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Life Stress, Negative Mood States, and Antibodies to Heat Shock Protein 70 in Endometrial Cancer

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Abstract

Heat shock protein 70 (HSP70), an intracellular chaperone “stress protein,” has been identified in the extracellular milieu, where it may exert regulatory effects upon monocytes. HSPs are overexpressed in many cancers and implicated in tumorigenesis. Few studies have examined the relationship between psychosocial factors and HSP levels, particularly in cancer. The purpose of the present study was to examine the relationship between negative psychosocial states (life events stress and negative mood states) and serum concentration of HSP70 antibodies among women with endometrial cancer, the fourth most common cancer among women in the United States. Thirty-six women scheduled to undergo surgery for suspected endometrial adenocarcinoma underwent a psychosocial assessment and peripheral venous blood draw. Life events stress was assessed using an abbreviated version of the Life Experiences Survey; negative mood states were assessed using abbreviated versions of the Structured Interview Guide for the Hamilton Anxiety and Depression Scales and the Profile of Mood States. HSP70 antibody levels were regressed sequentially on life events stress and negative mood variables while controlling for body mass index (BMI) and cancer stage. Results revealed that greater HSP70 antibody concentrations were associated with greater impact of recent negative life events ($p = .04$), anxious symptomatology ($p = .007$), depressive symptomatology ($p = .03$), and total mood disturbance ($p = .001$) after controlling for BMI and cancer stage. While based on a modest sample size, these preliminary results suggest that larger-scale research exploring the relationships among psychosocial factors and HSP70 in cancer patients may be warranted.

Keywords

stress; mood; cytokines; cancer; women; heat shock proteins

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Introduction

Molecular chaperones are a family of cellular proteins that assist polypeptides with correct assembly and disassembly. There are several classes of molecular chaperones, including chaperonins and heat shock proteins (HSPs). HSPs have both intracellular and extracellular functions. Intracellularly, HSPs chaperone misfolded proteins and protect cells from stressful environmental and physiological stimuli, while extracellularly, HSPs act as cytokines by modulating immunity (Asea et al., 2000).

HSPs have been implicated in tumorigenesis (Ciocca and Calderwood, 2005). HSP70, one of the most thoroughly studied small (70 kDa) chaperone proteins, is overexpressed in many cancers, including endometrial cancer. Endometrial cancer is the fourth most prevalent cancer and the eighth leading cause of cancer-related death among U.S. women (American Cancer Society, 2007). In endometrial cancer, HSP70 overexpression is associated with p53 tumor suppressor gene mutation/overexpression, poorly differentiated tumor grade, more aggressive variants, more advanced tumor stages, estrogen and progesterone receptor (ER/PR) negative tumors, and poorer survival rates (Nanbu et al., 1996; Nanbu et al., 1998).

HSP70 overexpression may contribute to endometrial cancer progression in several ways. Although HSP70 overexpression protects cells from proteotoxic damage, it also inhibits apoptosis, allowing tumor cells to escape immune surveillance and develop chemotherapy resistance (Morano, 2007). In the extracellular milieu, exogenous HSP70 has been found to bind to human monocytes, where it can activate nuclear factor (NF)- κ B and upregulate proinflammatory cytokine expression (Asea et al., 2000) implicated in endometrial cancer progression (Bellone et al., 2005; Chopra et al., 1997).

There is emerging evidence that activation of the stress-response systems may induce HSP70 expression. HSP70 expression can be induced via cellular and metabolic stress-induced hypothalamic pituitary adrenal (HPA) axis-mediated release of cortisol (Deane et al., 2006) and sympathetic nervous system (SNS)-mediated release of norepinephrine (Matz et al., 1995). Psychological stress may also induce molecular chaperone expression. In one study, psychological stress induced HSP expression in rats following restraint stress via adrenocorticotrophic hormone (ACTH) dependent HPA axis and adrenergic dependent SNS activation (Udelsman et al., 1993; Udelsman et al., 1994).

