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To cite this article: Michael Jan, Stephanie E. Bonn, Arvid Sjölander, Fredrik Wiklund, Pär Stattin, Erik Holmberg, Henrik Grönberg & Katarina Bälter (2016) The roles of stress and social support in prostate cancer mortality, *Scandinavian Journal of Urology*, 50:1, 47-55, DOI: [10.3109/21681805.2015.1079796](https://doi.org/10.3109/21681805.2015.1079796)

To link to this article: <https://doi.org/10.3109/21681805.2015.1079796>

Published online: 07 Sep 2015.

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ORIGINAL ARTICLE

The roles of stress and social support in prostate cancer mortality

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Abstract

Objective: This study aimed to evaluate the association between perceived stress, social support, disease progression and mortality in a nationwide population-based cohort of men with prostate cancer. **Materials and methods:** The study surveyed 4105 Swedish men treated for clinically localized prostate cancer regarding stress, grief, sleep habits and social support. Associations between these factors and mortality were assessed using multivariate Cox regression analysis. **Results:** Men with the highest levels of perceived stress had a statistically significantly increased rate of prostate cancer-specific mortality compared with men with low stress levels (hazard ratio 1.66, 95% confidence interval 1.05–2.63). Men with high stress levels also had a high frequency of grieving and sleep loss. They also had fewer people with whom to share their emotional problems and felt an inability to share most of their problems with partners, friends and family. **Conclusions:** This study contributes to the growing field of psychosocial quality of life research in men with prostate cancer. The findings show a significant association between prostate cancer-specific mortality and perceived stress in patients initially diagnosed with localized, non-metastatic prostate cancer. Significant associations between perceived stress and various psychosocial factors were also seen. The findings of this study could prove useful to target interventions to improve quality of life in men with prostate cancer.

Keywords:

Oncology, perceived stress, prostate cancer, quality of life, social support

History

Received 29 January 2015

Revised 13 July 2015

Accepted 1 August 2015

Introduction

Prostate cancer is the leading cause of cancer death among men in Sweden [1]. Nonetheless, the survival rate following diagnosis has greatly improved and research is focusing more and more on improving quality of life (QoL) and prognosis. Previous studies have examined QoL in terms of patient satisfaction [2,3], pain [4], depression, anxiety [5], perceived stress [6–8], social status [7] and sleep disruption [9], among other factors. The role of QoL in prostate cancer research has been evaluated both as a risk factor for incidence [5–7,10] and as a prognostic factor for morbidity and mortality [3,6]. Prospective cohorts have examined prostate cancer incidence and progression [5–7], physical (urinary, sexual) and social functioning after treatment [11] and mortality [6].

Psychosocial aspects of QoL in prostate cancer patients have been evaluated using various indices of satisfaction [2,3], depression, anxiety, distress [5,12], perceived stress [6–8,13] and social support [8,13]. Perceived stress has been studied largely in relation to prostate cancer incidence, with mixed results [5–7]. Only Metcalfe et al. [6] examined mortality as

an outcome after surveying perceived stress, finding an association between increased stress and increased prostate-related mortality, but the study's participants were only surveyed before prostate cancer diagnosis, not afterwards.

Several factors have been shown to be related to both perceived stress and prostate cancer. Relapse has been demonstrated to have significant associations with both stress [12] and prostate cancer-specific mortality [14]. Lis et al. [9] found that insomnia in cancer patients is strongly correlated with patient satisfaction and QoL, while other studies have shown that sleep disruption contributes to mortality in patients with prostate cancer [15,16]. Stone et al. [8] noted the impact of declining social support in patients with prostate cancer. Zhou et al. [13], moreover, suggested that perceived stress mediates the effects of social support on QoL in men with prostate cancer.

To date, few studies have assessed the prognostic significance of QoL for men with prostate cancer after diagnosis [2–4,17,18]. This study evaluated the association between perceived stress, social support, disease progression and mortality after diagnosis of prostate cancer using a larger ($n = 4105$) cohort than has previously been studied.

