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Post-traumatic disorder symptoms and blunted diurnal cortisol production in partners of prostate cancer patients

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Summary Prostate cancer (PC) is the most common cancer diagnosed in men, and research suggests that coping with this illness can cause significant distress in patients as well as their partners. This study examined the relationship of caregiving for a partner with PC with diurnal cortisol output in women between the ages of 42 and 75 years old. Participants were women whose partners had PC ($n = 19$) and women who were in relationships with men with no diagnosed medical illness ($n = 26$). Women provided saliva samples (4 times per day over 3 days) in their natural environment. The Structured Clinical Interview for DSM-IV Axis-I Disorders was also conducted to assess for the presence of post-traumatic stress disorder (PTSD) and major depression. Partners of men with PC had lower daily cortisol output across the three days than controls, $F(1,444.08) = 20.72$, $p < .001$). They were also more likely to report PTSD symptoms with 68.4% of PC partners fulfilling criteria for sub-threshold PTSD as compared to 23.1% of controls ($\chi^2 = 11.30$, $p = .01$). Mixed model analyses revealed that the presence of sub-threshold PTSD symptoms significantly predicted cortisol production, $F(1,419.64) = 5.10$, $p < .01$). Regardless of caregiver status, women who reported at least sub-threshold PTSD symptoms had lower cortisol production than those with no PTSD symptoms. Major depression did not explain differences in cortisol production between partners of PC patients and controls. Although these findings are preliminary, they highlight the importance of developing interventions aimed at reducing risk of psychopathology in partners of men with PC.
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1. Introduction

Prostate cancer (PC) is the most common cancer diagnosed in men, with 1 in 6 men being at risk for developing prostate cancer during their lifetime (National Cancer Institute, 2011). Partners of men with PC report significant distress (Carter et al., 2010; Eton et al., 2005; Fletcher et al., 2008; Garos et al., 2007). In fact, some studies have found that partners report more distress than the patients themselves (Couper et al., 2006, 2009; Eton et al., 2005; Garos et al., 2007). In a study examining psychological functioning in PC patients and their spouses, Eton et al. (2005) found that spouses were more likely than patients to report cancer-specific distress, including more avoidance and intrusive thoughts. Spouses report distress associated with the demands of caregiving for a cancer patient (Northouse et al., 2007a; Sterba et al., 2010), the threat of losing a loved one (Eton et al., 2005; Northouse et al., 2007b), and social isolation (Carter et al., 2010; Williamson et al., 1998).

Although research in this area is limited, several studies have documented that cancer caregivers have higher rates of psychiatric disorders than individuals in the general population (Alderfer et al., 2009; Balluffi et al., 2004; Kazak et al., 2004a,b; Patino-Fernandez et al., 2008; Stehl et al., 2009), with panic disorder and post-traumatic stress disorder (PTSD) being among the most commonly reported disorders in this group (Kazak et al., 2004a; Patino-Fernandez et al., 2008; Vanderwerker et al., 2005). Additionally, post-traumatic stress symptoms are common in cancer caregivers, with intrusive thoughts and hyperarousability being frequently reported symptoms (Eton et al., 2005; Glover and Poland, 2002; Kazak et al., 2004a). In a study examining the prevalence of PTSD in parents of children with cancer, Kazak et al. (2004a) found that nearly 20% of parents sampled met DSM-IV criteria for this disorder. Other studies have found that cancer caregivers are more likely to report clinically significant depressive symptoms than non-caregiving controls (Carter and Chang, 2000; Rhee et al., 2008).

No studies have examined the prevalence of PTSD in female caregivers of PC patients. However, in a study examining the prevalence of psychiatric symptoms in this group, Fletcher et al. (2008) found that 40% of female PC caregivers sampled in their study reported clinically significant anxiety symptoms. Further, Eton et al. (2005) found that spouses of PC patients were more likely than the patients themselves to report intrusive thoughts and avoidance following their PC husband's diagnosis. Thus, PC partners may experience more post-traumatic stress symptoms than women in the general population.

Recent studies suggest that cancer caregivers have worse physical health than non-caregiving controls (Beesley et al., 2011; Cora et al., 2012; Kim et al., 2010; Klassen et al., 2010; Lucini et al., 2008; Witt et al., 2010). However, no published study has examined the underlying psychobiological pathways through which distress might impact health in partners of men with PC. Altered Hypothalamic-Pituitary-Adrenal Axis (HPA) activity may be an underlying mechanism explaining poor health in caregivers. High cortisol production is associated with heightened risk for a number of health conditions, including coronary heart disease (Dekker et al., 2008; Matthews et al., 2006; Seeman et al., 2010), type 2 diabetes (Rosmond and Bjorntorp, 2000) and stroke (Rosmond and Bjorntorp, 2000). Further, stress-induced increases in glucocorticoid production is linked to altered immune activity, which is a risk factor for a number of negative health outcomes (Glaser and Kiecolt-Glaser, 2005).

