Inflammatory Biomarkers and Fatigue during Radiation Therapy for Breast and Prostate Cancer

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Abstract

Purpose: Biomarkers of radiation-induced behavioral symptoms, such as fatigue, have not been identified. Studies linking inflammatory processes to fatigue in cancer survivors led us to test the hypothesis that activation of the proinflammatory cytokine network is associated with fatigue symptoms during radiation therapy for breast and prostate cancer.

Experimental Design: Individuals with early-stage breast ($n = 28$) and prostate cancer ($n = 20$) completed questionnaires and provided blood samples for determination of serum levels of interleukin 1β (IL-1β) and IL-6 at assessments conducted before, during, and after a course of radiation therapy. Serum markers of proinflammatory cytokine activity, including IL-1 receptor antagonist and C-reactive protein, were examined in a subset of participants. Random coefficient models were used to evaluate the association between changes in cytokine levels and fatigue.

Results: As expected, there was a significant increase in fatigue during radiation treatment. Changes in serum levels of inflammatory markers C-reactive protein and IL-1 receptor antagonist were positively associated with increases in fatigue symptoms (Ps < 0.05), although serum levels of IL-1β and IL-6 were not associated with fatigue. These effects remained significant (Ps < 0.05) in analyses controlling for potential biobehavioral confounding factors, including age, body mass index, hormone therapy, depression, and sleep disturbance.

Conclusions: Results suggest that activation of the proinflammatory cytokine network and associated increases in downstream biomarkers of proinflammatory cytokine activity are associated with fatigue during radiation therapy for breast and prostate cancer. (Clin Cancer Res 2009;15(17):5534–40)

There is considerable interest in the identification of clinical biomarkers associated with radiation therapy and their role in clinical outcomes (1). Exposure to radiation initiates a programmed molecular and cellular response to promote tissue repair, which includes induction of nuclear factor κB activity and up-regulation of proinflammatory cytokines (2–4). Clinical reports have shown elevations in circulating levels of proinflammatory cytokines during radiation therapy; in some cases, these are associated with treatment-related toxicities such as radiation pneumonitis in lung cancer (5) and acute proctitis in prostate cancer (6). However, the role of proinflammatory cytokines in behavioral toxicities associated with radiation therapy has not been determined.

Fatigue is increasingly recognized as one of the most common and disabling side effects of radiation and other cancer treatments (7). However, the etiology of cancer-related fatigue is poorly understood. Although biological [e.g., hemoglobin, albumin (8, 9) and psychological (e.g., depression (10)] correlates of fatigue have been identified, these factors are not consistently associated with fatigue and do not fully explain the occurrence of fatigue in cancer populations. Basic research on neuroimmune interactions has shown that proinflammatory cytokines can signal the central nervous system to generate fatigue and other behavioral changes (11). In cross-sectional studies conducted with breast cancer survivors, we have shown that persistent posttreatment fatigue is associated with elevations in markers of proinflammatory cytokine activity and alterations in the cellular immune system, suggesting a chronic inflammatory process (12–14). Of note, most women in these studies received radiation therapy, often combined

Translational Relevance

Behavioral symptoms are increasingly recognized as a common and disabling side effect of cancer treatment. Understanding the etiology of these symptoms and developing targeted therapies is critical for improving treatment adherence and overall quality of life. This work provides insight into the biological mechanisms underlying radiation-induced fatigue and suggests potential avenues for treatment, including use of cytokine antagonists.

with chemotherapy or endocrine therapy. Similar findings have been observed by other investigators (15, 16). These studies provide preliminary evidence for a role of proinflammatory cytokines in cancer-related fatigue, but the role of cancer treatment in initiating these dynamics remains unclear.

