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Cytokine gene variation is associated with depressive symptom trajectories in oncology patients and family caregivers

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A B S T R A C T

Purpose: Depressive symptoms are common in cancer patients and their family caregivers (FCs). While these symptoms are characterized by substantial interindividual variability, the factors that predict this variability remain largely unknown. This study sought to confirm latent classes of oncology patients and FCs with distinct depressive symptom trajectories and to examine differences in phenotypic and genotypic characteristics among these classes.

Method: Among 167 oncology outpatients with breast, prostate, lung, or brain cancer and 85 of their FCs, growth mixture modeling (GMM) was used to identify latent classes of individuals based on Center for Epidemiological Studies-Depression (CES-D) scores obtained prior to, during, and for four months following completion of radiation therapy. One hundred four single nucleotide polymorphisms (SNPs) and haplotypes in 15 candidate cytokine genes were interrogated for differences between the two largest latent classes. Multivariate logistic regression analyses assessed effects of phenotypic and genotypic characteristics on class membership.

Results: Four latent classes were confirmed: Resilient (56.3%), Subsyndromal (32.5%), Delayed (5.2%), and Peak (6.0%). Participants who were younger, female, non-white, and who reported higher baseline trait and state anxiety were more likely to be in the Subsyndromal, Delayed, or Peak groups. Variation in three cytokine genes (i.e., interleukin 1 receptor 2 [IL1R2], IL10, tumor necrosis factor alpha [TNFA]), age, and performance status predicted membership in the Resilient versus Subsyndromal classes.

Conclusions: Findings confirm the four latent classes of depressive symptom trajectories previously identified in a sample of breast cancer patients. Variations in cytokine genes may influence variability in depressive symptom trajectories.

Introduction

Depressive symptoms are experienced by 10%–40% of oncology patients (Massie, 2004; Pirl, 2004), have deleterious effects on quality of life (QOL) (Given et al., 2008; Rabin et al., 2008), and are associated with increased mortality (Satin et al., 2009). Family caregivers (FCs), who provide substantial physical and emotional support to patients (Yabroff and Kim, 2009), are at heightened risk for depressive symptoms (Institute of Medicine, 2007; Kim et al., 2005; Rhee et al., 2008), with similar negative consequences (Couper et al., 2006a, 2006b).

Despite the prevalence and impact of depressive symptoms in patients and FCs, most studies have examined these groups separately, based on assumptions that the stressors experienced by patients and FCs differ. However, recent evidence suggests that demographic, dispositional, and personality-related characteristics explain substantial variability in distress and depression in cancer patients (Deimling et al., 2006; Schou et al., 2004) and FCs (Carter and Acton, 2006), while disease characteristics explain relatively little (Bardwell et al., 2006; Deshields et al., 2006). Moreover, as underscored by the Stress Process model (Pearlin et al., 1990) and supported by both cancer and non-cancer literature (Gottlieb and

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Rooney, 2004; Hooker et al., 1998; Kim et al., 2008; Kurtz et al., 1997), FC stress is influenced by a FC's individual characteristics.

Cancer treatment and follow-up typically occur over long time periods (Deshields et al., 2006; Helgeson et al., 2004; Kurtz et al., 2004). While longitudinal studies have evaluated for changes in mean symptom scores, such approaches obscure underlying patterns (i.e., subgroups of individuals with similar symptom trajectories). Growth mixture modeling (GMM) is an approach that identifies latent classes with similar patterns of change (Muthen and Muthen, 2000). Few studies have employed GMM to identify latent classes of oncology patients with distinct symptom trajectories (Donovan et al., 2007; Helgeson et al., 2004; Henselmans et al., 2010; Hou et al., 2010; Lam et al., 2010, 2012; Legler et al., 2004; Rose et al., 2009).

In our previous study of patients with breast cancer ($n = 398$), four latent classes were identified using Center for Epidemiological Studies-Depression (CES-D) scores assessed prior to and for six months after surgery (Dunn et al., 2011). The classes were named Resilient (38.9%), Subsyndromal (45.2%), Delayed (11.3%), and Peak (4.5%), based on the shape of the trajectories. Compared to the Resilient class, patients in the Subsyndromal class were younger and had higher anxiety scores prior to breast cancer surgery. However, differences in genotypic predictors between the two classes were not evaluated.

