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ORIGINAL ARTICLE

Educational level and the risk of depression after prostate cancer

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ABSTRACT

Background: The risk of depression is inversely associated with socioeconomic position in the general population; however, studies on the association in cancer populations are limited. The aim was to investigate if shorter education was associated with a higher risk of depression following prostate cancer diagnosis.

Material and methods: This is a cohort study among participants in the Danish prospective Diet, Cancer and Health (DCH) study including 2337 men diagnosed with prostate cancer between 1997 and 2014. Primary outcome was indication of moderate to severe depression, defined as either a first hospital contact for depression or first use of antidepressants. The main indicator of socioeconomic position was education categorized into short (<9 years of education), medium (9–12 years) and long (>12 years). We retrieved information on education, depression and cohabitation status from Danish National Registries. Information on stage, primary treatment, lifestyle and anthropometry was obtained from medical records and questionnaires. Data were analyzed using Cox proportional hazards models adjusted for possible confounders and mediators.

Results: The hazard of first depression was 1.86-fold higher (95% CI, 1.36–2.54) in prostate cancer patients with short education compared to those with long education. Adjustment for stage and primary treatment did not change the HRs, while adding comorbidity and lifestyle factors resulted in an HR of 1.65 (95% CI, 1.19–2.29). Men with medium education had a non-statistically significant 1.23-fold higher hazard of depression (95% CI, 0.95–1.59) than men with long education in the fully adjusted model. Educational differences were present in the cumulative incidence of first depression among cancer-free DCH study participants, but the level of first depression was substantially lower in this population than in prostate cancer patients.

Conclusions: We found indication of social inequality in depression following prostate cancer. Patients and particularly men with short education might benefit from psychosocial intervention and support.

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Introduction

Rates of depression in the elderly population increase with lower socioeconomic position [1,2]. Few studies of depressive symptoms have indicated a similar association in cancer patients [3], but it remains unknown if cancer patients' socioeconomic position is associated with moderate to severe clinical depression.

Prostate cancer is the most common cancer among men in Western parts of the world [4]. Previous studies have found an increased risk of depressive symptoms, hospitalization for depression, and use of antidepressant medication in this population [5–7]. Concurrent with prostate cancer, depression has been associated with a lower adherence to treatment, increased periods of hospitalization and decreased overall survival [8,9]. If the incidence of depression differs by socioeconomic group, this might help to identify a vulnerable prostate cancer patient group, increase focus on depressive symptoms, and prevent consequences of the disease by applying timely treatment.

Socioeconomic position may be measured by several indicators [10]; we chose education as generic indicator as prostate cancer patients are at an age where change of education level during follow-up is unlikely as opposed to other indicators such as income and occupation. With this study, we investigated the association of the education of

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prostate cancer patients with development of depression indicated by either use of antidepressants mainly prescribed in general practice or somatic or psychiatric hospital contact for depression. We further investigated if such an association was affected by stage at diagnosis, primary treatment, comorbidity and lifestyle.

Material and methods

Study design and setting

We performed a cohort study of prostate cancer patients identified in the Danish Diet, Cancer and Health (DCH) study. All previously cancer-free citizens aged 50–64 years, born in Denmark and living in the area of Aarhus and Copenhagen were invited to participate in the DCH. Enrolment took place from December 1993 to May 1997 at which point all participants filled questionnaires on diet and lifestyle. Further, anthropometric measures including height and weight were collected. A detailed description of the cohort is provided elsewhere [11].

Participants

We included men with prostate cancer reported as their first cancer diagnosis (except non-melanoma skin cancer) in the Danish Cancer Registry that has recorded incident cases of cancer on a nationwide basis since 1943 and is considered accurate and almost complete [12]. We restricted the study population to men diagnosed with prostate cancer between 1 January 1997 and 31 December 2014. This allowed for information on antidepressant medication two years prior to diagnosis in all participants as the Danish Prescription Registry holds information on all redeemed prescriptions of medication in Denmark since 1995 [13].

All men were followed from date of prostate cancer diagnosis until date of redeemed prescription of antidepressant medication, date of hospital admission for depression, date of hospital admission for other major psychiatric disorders, date of new cancer, emigration date, date of death, or end of follow-up on 31 December 2014 whichever came first.