Materials and methods

Study population

Participants in this study come from the PROgression in CANcer of the Prostate (PROCAP) Study, which follows from the National Prostate Cancer Register (NPCR) of Sweden Follow-Up Study. The NPCR of Sweden Follow-Up Study is a retrospective nationwide cohort study consisting of men diagnosed with localized prostate cancer between 1 January 1997 (from 1 January 1998 in one of six regions) to 31 December 2002, as detailed previously [19–21]. The NPCR contains data on prostate-specific antigen (PSA) level at diagnosis, tumor, node, metastasis (TNM) staging, tumor differentiation and primary treatment within 6 months of diagnosis for 98% of all Swedish men diagnosed with prostate cancer [22,23].

The NPCR was used to identify 8304 men up to 70 years of age at diagnosis with serum PSA less than 20 ng/ml, local tumor stage T1–T2, and neither lymph-node (NX or N0) nor bone metastases (MX or M0). Of all eligible men, 7960 (96%) accepted inclusion into this study. From these men, those alive in 2007 were invited to participate in the PROCAP Study to assess the roles of genetics and lifestyle on localized prostate cancer prognosis [24–26]. Of those invited, 5779 (82%) of 7074 eligible men accepted inclusion by donating a blood sample for DNA extraction and by completing a questionnaire regarding lifestyle factors. Questionnaires were returned between January 2007 and June 2008 and participants were followed for mortality until 8 June 2012 using the Swedish National Cause of Death Registry. Participants with missing clinical data ($n = 908$) or missing questionnaire data ($n = 284$) were excluded. Further, since perceived stress was one of the primary interests in the present study, participants missing any of the 14 components of the perceived stress scale ($n = 306$) and those with improperly completed stress scales ($n = 24$) were excluded. Finally, since disease progression and relapse were considered in the analyses, men primarily receiving hormone therapy ($n = 152$) were also excluded because hormone therapy was initiated when disease was more advanced and relapse could not be assessed (Figure 1). Thus, 4105 men in total were included in the analyses.

All participants provided written informed consent and the study was approved by the Research Ethics Board at Karolinska Institutet.

Clinical data collection

Clinical follow-up data for this study come from the NPCR of Sweden Follow-Up Study, which has been described previously [24–26]. In brief, research nurses in each of Sweden's six healthcare regions extracted information regarding PSA levels, local tumor progression, distant metastases, date of and reasoning for termination of surveillance, and date of last follow-up from medical records at a median of 4 years after the date of diagnosis. Recurrence was defined based on type of primary treatment: (i) radiation therapy – doubling of post-treatment PSA levels in excess of at least 1 ng/ml; or (ii) radical prostatectomy – PSA level greater than 0.2 ng/ml on two subsequent PSA tests (date of first test

considered date of recurrence) or PSA level greater than 0.5 ng/ml on one subsequent PSA test. For men who underwent clinical intervention, prostate cancer progression was defined by recurrence, local progression or distant metastases. For men on surveillance, prostate cancer progression was defined by termination of watchful waiting, citing progression as the reason.

Questionnaire data collection

Participants in PROCAP were surveyed between January 2007 and June 2008 with a single questionnaire regarding lifestyle factors including dietary intake, physical activity and QoL (stress, sleep, grieving, social support). These questions have been used in a number of Swedish studies and have also been validated [27–30]. The dietary questions aimed to assess habitual food intake whereas the physical activity questions assessed both prediagnosis and postdiagnosis habits of physical activity. The questionnaire was made available to participants in both paper and electronic formats.

Figure 1. Study participant selection criteria. All participants available from the National Prostate Cancer Register (NPCR) of Sweden Follow-Up Study were invited to join the PROgression in Cancer of the Prostate (PROCAP) Study. Of those who accepted inclusion, this diagram summarizes the exclusion criteria used to reach the final sample for analysis.

Assessment of perceived stress

A 14-item Perceived Stress Scale developed by Cohen et al. was used to assess stress [27]. This tool has been validated among populations in different locations as well as longitudinally over time [31]. The present study employed a Swedish language translation of the Perceived Stress Scale questionnaire, as used previously [32]. The 14 questions, each scored 0–4, ask the participant to assess the degree to which life situations are stressful. Summed together, the total perceived stress score was used as an index of stress and categorized into tertiles in the analyses.

