Fatigue is a common side effect of cancer treatment and may persist for months or years after treatment is completed (1–5). Approximately 30% of breast cancer survivors report persistent fatigue of unknown origin (6–9). Fatigue after cancer therapy is not consistently associated with treatment modality (4,6,8,10), and there is no evidence of residual or recurrent neoplastic disease in fatigued breast cancer survivors. Basic research on neuro-immune signaling has shown that inflammatory stimuli can signal the central nervous system to generate fatigue, as well as changes in sleep, appetite, social behavior, and reproduction (11). In a previous study of fatigued breast cancer survivors (12), we found elevated levels of several inflammatory markers in circulating blood, including interleukin 1 receptor antagonist (IL-1ra), soluble tumor necrosis factor receptor type II (sTNF-RII), and neopterin. We designed this study to identify the immunologic basis for these elevations. In particular, we evaluate the hypothesis that these soluble inflammatory markers and associated symptoms of fatigue stem from an underlying chronic cellular immune response involving the T-cell compartment.

We contacted 332 potential participants from a larger study of breast cancer survivors (13,14) and screened 132 responders for study eligibility. From this group, we identified 20 breast cancer survivors who reported enduring fatigue and a matched control group of 19 non-fatigued breast cancer survivors. Fatigue was assessed by use of the RAND SF-36 energy/fatigue scale (15,16). Survivors were considered eligible if they reported moderate-to-severe fatigue at the initial assessment (mean = 1.85 years after diagnosis, range = 1–5 years) and at the assessment for this study (mean = 5.25 years after diagnosis, range = 3–7 years; mean number of years between first and second assessment = 3.4 years, range = 2–5 years). Control group participants scored in the non-fatigued range at both assessment points. All participants had completed primary cancer treatments (surgery, radiation therapy, and/or chemotherapy) at least 2.5 years earlier, showed no evidence of recurrence, and had no history of an immunologic disease. Nine participants were still undergoing tamoxifen. Fatigued and non-fatigued breast cancer survivors did not differ by age, ethnicity, menopausal status, primary cancer treatment, and other medical comorbidities. Fatigued survivors, compared with non-fatigued survivors, had statistically significantly higher body mass indexes and lower incomes and reported higher levels of depressed mood. This sample of breast cancer survivors was the focus of a previous study (12) that includes more detailed information about recruitment and sample characteristics. In this communication, we report additional immune analyses conducted on blood samples collected from this cohort.

Fasting blood samples were drawn and subjected to a complete blood count and flow cytometric determination of circulating lymphocytes, including T lymphocytes (CD3+), B lymphocytes (CD19+), natural killer cells (CD3+/CD16+ or CD3+/CD56+), CD4+ T lymphocytes, CD8+ T lymphocytes, activated T lymphocytes (CD3+/HLA-DR+/CD38+), and effector T lymphocytes (CD3+/CD56+). Blood was not collected from three subjects (one fatigued and two control survivors) because of technical difficulties or subject refusal. The investigation was approved by the Institutional Review Board of the University of California, Los Angeles, and informed, written consent was obtained from all subjects. Immunologic parameters in fatigued breast cancer survivors were compared with those of non-fatigued control survivors by analysis of

