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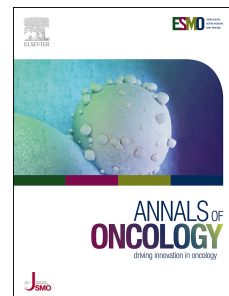
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HIGHLIGHTS

- • 34.4% of 1208 stage I-III breast cancer survivors had cancer-related fatigue of clinical importance 2 years after diagnosis
- • High pre-treatment levels of the pro-inflammatory cytokine IL-6 were associated with global fatigue 2 years later
- • Individuals with high levels of IL-6 had higher body mass index and were less physically active than those with lower levels
- • Higher pre-treatment IL-2 and IL-10 were also associated with higher and lower likelihood of global fatigue, respectively
- Higher C-reactive protein was associated with higher likelihood of cognitive fatigue

ABSTRACT

Background: We aimed to generate a model of cancer-related fatigue (CRF) of clinical importance two years after diagnosis of breast cancer building on clinical and behavioral factors and integrating pre-treatment markers of systemic inflammation.

Methods: Women with stage I-III HR+/HER2- breast cancer were included from the multimodal, prospective CANTO cohort (NCT01993498). The primary outcome was global CRF of clinical importance (EORTC QLQ-C30 \geq 40/100) two years after diagnosis (year-2). Secondary outcomes included physical, emotional, and cognitive CRF (EORTC QLQ-FA12). All pre-treatment candidate variables were assessed at diagnosis, including inflammatory markers (interleukin [IL]-1a, IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, interferon gamma, IL-1 receptor antagonist, TNF- α , and C-reactive protein), and were tested in multivariable logistic regression models implementing multiple imputation and validation by 100-fold bootstrap resampling.

Results: Among 1208 patients, 415 (34.4%) reported global CRF of clinical importance at year-2. High pre-treatment levels of IL-6 (Quartile 4 vs.1) were associated with global CRF at year-2 (adjusted Odds Ratio [aOR]: 2.06 [95% Confidence Interval 1.40-3.03]; $p=0.0002$; AUC=0.74). Patients with high pre-treatment IL-6 had unhealthier behaviors, including being frequently either overweight or obese (62.4%; mean BMI 28.0 [SD 6.3] Kg/m²) and physically inactive (53.5% did not meet WHO recommendations). Clinical and behavioral associations with CRF at year-2 included pre-treatment CRF (aOR vs no: 3.99 [2.81-5.66]), younger age (per 1-year decrement: 1.02 [1.01-1.03]), current smoking (vs never: 1.81 [1.26-2.58]), and worse insomnia or pain (per 10-unit increment: 1.08 [1.04-1.13], and 1.12 [1.04-1.21], respectively). Secondary analyses indicated additional associations of IL-2 (aOR per log-unit increment:1.32 [CI 1.03-1.70]) and IL-10 (0.73 [0.57-0.93]) with global CRF and of C-reactive protein (1.42 [1.13-1.78]) with cognitive CRF at year-2. Emotional distress was consistently associated with physical, emotional, and cognitive CRF.

Conclusions: This study proposes a bio-behavioral framework linking pre-treatment systemic inflammation with CRF of clinical importance two years later among a large prospective sample of survivors of breast cancer.

KEYWORDS: breast cancer, cancer-related fatigue, inflammatory markers, health behaviors, symptom management, survivorship

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MANUSCRIPT

Introduction

Cancer-related fatigue (CRF) is almost universal during primary treatment for breast cancer, however long-term CRF can be prevalent up to several years after treatment completion.¹⁻³ CRF is usually defined as more disabling than fatigue due to sleep deprivation or overexertion, with a substantial proportion of patients (30-60%) describing this symptom as moderate to severe, causing great detriment to quality of life (QOL).⁴⁻⁶

Extensive work has studied clinical, psychological, behavioral, environmental, socio-demographic, tumor-, and treatment-related correlates of CRF.^{1,7-11} Dissecting its multidimensional characteristics, several studies have also suggested that the physical, emotional, and cognitive manifestations of CRF may have distinct etiology, courses, and determinants, including different pathophysiology, and a “subtype-specific” approach to better tailor the management of CRF was proposed.¹²⁻¹⁴ Joining this effort to improve assessment and management of CRF, our group previously developed and validated predictive models building on clinical and behavioral characteristics¹⁵ and generated an online screening tool to estimate individual risk of long-term CRF after breast cancer.¹⁶

Nevertheless, CRF remains a complex and multifactorial syndrome, and most of its mechanisms and biological underpinnings are still elusive.^{1,9} Multiple pathways have been studied in relation to CRF. Inflammation, dysregulation of the hypothalamic–pituitary–adrenal axis, and/or activation of the autonomic nervous system have traditionally been advocated as potential mechanisms of CRF, being able to influence each other and to activate additional systems such as oxidative stress cascades, endocannabinoids, and gut microbiota.^{1,17} Over the past few years, the link between cancer-related inflammation and CRF received the greatest empirical attention. It has been suggested that CRF and other “sickness behaviors”, including emotional distress, cognitive dysfunction, pain, and insomnia, may stem from central stimulation resulting from peripheral activation of the inflammatory axis and the production of pro-inflammatory cytokines.¹⁸⁻²⁰ Carrol and colleagues also suggested that variation in

individual susceptibility to symptoms including CRF may be substantially driven by cellular senescence and accelerated ageing resulting from tumor-host-treatment interactions.²¹ Pre-existing factors including psychosocial and lifestyle traits, with mediation exerted by cancer treatment, may influence inflammatory pathways, and facilitate the accumulation of cells enriched with an inflammation-biased secretome.^{22–26} Particularly, several interleukins (IL; such as IL-1 and IL-6), C-reactive protein, and tumor necrosis factor-alpha (TNF- α) seemed to have implications in orchestrating local and systemic effects leading to a wide spectrum of host defense responses on energy levels.^{1,17} By signaling across the blood-brain interface, increased inflammation can then impair several bodily systems, being a shared biological substrate across oncologic, cardiovascular, and metabolic comorbidities.²¹ It is also plausible that the effect of initial systemic inflammation keeps manifesting on CRF for years after cancer diagnosis, as a combined result of physiological and accelerated aging, accumulation of greater comorbidity, disrupted compensatory capacities, long-term treatment burden, and perpetuating factors such as poor diet, physical inactivity and sleep disturbance.^{4,27–29}

