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Inflammation And Cancer-Related Fatigue In Breast Cancer Survivors

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ABSTRACT

Purpose: Cancer-related fatigue negatively impacts quality of life and possible recurrence and overall mortality in breast cancer survivors. This study aimed to investigate the associations between inflammation and cancer-related fatigue in breast cancer survivors using methods of systematic review and quantitative assessment of the Hormones and Physical Exercise (HOPE) Study in a high-risk population. **Methods:** A PubMed search was conducted to identify peer-reviewed studies that assessed the associations among inflammatory markers, CRP, IL-6, and TNF-α, and cancer-related fatigue in breast cancer survivors. The HOPE Study was a randomized control trial in 121 postmenopausal Stage I-IIIC breast cancer survivors, who were taking Aromatase Inhibitors (AIs) and experiencing arthralgia. This study investigated the associations of baseline (N = 69) pro-inflammatory markers CRP, IL-6, and TNF-α and self-reported fatigue. **Results:** Fifteen studies with more than 1,900 participants were included in the systematic review. The literature inconclusively supported the CRP and cancer-related fatigue association. TNF-α and IL-6 were not associated with cancer-related fatigue. In the HOPE Study, CRP, IL-6, and TNF-α, fatigue, and sleep duration were not significantly associated. There was the suggestion of a positive trending association between CRP and cancer-related fatigue among women with higher stage of disease. BMI status and joint pain intensity were significant risk factors of cancer-related fatigue. **Conclusion:** A growing body of literature inconclusively supports the link between downstream inflammatory activity and cancer-related fatigue. There may be subgroups of women, e.g. those with higher stage of disease, for whom this may be particularly important. A further understanding of cancer-related fatigue mechanisms and the development of effective interventions are necessary to improve the quality and duration of life in the increasing population of cancer survivors.

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INTRODUCTION

Cancer-related fatigue is the most common and distressing symptom reported by women diagnosed with breast cancer,[1-3] even more distressing than cancer-related pain, nausea, or vomiting.[4] Prevalence estimates of cancer-related fatigue range from 25% to 99%, depending on the sample, treatment type, and assessment methodology,[5] with more than 60% of cancer survivors reporting moderate to severe fatigue.[6] While fatigue often improves within a year following treatment, cancer-related fatigue may continue months and years after successful completion of treatment. One third of those in remission experience cancer-related fatigue for up to 10 years post-cancer diagnosis, and 40% to 50% report sleep disturbance.[7] Insomnia is a strong predictor of cancer-related fatigue, and over 50% of cancer patients experience sleep disturbance (difficulty falling asleep and maintaining sleep, awakening too early from sleep, and daytime sleepiness), as confirmed by polysomnographic data.[8] However, cancer-related fatigue is more chronic and debilitating than non-cancer-related fatigue and is not relieved with adequate sleep.[9]

Not only does cancer-related fatigue negatively impact mental and physical wellbeing and overall quality of life,[1] but cancer-related fatigue may also be associated with recurrence ($p = 0.0004$) and overall mortality ($p = 0.0101$) in newly diagnosed breast cancer patients ($N = 1,588$) followed for a median of 12.9 years.[10] While this finding has not been repeated in the literature [possibly due to methodology, smaller sample sizes ($N = 398$ and $N = 448$, respectively), and shorter median follow-up (5.8 and 5.5 years, respectively)],[11,12] identifying the mechanisms behind cancer-related fatigue will significantly advance the development of targeted interventions and improve the lives of cancer survivors.

Cancer-related fatigue has a complex etiology.[13] While white blood cell count and hemoglobin do not fully explain cancer-related fatigue, recent studies support the role of inflammatory mediators in cancer-related fatigue, as these mediators are often elevated in cancer patients and are known to induce fatigue.[1] The innate immune response has been shown in animal and human studies to induce "sickness behavior," which includes depression, fatigue, impaired sleep, and cognitive dysfunction.[8] This may be the result of cytokine-induced inflammatory responses within the brain that are associated with metabolic alteration and synaptic availability of relevant neurotransmitters, including serotonin, norepinephrine, and dopamine.[8] Additional mechanisms involved in the link between inflammation and cancer-related fatigue may include: 1) genetic polymorphisms (single-nucleotide polymorphisms in cytokine genes, e.g. polymorphisms in TNF-α and IL-6 were associated with cancer-related fatigue in breast, prostate, and lung cancer patients),[14-17] 2) alterations in the hypothalamic-pituitary-adrenal axis and alterations in immune factors (e.g. cellular immune system and latent herpes viruses), and 3) biobehavioral factors (e.g. history of depression, sleep disturbance, early life stress, and body mass index).[1]

The purpose of this study was to examine the associations between inflammation and cancer-related fatigue using 1) methods of systematic review [to update the Saligan et al (2012) review[18] and focus on breast cancer survivors] and 2) quantitative, observational data analysis in a high risk population: breast cancer survivors taking AIs and experiencing arthralgia. AIs cause arthralgias and myalgias of elusive etiology suggestive of inflammatory association.[19] AIs have been shown to improve disease-free survival in postmenopausal women diagnosed with hormone-receptor positive disease, by significantly lowering estrogen levels. AIs are now the current standard of care for treating hormone receptor-positive breast cancer.[20] The most

common side effect of AIs, arthralgia or joint pain, may cause increased inflammation, cancer-related fatigue, and poor sleep habits. To our knowledge, no study has examined the relationship between inflammation and cancer-related fatigue in breast cancer survivors taking AIs.

We conducted the National Cancer Institute funded "Hormones and Physical Exercise (HOPE) Study," a randomized control trial examining the effect of 12 months of moderate-intensity aerobic and resistance training exercise vs. usual care on improving side effects of aromatase inhibitors, including arthralgia severity, endocrine-related quality of life, and bone mass, in women taking AIs and reporting arthralgia. Baseline data on inflammation, cancer-related fatigue, and sleep were obtained from all women enrolled. The purpose of this analysis was to examine the baseline cross-sectional associations among the inflammatory markers, C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), and cancer-related fatigue in breast cancer survivors taking AIs and enrolled in the HOPE Study. As this population may have an increased risk for inflammation, assessing the association between inflammatory levels and fatigue and sleep could be critical to treatment adherence and the development of targeted interventions.

METHODS

Systematic Review

PubMed was utilized to identify relevant studies. MeSH headings "c-reactive protein AND fatigue AND breast cancer," "interleukin AND fatigue AND breast cancer" and "tumor necrosis factor AND fatigue AND breast cancer" were utilized to identify studies. Inclusion criteria included the following: English-language and quantitative assessment of the associations

between inflammatory markers CRP, IL-6, and/or TNF-α and cancer-related fatigue in breast cancer survivors.

HOPE Study

Participants

The study enrolled 121 postmenopausal AJCC Stages I-IIIC hormone receptor positive breast cancer survivors under the age of 76 years who had been taking an AI for at least six months and were currently experiencing at least mild arthralgia associated with AI use (defined as ≥ 3 on the Brief Pain Inventory Short Form Questionnaire).[21] Eligible participants were physically inactive (< 90 mins/week of moderate-to-vigorous intensity aerobic exercise and no strength training within the past year), were able to exercise, agreed to random assignment, provided informed consent to participate in all study activities, were mentally competent, and were able to come for baseline, 6-, and 12-month clinic visits and twice-weekly strength training sessions. The exclusion criteria included a history of other malignancies (other than non-melanoma skin cancer or in situ cervical cancer) or recurrence of breast cancer.

