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Research report

A one year longitudinal study of cytokine genes and depression in breast cancer

Jae-Min Kim [a,*], Robert Stewart [b], Seon-Young Kim [a], Hee-Ju Kang [a], Ji-Eun Jang [a], Sung-Wan Kim [a], Il-Seon Shin [a], Min-Ho Park [c], Jung-Han Yoon [c], Sung-Woo Park [d], Young-Hoon Kim [d], Jin-Sang Yoon [a]

[a] Department of Psychiatry, Chonnam National University Medical School, and Depression Clinical Research Center, Chonnam National University Hospital, Gwangju, Republic of Korea
[b] Institute of Psychiatry, King's College London, London, UK
[c] Breast and Endocrine Tumor Clinic, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea
[d] Department of Neuropsychiatry, School of Medicine, Haeundae Paik Hospital, and Paik Institute for Clinical Research & FIRST research group, Inje University, Busan, Republic of Korea

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ABSTRACT

Background: Since inflammatory cytokines have been implicated in the pathophysiology of both cancer and depression, genes that contribute to determining cytokine functional activity are reasonable candidate risk factors for depression related to cancer. This study aimed to investigate whether alleles related to higher pro-inflammatory and/or lower anti-inflammatory cytokine production would associate with depression in a cohort with breast cancer.

Methods: A total of 309 women with breast cancer were evaluated one week after surgery, and 244 (79%) were followed one year later. Depression (major+minor depressive disorders) was diagnosed according to DSM-IV criteria using the Mini International Neuropsychiatric Interview on both occasions. Six pro-(TNF-α-850C/T and -308G/A, IL-1β-511C/T and +3953C/T, IL-6-174G/C, IL-8-251T/A) and two anti-inflammatory (IL-4 +33T/C, IL-10-1082G/A) cytokine polymorphisms were assayed, and total numbers of potential risk alleles were calculated for pro- and anti-inflammatory cytokine genes. Adjustments were made for demographic and clinical characteristics.

Results: At baseline, 74 (24%) patients were classified with prevalent depression; and at follow-up, 19 (8%) and 25 (10%) patients were classified with persistent and incident depression, respectively. A higher number of pro-inflammatory cytokine risk alleles, and IL-1β-511*T*/*T* genotype individually, were independently associated with both prevalent depression at baseline and persistent depression at one year follow-up.

Limitations: Sample size was relatively small.

Conclusions: Our findings support the role of pro-inflammatory cytokines in the etiology of depression related to breast cancer, and provide novel evidence of a potential genetic basis for this.

1. Introduction

Breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cases diagnosed worldwide in 2008, constituting 23% of all cancers (Ferlay et al., 2010). With advances in detection and treatment, the number of women who survive breast cancer has increased significantly in recent years, and 5 year survival rates have climbed to 89% (Jemal et al., 2010). However, a considerable number of breast cancer survivors continue to suffer from psychological problems and unmet needs (Bower, 2008). Depression is particularly common (Massie, 2004) and substantially impairs quality of life (Shim et al., 2008), as well as being potentially associated with cancer progression or survival (Giese-Davis et al., 2011).

Both psychosocial and biological factors are important in the etiology of depression. Of these, the inflammatory hypothesis was proposed as a biological pathway for the etiology of depression, proposing that major depression is related to monocytic (M1) and cell mediated immune (T-helper 1 and T-helper 17 cells) activation (Maes et al., 1990, 1991; Maes, 1991). Cytokine production largely depends on the state of immune activation, and has an important role in the pathophysiology of depression (Maes, 1993, 1995). Cytokines have also been hypothesized as potential candidates responsible for at least some cases of depression in people with cancer (Reyes-Gibby et al., 2008). Increased circulating levels of cytokines are associated with cancer progression and/or treatment (Seruga et al., 2008). Cytokines can be classified by their producer cells, family, and functional

* Correspondence to: Department of Psychiatry, Chonnam National University Medical School, 160 Baekseoro, Dong-Ku, Gwangju 501-746, Republic of Korea. Tel.: +82 62 220 6143; fax: +82 62 225 2351.
E-mail address: jmkim@chonnam.ac.kr (J.-M. Kim).

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category, and have recently been subdivided according to M1, M2, T-helper 1, T-helper 2, *etc*. cytokines, as commonly used (Schiepers et al., 2005). However, we employed a functional division of cytokine genes into pro-inflammatory (facilitating inflammatory process) and anti-inflammatory (dampening immune response) categories. Circulating levels of both pro-inflammatory cytokines (e.g., tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6 and IL-8) and anti-inflammatory cytokines (e.g., IL-4 and IL-10) have been found to be altered in some cancer subtypes, including breast cancer, compared to healthy controls (Benoy et al., 2004; Meyers et al., 2005; Tsimberidou et al., 2008). In addition, there has been growing evidence for an etiological role of cytokines in depression, in that exogenous administration of cytokines with a pro-inflammatory response has been found to induce depressive behavior both in cancer patients (Friebe et al., 2010) and in animals (Kubera et al., 1995; Song and Leonard, 1994). Also, pro-inflammatory cytokine levels have been found to be increased in depression (Anisman et al., 1999; Maes et al., 1993), and some antidepressants have been suggested to have a cytokine-linked anti-inflammatory effect (Maes et al., 1999; Musselman et al., 2001a; Xia et al., 1996).

