.001$), fractures (10.7 *vs*. 8.7% $p = 0.022$), and diabetes (11.6 *vs*. 9.9%, $p = 0.056$) to a greater extent compared to the healthy controls (Table 1). Educational level for the two groups was similar ($p = 0.041$). The median follow-up time in the CVD analysis was 0.6 years (IQR: 0.2–1.4), 1.0 year (IQR: 0.4–2.0) in the fracture analysis and 0.9 years (IQR: 0.3–1.9) in the diabetes analysis for the CRPC population.

The majority of patients were primarily diagnosed with advanced PC with Gleason grade >7, T-stage >2 or more, and PSA >20 (Table 2). 81% of men were on ADT for less than 36 months prior to CRPC diagnosis, and 40% were on ADT for less than 13 months before entering their CRPC phase.

CRPC was associated with an increased rate of CVD (IRR = 1.99 (1.68–2.37)), fracture (IRR = 1.94, 95% CI: 1.79–2.12), and diabetes (IRR = 2.00, 95% CI: 1.31–3.05) when compared to healthy controls (Table 3).

The Kaplan–Meier estimations in Figure 1 indicated that the men in the comparator cohort remained free from events of CVD and fracture longer than men with CRPC (log-rank $p < 0.001$). These results appeared unrelated to risk category at primary PC diagnosis and duration of ADT exposure before development of CRPC.

The difference in cumulative incidence of CVD-related events was higher in men belonging to the two younger age groups (<65 and 65–74 years) at diagnosis of CRPC when compared to their matched comparators (Figure 2). For men diagnosed with CRPC < 65 years the cumulative incidence of CVD was 0.31 (CI: 0.24–0.38) and 0.11 (CI: 0.09–0.14) for the comparators at 12 months of follow-up. For men diagnosed

Table 1. Baseline characteristics of 1464 men with castration-resistant prostate cancer (CRPC) and 4392 matched comparators in Stockholm, Sweden between the years 2006 and 2014.

	CRPC cohort				Matched cohort			
Covariates	Patients, *N*	CVD, *N* (%)	Fracture, *N* (%)	Diabetes, *N* (%)	Number, *N*	CVD, *N* (%)	Fracture, *N* (%)	Diabetes, *N* (%)
Total	1464	786	142	177	4392	1989	387	470
Age (CRPC/matching)								
<65 years	173 (11.8)	78 (9.9)	13 (9.2)	16 (9.0)	531 (12.1)	142 (7.1)	26 (6.7)	56 (11.9)
65–74 years	449 (30.7)	212 (27.0)	33 (23.2)	57 (32.2)	1327 (30.2)	474 (23.8)	73 (18.9)	157 (33.4)
75–84 years	558 (38.1)	329 (41.9)	51 (35.9)	80 (45.2)	1689 (38.5)	879 (44.2)	177 (45.7)	200 (42.6)
>84 years	284 (19.4)	167 (21.3)	45 (31.7)	24 (13.6)	845 (19.2)	494 (24.8)	111 (28.7)	57 (12.1)
Education								
Low (<10 years)	443 (30.3)	236 (30.0)	53 (37.3)	57 (32.2)	1195 (27.2)	593 (29.8)	114 (29.5)	144 (30.6)
Intermediate (10–12 years)	575 (39.3)	311 (39.6)	52 (36.6)	66 (37.3)	1731 (39.4)	763 (38.4)	160 (41.3)	190 (40.4)
High (>12 years)	385 (26.3)	201 (25.6)	30 (21.1)	49 (27.7)	1300 (29.6)	547 (27.5)	98 (25.3)	115 (24.5)
Missing	61 (4.2)	38 (4.8)	7 (4.9)	5 (2.8)	166 (3.8)	86 (4.3)	15 (3.9)	21 (4.5)
Calendar period								
2006–2008	271 (18.5)	168 (21.4)	28 (19.7)	27 (15.3)	813 (18.5)	510 (25.6)	127 (32.8)	101 (21.5)
2009–2011	515 (35.2)	316 (40.2)	67 (47.2)	67 (37.9)	1545 (35.2)	844 (42.4)	171 (44.2)	203 (43.2)
2012–2014	678 (46.3)	302 (38.4)	47 (33.1)	83 (46.9)	2034 (46.3)	635 (31.9)	89 (23.0)	166 (35.3)
History of CVD[a]								
Yes	813 (55.5)	557 (70.9)	NA	NA	2037 (47.2)	1356 (68.2)	NA	NA
No	654 (44.5)	229 (29.1)	NA	NA	2319 (52.8)	633 (31.8)	NA	NA
History of fracturess[a]								
Yes	157 (10.7)	NA	27 (19.0)	NA	383 (8.7)	NA	86 (22.2)	NA
No	1307 (89.3)	NA	115 (81.0)	NA	4009 (91.3)	NA	301 (77.8)	NA
History of diabetes[c]								
Yes	170 (11.6)	NA	NA	146 (82.5)	433 (9.9)	NA	NA	388 (82.6)
No	1294 (88.4)	NA	NA	31 (17.5)	3959 (90.1)	NA	NA	82 (17.5)
Previous statin use[d]								
Yes	372 (25.4)	255 (32.4)	NA	NA	1101 (25.1)	674 (33.9)	NA	NA
No	1092 (74.6)	531 (67.6)	NA	NA	1315 (74.9)	1315 (66.1)	NA	NA

