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The risk of developing cardiovascular disease is increased for patients with prostate cancer who are pharmaceutically treated for depression

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Objective

To examine the associations between pharmaceutically treated anxiety and depression and incident cardiovascular disease (CVD) among 1-year prostate cancer survivors.

Patients and methods

A registry-based cohort study design was used to describe the risk of incident CVD in adult 1-year prostate cancer survivors without a history of CVD. Patients with prostate cancer diagnosed between 1999 and 2011 were selected from the Netherlands Cancer Registry. Drug dispenses were retrieved from the PHARMO Database Network and were used as proxy for CVD, anxiety, and depression. Data were analysed using Cox regression analysis to examine the risk associations between pharmaceutically treated anxiety and depression entered as a time-varying predictor with incident CVD in 1-year prostate cancer survivors, while controlling for age, traditional CVD risk factors, and clinical characteristics.

Results

Of the 5262 prostate cancer survivors, 327 (6%) developed CVD during the 13-year follow-up period. Prostate cancer survivors who were pharmaceutically treated for depression had an increased risk of incident CVD after full adjustment compared to prostate cancer survivors who were not pharmaceutically treated for depression (hazard ratio [HR] 1.51, 95% confidence interval [CI] 1.06–2.15). The increased risk of incident CVD amongst those pharmaceutically treated for depression compared to those who were not pharmaceutically treated for depression, was only valid among: prostate cancer survivors who were aged ≤65 years (HR 2.91; 95% CI 1.52–5.55); those who were not treated with radiotherapy (HR 1.63; 95% CI 1.01–2.65); those who were treated with hormones (HR 1.76; 95% CI 1.09–2.85); those who were not operated upon (HR 1.55; 95% CI 1.07–2.25); and those with tumour stage III (HR 2.21; 95% CI 1.03–4.74) and stage IV (HR 2.47; 95% CI 1.03–5.89).

Conclusion

Patients with prostate cancer who were pharmaceutically treated for depression had a 51% increased risk of incident CVD after adjustment for anxiety, age, traditional CVD risk factors, and clinical characteristics. The results emphasise the need to pay attention to (pharmaceutically treated) depressed patients with prostate cancer prior to deciding on prostate cancer treatment and for a timely detection and treatment of CVD.

Keywords

cardiovascular disease, depression, anxiety, risk factors, #PCSM, #ProstateCancer

Introduction

A considerable proportion of prostate cancer survivors experience late effects from the cancer itself and its treatment, such as co-morbid cardiovascular disease (CVD) and psychological distress [1,2]. A recent case-control study by our group concluded that prostate cancer survivors have an increased risk of incident CVD compared to their age-matched cancer-free controls [3]. This increased risk may be the result of cardiotoxic cancer treatment, as several chemotherapeutic agents and hormone treatments can lead to a heterogeneous group of CVDs [4]. As more patients with prostate cancer survive their cancer, cardiotoxic side-effects demand consideration. Moreover, there are similar underlying behavioural risk factors for both prostate cancer and CVD, like obesity and smoking [5].

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The incidence rate of cardiac co-morbidity in prostate cancer survivors who received cardiotoxic treatment is ~3% [3]. This suggests that there are additional factors involved in the pathogenesis of incident CVD amongst prostate cancer survivors. Knowledge on predictors of incident CVD is vital as a prostate cancer patient's individual risk should be considered when opting for a cancer treatment that has a high probability of cardiac complications.

Little is known about risk factors for incident CVD amongst prostate cancer survivors. However, there is ample knowledge on predictors for CVD in non-cancer populations. First, traditional CVD risk factors such as hypertension, hypercholesterolaemia, and diabetes mellitus, are known to play an important role in the pathogenesis of CVD [6,7]. The involvement of these risk factors has been confirmed to play a role in incident CVD among various malignancies as well [3,8,9]. More recently, several studies have shown that psychological distress, such as being anxious or depressed, also increases the risk of the development and progression of CVD among non-cancer populations, independent of traditional biomedical risk factors [10–13].