In spite of recent calls to examine biobehavioral influences on HSPs in humans (Cohen, 2006; Fleshner and Laudenslager, 2004), few studies have done so. One study found that higher plasma levels of HSP60, a widely studied chaperonin, were associated with greater psychological distress in healthy female British civil servants (Lewthwaite et al., 2002). No published research, to our knowledge, has examined the relationship between psychological factors and HSP expression in cancer. Given that stress-related psychological factors are associated with (a) HSP overexpression (Udelsman et al., 1994), and (b) greater cancer incidence and mortality (Chida et al., 2008), the possibility exists that stress/distress may be associated with poorer cancer outcomes via HSP70 overexpression.

As an initial step toward exploring this hypothesis, the present study examined the relationship between negative psychosocial states and HSP70 antibody levels in endometrial cancer. Life stress, anxious symptomatology, and depressive symptomatology were examined due to the prevalence of these mental health concerns among individuals undergoing diagnosis/treatment for cancer (Breitbart, 1995) and their association with poorer health outcomes in cancer (Chida et al., 2008).

Methods

Participants

Participants were women scheduled to undergo total abdominal hysterectomy and bilateral salpingo oophorectomy (TAH-BSO) for suspected endometrial adenocarcinoma who were fluent in spoken English. Exclusion criteria included pre-menopausal status, recurrent endometrial cancer, neoadjuvant chemotherapy, presurgical radiation therapy, primary cancer originating from a site other than the uterine corpus, and medical record documented current severe psychiatric illness.

Procedures

Recruitment occurred in a gynecologic oncology clinic at a large academic health science center in the Southeastern United States from June 2004 until January of 2007. Women attending the clinic for consultation following an abnormal endometrial biopsy were screened for preliminary study eligibility. Eligible women who were interested in participating completed University of Florida Institutional Review Board approved informed consent procedures. Participants were scheduled to return to the clinic one week later for a presurgical medical evaluation and provided a packet of psychosocial questionnaires to complete and return at this visit. At the presurgical evaluation, study staff administered a psychosocial interview to assess depressive and anxious symptomatology. Participants underwent peripheral venous blood draw¹ and received \$20 compensation for study participation. Blood samples were immediately transported to the laboratory for processing and storage. Following participants' surgeries, study staff reviewed participants' medical charts and abstracted history of comorbid medical conditions and tumor cellular classification, stage, and grade data.

Assessment

Control Variables—Demographic (age, race/ethnicity, education level, and yearly income) and behavioral factors (tobacco, alcohol, and other substance use) were assessed via face-to-face interview and self-report instruments. Health factors possibly associated with HSP70 were assessed via face-to-face interview and data abstraction from medical chart reviews. Health factors assessed included length of time since abnormal endometrial biopsy was obtained; body mass index (BMI) (Ghayour-Mobarhan et al., 2007); tumor cellular classification, grade, and stage (Nanbu et al., 1998); and comorbid connective tissue disease (Sedlackova et al., 2009). Medical comorbidity severity was assessed using the Charlson Comorbidity Index (Charlson et al., 1987).

Psychosocial Variables

Life events stress: Life events stress was measured using a version of the Life Experiences Survey (LES) (Sarason et al., 1978) previously abbreviated/modified to assess the incidence and impact of recent moderate to severe life stressors among individuals with a chronic/life-limiting illness (Leserman et al., 2005). The degree of stressfulness of each endorsed stressor was rated on a scale from 0 (*not at all stressful*) to 4 (*extremely stressful*). Scores were summed to yield a total impact of negative life events score.

Negative Mood States: Depressive symptomatology, anxious symptomatology, and total mood disturbance were assessed. Depressive and anxious symptomatology were assessed using the Structured Interview Guide for the Hamilton Anxiety and Depression scales (SIGH-AD) (Williams, 1988), a widely used mood assessment instrument in medical populations. An abbreviated SIGH-AD, consisting of 15 depression items and 9 anxiety items, was used to

¹15 participants recruited for the study did not undergo blood draw procedures (cf., Results section, for detail).

minimize patient burden and remove items confounded with endometrial cancer symptomatology. Symptom severity ratings were summed to yield depressive symptomatology (possible range of 0 to 44) and anxious symptomatology (possible range of 0 to 29) scores. Scores for depressive symptoms judged as possibly/definitely organic in origin were subtracted from total depressive symptomatology scores to minimize confounding by health/treatment factors.