Taken together, previous research has generated evidence about inflammation, neuroimmune interactions, and immune mechanisms for CRF. However, this evidence is not always consistent and often limited by the cross-sectional nature and small sample size of studies that are therefore sensitive to a number of biases.^{17,30} In the present analysis, we evaluated the contribution of pre-treatment markers of systemic inflammation or inflammatory axis activation (i.e., assessed at breast cancer diagnosis, before any treatment for breast cancer) to models of CRF considered of clinical importance^{31,32} two years later, using a large, prospective cohort of survivors of early-stage breast cancer. Our study builds on previous knowledge suggesting an inflammatory basis for CRF and on existing evidence of the interplay between health behaviors and CRF, also aiming to find potential interventional targets

PATIENTS AND METHODS

Study design

We used CANTO (CANcer TOxicity; ClinicalTrials.gov identifier: NCT01993498), a large, prospective cohort of survivors of stage I-III breast cancer. Briefly, clinical, socio-economic, behavioral, tumor and treatment characteristics, and patient-reported outcome data are collected at diagnosis of breast cancer (pre-treatment, i.e., before any primary breast cancer treatment including surgery, chemo-, or radiotherapy, as appropriate), then longitudinally reassessed at approximately one, two, four, and six years after diagnosis. Endocrine therapy and targeted therapies are allowed to be ongoing during the follow-up time points. Patients experiencing disease recurrence, metastatic relapse, or death, exit the study and do not contribute to the analyses from the event date forward. All patients provided written informed consent. The study design was previously described (Ethics committee approval: ID-RCB:2011-A01095-36,11-039).³³

Cohort definition

This analysis included patients with hormone-receptor (HR)-positive, human epidermal growth factor receptor (HER) 2-negative breast cancer diagnosed from 2012-2013, who had a pre-treatment blood sample available for quantification of inflammatory markers. The final analytic cohort included patients providing data on CRF at the year-2 time point (N= 1208 for the primary outcome; the full study flowchart is presented in **Supplementary Figure 1**).

Outcome assessment

Our primary outcome of interest was global CRF at year-2 after diagnosis, assessed using the three-item scale of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30. A higher score on this scale indicates a higher level of symptomatology. Scores were dichotomized using a threshold of $\geq 40/100$, typically defining clinically important CRF.^{31,32}

In addition, we assessed the physical, emotional, and cognitive dimensions of CRF at year-2 after diagnosis as secondary outcomes, using the EORTC module measuring CRF

(EORTC QLQ-FA12), a multidimensional instrument to be used in conjunction with the core EORTC QLQ-C30.³⁴ The questionnaire includes five items for physical (Item 1-5), three for emotional (Item 6-8), and two for cognitive CRF (Item 9-10). While there is no threshold for clinical importance for the QLQ-FA12 scores, a cut-off value of 40/100 was used to identify CRF dimensional symptoms of clinical relevance, consistent with a previous study.¹⁵

Additional information on the outcome assessment instruments and score calculation is available in the **Supplementary Methods**.

Clinical and behavioral variables of interest

Based on clinical expertise and prior evidence of association with CRF^{1,7-11}, we included clinical, socio-demographic, behavioral, tumor- and treatment-related factors, and symptoms (including pre-treatment fatigue) in our analyses. Variables were defined and categorized as described in **Table 1**. These variables were collected at study entry (breast cancer diagnosis, equivalent to pre-treatment in the CANTO study) during dedicated visits with trained study nurses as per study protocol, and included the following: age at diagnosis of breast cancer, Body Mass Index (BMI; objectively assessed during clinical study visits), menopausal status, comorbidities (Charlson comorbidity index), previous mental health problems, marital status, education, and income (*ad hoc* socio-economic questionnaire), alcohol consumption, tobacco use, physical activity (Global Physical Activity Questionnaire-16)³⁵, breast cancer stage, axillary and breast surgery, receipt of chemotherapy, radiotherapy, hormonal therapy, anxiety and depression (Hospital Anxiety and Depression Scale [HADS; non-case, score 0-7; doubtful case, score 8-10; case, score 11-21])³⁶, CRF, insomnia, pain (EORTC QLQ-C30)³⁷, and menopausal symptoms (i.e., hot flashes; Common Terminology Criteria for Adverse Events [CTCAE v 4.0, Yes= any grade]).³⁸

Biological variables of interest: serum inflammatory markers

Fasting blood samples were obtained pre-treatment, kept at room temperature for 30-60 minutes, then centrifuged for 15 minutes at 1800g to obtain 200 to 400 uL of serum, which was stored in two aliquots at -180°C for long-term preservation until analyzed.

The High Sensitivity Cytokine Custom array (CTK CST X, EV3881/EV3623), the Metabolic Syndrome array I (METS I, EV3755), and the Metabolic Syndrome array II (METS II, EV3759/A) were used for the quantification of the following serum inflammatory markers: IL-1 α , IL-1 β , IL-2, IL-4, IL-8, IL-10, interferon gamma (IFN γ), IL-1 receptor antagonist (IL-1Ra) (CTK), IL-6, TNF- α (METS I), and C-reactive protein (METS II) (RANDOX Laboratories Limited, UK). Previous studies suggested the implication of these markers in inflammatory responses linked with CRF and other behavioral symptoms.^{1,13,17} All samples from a single subject were assayed together on the same ELISA plate to minimize effects of inter-assay variation, with internal quality controls applied twice, once at the beginning and once at the end of each run, using the RANDOX Evidence Investigator™ Biochip Array technology.³⁹

For the primary analysis focused on global CRF at year-2 (EORTC QLQ-C30), concentrations were dichotomized as “low” vs “high” according to the lower limit of quantification for the individual assay (sensitivity threshold). If the sensitivity threshold was sufficiently low (i.e., $\leq 15^{\text{th}}$ percentile), categories were defined according to the quartile (Q) distribution as “low” (Q1), “middle low” (Q2), “middle high” (Q3), and “high” (Q4), to allow for a more granular quantification. Similar approaches were previously used.⁴⁰ C-reactive protein values were categorized according to levels with clinical meaning (Normal/low [< 1 mg/L], moderately elevated [1 to < 3 mg/L], and high [≥ 3 mg/L]).⁴¹ Categorization is shown in **Table 2**.