In addition to overall cortisol levels, the diurnal pattern of cortisol production may also play a critical role in health outcomes. Studies have found that flattened diurnal cortisol rhythm is associated with cardiovascular morbidity in otherwise healthy adults (Matthews et al., 2006) as well as lower survival rates in breast cancer patients (Sephton et al., 2000). Little is known about whether the cancer caregiving experience has a similar impact on HPA activity. The majority of studies examining associations between chronic caregiver stress and HPA dysregulation have been conducted with elderly dementia caregivers (Epel et al., 2010; Fonareva et al., 2011; Vedhara et al., 2002). Findings from these studies indicate that dementia caregivers tend to have increased cortisol production (Cacioppo et al., 2000; Da Roza Davis and Cowen, 2001; Davis et al., 2004; de Vugt et al., 2005; Fonareva et al., 2011; Wahbeh et al., 2008) and more flattened diurnal cortisol slopes (Brummett et al., 2008) compared to non-caregiving controls.

Only a few studies have examined diurnal cortisol patterns in family members of cancer patients, and those that have been conducted in this population have yielded mixed results (Cohen et al., 2002; Glover and Poland, 2002; Miller et al., 2002; Rohleder et al., 2009). Although some studies have found higher cortisol and more flattened diurnal patterns in family members of cancer patients (Cohen et al., 2002; Miller et al., 2002), other researchers have failed to replicate these findings and instead report similar cortisol patterns or lower cortisol output in cancer caregivers compared to controls (Glover and Poland, 2002; Rohleder et al., 2009). The presence and nature of clinically relevant psychological symptoms experienced by cancer caregivers may help explain these divergent findings. Whereas cancer caregivers with PTSD symptoms seem to have lower cortisol production than controls (Glover and Poland, 2002), those who report elevated perceived stress and depressive symptoms have higher daily output and more flattened diurnal cortisol patterns (Miller et al., 2002). However, given the small number of studies examining HPA activity in family members of cancer patients, more research is needed to elucidate the impact of cancer caregiving on diurnal cortisol secretion.

This study was conducted to understand whether caregiving for a spouse/partner with PC is associated with HPA activity in women. Based on research finding differences in salivary cortisol output between cancer caregivers and controls (Miller et al., 2002), we hypothesized that diurnal cortisol production would be significantly different in spouses of PC patients (PC partners) and a control group of women in relationships with men who are medically healthy. Additionally, we suspected that the pattern of cortisol production in PC partners would be dependent on the psychological symptoms experienced in this group. Specifically, based on research finding that cancer caregivers with subthreshold PTSD symptoms have lower cortisol output (Glover and Poland, 2002), we predicted that PTSD symptoms would be associated with lower cortisol production. In contrast, based on research finding that cancer caregivers with depressive symptoms have more flattened diurnal cortisol patterns (Miller et al., 2002), we suspected that depressive symptoms

would be associated with higher and more flattened diurnal cortisol production.

2. Methods

2.1. Participants

Participants were women whose partners had PC (n = 19) and women who were in relationships with men with no diagnosed medical illness (n = 26). Women were recruited between June 2008 and August 2010. Women were eligible if they met one of two inclusion criteria: (1) PC partners were eligible for the study if their mates had been diagnosed with PC and was either currently undergoing treatment or had completed treatment for this disease within the last 2 years; (2) Control participants were eligible if they were at least 42 years old and were married to or cohabitating with a man who was medically healthy. Exclusion criteria included current pregnancy, cognitive impairment, an autoimmune disease, insulin-dependent diabetes, habitual use of tobacco, substance abuse or dependence, or currently taking sleep medication.

PC partners were identified through flyers posted at urology clinics in Los Angeles, CA and surrounding areas (n = 11) as well as through tumor registry information collected on PC patients at University of California, Los Angeles (n = 8). Patients identified through tumor registry information were sent an initial letter outlining the study and providing researchers' contact information. Spouses and female domestic partners who were interested in participating in the study were asked to call the research office to undergo screening. Approximately 50 PC partners contacted the study for screening. Eleven partners were ineligible due to medical conditions. Twenty partners were eligible but refused participation due to time demands or general lack of interest.