It is well known, that many prostate cancer survivors experience high levels of psychological distress, which can persist for years after cancer treatment has finished [14]. Prevalence rates for anxiety and depression range from 15% to 27%, hence one in every five prostate cancer survivors are afflicted [14,15]. Consequently, prostate cancer survivors may have an increased risk of incident CVD if only by these elevated levels of psychological distress after cancer diagnosis [16]. Indeed, a study by our group amongst breast cancer survivors showed that pharmaceutically treated anxiety prior to cancer diagnosis increases the risk of incident CVD, while controlling for depression, traditional cardiovascular risk factors, and clinical factors [17]. Interestingly, the predictive value of anxiety and depression for incident CVD, in addition to the traditional CVD risk factors and cancer treatments, is a key clinical objective in the field of CVD but has never been studied within the field of prostate cancer survivorship.

The aim of the present study was therefore to examine the associations between pharmaceutically treated anxiety and depression and incident CVD in 1-year prostate cancer survivors.

Patients and methods

Study design and setting

A registry-based cohort study design was used to describe the risk of incident CVD in adult 1-year prostate cancer survivors without a history of CVD. Patients with prostate cancer diagnosed in the Southern Region of the Netherlands between 1 January 1999 and 31 December 2011 were selected from the Netherlands Cancer Registry (NCR). The NCR includes all newly diagnosed patients with cancer and registers type of malignancy, date of diagnosis, stage, and primary cancer treatment [18]. For patients with cancer diagnosed from 1998 and onwards the PHARMO database network was linked to data from the NCR, see a detailed description of this linkage elsewhere [19]. PHARMO is a large, patient-centric multi-linked data network, which entails longitudinal data on drugs dispensed by community pharmacies, date, and amount of dispensing [19]. Drug prescriptions are coded according to the international Anatomical Therapeutic Chemical (ATC) Classification developed by the WHO [20], and were used as a proxy for CVD, anxiety and depression in this study.

This study does not fall under the medical Research Involving Human Subjects Act in the Netherlands, as anonymous observational patient information was used. Therefore, this study was exempted from medical ethics review and no informed consent was required. The procedures of the study were in accordance with the Declaration of Helsinki.

Participants

Adult patients with prostate cancer diagnosed between 1 January 1999 and 31 December 2011 were selected from the NCR. The aim of the study was to examine risk of incident CVD secondary to prostate cancer diagnosis. Therefore, prostate cancer survivors who had a history of CVD in the year prior to cancer diagnosis were not eligible. Start of follow-up was set at 1 year after diagnosis because cancer treatment is generally finished within the first year. This moment allowed avoidance of CVD detection due to increased medical evaluations and exempted inclusion of the direct and sometimes reversible effects of cardiotoxic treatment. Follow-up time was measured until CVD, death, loss to follow-up, or until the end of the study period (31 December 2011), whichever occurred first.

Data measurements

Drug prescriptions for CVD

The following algorithm to define CVD was used: ≥2 drug dispenses of 'cardiac therapeutics' (i.e., ATC code C01 [21]) at unique dates within 6 months. When participants dispensed two ATC code C01 drugs within a 2-week period (<15 days in between) they were classified as having CVD only if they had at least three ATC code C01 dispenses at unique dates. To avoid false classifications of CVD, our definition was solely based on the use of cardiac therapeutics (ATC code C01). Usage of drugs that have a broad treatment range including non-cardiac indications, such as diuretics (ATC code C03), or β-blockers (ATC code C07), was insufficient to be classified as having CVD.

Psychological factors; anxiety and depression

Drug dispensing information for anxiety (ATC code N05B) and depression (ATC code N06A) in the year prior to and after cancer diagnosis was included. Survivors were classified as being anxious or depressed (yes/no) as indicated by using ≥1 drug prescriptions.

Traditional risk factors for CVD

Information on traditional CVD risk factors was obtained based on prescription drugs for the duration of follow-up for hypertension (ATC code C02, C03 [except C03c], C07, C08, C09 [except C09x]), hypercholesterolaemia (ATC code C10), and diabetes mellitus (ATC code A10). Having one of the traditional cardiovascular risk factors (yes/no) was defined as ≥1 drug prescription.

Demographics and clinical characteristics

Demographics at index date were extracted from the PHARMO database. Clinical information on tumour stage and primary cancer treatment (having received chemo-, radio-, hormone therapy, or surgery [yes/no]) was obtained from the NCR.