Secondary analyses were performed using continuous log-transformed values of the markers and including the ratio IL1Ra/IL-6, both for the primary outcome of global CRF (EORTC QLQ-C30) and for outcomes of dimensions of CRF (EORTC QLQ-FA12). Continuous values of the markers are available in **Supplementary Table 1** and **2**.

Statistical analysis

Cohort and outcome description. Descriptive statistics summarized distribution of clinical and behavioral characteristics, and serum concentrations of inflammatory markers at breast cancer diagnosis, as well as outcome distribution at year-2 after diagnosis.

Selection of factors to be included in the multivariable model. To assess clinical, behavioral, and biological factors that could explain the variability in CRF of clinical importance at year-2, we used multivariable logistic regression implementing automatic backward variable selection under multiple imputation (MI), combined with bootstrapping, as described by Heymans MW et al, to account both for variation linked to missing data and sampling.⁴² Missing covariate data were handled generating 15 complete data replicates by MICE (Multivariate Imputation by Chained Equations).⁴³ The imputation model included (a) all variables that would be part of the subsequent analytic model (as listed in Table 1, 2, and 3); (b) the outcome variables (of note, missing outcome variables were not imputed, outcome data was used to impute missing values in other covariates); and (c) auxiliary variables, included to help minimize bias and improve precision of the estimates. These variables were identified using domain knowledge or through association with incomplete variables, and included menopausal status, health behaviors (BMI, physical activity, smoke, alcohol), presence of concomitant medical conditions (i.e., history of previous cardio-circulatory, respiratory, gastrointestinal, renal, hepatic, endocrine, muscle-articular, urologic, hematologic, dermatologic, neurologic, allergic, gynecological disease), socioeconomic variables (marital status, professional status, level of education), household income, and patient-reported health (EORTC QLQ-C30 domains, continuous scores). For each replicate, we constructed 100 bootstrap sets by randomly drawing with replacement, therefore the total number of data sets equaled 1500 (15-MI*100-bootstrap). For the primary analysis focused on global CRF (EORTC QLQ-C30), we used strict selection criteria to define factors for the final multivariable model, including categorical inflammatory markers. First, the automatic stepwise method used a p-value cut-off of ≥ 0.05 to remove variables. Then, we calculated the proportion of times each variable appeared in the models (i.e., the inclusion frequency) and retained in the final

multivariable model only variables for which the inclusion frequency exceeded 70%. These criteria allow to exploit the wealth of data from the CANTO study without overfitting the models and minimize the risk of including noise variables.⁴² Results obtained across imputed data sets were combined using Rubin's rules to produce Odds Ratio (OR) estimates and Confidence Intervals (CIs) that incorporate uncertainty of imputed values.⁴⁴

For secondary analyses, focused both on global CRF (EORTC QLQ-C30) and dimensions of CRF (EORTC QLQ-FA12), we incorporated continuous log-transformed values of the markers using a more lenient inclusion frequency of 50%, while keeping the probability to remove variables strictly set at ≥ 0.05 in the stepwise procedure. This strategy would allow us to obtain a less parsimonious model while limiting the inclusion of an excessive number of non-informative variables.^{42,45}

Model performance and bootstrap validation. The discriminative ability of the model was assessed by c-index, equal to the Area Under the Receiver Operating Characteristic Curve (AUC). Calibration was visually explored by plotting the observed and estimated probabilities of clinically important CRF. The optimism-corrected AUC and calibration were obtained by bootstrap.⁴⁶

Sensitivity analyses. We aimed at testing whether different definitions, categorizations, and selection criteria for variables of interest would impact modelling findings. Therefore, several sets of sensitivity analysis were conducted for the primary outcome and additional models were fit i) using pain and insomnia as categorical variables (i.e., dichotomizing according to thresholds of clinical importance: a cut-off of 50/100 and 25/100 defined clinically important insomnia and pain, respectively^{31,32}; and ii) irrespective of statistical variable selection (to correct for the potential confounding effect of age, health behaviors such as BMI, tobacco smoke, and physical activity, and anxiety and depression). Finally, acknowledging the importance of emotional distress in relation with CRF, iii) we fit models not including pre-treatment CRF of clinical importance and including anxiety and depression either as (a) categorical (HADS standard cut-off definitions) or (b) continuous variables.

Power considerations. With a binary outcome prevalence of approximately 35%, a minimal sample size of 1022 patients was needed to minimize overfitting (expected shrinkage of 10% or lower) and to ensure precise estimation of key parameters in a model with 15 variables (including an absolute difference of 0.05 in the model apparent and adjusted R-squared value).⁴⁷

Statistical analysis was performed using SAS statistical software Version 9.4. Statistical significance was defined with a two-sided p -value <0.05 .

RESULTS

Cohort characteristics

In the overall cohort, mean age was 57.9 years (Standard Deviation [SD] 11.1), 191 patients (16.3%) had a history of previous mental health problems (i.e., mostly anxiety–depressive disorders), 253 (21.2%) reported pre-treatment CRF of clinical importance, 425 (35.6%) and 82 (6.9%) had clinically suggestive symptoms of anxiety and depression at diagnosis (cases), respectively. In addition, mean BMI was 25.9 Kg/m² (SD 5.2), 204 patients (17.3%) reported current smoking at diagnosis, and median total physical activity level was 14.0 Metabolic-equivalent of task-hour (MET-h)/week; Q1-Q3 0.0-40.0). Five hundred and thirty three patients (44.1%) received (neo)adjuvant chemotherapy and 1109 (91.8%) were treated with adjuvant hormonal therapy (**Table 1**).