Control participants were recruited through newspaper advertisements, referrals, and flyers posted throughout the medical center at University of California, Los Angeles. Approximately 120 women were screened for the control arm of study. Of these 46, women were ineligible due to age, medical conditions, or tobacco use. Forty-eight women were eligible but refused participations due to time demands or general lack of interest.

All participants signed an informed consent form that was approved by the Institutional Review Board at University of California, Los Angeles and Pitzer College in Claremont, California. Additionally, they received $50 compensation for completing the study.

2.2. Diurnal cortisol assessment

Diurnal rhythm in salivary cortisol was measured over three days. Participants provided saliva samples in their natural environment. Samples were provided upon awakening, 30 min later, 8 h later, and at bedtime (defined as the time when they get into bed and turn off the lights to go to sleep). Participants were instructed to go about their normal daily activities during the three days of data collection. During this time, they also completed a diary that assessed relevant health behaviors (e.g., caffeine intake, tobacco usage, alcohol consumption, sugar intake, physical activity, and sleep patterns) as well as daily stress levels. Participants were instructed to call the laboratory's voicemail after each sample collection to ensure compliance with the sample schedule. To avoid sample contamination, they were also instructed to avoid brushing their teeth, eating, or drinking within 20 min before providing saliva samples. Participants kept samples refrigerated prior to returning them to the research laboratory. Average sample collection times were as follows: waking: 6:59 am (SD = 1:19); 30 min post-waking: 7:27 am (SD = 1:26); 8 h post-waking: 3:04 pm (SD = 1:30); bedtime: 10:56 pm (SD = 1:32). The returned salivettes were stored in a $-20\ ^{\circ}C$ freezer until they were analyzed. After data collection, salivary cortisol was analyzed with a time-resolved fluorescence immunoassay (Dressendorfer et al., 1992) at the Biological Psychology laboratory directed by Dr. Clemens Kirschbaum at the Technical University of Dresden in Dresden, Germany.

2.3. SCID PTSD and depression

The *Structured Clinical Interview for DSM-IV Axis-I Disorders* (SCID-I) was used to identify participants who met criteria for a major depressive episode (MDE) and PTSD. The SCID-I is a well-validated, semistructured interview that has been widely used to assess for the presence of psychopathology (Spitzer et al., 1992).

In the PTSD module of the SCID, participants are asked whether they have experienced a significant trauma in their lifetime. If multiple traumas are reported, participants are asked to identify the event that affected them most. Subsequent questions about PTSD symptoms are rated with respect to this event. Participants who rated the traumatic event as producing intense fear, helplessness, or horror and also had symptoms above the clinical threshold in each of three symptom clusters (intrusive thoughts, avoidance, hyperarousability) met criteria for PTSD. Participants who rated the traumatic event as producing intense fear, helplessness, or horror, met all criteria for at least one symptom cluster, and reported at least one symptom in one of the remaining two symptom clusters were classified as having subthreshold PTSD (Glover and Poland, 2002).

In the MDE module, participants who report experiencing depressed mood/anhedonia during a two week period in the last month are asked a series of follow-up questions to determine whether they meet criteria for a current MDE. Those who report experiencing at least 5 of the 9 symptoms are identified as having a current MDE. For the purposes of the current study, participants who did not meet these criteria but reported depressed mood/anhedonia during $\geq$ a a two week period and reported $\geq$ two additional symptoms of depression were classified as having subthreshold depression.

2.4. Self-report measures of psychological distress

Depressive symptoms were also assessed using the *Centers for Epidemiologic Studies Depression Scale* (CESD, Radloff, 1977). This 20-item scale is designed to measure depressive symptoms in the general population. Each item has a 0—3 range, with higher scores representing more severe depres-

sive symptoms. Scores of 16 and above are suggestive of clinical depression. The internal consistency reliability coefficient ranged from .84 to .90 in validation research (Radloff, 1977) and is .93 for the current sample.

Perceived stress was assessed using the *Perceived Stress Scale*-10 (PSS, Cohen et al., 1983). This 10-item scale provides a global measure of the extent to which situations in an individual's life are appraised as stressful. Higher scores indicate a greater report of stress. This scale has strong psychometric properties and has been widely used in studies examining the relationship between stress and health outcomes (Cohen et al., 1983). The internal consistency reliability coefficient was .93 for the current sample.

Caregiver strain was assessed using the *Modified Caregiver Strain Index* (MCSI, Thornton and Travis, 2003). This 13-item questionnaire assesses caregiver strain across the following domains: employment, financial, time, physical and social. Higher scores represent more strain. This scale has sound psychometric properties, with the reliability coefficient equaling .90 in the validation sample (Thornton and Travis, 2003) and .91 in the current sample.