Variables and data sources

The primary outcome of the study was the incidence of depression. Depression is a chronic disease with recurrent episodes. We aimed to study the incidence of depression; accordingly, men with hospital contacts for depression or other major psychiatric disorders (International Classification of Diseases, 10th revision (ICD-10): F00–F31) before their prostate cancer diagnosis were excluded. Also, men were excluded if they used antidepressant medication up to two years before prostate cancer diagnosis.

Depression was assessed by registrations of hospital contact for depression (ICD-10: F32–F33) in the Danish National Patient Registry containing information on all hospital admissions since 1978 and since 1995 out-patient contacts as well and both in- and out-patient contacts in psychiatric hospitals [14]. Hospital contact for depression is a rare event and primarily occurs in case of severe depression. Accordingly, we further assessed the incidence of depression by using redeemed prescriptions of antidepressant medication (ATC N06A, except for Bupropion, which is used for smoking cessation). This proxy for depression was applied under the assumption that according to Danish guidelines antidepressant medication prescribed by a physician indicates moderate to severe depression – independently of how many redeemed prescriptions follow.

The primary exposure was length of education divided into three levels: short (<9 years, basic school), medium (9–12 years, upper secondary school or vocational education) and long (>12 years, higher education). Information on education was assessed the year before prostate cancer diagnosis and was obtained from the Danish education registers [15].

We included age as a continuous covariate and assessed time of diagnosis as a categorical covariate with four time periods: 1997–2000, 2001–2005, 2006–2010 and 2011–2014. Information on cohabitation status was obtained from the Danish Civil Registration System, administered by Statistics Denmark [16]; this variable was defined as living with a partner (married or cohabiting) or living alone (single, divorced, widowed) by 1 January the year of diagnosis. To get a comprehensive measure of patients' somatic comorbidity before and after diagnosis, we obtained the history of hospital contacts (in- and outpatient) for all participants for a period of 10 years prior to prostate cancer diagnosis by linking to the National Patient Registry. We computed Charlson comorbidity index (CCI) scores by cumulatively adding up 19 weighted conditions [17]. We categorized the CCI scores into 0, 1 or $\geq$2.

Clinical information on stage, prostate-specific antigen (PSA) at time of diagnosis, and primary treatment was obtained from medical records. We assessed stage of the disease reported by the TNM classification system in medical records. In case of no record of stage, information was obtained from the Danish Cancer Registry. To include stage of disease recorded prior to the introduction of TNM in 2003, we merged TNM with the previously used classification system, resulting in two-stage categories ('localized disease' and 'non-localized disease') which were used in the statistical analyses (for further details on algorithm, see Appendix). Primary treatment was obtained from medical records and divided into three groups: no active treatment (including watchful waiting and active surveillance), treatment with curative intent (including radical prostatectomy and radiotherapy), and palliative care (primarily androgen deprivation therapy).

Lifestyle factors were self-reported and measured at time of enrollment in the DCH and consisted of body mass index (BMI) (continuous variable), physical activity measured by the metabolic equivalent (MET) in kcal/kg/h (continuous variable), alcohol consumption (none, below recommended amount at the time (21 units/week), above recommended amount), and smoking status divided into current, former and never smokers.