Bio-behavioral model of global CRF at year-2

Four hundred fifteen patients (34.4%) reported CRF of clinical importance at year-2 post diagnosis of breast cancer.

The main model of CRF included a combination of clinical, behavioral, and biological characteristics (inclusion frequencies are presented in **Supplementary Table 3**). IL-6 was the only inflammatory marker selected with strict inclusion frequency $>70\%$ and therefore tested in the main multivariable model of CRF at year-2. A larger proportion of patients among those that reported CRF of clinical importance at year-2 had high levels of pre-treatment IL-6

compared to those that did not (30.8% and 21.9% respectively; **Table 2**), and this difference was consistent across age groups and menopausal status (not shown). After correction for clinical and behavioral characteristics, high pre-treatment IL-6 levels were associated with CRF of clinical importance at year-2 (adjusted OR vs low IL-6: 2.06 [95% CI 1.40-3.03]; $p=0.0002$). The model AUC was 0.75 (95% CI 0.72-0.78; Optimism-corrected AUC=0.74; **Table 3; Supplementary Figure 2**). Patients with high pre-treatment levels of IL-6 had unhealthier behaviors compared to those with lower levels, including that they were frequently either overweight or obese (62.4%; mean BMI 28.0 [SD 6.3] Kg/m²), did not meet WHO physical activity recommendations (53.5% reported <10 MET-hours/week; median time: total activity 8.0 [Q1-Q3 0.0 to 28.0] MET-hours/week, transport and leisure-time activity 4.0 [0.0 to 18.3]), and several among them (20.1%) were current smokers (**Supplementary Figure 3**, additional clinical characteristics are presented in **Supplementary Table 4**).

Pre-treatment clinical and behavioral factors that were associated with CRF of clinical importance at year-2 in the main model included reporting pre-treatment fatigue of clinical importance (OR vs no: 3.99 [95% CI 2.81-5.66]), younger age (per 1-year decrement: 1.02 [1.01-1.03]), being a current smoker (vs never: 1.81 [1.26-2.58]), and CRF-associated symptom burden at diagnosis including worse insomnia (per 10-unit increment: 1.08 [1.04-1.13]) and pain (per 10-unit increment: 1.12 [1.04-1.21]). Treatment-related factors and pre-treatment physical activity were not retained in the model of global CRF.

Models using inflammatory markers as log-transformed continuous variables identified several associations of CRF of clinical importance at year-2, including with pre-treatment IL-6 (OR per log-unit increment: 1.33 [1.11-1.60]), IL-2 (1.32 [95% CI 1.03-1.70]), and IL-10 (0.73 [95% CI 0.57-0.93]). Additional associations with clinical and behavioral factors were consistent with the main model. Inclusion frequencies for this model are presented in **Supplementary Table 5**, the full model is presented in **Supplementary Table 6**.

Models of CRF dimensions at year-2: physical, emotional, and cognitive CRF

At year-2 after diagnosis, 426 (35.1%), 268 (22.1%), and 165 patients (13.6%) reported physical, emotional, and cognitive CRF of clinical importance, respectively. A descriptive summary of clinical, behavioral and biological characteristics is provided in **Supplementary Table 7** and **8**.

Focusing on the contribution of inflammatory markers to models of CRF dimensions, significant associations were observed between increasing levels of C-reactive protein and cognitive CRF (OR per log-unit increment in C-reactive protein 1.42 [95%CI 1.13-1.78]), whereas there were no specific associations with physical or emotional CRF. Additional relevant clinical and behavioral factors emerged from these models. Among these, pre-treatment, clinically suggestive symptoms of depression were significantly associated with the three dimensions of physical (OR case vs. normal 2.19 [95% CI 1.25-3.84]), emotional (OR case vs. normal 1.97 [95% CI 1.13-3.42]), and cognitive CRF of clinical importance (OR case vs. normal 1.92 [95% CI 1.05-3.49]), after multivariable correction that also included pre-treatment CRF. In addition, pre-treatment, clinically suggestive symptoms of anxiety were significantly associated with emotional CRF (OR case vs. normal 1.91 [95% CI 1.26-2.90]). Finally, previous mental health problems were associated with physical (OR vs. no 1.72 [95% CI 1.22-2.43]) and cognitive (OR vs. no 1.66 [95% CI 1.07-2.57]) CRF. Mastectomy was associated with physical CRF (OR vs. conservative surgery 1.38 [95%CI 1.03-1.85]). Full models are presented in **Supplementary Table 9**.

Sensitivity analyses

Models indicated consistent associations between higher pre-treatment levels of IL-6 and CRF of clinical importance at year-2 across all sensitivity analyses, namely i) using insomnia and pain as categorical variables (**Supplementary Table 10**); and ii) fitting a model by including age, health behaviors, and emotional distress without variable selection (**Supplementary Table 11**). Finally, iii) in a last set of sensitivity models not including pre-treatment CRF, associations emerged also between pre-treatment depression and global CRF of clinical importance at year-2 (OR for clinically suggestive case vs. non-case 2.06 [95% CI

1.24-3.43]; OR per unit increment in continuous depression score 1.07 [95% CI 1.03-1.11]; full models not shown).

DISCUSSION

This large, prospective study of women with HR+/HER2- breast cancer adds a biological dimension focused on pre-treatment inflammation to clinical and behavioral models of CRF. We found consistently increased likelihood of reporting global CRF of clinical importance two years after breast cancer diagnosis among women with high pre-treatment levels of IL-6, compared to those with low levels. Capitalizing on the role of behavioral factors, we also report that pre-treatment excess weight and physical inactivity were prevalent among women with high circulating levels of inflammatory marker. Additional biological associations emerging from this study included those of pre-treatment IL-2 and IL-10 with global CRF as well as of C-reactive protein with cognitive CRF. Clinical and behavioral factors associated with global CRF included pre-treatment fatigue, younger age, current smoking, and worse insomnia or pain. Models of physical, emotional, and cognitive dimensions of CRF were significantly informed by metrics of pre-treatment emotional distress.