To determine whether radiation-induced inflammation might contribute to cancer-related fatigue, this study tested the hypothesis that elevations in circulating levels of proinflammatory cytokines would be associated with fatigue symptoms during radiation treatment for breast and prostate cancer. A handful of previous reports on this topic have yielded mixed results (17–20), possibly because of constraints of the respective study designs (e.g., small sample sizes, use of nonstandard measures to detect cytokine levels) and the focus on cross-sectional associations between cytokine levels and fatigue, which may not adequately capture the dynamic changes that occur in these systems over the course of treatment. In the current study, random coefficient models were used to examine within-subject relationships between inflammatory markers and fatigue assessed at multiple times before, during, and after treatment. We focused on changes in two proinflammatory cytokines, interleukin 1β (IL-1β) and IL-6, which have been identified as key mediators of neuroimmune interactions. In addition, we examined changes in IL-1 receptor antagonist and C-reactive protein (CRP) in a subset of study participants as a secondary study aim. These markers were of interest because they provide a measure of the cumulative activity of IL-1β and IL-6, respectively, and have been correlated with posttreatment fatigue in our research with cancer survivors (12).

Materials and Methods

Participants. Patients with breast or prostate cancer who were scheduled to receive external beam radiation therapy were recruited from the University of California at Los Angeles Radiation Oncology Clinic. Patients were eligible for study participation if they met the following criteria: (*a*) age of 25 to 75 y, (*b*) newly diagnosed with localized breast cancer (stage 0, I, or II) or prostate cancer (T_1-T_3, N_0, M_0), (*c*) external beam radiation therapy as part of the primary treatment plan, (*d*) completion of definitive primary surgery (for breast cancer patients), and (*e*) ability to read and write English. Exclusion criteria included (*a*) recurrent cancer, (*b*) previous or planned treatment with chemotherapy, and (*c*) regular use of immunosuppressive medication or tobacco.

Of the 107 patients screened for study eligibility, 41 were not eligible because of medical conditions (e.g., previous cancer treatment) or use of tobacco. Fifteen patients were eligible but refused participation because of concerns about blood draws, time demands, or general lack of interest, and three withdrew within 2 wk after treatment onset. Thus, the final sample for these analyses included 48 patients (*n* = 28 breast cancer patients, *n* = 20 prostate cancer patients). The University of California at Los Angeles Institutional Review Board approved the study procedures, and written informed consent was obtained from all participants.

Procedures. Potential participants were screened for eligibility during initial consultations at the University of California at Los Angeles Radiation Oncology Clinic. After determination of eligibility, subjects completed a baseline assessment before treatment onset. Patients with localized breast and prostate cancer typically receive radiation therapy 5 d per week, Monday through Friday, for a 6- to 8-wk course of treatment. Study assessments were conducted at specific points in the treatment trajectory: after 5 d of treatment, after 10 d of treatment, after 20 d of treatment, during the final week of treatment, and at two regularly scheduled follow-up visits targeted at 2 wk and 2 mo after treatment completion. This intensive assessment schedule was designed to capture the initial increase and peak in fatigue symptoms that have been observed in previous research (21–24), as well as the initial inflammatory response to treatment and the more persistent effects of daily radiation therapy on inflammatory markers.

Assessments were scheduled to coincide with treatment appointments and thus did not occur at the same time of day for all participants; however, appointments for individual participants typically did occur at the same time of day. At each assessment, subjects completed self-report questionnaires and provided blood samples for immune analysis. Assessments were not conducted on weeks when participants reported an active illness or infection.

Measures. Fatigue was assessed using the Fatigue Symptom Inventory, a 14-item measure that assesses fatigue frequency, severity, and interference with daily functioning during the past week (25). The Fatigue Symptom Inventory was specifically designed to assess fatigue in cancer populations, has acceptable psychometric properties, and is responsive to cancer treatments, including radiation therapy (21). We focused on two dimensions of fatigue: severity and duration. Fatigue severity is measured by the item "Rate your level of fatigue on the day you felt most fatigued in the last week," scored on a 11-point scale ranging from "not at all fatigued" to "as fatigued as I could be." Fatigue duration is measured by the item "Indicate how many days in the last week you felt fatigued for any part of the day," scored on an eight-point scale ranging from 0 to 7 d. Higher scores on both dimensions indicate greater fatigue.

Two other cancer-related behavioral comorbidities were assessed that may confound associations between inflammatory markers and fatigue. Sleep problems were assessed using the Medical Outcomes Study Sleep Scale, a 12-item measure that assesses important dimensions of sleep, including sleep initiation, maintenance, and quantity; perceived adequacy of sleep; respiratory problems; and somnolence (26). This scale has been validated in the general U.S. population and among chronically ill individuals (26), and has also been used in our previous research with cancer patients (27). Depressed mood was assessed using the Center for Epidemiologic Studies–Depression scale, a 20-item measure with excellent reliability and validity designed to assess depressive symptomatology in the general population (28). Demographic and medical variables were assessed by self-report questionnaire and validated by review of medical records.