Statistical analyses

Differences in demographics, clinical characteristics, traditional CVD risk factors, pharmaceutically treated anxiety and depression between prostate cancer survivors with and without incident CVD were tested using ANOVA, the chi-squared and *t*-tests for independent samples.

To examine the associations between pharmaceutically treated anxiety and depression and incident CVD in 1-year prostate cancer survivors Cox proportional hazard regression analyses were performed. In other words, we examined whether the risk of incident CVD between those pharmaceutically treated for anxiety and depression was different compared to the risk for prostate cancer survivors who were not pharmaceutically treated for anxiety and depression. Anxiety and depression were entered in a time-dependent manner and the used time-scale was the follow-up time since diagnosis starting at 1 year after diagnosis. Separate analyses were performed to examine the associations between pharmaceutically treated anxiety and depression with incident CVD. Additionally, both pharmaceutically treated anxiety and depression were entered together. Analyses included covariates that were entered in three steps. First, we adjusted for age (continuous). Second, we added the traditional CVD risk factors (i.e., hypertension, hypercholesterolaemia, and diabetes mellitus) as time-varying covariates. Finally, in the fully adjusted model, clinical characteristics (i.e., tumour stage and cancer treatment) were added to the model.

The test assumption of the Cox proportional hazard regression analyses was evaluated using visual inspection of the Kaplan–Meier curve. The assumptions of linearity of continuous covariates were checked by plots of residuals.

Sensitivity analyses were conducted to examine whether the associations between pharmaceutically treated anxiety and depression with incident CVD risk in the fully adjusted model differed by the timing of the development of anxiety or depression (prior or secondary to the cancer diagnosis) by means of stratified analyses. Furthermore, to explore whether the relation between pharmaceutically treated anxiety and depression with incident CVD was similar across subgroups, stratified analyses were performed for age (≤65 vs >65 years at cancer diagnosis), the presence of traditional CVD risk factors, cancer treatment category (chemo-, radio-, hormone therapy, and surgery), and tumour stage in the fully adjusted model.

Missing data were handled in previous steps and described elsewhere [19]. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS®), version 22 (SPSS Inc., IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$. We chose not to use a more stringent α level, as this is the first study relating both pharmaceutically treated anxiety and depression to incident CVD in prostate cancer survivors, hence we wanted to avoid making a type-2 error.

Results

Patient characteristics

Of the 5924 eligible prostate cancer survivors included in the NCR, 541 survivors were excluded as they had received CVD medications in the year prior to or after their cancer diagnosis. Additionally, 121 were excluded as they were deceased or lost to follow-up in the first year after cancer diagnosis. In total, 5262 were included in the present analyses. The excluded survivors were older, had more traditional CVD risk factors, had less often tumour stage I, were more often treated with hormone therapy and less often with radiotherapy or surgery, but most importantly they were not different in prevalence for pharmaceutically treated anxiety and depression (data not shown).

The follow-up time ranged from 1 to 13 years (Table 1). During this period 6% of the prostate cancer survivors developed CVD ($n = 327$). The prostate cancer survivors who developed CVD differed from those who did not; see Table 1 for the specific differences.

Table 1 Patients' characteristics stratified by CVD status.

Characteristic	Total (*n* = 5262)	No CVD (*n* = 4935)	CVD (*n* = 327)
Follow-up, years, median (range)	4 (1–13)	4 (1–13)	3 (1–12)*
Deceased, *n* (%)	1108 (21)	993 (20)	115 (35)*
Demographics			
Age, years, median (range)	68 (42–96)	68 (42–96)	71 (50–91)*
Age dichotomised >65 years, *n* (%)	3356 (64)	3097 (63)	259 (79)
Traditional cardiovascular risk factors†, *n* (%)	3202 (61)	2884 (58)	318 (97)*
Hypertension	2784 (53)	2468 (50)	316 (97)*
Hypercholesterolaemia	1949 (37)	1712 (35)	237 (73)*
Diabetes mellitus	598 (11)	531 (11)	67 (21)
Clinical characteristics, *n* (%)			
Tumour stage			
I	498 (10)	491 (10)	7 (2)
II	2924 (57)	2703 (57)	221 (69)
III	847 (17)	791 (17)	56 (18)
IV	839 (16)	803 (17)	36 (11)
Treatment, *n* (%)			
Chemotherapy	22 (0)	21 (0)	1 (0) na
Radiotherapy	1907 (36)	1745 (35)	162 (50)*
Surgery	1267 (24)	1229 (25)	38 (12)*
Hormone treatment	2087 (40)	1923 (39)	164 (50)*
Psychological factors, *n* (%)			
Total number‡			
Pharmaceutically treated for anxiety	859 (16)	761 (15)	98 (30)*
Pharmaceutically treated for depression	546 (10)	483 (10)	63 (19)*
Before prostate cancer diagnosis§			
Pharmaceutically treated for anxiety	235 (4)	211 (4)	24 (7)
Pharmaceutically treated for depression	172 (3)	155 (3)	17 (5)
After prostate cancer diagnosis§			
Pharmaceutically treated for anxiety	624 (12)	550 (11)	74 (23)*
Pharmaceutically treated for depression	374 (7)	328 (7)	46 (14)*