Assessment of psychosocial factors

Participants were asked questions regarding grieving over loss of loved ones, difficulty sleeping, and ability to talk about emotional problems with partners, friends and family [33,34]. Grief and sleep questions were categorized by frequency (never, seldom, sometimes, fairly often, very often). Sharing of emotional problems with others was categorized by quantity shared (few, half, most) and with whom (partner, other). Sharing of emotional problems was also categorized by number of people with whom to share (0, 1–2, 3–5, > 5). These questions have been used in large-scale national Swedish surveys such as LifeGene [35].

Assessment of outcome

Swedish citizens have a unique personal identification number (PIN) with which national registries can keep track of health records. This study began as a follow-up to the NPCR [22,23], and by using these unique PINs, 100% follow-up can be achieved using the Swedish National Cause of Death Registry. Studies have shown that cause of death reporting in the death certificates of Swedish males with prostate cancer is reliable [36,37]. Person-time was counted from the date of questionnaire return (January 2007 to June 2008) until the date of death or censoring (the final date of follow-up was 8 June 2012, at which time all active participants were censored). The role of perceived stress was considered in two different ways. First, stress was evaluated as a potential consequence of prostate cancer relapse. Then, stress was considered as an exposure for the outcome of mortality.

Statistical analyses

Descriptive statistics for participant characteristics are presented as raw numbers (*n*) and proportions (%) for categorical variables, and as means and standard deviations for continuous variables. For descriptive statistics grouped by stress levels, chi-squared testing was used to determine significant differences in categorical variables, while one-way analysis of variance (ANOVA) was used to determine significant differences in continuous variables. The relationship between relapse and perceived stress was evaluated using ANOVA while the relationships between relapse and psychosocial factors (grief, sleep, social support) were evaluated using non-parametric testing and correlation with Spearman's ρ . Non-parametric testing and Spearman's ρ were also used to examine psychosocial factors consequent to perceived stress.

The relationships between mortality and perceived stress, grieving, sleep loss and social support were examined using Cox proportional hazards models. Since the date of prostate cancer diagnosis preceded inclusion into this study, left-truncated Cox proportional hazards models were used to estimate hazard ratios of death from prostate cancer, non-prostate cancer and all causes. Here, the time from diagnosis to questionnaire return has been truncated, and since each participant filled in the questionnaire at approximately the same time, truncation time corresponds to time of diagnosis, which is likely to be random and therefore free of bias. Confounders were determined from prior subject matter knowledge and statistically if they were significantly associated with the exposures (stress, grieving, sleep loss, social support) as well as with the outcome (mortality). These associations were determined by fitting a linear regression for the exposure and the covariate. The final multivariate model was adjusted for age at diagnosis, current body mass index (BMI) category, physical activity after diagnosis, smoking status, education and primary treatment. Adjusting for PSA at diagnosis, Gleason score at diagnosis, tumor staging and relapse was also considered, but not included in the final model since there was little evidence of confounding by these factors. Sensitivity analyses were performed to ensure that the model was not biased by rapidly deteriorating health and/or hastened mortality. In one sensitivity analysis, men who died of prostate cancer within 6 months of responding to the questionnaire were excluded. In another sensitivity analysis, men who died within 1 year of responding to the questionnaire were excluded.

All *p* values were two-sided and *p* values less than 0.05 were considered significant. All statistical analyses were performed using Stata 12.0 (StataCorp, College Station, TX, USA).

Results

Participant characteristics

Participant characteristics by tertiles of perceived stress are presented in Table 1. Compared to participants with low stress, those with high stress had higher BMI at the time of questionnaire response, higher BMI at diagnosis and less physical activity after diagnosis. Those with high stress levels were more often former or current smokers and had less formal education. Moreover, the proportion of men who died from prostate cancer was greater in the most highly stressed group of men compared to men with the lowest stress level.

Relapse and psychosocial factors

The relationships between early prostate cancer relapse (within 2 years of diagnosis) and perceived stress and social support are shown in Table 2. There were no statistically significant associations between prostate cancer relapse and total perceived stress, grieving, difficulty sleeping, or the ability to share emotional problems with partners or with friends or family. However, men with reported relapse had fewer people with whom to share emotional problems.

Table 1. Baseline characteristics of participants in the PROgression in CAncer of the Prostate (PROCAP) Study according to tertiles of perceived stress.