There is convergence between our findings and those from previous studies supporting an inflammatory basis for CRF and other behavioral symptoms among cancer patients and suggesting that perturbation of immune system homeostasis may help structure elevations in circulating inflammatory markers in survivors with persistent CRF.^{1,20,48} Such alterations may manifest in multiple ways, including reactivation of latent infections, deregulation of glucocorticoid signaling and alterations in lymphocyte subsets.^{1,17} Several authors reported, at various points across the survivorship trajectory, associations between pro-inflammatory cytokine activity with CRF, especially in the post-treatment period. Our study validates and extends the findings of many smaller samples. Noteworthy, high levels of IL-6 across the distribution were associated with CRF in our main models, and additional identified markers included C-reactive protein, IL-10, and IL-2. While previous studies usually assessed panels

of inflammatory markers¹⁷, several reported associations between IL-6⁴⁹⁻⁵² and/or C-reactive protein^{30,53-55} with CRF. IL-6 is a pleiotropic cytokine produced by a variety of cell types, involved in antigen-specific immune responses and inflammatory responses, mediation of acute phase reactions, and in host-defense mechanisms⁵⁶⁻⁵⁸, whereas C-reactive protein is a sensitive downstream indicator of inflammation, and its concentrations have clinical meaning in several settings.^{59,60} Some evidence also indicated associations of CRF with IL-10⁶¹, suggested to increase in response to pro-inflammatory cytokines and to exert an anti-inflammatory effect by modulating their levels.⁶² This is consistent with our findings indicating a reverse relationship between higher levels of IL-10 and lower likelihood of CRF. Finally, the association between the pro-inflammatory cytokine IL-2 and CRF was observed less frequently in previous studies, and its increase in fatigued survivors could be put in relation with elevation of multiple cytokines involved in the inflammatory process rather than of a single marker.^{17,63} Previous literature has also examined the IL-6 gene single nucleotide polymorphisms (SNPs) and CRF. Associations with CRF were described before, during, and after cancer treatment, extending also to SNPs in genes encoding IL-1, IL-10, and TNF- α , and expression of Type I interferon genes.⁶⁴⁻⁶⁸ Furthermore, evidence is available linking circulating levels of IL-6 and its genetic polymorphisms with other behavioral symptoms such as depression and memory problems, which are common in severely fatigued survivors.⁶⁹

While inflammation is among the most discussed mechanisms of fatigue, including in the non-cancer realm (e.g., for fatigue associated with autoimmune, neurological, and musculoskeletal diseases)⁷⁰, scenarios have been proposed where its contribution is less clear. Results of several studies, either with longitudinal or cross-sectional designs, were controversial or failed to demonstrate a relationship between inflammatory markers and CRF independently of other clinical, behavioral or socio-demographic risk factors.^{71,72} Of note, these studies are heterogeneous in terms of design, analytic methods, and CRF outcomes, assessment instruments, and time-points.¹⁷ Cluster analyses may help further dissect subgroups of CRF driven by concomitant clinical conditions (e.g., psychological disturbance,

sleep dysregulation and pain, obesity), from those associated with inflammatory or different biological patterns. By looking at a post-diagnosis survivors population, Schmidt et al.¹³ delineated different subgroups of CRF, including one occurring along a history of depression, a second associated with inflammation (i.e., with high levels of inflammatory markers including IL-6, but also TNF- α , IL-1 β , resistin, VEGF-A and GM-CSF), and a third characterized by metabolic markers such as leptin. The inflammation-associated cluster also expressed high levels of pain and high BMI, findings that echo the associations with other symptoms (e.g., insomnia, pain) and bio-behavioral factors (e.g. increased BMI, inactivity) observed in our cohort. These authors have therefore proposed targeting fatigue phenotypes that are driven by different mechanisms with specific interventions, modeling fatigue management upon patient features and biological hallmarks of CRF subtypes.^{8,13} Nevertheless, the contributing mechanisms and biological substrates of the different CRF dimensions still need further elucidation.⁷⁰ For example, there were higher manifestations of physical CRF in the cluster associated with inflammation¹³, consistent with other studies.^{53,73,74} Conversely, in our cohort with a different design, the only dimension that seemed associated with inflammation was cognitive CRF, for which a relationship with pre-treatment C-reactive protein was evident. In the CANTO-Cog sub-study focused on cognition, we also reported associations between high levels of C-reactive protein assessed at diagnosis of breast cancer and overall cancer-related cognitive impairment, processing speed and episodic memory impairments two years later.⁷⁵ Others recently suggested longitudinal relationships between C-reactive protein and cognitive complaints in older breast cancer survivors.⁷⁶ Such findings can help contextualize the associations between C-reactive protein and the feelings of “having trouble thinking clearly” and “confusion”³⁴ reported by survivors with elevated cognitive CRF in our cohort.

Development and validation of a model of clinical and behavioral risk factors for CRF and related discussion was the focus of a previous manuscript¹⁵, however the associations between emotional distress and CRF reported herein merit further discussion. Clustering of emotional distress with fatigue was reported by numerous previous studies^{7,8,13,77–80}, including

ours^{6,15}, and CRF characterized by depressive symptoms/anxiety was suggested to manifest with more severe and persisting physical, emotional, and cognitive symptoms compared to CRF not linked with depression. In our main model, emotional distress variables were not retained in association with global CRF two years later. This association might have been masked by the inclusion of pre-treatment CRF of clinical importance in the models, as also suggested by sensitivity analyses. However, pre-treatment CRF is one of the strongest and most consistent predictors of post-treatment CRF and may set the stage for elevated CRF years after treatment completion, therefore including this metric in a pre-treatment model is particularly relevant. Some authors also suggested that most studies looking at predictors of CRF did not control for pre-treatment CRF and therefore the independent contribution of depression (and other clinical factors) above pre-existing CRF might be not entirely clear.¹ In general, models including a baseline measurement of the outcome yield better performance and more accurate estimates.⁸¹⁻⁸⁴ As opposed to models of global CRF, our models of the physical, emotional, and cognitive dimensions of CRF had very consistent associations with symptoms suggestive of anxiety or depression at the moment of diagnosis or with mental health problems that pre-existed breast cancer diagnosis. These disorders may determine poorer psychological adjustment to cancer and increase vulnerability to long-term CRF.⁸ Beyond impairing coping capacity, emotional vulnerability was also linked to increased inflammatory responses to stress.^{19,85,86} Confirming what previously suggested, our findings underpin the role of emotional distress in defining a CRF phenotype with multidimensional manifestations (e.g., slowing down, having trouble getting things started, helplessness, frustration, impaired thinking ability) rather than just general feelings of weakness and need to rest.⁸