Information is provided in n (%)for categorical variables, whereas follow-up time and age are presented in median years (range). There were missing values across all variables. As patients with prostate cancer could have received more than one treatment the total number does not add up to 5262. ANOVA *was used for the categorical variables, chi-squared tests were used for dichotomous variables and t-tests were used for continuous variables. *Significant difference ($P < 0.05$) between those with and without incident CVD. †Being pharmaceutically treated for at least one of the traditional cardiovascular risk factors (i.e., hypertension, hypercholesterolaemia, or diabetes mellitus) during the 1 year prior to cancer diagnosis, yes/no. ‡The total number of survivors who were classified as pharmaceutically treated for anxiety/depression regardless of when they started taking medication, either before or after prostate cancer diagnosis. §The total number of survivors who were classified as pharmaceutically treated for anxiety/depression before and after prostate cancer diagnosis.*

Number of prostate cancer survivors who were pharmaceutically treated for anxiety and depression before and after prostate cancer diagnosis

In total, 859 (16%) prostate survivors were pharmaceutically treated for anxiety, of which 235 (4%) men started taking medication for anxiety before cancer diagnosis and 624 (12%) started taking medication for anxiety after their cancer diagnosis (Table 1). In addition, 546 survivors (10%) were pharmaceutically treated for depression, of which 172 (3%) men started taking antidepressants before cancer diagnosis and 374 (7%) started taking antidepressants after their prostate cancer diagnosis.

Associations between anxiety and depression with incident CVD

The association between pharmaceutically treated anxiety and depression, entered as time-varying predictors, with incident CVD risk was analysed separately (data not shown). Hence, we analysed whether prostate cancer survivors who were pharmaceutically treated for anxiety or depression had an increased risk of incident CVD compared to the risk of prostate cancer survivors who were not pharmaceutically treated for anxiety or depression. Pharmaceutically treated anxiety was positively associated with incident CVD risk in all three models: age-adjusted (hazard ratio [HR] 1.61, 95% CI 1.18–2.16), partially adjusted (adjusted for age and traditional CVD risk factors; HR 1.39, 95% CI 1.03–1.87) and the fully adjusted model (adjusted for age, traditional CVD risk factors and clinical factors; HR 1.42; 95% CI 1.05–1.91). Pharmaceutically treated depression was also positively associated with incident CVD risk in all three models (age-adjusted: HR 1.74, 95% CI 1.24–2.45; partially adjusted: HR 1.60, 95% CI 1.14–2.24; and fully adjusted model: HR 1.63; 95% CI 1.16–2.29).

Associating pharmaceutically treated anxiety and depression simultaneously to CVD risk (Table 2) showed that anxiety (HR 1.45, 95% CI 1.06–1.98) and depression (HR 1.54, 95% CI 1.08–2.21) were significantly associated with an increased

Table 2 Associations between pharmaceutically treated anxiety and depression with incident CVD risk.