Inflammatory markers. Serum samples were separated according to standard procedures and stored at -70°C for subsequent batch testing. Serum levels of IL-1β and IL-6 cytokines were measured using Quantikine High Sensitivity Immunoassay kits (R&D Systems). Serum levels of IL-1 receptor antagonist and CRP were measured in a subset of study participants (*n* = 12 breast cancer patients, *n* = 10 prostate cancer patients) with Quantikine Immunoassay kits for IL-1 receptor antagonist (R&D Systems) and high sensitivity Immunodiagnostik kits for CRP (ALPCO Diagnostics). These assays were conducted as part of an initial validation study designed to identify inflammatory responses to treatment. The measurement of cytokine levels was done according to the

Table 1. Demographic characteristics of study participants

Characteristic	Breast cancer (*n* = 28)	Prostate cancer (*n* = 20)
Mean age, y (range)	57.1 (29-75)	70.6 (54-79)
Ethnicity		
White	20	12
Hispanic	1	2
African American	2	4
Asian	3	2
Other	2	0
Married/committed relationship		
Yes	16	16
No	12	4
Education status		
High school graduate	9	8
College graduate	11	7
Graduate degree	8	5
Employment status		
Employed full or part time	15	8
Homemaker or student	4	0
Retired	7	11
Unemployed or medical leave	2	1
Yearly income*		
≤$45,000	4	4
$45,000-$100,000	8	8
≥$100,000	14	7
Mean radiation dose, Gy (range)	5796 (5040-6640)	7165 (4500-7560)

*Numbers based on available data.

manufacturer's instructions. Quality control procedures for our laboratory were conducted in the manner reported by Aziz et al. (29, 30). The intra-assay precision of all tests was ≤15% for in-house quality control samples. All samples for a given participant were run in parallel to minimize interassay variability.

The lower limit of assay detection in our laboratory is 0.02 pg/mL for IL-1β, 0.025 pg/mL for IL-6, 0.20 mg/L for CRP, and 14 pg/mL for IL-1 receptor antagonist. Of the 319 samples collected for IL-1β and IL-6, 25 (13%) were undetectable for IL-1β and assigned a score of 0. None of the samples were below the lower limit of detection for IL-6. Of the 143 samples collected for IL-1 receptor antagonist and CRP, none were below the lower limit of detection.

Statistical analyses. Analyses were conducted using random coefficient models (Hierarchical Linear Modeling 6.04; ref. 31) to account for correlated measures on individuals over time. To evaluate changes over time in fatigue and inflammatory markers, we first fit models testing linear (days since treatment start) and quadratic (days since treatment start squared) trends. Next, we fit models to test the hypothesis that increases in proinflammatory cytokines and markers of inflammatory cytokine activity would be associated with increases in fatigue during treatment. The study was conceived as a two-level nested design, with time (level 1) nested within subjects (level 2). Fatigue and inflammatory markers were measured at level 1. Demographic and biobehavioral variables that may impact inflammation and fatigue were examined as potential confounding factors. These included depressive symptoms and sleep disturbance (measured at level 1), as well as age, body mass index, and use of hormone therapy (measured at level 2). Breast and prostate cancer patients were combined in analyses, with preliminary analyses incorporating a moderating effect of gender (level 2) that was omitted from final models because of lack of significance. Predictor variables were grand-mean centered, which enabled us to determine how deviations from the average score on a particular predictor variable were associated with changes in the outcome variable. Because their distributions were clearly nonnormal and highly skewed, all inflammatory marker measures were transformed before analyses using a log transformation. All tests of statistical significance were two sided.