	Perceived stress			<i>P</i>
	< 18	18 to < 23	≥ 23	
No. of men (%)	1442 (35.1)	1359 (33.1)	1304 (31.8)	
<i>Clinical data at diagnosis^a</i>				
Age (years)	62.9 ± 4.9	62.8 ± 5.1	63.1 ± 5.3	0.4771
BMI (kg/m ²)	26.1 ± 3.1	26.2 ± 3.0	26.4 ± 3.3	0.0070
PSA (ng/ml) at diagnosis	8.4 ± 4.2	8.3 ± 4.2	8.4 ± 4.2	0.9987
Gleason score at diagnosis	5.9 ± 1.1	5.8 ± 1.1	5.8 ± 1.1	0.4795
<i>Gleason score at diagnosis</i>				0.4806
< 7	956 (77.0)	909 (79.3)	852 (77.0)	
7	240 (19.3)	192 (16.7)	213 (19.3)	
> 7	45 (3.6)	46 (4.0)	41 (3.7)	
<i>Tumor staging</i>				0.2165
T1a	64 (4.4)	58 (4.3)	65 (5.0)	
T1b	34 (2.4)	28 (2.1)	29 (2.2)	
T1c	780 (54.1)	686 (50.5)	644 (49.4)	
T2	564 (39.1)	587 (43.2)	566 (43.4)	
<i>Primary treatment</i>				0.0001
Watchful waiting	336 (23.3)	323 (23.8)	320 (24.5)	
Radical prostatectomy	827 (57.4)	783 (57.6)	659 (50.5)	
Radiation therapy	279 (19.3)	253 (18.6)	325 (24.9)	
<i>Follow-up and questionnaire data^b</i>				
Age (years)	70.2 ± 5.0	70.2 ± 5.2	70.4 ± 5.4	0.5337
BMI (kg/m ²)	26.2 ± 3.2	26.4 ± 3.2	26.7 ± 3.5	0.0014
<i>BMI</i>				0.0025
Normal (< 25 kg/m ²)	531 (37.1)	467 (34.7)	436 (33.8)	
Overweight (25 to < 30 kg/m ²)	752 (52.5)	710 (52.8)	654 (50.7)	
Obese (≥ 30 kg/m ²)	150 (10.5)	168 (12.5)	200 (15.5)	
<i>Physical activity</i>				
MET-hours at age 50	24.1 ± 8.2	24.3 ± 7.9	24.3 ± 8.2	0.7368
MET-hours after diagnosis	24.3 ± 7.0	24.1 ± 6.9	23.3 ± 7.1	0.0014
<i>Smoking status</i>				0.0001
Current	100 (7.0)	102 (7.6)	116 (8.9)	
Former	663 (46.4)	666 (49.3)	694 (53.5)	
Never	666 (46.6)	583 (43.2)	487 (37.6)	
<i>Education</i>				< 0.0001
Elementary/primary (≤ 9 years)	505 (35.1)	555 (41.2)	587 (45.2)	
Upper secondary (> 9, < 12 years)	537 (37.3)	484 (35.9)	472 (36.3)	
University (≥ 12 years)	396 (27.5)	308 (22.9)	240 (18.5)	
<i>Occupation</i>				0.0003
Retired full time	1156 (83.2)	1087 (82.2)	1002 (79.5)	
Working full time	149 (10.7)	153 (11.6)	127 (10.1)	
Working part time	80 (5.8)	79 (6.0)	123 (9.8)	
Unemployed	4 (0.3)	3 (0.2)	9 (0.7)	
Early relapse	205 (14.2)	181 (13.3)	212 (16.3)	0.0890
<i>Mortality</i>				
Prostate cancer-specific	38 (2.6)	34 (2.5)	55 (4.2)	
Non-prostate cancer	89 (6.2)	89 (6.5)	98 (7.5)	
All-cause	127 (8.8)	123 (9.1)	153 (11.7)	

Data are shown as mean ± SD or *n* (%).

^aClinical data were gathered during the National Prostate Cancer Register (NPCR) of Sweden Follow-Up Study between 1 January 1997 and 31 December 2002. ^bQuestionnaire data were gathered from the PROCAP Study between January 2007 and June 2008. Relapse was determined from the date of last follow-up from medical records at a median of 4 years after date of diagnosis. Mortality was determined from the National Cause of Death Registry until 8 June 2012.