Recruitment

Women diagnosed with hormone receptor positive breast cancer at one of four Connecticut (CT) hospitals: 1) Smilow Cancer Hospital at Yale-New Haven, 2) Hospital of St. Raphael, 3) Bridgeport Hospital, and 4) Greenwich Hospital, were recruited through the Rapid Case Ascertainment (RCA) Shared Resource of the Yale Cancer Center, a field arm of the CT Tumor Registry. The RCA provided a list of potential participants and their physicians. Upon receipt of physician approval, invitation letters, detailing the study and informing the potential participant

of a phone call from the Principal Investigator to solicit interest and eligibility within a week, were mailed to potential participants. Eligibility was assessed via phone, and eligible participants received a baseline clinic visit. A total of 1,020 screening telephone calls were completed between April 1, 2010, and December 23, 2012, and 121 participants were enrolled in the study (Figure 1).

Measures

This study utilized HOPE baseline data, where participants completed questionnaires and were subject to physical measurements and a fasting (> 12 hours) blood draw. Three sets of measures were used in this secondary analysis: inflammatory biomarkers, cancer-related fatigue, and sleep, and the demographic measures and covariates assessed include: age, BMI, race/ethnicity, education, cancer stage at diagnosis, treatment (radiation and/or chemotherapy), pain intensity (as measured by the Brief Pain Inventory) and time since cancer diagnosis.

Demographics and Medical History

Baseline visit information was collected via an interviewer-administered questionnaire. All medical history information was self-reported and later confirmed by the participant's physician and medical record review.

Anthropometry

Height without shoes was measured using a stadiometer. Weight with light clothing and without shoes was measured on a digital scale. Height and weight measurements were the average of

two measurements taken in succession by the same technician and were rounded up to the next 0.5 cm and 0.1 kg, respectively.

Fatigue

Fatigue was measured using the Functional Assessment of Cancer Therapy fatigue subscale (FACIT-F). FACIT-F is a 13 item questionnaire assessing fatigue with high internal consistency (Cronbach's $\alpha = 0.93\text{-}0.95$),[22,23] convergent and discriminant validity revealing a positive correlation with other fatigue-questionnaires, and was found to be stable on test-retest ($r = 0.87$).[23]

Sleep

Sleep was measured using an abbreviated, 8-item, Pittsburgh Sleep Quality Index (PSQI). PSQI has high overall reliability and internal consistency (Cronbach's $\alpha = 0.83$) and validity (MANCOVA $p < 0.001$) and has a specificity and sensitivity of 89.6% and 86.5%, respectively (kappa = 0.75, $p < 0.001$).[24]

Inflammation

The serum inflammatory measures assessed include: CRP, IL-6, and TNF-α. Serum samples were collected, centrifuged at 2,000 rpm for 15 minutes at 4˚C, separated into plasma and buffy coat, stored temporarily for transportation at -20˚C, and stored at -70˚C until analyzed. Samples were measured in duplicate to improve reliability, and quality control samples were included in each batch. CRP was measured with an ACE chemistry analyzer (Alfa Wassermann Inc). IL-6

and TNF-α were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).

Statistical Analysis

The analyses were carried out with SAS for Windows PC, version 9.2. Descriptive characteristics are presented as means and standard deviations for continuous variables and number and percentage of total for categorical variables. Pearson correlations were performed to determine the associations between inflammatory biomarkers, cancer-related fatigue, and sleep duration. Given the larger published evidence supporting a potential relationship between CRP and fatigue, we determined unadjusted and adjusted associations between CRP tertiles and FACIT-fatigue scores using linear regression. The adjustment covariates included: age, BMI, cancer stage at diagnosis, radiation, chemotherapy, pain intensity, and time since cancer diagnosis, with stratification variables removed in respective adjustments. We repeated these analyses stratified by *a priori* determined factors: cancer stage at diagnosis, radiation, chemotherapy, BMI status, and pain intensity. Additionally, adjusted and unadjusted linear regressions were performed to determine which covariate(s) (cancer stage at diagnosis, radiation, chemotherapy, BMI status, pain intensity, and sleep quality) were the greatest risk factor(s) of fatigue. Pearson correlation coefficients and linear regression adjusted and unadjusted p values denote the strength of associations. The significance level was set at $p < 0.05$. All tests were two-sided.

RESULTS

Systematic Review

As of April 22, 2013, forty-five total studies were identified through the initial search, twelve of which were excluded due to duplication (three studies in triple duplicate)[7,17,25-37] and thirty of which were examined for inclusion (Figure 2).[7,17,25-52] Thirteen citations were excluded at the title and abstract level[26,30,34,39,40,42,44-49,51] and two studies were excluded at the full article review[36,50] for not meeting the inclusion criteria. Fifteen were included in the systematic review.

A growing body of literature supports the hypothesis that downstream inflammatory activity, e.g. soluble tumor necrosis factor receptor Type II (sTNF-RII), interleukin-1 receptor antagonist (IL-1RA), and C-reactive protein (CRP), are associated with cancer-related fatigue.[1] The literature cites 15 studies in this field related to the inflammatory biomarkers CRP, IL-6, and TNF-α and cancer-related fatigue in breast cancer survivors (Table 1). CRP was significantly and positively associated with many factors of fatigue: fatigue duration, behavioral changes due to fatigue, emotional meaning and symptoms of fatigue, and total fatigue [$\beta = 0.32$; SE = 0.14; $p = 0.022$],[27] [all $p < 0.02$],[38] [$\beta = 0.120$, $p = 0.020$],[33] [$p = 0.003$],[35] [$r = 0.47$, $p = 0.004$],[32] [Spearman's correlation coefficient-0.456, $p < 0.01$][52] (Table 1 & 2). In other studies, however, CRP, was only associated with total nighttime wake time but was not associated with total fatigue, total sleep, total nighttime sleep time, or total nap time in newly diagnosed breast cancer survivors scheduled to receive chemotherapy,[31] in breast cancer patients three months post primary cancer treatment,[7] or in those newly diagnosed.[28] The association between IL-6 and fatigue are unclear. IL-6 is shown to be positively associated ($\beta = 14.027$, SE = 4.194, $p = 0.002$),[31] negatively associated (Spearman's correlation coefficient = 0.311, $p = 0.05$),[52] and not associated with

fatigue.[27,29,41,43,53] While sTNF-RII has been shown to be significantly associated with fatigue,[25] TNF-α has not.[29,37,41,43,52]

HOPE Study

Baseline Characteristics

As of April 10, 2013, baseline inflammatory data were available for the first 69 women enrolled into the HOPE Study. Among the 69 women included in this analysis, study participants were an average of 61.8 years (Table 3). The majority of participants were non-Hispanic white (89.9%) and college graduates or above (50.7%). Approximately two-thirds of participants were overweight (36.2%) or obese (37.7%), with an average BMI of 29.5 kg/m^2. The majority of participants were diagnosed with Stage I cancer (62.3%) and had received chemotherapy (53.6%). Only 20.3% of participants had received radiation therapy. The average time since diagnosis was 3.04 ± 2.14 years. Participants slept, on average, 6.5 hours per night and described their sleep quality as follows: very good (10.2%), fairly good (50.7%), fairly bad (34.8%), and very bad (2.9%). On a scale from 0 to 52, with a higher score denoting better quality of life, the average participant FACIT-Fatigue score was 37.4. Mean serum CRP was 3.1 mg/L. HOPE Study participants had higher inflammatory markers and fatigue (lower FACIT-fatigue scores), as compared to a normal, healthy population (Table 4).