Complete data for the primary study variables (i.e., fatigue, IL-1β, IL6) were available for all 48 participants at baseline and week 1, for 46 participants at weeks 2 and 4, for 45 participants at week 3 and 2 weeks post-tx, and for 41 participants at 2 months post-tx. Missing values were primarily due to problems with blood draws, participant illness, or scheduling difficulties (e.g., subject changed appointment time without notifying research assistant). In addition, three of the prostate cancer patients began brachytherapy after their first posttreatment
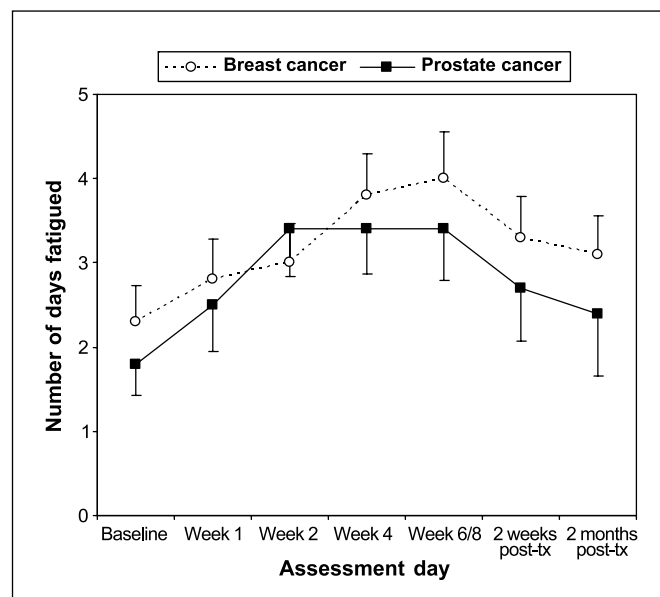

Fig. 1. Fatigue symptoms during radiation therapy. There was a significant increase in number of days fatigued in breast and prostate cancer patients during treatment, followed by a decrease in fatigue after treatment completion.

follow-up appointment and were withdrawn from the study before the second follow-up.

Results

Demographic characteristics of study participants are reported in Table 1. Twenty-six women in the current sample had undergone lumpectomy before study enrollment, and two women had undergone mastectomy with immediate reconstruction. Nine of the prostate cancer patients were treated with hormone therapy, and one breast cancer patient was treated with tamoxifen during radiation therapy.

Changes in fatigue and proinflammatory cytokines during treatment. Random coefficient models were used to evaluate changes in fatigue and serum inflammatory markers over the course of radiation treatment. There was a significant linear (β = 0.24; SE = 0.07; P = 0.001) and quadratic (β = -0.013; SE = 0.004; P = 0.001) trend for fatigue duration and a significant quadratic trend for fatigue severity (β = -0.008; SE = 0.003; P = 0.024). Figure 1 plots the number of days fatigued in breast and prostate cancer patients, both of which exhibit an inverted-U shape consistent with the negative quadratic coefficient. These results indicate an increase in fatigue over the course of treatment, followed by a decline in the posttreatment period, consistent with previous research (22, 23).

For the inflammatory markers, there was a significant quadratic trend for IL-1β (β = -0.002; SE = 0.001; P = 0.034), significant linear (β = 0.11; SE = 0.04; P = 0.007) and quadratic (β = -0.006; SE = 0.002; P = 0.003) trends for IL-6, and a marginally significant quadratic trend for CRP (β = -0.004; SE = 0.002; P = 0.079); see Fig. 2 for box plots of cytokine responses to treatment on the untransformed scales of the original measurements. These results indicate an increase in IL-6 levels during treatment, with a decline by 2 months posttreatment, and a plateau in levels of IL-1β and CRP, followed by a general decrease over time. There were no significant time trends for IL-1 receptor antagonist. Unlike the relatively stable plasma biomarkers of cumulative cytokine activity (IL-1 receptor antagonist and CRP), instantaneous levels of IL-1β and IL-6 showed substantial intraindividual fluctuation.