In terms of other clinical and behavioral factors, receipt of more extensive breast surgery was previously associated with CRF⁸⁷, a finding that we also report. It is important to highlight that the timing of outcome assessment in our study may be responsible for the lack of observed associations between CRF and other treatment-related factors. CRF was

assessed at least one year after primary treatment completion in our cohort. We previously reported an early association of chemotherapy with global and physical CRF at approximately 3-6 months after treatment.¹⁵ Consistently, previous studies had pointed at chemotherapy as a precipitating factor for CRF (i.e. arising during treatment), with weaker effects on long-term, persistent CRF.⁷ On the contrary, several studies, including ours, had identified hormonal therapy as a factor perpetuating CRF later during follow-up.^{15,27} Associations with hormonal therapy might not be evident in the present HR+/HER2-cohort, as the overwhelming majority received adjuvant hormonal therapy. Further research should look at interactions between cancer treatment and inflammation on long-term symptoms, as these may not be manifested until several years after initial treatment, including until longer term exposures to hormonal therapy. In addition, we did not find associations between pre-treatment levels of physical activity and CRF, which might partly be explained by the observational nature of the cohort with self-reported activity and subject to over-reporting, and by the time elapsed between exercise exposure and outcome assessment.

A relevant question is whether we can implement our -or similar- models to improve patient stratification, targeted provision of behavioral interventions, and monitoring strategies to prevent CRF deterioration in clinical practice. In addition to actionable clinical factors such as baseline symptom burden, excess adiposity and inactivity were common among individuals with increased markers of inflammation in our analysis, suggesting potential modifiable targets for interventions. As previously indicated, an expanded, reprogrammed, and metabolically active adipose tissue may alter systemic physiology of individuals with obesity, by enhancing secretion of cytokines, including IL-6, and adipokines, and activate key pathways that trigger or precipitate the CRF cascade.^{1,88} Analogously, dysregulation in systemic inflammation is observed in sedentary individuals.¹ The link between inflammation, behaviors, and CRF symptoms is further reinforced by data from interventional research. Although there is still uncertainty about whether a shared inflammatory substrate is consistently present or not, several behavioral interventions, including those focused on exercise, psychological support,

mindfulness, and yoga, have shown a positive impact on CRF and the associated spectrum of behavioral symptoms that include cognitive disturbance, emotional distress, social withdrawal, and sleep troubles, suggesting a common biological basis.^{24–26,48,89–95} By acting on modifiable host-specific factors such as sedentary behavior, but also on poor sleep, psychosocial stress and catastrophizing, behavioral interventions can target inflammation, disrupt its feed-forward pathways, and mitigate symptoms.⁹⁶ It is evident that one-size-fits-all approaches may not be sufficient facing the complexity and multidimensionality of CRF subtypes and its entanglement with other behavioral symptoms. Our models are not intended to point at a single (or few) diagnostic biomarker(s) of CRF. They rather provide a bio-behavioral framework for thorough evaluation of potential risk factors for CRF since diagnosis, including screening for the presence of pre-treatment CRF and past medical history with a focus on previous mental health problems, and addressing acute emotional vulnerability and additional symptoms such as insomnia and pain. Behavioral factors should also be thoroughly assessed and options to improve an unhealthy lifestyle (e.g., excess weight, inactivity, tobacco smoking) offered as appropriate. When moderate-to-severe pre-treatment CRF is present, it should be treated. These recommendations are reflected in current CRF guidelines for patients and survivors across the disease spectrum^{96–99} and many of them represent cornerstones of optimal survivorship care beyond the management of CRF.¹⁰⁰ There is still no evidence demonstrating that “intercepting the risk” of post-treatment symptoms early along the cancer trajectory and correcting modifiable factors may alter the course of CRF. However, refined knowledge of symptom science, including leveraging bio-behavioral models of CRF, paves the way and sets out the rationale for prospective studies testing these hypotheses.¹⁰¹ Examples of such studies, assessing feasibility, acceptability, and effectiveness of risk stratification and personalized supportive care pathways are ongoing or in the pipeline at our institution¹⁰², and similar efforts are in place elsewhere, aiming at implementing CRF screening in routine care to provide early treatment options.¹⁰³

We acknowledge that the model we propose is only “a” bio-behavioral model that may explain CRF. It focuses on pre-treatment factors and on outcomes reported two years later. Some factors such as childhood trauma, or biochemical parameters such as cortisol and hormonal levels could not be investigated. We included a relatively homogeneous population of breast cancer survivors from the CANTO study without a healthy control group that could have allowed comparisons with individuals that did not receive cancer treatment. We also acknowledge a potential impact of variability linked to stability of the analyte in the samples and measurement error that is intrinsically linked to the evaluation methods implemented in any biological analysis. However, all analytic procedures underwent strict quality control at a reference center (Gustave Roussy, Villejuif, France), ensuring collection, storage, and profiling standards are met¹⁰⁴, and that quantifications are consistent with studies using similar assays.^{39,105} Despite measures taken to optimize variable selection, some may have not been retained due to inclusion thresholds. Nevertheless, we used an established methodology⁴² and results are strengthened by several sensitivity analyses. Additional specific strengths include a prospective and longitudinal design, and the wealth of available data, including a baseline, pre-treatment evaluation of serum inflammatory markers and of the outcome.