Fatigue, Inflammation, and Sleep

There was no association between FACIT-fatigue scores, CRP, IL-6, TNF-α, and sleep hours (Pearson's correlation, $p > 0.05$, data not shown). Overall, CRP tertiles were not significantly associated with cancer-related fatigue in both the adjusted and unadjusted linear regression

models ($p > 0.05$) (Table 5). When stratified by covariates, associations between CRP tertiles and cancer-related fatigue were significant and moderately significant in those with higher stage of disease at diagnosis in the unadjusted ($p = 0.019$) and adjusted ($p = 0.080$) models, respectively. All other stratified analyses were non-significant. BMI status (unadjusted $p = 0.013$) and pain intensity (unadjusted $p = 0.002$, adjusted $p = 0.011$) were significant risk factors of cancer-related fatigue (Table 6).

DISCUSSION

A growing body of literature supports the hypothesis that downstream inflammatory activity, e.g. C-reactive protein (CRP),[27,32,33,35,38,52] is associated with cancer-related fatigue, yet the data is not entirely conclusive.[1] The association between IL-6 and fatigue is unclear (with evidence to support positive,[31] negative,[52] and no association[27,29,43,53]), and TNF-α is consistently not associated with fatigue.[29,37,43,52] Limitations to these studies include small sample sizes,[25,27,29,31,32,37,41,43,52,53] potential selection bias towards healthier, less fatigued individuals,[28,38] and not assessing the associations between inflammation, fatigue, and sleep as the primary outcome.[41] Further, many studies did not adjust for BMI or cancer stage at diagnosis, and none adjusted for pain.

Our study examined associations among inflammation, cancer-related fatigue, and sleep in a sample of breast cancer survivors at high risk for inflammation, lack of sleep, and fatigue, given participants had been experiencing arthralgia originating during AI treatment. Our findings showed no significant association between cancer-related fatigue, CRP, IL-6, TNF-α, and sleep hours, adjusting for potential confounders. However, the data suggested an association between

cancer-related fatigue and CRP among women with higher stage disease, and BMI status and pain intensity were the most significant predictors of cancer-related fatigue.

While this study assessed a potentially higher risk population due to arthralgia, the mechanisms of AI-associated arthralgia are unclear but suggest estrogen deprivation as an etiologic explanation. While AI-induced arthralgia is associated with normal levels of CRP, estrogen deficiency results in elevated IL-6 and TNF-α.[54] Normalized CRP levels may contribute to this population's CRP homogeneity, as compared to previously published studies demonstrating a fatigue-CRP association.[33,35,38] Non-steroidal anti-inflammatory drugs are the most widely used treatment for arthralgia and may further homogenize the study population with regards to circulating inflammatory markers.[54] Further, statins suppress CRP at the transcriptional level and may contribute to lower, more homogenous CRP levels among HOPE study participants.[55]

Limitations include the lack of variability in the fatigue and CRP scores, lack of adjustment for anti-inflammatory, statin, and pain medications, as well as the fact that the cross-sectional study design precludes the establishment of temporal or causal relationships. However, a significant study strength is that this is the first study to examine the associations among inflammation and fatigue in this high-risk population.

While Groenvold et al (2007) show that cancer-related fatigue predicts recurrence and overall mortality in breast cancer patients,[10] the principle mechanisms underlying this relationship remain unclear and may derive from biological (e.g. inflammation), psychological (e.g. depression), or process (e.g. medication compliance) factors. Our data indicate that there may be

subgroups of women, e.g. those with higher stage of disease, who may serve to benefit from inflammation-reducing interventions. Further, as our data demonstrated that BMI status and pain intensity are the strongest predictors of fatigue, future studies should assess the affects of weight loss and pain management interventions on cancer-related fatigue, recurrence, and survivorship. While a growing body of literature supports the link between downstream inflammatory activity and cancer-related fatigue, future research is required to understand the mechanisms and causal pathway underlying these associations.[1] A better understanding of cancer-related fatigue and the subsequent development of effective interventions will serve to improve the duration and quality of life in an increasing population of cancer survivors.[56]

REFERENCES

1. Bower JE, Lamkin DM. Inflammation and cancer-related fatigue: Mechanisms, contributing factors, and treatment implications. *Brain, behavior, and immunity.* Jul 6 2012.

2. Knobf MT. Physical and psychologic distress associated with adjuvant chemotherapy in women with breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* May 1986;4(5):678-684.

3. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *The oncologist.* 2007;12 Suppl 1:4-10.

4. Blohmer JU, Dunst J, Harrison L, et al. Cancer-related anemia: biological findings, clinical implications and impact on quality of life. *Oncology.* 2005;68 Suppl 1:12-21.

5. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *European journal of cancer.* Jan 2002;38(1):27-43.

6. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Feb 2000;18(4):743-753.

7. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Sep 10 2011;29(26):3517-3522.

8. Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Feb 20 2008;26(6):971-982.

9. Poulson MJ. Not just tired. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Nov 1 2001;19(21):4180-4181.

10. Groenvold M, Petersen MA, Idler E, Bjorner JB, Fayers PM, Mouridsen HT. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. *Breast cancer research and treatment.* Oct 2007;105(2):209-219.

11. Goodwin PJ, Ennis M, Bordeleau LJ, et al. Health-related quality of life and psychosocial status in breast cancer prognosis: analysis of multiple variables. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Oct 15 2004;22(20):4184-4192.

12. Efficace F, Therasse P, Piccart MJ, et al. Health-related quality of life parameters as prognostic factors in a nonmetastatic breast cancer population: an international multicenter study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Aug 15 2004;22(16):3381-3388.

13. Blesch KS, Paice JA, Wickham R, et al. Correlates of fatigue in people with breast or lung cancer. *Oncology nursing forum.* Jan-Feb 1991;18(1):81-87.

14. Aouizerat BE, Dodd M, Lee K, et al. Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. *Biological research for nursing.* Jul 2009;11(1):27-41.

15. Miaskowski C, Dodd M, Lee K, et al. Preliminary evidence of an association between a functional interleukin-6 polymorphism and fatigue and sleep disturbance in oncology patients and their family caregivers. *Journal of pain and symptom management.* Oct 2010;40(4):531-544.

16. Jim HS, Park JY, Permuth-Wey J, et al. Genetic predictors of fatigue in prostate cancer patients treated with androgen deprivation therapy: preliminary findings. *Brain, behavior, and immunity.* Oct 2012;26(7):1030-1036.

17. Collado-Hidalgo A, Bower JE, Ganz PA, Irwin MR, Cole SW. Cytokine gene polymorphisms and fatigue in breast cancer survivors: early findings. *Brain, behavior, and immunity.* Nov 2008;22(8):1197-1200.

18. Saligan LN, Kim HS. A systematic review of the association between immunogenomic markers and cancer-related fatigue. *Brain, behavior, and immunity.* Aug 2012;26(6):830-848.

19. Henry NL, Giles JT, Ang D, et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. *Breast cancer research and treatment.* Sep 2008;111(2):365-372.

20. Clarke M. Meta-analyses of adjuvant therapies for women with early breast cancer: the Early Breast Cancer Trialists' Collaborative Group overview. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* Sep 2006;17 Suppl 10:x59-62.