Although this was a relatively homogenous patient population, there was variability in the total dose of radiation received
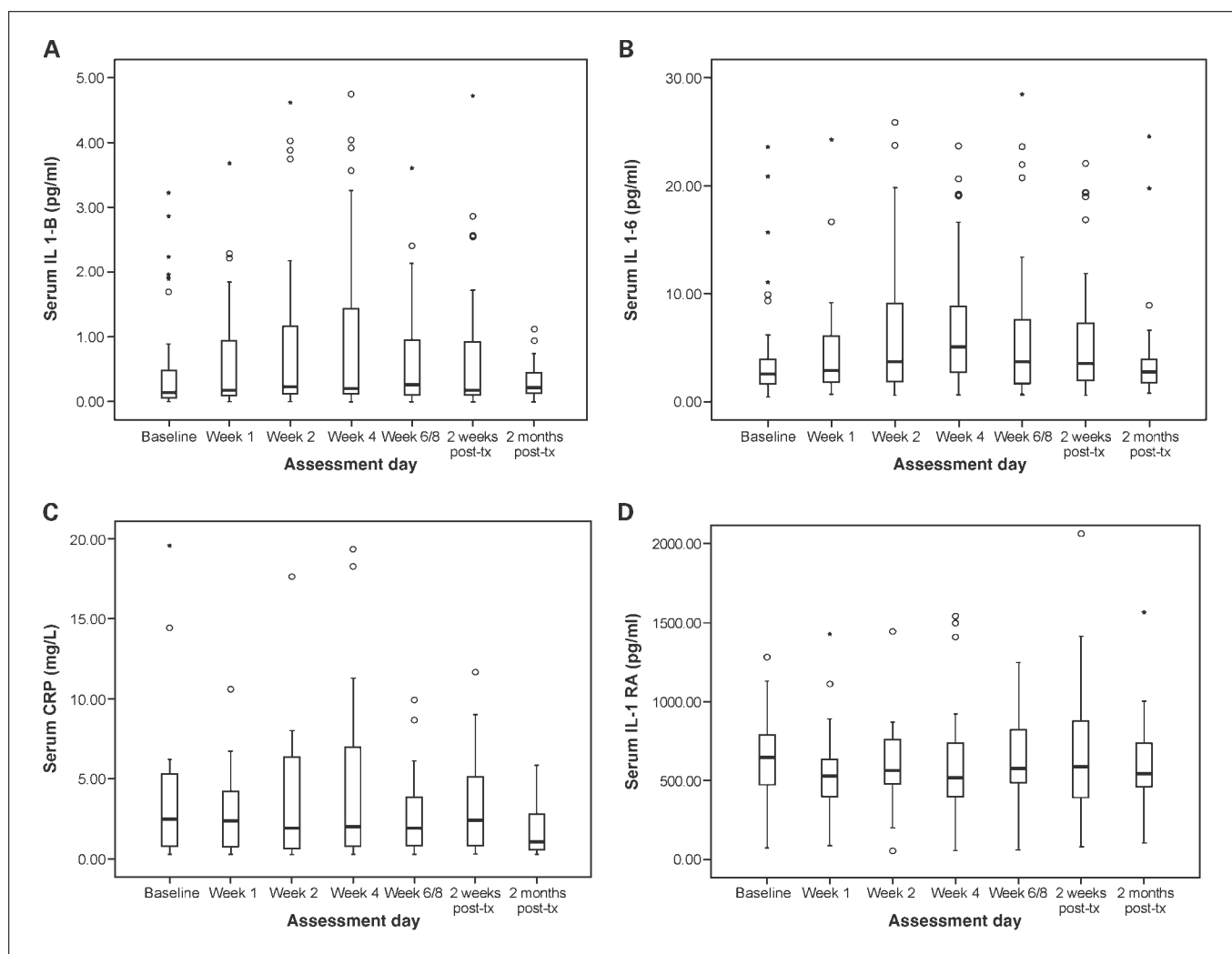

