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Associations between cytokine gene variations and self-reported sleep disturbance in women following breast cancer surgery

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A B S T R A C T

Purpose of the research: To attempt to replicate the associations found in our previous study of patients and family caregivers between interleukin 6 (IL6) and nuclear factor kappa beta 2 (NFKB2) and sleep disturbance and to identify additional genetic associations in a larger sample of patients with breast cancer.

Methods and sample: Patients with breast cancer ($n = 398$) were recruited prior to surgery and followed for six months. Patients completed a self-report measure of sleep disturbance and provided a blood sample for genomic analyses. Growth mixture modeling was used to identify distinct latent classes of patients with higher and lower levels of sleep disturbance.

Key results: Patients who were younger and who had higher comorbidity and lower functional status were more likely to be in the high sustained sleep disturbance class. Variations in three cytokine genes (i.e., IL1 receptor 2 (IL1R2), IL13, NFKB2) predicted latent class membership.

Conclusions: Polymorphisms in cytokine genes may partially explain inter-individual variability in sleep disturbance. Determination of high risk phenotypes and associated molecular markers may allow for earlier identification of patients at higher risk for developing sleep disturbance and lead to the development of more targeted clinical interventions.

Introduction

Findings from several studies suggest that women with breast cancer experience a significant amount of sleep disturbance or insomnia (Davidson et al., 2002; Palesh et al., 2010; Savard et al., 2011, 2009). For example, in one large cross sectional study that evaluated the prevalence of sleep disturbance in patients with a variety of cancer diagnoses (Davidson et al., 2002), patients with breast cancer reported the highest rate of insomnia (37.8%). In another study of a heterogeneous sample of oncology patients receiving chemotherapy (CTX) (Palesh et al., 2010), breast cancer patients had the highest rates of insomnia (i.e., 84% reported insomnia symptoms). Of the patients who reported insomnia symptoms, 45% met the diagnostic criteria for insomnia.

Recent work from our research team used growth mixture modeling (GMM) to identify subgroups of patients with distinct self-reported sleep disturbance trajectories prior to and for six months following breast cancer surgery (Van Onselen et al., 2012). Three distinct latent classes of patients were identified (i.e., high sustained (55.0%), low sustained (39.7%), and decreasing (5.3%) levels of sleep disturbance). Women in the high sustained class were significantly younger and had more comorbidities and poorer functional status than women in the low sustained class. These findings suggest that GMM can be used to identify subgroups of patients with distinct sleep disturbance trajectories, as well as specific phenotypic characteristics associated with increased risk for higher levels of sleep disturbance.

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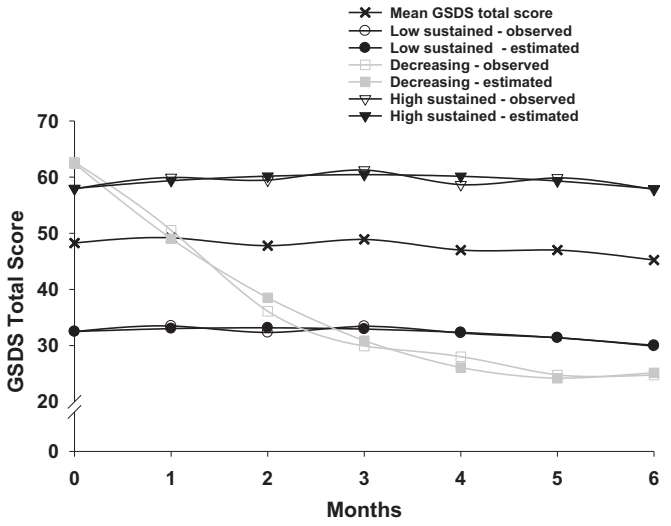

Fig. 1. Observed and estimated General Sleep Disturbance Scale (GSDS) trajectories for patients in each of the latent classes, as well as the mean GSDS scores for the total sample (Adapted from Van Onselen et al., 2012).

While an evaluation of differences in phenotypic characteristics is important to identify patients at highest risk for sleep disturbance before and during cancer treatment, an equally important consideration is whether genomic markers can distinguish among these patient subgroups. As noted by Cirelli (2009), specific candidate genes are associated with sleep regulation and sleep disorders like restless leg syndrome and narcolepsy. In addition, recent evidence suggests that cytokine dysregulation is associated with sleep disturbance in humans (for reviews see Cirelli (2009) and Sehgal and Mignot (2011)).