Total mood disturbance was assessed using the Incredibly Short Profile of Mood States (ISPOMS) (Dean et al., 1990), a six-item version of the Profile of Mood States (POMS) (McNair et al., 1981) used as a brief mood assessment in medical populations. Participants rated the degree of severity of six mood states on a scale from 0 (*not at all*) to 4 (*extremely*). These ratings were summed to yield a total mood disturbance score.

HSP70 Antibody Concentrations: Whole blood was collected using a serum separator tube, and samples were allowed to clot at room temperature for 30 minutes. Samples were then centrifuged at $1000 \times g$ for 10 minutes. Serum was removed, aliquotted, and stored at -80°C until assayed. HSP70 antibody concentrations were measured in sera using a commercially available Enzyme Linked Immunosorbent Assay (ELISA) kit (StressGen, Assay Designs, Ann Arbor, MI). This kit utilized recombinant human HSP70 precoated to the wells of the recombinant HSP70 immunoassay plate to capture anti-HSP70 antibodies present in human serum. Captured anti-HSP70 antibodies were then detected with a horseradish peroxidase conjugated goat polyclonal antibody specific for human IgG/A/M. After the substrate produced a readable change in optical density, color intensity was measured in a microplate reader at 450nm. Samples were assayed in duplicate. This HSP70 antibody ELISA kit generated a standard curve using a calibrated standard of anti-HSP70 (IgG/A/M) antibodies isolated from pooled human sera. The resulting predicted values of HSP70 antibody concentrations were reported in ng/mL, and these values were multiplied by a dilution factor of 1:1000. Final sample HSP70 antibody concentrations were reported in $\mu\text{g/mL}$.

Statistical Analyses

Descriptive statistics for this cross-sectional study were calculated on all variables of interest, and the distribution of HSP70 antibody concentrations was examined for normality. Participants who completed blood draw procedures were compared to those who did not complete blood draw procedures on control/psychosocial variables in order to assess for the presence of systematic differences between the subsamples. Relationships between control variables and HSP70 antibody concentrations were explored using bivariate correlational analyses and univariate analysis of variance (ANOVA). Control variables associated with HSP70 antibody concentrations at $p < .10$ were controlled for in subsequent regression analyses. Using hierarchical linear regression analysis, HSP70 antibody concentrations were then regressed on each of the five psychosocial factors of interest independently while controlling for any variable(s) associated with HSP70 in this sample. Thus, five separate regression analyses were conducted.

Results

Participant Characteristics

One hundred and four women undergoing evaluation for suspected endometrial cancer were screened for study eligibility. Twenty-three women declined to participate in the study, the majority of whom cited “stress” or “I’m not interested in research” as reasons. An additional 19 individuals did not meet study eligibility criteria due to pre-menopausal status, nonfluency in English, non-surgical candidacy, and/or comorbidity with other cancers. The remaining 59 individuals signed informed consent and were enrolled in the study. Of these 59 individuals,

8 withdrew prior to initiation of study procedures due to “feeling overwhelmed by my cancer.” Of the remaining 51 participants, 2 were assessed prior to IRB approval and availability of study-related phlebotomy services, and 13 declined to participate in the blood draw or did not undergo outpatient pre-surgical phlebotomy due to medical contraindication (e.g., coagulation disorder, recent heparin use). The remaining 36 participants completed psychosocial assessment and blood draw procedures. These 36 participants did not differ from the 15 who did not complete blood draw procedures on any control or psychosocial variables examined at $p < .10$, except that women with blood draws had marginally fewer days between biopsy and study entry than women without blood draws, $p = .08$.