Fig. 2. Circulating inflammatory markers during radiation therapy. Box-and-whisker plots represent data with boxes ranging from the 25th to the 75th percentile of the observed distribution of values. Horizontal lines, the median value for serum levels of IL-1B (*A*), IL-6 (*B*), CRP (*C*), and IL-1 receptor antagonist (*D*). Whiskers span minimum to maximum observed values, with algorithm-defined outliers identified by open circles and stars.
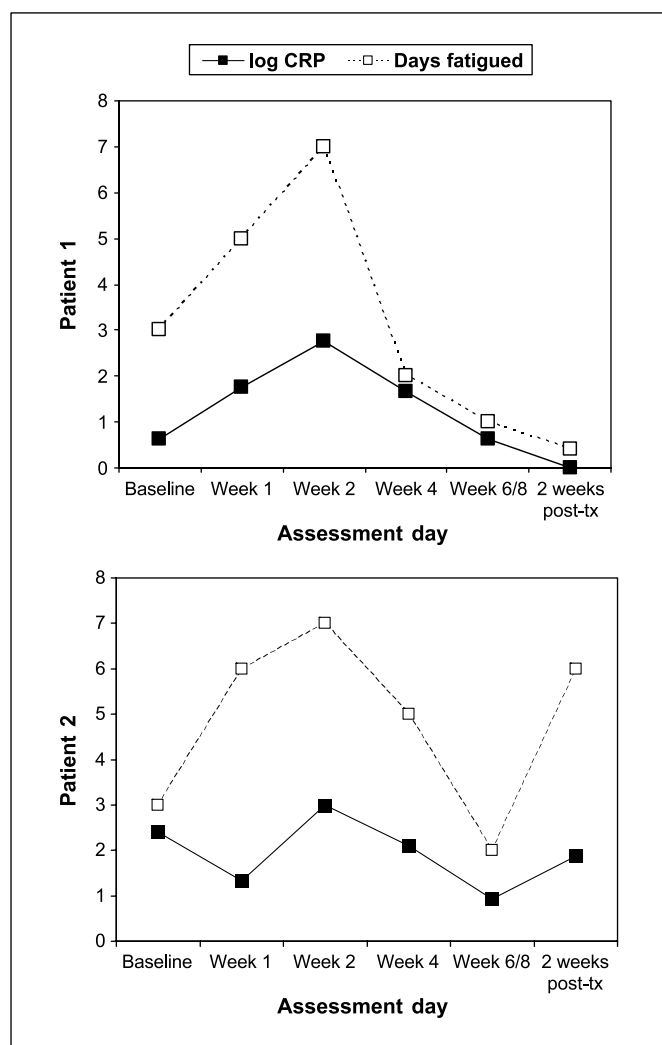
Fig. 3. Association between CRP and fatigue symptoms. Representative data from two participants showing that, on weeks when serum levels of CRP were elevated, there was a corresponding elevation in the number of days fatigued.

(see Table 1). A higher dose of radiation was associated with significantly higher levels of IL-6 and CRP over the assessment period ($Ps < 0.05$), consistent with a causal effect of radiation exposure on production of IL-6 and associated markers. Treatment dose was not associated with levels of IL-1β or IL-1 receptor antagonist.

Association between fatigue and proinflammatory cytokines. Random coefficient models were used to examine the association between proinflammatory cytokines and fatigue. There was no evidence that changes in serum levels of IL-1β or IL-6 were associated with changes in fatigue severity or duration over the assessment period (all $Ps > 0.30$).

Association between fatigue and markers of proinflammatory cytokine activity. As a secondary study aim, we examined the association between serum markers of cytokine activity and fatigue in a subset of study participants. Increases in circulating levels of the stable IL-6 biomarker CRP were significantly associated with increases in fatigue duration ($\beta = 0.32$; SE = 0.14; $P = 0.022$). Participants reported experiencing more days of fa-

tigue on weeks when CRP was elevated. This association is illustrated in Fig. 3, which shows fatigue and CRP data from two representative study participants. The association between CRP and number of days fatigued remained significant in analyses controlling for sleep disturbance and depressive symptoms, although each of these variables was independently associated with fatigue (for Center for Epidemiologic Studies–Depression, $P < 0.0001$; for Medical Outcomes Study sleep, $P = 0.093$). In addition, this association remained significant in analyses controlling for age, body mass index, and hormone therapy.

Increases in circulating levels of the IL-1β exposure biomarker IL-1 receptor antagonist were associated with increases in fatigue severity ($\beta = 0.63$; SE = 0.26; $P = 0.016$.). Participants reported experiencing more severe fatigue on weeks when IL-1 receptor antagonist was elevated. This association remained significant after controlling for sleep and depressive symptoms, both of which were associated with fatigue (for Center for Epidemiologic Studies–Depression, $P = 0.001$; for Medical Outcomes Study sleep, $P < 0.0001$), and after controlling for age, body mass index, and hormone therapy. Of note, neither IL-1 receptor antagonist nor CRP was independently associated with depressive symptoms, although increases in circulating levels of IL-1 receptor antagonist were associated with greater sleep disturbance.