Approximately 30% of women successfully treated for breast cancer suffer persistent fatigue of unknown origin. Recent studies linking inflammatory processes to central nervous system–mediated fatigue led us to examine cellular immune system status in 20 fatigued breast cancer survivors and 19 matched non-fatigued breast cancer survivors. Fatigued survivors, compared with non-fatigued survivors, had statistically significantly increased numbers of circulating T lymphocytes (mean 31% increase, 95% confidence interval [CI] = 6% to 56%; \( P = .015 \) by two-sided analysis of variance [ANOVA]), with pronounced elevation in the numbers of circulating lymphocytes, including T cells, natural killer cells, granulocytes, and monocytes were not altered. The increased numbers of circulating T cells correlated with elevations in the level of serum interleukin 1 receptor antagonist (for CD3+ cells, \( r = .56 \) and \( P = .001 \); for CD3+/CD4+ cells, \( r = .68 \) and \( P < .001 \), by Spearman rank correlation). Results of this study suggest that persistent fatigue in breast cancer survivors might be associated with a chronic inflammatory process involving the T-cell compartment. These results require confirmation in a larger study that is specifically designed to address this hypothesis. [J Natl Cancer Inst 2003;95:1165–8]
variance (ANOVA), and relationships among various immunologic parameters were determined by the Spearman rank correlation coefficient. Analyses of covariance (ANCOVA) were used to control for possible confounders in comparisons between fatigued survivors and controls. All statistical tests were two-sided.

Fatigued breast cancer survivors did not differ from non-fatigued survivors in total numbers of white blood cells, granulocytes, or monocytes (Fig. 1). Fatigued breast cancer survivors, compared with non-fatigued control survivors, had approximately 28% more lymphocytes per cubic millimeter of circulating blood (95% confidence interval [CI] = 7% to 49%; \(P = .011\)). Within the lymphocyte population, numerical expansion was confined to the T-cell subset. Fatigued breast cancer survivors, compared with non-fatigued survivors, had 31% more CD3+ T lymphocytes (95% CI = 6% to 56%; \(P = .015\)), 41% more CD4+ T lymphocytes (95% CI = 15% to 68%; \(P = .003\)), and 52% more CD3+/CD56+ lymphocytes (95% CI = 4% to 99%; \(P = .027\)), which are more likely to represent terminally differentiated cytotoxic effector cells (17). Fatigued breast cancer survivors also had 31% more CD8+ T lymphocytes, but this difference failed to reach statistical significance (95% CI = −9% to 80%; \(P = .124\)). The fractions of T lymphocytes expressing CD38 and HLA-DR involved in the association of IL-1ra were not altered in fatigued breast cancer survivors. Although the present results are consistent with a chronic viral infection, they could also be induced by a generalized alteration in homeostatic set points that control T-cell development, survival, proliferation, or maturation. The CD56+ T-cell subset, in particular, is known to be resistant to proliferative and apoptotic signals and to include an appreciable fraction of senescent CD57+ cells (20). These alterations may be related to changes in immune regulatory systems, including the autonomic nervous system and the hypothalamic–pituitary–adrenal axis. For example, fatigued survivors have lower levels of morning serum cortisol (12) and flatter diurnal cortisol slopes (Bower J, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL: unpublished data) than non-fatigued survivors, which could conceivably play a role in the inflammatory phenotype observed in fatigued breast cancer survivors. The processes that initiate and maintain immune alterations associated with fatigue are an important topic for future research.

![Fig. 1. Distribution of circulating leukocyte subsets in fatigued and non-fatigued (control) breast cancer survivors. Cells obtained from antecubital venipuncture were assessed by complete cell blood counts and flow cytometry for major lymphocyte subsets. Difference between persistently fatigued (open bars) and non-fatigued (solid bars) breast cancer survivors were analyzed by two-sample \(t\) test (after logarithmic transformation when necessary to normalize distributions). All statistical tests were two-sided. Gran. = granulocytes; Mono. = monocytes; Lymph. = lymphocytes; B = B cells; T = T cells; NK = natural killer cells. Error bars = 95% confidence intervals for the mean value of each parameter.](image-url)
It has long been known that some physiologic responses to infection such as fever originate in brain structures that receive input from circulating cytokines (25). In the past three decades, it has also become clear that inflammatory mediators can regulate more complex central nervous system and behavioral processes including affective, motivational, and cognitive variables (26–28). Results presented in this paper lead us to establish the hypothesis that subclinical immunologic alterations may underlie cancer-related fatigue syndromes. Priority should be given to larger studies that specifically address this hypothesis.

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NOTES

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