Daily health behaviors that may influence cortisol levels were assessed using a brief questionnaire adapted from (Sephton et al., 2000). This measure includes questions about physical activity, stress, sleep quality, tobacco usage, and consumption of fat, sugar, alcohol, and caffeine on each sampling day.

A demographic questionnaire developed for the study assessed age, medical history, ethnicity, education, income, and living situation. In addition, PC partners provided prostate cancer-related information about their partner (e.g., disease stage, type of treatment, time since diagnosis) in the demographic questionnaire.

2.5. Statistical analyses

2.5.1. Differences between spouses of PC patients and controls

T-tests were conducted to examine differences between PC partners and controls on measures of psychological distress and demographic variables (age, BMI, education, income, and CVD). In these analyses, caregiver status was entered as the independent variable and measures of psychological distress and demographic variables were entered as outcome variables. Chi-square analyses examined differences in major depression and PTSD between PC partners and controls.

2.5.2. Diurnal cortisol production

Data were analyzed using SPSS 17.0 software. Prior to conducting the analyses, cortisol data were log transformed to control for skewness. In order to determine whether PC partners and controls differed in the diurnal slope of their cortisol values, multilevel modeling was performed using Day, Sample Time of day and Caregiver Status (i.e., PC partner versus control) as fixed variables. Age (Kumari et al., 2010), daily sleep efficiency (Kumari et al., 2010), as well as daily tobacco (Lovallo, 2006) and caffeine usage (Ice et al., 2004) were controlled as covariates in analyses based on research demonstrating that these factors are associated with altered HPA activity.

Analyses were also conducted examining differences in cortisol awake response (CAR) between PC partners and controls. CAR was assessed by subtracting Sample 1 cortisol levels from Sample 2 cortisol levels. Independent samples *T*-tests were conducted to examine differences in CAR based on caregiver status.

As a follow-up, mixed model analyses were performed to determine whether the presence of at least subthreshold SCID depression and SCID post traumatic stress explained differences in diurnal cortisol between PC partners and controls (Hypothesis 2). SCID depression and SCID post traumatic stress were each entered as fixed variables along with Day, Sample Time of day, and Caregiver Status. Age, daily sleep efficiency, as well as daily tobacco and caffeine usage were controlled in these analyses.

2.5.3. Caregiver characteristics and cortisol production

Correlation analyses were conducted on data from the sample of PC partners to determine which caregiver characteristics might explain altered HPA activity in spouses of men with PC. Caregiver strain, time since diagnosis, and prostate cancer stage at the time of diagnosis were entered as predictor variables. Outcome variables included measures of psychological distress. To assess differences in the diurnal pattern of cortisol based on these caregiver characteristics, multilevel analyses were conducted. Caregiver strain, time since diagnosis, and prostate cancer stage at the time of diagnosis were each entered as fixed variables in separate analyses. In each of these analyses, Day and Sample time of day were also included as fixed variables with cortisol values entered as outcome variables.

3. Results

3.1. Sample characteristics

Sample characteristics are displayed in Table 1. The sample was 60% Caucasian American, 11.1% African American, 6.7% Asian American, 15.6% Hispanic, and 6.7% other. Approximately half of the sample had at least a bachelor's degree and an annual income of $60,000 or more. Participants were between the ages of 42 and 75 (M = 60.89, SE = 1.34) with body mass indices between 17.36 and 40.56 (M = 25.83, SE = 0.96). Seven women reported current use of antidepressants (4 partners, 3 controls). There were no significant differences between PC partners and the control group on age, ethnicity, education, income, antidepressant usage, or BMI (p's $> .15$).

PC partners were more likely than controls to have been diagnosed with hypertension ($\chi^2 = 4.35$, $p = .037$). There were no other significant differences in medical history between the two groups. As noted in Table 1, PC partners reported getting fewer hours of sleep than controls ($t(1,44) = -3.22$, $p < .05$). There were no other significant differences in daily health behaviors. Concerning self-report measures of psychological distress, there was no significant difference between spouses of PC patients and controls on the CESD ($p = .20$) or the Perceived Stress Scale ($p = .15$).

3.2. SCID PTSD symptoms

Whereas criteria for PTSD were fulfilled in only 3 subjects (1 partner and 2 controls), subthreshold PTSD (i.e., meeting all

Table 1 Sample characteristics.