	Age-adjusted HR (95% CI)	Partially adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Psychological factors			
Pharmaceutically treated anxiety	1.45 (1.06–1.98)*	1.28 (0.94–1.74)	1.30 (0.95–1.77)
Pharmaceutically treated depression	1.54 (1.08–2.21)*	1.48 (1.04–2.11)*	1.51 (1.06–2.15)*
Demographics			
Age (continuous)	1.05 (1.04–1.06)*	1.04 (1.03–1.06)*	1.03 (1.02–1.05)*
Traditional cardiovascular risk factors			
Hypertension	–	4.89 (3.41–7.03)*	4.84 (3.37–6.95)*
Hypercholesterolaemia	–	1.81 (1.42–2.34)*	1.81 (1.41–2.33)*
Diabetes mellitus	–	1.00 (0.72–1.38)	0.99 (0.72–1.37)
Clinical characteristics			
Tumour stage	–		
I	–	–	Reference
II	–	–	1.70 (0.98–2.95)
III	–	–	1.57 (0.85–2.92)
IV	–	–	1.19 (0.62–2.30)
Treatment			
Chemotherapy	–	–	0.77 (0.11–5.51)
Radiotherapy	–	–	1.04 (0.80–1.35)
Surgery	–	–	0.61 (0.41–0.92)
Hormone treatment	–	–	1.32 (1.01–1.72)*

*Age-adjusted model: adjusted for age. Partially adjusted model: adjusted for age and traditional CVD risk factors (i.e., hypertension, hypercholesterolaemia, and diabetes mellitus). Fully adjusted model: adjusted for age, traditional CVD risk factors and clinical characteristics (i.e., tumour stage and received cancer treatment). In total, 5262 patients with prostate cancer were included in the analysis, with a total of 18.732 person-years at risk. Reference category = not being pharmaceutically treated for anxiety/depression; being aged ≤65 years; not being pharmaceutically treated for hypertension/hypercholesterolaemia/diabetes mellitus; tumour stage I; not being treated with chemotherapy/radiotherapy/surgery/hormone treatment. *$P < 0.05$.*

risk of incident CVD in the age-adjusted model (both $P < 0.05$). The increased risk of incident CVD for pharmaceutically treated depression attenuated slightly but remained significant when controlling for traditional CVD risk factors in the partially adjusted model (HR 1.48, 95% CI 1.04–2.11). Pharmaceutically treated anxiety was no longer significantly related to incident CVD risk when controlling for traditional CVD risk factors. In the full model, after additionally controlling for clinical cancer characteristics, the positive association between pharmaceutically treated depression and incident CVD risk remained significant (HR 1.51, 95% CI 1.06–2.15). Cumulative incidence plots illustrating the risk of incident CVD among those pharmaceutically treated for depression compared to those who were not during the follow-up period of 13 years are presented in Appendix S1.

Results of the sensitivity analyses showed that the associations between pharmaceutically treated anxiety and depression with incident CVD risk amongst prostate cancer survivors was not different in those with anxiety or depression present prior to or developed after prostate cancer diagnosis (data not shown).

Stratified analyses for age, traditional CVD risk factors, cancer treatment, and tumour stage

Results of the analyses examining whether the relation between pharmaceutically treated depression and incident CVD was similar across subgroups on age (≤65 vs >65 years at the time of cancer diagnosis), traditional CVD risk factors, cancer treatment categories, and tumour stage are presented in Table 3 and Fig. 1. Stratified analyses showed that the increased risk of incident CVD amongst those pharmaceutically treated for depression compared to those who were not pharmaceutically treated for depression, was only valid amongst younger (HR 2.91, 95% CI 1.52–5.55) but not in older prostate cancer survivors (HR 1.21, 95% CI 0.78–1.86). When stratifying for the absence or presence of one or more traditional risk factors (i.e., hypertension, hypercholesterolaemia, or diabetes mellitus), only nine prostate survivors developed CVD in the category 'no traditional CVD risk factors', hence stratified analysis was not possible. Stratified analysis for chemotherapy was not possible due to the limited number of subjects that developed CVD in the category 'was treated with chemotherapy'. Additionally, the increased risk of incident CVD amongst those pharmaceutically treated for depression compared to those who were not pharmaceutically treated depression was only valid amongst those who were not treated with radiotherapy (HR 1.63, 95% CI 1.01–2.65); those who were treated with hormones (HR 1.76, 95% CI 1.09–2.85); those who were not operated upon (HR 1.55, 95% CI 1.07–2.25); and those with tumour stage III (HR 2.21, 95% CI 1.03–4.74) and stage IV (HR 2.47, 95% CI 1.03–5.89). The relation between pharmaceutically treated anxiety and incident CVD was not significant in the fully adjusted model; therefore, no stratified analyses for anxiety were performed.