[a]Defined as a record up to five years before start of follow-up.
[c]Defined as having bought a prescription of a diabetic drug within 6 months before start of follow-up.
[d]Defined as having used statins within 6 months before start of follow-up.

with CRPC > 84 years, the cumulative incidence of CVD was 0.50 (CI: 0.44–0.56) and 0.39 (CI: 0.35–0.42) for the comparators at 12 months of follow-up. There was no clear difference in the cumulative incidence of fracture and diabetes between men diagnosed with CRPC and the comparators.

Discussion

Key findings

In this follow up of a large cohort of men with CRPC, we found that CVD was the most frequently occurring late effect in this patient cohort. The occurrence of fractures and diabetes was less pronounced in this group compared with the matched comparators, when competing risks were taken into account.

Cardiovascular disease

The higher rate of CVD among men with CRPC was observed in the beginning of the CRPC phase, within the first 12 months. O'Farrell et al. showed that the highest risk of having an event of CVD was during the first 6 months of ADT among PC patients on ADT [12]. According to Hemelrijck et al. [13] their absolute risk differences of CVD among PC patients on endocrine therapy were also rather small. This was in concordance with our results (Figure 2) even though the men diagnosed with CRPC of this cohort were not in a hormone naïve phase of disease in contrast to these two publications. It seems like the risk of CVD may be rather persistent regardless of which phase of PC these men are in.

The competing risk analysis reflects that men in the comparator group belonging to age groups 75–84 and age > 84 have a higher incidence of CVD at the end of follow-up where the curves cross. A possible explanation for the observed differences in the absolute risk when contrasting the men diagnosed with CRPC and the comparator cohort may merely be the differential risk of experiencing the competing event (death). This explanation reflects the situation when healthy men live comparatively longer than men with CRPC, thus remaining at risk for CVD.

Fracture

Fractures in the CRPC population were around twice as prevalent as in the comparator group, but this did not translate into a higher absolute risk when estimated in the presence of competing risks. Thorstenson et al. demonstrated similar results in a population-based study of PC patients on ADT, with rather small absolute risk incidence of fractures leading to hospitalization [14]. In a study of 181 patients with PC on ADT, fracture-free rates were 96 and 80% for men on ADT for 5 and 10 years, respectively [15], indicating the slow process of fracture development. According to a study cohort of 235 patients with advanced PC, orchiectomy resulted in a 13.6% 7-year cumulative fracture incidence compared to 1.1% in men who did not undergo ADT-associated surgery [16]. In a retrospective study of 50,000 patients

Table 2. PC characteristics of 1464 men before the onset of castration-resistant prostate cancer (CRPC) in Stockholm, Sweden between the years 2006 and 2014.

