Can the Cancer-related Fatigue Case-definition Criteria Be Applied to Chronic Medical Illness? A Comparison between Breast Cancer and Systemic Sclerosis

Linda Kwakkenbos, Ollie Minton, Patrick C. Stone, Susanna Alexander, Murray Baron, Marie Hudson, Brett D. Thombs, and the Canadian Scleroderma Research Group

ABSTRACT. ***Objective.*** Fatigue is a crucial determinant of quality of life across rheumatic diseases, but the lack of agreed-upon standards for identifying clinically significant fatigue hinders research and clinical management. Case definition criteria for cancer-related fatigue were proposed for inclusion in the International Classification of Diseases. The objective was to evaluate whether the cancer-related fatigue case definition performed equivalently in women with breast cancer and systemic sclerosis (SSc) and could be used to identify patients with chronic illness-related fatigue.

Methods. The cancer-related fatigue interview (case definition criteria met if ≥ 5 of 9 fatigue-related symptoms present with functional impairment) was completed by 291 women with SSc and 278 women successfully treated for breast cancer. Differential item functioning was assessed with the multiple indicator multiple cause model.

Results. Items 3 (concentration) and 10 (short-term memory) were endorsed significantly less often by women with SSc compared with cancer, controlling for responses on other items. Omitting these 2 items from the case definition and requiring 4 out of the 7 remaining symptoms resulted in a similar overall prevalence of cancer-related fatigue in the cancer sample compared with the original criteria (37.4% vs 37.8%, respectively), with 97.5% of patients diagnosed identically with both definitions. Prevalence of chronic illness-related fatigue was 36.1% in SSc using 4 of 7 symptoms.

Conclusion. The cancer-related fatigue criteria can be used equivalently to identify patients with chronic illness-related fatigue when 2 cognitive fatigue symptoms are omitted. Harmonized definitions and measurement of clinically significant fatigue will advance research and clinical management of fatigue in rheumatic diseases and other conditions. (First Release June 1 2015; J Rheumatol 2015;42:1156–62; doi:10.3899/jrheum.141421)

Key Indexing Terms:
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From the Department of Psychiatry, Department of Medicine, Department of Epidemiology, Biostatistics and Occupational Health, Department of Educational and Counselling Psychology, Department of Psychology, and School of Nursing, McGill University; Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, Québec, Canada; Division of Population Health Sciences and Education, St. Georges University of London; Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London; Norfolk and Norwich University Hospitals National Health Service (NHS) Foundation Trust, Norwich, UK.

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L. Kwakkenbos, PhD, Department of Psychiatry, McGill University, and Lady Davis Institute for Medical Research, Jewish General Hospital; O. Minton, PhD, Division of Population Health Sciences and Education, St. Georges University of London; P.C. Stone, MD, Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London; S. Alexander, PhD, Norfolk and Norwich University Hospitals NHS Foundation Trust; M. Baron, MD; M. Hudson, MD, Lady Davis Institute for Medical Research, and Department of Medicine, McGill University; B.D. Thombs, PhD, Department of Psychiatry, Department of Medicine, Department of Epidemiology, Biostatistics and Occupational Health, Department of Educational and Counselling Psychology, Department of Psychology, and School of Nursing, McGill University, and Lady Davis Institute for Medical Research, Jewish General Hospital.

Address correspondence to Dr. L. Kwakkenbos, Jewish General Hospital, 4333 Cote Ste. Catherine Road, Montreal, Quebec H3T 1E4, Canada. E-mail: kwakkenbosL@gmail.com

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Persistent fatigue from chronic medical disease involves exhaustion disproportionate to exertion that is not relieved by rest and can have a major effect on health-related quality of life (HRQOL)[1,2]. Clinicians, however, are often unsure how to address fatigue[3,4,5]. Almost 90% of rheumatologists never assess fatigue[6], and most patients with cancer do not discuss fatigue with their physicians[7,8].

Most studies of fatigue in medical illness use single items or scores above a cutoff threshold on continuous scales to define fatigue. These methods, however, are not benchmarked to any case-definition standard and do not necessarily identify clinically significant fatigue levels that warrant investigation and treatment[9,10]. Researchers in cancer have developed cancer-related fatigue case definition criteria that have been proposed for inclusion in the International Classification of Diseases[11]. Cancer-related fatigue is based on 4 criteria: (1) the presence of ≥ 5 of 9 fatigue symptoms with "significant fatigue, lack of energy, or an increased need to rest" on (nearly) every day in a 2-week period in the last month; (2) effect on daily activities; (3) evidence that symptoms are a consequence of cancer or cancer therapy; and (4) not primarily a consequence of comorbid psychiatric disorders[11].

Establishing a common fatigue case definition across diseases would enhance comparability of research results and could help improve clinical management. The cancer-related fatigue case definition, however, has not been tested in any other patient groups. To apply the criteria more broadly to define chronic illness-related fatigue, criteria items must be measurement equivalent across disease groups, meaning that patients across groups with similar levels of fatigue will respond similarly to the items[12]. Differential item functioning (DIF), on the other hand, is said to occur when patients from different disease groups with similar levels of fatigue score differently on items assessing fatigue. DIF between disease groups may occur because of underlying differences in item relevance or in the way specific items are perceived or interpreted[13]. DIF analyses can help inform whether the cancer-related fatigue case definition operates consistently across diseases or whether there may be cross-disease measurement differences that reflect elements of fatigue specific to a certain illness, but less relevant to others.