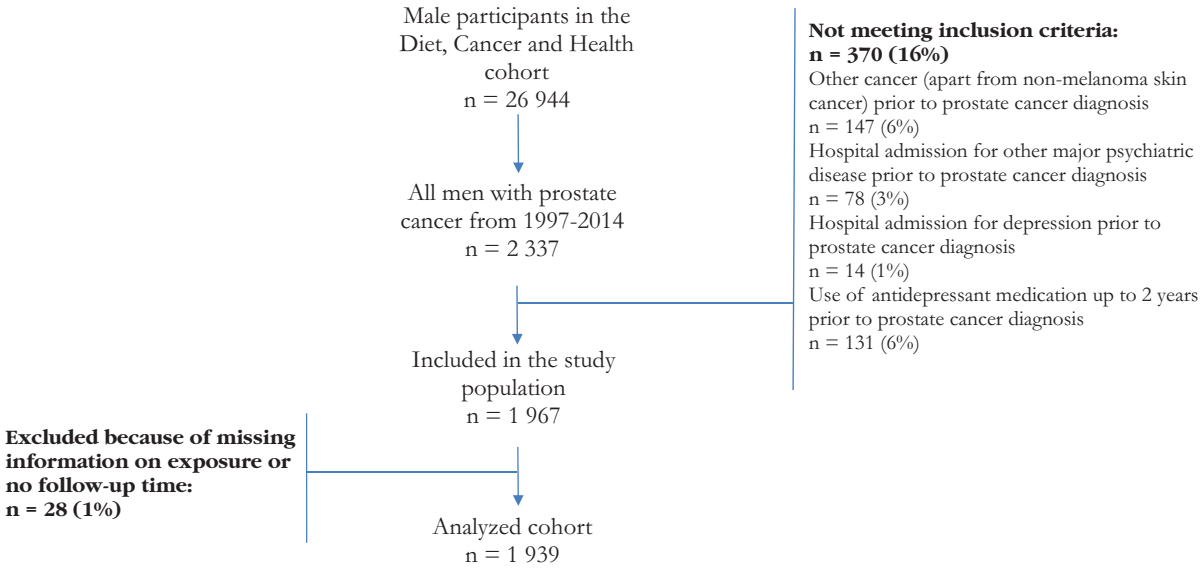

Figure 1. Flowchart of the formation of the study population of 1939 men diagnosed with prostate cancer from 1997 to 2014 among participants in the Danish prospective Diet Cancer and Health Study in the area of Aarhus and Copenhagen, Denmark.

Statistical analysis

The cumulative incidence of depression was estimated non-parametrically by education group taking death into account as a competing event. For descriptive comparison, we further plotted the cumulative incidence of depression in cancer-free men in the DCH.

To determine the risk of depression by educational group, Cox's proportional hazards analyses were conducted with inclusion of identified possible confounders and mediators. Time since diagnosis was used as underlying time scale. First, we included age, time period of diagnosis, and cohabitation status as possible confounders (model 1); then, we further included stage at diagnosis as a possible mediator (model 2). Next, primary treatment was included as a possible mediator (model 3) and finally, we added comorbidity and lifestyle factors as possible mediating factors in the fully adjusted model 4.

The assumptions of proportional hazards and linearity were checked using Martingale residuals. If the proportionality assumption did not hold, the baseline hazard was stratified accordingly.

To explore possible effect modification of the exposure effect by time since diagnosis, we did a sub-analysis splitting time in three periods (0–1, 2–5 and >5 years after diagnosis). This resulted in a model estimating the hazard ratios (HRs) of depression in three intervals: the first year post-diagnosis, from 1 to 5 years post diagnosis, and from five years post diagnosis and forward.

The main analysis was based on the full dataset following multiple imputation assuming the data were missing at random. This assumption was evaluated by comparing these estimates with those of the analyses based on complete cases.

Data were analyzed in R Version 3.4.2 using the packages 'prodlim', 'survival' and 'cmprsk'. Proportional hazards assumption and linearity of quantitative covariates were checked by using the package 'timereg'. Multiple imputation was carried out using the packages 'smcfcs' and 'mitools'. See Appendix for R package credentials.

Ethics

The DCH was approved by the regional ethical committees on human studies in Copenhagen and Aarhus (file number (KF) 11-037/01) and by the Danish Data Protection Agency (2013-41-4232).

Results

Among the 26,944 men included in the DCH, 2337 men developed prostate cancer from 1997 to 2014. Inclusion criteria were not met in 370 (16%) of the men: 147 (6%) had a previous cancer, 92 (4%) had a previous hospitalization for depression or other major psychiatric disorders and 131 (6%) used antidepressant medication within two years prior to prostate cancer diagnosis (Figure 1). Twenty-eight men (~1%) had missing information on education or no follow-up time and were excluded.

Of the 1939 men included in the present study, 14% had short education, 52% medium education and 33% long education and the median follow-up time was 4.5 years (IQR, 1.7–7.2 years) (Table 1). A median of 12 years (IQR, 9–15 years) had passed from measurement of lifestyle factors to prostate cancer diagnosis. More men with short education were registered with metastatic disease (M stage) and received palliative care compared to men with medium or long education. Only five men had an event of hospital contact for depression, while 228 men redeemed prescriptions of antidepressant medication.