Abbreviations: BMI = Body mass index; PSA = Prostate-specific antigen; MET = Metabolic equivalent task.

Perceived stress and social support

The relationships between perceived stress and grieving, sleep habits and social support are presented in Table 3. Compared to low stress levels, high stress levels were significantly associated with increased frequency of grieving over the loss of loved ones. High stress levels were also significantly associated with increased difficulty sleeping, compared with low stress levels. Participants with high stress reported more difficulty in sharing emotional problems with their

partners compared to those with low stress. A similar trend was seen for an inability to share emotional problems with other friends and family, but this did not reach statistical significance. High stress levels were associated with the number of people with whom emotional problems could be shared, and men with few or no friends or family members with whom to share had higher stress levels than men who could share emotional problems with several close friends or family members.

Table 2. Stress, grief, sleep loss and social support according to prostate cancer relapse.

	Relapse		<i>p</i>
	Yes	No	
No. of men (%)	598 (14.6)	3507 (85.4)	
Age at questionnaire (years)	70.8 ± 5.0	70.2 ± 5.3	0.0095
Total perceived stress	20.3 ± 6.8	19.9 ± 6.4	0.2315
<i>Frequency of grieving from loss</i>			0.7103
Never	103 (17.4)	611 (17.5)	
Seldom	125 (21.1)	714 (20.5)	
Sometimes	228 (38.4)	1421 (40.7)	
Fairly often	96 (16.2)	496 (14.2)	
Very often	41 (6.9)	248 (7.1)	
<i>Frequency of sleep problems</i>			0.9494
Never	135 (22.6)	750 (21.4)	
Seldom	219 (36.6)	1302 (37.1)	
Sometimes	153 (25.6)	930 (26.5)	
Fairly often	61 (10.2)	361 (10.3)	
Very often	30 (5.0)	162 (4.6)	
<i>Sharing emotional problems with partner</i>			0.2266
Few/no problems shared	50 (8.4)	241 (7.0)	
Half problems shared	151 (25.4)	791 (22.8)	
Most problems shared	329 (55.4)	2057 (59.4)	
No partner	64 (10.8)	374 (10.8)	
<i>Sharing emotional problems with others</i>			0.1982
Few/no problems shared	396 (68.2)	2274 (66.3)	
Half problems shared	126 (21.7)	853 (24.9)	
Most problems shared	59 (10.2)	304 (8.9)	
<i>People with whom to share emotional problems</i>			0.0331
No one	43 (7.2)	159 (4.5)	
1–2 close friends/family members	219 (36.7)	1283 (36.7)	
3–5 close friends/family members	208 (34.8)	1219 (34.9)	
> 5 close friends/family members	127 (21.3)	834 (23.9)	
<i>Mortality</i>			
Prostate cancer-specific	72 (12.0)	55 (1.6)	
Non-prostate cancer	54 (9.0)	222 (6.3)	
All-cause	126 (21.1)	277 (7.9)	

Data are shown as mean ± SD or *n* (%).

Psychosocial factors and mortality

During a mean follow-up of 51.3 months (range 0.4–64.5 months) after questionnaire return among 4105 men with prostate cancer, 127 (3.1%) died from prostate cancer and 276 (6.7%) died from other causes. As shown in Table 4, men in the highest tertile of perceived stress had a 66% increased risk of prostate cancer-specific mortality compared to men in the lowest tertile. A sensitivity analysis was performed to ensure that this observation was not biased by men with increased stress in the face of rapidly deteriorating health and hastened mortality. After excluding men who died of prostate cancer within 6 months of responding to the questionnaire, the result did not change. When excluding men who died within 1 year, the result became only slightly weaker. Performing this sensitivity analysis for men who died from all causes did not significantly change the observations at 6 months and 1 year (data not shown).

A high frequency of grieving over the loss of a loved one was associated with an increased risk of all-cause mortality compared to no grieving at all. A similar result was seen for frequent grieving and non-prostate cancer-specific mortality, whereas no association was seen between frequency of grieving and prostate cancer-specific mortality. Frequency of sleep problems was also not seen to have any association with any

type of mortality (all-cause, non-prostate cancer or prostate cancer-specific).