21. Cleeland CS. The Brief Pain Inventory. 1991; http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html.

22. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet.* Aug 23 2003;362(9384):640-650.

23. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of pain and symptom management.* Feb 1997;13(2):63-74.

24. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* May 1989;28(2):193-213.

25. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosomatic medicine.* Jul-Aug 2002;64(4):604-611.

26. Bower JE, Ganz PA, Aziz N, Fahey JL, Cole SW. T-cell homeostasis in breast cancer survivors with persistent fatigue. *Journal of the National Cancer Institute.* Aug 6 2003;95(15):1165-1168.

27. Bower JE, Ganz PA, Tao ML, et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Sep 1 2009;15(17):5534-5540.

28. Fagundes CP, Glaser R, Alfano CM, et al. Fatigue and herpesvirus latency in women newly diagnosed with breast cancer. *Brain, behavior, and immunity.* Mar 2012;26(3):394-400.

29. Geinitz H, Zimmermann FB, Stoll P, et al. Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. *International journal of radiation oncology, biology, physics.* Nov 1 2001;51(3):691-698.

30. Gelinas C, Fillion L. Factors related to persistent fatigue following completion of breast cancer treatment. *Oncology nursing forum.* Mar-Apr 2004;31(2):269-278.

31. Liu L, Mills PJ, Rissling M, et al. Fatigue and sleep quality are associated with changes in inflammatory markers in breast cancer patients undergoing chemotherapy. *Brain, behavior, and immunity.* Jul 2012;26(5):706-713.

32. Lyon DE, Schubert C, Taylor AG. Pilot study of cranial stimulation for symptom management in breast cancer. *Oncology nursing forum.* Jul 2010;37(4):476-483.

33. Orre IJ, Reinertsen KV, Aukrust P, et al. Higher levels of fatigue are associated with higher CRP levels in disease-free breast cancer survivors. *Journal of psychosomatic research.* Sep 2011;71(3):136-141.

34. Pusztai L, Mendoza TR, Reuben JM, et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. *Cytokine.* Feb 7 2004;25(3):94-102.

35. Reinertsen KV, Grenaker Alnaes GI, Landmark-Hoyvik H, et al. Fatigued breast cancer survivors and gene polymorphisms in the inflammatory pathway. *Brain, behavior, and immunity.* Oct 2011;25(7):1376-1383.

36. Starkweather AR, Lyon DE, Schubert CM. Pain and inflammation in women with early-stage breast cancer prior to induction of chemotherapy. *Biological research for nursing.* Apr 2013;15(2):234-241.

37. Von Ah DM, Kang DH, Carpenter JS. Predictors of cancer-related fatigue in women with breast cancer before, during, and after adjuvant therapy. *Cancer nursing.* Mar-Apr 2008;31(2):134-144.

38. Alfano CM, Imayama I, Neuhouser ML, et al. Fatigue, inflammation, and omega-3 and omega-6 fatty acid intake among breast cancer survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Apr 20 2012;30(12):1280-1287.

39. Baidas SM, Winer EP, Fleming GF, et al. Phase II evaluation of thalidomide in patients with metastatic breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jul 2000;18(14):2710-2717.

40. Body JJ, Greipp P, Coleman RE, et al. A phase I study of AMGN-0007, a recombinant osteoprotegerin construct, in patients with multiple myeloma or breast carcinoma related bone metastases. *Cancer.* Feb 1 2003;97(3 Suppl):887-892.

41. Bower JE, Ganz PA, Aziz N, Olmstead R, Irwin MR, Cole SW. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. *Brain, behavior, and immunity.* Mar 2007;21(3):251-258.

42. Budd GT, Green S, Baker LH, Hersh EP, Weick JK, Osborne CK. A Southwest Oncology Group phase II Trial of recombinant tumor necrosis factor in metastatic breast cancer. *Cancer.* Oct 15 1991;68(8):1694-1695.

43. Cameron BA, Bennett B, Li H, et al. Post-cancer fatigue is not associated with immune activation or altered cytokine production. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* Nov 2012;23(11):2890-2895.

44. Lof M, Bergstrom K, Weiderpass E. Physical activity and biomarkers in breast cancer survivors: a systematic review. *Maturitas.* Oct 2012;73(2):134-142.

45. Madhusudan S, Foster M, Muthuramalingam SR, et al. A phase II study of etanercept (Enbrel), a tumor necrosis factor alpha inhibitor in patients with metastatic breast cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Oct 1 2004;10(19):6528-6534.

46. Parihar R, Nadella P, Lewis A, et al. A phase I study of interleukin 12 with trastuzumab in patients with human epidermal growth factor receptor-2-overexpressing malignancies: analysis of sustained interferon gamma production in a subset of patients. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Aug 1 2004;10(15):5027-5037.

47. Rauthe G, Sistermanns J. Pleurodesis with recombinant tumour necrosis factor in gynaecological neoplasms. *European journal of gynaecological oncology.* 1998;19(2):108-112.

48. Schubert C, Neises M, Fritzsche K, et al. Mood and fatigue in everyday life are temporally related to cellular immune activity. Preliminary evidence from an extensive observation of a patient with prior breast cancer. *Psychopathology.* 2009;42(1):67-68.

49. Singhal S, Mehta J. Thalidomide in cancer. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie.* Feb 2002;56(1):4-12.

50. Standish LJ, Torkelson C, Hamill FA, et al. Immune defects in breast cancer patients after radiotherapy. *Journal of the Society for Integrative Oncology.* Summer 2008;6(3):110-121.

51. Witt PL, Zahir S, Ritch PS, McAuliffe TM, Ewel CH, Borden EC. Phase I/IB study of polyadenylic-polyuridylic acid in patients with advanced malignancies: clinical and biologic effects. *Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research.* Aug 1996;16(8):631-635.

52. Wratten C, Kilmurray J, Nash S, et al. Fatigue during breast radiotherapy and its relationship to biological factors. *International journal of radiation oncology, biology, physics.* May 1 2004;59(1):160-167.

53. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clinical cancer research : an official journal of the American Association for Cancer Research.* May 1 2006;12(9):2759-2766.

54. Burstein HJ. Aromatase inhibitor-associated arthralgia syndrome. *Breast.* Jun 2007;16(3):223-234.

55. Demierre MF, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. *Nature reviews. Cancer.* Dec 2005;5(12):930-942.

56. Bower JE, Lamkin DM. Inflammation and cancer-related fatigue: Mechanisms, contributing factors, and treatment implications. *Brain, behavior, and immunity.* Mar 2013;30 Suppl:S48-57.

57. Risk NoMoB. Biomarkers. 2005; http://gero.usc.edu/CBPH/biomarker/biomarkers-index3.htm.

58. FACIT.org. 2010; http://www.facit.org/FACITOrg/Questionnaires.

APPENDIX 1

FACIT-fatigue

Below is a list of statements that other people with cancer have said are important to their quality of life. Please indicate the extent to which you have experienced each of the statements during the past 7 days by circling the appropriate number using the following scale.