We found an increased cumulative incidence of depression in men with short education: five years after diagnosis, 20% of prostate cancer patients with short education had a first depression compared with 13% of patients with medium and long education (Figure 2). The incidence remained

Table 1. Characteristics of 1939 men diagnosed with prostate cancer from 1997 to 2014 among participants in the Danish prospective Diet, Cancer and Health Study, Aarhus and Copenhagen, Denmark.

	Highest attained education		
	Short *n* (%)	Medium *n* (%)	Long *n* (%)
Patients included	275 (14)	1017 (52)	647 (33)
Events of depression	70 (26)	171 (17)	92 (14)
Patient characteristics			
Follow up time			
Median, years (IQR)	3.8 (1.4–7.2)	4.7 (2.0–7.1)	4.5 (1.8–7.3)
Age at diagnosis			
Median, years (IQR)	70.2 (67–74)	69.3 (66–73)	69.0 (66–73)
53–64 years	33 (12)	159 (16)	101 (16)
65–69 years	101 (37)	401 (39)	271 (42)
70–74 years	91 (33)	314 (31)	193 (30)
75–84 years	50 (18)	143 (14)	82 (13)
Calendar period of diagnosis			
1997–2000	23 (8)	80 (8)	42 (7)
2001–2005	64 (23)	208 (21)	150 (23)
2006–2010	116 (42)	461 (45)	259 (40)
2011–2014	72 (26)	268 (26)	196 (30)
Disposable income, quintiles			
1 (lowest)	58 (21)	161 (16)	35 (5)
2	54 (20)	153 (15)	49 (8)
3	63 (23)	239 (24)	93 (14)
4	57 (21)	307 (30)	265 (41)
5 (highest)	43 (16)	157 (15)	205 (32)
Cohabitation status			
Cohabiting	208 (76)	831 (82)	546 (84)
Living alone	67 (24)	186 (18)	101 (16)
Charlson comorbidity index			
0	167 (61)	726 (71)	475 (73)
1	62 (23)	177 (17)	120 (19)
≥2	46 (17)	114 (11)	52 (8)
Disease characteristics			
T stage at diagnosis			
T1	121 (44)	436 (43)	259 (40)
T2	63 (23)	209 (21)	158 (24)
T3–T4	55 (20)	250 (24)	145 (22)
TX	16 (6)	69 (7)	46 (7)
Missing = 112 (6%)	20 (7)	53 (5)	39 (6)
N status at diagnosis			
N0/Nx/NA	258 (94)	930 (91)	599 (93)
N1	17 (6)	87 (9)	48 (7)
M status at diagnosis			
M0/Mx/NA	229 (83)	879 (86)	559 (86)
M1	46 (17)	138 (14)	88 (14)
Tumor spread			
Localized	185 (67)	657 (65)	423 (65)
Non-localized	79 (29)	300 (30)	179 (28)
Missing = 116 (6%)	11 (4)	60 (6)	128 (7)
Gleason score			
≤6	72 (26)	299 (29)	191 (30)
7	76 (28)	288 (28)	180 (28)
≥8	75 (27)	245 (24)	141 (22)
Missing = 372 (19%)	52 (19)	185 (18)	135 (21)
PSA at time of diagnosis			
Median (IQR)	14.9 (8–50)	12.3 (7.2–31.7)	11.7 (7–28)
Primary treatment			
No immediate treatment	62 (23)	237 (23)	143 (22)
Curative intent	91 (33)	358 (35)	259 (40)
Palliative care	519 (31)	284 (28)	149 (23)
Missing = 270 (14%)	36 (13)	138 (14)	96 (15)
Lifestyle characteristics[a]			
Physical activity score (Met-score)			
Median (IQR)	23.7 (10.0–46.8)	26.0 (13.0–45.0)	26.0 (15.2–40.5)
Body mass index			
Mean (SD)	27.4 (4)	26.5 (3)	25.8 (3)
Alcohol intake			
Median, units (12 g)/day (IQR)	1.1 (0.5–2.1)	1.3 (0.7–2.3)	1.4 (0.8–2.5)
0 g/day	22 (8)	37 (4)	14 (2)
Less than 36 g/day	209 (75)	821 (81)	516 (80)
More than 36 g/day	43 (16)	156 (15)	112 (17)
Smoking			
Never	73 (27)	313 (31)	220 (34)
Former	87 (32)	351 (35)	252 (39)
Active	115 (42)	352 (35)	173 (27)

[a]Lifestyle characteristics were assessed at time of enrolment in the Danish Diet, Cancer and Health study.