The final sample ($N = 36$) was comprised of predominantly overweight/obese (BMI $M = 36.91$, $SD = 10.55$), White ($n = 33$), non-Hispanic ($n = 35$) women (age $M = 61.92$ years, $SD = 10.05$ years) without comorbid connective tissue disease ($n = 34$). Most participants were diagnosed with well- or moderately differentiated ($n = 32$) surgical Stage I ($n = 26$) endometrioid adenocarcinoma ($n = 35$).²

Psychosocial Variables

Descriptive statistics on the psychosocial variables of interest are embedded in Table 1. The prevalence of negative life events in the prior 6 months was high; 30 participants (83%) reported experiencing at least 1 negative life event while only 4 (11%) denied experiencing any negative life events in the prior 6 months.³

HSP70 Antibody Concentrations

The distribution of HSP70 antibody concentrations was examined for normality using a normal probability plot. The plot revealed that the values were approximately normally distributed. The mean HSP70 antibody concentration was 225.42 $\mu\text{g/mL}$ ($SD = 195.26 \mu\text{g/mL}$) and consistent with mean values obtained in other cancer samples (Fujita et al., 2008).

Relations between Control Variables, Psychosocial Variables, and HSP70 Antibody Concentrations

Of the demographic, behavioral, and health factors examined as possible control variables in this study, only BMI was associated (marginally) with HSP70 antibody concentrations, $r = -0.33$, $p = .06$. Thus, BMI was retained as a control variable. Although univariate ANOVA did not reveal an association between cancer stage and HSP70 antibodies in this sample, $F(2, 33) = .29$, $p = .76$, $\eta_p^2 = .02$, cancer stage was retained as a control variable in subsequent regression equations based on its association with HSP70 in published research (Nanbu et al., 1998). Impact of negative life events, anxious symptomatology, depressive symptomatology, and total mood disturbance were all significantly correlated with HSP70 antibodies at $p \leq .05$, $r_s = 0.33$ (depressive symptomatology) to 0.48 (anxious symptomatology).

Regression of HSP70 Antibody Concentrations on Psychosocial Variables

Greater impact of negative life events, anxious symptomatology, depressive symptomatology, and total mood disturbance were all significantly associated with greater HSP70 antibodies above and beyond the effects of BMI and cancer stage on HSP70 ($\beta_s = 0.35$ to 0.58, $p_s \leq .04$) (Table 1). The largest effect size was obtained between HSP70 antibody concentrations and total mood disturbance, $\beta = 0.58$, $p = .001$. The linear combination of BMI, cancer stage, and

²One woman was diagnosed with uterine papillary serous adenocarcinoma, an aggressive endometrial cancer variant. Exclusion of her data did not alter the study's findings.

³Two participants (6%) did not complete the LES. Deidre B. Pereira, PhD Life Stress, Negative Mood States, and HSP70 in Endometrial Cancer

total mood disturbance accounted for 44% of the variance in HSP70 antibodies, $F(3, 29) = 7.66, p = .001$.

Discussion

A recent meta-analytic review concluded that stress and distress are associated with greater cancer incidence and mortality (Chida et al., 2008). Given that HSP70 overexpression is implicated in carcinogenesis (Ciocca and Calderwood, 2005) and stress can induce HSP70 expression via activation of HPA and SNS activity (Udelsman et al., 1993; Udelsman et al., 1994), the possibility exists that stress/distress and cancer outcomes may be mediated by stress-induced HSP70 overexpression. While this may be a plausible hypothesis, no published research, to our knowledge, has taken the initial step of examining whether psychosocial factors are in fact associated with HSPs in cancer. The present study examined stress/distress and HSP70 antibodies in women with endometrial cancer. As hypothesized, life events stress and negative mood states were significantly associated with higher concentrations of HSP70 antibodies in women with endometrial cancer, and that these relationships persisted after controlling for BMI and cancer stage.