During the PAST WEEK:

0 Not at all	1 A little bit	2 Somewhat	3 Quite a bit	4 Very Much

FATIGUE AND ENERGY

1. I feel fatigued	0	1	2	3	4
2. I feel weak all over	0	1	2	3	4
3. I feel listless ("washed out")	0	1	2	3	4
4. I feel tired	0	1	2	3	4
5. I have trouble starting things because I am tired	0	1	2	3	4
6. I have trouble finishing things because I am tired	0	1	2	3	4
7. I have energy	0	1	2	3	4
8. I am able to do my usual activities	0	1	2	3	4
9. I need to sleep during the day	0	1	2	3	4
10. I am too tired to eat	0	1	2	3	4
11. I need help doing my usual activities	0	1	2	3	4
12. I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13. I have to limit my social activity because I am tired	0	1	2	3	4

Table 1: Associations between inflammatory markers, fatigue, and sleep

Study	Design	Participants	Measures	Results
Alfano et al 2012	Multicenter prospective cohort study (HEAL Study); assessed inflammation biomarkers (30 months after diagnosis) and fatigue measures (39 months after diagnosis)	Stage I to IIIA breast cancer survivors (n = 633) with a mean age of 56 years	Inflammatory: CRP and SAA Fatigue: Revised Piper Fatigue Scale Short Form-36 (assess severity of fatigue) Covariates: age, race/study site, tamoxifen use, menopausal status	Higher CRP levels were significantly and linearly associated with higher behavioral (p_{trend} = 0.003), sensory (p_{trend} = 0.001), and total fatigue (p_{trend} = 0.02), which were attenuated after adjusting for medication use, comorbidity, and BMI.
Cameron et al 2012	Nested case-control study derived from a prospective cohort study where participants were assessed before, during, and after adjufant treatment	Early-stage breast cancer survivors (n = 28, 13 cases with confirmed post-cancer fatigue and 15 controls who did not develop post-cancer fatigue)	Inflammatory: IL1β, IL2, IL4, IL6, IL10, IL12, TNF-α, IFN-γ, neopterin, IL1ra, sIL6R, sTNF-rII, leukocytes Fatigue: Somatic and Psychological Health Report (SPHERE, 43-item tool with a fatigue subscale, the SOMA) Sleep: Sleep Assessment Questionnaire Covariates: none mentioned	Cytokine levels did not significantly differ between cases and controls (all p > 0.01).
Fagundes et al 2012	Cross-sectional	Newly diagnosed breast cancer survivors or those awaiting a positive diagnosis result (n = 158)	Inflammatory: CRP Fatigue: RAND SF-36 vigor/vitality scale Sleep: Insomnia Severity Index Covariates: none mentioned	CRP was not statistically associated with being fatigued, as compared to not being fatigued (p = 0.88).
Liu et al 2012	Prospective; data was collected at baseline and during cycles 1 and 4 of chemotherapy	Newly diagnosed, stage I-III breast cancer survivors scheduled to receive adjuvant or neoadjuvant anthracycline-based chemotherapy and with a mean age of 50.3 years (n = 53).	Inflammatory: IL6, IL1RA, CRP Fatigue: Multidimensional Fatigue Symptom Inventory-Short Form Sleep: Pittsburgh Sleep Quality Index (PSQI); Actillume actigraph data hand-edited with additional self-report sleep log information	CRP was significantly associated with total nighttime wake time (β = 0.774, SE = 0.261, p = 0.01), but was not significantly associated with total MFSI-SF score, total PSQI score, total nighttime sleep time, or total nap time. IL6 was significantly associated with total MFSI-SF score (β = 14.027, SE = 4.194, p = 0.002) and total PSQI score (β = 1.740, SE = 0.690, p = 0.02). IL1RA was significantly associated

			Covariates: time, race, use of antacids (in inflammatory marker and MFSI-SF association)	with total PSQI score (β = 0.974, SE = 0.423, p = 0.03).
Bower et al 2011	Cross-sectional	Stage 0-IIIA breast cancer survivors, 3 months post primary cancer treatment completion but prior to endocrine therapy (n = 103)	Inflammatory: IL1RA, TNF, sTNF-RII, CRP Fatigue: Fatigue Symptom Inventory Sleep: Pittsburgh Sleep Quality Index Covariates: age, time since diagnosis, cancer treatment prior to gene analysis	Fatigue was not associated with IL1RA or CRP (both p > 0.9).
Orre et al 2011	Cross-sectional; participants assessed at a mean 4 years post diagnosis	breast cancer survivors treated with postoperative locoregional radiotherapy for stage II-III breast cancer with a mean age of 55 years (n = 299)	Inflammatory: Hemoglobin, leukocytes, hsCRP, sTNF-R1 Fatigue: Fatigue Questionnaire (FQ; 11-items assessing both physical and mental fatigue) Sleep: Insomnia symptoms (2-items) Covariates: age, educational level	Of the inflammatory biomarkers assessed, only hsCRP was significantly and positively associated with total fatigue, adjusted (β = 0.120, p = 0.020). Insomnia was significantly associated with fatigue (β = 0.236, p < 0.001).
Reinertsen et al 2011	Cross-sectional	Stage II/III breast cancer survivors under the age of 75 (n = 302)	Inflammatory: Leukocytes, CRP Fatigue: Fatigue questionnaire (7-item tool to assess both mental and physical fatigue) Covariates: treatment strategies, BMI, treatment-area related fibrosis	CRP was significantly associated with both chronic fatigue (p = 0.003) and persistent fatigue (p < 0.001), as compared to those without chronic fatigue and those never fatigued, respectively.
Lyon et al 2010	Prospective, three-group (cranial electrical stimulation [CES], CES-sham, control), randomized, double-blinded, longitudinal pilot feasibility study	Stage I-IIIA breast cancer survivors receiving adjuvant chemotherapy or neoadjuvant therapy with an anthracycline-containing chemotherapy regimen (n = 36)	Inflammatory: IL6, TNF-α, IL-1β, CRP Fatigue: Brief Fatigue Inventory Sleep: General Sleep Disturbance (GSDS, 21-item tool, assesses frequency of sleep problems) Covariates: none mentioned	Fatigue was significantly associated with CRP (r = 0.47, p = 0.004).
Bower et al	Prospective cohort	Newly diagnosed breast	Inflammatory:	Fatigue duration:

2009	study; assessed self-report fatigue and sleep measures and inflammation biomarkers before, during, and after a course of radiation therapy	(n = 28) or prostate cancer (n = 20) survivors 25-75 years of age undergoing radiation therapy	Serum IL1β, IL6, IL1 receptor antagonist, CRP Fatigue: Fatigue Symptom Inventory Sleep: Medical Outcomes Study Sleep Scale Covariates: sleep disturbance, depressive symptoms, age, BMI, hormone therapy	IL1β and IL6 were not associated with fatigue (all Ps > 0.30). CRP was significantly associated with fatigue duration (β = 0.32; SE = 0.14; p = 0.022). The association remained significant after controlling for sleep disturbance, depressive symptoms, age, body mass index, and hormone therapy. Fatigue severity: IL1 receptor antagonist was associated with increased fatigue severity (β = 0.63, SE = 0.26, p = 0.016) controlling for sleep and depression measures, age, body mass index, and hormone therapy.
Von Ah et al 2008	Prospective longitudinal cohort study; assessed measures before, during, and after adjuvant therapy	Newly diagnosed stage 0-IIIA breast cancer survivors at least 1 week post surgery but prior to adjuvant therapy (n = 57)	Inflammatory: IL-1β, TNF-α Fatigue: Piper Fatigue Scale-Revised Covariates: type of adjuvant therapy, mood, network support, satisfaction, cortisol, perceived stress, optimism	Before adjuvant therapy, IL1β was significantly associated with cancer-related fatigue (β = 0.35, p < 0.01).
Bower et al 2007	Longitudinal cohort study	Stage 0-II breast cancer survivors (N = 25, 10 fatigued and 15 non-fatigued)	Inflammatory: IL-6, TNF-α Fatigue: SF-36 Validity Scale Covariates: time between blood draw, age, marital status, cancer treatment, BMI, depressed mood score	IL-6 and TNF-α did not significantly differ among those fatigued and not-fatigued at baseline.
Collado-Hidalgo et al 2006	Case-control study	Breast cancer survivors originally diagnosed with stage 0-II breast cancer, completed all cancer treatment, and were 1-5 years post diagnosis (n = 50, 32 fatigued cases, 18 nonfatigued controls)	Inflammatory: Plasma IL6, sIL6R, IL1ra, TNF-rII, monocyte intracellular production of IL6 and TNF-α Fatigue status: Validity scale of the SF-36 Covariates: age, BMI, time since treatment, treatment mode, depressive symptom scores	Plasma IL6 did not significantly differ between cases and controls.