Discussion

This study was designed to identify mechanisms of fatigue in cancer patients undergoing radiation therapy, focusing on inflammatory processes. Although there was no evidence for an association between fatigue and the proinflammatory cytokines IL-1β and IL-6, results did support an association between fatigue and downstream biomarkers of cytokine activity. In particular, increases in circulating levels of the IL-6 cumulative exposure biomarker CRP and the IL-1β cumulative exposure biomarker IL-1 receptor antagonist were associated with increased frequency and severity of fatigue symptoms. These effects could not be accounted for by other variables, including age, body mass index, depressed mood, or sleep disturbance.

As noted above, circulating levels of IL-1β and IL-6 were not associated with fatigue in this sample. Proinflammatory cytokines are typically produced locally and in small quantities, and can be difficult to detect in serum. In contrast, CRP and IL-1 receptor antagonist are produced in larger quantities as acute phase proteins by the liver and can often be quantified more reliably than the cytokines that induce their production; they may also provide a more accurate reflection of cytokine activity (32). Thus, downstream markers such as CRP and IL-1 receptor antagonist may be more reliable and sensitive indicators of systemic inflammation, facilitating the detection of relationships with behavioral states. Indeed, our research with breast cancer survivors has shown elevations in stable plasma markers of cumulative cytokine activity (e.g., IL-1 receptor antagonist) among patients with posttreatment fatigue but no differences in noisier instantaneous plasma cytokine levels (e.g., IL-1β and IL-6; refs. 12, 13). Of note, inflammatory biomarkers were assessed in a subset of participants in the current study; thus, our significant results should be viewed as having been derived from secondary data analysis and as such would benefit from confirmation in other settings.

Previous studies investigating the association between proinflammatory cytokines and fatigue in cancer patients during radiation therapy have yielded mixed results (17–20). Our trial differs from earlier research because we included more frequent assessments, used random coefficient models to examine within-subject associations between cytokines and fatigue, and assayed markers of inflammatory activity in addition to proinflammatory cytokines. This more intensive approach to intraindividual measurement and analysis may provide greater resolution of relationships between inflammation and fatigue. Future research may benefit from inclusion of systemic markers of inflammatory activity and use of statistical methods that account for correlated measures on individuals over time. In addition, if the goal is to capture the dynamic response of the immune system to radiation, it may be necessary to conduct even more frequent blood draws (e.g., daily blood sampling).

The pattern of results observed in this study suggests that inflammatory processes play a role in radiation-induced fatigue, although the observational nature of the study design precludes conclusions about the causal nature of this association. Induction of proinflammatory cytokines in the periphery is known to induce production and release of cytokines in the central nervous system (33), which have a host of effects on brain function. Persistent exposure to cytokines can produce changes in neural activity (34, 35), similar to effects seen with glucocorticoids (36); if these neural changes persist, they might account for the chronic posttreatment fatigue observed in a subgroup of cancer survivors (27). Host factors may also play an important role in determining the extent and duration of inflammatory processes in cancer patients and associated symptoms of fatigue; for example, we have shown an association between cytokine gene polymorphisms and persistent fatigue in breast cancer survivors (37), and between neuroendocrine function and fatigue in this population (38–40). Identifying risk factors for cytokine-induced fatigue and determining the neural substrates of this symptom are important topics for future research. In addition, insight into the mechanisms responsible for inducing fatigue would benefit from further research wherein exposures affecting inflammatory processes are under experimental control.

The identification of inflammatory processes as potential mediators of radiation-induced fatigue has important treatment implications for cancer patients. Initial trials with cytokine antagonists have shown beneficial effects on fatigue (41), including trials conducted with cancer patients designed to improve the tolerability of chemotherapy (41, 42). Although these agents have not yet been investigated in patients undergoing radiation therapy, they may be indicated if fatigue is of sufficient severity to merit discontinuation of treatment, leads to significant decrements in quality of life, and/or persists for months or years after treatment completion.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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