Table 3 Associations between prostate cancer survivors pharmaceutically treated for depression compared to those not pharmaceutically treated for depression with incident CVD per subgroup.

Characteristic	Number of survivors		Person-years at risk		Pharmaceutically treated depression, HR (95% CI)
	N	Persons with CVD, *n*	Not depressed	Depressed	
Age, years					
≤65	1906	68	6574	879	2.91 (1.52–5.55)*
>65	3356	258	9852	1430	1.21(0.78–1.86)
Traditional CVD risk factors					
No	2050	9	–	–	1.86 (0.20–17.40)
Yes	3202	317	–	–	1.43 (1.00–2.05)
Radiotherapy					
No	3351	164	9188	1287	1.63 (1.01–2.65)*
Yes	1907	162	7220	1019	1.41 (0.84–2.38)
Hormone treatment					
No	3171	162	10 233	1375	1.26 (0.75–2.14)
Yes	2087	164	6175	931	1.76 (1.09–2.85)*
Surgery					
No	3991	288	12 202	1749	1.55 (1.07–2.25)*
Yes	1267	38	4206	557	1.36 (0.44–4.22)
Tumour stage					
Stage I	498	7	637	48	2.96 (0.29–30.4)
Stage II	2921	220	11 196	1544	1.14 (0.70–1.84)
Stage III	846	56	2700	377	2.21 (1.03–4.74)*
Stage IV	839	36	1689	301	2.47 (1.03–5.89)*

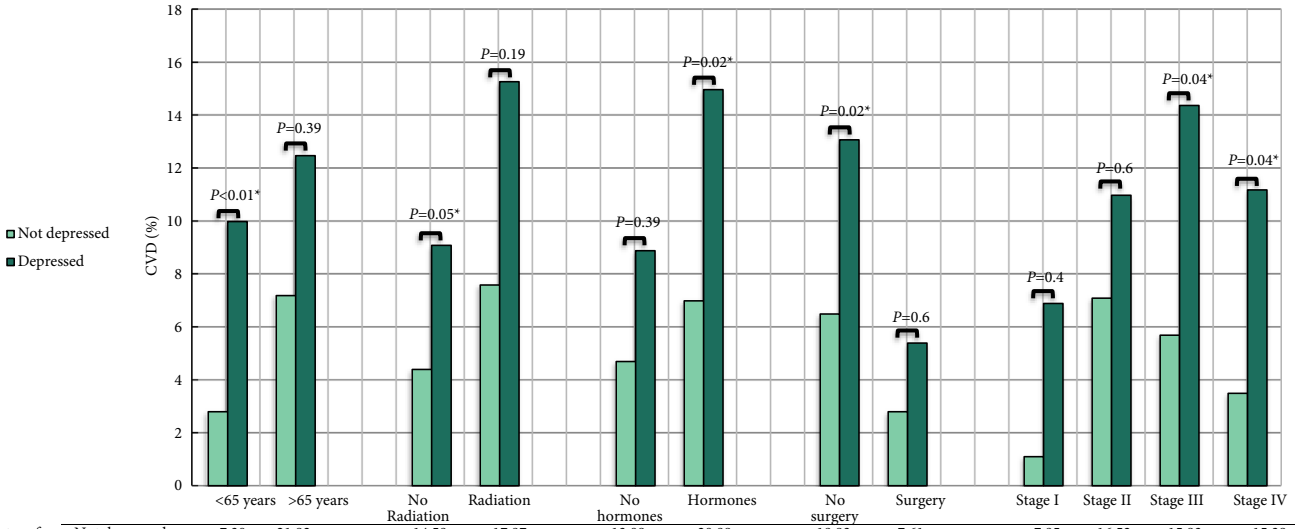
*HR comparing the risk of incident CVD for those pharmaceutically treated for depression vs those not pharmaceutically treated for depression across subgroups: age (≤65 vs >65 years at the time of cancer diagnosis), the presence of traditional CVD risk factors, cancer treatment category (radio-, hormone therapy, and surgery), and tumour stage. Stratification on chemotherapy was not applicable as only 22 individuals received this treatment. *P < 0.05.*

Discussion

In the present study, we found that pharmaceutically treated depression and anxiety increased the risk of incident CVD in 1-year prostate cancer survivors when controlling for age.