Based on these findings, it can be postulated that cancer-related changes in cytokine expression are important in the pathophysiology of depression in cancer. However, previous studies investigating this issue have had inconsistent findings. Some reported that levels of pro-inflammatory cytokines such as IL-6 or soluble IL-2 receptors were increased among depressed patients with cancer (Jacobson et al., 2008; Musselman et al., 2001b), while others found that pro-inflammatory cytokine levels were increased in patients with cancer who demonstrated positive moods (Blomberg et al., 2009; Sepah and Bower, 2009), and another studies found no significant associations between cytokine levels and depression (Steel et al., 2007). This discrepancy might be due to the pleiotropic actions of cytokines or confounding effects of the paraneoplastic immune reaction, cancer stage, and treatment modalities such as chemotherapy (Loftis et al., 2010).

It has been suggested that individual differences in cytokine production profiles have substantial genetic origin (de Craen et al., 2005), influenced by the transcriptional activity of cytokine gene polymorphisms [see online supplement for references]. Genetic liability is also likely to play a substantial role in determining vulnerability to depressive disorders (Sullivan et al., 2000). With respect to cytokine hypothesis, there are several studies that genetic polymorphisms in cytokine genes such as IL-1 were associated with major depression (Borkowska et al., 2011; Hwang et al., 2009; Yu et al., 2003). Thus, it could be hypothesized that cytokine genes, causing changes in cytokine production in relation to cancer progression or treatment, may confer risk for depression in cancer. However to our knowledge, this hypothesis has not been tested to date.

Cytokines have shown additive, synergistic or sometimes antagonistic actions on depression (Schiepers et al., 2005). Therefore, investigating one or a few selected polymorphisms at a time based on the knowledge of candidate gene function may give rise to conflicting results (NCI-NHGRI Working Group on Replication in Association Studies et al., 2007), and examining a broader set of cytokines may be preferential to understand the pathophysiology of depression in cancer. Polymorphisms in six cytokine network genes were investigated in the study presented here: those coding four pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8), and those for two anti-inflammatory cytokines (IL-4 and IL-10). This study aimed to investigate whether functional polymorphisms in these cytokine genes are associated with depression independently and/or interactively in a Korean sample of patients with breast cancer.

2. Methods

2.1. Participants

This analysis was carried out as a component of a larger parent study, which seeks to investigate mental disorders in breast cancer using a naturalistic prospective design. The detailed design has been published (Kim et al., 2012a). In brief, participants were consecutively recruited from all women with breast cancer undergoing surgery within the Breast and Endocrine Tumor Clinic of Chonnam National University Hwasun Hospital, Hwasun, South Korea. Assessments are made at one week and one year after the surgery to investigate both acute and chronic outcomes. The recruitment period for the initial baseline assessment was from March 2008 to May 2009 and for the follow-up evaluation was one year thereafter.

All women with breast cancer undergoing surgery at the study site were approached regarding participation. Inclusion criteria were: (i) confirmed breast cancer by histological examination; (ii) ability to complete the necessary investigations and questionnaires; and (iii) capacity to understand the objective of the study and provide informed consent. Exclusion criteria were: (i) secondary breast cancer; (ii) benign breast tumor; and (iii) male gender. This study was approved by the Chonnam National University Hwasun Hospital institutional review board. All participants gave written informed consent.

2.2. Depression ascertainment

Depression diagnoses were ascertained at one week and one year after surgery, using the Mini International Neuropsychiatric Interview (MINI), a structured diagnostic psychiatric interview for DSM-IV giving rise to major or minor depression categories as outputs (Sheehan et al., 1988). According to these criteria, patients were diagnosed as having major depression if they had at least one core symptom (i.e., depressed mood or loss of interest) and at least four other symptoms of depression. A diagnosis of minor depression (one of the diagnostic categories of 'depressive disorder not otherwise specified' in DSM-IV) was made if patients had at least one core symptom and at least two but less than five symptoms in total. Cases of major depression were too rare in this sample to analyze separately, and therefore were combined with minor depression into a single category. The MINI has been formally translated and standardized in Korean (Yoo et al., 2006).

2.3. Selection of polymorphism and genotyping

Blood samples for genotyping were obtained in a subsample who gave consent. The blood samples were stored in the Chonnam National University Hwasun Hospital National Biobank of Korea, a member of the National Biobank of Korea, which is supported by the Ministry of Health, Welfare and Family Affairs. Polymorphism selection and allele detection methods are conducted using standard procedures. Polymorphisms were selected based on evidence for functionality. DNA was extracted from venous blood using standard procedures. Polymerase chain reaction (PCR) and PCR-based restriction fragment length polymorphism assays were performed. The amplification conditions were pre-denaturation at 95 °C for 5 min, followed by 30 cycles consisting of denaturation at 95 °C for 35 s, 55 °C for 35 s and 72 °C for 35 s, and post-elongation at 72 °C for 5 min, with a final maintenance step at 4 °C. The polymorphisms investigated have all been characterized as promoter region regulatory variants based on allele specific differences in nuclear-factor binding activity and/or allele specific differences in transcriptional activity exhibited in functional assays. A more detailed account of relationships between