Covariates	Patients, *N*	CVD, *N* (%)	Fracture, *N* (%)	Diabetes, *N* (%)
Gleason score at PC diagnosis				
Low (<7)	69 (4.7)	37 (4.7)	7 (4.9)	12 (6.8)
Middle (7)	344 (23.5)	178 (22.7)	31 (21.8)	50 (28.3)
High (>7)	655 (44.7)	353 (44.9)	60 (42.3)	76 (42.9)
Missing	396 (27.1)	218 (27.7)	44 (31.0)	39 (22.0)
PSA at PC diagnosis				
<10	25 (1.7)	10 (1.3)	0 (-)	4 (2.3)
[10–20)	101 (6.9)	51 (6.5)	11 (7.8)	14 (7.9)
[20,50)	304 (20.8)	174 (22.1)	42 (29.6)	40 (20.6)
>50	912 (62.3)	485 (61.7)	79 (55.6)	102 (57.6)
Missing	122 (8.3)	66 (8.4)	10 (7.0)	17 (9.6)
T-stage at PC diagnosis				
T1–2	568 (38.8)	303 (38.6)	56 (39.4)	84 (47.5)
T3	602 (41.1)	339 (43.1)	52 (36.6)	63 (35.6)
T4	173 (11.8)	79 (10.1)46	22 (15.5)13	14 (7.9)8
Missing	121 (8.3)	65 (8.3)	12 (8.5)	161 (9.0)
N-stage at PC diagnosis				
N0	61 (4.2)	33 (4.2)	3 (2.1)	8 (4.5)
N1	105 (7.2)	46 (5.9)	6 (4.2)	9 (5.1)
NX	1200 (82.0)	653 (83.1)	122 (85.9)	149 (84.2)
Missing	98 (6.7)	54 (6.9)	11 (7.8)	11 (6.2)
M-stage at PC diagnosis				
M0	379 (25.9)	210 (26.7)	34 (22.9)	53 (29.9)
M1	415 (28.4)	185 (23.5)	25 (17.6)	29 (16.4)
Mx	565 (38.6)	333 (42.4)	71 (50.0)	82 (46.3)
Missing	105 (7.2)	58 (7.4)	12 (8.5)	13 (7.3)
Riskgroup at PC diagnosis				
Low	3 (0.2)	2 (0.3)	0 (-)	1 (0.6)
Intermediate	33 (2.3)	13 (1.7)	1 (0.7)	4 (2.3)
High	268 (18.3)	160 (20.4)	37 (26.31)	36 (20.3)
Regionally metastatic/locally advanced	257 (17.6)	152 (19.3)	32 (22.5)	34 (19.2)
Distant metastasis	767 (52.4)	384 (48.9)	56 (39.4)	80 (45.2)
Missing	136 (9.3)	75 (9.5)	16 (11.3)	22 (12.4)
Duration of ADT treatment prior to CRPC				
<13 months	581 (39.7)	321 (40.8)	55 (38.7)	53 (29.9)
13–36 months	608 (41.5)	332 (42.2)	58 (40.6)	87 (49.2)
37–60 months	148 (10.1)	73 (9.3)	24 (16.9)	24 (13.6)
>60 months	40 (2.7)	18 (2.7)	3 (2.1)	2 (1.1)
Missing	87 (5.9)	42 (5.3)	2 (1.4)	11 (6.2)

Table 3. Incidence rate ratios and 95% confidence intervals (CI) of cardiovascular disease (CVD), fracture, and diabetes among 1464 men with castration-resistant prostate cancer (CRPC) as compared to the 4392 matched comparators.

	CVD		Fracture		Diabetes	
	IRR (95% CI) unadjusted	IRR (95% CI) adjusted[a]	IRR (95% CI) unadjusted	IRR (95% CI) adjusted[b]	IRR (95% CI) unadjusted	IRR (95% CI) adjusted[c]
Overall						
Comparators	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
CRPC	2.12 (1.78–2.53)	1.99 (1.68–2.37)	2.13 (1.75–2.60)	2.08 (1.70–2.53)	2.00 (1.31–3.05)	2.00 (1.31–3.05)
By risk group at PC						
Comparators	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Localized	2.56 (1.90–3.46)	2.01 (1.49–2.72)	2.45 (1.75–3.43)	2.14 (1.53–3.00)	2.87 (1.48–5.57)	3.08 (1.58–6.00)
Regional metastasis	2.68 (1.95–3.69)	2.49 (1.81–3.43)	2.49 (1.73–3.58)	2.54 (1.77–3.65)	1.00 (0.32–3.19)	0.99 (0.31–3.14)
Distant metastasis	1.84 (1.44–2.34)	1.94 (1.52–2.47)	1.77 (1.33–2.35)	1.86 (1.40–2.47)	1.61 (0.87–2.97)	1.58 (0.85–2.92)
Missing	1.61 (0.96–2.70)	1.37 (0.81–2.29)	2.38 (1.44–3.93)	2.02 (1.22–3.34)	3.75 (1.63–8.61)	3.60 (1.56–8.29)
By ADT treatment duration prior to CRPC						
Comparators	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<13 months	2.36 (1.84–3.04)	2.46 (1.92–3.17)	2.31 (1.73–3.07)	2.45 (1.84–3.26)	1.90 (1.00–3.59)	1.79 (0.94–3.39)
13–36 months	1.83 (1.42–2.35)	1.75 (1.37–2.26)	1.91 (1.45–2.53)	1.87 (1.42–2.48)	2.24 (1.28–3.92)	2.25 (1.29–3.94)
≥37 months	2.03 (1.35–3.07)	1.54 (1.02–2.33)	2.89 (1.95–4.28)	2.39 (1.60–3.55)	1.32 (0.42–4.20)	1.52 (0.48–4.88)
Missing	3.30 (1.97–5.53)	2.35 (1.40–3.94)	0.63 (0.16–2.51)	0.53 (0.13–2.13)	2.70 (0.66–11.04)	2.69 (0.66–11.04)

Only I63x/I50x/I21x/I25x-codes are included in this analysis. Sensitivity analyses for the diagnoses included are presented in Supplementary Material 3.
[a]Adjusted for age at CRPC/match date, education level, period of diagnosis, prior history of CVD, and statin use.
[b]Adjusted for age at CRPC/match date, education level, period of diagnosis, and prior history of fractures.
[c]Adjusted for age at CRPC/match date, education level, period of diagnosis. Men with a prior history of diabetes were excluded ($n = 603$).

diagnosed with PC and an overall 5-year survival, 19.4% of patients receiving ADT had a fracture *vs.* 12.6% in those not receiving ADT [17].