Wratten et al 2004	Prospective cohort study	Breast cancer survivors (n = 52)	Inflammatory: Transforming growth factor-β, fibroblast growth factor-β, IL6, TNF-α, intercellular adhesion molecule-1, platlet derived growth factor, CRP Fatigue: FACT fatigue subscale (subscale of FACT G quality-of-life questionnaire, a 13-item tool assessing fatigue severity) Covariates: BMI	The baseline values of CRP (Spearman's correlation coefficient-0.456, $p < 0.01$) and IL6 (Spearman's correlation coefficient -0.311, $p = 0.05$) were significantly correlated with baseline values of fatigue. The week 5 CRP values (Spearman's correlation coefficient -0.215, $p = 0.19$) were not correlated with fatigue, but the week 5 IL6 values were (Spearman's correlation coefficient -0.367, $p = 0.03$).
Bower et al 2002	Cross-sectional	Stage 0-II (at diagnosis) breast cancer patients 1-5 years post diagnosis who completed adjuvant therapy and were currently disease free (n = 40)	Inflammatory: IL-1β, IL-1RA, sTNF-RII, neopterin, lymphocytes Fatigue: RAND 36-Item Health Survey fatigue subscale (4-item) and Fatigue Symptom Inventory (13-item) Covariates: caffeine, alcohol use, smoking	Compared with non-fatigued breast cancer survivors, fatigued breast cancer survivors had significantly higher levels of IL-1RA ($p = 0.006$), neopterin ($p = 0.018$), and sTNF-RII ($p = 0.005$).
Geinitz et al 2001	Prospective cohort study; participants were assessed at 5 weekly intervals during and 2 months after the end of radiotherapy	Breast cancer survivors who underwent postoperative radiotherapy after breast-conserving surgery (n = 41)	Inflammatory: IL1β, IL6, TNFα Fatigue: Fatigue Assessment Questionnaire (20-item tool to assess physical, affective, and cognitive factors of fatigue) and visual analog scale on fatigue intensity Sleep: Self-report daily hours of sleep Covariates: none mentioned	None of the cytokines (IL1β, IL6, TNFα) correlated with fatigue.

Table 2: Systematic-review of inflammatory markers and fatigue association

	Significantly Associated with Fatigue	Not Significantly Associated with Fatigue
CRP	Alfano et al 2012 CRP mean = 4.4 ± 8.6 mg/L 40% of participants had a CRP > 3 mg/L Lowest tertile 0.5 mg/L, middle tertile 2.1 mg/L, highest tertile 8.0 mg/L; OR highest tertile vs. lowest tertile of 1.8 to 2.4, depending on the model, $p < 0.05$ Fatigue Measure: Piper Fatigue Scale Strength: N = 633 Limitation: cross-sectional, only one assessment of each construct, so unable to determine how changes in inflammation affect fatigue; selection bias towards healthier survivors Orre et al 2011 β adj = 0.120, p = 0.020 Mean hsCRP = 3.1±3.9 mg/L [0.2-31.0] Fatigue Measure: Fatigue Questionnaire (FQ; 11-items assessing both physical and mental fatigue) N = 299 Reinertsen et al 2011 Median with chronic fatigue 2.5 mg/L [0.2-23.0] Median without chronic fatigue 1.6 mg/L [0.2-31.0], p = 0.003 Fatigue Measure: Fatigue questionnaire (7-item tool to assess both mental and physical fatigue) Strength: N = 302 Lyon et al 2010 r = 0.47, p = 0.004 CRP mean = 3.75 mg/L ± 3.94 Fatigue Measure: Brief Fatigue Inventory N = 36 Bower et al 2009 Fatigue duration: β = 0.32; SE = 0.14; p = 0.022 Effect sizes not reported. Fatigue Measure: Fatigue Symptom Inventory N = 28 Wratten et al 2004 Spearman's correlation coefficient-0.456, $p < 0.01$ Effect sizes not reported. Fatigue Measure: FACT-F N = 52	Fagundes et al 2012 (p = 0.08) Fatigued CRP mean = 3.13 mg/L ($\log_{10}$ 0.14), Non-fatigued CRP mean = 3.24 ($\log_{10}$ 0.15); $\log_{10}$ p = 0.88 Bower et al 2011 (p > 0.09) Fatigue Measure: RAND SF-36 Strength: N = 167 Limitation: Selection biased possibly towards less-fatigued individuals; mostly white sample Liu et al 2012 β = 5.124, SE = 4.703, p = 0.3 Size effects before and during chemotherapy: Mean CRP at Baseline 3.09 mg/L, Cycle 1 Week 2 1.54 mg/L, Cycle 1 Week 3 3.61 mg/L, Cycle 4 Week 2 4.76 mg/L, Cycle 4 Week 3 3.24 mg/L (p > 0.05) Fatigue Measure: Multidimensional Fatigue Symptom Inventory-Short Form N = 53 Bower et al 2011 p > 0.9 Effect sizes not reported. Fatigue Measure: Fatigue Symptom Inventory Strength: N = 103 Wratten et al 2004 Week 5 values: Spearman's correlation coefficient -0.215, p = 0.19 Effect sizes not reported. Fatigue Measure: FACT-F N = 52
IL-6	Liu et al 2012 β = 14.027, SE = 4.194, p = 0.002 Size effects before and during chemotherapy: Baseline mean 2.93 pg/ml compared to Cycle 4 Week 2 mean 4.21 pg/ml (p < 0.001); baseline compared to Cycle 4 Week 3 3.37 pg/ml (p < 0.05) Fatigue Measure: Multidimensional Fatigue Symptom Inventory-Short Form Wratten et al 2004 Baseline values: Spearman's correlation coefficient -0.311, p	Cameron et al 2012 Non-significant effect sizes not reported. Fatigue Measure: SOMA Strength: prospective nested-case control design Limitation: N = 28, allowing for less statistical power; greatly varied period between cancer treatment and analysis Orre et al 2011 β adj = -0.015, p = 0.760 Mean IL-6 among all participants: 0.3 pg/ml Bower et al 2009