In conclusion, we generated a bio-behavioral model of CRF incorporating pre-treatment clinical, behavioral, and biological factors. While our results build and strengthen an evidence base about the inflammatory biology involved in CRF, future studies should be encouraged to unveil additional mechanisms underlying symptom onset and evolution. Novel technologies such as wearable biosensors could be exploited to test the clinical utility of devices allowing for a continuous monitoring of systemic inflammation and behaviors, providing data regarding potential “dynamic markers”.^{106–108} An agnostic approach, delving into multi-omics, may also unlock a more comprehensive understanding of alternative biological pathways and substrates that extend beyond cancer-related inflammation, providing further actionable mechanistic targets.¹⁰¹

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TABLES

Table 1. Descriptive statistics on the distribution of clinical and behavioral characteristics of the cohort at breast cancer diagnosis.			
Variable (all assessed at diagnosis of breast cancer)	Whole cohort (N=1208)	Reporting fatigue of clinical importance at year-2 (EORTC QLQC-30)	
		Yes (N=415; 34.4%)	No (N=793; 65.6%)
Age, years			
Mean (SD)	57.9 (11.1)	56.2 (11.4)	58.9 (10.8)
Min-Max	22.3–88.2	28.6–88.2	22.3–85.5
Missing	-	-	-
BMI, Kg/m²			
Mean (SD)	25.9 (5.2)	26.1 (5.5)	25.8 (5.1)
Missing	3	2	1
Menopausal status, N (%)			
Premenopausal	413 (34.4)	163 (39.6)	250 (31.7)
Postmenopausal	788 (65.6)	249 (60.4)	539 (68.3)
Missing	7	3	4
Charlson comorbidity index, N (%)			
0	867 (78.6)	283 (77.1)	584 (79.3)
>=1	236 (21.4)	84 (22.9)	152 (20.7)
Missing	105	48	57
Previous mental health problems, N (%)			
No	983 (83.7)	321 (79.3)	662 (86.1)
Yes	191 (16.3)	84 (20.7)	107 (13.9)
Missing	34	10	24
Marital Status, N (%)			
Not partnered	275 (23.8)	109 (27.5)	166 (21.9)
Partnered	880 (76.2)	287 (72.5)	593 (78.1)
Missing	53	19	34
Education level, N (%)			
Primary school	192 (16.6)	67 (16.8)	125 (16.5)
High school	532 (46.0)	185 (46.5)	347 (45.8)
College or higher	432 (37.4)	146 (36.7)	286 (37.7)
Missing	52	17	35
Household income, N (%)			
<1500	166 (15.2)	73 (19.5)	93 (12.9)
>=1500 and <3000	442 (40.4)	156 (41.6)	286 (39.8)
>=3000	486 (44.4)	146 (38.9)	340 (47.3)
Missing	114	40	74
Alcohol consumption behavior, N (%)			
Less than daily consumption	970 (84.3)	332 (84.7)	638 (84.2)
Daily consumption	180 (15.7)	60 (15.3)	120 (15.8)
Missing	58	23	35
Tobacco use behavior, N (%)			
Current smoker	204 (17.3)	108 (26.9)	96 (12.4)
Former smoker	240 (20.4)	76 (18.9)	164 (21.2)
Never smoker	733 (62.3)	218 (54.2)	515 (66.5)
Missing	31	13	18
Physical activity (MET-h/week)			
Median (Q1-Q3)	14.0 (0.0–40.0)	12.0 (0.0–40.0)	16.0 (0.7–38.0)
Missing	31	7	24
Breast cancer stage, N (%)			
Stage I	651 (54.1)	201 (48.8)	450 (56.8)
Stage II	439 (36.5)	166 (40.3)	273 (34.5)
Stage III	114 (9.5)	45 (10.9)	69 (8.7)

Missing	4	3	1
Axillary surgery, N (%)			
None or sentinel node biopsy	733 (60.7)	243 (58.6)	490 (61.8)
Dissection	475 (39.3)	172 (41.4)	303 (38.2)
Missing	-	-	-
Breast cancer surgery, N (%)			
Conservative	898 (74.3)	294 (70.8)	604 (76.2)
Mastectomy	310 (25.7)	121 (29.2)	189 (23.8)
Missing	-	-	-
Chemotherapy, N (%)			
No	675 (55.9)	214 (51.6)	461 (58.1)
Yes	533 (44.1)	201 (48.4)	332 (41.9)
Missing	-	-	-
Radiotherapy, N (%)			
No	111 (9.2)	37 (8.9)	74 (9.3)
Yes	1097 (90.8)	378 (91.1)	719 (90.7)
Missing	-	-	-
Hormonal therapy, N (%)			
No	99 (8.2)	30 (7.2)	69 (8.7)
Yes	1109 (91.8)	385 (92.8)	724 (91.3)
Missing	-	-	-
Anxiety, N (%)			
Non-case	445 (37.3)	119 (28.8)	326 (41.7)
Doubtful case	324 (27.1)	107 (25.9)	217 (27.8)
Case	425 (35.6)	187 (45.3)	238 (30.5)
Missing	14	2	12
Depression, N (%)			
Non-case	990 (83.0)	309 (74.8)	681 (87.3)
Doubtful case	121 (10.1)	51 (12.3)	70 (9.0)
Case	82 (6.9)	53 (12.8)	29 (3.7)
Missing	15	2	13
Fatigue			
Mean (SD)	25.8 (23.9)	38.8 (25.9)	18.9 (19.5)
Missing	17	3	14
Fatigue of clinical importance, N (%)			
No	938 (78.8)	236 (57.3)	702 (90.1)
Yes	253 (21.2)	176 (42.7)	77 (9.9)
Missing	17	3	14
Insomnia			
Mean (SD)	40.7 (33.1)	51.0 (34.4)	35.2 (31.0)
Missing	19	3	16
Pain			
Mean (SD)	14.1 (20.6)	21.7 (24.3)	10.1 (17.1)
Missing	13	3	10
Hot flashes, N (%)			
No	859 (74.5)	274 (70.1)	585 (76.8)
Yes	294 (25.5)	117 (29.9)	177 (23.2)
Missing	55	24	31

SD: Standard Deviation; Q: Quartile; BMI: Body Mass Index; MET-h: Metabolic-equivalent of task-hour; HR: hormone receptor, HER2: Human epidermal growth factor receptor 2. Total physical activity scored as a continuous variable according to the Global Physical Activity Questionnaire (GPAQ)-16. Anxiety and Depression scored according to the Hospital Anxiety and Depression Scale: non-case (score 0-7), Doubtful case (8-10), case (11-21). Fatigue, insomnia, and pain scored using the EORTC QLQ-C30; Hot flashes assessed by the Common Terminology Criteria for Adverse Events –CTCAE- v 4.0 (Yes= any grade).