	Caregivers (n = 19) n (%)	Controls (n = 26) n (%)
Education		
High school	1 (5.3%)	2 (7.7%)
Some college	6 (31.6%)	9 (34.6%)
BA degree	3 (15.8%)	5 (19.2%)
Graduate training	9 (47.4%)	10 (38.4%)
Income		
<30,000	3 (16.7%)	3 (12.0%)
30,000–60,000	4 (22.3%)	8 (32.0%)
>60,000	11 (61.1%)	14 (56.0%)
Ethnicity		
African-American	3 (15.8%)	2 (8.0%)
Asian-American	3 (15.8%)	0
Caucasian-American	11 (57.9%)	15 (60.0%)
Hispanic	2 (10.5%)	5 (20.0%)
Other	0	3 (12.0%)
Tobacco usage	0	7.6%
Hypertension*	9 (47.3%)	5 (19.2%)

	Caregivers (n = 19) Mean (SD)	Controls (n = 26) Mean (SD)
Age	62.16 (4.94)	59.96 (11.06)
Body Mass Index	27.10 (7.04)	25.21 (5.19)
Blood pressure		
Systolic	128.80 (17.03)	122.67 (17.12)
Diastolic	77.30 (9.06)	73.00 (11.50)
Hours of sleep*	6.38 (1.09)	7.48 (1.57)
Perceived stress scale	25.82 (8.35)	23.31 (7.28)
CESD-depressive symptoms	11.13 (11.80)	7.79 (8.22)
Cortisol awake response	0.61 (5.1)	2.7 (4.5)
Total cortisol output[a]	4.26 (2.6)	6.87 (4.1)

[a] Averaged across the 3 sample collection days.
* $p < .05$.

criteria for at least one symptom cluster and reporting at least one symptom in one of the remaining two symptom clusters) was identified in 19 subjects. As shown in Table 2, PC partners were more likely than control participants to have subthreshold PTSD in response to a traumatic event, with thirteen PC partners (68.4%) versus six control participants (23.1%) reporting such symptoms (χ^2 = 11.3, $p < .01$). For PC partners, the traumatic events identified as causing intense fear or helplessness were mate's PC diagnosis (n = 10), death of loved one (n = 1), witnessed a violent attack (n = 1), victim of robbery (n = 1). For controls, the traumatic events causing intense fear or helplessness were death of a loved one (n = 2), rape (n = 1), assault (n = 2), and involvement in a serious car accident (n = 1). Intrusive thoughts were the most frequently reported post-traumatic stress symptoms among women with subthreshold PTSD, followed by hyperarousability and avoidance (see Table 2).

Table 2 SCID interview classification.

	Caregivers (n = 19) n (%)	Controls (n = 26) n (%)
Post-traumatic stress disorder	1 (5.3%)	2 (7.7%)
Sub-threshold post-traumatic stress symptoms[a]	13 (68.4%)	6 (23.1%)
Intrusive thoughts	9 (47.3%)	7 (26.9%)
Avoidance	1 (5.3%)	1 (3.8%)
Hyperarousal	5 (26.3%)	6 (23.1%)
Current major depression	2 (10.5%)	0
Sub-threshold depression	7 (36.8%)	3 (11.5%)

[a] $p < .05$.

3.3. SCID major depression

Three partners of PC patients met the full criteria for a current MDE, whereas no control participants met these criteria (χ^2 = 5.674, $p < .05$). Furthermore, as can be seen in Table 2, PC partners (n = 7; 36.8%) were more likely than control participants (n = 2; 7.6%) to have at least subthreshold SCID depression (χ^2 = 4.675, $p < .05$).

3.4. Caregiver status and cortisol production

Mixed model analyses were conducted to test our hypothesis that diurnal cortisol production would be significantly different in PC partners and control participants. Covariates (age, daily sleep efficiency, daily usage of tobacco and caffeine) were controlled for in these analyses. Fig. 1 depicts that across the three days, spouses of men with PC had lower cortisol production than controls, $F(1,379.07) = 9.14$, $p < .01$). However, there was no difference between the two groups in the diurnal slope of cortisol production, $F(3,201.74) = 0.58$, $p = .63$. Regardless of caregiver status, there was a significant linear trend in cortisol production characterized by higher morning and lower evening cortisol levels $F(3,184.84) = 39.97$, $p < .001$).

On average, PC partners had a 13% increase in cortisol levels compared to 39% in control participants 30 min after awakening. This difference in CAR was non-significant ($t(1,44) = -1.13$, $p = .263$).