Sharing only half of one's problems with a partner was associated with an increased risk of prostate cancer-specific mortality, and participants who shared problems with people other than their partners had a significantly increased risk of all-cause mortality. They also had a significantly increased risk of non-prostate cancer mortality. There were no associations between the number of people with whom to share emotional problems and any type of mortality.

Discussion

From this large cohort study of men with localized prostate cancer, it was found that the highest levels of perceived stress were associated with a significantly increased rate of prostate cancer-specific mortality. Men with high stress levels were also seen to have high frequencies of grieving and sleep loss, as well as lessened social support in terms of people with whom to share their emotional problems, contributing negatively to their QoL.

The importance of QoL assessment is gaining recognition, as indicated by the fact that some clinical cancer trials now include QoL assessment as a primary measure alongside

Table 3. Grief, sleep loss and social support according to tertiles of perceived stress.

	Perceived stress			<i>r</i>	<i>p</i>
	< 18	18 to < 23	≥ 23		
<i>Frequency of grieving from loss</i>				0.12	< 0.0001
Never	335 (23.4)	193 (14.3)	186 (14.3)		
Seldom	292 (20.4)	292 (21.6)	255 (19.7)		
Sometimes	574 (40.1)	572 (42.3)	503 (38.8)		
Fairly often	152 (10.6)	202 (14.9)	238 (18.4)		
Very often	80 (5.6)	94 (6.9)	115 (8.9)		
<i>Frequency of sleep problems</i>				0.28	< 0.0001
Never	466 (32.3)	245 (18.0)	174 (13.4)		
Seldom	588 (40.8)	544 (40.1)	389 (29.9)		
Sometimes	286 (19.8)	396 (29.2)	401 (30.8)		
Fairly often	73 (5.1)	124 (9.1)	225 (17.3)		
Very often	29 (2.0)	49 (3.6)	114 (8.7)		
<i>Sharing emotional problems with partner</i>				–0.13	< 0.0001
Few/no problems shared	79 (5.5)	81 (6.0)	131 (10.2)		
Half problems shared	251 (17.6)	322 (24.0)	369 (28.7)		
Most problems shared	957 (67.0)	791 (58.9)	638 (49.6)		
No partner	141 (9.9)	150 (11.2)	147 (11.4)		
<i>Sharing emotional problems with others</i>				–0.01	0.4196
Few/no problems shared	954 (67.0)	861 (65.2)	855 (67.4)		
Half problems shared	312 (21.9)	347 (26.3)	320 (25.2)		
Most problems shared	157 (11.0)	113 (8.6)	93 (7.3)		
<i>People with whom to share emotional problems</i>				–0.14	< 0.0001
No one	50 (3.5)	52 (3.8)	100 (7.7)		
1–2 close friends/family members	450 (31.3)	506 (37.4)	546 (42.0)		
3–5 close friends/family members	522 (36.3)	488 (36.1)	417 (32.1)		
> 5 close friends/family members	416 (28.9)	307 (22.7)	238 (18.3)		

Data are shown as *n* (%).

tumor response and survival [2]. QoL has many contributory components, and among its psychosocial facets, perceived stress, depression, anxiety, social support and coping have often been studied [10]. A meta-analysis considering more than 150 studies found that psychosocial factors reliably predict cancer prognosis and not incidence, independent of tumor staging and other confounders [38]. To date, few studies have assessed the prognostic significance of QoL for men with prostate cancer after diagnosis [2–4,17,18]. However, this is an important consideration given that survival after prostate cancer has increased as a result of improved treatments [39,40] and that many men diagnosed with prostate cancer will never progress to clinical significance [2,41].

The present study examined the roles of perceived stress and other psychosocial factors in the mortality of men with localized prostate cancer. Those with the highest levels of perceived stress had a statistically significantly increased risk of prostate cancer-specific mortality. To ensure that this result was not biased by high stress immediately preceding death, men who died within 6 months of the survey were excluded, and the result did not change. The sensitivity analyses showed that excluding men who died within 1 year of questionnaire return slightly weakened the association between perceived stress and prostate cancer-specific mortality. This was probably due to a loss of power. It should be noted, however, that the sensitivity analyses do not completely preclude the possibility of reverse causation.

