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Associations Between Cytokine Gene Variations and Severe Persistent Breast Pain in Women Following Breast Cancer Surgery

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Abstract: **Persistent pain following breast cancer surgery is a significant clinical problem. Although immune mechanisms may play a role in the development and maintenance of persistent pain, few studies have evaluated for associations between persistent breast pain following breast cancer surgery and variations in cytokine genes. In this study, associations between previously identified extreme persistent breast pain phenotypes (ie, no pain vs severe pain) and single nucleotide polymorphisms (SNPs) spanning 15 cytokine genes were evaluated. In unadjusted analyses, the frequency of 13 SNPs and 3 haplotypes in 7 genes differed significantly between the no pain and severe pain classes. After adjustment for preoperative breast pain and the severity of average postoperative pain, 1 SNP (ie, interleukin [IL] 1 receptor 2 rs11674595) and 1 haplotype (ie, IL10 haplotype A8) were associated with pain group membership. These findings suggest a role for cytokine gene polymorphisms in the development of persistent breast pain following breast cancer surgery.**

Perspective: ***This study evaluated for associations between cytokine gene variations and the severity of persistent breast pain in women following breast cancer surgery. Variations in 2 cytokine genes were associated with severe breast pain. The results suggest that cytokines play a role in the development of persistent postsurgical pain.***

Key words: *Cytokines, polymorphism, breast cancer surgery, candidate genes, persistent pain.*

Persistent pain in women following breast cancer surgery is common, with an estimated prevalence between 21 and 55%.[6,23,40,50,51,64,66,72,73] Persistent pain is associated with depressed mood,[66] sleep disturbance,[15,31] decreased quality of life,[6,50,64] and disability.[40,72] Persistent postsurgical pain may result

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C.M. and B.E.A. contributed equally to the study.

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from ongoing nociceptor activation and/or nerve injury.[43] During the early postoperative period, release of numerous inflammatory mediators produces peripheral sensitization in and around the surgical site.[74] These reversible changes in sensitivity to innocuous and noxious stimuli discourage stimulation of the surgical incision and facilitate healing. However, sustained activation of nociceptors may lead to the maintenance of central sensitization and phenotypic changes that alter the normal stimulus-response relationship and produce persistent pain. Evidence suggests that ongoing activation of inflammatory and glial cells[46] and spinal inhibitory mechanisms[77] plays a role in the establishment of persistent pain. In addition, peripheral nerve injury prompts the aggregation of immune cells, which increases the local concentration of proinflammatory cytokines.[44] These mediators participate in the initiation and maintenance of persistent pain by generating ectopic activity,[24] altering neuronal connectivity,[30] and reducing the number of inhibitory neurons.[26]

Although several studies have identified phenotypic characteristics that predispose patients to the development of persistent pain following breast cancer surgery,[2,20,34,39,71] less is known about the molecular mechanisms associated with this significant clinical problem. In fact, despite the strong evidence that persistent activation of immune mechanisms results in persistent pain,[44] only 4 studies evaluated for associations between polymorphisms in cytokine genes and cancer-related pain.[45,56-58,72] Three of these studies[56-58] assessed pain intensity prior to the initiation of cancer treatment. Associations were found between severe pain (ie, pain rated >6 on a 0 to 10 numeric rating scale [NRS]) and interleukin (IL) 1 beta (IL1B) rs1143627,[56] IL8 rs4073,[56,57] and tumor necrosis factor alpha (TNFA) rs1800629.[58] However, findings from these studies are difficult to interpret because the pain phenotype was characterized using only a dichotomized pain severity rating, it had modest sample sizes, and the number of polymorphisms evaluated was not optimal. Recent work from our group evaluated for associations between variations in cytokine genes and pain in the affected breast of women prior to breast cancer surgery.[45] Associations were found between the presence of preoperative pain and IL1 receptor 1 (IL1R1) rs2110726 and IL13 rs1295686. Of note, no studies were found that evaluated for associations between cytokine gene polymorphisms and persistent postsurgical pain.

In this same sample of women assessed for pain prior to breast cancer surgery,[45] growth mixture modeling (GMM) was used to identify subgroups of women with distinct persistent breast pain trajectories prior to and for 6 months following breast cancer surgery.[47] In brief, 3 distinct classes were identified using patients' ratings of worst pain in their breast (ie, mild, moderate, severe). A fourth pain class was identified of women who did not experience breast pain preoperatively or at any of the postoperative assessments. An evaluation of associations between extreme pain phenotypes may increase the effect size that can be detected in genetic association studies.[41] Therefore, using the extreme pain phenotypes identified in this GMM analysis, the purposes of this study were to evaluate for differences in demographic and clinical characteristics, as well as for variations in cytokine genes, between the no pain and severe pain classes.

Methods

Patients and Settings

This study is part of a larger, longitudinal study that evaluated for neuropathic pain and lymphedema in a sample of women who underwent breast cancer surgery.[45,47] Patients were recruited from breast care centers located in a Comprehensive Cancer Center, 2 public hospitals, and 4 community practices. Patients were eligible to participate if they were adult women (≥18 years) who would undergo breast cancer surgery on 1 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 to participate, and 410 were enrolled in the study (response rate 79.5%). The major reasons for refusal were too busy, overwhelmed with the cancer diagnosis, or insufficient time available to do baseline assessment prior to surgery.

Subjective Measures

The demographic questionnaire obtained information on age, education, ethnicity, marital status, employment status, living situation, and financial status. The Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well established validity and reliability.[36,37] 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). Patients were asked to indicate if they exercised on a regular basis (yes/no format).

The Self-Administered Comorbidity Questionnaire is a short and easily understood instrument that was developed to measure comorbidity in clinical and health service research settings.[62] 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 3 additional conditions not listed on the instrument. For each condition, a patient can receive a maximum of 3 points. Because there are 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 Self-Administered Comorbidity Questionnaire has well-established validity and