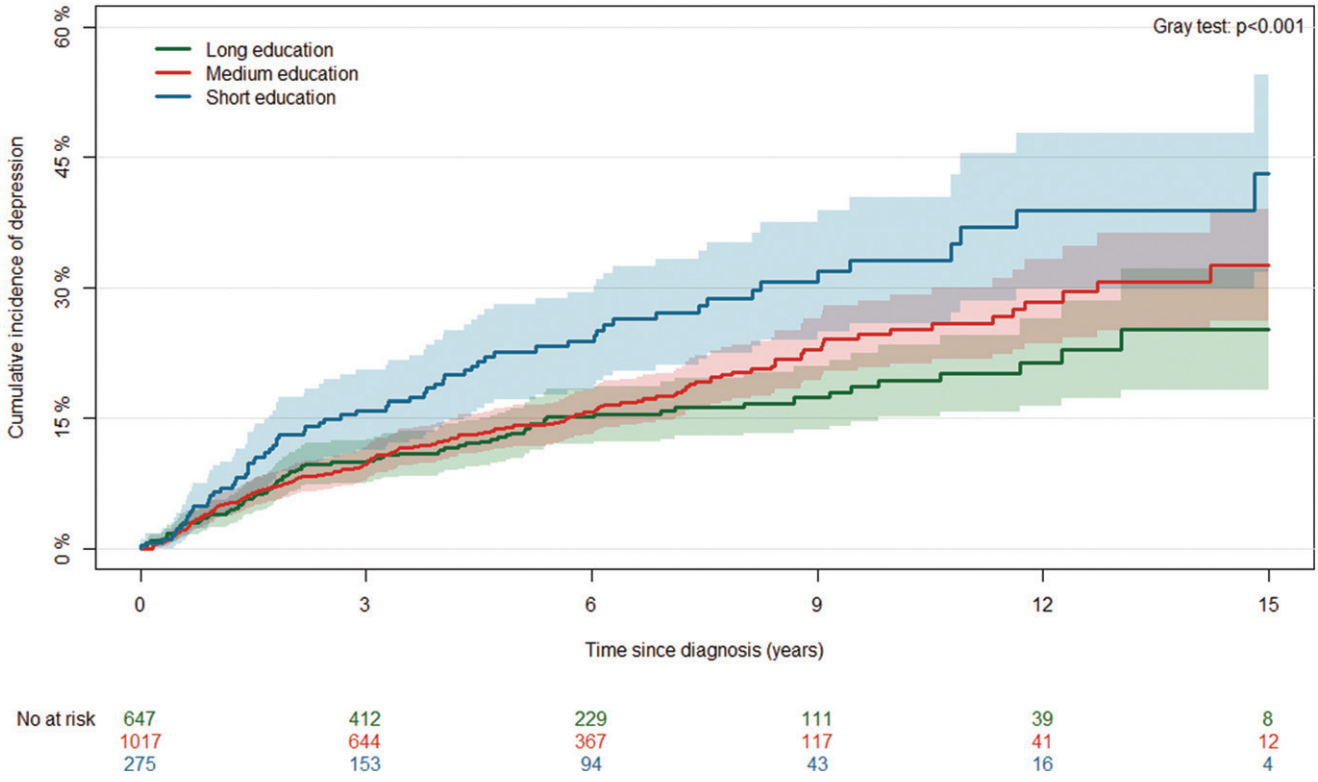

Figure 2. Illustration of the cumulative incidence of depression following prostate cancer diagnosis, stratified on educational level among the 1939 men diagnosed with prostate cancer from 1997 to 2014 who participated in the Danish prospective Diet Cancer and Health Study in the area of Aarhus and Copenhagen, Denmark.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for depression according to education and cohabitation status, among 1939 men who participated in the Danish prospective Diet Cancer and Health Study and diagnosed with prostate cancer from 1997 to 2014.