Genetic variation accounts for substantial heterogeneity in risk for depression (Levinson, 2006), primarily through mediation of neuroendocrine and immune pathways (Feder et al., 2009; Maes et al., 2009; Miller et al., 2009). Specifically, the cytokine signaling pathway is associated with inflammation, stress, and depression (Haroon et al., 2012; Miller et al., 2009). The "cytokine hypothesis of depression" is supported by findings of increased levels of cytokines in adults with major depression and in those with treatment-resistant depression (Maes et al., 1997; Zorrilla et al., 2001), as well as reductions in cytokine levels in individuals who respond to antidepressants (Miller et al., 2009). Pro-inflammatory cytokines may influence vulnerability to depression by reducing synthesis and increasing reuptake of key neurotransmitters associated with depression (Miller et al., 2009). For instance, pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin-1-beta (IL1β), upregulate the serotonin transporter (5-HTT) (Zhu et al., 2006). Sickness behavior, which includes symptoms of depression, is hypothesized to be associated with cytokine pathway dysregulation (Dantzer et al., 2008a; Dantzer and Kelley, 2007) and can be induced by administration of pro-inflammatory cytokines (Capuron et al., 2002; Dantzer et al., 2008b; Haroon et al., 2012; Raison et al., 2006; Reichenberg et al., 2001). For instance, administration of interferon-alpha to patients with melanoma or hepatitis C can induce depressive symptoms (Raison et al., 2006).

Preliminary evidence suggests that an underlying genetic predisposition exists for different levels of symptom severity in response to inflammation or other stressors. For instance, a common functional promoter polymorphism in the TNFA gene (c.G-308A) is associated with inflammatory diseases (Lee et al., 2007) and increased sleep disturbance (Aouizerat et al., 2009). However, relationships between cytokine gene variation and depressive symptoms in cancer patients and their FCs have not been evaluated.

Therefore, the purposes of this study, in a sample of oncology patients and their FCs, were to: confirm previously identified (Dunn et al., 2011) latent classes with distinct depressive symptom trajectories from the beginning to four months after the completion of RT; evaluate for differences in demographic, clinical, and underlying trait characteristics among these latent classes; and examine whether latent classes differed with respect to variation in a number of pro- and anti-inflammatory cytokine genes. Based on our prior work (Dunn et al., 2012), we predicted that latent classes would not be dependent on patient or FC status. Given substantial evidence for cytokine-induced sickness behavior (Aouizerat et al., 2009; Capuron et al., 2002; Cerri et al., 2010; Collado-Hidalgo et al., 2008; Dantzer et al., 2008b; Haroon et al., 2012; Miaskowski et al., 2010; Raison et al., 2006; Reichenberg et al., 2001), we also hypothesized that variation in candidate cytokine genes would be associated with latent class membership.

Methods and materials

Participants and settings

Patients and their FCs were recruited from two radiation therapy (RT) departments located in a Comprehensive Cancer Center and a community-based oncology program at the time of the patient's simulation visit. Patients were eligible to participate if they were ≥18 years of age; were scheduled to receive primary or adjuvant RT for one of four cancer diagnoses (i.e., breast, prostate, lung, brain); were able to read, write, and understand English; gave written informed consent; and had a Karnofsky Performance Status (KPS) score of ≥60. Patients were excluded if they had metastatic disease, more than one cancer diagnosis, or a diagnosed sleep disorder. FCs were eligible to participate if they were adult (≥18 years of age); were able to read, write, and understand English; gave written informed consent; had a KPS score of ≥60; were living with the patient; and did not have a diagnosed sleep disorder.

Self-report instruments

A demographic questionnaire obtained information on age, gender, marital status, education, ethnicity, employment status, and the presence of co-morbidities. Depressive symptoms were assessed using the CES-D scale (Radloff, 1977). A score of ≥16 is considered indicative of the need for clinical evaluation for major depression. State and trait anxiety were measured using the Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) (Spielberger, 1983). Functional status was assessed using the KPS scale (Karnofsky et al., 1948). Additional information on each of the measures is included in the Online Supplement.

Study procedures

The study was approved by the institutional review boards at each of the research sites. At the time of simulation (i.e., approximately one week prior to the initiation of RT), patients and FCs were invited to participate. A research nurse explained the study protocol, determined eligibility, and obtained written informed consent.

At the time of the simulation visit (enrollment), participants completed self-report questionnaires. Subsequently, participants completed the CES-D at 4 weeks after the initiation of RT, at the end of RT (approximately 6–9 weeks later), and at 4, 8, 12, and 16 weeks after the completion of RT (i.e., 7 assessments over 6 months). In addition, patients' medical records were reviewed for disease and treatment information.

Analysis of the phenotypic data

Additional details on the phenotypic analyses are provided in the Online Supplement. Data were analyzed using SPSS version 19 (SPSS, 2010) and Mplus version 6.11 (Muthen and Muthen, 1998–2010). Descriptive statistics and frequency distributions were generated for the sample characteristics and symptom data. Independent samples *t*-tests, analyses of variance, and chi-square