Biologically, stress involves a myriad of interrelated pathways, many of which have implications in prostate cancer progression [42]. The (β-adrenergic pathways mediate the

sympathetic stress response – so-called “fight or flight”. In cohort studies, it has been seen that attenuation of these pathways via (β-blockers decreases prostate cancer-specific mortality [43]. Glucocorticoid hormones such as cortisol also mediate stress pathways and have been found to have a role in prostate cancer progression in *ex vivo* human prostate cancer cell models [44]. Recent animal studies have even suggested molecular mechanisms by which stress can affect apoptotic pathways of prostate cancer cells themselves [45]. This group demonstrated that increased stress directly leads to prostate cancer cell-type specific proliferation using an *in vivo* murine model. Although stress operates through a number of different pathways, approaches to limiting stress along even singular pathways have generally been associated with benefit.

The present study did not observe a relationship between prostate cancer relapse and perceived stress. Given the association between stress and relapse from the literature [12], this result may seem counterintuitive, but it can be potentially explained by the inherent selection bias that participants in the study must necessarily have survived with prostate cancer sufficiently long to participate. Since stress was assessed with questionnaires distributed after diagnosis and relapse had already been determined, men who relapsed and died could not be surveyed. Thus, this study considers only men who did not relapse and men who relapsed and survived until questionnaire return.

Several studies have suggested that circadian rhythm disruption and sleep loss are associated with increased risk of prostate cancer incidence and mortality [15,16,33,46]. The

Table 4. Multivariate hazard ratios of mortality according to cause of death.

Measure	Mortality		
	All-cause	Non-PCa	PCa-specific
No. of men (%)	403 (9.8)	276 (6.7)	127 (3.1)
<i>Stress</i>			
Lowest tertile	1.0	1.0	1.0
Middle tertile	1.06 (0.82–1.39)	1.08 (0.79–1.48)	1.02 (0.61–1.69)
Highest tertile	1.21 (0.93–1.56)	1.03 (0.75–1.42)	1.66 (1.05–2.63)
			1.64 (1.02–2.62) ^a
			1.58 (0.96–2.59) ^b
<i>Frequency of grieving from loss</i>			
Never	1.0	1.0	1.0
Seldom	1.39 (0.93–2.07)	1.16 (0.72–1.89)	1.96 (0.96–3.99)
Sometimes	1.61 (1.13–2.29)	1.58 (1.04–2.39)	1.71 (0.88–3.33)
Often	1.60 (1.10–2.35)	1.49 (0.95–2.34)	1.90 (0.93–3.87)
<i>Frequency of sleep problems</i>			
Never	1.0	1.0	1.0
Seldom	0.93 (0.70–1.24)	0.97 (0.69–1.37)	0.83 (0.50–1.40)
Sometimes	1.08 (0.80–1.45)	1.06 (0.74–1.52)	1.14 (0.68–1.93)
Often	1.05 (0.74–1.49)	1.04 (0.68–1.59)	1.07 (0.58–1.99)
<i>Sharing emotional problems with partner</i>			
Few/no problems shared	1.0	1.0	1.0
Half problems shared	1.24 (0.79–1.94)	0.89 (0.53–1.49)	3.05 (1.08–8.59)
Most problems shared	1.02 (0.66–1.56)	0.86 (0.54–1.39)	1.81 (0.65–5.02)
<i>Sharing emotional problems with others</i>			
Few/no problems shared	1.0	1.0	1.0
Half problems shared	1.16 (0.90–1.49)	1.35 (1.00–1.82)	0.81 (0.50–1.32)
Most problems shared	1.46 (1.05–2.03)	1.61 (1.09–2.40)	1.18 (0.64–2.17)
<i>People with whom to share emotional problems</i>			
No one	1.0	1.0	1.0
1–2 close friends/family members	0.79 (0.49–1.27)	0.96 (0.52–1.76)	0.55 (0.25–1.20)
3–5 close friends/family members	0.97 (0.60–1.56)	1.16 (0.63–2.13)	0.71 (0.33–1.54)
> 5 close friends/family members	1.04 (0.64–1.69)	1.23 (0.66–2.29)	0.78 (0.35–1.71)

Data are shown as hazard ratio (95% confidence interval).