	PYRS at risk $n = 9509$	No. of events $n = 333$	Model 1 Age and time period	Model 3 Age, time period, stage and treatment	Fully adjusted model Age, time period, stage, treatment, comorbidity and lifestyle[a]
			HR (95% CI)	HR (95% CI)	HR (95% CI)
Education					
Long	3273	92	1.00 (ref)	1.00 (ref)	1.00 (ref)
Medium	4955	171	1.23 (0.95–1.59)	1.19 (0.92–1.53)	1.15 (0.89–1.50)
Short	1281	70	1.86 (1.36–2.54)	1.83 (1.34–2.51)	1.65 (1.19–2.29)
Cohabitation status					
Cohabiting	8006	267	1.00 (ref)	1.00 (ref)	1.00 (ref)
Living alone	1503	66	1.27 (0.95–1.67)	1.24 (0.94–1.62)	1.13 (0.85–1.49)

[a]Lifestyle includes body mass index, alcohol consumption, physical activity score (MET) and smoking status. Model 4 is stratified for smoking status because of violation of the proportional hazards assumption.

increased in men with short education throughout the follow-up period. Among the cancer-free men in the DCH, we found that cumulative incidences were lower than that of prostate cancer patients but that clear differences existed by education group (Figure 3 in Appendix).

The time-to-event analysis resulted in an HR of 1.86 (95% CI, 1.36–2.53) for depression in men with short education compared to men with long education (model 1, Table 2). These results were consistent when analyzing all four models; adjustments for stage and primary treatment only changed the HR slightly, and further adding comorbidity and lifestyle factors resulted in an HR of 1.65 (95% CI, 1.19–2.29) (model 4) for depression in men with short education compared with men with long education. Our results showed a consistently graded association between education group and the risk of depression: the shorter education, the higher risk of depression. This hazard of depression was however not statistically significantly higher in men with medium length education compared with men with long education. There was no difference in risk of depression with cohabitation status.

None of the continuous covariates violated the linearity assumption. However, smoking status violated the proportional hazards assumption in the fully adjusted model; consequently, we stratified the baseline hazard for this variable. The estimates based on the multiple imputation model did not differ substantially from the estimates based on analyses of the incomplete dataset.

The hazard of depression increased with time since diagnosis in men with short education compared with those with

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for depression at three time points, among the 1939 men who participated in the Danish prospective Diet, Cancer and Health study and diagnosed with prostate cancer from 1997 to 2014 according to education and cohabitation status at diagnosis.

	First year post-diagnosis	From one to five years post-diagnosis	After five years post-diagnosis	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	$P_{interaction}$
Education				0.3
Long	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Medium	1.14 (0.70–1.85)	1.03 (0.72–1.47)	1.93 (1.13–3.29)	
Short	1.57 (0.85–2.92)	1.83 (1.18–2.84)	2.32 (1.22–4.43)	
Cohabitation status				0.2
Cohabiting	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Living alone	1.67 (1.04–2.70)	0.98 (0.65–1.48)	1.53 (0.88–2.65)	

The model is adjusted for age and time period of diagnosis.

long education. From five years post-diagnosis and onwards, men with medium education had a statistically significant increased hazard of depression compared with men with long education (HR, 2.32, 95% CI, 1.22–4.43). Moreover, men living alone at time of diagnosis had an increased hazard within the first year post-diagnosis compared with men living with a partner (Table 3); however, we found no statistically significant association with cohabitation status after the first year.

Discussion

We found an educational gradient in the risk of depression with a 1.86-fold higher hazard in prostate cancer patients with short education compared to those with long education. The hazard of depression was, however, statistically non-significant in men with medium education compared with men with long education. Some, but not all, of the observed inequality in depression could be explained by differences in comorbidity and lifestyle factors, while stage and primary treatment did not seem to contribute to the increased hazard.

To our knowledge, this is the first study of the association between education and moderate to severe clinical depression in cancer patients in general. However, our data indicate that there are disparities by education in depression among the cancer-free men in the DCH, supporting a social inequality in depression in general. Although rates of depression are higher in prostate cancer patients, the educational differences may be similar to those in cancer-free men.

Previous research has investigated other socioeconomic differences in prostate cancer patients: PSA testing without clinical indication has been associated with longer education [18] which might be reflected in the recognized association between high socioeconomic position and higher prostate cancer incidence. Conversely, prostate cancer patients with low socioeconomic position have a higher risk of dying from the disease [19,20]; this may be due to socioeconomic differences in diagnostics, comorbidity, treatment and rehabilitation [19,21].