This increased risk for incident CVD amongst pharmaceutically treated depressed prostate cancer survivors remained statistically significant after controlling for anxiety, traditional CVD risk factors and clinical characteristics, and was limited to younger prostate cancer survivors, those who

Fig. 1 Percentage of incident CVD and incidence rates of CVD according to pharmaceutically treated depression by subgroup. Subgroup analyses between pharmaceutically treated depression and incident CVD amongst younger (≤65 years) and older (>65 years) men (age at the time of cancer diagnosis), cancer treatment category (radio-, hormone therapy, and surgery), and tumour stage. Incidence rates of CVD per 1000 person-years per subgroup. *$P < 0.05$.



Incidence rates of CVD per 1000 person-years	<65 years	>65 years	No Radiation	Radiation	No hormones	Hormones	No surgery	Surgery	Stage I	Stage II	Stage III	Stage IV
Not depressed	7.30	21.92	14.58	17.87	13.09	20.89	18.93	7.61	7.85	16.52	15.93	15.39
Depressed	22.83	30.07	23.31	32.38	20.36	37.59	32.59	10.77	41.67	23.32	34.48	33.22

received no radiation, those who were treated with hormones, those who were not operated upon, and those with tumour stages III and IV.

The increased risk for developing CVD when pharmaceutically treated for depression in our present study (51%) is consistent with a meta-analysis among healthy individuals where the effect sizes of various populations and methodological characteristics varied between 32% and 57% [13]. The association between pharmaceutically treated depression and incident CVD risk amongst prostate cancer survivors did not differ with respect to timing of the development, that is, prior or secondary to the prostate cancer diagnosis. It is well known that the diagnosis of cancer and the additional cancer treatment is associated with increased risk of developing depression [16,22]. Apparently, patients who have a depression before cancer diagnosis already have a higher risk for developing CVDs regardless of cancer and cancer treatment [16,23,24]. Various behavioural and pathophysiological mechanisms are suggested to be underlying the association between depression and the risk of CVD [24,25]. A possibility is that prostate cancer survivors who are pharmaceutically treated for depression, smoke more often, and perform limited exercise compared to prostate cancer survivors who are not pharmaceutically treated for depression [26–28]. As the majority of studies in cardiovascular research have shown that smoking and limited exercise increases the risk of CVD amongst non-cancer populations, smoking and limited exercise have been included in the European Guidelines of cardiovascular risk prevention in clinical practice [29]. Although previously found increased CVD risks amongst (prostate) cancer survivors may not be attributed to lifestyle factors [30], other mechanisms (i.e., pathophysiological) may be relevant amongst cancer populations. Pathophysiological mechanisms (e.g., high cortisol levels, impairment in platelet function, reduced heart rate variability, immune functioning, oxidative stress) could be involved as they are known for their association with depression and contribute to reduced cardiac reserve possibly resulting in CVD [23,24,31]. In addition, direct pharmacological pathways could play a role in the association between depression and the risk of CVD [32–34]. The two most common pharmacological treatments for depression in the Netherlands are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) [35,36]. As it is clear that TCAs have cardiovascular side-effects, TCAs are no longer prescribed in patients with or at risk for CVD. SSRIs are the preferred antidepressants; however, the literature is heterogeneous about whether SSRIs have a small negative or even a positive effect on CVD [32–34]. As we have no data on the type of antidepressants used, we were unable to explain the pharmacological relation in the present study.

The lack of an association between pharmaceutically treated anxiety and an increased risk for CVD was surprising, as previous studies demonstrated that anxiety is a risk factor for the development of CVD [10,37]. This difference could be because most studies relate depression and anxiety separately to CVD risk instead of simultaneously.