Diabetes

There was a relative risk increase for diabetes in the CRPC cohort, but the CIs were wide (IRR = 2.00, 95% CI 1.31–3.05)

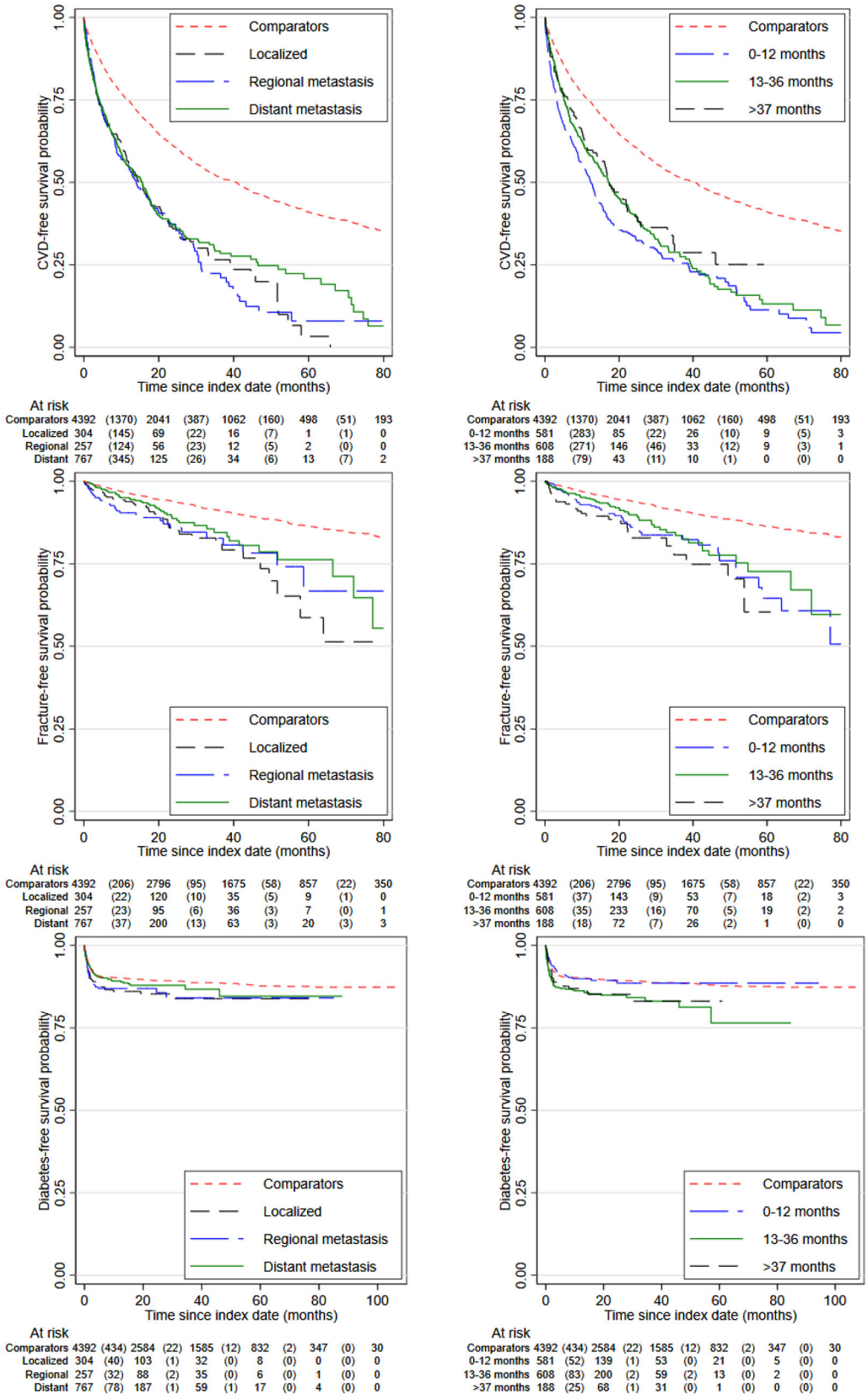
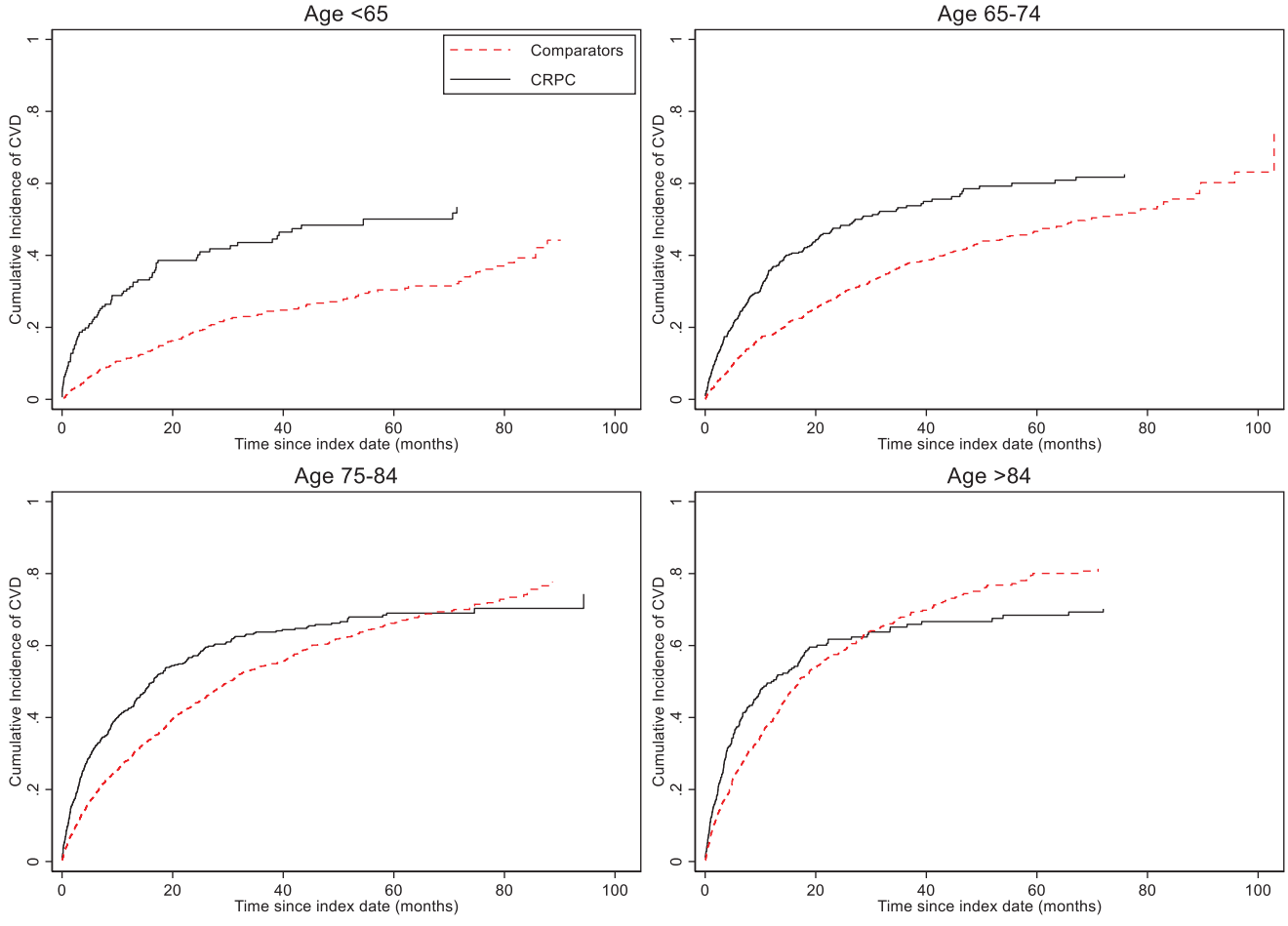