Sensitivity analysis was performed for prostate cancer (PCa)-specific mortality in patients with the highest tertile of stress. Results are shown after excluding patients who died within ^a6 months or ^b1 year after responding to the questionnaire.

present study did not examine incidence, nor did it confirm an association between sleep loss and mortality. Of note, the studies that did identify an association between sleep loss and mortality in men with prostate cancer relied on cohorts of pilots, who may experience additional confounding occupational hazards [15,16]. This study, however, did confirm a statistically significant association between sleep loss and high stress. This accords with the finding of Lis et al., that sleep loss affects QoL in cancer patients [9].

In their structured review of the literature, Paterson et al. call for more investigations of social support and coping in men with prostate cancer, claiming that the field is “underdeveloped at present” [40]. Bellardita et al. found that lack of a partner impaired QoL in men with prostate cancer under active surveillance [47]. In the present study, it was seen that highly stressed men had fewer people with whom to share their emotional problems and moreover felt an inability to share most of their problems with partners, friends and family. The finding that increased sharing of emotional problems with friends and family other than with one’s partner was associated with increased all-cause and non-prostate cancer mortality may be explained severally by potential limitations of the question. One consideration may be that a participant may not have emotional problems or may be unwilling to share them. In addition, it was not possible to determine whether participants interpreted this question as

positing friends and family as sources of social support in addition to their partners or as sources of support in lieu of their partners. Moreover, given the negative impact of not having a partner at all, this may have confounded the answering of this question for men who had lost partners.

This study thus contributes new results, while confirming some previously reported ones, to the growing field of psychosocial QoL research in men with prostate cancer. Direct comparisons between this study and others cited above are not possible owing to differences in the measures of QoL and psychosocial factors used. The results of this study have important clinical and research implications. While the utility of designing psychosocial interventions to increase survival in cancer patients is controversial [48–50], it is not unreasonable to apply psychosocial therapy where applicable to improve QoL [51,52]. In addition to investigating mortality, this study examined perceived stress in relation to a number of commonly studied psychosocial factors. Such results can be used to identify patients who may benefit from individualized attention to stress reduction, sleeping habits and social support.

While this study presents interesting findings and raises additional questions for further investigation, several limitations require acknowledgement. The patient cohort represented men with localized, non-metastatic prostate cancer. As a result, generalizing the results for men with late-stage

disease may be questionable. Limited clinical follow-up did not allow for thorough documentation of relapse. Also, a one-time questionnaire did not allow for follow-up of reported psychosocial factors. Nevertheless, this study also has several strengths, including a population-based design, a large sample size and complete mortality follow-up.

In conclusion, this study shows a significant association between prostate cancer-specific mortality and perceived stress, as measured by the Cohen Stress Scale, in patients initially diagnosed with localized, non-metastatic prostate cancer. The study also reports significant associations between perceived stress and various psychosocial factors that merit follow-up and confirmation. While this study cannot prescribe specific interventions, it does affirm previous studies' recommendations to target improvements in QoL.

Acknowledgements

We would like to thank the Swedish Cancer Foundation, the Swedish Council for Working Life and Social Research, and the Fulbright US Student Program for financial support. Thank you to all of the participants in the PROCAP Study and the research nurses who extracted the clinical follow-up data. Thank you to Robert Szulkin for helping to program the progression variables. Finally, we would like to acknowledge that this project was made possible by the continuous work of the NPCR steering group: Pär Stattin (chairman), Anders Widmark, Lars Egevad, Magnus Törnblom, Stefan Carlsson, Jan Adolfsson, Anna Bill-Axelsson, Jan-Erik Johansson, Ove Andrén, Mats Lambe, Erik Holmberg, David Robinson, Bill Pettersson, Jonas Hugosson, Jan-Erik Damber, Ola Bratt, Göran Ahlgren, Karin Hellström and Maria Nyberg.

Funding

Supported by funds from the Swedish Cancer Foundation, the Swedish Council for Health, Working Life, and Social Research (FAS), and the Fulbright US Student Program.

Declaration of interest: The authors have no conflicts of interest to disclose.

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