3.5. SCID PTSD symptoms and cortisol production

To examine the relationship of with cortisol, individuals who met criteria for PTSD were combined with those who reported subthreshold PTSD. Mixed model analyses examined whether the presence of PTSD symptoms was associated with the lower cortisol production (Hypothesis 2), controlling for covariates. As predicted, women with at least subthreshold PTSD had lower cortisol production than those with no PTSD symptoms, $F(1,344.33) = 3.89$, $p < .01$, as displayed in Fig. 2. Further, presence of PTSD symptoms explained differences in cortisol between PC partners and controls; when presence of PTSD symptoms was entered in the model, the effect of caregiver status on cortisol production was no longer significant. The absence of a 3-way interaction between PTSD symptoms, caregiver status, and sample time of day suggests that this effect was the same in PC partners and controls, $F(3,168.46) = 1.53$, $p = .18$.

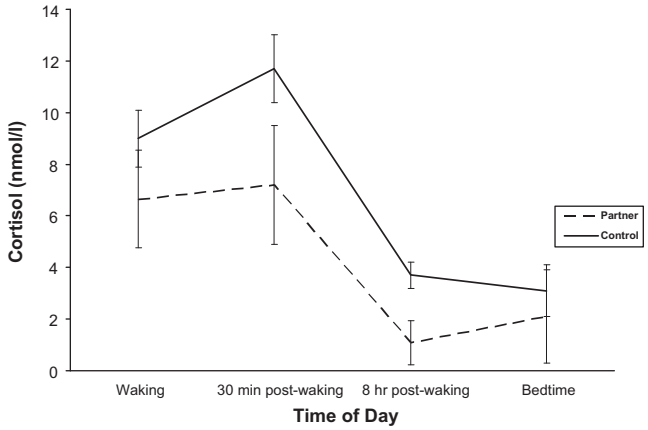

Figure 1 Differences between PC partners and controls on diurnal cortisol production. PC partners had lower overall cortisol production (all figures depict raw cortisol data) than controls throughout the day ($p < .05$).

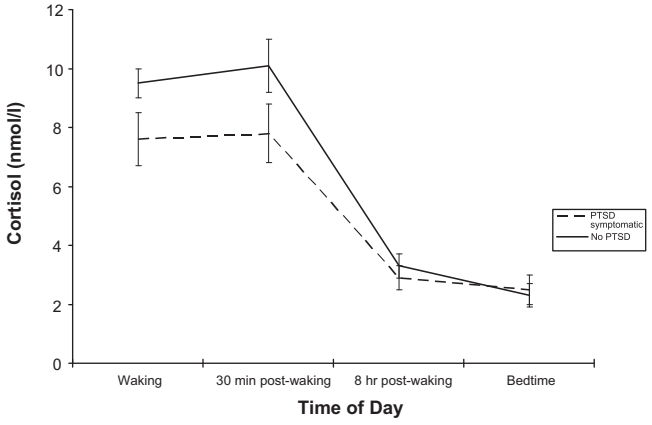

Figure 2 Differences in diurnal cortisol production between women with subthreshold PTSD and those in the No-PTSD group. PTSD symptomatic women had lower cortisol production than women with no PTSD symptoms ($p < .05$).

3.6. SCID depression and cortisol production

Individuals who met criteria for a current major depressive episode were combined with those who reported subthreshold depression. Mixed model analyses were conducted to examine the relationship between presence of SCID depressive symptoms and cortisol production in partners and controls (Hypothesis 2), controlling for covariates. There was a significant interaction between SCID depressive symptoms and sample time of day on cortisol, $F(3,179.30) = 4.48$, $p < .05$. Fig. 3 depicts that women who reported at least subthreshold depression had lower morning and higher evening cortisol than those with no depressive symptoms, resulting in flattened diurnal cortisol slopes, $F(3,179.30) = 4.48$, $p < .05$. The presence of SCID depressive symptoms did not explain differences in cortisol between partners of PC patients and controls. Even with the presence of SCID depressive symptoms in the model, caregiver status remained a significant predictor of cortisol, with partners having lower overall cortisol production than controls, $F(1,368.33) = 15.44$, $p < .001$.

The absence of a 3-way interaction between SCID depressive symptom, caregiver status, and Sample time of day suggests that this effect was the same in PC partners and controls, $F(3,187.68) = 1.52$, $p = .21$.