Figure 1. Kaplan–Meier estimates of CVD-, fracture-, and diabetes-free survival among 1464 men with CRPC, by risk group at prostate cancer and duration of ADT use prior to the diagnosis of CRPC, as compared to the 4392 matched comparators.

as few events were recorded in both the CRPC cohort and among the comparators. When analyzed in the presence of competing risks, the cumulative incidence for men diagnosed with CRPC and their matched comparators were similar, again possibly explained by differences in mortality between the groups.

A possible reason for the generally low incidence of diabetes may be that the prevalence of diabetes was relatively high before entering the CRPC phase. Additionally, our study may suffer from some degree of underreporting due to the definition of the diabetes outcome which assumes that the men had been prescribed drugs for their diabetes, while men having diabetes without medication were not classified as events. To contrast our findings, an observational study of PC patients on ADT showed a significantly higher absolute risk of diabetes compared to patients not on ADT. That study ascertained the diagnosis through a diagnosis code, which may partly explain the fewer events of this study [18].

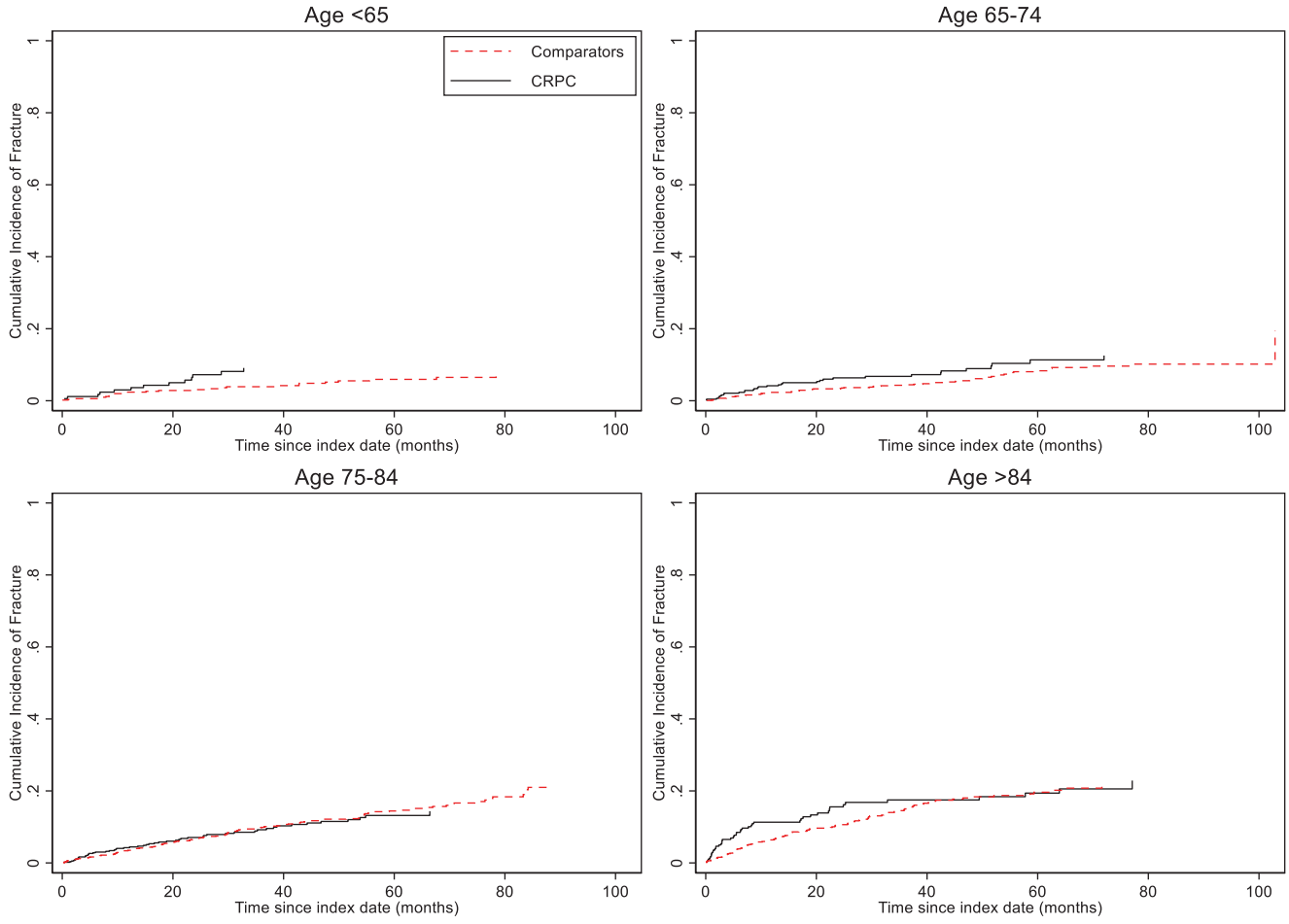
During the study period, the use of treatment with abiraterone acetate in combination with prednisone was less common, which in theory can explain the similar incidence of diabetes between men having CRPC and the comparators as men having CRPC experienced the possible adverse event of glucocorticoid treatment to a lower extent. However, a



Age at CRPC*	CRPC/Comparator status	12-month cumulative incidence (%)	95% Confidence interval	24-month cumulative Incidence	95% Confidence interval
<64	CRPC	0.307	(0.239 - 0.377)	0.386	(0.312- 0.459)
<64	Comparators	0.112	(0.087 - 0.141)	0.184	(0.151 - 0.220)
65-74	CRPC	0.363	(0.317 - 0.410)	0.476	(0.423 - 0.525)
65-74	Comparators	0.179	(0.158 - 0.201)	0.287	(0.260 - 0.313)
75-84	CRPC	0.424	(0.381 - 0.466)	0.572	(0.527 - 0.614)
75-84	Comparators	0.283	(0.261 - 0.306)	0.440	(0.415 - 0.466)
>84	CRPC	0.500	(0.438 - 0.559)	0.618	(0.553 - 0.676)
>84	Comparators	0.389	(0.354 - 0.423)	0.575	(0.536 - 0.612)

*Matching date for comparators

Figure 2. Cumulative incidence with CIs in the presence of competing risk (e.g., death) for CVD, fracture, and diabetes in 1464 men with CRPC, as compared to the 4392 matched comparators.