	= 0.05 Week 5 values: Spearman's correlation coefficient -0.367, p = 0.03 Effect sizes not reported. Fatigue Measure: FACT-F	p > 0.30 Effect sizes not reported. Fatigue Measure: Fatigue Symptom Inventory Bower et al 2007 Baseline IL-6 in fatigued participants: 1.99±0.21 Baseline IL-6 in non-fatigued participants: 2.11±0.16 p > 0.05 Fatigue Measure: SF-36 Collado-Hidalgo et al 2006 p > 0.05 Effect sizes not reported. Fatigue Measure: SF-36 Geinitz et al 2001 p > 0.05 Effect sizes not reported. Fatigue Measure: Fatigue Assessment Questionnaire
TNF-α		Cameron et al 2012 Non-significant effect sizes not reported. Fatigue Measure: SOMA Strength: prospective nested-case control design Limitation: N = 28, allowing for less statistical power; greatly varied period between cancer treatment and analysis Bower et al 2007 Baseline TNF-α in fatigued participants: 1.20±0.43 Baseline TNF-α in non-fatigued participants: 1.21±0.31 p > 0.05 Fatigue Measure: SF-36 Geinitz et al 2001 p > 0.05 Effect sizes not reported Fatigue Measure: Fatigue Assessment Questionnaire

Table 3: Baseline characteristics

Characteristics	N (%)*
Race/ethnicity	
Non-Hispanic white	60 (88.2)
Non-Hispanic black	6 (8.8)
Hispanic	2 (2.9)
Age (years), mean ± SD	61.8 ± 7.2
Weight (kg), mean ± SD	77.5 ± 15.8
BMI (kg/m^2)	29.5
Normal (18.5 – 25 kg/m^2)	16 (23.2)
Overweight (25 – 30 kg/m^2)	25 (36.2)
Obese (> 30 kg/m^2)	26 (37.7)
Education	
Less than high school	1 (1.5)
High school graduate	32 (46.4)
College graduate	16 (23.2)
Masters/Doctorate graduate	19 (27.5)
Stage of cancer at diagnosis	
Stage I	43 (62.3)
Stage II	18 (26.1)
Stage III	6 (8.7)
Stage IV	0 (0)
Received radiation therapy	14 (20.3)
Received chemotherapy	37 (53.6)
Pain Severity (Range 0-10)	
None (0-3)	17 (24.6)
Mild (3-4)	20 (29.0)
Moderate (5-7)	27 (39.1)
Severe (8-10)	5 (7.3)
Pain Intensity (Range 0-10)	
None (0-3)	37 (53.6)
Mild (3-4)	15 (21.7)
Moderate (5-7)	12 (17.4)
Severe (8-10)	5 (7.3)
Worst Pain Score (Range 0-10)	
No Pain (0-3)	2 (2.9)
Mild (3-4)	17 (24.6)
Moderate (5-7)	35 (50.7)
Severe (8-10)	15 (21.7)
Sleep per night (hours), mean ± SD	6.5 ±1.3
Quality of sleep	
Very good	7 (10.2)
Fairly good	25 (50.7)

Fairly bad	24 (34.8)
Very bad	2 (2.9)
FACIT-Fatigue score,** mean ± SD	37.4 ± 10.6
Not-fatigued (< 37)	30 (43.5)
Fatigued (≥ 37)	38 (55.1)
CRP1 (mg/L), mean ± SD	3.1 ± 3.7
IL6, mean ± SD	2.0 ± 2.1
TNF-α, mean ± SD	2.2 ± 2.9

* Numbers may not sum to 69 due to missing data, and percentages may not sum to 100% due to rounding.
**The higher the FACIT-Fatigue score (range 0-52), the better the quality of life.

Table 4: Clinical measures in HOPE Study participants and healthy population

	HOPE Study	Healthy Population
Inflammatory Biomarkers		
CRP (mg/L) mean ± SD (range)	3.13 ± 3.71 (0.08-18.47)	<1[57]
IL-6 (μg/mL) mean ± SD (range)	2.04 ± 2.11 (0.61-16.64)	<1-2[57]
TNF-α (pg/mL) mean ± SD (range)	2.17 ± 2.90 (0.74-25.19)	<1
FACIT-Fatigue		
Mean ± SD	37.38 ±10.63	44.1±7.6*[58]
Minimum Observed Score	11.0	18.0
25th Percentile	29.5	41.0
50th Percentile (median)	39.0	46.5
75th Percentile	47.0	50.0
Maximum Observed Score	52.0	52.0

* General female population norm: healthy sub-population

Table 5: Associations between CRP tertiles and cancer-related fatigue overall and stratified by covariates

	CRP Tertile†	N (%)*	Unadjusted mean ± SE p-value	Adjusted** mean ± SE p-value
Overall	1	23 (33.3)	40.71 ± 1.66	39.61 ± 2.91
	2	22 (31.9)	36.77 ± 2.81	36.44 ± 3.47
	3	24 (34.8)	34.89 ± 2.01	38.11 ± 3.30
			0.169	0.657
Cancer Stage				
Lower Stage	1	12 (27.9)	41.45 ± 2.86	36.73 ± 4.00
(Stage I)	2	17 (39.5)	35.47 ± 3.46	33.31 ± 3.52
	3	14 (32.6)	38.00 ± 2.57	39.14 ± 3.30
			0.427	0.391
Higher Stage	1	10 (41.67)	39.77 ± 2.00	39.38 ± 3.25
(Stage II – III)	2	4 (16.7)	42.25 ± 4.53	46.23 ± 5.29
	3	10 (41.7)	30.50 ± 2.79	30.33 ± 4.14
			0.019	0.080
Radiation				
Yes	1	6 (42.9)	40.33 ± 3.17	34.95 ± 5.43
	2	3 (21.4)	31.67 ± 10.53	38.66 ± 6.40
	3	5 (35.7)	40.20 ± 4.42	42.07 ± 4.91
			0.514	0.692
No	1	17 (30.9)	40.85 ± 2.02	39.61 ± 3.10
	2	19 (34.6)	37.58 ± 2.91	37.10 ± 3.21
	3	19 (34.6)	33.47 ± 2.20	36.62 ± 3.30
			0.121	0.745
Chemotherapy				
Yes	1	13 (35.1)	41.25 ± 2.52	37.54 ± 5.19
	2	16 (43.2)	38.56 ± 3.12	37.75 ± 6.50
	3	8 (21.6)	35.63 ± 3.28	39.72 ± 7.24
			0.518	0.922
No	1	10 (31.3)	40.07 ± 2.19	44.07 ± 4.68
	2	6 (18.8)	32.00 ± 6.15	35.82 ± 5.91
	3	16 (50.0)	34.50 ± 2.60	40.09 ± 4.48
			0.277	0.440

BMI Status				
Normal Weight	1	12 (75.0)	42.31 ± 1.91	49.93 ± 2.64
(18.5-25 kg/m^2)	2	3 (18.8)	41.67 ± 4.48	44.71 ± 4.80
	3	1 (6.3)	46.00 ± 0.00	45.89 ± 6.16
			0.855	0.567
Overweight	1	9 (36.0)	39.50 ± 3.38	38.96 ± 6.41
(25-30 kg/m^2)	2	9 (36.0)	37.67 ± 4.23	24.71 ± 11.30
	3	7 (28.0)	36.71 ± 4.60	41.88 ± 7.26
			0.893	0.282
Obese	1	2 (7.7)	36.00 ± 6.00	31.53 ± 8.41
(> 30 kg/m^2)	2	8 (30.8)	31.00 ± 5.36	30.06 ± 5.03
	3	16 (61.5)	33.38 ± 2.20	28.66 ± 4.68
			0.813	0.910
Joint Pain Intensity				
None – Mild	1	19 (37.3)	42.26 ± 1.78	42.04 ± 3.96
	2	15 (29.4)	39.40 ± 2.78	39.50 ± 5.67
	3	17 (33.3)	36.00 ± 2.43	37.99 ± 4.82
			0.158	0.684
Moderate –	1	4 (22.2)	33.75 ± 2.50	45.90 ± 13.55
Severe	2	7 (38.9)	31.14 ± 6.37	34.61 ± 10.91
	3	7 (38.9)	32.14 ± 3.6	41.73 ± 10.45
			0.946	0.690

† CRP tertiles: first tertile ≤ 1.235 mg/L, second tertile > 2.321 mg/L and < 2.321 mg/L, third tertile ≥ 2.321 mg/L

* Numbers may not sum to 69 due to missing data, and percentages may not sum to 100% due to rounding.