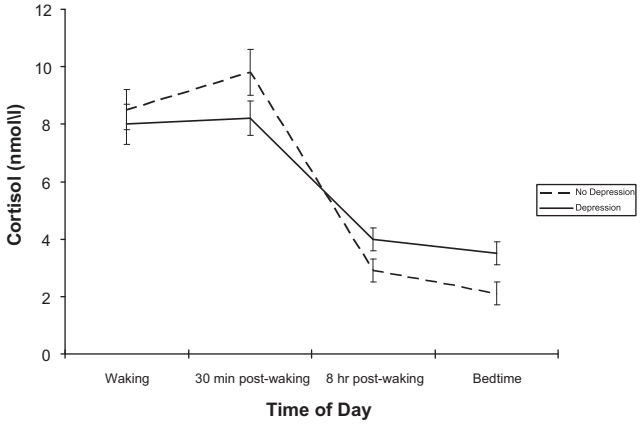

Figure 3 Differences in diurnal cortisol production between women with subthreshold symptoms of major depression and women with no depressive symptoms. Women with subthreshold symptoms of major depression had flattened diurnal cortisol production characterized by lower morning and higher evening cortisol levels ($p < .05$).

3.7. Caregiver characteristics and cortisol production

Within the PC partner sample, 53% of women reported that their spouse was diagnosed with PC at Stage 1. The remainder reported that they were diagnosed at Stage 2 (23%), and Stage 3 or 4 (23%). Women whose partners were diagnosed at later cancer stages had more CESD depression ($r = 0.76$, $p < .05$) and perceived stress ($r = .74$, $p < .05$) than women whose partners were diagnosed at Stage 1. Further, multilevel modeling showed that a later stage PC diagnosis was associated with lower cortisol production in women throughout the day compared to women whose mates were diagnosed at Stage 1, $F(2,30.93) = 4.76$, $p < .05$. Time since spousal PC diagnosis ranged between 3 and 58 months ($M = 22.4$, $SD = 12.37$) and was unrelated to partners' psychological distress or diurnal cortisol output. Caregiver strain was also unrelated to depression, perceived stress, or diurnal cortisol production.

4. Discussion

This study examined whether cancer caregiving is associated with altered HPA activity in partners of men with prostate cancer. As predicted, cortisol production differed in PC partners and the control group. Specifically, PC partners had lower salivary cortisol production throughout the day compared to women whose mates were medically healthy. This finding is consistent with that of Glover and Poland (2002), in which cancer caregivers who reported post-traumatic stress symptoms had lower plasma cortisol levels than controls.

PC partners were more likely to report subthreshold PTSD than women whose spouses were medically healthy. In the majority of cases, these symptoms were related to their partner's cancer diagnosis. As hypothesized, the presence of PTSD symptoms was associated with lower cortisol production, explaining differences in cortisol patterns between PC partners and controls. When PTSD symptomatology was entered in the mixed model analysis, there was no longer a significant difference in cortisol production between PC partners and controls. Instead, women with subthreshold PTSD had lower cortisol levels than controls.

This pattern of cortisol production in spouses of men with PC follows a similar pattern to that observed in individuals with PTSD. Several studies have shown that individuals who have been diagnosed with PTSD and those with post-traumatic stress symptoms have lower cortisol production than non-PTSD patients (Gill et al., 2008; Glover and Poland, 2002; Hauer et al., 2009; Miller et al., 2007; Yehuda, 2001; Yehuda et al., 1990). In contrast, depression is associated higher overall cortisol production and more flattened cortisol slopes, characterized by lower morning and increased evening cortisol levels (Miller et al., 2007).

Low cortisol in PTSD patients may result from enhanced negative feedback inhibition in the pituitary and hypothalamus (Yehuda, 2001). In addition to facilitating the ability to respond to stressors by providing energy to cells in the body when a threat is detected, cortisol also functions to turn off the stress response by suppressing the further release of cortisol and catecholamines when the negative feedback loop is activated by the amygdala (Yehuda, 2001).

Evidence for enhanced negative feedback inhibition in PTSD has been found in studies demonstrating that individuals with this disorder have increased glucocorticoid receptor sensitivity to dexamethasone (DST), a substance that mimics the effects of cortisol in the body (Yehuda, 2001). Following administration of DST, PTSD patients have lower cortisol levels than non-PTSD controls. Consequently, lower cortisol production may disrupt recovery from stress by failing to inhibit corticotrophin releasing factor (CRF) and adrenocorticotropic hormone (ACTH), leading to increased stimulation of the sympathetic nervous system and greater catecholamine production (Yehuda, 2001, 2003). Heightened SNS stimulation might increase the risk for stress-related diseases in individuals with clinically significant symptoms of PTSD. This process may contribute to worse physical health in cancer caregivers. Chronic increases in catecholamine production in response to sympathetic nervous system activation may lead to an overactive inflammatory immune response, increasing the risk for cardiovascular disease, diabetes, as well as rheumatologic and other diseases (Miller et al., 2002). In light of our findings that partners of men with prostate cancer have lower cortisol production and are more likely to report symptoms of PTSD than controls, future research should explore links between glucocorticoid and catecholamine production, inflammation, and health outcomes in spouses of men with PC.