Age at CRPC*	CRPC/Comparator status	12-month cumulative incidence (%)	95% Confidence interval	24-month cumulative incidence	95% Confidence interval interval)
<64	CRPC	0.030	(0.011 - 0.065)	0.072	(0.038 - 0.121)
<64	Comparators	0.023	(0.013 - 0.040)	0.031	(0.018 - 0.049)
65-74	CRPC	0.042	(0.025 - 0.064)	0.064	(0.042 - 0.091)
65-74	Comparators	0.023	(0.016 - 0.033)	0.033	(0.024 - 0.044)
75-84	CRPC	0.042	(0.027 - 0.062)	0.071	(0.050 - 0.096)
75-84	Comparators	0.035	(0.027 - 0.045)	0.067	(0.054 - 0.080)
>84	CRPC	0.113	(0.079 - 0.155)	0.156	(0.113 - 0.205)
>84	Comparators	0.064	(0.048 - 0.083)	0.104	(0.083 - 0.129)

*Matching date for comparators

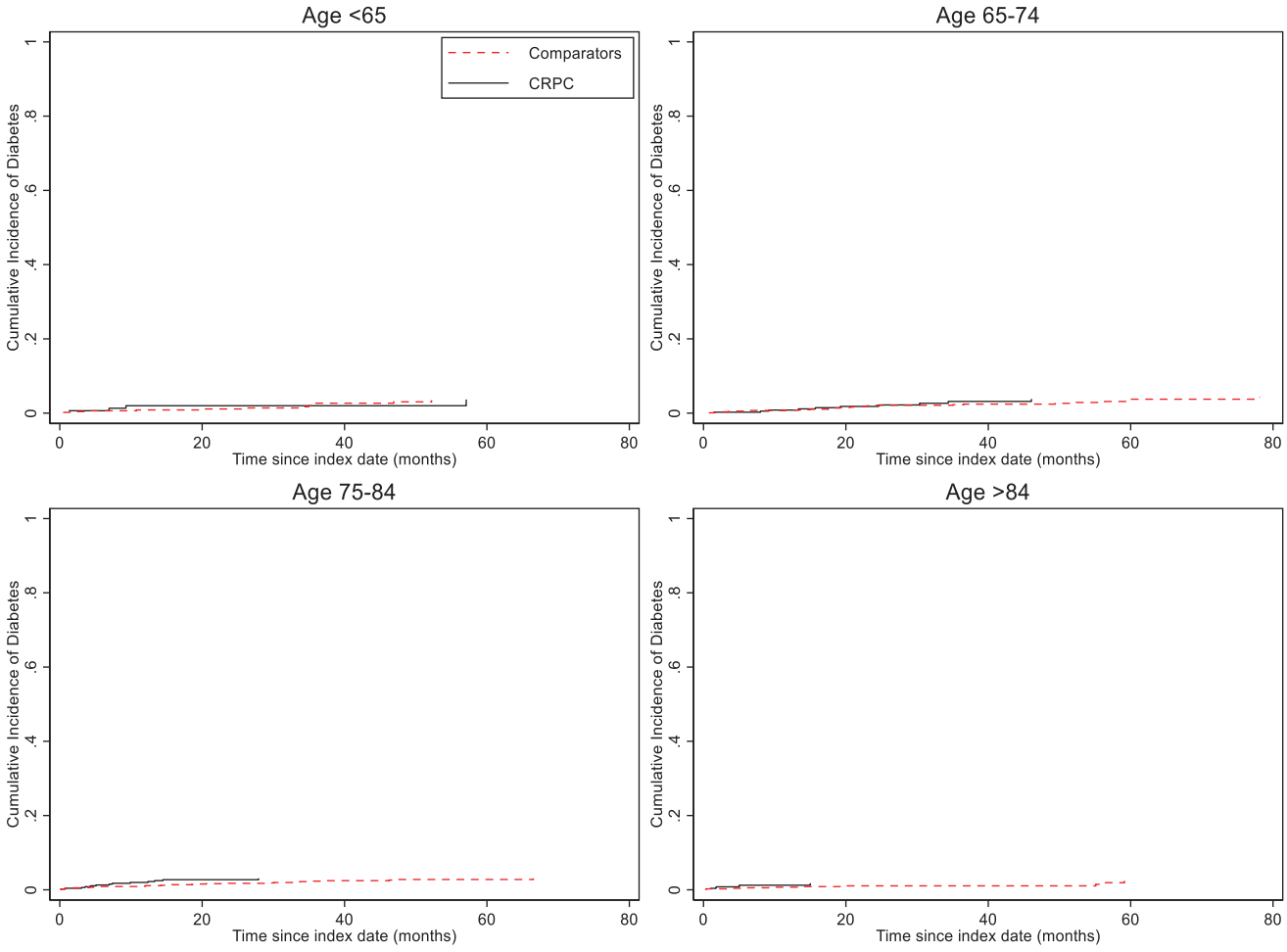
Figure 2. Continued.