Interestingly, the increased risk of incident CVD associated with pharmaceutically treated depression was present amongst younger but not amongst older prostate cancer survivors. This finding is consistent with previous research, where psychological distress plays a greater role in younger individuals, as older individuals already have a higher CVD risk due to biological ageing, which limits the likely course of psychological distress [38]. Furthermore, the association between pharmaceutically treated depression and incident CVD was limited to those who were not treated with radiotherapy, those who received hormone treatment, and those who were not operated upon. Prostate cancer survivors who did not receive radiotherapy were generally younger and were less often diagnosed with one or more traditional CVD risk factors. Hence, these men had a relatively lower a priori risk for developing CVD, which means there was room for the increased risk of developing CVD by being pharmaceutically treated for depression. As previously demonstrated in this patient sample, there is an increased risk of receiving hormone treatment for incident CVD [3]. The present results show that there might be an additive effect, as pharmaceutically treated depression increases the risk of CVD only amongst men who are treated with hormones. However, there is controversy on the association between patients with prostate cancer treated with hormones and the risk of CVD and cardiovascular death. A meta-analysis of randomised studies found no association between cardiovascular death in patients with prostate cancer treated with hormones vs controls [39], although several observational studies have found the opposite [40–43]. According to a large observational study, the risk of CVD is increased for men with a history of CVD during the first 6 months of androgen-deprivation therapy [40]. Unfortunately, we were not able to investigate in the present study whether the duration of hormonal therapy was associated with the risk of CVD. Overall you have to live long enough to develop CVD after cancer (immortal bias), that is lower tumour stage is associated with longer survival, hence more time to develop CVD. Nevertheless, we additionally saw that pharmaceutically treated depression was associated with newly developed CVD amongst patients with prostate cancer with the higher tumour stages III and IV. This can be explained by both lifestyle and biological factors. Lifestyle factors like obesity, physical activity, and smoking are associated with advanced, and less with non-advanced prostate cancer, and are also known risk factors for CVD [5]. Biological factors like increased levels of inflammation and accelerated cellular ageing are also associated with both advanced prostate cancer and increased risk for CVD [44].

The present study has several limitations. First, there was a lack of information on residual confounders due to the observational nature of our study. Second, we used drug dispenses as a proxy for CVD, anxiety, and depression. Nevertheless, the specificity of algorithms is greater when they are based on pharmacy drugs, although sensitivity is greater when based on medical diagnosis [45]. Furthermore, we used a tight algorithm to define CVD-related drug dispenses, as this was based on a minimum number of two ATC code C01 drug dispenses within a 6-month period. This may have led to an underestimation of the incidence of CVD. Additionally, we could have missed a number of patients with CVD who used other drugs, e.g., angiotensin-converting enzyme inhibitors or β-blockers, but no ATC code C01 drug. Finally, we excluded prostate cancer survivors with CVD in the year prior to their cancer diagnosis, as we were interested in incident CVD. Hence, the present study investigated a subpopulation of 1-year prostate cancer survivors.

An important strength of the study is the inclusion of a large population-based sample of prostate cancer survivors of high-quality databases of the NCR and PHARMO allowing a 13-year follow-up period. Furthermore, the index date for CVD was set 1-year after prostate cancer diagnosis as the best compromise between not starting too late and missing incident CVD, which allowed us to exclude the effect of detecting incident CVD due to ongoing cancer treatment or increased clinical evaluations. Moreover, the present study is to our knowledge, the first to investigate whether pharmaceutically treated depression and anxiety are associated with incident CVD in prostate cancer survivors.

In conclusion, pharmaceutically treated depression, but not anxiety, increases the risk of incident CVD in 1-year prostate cancer survivors. Future studies should focus on understanding the behavioural and pathophysiological mechanisms that play a role in the development of incident CVD in depressed and anxious prostate cancer survivors. It is important that in addition to the current focus on traditional CVD risk factors, physicians pay sufficient attention to patients with prostate cancer who are pharmaceutically treated for depression or anxiety prior to deciding prostate cancer treatment and for a timely detection and treatment of CVD.

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None.

Conflict of Interest

None declared.

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Abbreviations: ATC, Anatomical Therapeutic Chemical; CVD, cardiovascular disease; HR, hazard ratio; NCR, Netherlands Cancer Registry; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Supporting Information

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

Appendix S1. Cumulative incidence plots illustrating the risk of CVD amongst depressed vs non-depressed patients with prostate cancer (N = 5262) for all three models (age-, partially, and fully adjusted).