In prostate cancer, the choice of primary treatment is based on an evaluation of both stage, age and somatic comorbidity; consequently, primary treatment might be more predictive of prognosis – and the possible level of stress in that relation – than stage of disease alone. Furthermore, treatment with androgen deprivation therapy has been associated with an increased risk of depression possibly explained by a global decrease in quality of life and low testosterone affecting central serotonin levels [22]. Treatment did not affect the association of education with risk of depression; however, introducing somatic comorbidity and lifestyle into the model affected the HRs. This aligns with findings of a three-fold risk of depression in patients with multimorbidity (including cancer) compared with people without any chronic physical condition [23]. Likewise, somatic comorbidity has been associated with a first prescription for antidepressants among breast cancer patients [24]. Moreover, socioeconomic inequalities have been shown to exist within many other non-communicable diseases such as diabetes and chronic obstructive pulmonary disease [25].

A previous study from PCBase Sweden touched upon the association of stage, primary treatment and comorbidity with the risk of hospitalization or use of antidepressants; in a large cohort ($n = 72{,}613$) of prostate cancer patients, they found an increased risk of hospital admission for depression (RR 1.29, 95% CI, 1.14–1.45) and use of antidepressants within the first year post-diagnosis (RR 1.65, 95% CI, 1.54–1.88) compared with cancer-free men. Risks were increased across stages and treatment types [6]. This could indicate that the main stressor is the cancer diagnosis and not the prognosis of the disease.

In the present study, adjustment for potential confounders and mediators did not fully explain the difference in the risk of depression between prostate cancer patients with short and long education. The remaining inequality can be explained by residual confounding and mediation; 'well-functioning social network', the ability to cope with stress and the burden of other late treatment effects of treatment or recurrence of disease are factors we were not able to consider – all aspects may be distributed differently by educational group.

Strengths and limitations

The present study is the first to examine the association of socioeconomic position and the risk of moderate to severe depression indicated by hospital contact for depression or use of antidepressants. A strength of this study is the use of nationwide and population-based registries. This minimizes recall bias and loss to follow up; further, misclassification is almost completely excluded by the detailed diagnostic information required by the Danish Cancer Registry. Another

strength is the use of a large cohort providing detailed information on lifestyle factors. Finally, audits of hospital records have provided us with clinical information on the disease and the received primary treatment.

Our results may be affected by limitations related to the specificity of the outcome measure. We combined receipt of antidepressant medication with hospital contact for depression; however, hospital admission for depression is rare: we found only five with a hospital contact as their first event indicating that persons participating in the DCH may be relatively healthy [26]. The lack of information on indications for antidepressant treatment may have led to inclusion of other outcomes such as treatment for anxiety and insomnia. Previous studies have found that 45–81% of prescribed antidepressant medication have an indication of depressive disorders [27–29]. Meanwhile, the inability to include non-pharmacologically treated depression potentially underestimates the number of events. Nevertheless, the observed associations between education and depression could be affected in case of differences by education in pharmacological treatment for depression.

Lack of lifestyle measurements at time of diagnosis may be considered a limitation. However, in a study of the DCH comparing lifestyle information at baseline with information at follow-up (survey conducted between 2000 and 2002), men with prostate cancer ($n = 129$) had a small but statistically significant increase in BMI, but no significant change in smoking and alcohol consumption [30]. Finally, a higher proportion of participants in the DCH had long education and a lower proportion had short education when compared to invited men who chose not to participate in the DCH [26]. Thus, external generalizability must be considered; in absolute terms, the degree of educational inequality in depression among prostate cancer patients might be less pronounced in this study than in a nationwide Danish study.

Conclusions

In conclusion, we found evidence of educational inequality in moderate to severe depression. The educational difference in the risk of depression was affected by comorbidity and lifestyle factors. Nevertheless, these possible mediators only explained part of the social inequality. This indicates that prostate cancer patients – and particularly men with short education – constitute a vulnerable patient group in regards to the risk depression. In perspective, this patient group may need intervention and support at time of diagnosis and throughout treatment to reduce the risk of depression and if necessary initiate timely treatment to minimize the physical and mental consequences of depression.

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Disclosure statement

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