study on the effect of prednisone or dexamethasone and the risk of diabetes showed that there was only an increased risk of diabetes in the group receiving dexamethasone, which is not regularly used as a combination with novel antiandrogens or generally to men having CRPC [19].

Strengths and limitations

All patients included were recorded in our population-based registers permeated by high-quality data. The real-life design of the study including patients with a larger burden of comorbidity and higher age in contrast to trial studies also made it more representative for clinical purposes and may increase generalizability.

The retrospective nature of this cohort was a limitation and as for all registry-based cohorts events may be misclassified. Men are followed in a real-life setting that may be less rigid than in a prospective study, meaning that PSA testing and indication for therapy was based on clinical decision making rather than by clinical study protocols. In this cohort, there was no information on prescription of specific chemotherapy drugs as they were hospital-administered, thus not captured in the prescribed drug register. We did not have



Age at CRPC*	CRPC/Comparator status	12-month cumulative incidence (%)	95% Confidence interval	24-month cumulative incidence	95% Confidence interval
<64	CRPC	0.020	(0.005 - 0.053)	0.020	(0.005 - 0.053)
<64	Comparators	0.009	(0.003 - 0.021)	0.011	(0.004 - 0.025)
65-74	CRPC	0.008	(0.002 - 0.023)	0.018	(0.008 - 0.037)
65-74	Comparators	0.008	(0.004 - 0.015)	0.021	(0.013 - 0.032)
75-84	CRPC	0.020	(0.010 - 0.036)	0.027	(0.015 - 0.046)
75-84	Comparators	0.010	(0.006 - 0.017)	0.017	(0.011 - 0.026)
>84	CRPC	0.012	(0.003 - 0.033)	Not available	Not available
>84	Comparators	0.007	(0.003 - 0.016)	0.011	(0.005 - 0.021)

*Matching date for comparators

Figure 2. Continued.

access to data regarding the use of bone-health agents, which should be more commonly used by the CRPC-patients compared to the ordinary population, which in turn might reduce and hide a larger (not observed) difference in fractures.

Due to the design of this study patients being on ADT prior to June 2005 were not included since the Swedish Prescribed Drug Register, despite its high validity [20], was established in July 2005. The men included in this patient cohort (years 2006–2014) first had to be diagnosed with PC and develop CRPC during the follow-up time, which is described in more detail in Supplementary Material 1. Men diagnosed with PC before June 2005 were not included in this cohort as we wanted to have control of their full disease history and prescribed drugs during the study, meaning that those men diagnosed prior to June 2005 and developing CRPC during the study period were excluded, thus likely leading us to selecting a more aggressive CRPC cohort in this study as the patients had to be diagnosed, treated, having a PSA failure and also fail on GNRH-treatment within 10 years of the study follow-up, in order to be included in this study.

Men with CRPC may be more likely to have regular check-ups and surveillance visits as they regularly meet health care providers, not being the case in the comparator cohort. A Danish study however shows there does not seem to be a difference in prescription rates between men having PC and cancer-free comparisons, although there is a difference with higher rates of prescriptions for PC patients one year before the men are diagnosed during the medical investigation for PC [21]. Thus, it is not likely that closer observation of men having PClead to an inflated rate of sub-clinical diagnostic coding resulting in false positives.

Conclusion

In this cohort of men diagnosed with CRPC CVD was a prevalent late effect when compared to healthy controls. This finding can potentially work as an aid in clinical decision making on CRPC patients, especially those with lower age having risk factors for CVD. Compared to men in the general population, men with CRPC did not have a higher absolute risk of fractures and diabetes in the real-world setting.

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Disclosure statement

Amy Leval, Johan Liwing, Anton Boman, and Martin Dahlkild are/where employees of Janssen during the work of this study. Frida Schain is a former employee of Janssen and an owner and employed by Schain Research (a consultancy service related to studies for Janssen).

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [YK], upon reasonable request.

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