The current results contribute to a growing body of literature positing that psychosocial factors contribute to biological processes known to influence cancer metastasis and progression (Antoni et al., 2006). Stress/distress-induced HPA axis activation may result in cortisol elevations and subsequent HSP70 overexpression and tumor cell apoptosis inhibition. Likewise, stress/distress-induced locus coeruleus/SNS activation may result in norepinephrine elevations, which have been shown to induce HSP70 expression (Matz et al., 1995). HSP70 binds to human monocytes, where it can activate NF- κ B and upregulate the expression of proinflammatory cytokines (Asea et al., 2000) implicated in endometrial cancer progression, such as tumor necrosis factor (TNF)- α (Chopra et al., 1997) and interleukin (IL)-6 (Bellone et al., 2005). Notably, this stress-induced beta-adrenergic activation of the tumor cAMP-PKA signaling pathway has been shown to result in greater tumor burden and more invasive cancer cell growth in ovarian cancer cell lines (Thaker et al., 2006). Future research should examine the impact of HPA axis and SNS activation on HSP70 expression and downstream effects on the tumor microenvironment using *in vitro* and non-human animal experimental models.

In contrast to the only other published study examining psychosocial factors and HSPs (Lewthwaite et al., 2002), the present study assessed HSP70 antibody levels, rather than circulating protein levels. While the presence and elevation of antibodies to HSPs may be novel biomarkers for various cancers (Luo et al., 2002), it remains unclear how well circulating autoantibody concentrations reflect circulating protein levels, monocyte receptor expression, or tumor surface expression of HSPs. HSP70 antibody levels and HSP70 tumor expression are significantly correlated in esophageal cancer patients (Nakajima et al., 2009); however, it is unclear whether these results are generalizable to endometrial cancer. Consequently, future research should examine how psychosocial factors may be associated with these physiologic outcomes involving HSPs in women with gynecologic cancers.

The results of this study must be interpreted with caution due to study design and sample limitations. The study had a modest sample size and minimal racial/ethnic diversity, both of which may have impacted the study's external validity. It is also possible that the most stressed or distressed individuals declined study participation; thus, the relationship between extremely high stress and HSP70 antibodies is unknown. The cross-sectional design precludes causal interpretations. Finally, data on participants' ER/PR tumor status were unavailable. Given that HSP70 overexpression is found in ER/PR negative tumors, future research should examine how the relationship between stress/distress and HSP70 overexpression may be influenced by

ER/PR tumor status. In light of these limitations, future research should attempt to replicate these findings with a larger and more diverse sample.

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Hierarchical Linear Regressions of HSP70 Antibody Concentrations (in $\mu\text{g/mL}$) on Psychosocial Factors Among Women Undergoing Surgery for Endometrial Cancer

Table 1

Equation No.	Psychosocial Predictor(<i>M</i> , <i>SD</i>)	β	R^2	ΔR^2	<i>F</i> of	<i>p</i>
1	Impact of Negative Life Events (<i>M</i> = 7.40, <i>SD</i> = 6.87)	0.36	.27	.13	5.01	.04
2	Anxious Symptomatology (<i>M</i> = 4.50, <i>SD</i> = 3.23)	0.43	.31	.18	8.25	.007
3	Depressive Symptomatology (<i>M</i> = 6.89, <i>SD</i> = 4.74)	0.35	.25	.12	5.18	.03
4	Depressive Symptomatology Excluding Organic Symptoms (<i>M</i> = 5.53, <i>SD</i> = 4.65)	0.38	.27	.14	6.20	.02
5	Total Mood Disturbance (<i>M</i> = 7.33, <i>SD</i> = 4.84)	0.58	.44	.29	14.84	.001

Note. All regression equations controlled for body mass index (BMI) and cancer stage in Block 1. $\Delta R^2 = \text{Change in } R^2 \text{ after controlling for BMI and cancer stage. Equation 1: } F(3, 28) = 3.43, p = .03. \text{ Equation 2: } F(3, 32) = 4.78, p = .007. \text{ Equation 3: } F(3, 32) = 3.60, p = .03. \text{ Equation 4: } F(3, 32) = 4.00, p = .02. \text{ Equation 5: } F(3, 29) = 7.66, p = .001.$