Table 2. Descriptive statistics on the distribution of inflammatory markers at breast cancer diagnosis.			
Variable (all assessed at diagnosis of breast cancer)	Whole cohort (N=1208)	Reporting fatigue of clinical importance at year-2 (EORTC QLQ-C30)	
		Yes (N=415; 34.4%)	No (N=793; 65.6%)
IL-1a, N (%)			
Low	928 (77.3)	307 (74.3)	621 (78.9)
High	272 (22.7)	106 (25.7)	166 (21.1)
Missing	8	2	6
IL-1b, N (%)			
Low	300 (25.0)	94 (22.8)	206 (26.2)
Middle low	305 (25.4)	113 (27.4)	192 (24.4)
Middle high	296 (24.7)	107 (25.9)	189 (24.0)
High	299 (24.9)	99 (24.0)	200 (25.4)
Missing	8	2	6
IL-2, N (%)			
Low	1057 (89.5)	354 (86.8)	703 (90.9)
High	124 (10.5)	54 (13.2)	70 (9.1)
Missing	27	7	20
IL-4, N (%)			
Low	1131 (95.8)	389 (95.3)	742 (96.0)
High	50 (4.2)	19 (4.7)	31 (4.0)
Missing	27	7	20
IL-6, N (%)			
Low	304 (25.3)	93 (22.5)	211 (26.7)
Middle low	300 (24.9)	96 (23.2)	204 (25.8)
Middle high	299 (24.9)	97 (23.5)	202 (25.6)
High	300 (24.9)	127 (30.8)	173 (21.9)
Missing	5	2	3
IL-8, N (%)			
Low	296 (25.1)	108 (26.5)	188 (24.3)
Middle low	296 (25.1)	103 (25.2)	193 (25.0)
Middle high	294 (24.9)	96 (23.5)	198 (25.6)
High	295 (25.0)	101 (24.8)	194 (25.1)
Missing	27	7	20
IL-10, N (%)			
Low	915 (76.3)	310 (75.1)	605 (76.9)
High	285 (23.8)	103 (24.9)	182 (23.1)
Missing	8	2	6
IFNg, N (%)			
Low	850 (82.6)	287 (81.1)	563 (83.4)
High	179 (17.4)	67 (18.9)	112 (16.6)
Missing	179	61	118
IL-1Ra*			
Low	579 (50.1)	184 (46.0)	395 (52.2)
High	577 (49.9)	216 (54.0)	361 (47.8)
Missing	52	15	37
TNF-a, N (%)			
Low	303 (25.1)	102 (24.6)	201 (25.3)
Middle low	305 (25.3)	103 (24.9)	202 (25.5)
Middle high	298 (24.7)	97 (23.4)	201 (25.3)
High	301 (24.9)	112 (27.1)	189 (23.8)
Missing	1	1	0
C-reactive protein, N (%)			
Normal/low	462 (38.2)	149 (35.9)	313 (39.5)

Moderately elevated	571 (47.3)	199 (48.0)	372 (46.9)
High	175 (14.5)	67 (16.1)	108 (13.6)
Missing	-	-	-

IL: Interleukin ; IFNg ; Interferon gamma ; IL1Ra : IL1 receptor antagonist ; TNF-a: tumor necrosis factor-alpha. The Cytokine Custom array HS (CTK CST X, EV3881/EV3623), the Metabolic Syndrome array I (METS I, EV3755) and Metabolic Syndrome array II (METS II, EV3759/A) were used for quantification of IL-1a, IL-1b, IL-4, IL-8, IL-10, IFNg, IL-1Ra (CTK), IL-6, TNFa (METS I), and CRP (METS II). If a significant proportion of marker values across the cohort distribution fell below the sensitivity threshold for the respective assay, continuous values were dichotomized as low vs high according to whether they were below vs above the sensitivity threshold, respectively. If the sensitivity threshold for an individual assay was relatively low respective to the distribution, continuous values were categorized according to the quartile (Q) distribution of the cohort as "low" (Q1), "middle low" (Q2), "middle high" (Q3), and "high" (Q4). *Sensitivity threshold not available, continuous values dichotomized according to median (i.e., "high" vs "low" according to whether they were above vs below median, respectively). Ranges and units for each category and variable are available in Supplementary Table 2.

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Table 3. Clinical and bio-behavioral model of global fatigue of clinical importance 2 years after diagnosis.

Variable (all assessed at diagnosis of breast cancer)	Odds Ratio	95% CI		p
		Lower	Upper	
Fatigue of clinical importance at diagnosis*, Yes vs. No	3.99	2.81	5.66	<.0001
Age, continuous (per 1-year decrement)	1.02	1.01	1.03	0.0021
Tobacco use behavior, Former vs. Never	0.96	0.68	1.35	0.7991
Tobacco use behavior, Current vs. Never	1.81	1.26	2.58	0.0012
Insomnia*, continuous (per 10-unit increment)	1.08	1.04	1.13	0.0002
Pain*, continuous (per 10-unit increment)	1.12	1.04	1.21	0.0023
IL-6, middle low vs. low	1.27	0.87	1.86	0.2234
IL-6, middle high vs. low	1.15	0.78	1.69	0.4957
IL-6, high vs. low	2.06	1.40	3.03	0.0002
Intercept	0.49	0.22	1.05	0.0672
<i>Naïve AUC (95% CI)</i>	0.75 (0.72-0.78)			
<i>Optimism-corrected AUC</i>	0.74			

CI: Confidence Interval; AUC: Area Under the Curve. *Scored according to the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (a score of $\geq 40/100$ indicates fatigue of clinical importance).