We also found evidence suggesting that the nature of psychological distress in cancer caregivers plays an important role in determining diurnal cortisol patterns. As hypothesized, MDE and PTSD differentially predicted cortisol patterns in participants. Although PTSD symptoms were associated with lower cortisol across the day, depression was associated with higher cortisol in the evening hours and a flattened diurnal cortisol slope. This may shed light on discrepant findings in the literature concerning cortisol production in cancer caregivers (Cohen et al., 2002; Glover and Poland, 2002; Miller et al., 2002; Rohleder et al., 2009). Research suggests that in depressed individuals diurnal cortisol tends to be flattened, with higher evening cortisol levels than those of non-depressed controls (Linkowski, 2003), consistent with our results. Studies finding higher evening cortisol in cancer caregivers have also reported higher depression in this group (Cohen et al., 2002; Miller et al., 2002). Thus, greater reports of depressive symptoms may explain flattened diurnal cortisol patterns in some cancer caregivers.

There are several limitations in the current study that should be considered when interpreting these findings. First, this study was conducted on a small community sample and findings need to be replicated in larger samples. Second, the sample of PC partners was made up of a heterogeneous group of women whose mates varied in terms of medical characteristics, including time since diagnosis, PC cancer stage, and type of treatment received. It is possible that these characteristics influenced partners' psychological well-being and HPA activity. However, given the small sample size in the current study, we were unable to fully explore relationships between these factors and HPA activity. Although follow-up analyses suggested that partners of later stage cancer patients had higher distress and lower cortisol production, only a small percentage of women in this study were in relationships with men who had Stage 3 or 4 cancer. Thus,

this finding could have been spurious. Ideally, this study would need to be conducted with large enough samples to examine systematic differences in psychological distress and HPA activity in PC partners whose mates differ based on medical characteristics. It remains unclear from the current study, which specific aspects of the cancer caregiving experience may have been considered traumatic to partners. For instance, we did not assess whether women were afraid that their partners were going to die, or whether they experienced distress related to their partners' treatments, hospitalization, or helping them cope with the side effects of medical interventions. This information would help us to understand why partners of men with PC were more likely to report subthreshold post-traumatic stress symptoms, which would be useful in developing treatments tailored to meet the needs of this caregiver group.

The cortisol awakening response was below 50% among participants in this study, which is lower than what is typically seen in normal individuals (Wust et al., 2000). Although the difference was non-significant, PC partners had a lower CAR than control participants (13% versus 39%). It is possible that non-compliance with the sampling schedule might explain the reduced CAR in PC partners. However, several studies have found lower CAR in individuals who suffer from PTSD (Chida and Steptoe, 2009; Rohleder et al., 2004; Wessa et al., 2006). Thus, it is also possible that the lower CAR in PC partners was due to the presence of post-traumatic stress symptoms in this group.

Given the correlational nature of this study, we cannot infer that a causal relationship exists between partner PC diagnosis, PTSD symptomatology, and cortisol production. Low cortisol production may have preceded PC diagnosis and increased risk for PTSD. To determine causality, a longitudinal study would be necessary with data collection ranging from pre-diagnosis to post-treatment.

To our knowledge, this is the first study to examine diurnal cortisol patterns in spouses of men with cancer. Although these findings are preliminary and require replication, they suggest that the pattern of cortisol production in partners of men with PC may be associated with symptoms of PTSD resulting from the experience of caring for a spouse with cancer. The threat of losing a loved one to cancer is a traumatic experience that might lead to PTSD in some individuals. Although no published studies have examined the prevalence of PTSD in PC partners, female PC caregivers report clinically significant anxiety symptoms (Fletcher et al., 2008) and are more likely to report PTSD symptoms (e.g., intrusive thoughts and avoidance) than PC patients (Eton et al., 2005). These findings, in conjunction with our findings of lower cortisol production in spousal cancer caregivers, provide evidence that caring for a spouse/partner with PC may have adverse psychobiological effects. Additionally, these findings highlight the importance of developing interventions aimed at reducing risk of psychopathology in this group.

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Conflicts of interest

The authors have no conflicts of interest considering this manuscript.

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