** Adjusted by age, BMI, cancer stage at diagnosis, radiation, chemotherapy, pain intensity, and time since cancer diagnosis, with stratification variables removed in respective adjustments.

Table 6: Potential risk factors for cancer-related fatigue

	N (%)*	Unadjusted mean ± SE	p-value	Adjusted** mean ± SE	p-value
Cancer Stage			0.575		0.839
Lower Stage (Stage I)	43 (62.3)	37.88 ± 1.81		37.68 ± 1.82	
Higher Stage (Stage II – III)	24 (34.8)	36.32 ± 1.86		37.09 ± 2.42	
Radiation			0.681		0.477
Yes	14 (20.3)	38.43 ± 2.90		39.40 ± 3.50	
No	55 (79.7)	37.10 ± 1.45		37.77 ± 2.59	
Chemotherapy			0.243		0.506
Yes	37 (53.6)	38.81 ± 1.77		39.52 ± 2.91	
No	32 (46.4)	35.77 ± 1.88		37.65 ± 2.74	
BMI Status			0.013		0.065
Normal Weight (18.5-25 kg/m^2)	16 (23.2)	42.42 ± 1.60		42.42 ± 3.07	
Overweight (25-30 kg/m^2)	25 (36.2)	38.00 ± 2.27		39.41 ± 3.06	
Obese (> 30 kg/m^2)	26 (37.7)	32.85 ± 2.11		34.88 ± 2.92	
Joint Pain Intensity			0.002		0.011
None	37 (53.6)	41.24 ± 1.50		41.68 ± 3.01	
Mild	15 (21.7)	34.20 ± 2.39		35.88 ± 3.56	
Moderate	12 (17.4)	35.25 ± 2.48		35.89 ± 3.53	
Severe	5 (7.3)	24.20 ± 7.43		24.52 ± 5.32	
Sleep Quality			0.114		0.112
Very good	7 (10.1)	44.57 ± 3.74		46.89 ± 4.95	
Fairly good	35 (50.7)	38.34 ± 1.69		40.15 ± 2.62	
Fairly bad	24 (34.8)	34.08 ± 2.31		37.63 ± 2.86	
Very bad	2 (2.9)	34.83 ± 0.17		30.00 ± 7.02	

* Numbers may not sum to 69 due to missing data, and percentages may not sum to 100% due to rounding.

***** Adjusted by age, BMI, cancer stage at diagnosis, radiation, chemotherapy, pain intensity, and time since cancer diagnosis, with stratification variables removed in respective adjustments.

Figure 1. Flow of participants through the HOPE Study

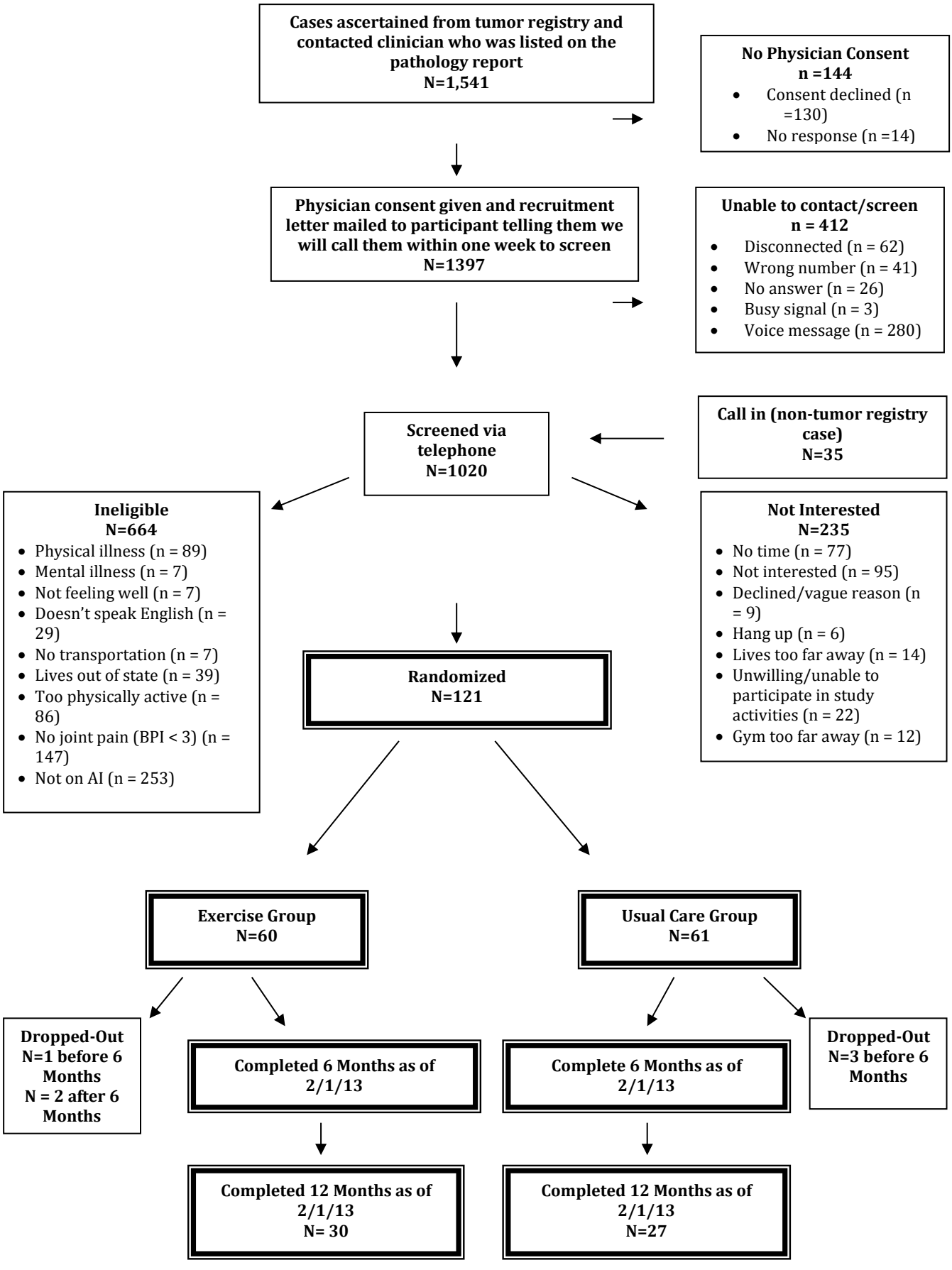

Figure 2. Literature Review Process