However, only a limited number of studies have evaluated the association between cytokine gene polymorphisms and sleep disturbance. For example, in one study that examined single nucleotide polymorphisms (SNPs) in interleukin 6 (IL6), IL1, and tumor necrosis factor alpha (TNFA) in patients newly diagnosed with obstructive sleep apnea syndrome (OSAS) (Popko et al., 2008), the only cytokine gene that was associated with OSAS was a polymorphism located in the promoter region of IL6 (rs1800795). In addition, this association was found only in male patients with OSAS compared to unaffected males. A higher percentage of men with OSAS (35.1%) were homozygous for the rare C allele compared to men in the control group (10.3%; $p = .004$). Recent work from our research team found associations between IL6 rs35610689 and nuclear factor kappa beta (NFKB2 rs7897947) and self-reported sleep disturbance in patients and family caregivers prior to and following radiation treatment. Carrying one or two doses of the rare allele for these two SNPs was associated with a decreased odds of belonging to the higher sleep disturbance class (Miaskowski et al., 2012b).

The purpose of the current study was to attempt to replicate the associations between IL6 and NFKB2 and sleep disturbance found in our previous study (Miaskowski et al., 2012b) and to identify additional associations in a larger sample of patients with breast cancer. To achieve this objective, we evaluated for differences in phenotypic and genotypic characteristics between breast cancer patients who were classified into the high sustained (58.1%) and low sustained (41.9%) GMM classes (Fig. 1). Patients in the decreasing class were not included in this analysis because the sample size ($n = 21$) was too small to allow for meaningful comparisons among the three latent classes (Miaskowski et al., 2012b).

Materials and methods

Patients and settings

This analysis is part of a larger, longitudinal study that evaluated neuropathic pain and lymphedema in women who underwent breast cancer surgery (McCann et al., 2012; Miaskowski et al., 2012a, 2013; Van Onselen et al., 2013). Patients were recruited from breast care centers located in a Comprehensive Cancer Center, two public hospitals, and four community practices.

Patients were eligible to participate if they: were adult women (≥18 years) who were scheduled to undergo breast cancer surgery on one breast; were able to read, write, and understand English; agreed to participate; and gave written informed consent. Patients were excluded if they were having breast cancer surgery on both breasts and/or had distant metastasis at the time of diagnosis. A total of 516 patients were approached, 410 were enrolled (response rate 79.5%), and 398 completed the baseline assessment. The most common reasons for refusal were: too busy, overwhelmed with the cancer diagnosis, or insufficient time available to do the baseline assessment prior to surgery.

Instruments

The demographic questionnaire obtained information on age, marital status, education, ethnicity, employment status, and living situation. The Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well-established validity and reliability (Karnofsky et al., 1948). Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).

The Self-administered Comorbidity Questionnaire (SCQ) is a short and easily understood instrument that was developed to measure comorbidity in clinical and health service research settings (Sangha et al., 2003). The questionnaire consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical knowledge. Patients were asked to indicate if they had the condition using a "yes/no" format. If they indicated that they had a condition, they were asked if they received treatment for it (yes/no; proxy for disease severity) and did it limit their activities (yes/no; indication of functional limitations). Patients were given the option to add two additional conditions not listed on the instrument. For each condition, a patient can receive a maximum of 3 points. Because the SCQ contains 13 defined medical conditions and 2 optional conditions, the maximum score totals 45 points if the open-ended items are used and 39 points if only the closed-ended items are used. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions (Brunner et al., 2008; Cieza et al., 2006).

The 21-item General Sleep Disturbance Scale (GSDS) was used to evaluate self-reported sleep disturbance during the past week. Each item is rated on a scale that ranges from 0 (never) to 7 (everyday). The total GSDS score can range from 0 (no disturbance) to 147 (extreme sleep disturbance). A total GSDS score of ≥43 indicates a clinically meaningful level of sleep disturbance (Fletcher et al., 2008; Lee, 1992). Cronbach's alpha for the GSDS total score was 0.86.

Study procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Boards at each of the study sites. During the patient's