Patients with systemic sclerosis (SSc; or scleroderma) provide an ideal population to test the viability of the cancer-related fatigue case definition paradigm as a general fatigue case definition for potential use in rheumatic diseases. SSc is a chronic, multisystem connective tissue disorder characterized by thickening and fibrosis of the skin, involvement of internal organs, substantially reduced HRQOL, and significant morbidity and mortality[14,15]. Fatigue in SSc is common, influences daily functioning more than any other symptom, and is independently associated with reduced capacity to carry out daily activities, work disability, and impaired physical function[16,17,18,19,20,21].

The objective of our study was to assess the measurement equivalence of the cancer-related fatigue case definition criteria between SSc and patients with breast cancer, and to examine whether this definition can be used to identify patients with SSc with clinically significant fatigue, and potentially more broadly, as a case definition for chronic illness-related fatigue.

MATERIALS AND METHODS

SSc sample. Data for the SSc sample were collected as part of a Canadian Scleroderma Research Group (CSRG) Registry substudy. Patients with an SSc diagnosis confirmed by a CSRG rheumatologist, ≥ 18 years of age, and fluent in English or French were recruited from 7 of 15 CSRG centers. Over 98% of patients in the registry met the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria[22,23]. Registry patients annually undergo physical evaluations and complete self-report questionnaires. Participants were recruited during their annual registry visit to participate in a telephone interview related to fatigue. The present study included data from the first of 2 interviews conducted between April 2009 and May 2012. We included women, but not men, because we compared data to women with breast cancer. The study was approved by the McGill University Institutional Review Board, and patients provided informed written consent.

Breast cancer sample. Data were collected in 2 separate studies conducted in a nurse-led followup clinic at St. George's Hospital, London, UK. Disease-free women ≥ 18 years of age diagnosed histologically with breast cancer (stages I-III) were included[24]. All women were clinically and radiologically disease-free and between 3 months and 2 years post-completion of primary breast cancer treatment (of any modality). Cancer-related fatigue interviews were conducted in person between January 2006 and January 2008, and between January 2009 and June 2011. For both studies, local ethics approval was obtained from Wandsworth regional ethics committee, and all patients provided informed written consent.

Demographics and disease characteristics. In patients with SSc, time since SSc diagnosis, extent of cutaneous involvement, and current use of immunosuppressive medications (methotrexate, cyclophosphamide, azatrophine, and mycophenolate) were recorded by a CSRG rheumatologist. Limited SSc was defined as skin involvement distal to the elbows and knees only, whereas diffuse SSc was defined as skin involvement proximal to the elbows and knees, and/or the trunk[25]. Patients with sine SSc were grouped with limited patients with SSc in analyses. Cancer comorbidity was self-reported by patients. In the cancer sample, time post-treatment and disease-related data, including histological stage and treatment history, were collected through medical records.

Fatigue interview. The cancer-related fatigue interview determined whether patients had experienced 2 weeks of significant fatigue in the preceding month (Criterion A1) and the presence of ≥ 5 of 9 fatigue-related symptoms (Criteria A2–A10). In addition, single items assessed whether fatigue had significantly affected work or self-care (Criterion B), were a consequence of cancer or cancer therapy (Criterion C), and were primarily a consequence of a comorbid psychiatric disorder, primarily depression (Criterion D)[10]. In the SSc sample, Criterion C was not explicitly assessed related to SSc or its treatment. In cancer samples, when Criterion C had been explicitly assessed[24], no patients had been excluded based on non-cancer sources of fatigue, and it seemed unlikely that patients with SSc would be excluded on this basis. Although the case definition permitted patients with coexisting psychiatric disorders to be classified as cases, provided the psychiatric condition was not the primary cause of the fatigue, we excluded all such patients from both samples because the inclusion of women with comorbid psychiatric disorders would have made it difficult to interpret the significance of any differences that were identified between the 2 groups.

Depression interview. In the SSc sample, the Depression Module of the

Composite International Diagnostic Interview[26] was administered by trained interviewers to assess whether patients met the criteria for current (30-day) Major Depressive Disorder (MDD) based on the Diagnostic and Statistical Manual-IV (DSM-IV) criteria[27].

In 1 of the cancer samples[28], eligible patients were first screened for psychiatric pathology clinically, and the remaining eligible patients completed the Structured Clinical Interview for the DSM-IV (SCID)[29]. In the other cancer sample[30], all eligible patients completed the SCID.

Statistical analyses. Demographic characteristics were compared between samples using the chi-square statistic for categorical variables and Student t tests for continuous variables. The factor structure of cancer-related fatigue criteria items was assessed for each sample separately using confirmatory factor analysis (CFA) with Mplus[31]. For DIF assessment, the simplest structure with reasonable fit was used. A previous study demonstrated that cancer-related fatigue can be considered unidimensional for measurement applications, such as DIF analysis[32]. Thus, a single-factor CFA model was constructed. Item responses for the case definition were binary and thus modeled using the weighted least squares estimator with a diagonal weight matrix, robust standard errors, and a mean- and variance-adjusted chi-square statistic with delta parameterization using full information maximum likelihood for missing data[31]. The chi-square test, the Tucker-Lewis index (TLI)[33], the comparative fit index (CFI)[34], and the root mean square error of approximation (RMSEA)[35] were used to assess model fit. Good-fitting models were indicated by a TLI and CFI ≥ 0.95 and RMSEA ≤ 0.06[36]. A CFI of 0.90 or above and an RMSEA of 0.08 or less[37] were also considered acceptable model fit. The chi-square test is highly sensitive to sample size and can lead to the rejection of well-fitting models[38]. Therefore, the TLI, CFI, and RMSEA were emphasized. Modification indices were used to identify pairs of items for which model fit would improve if errors were freed to covary. Once the factor structure was established for each sample separately, a CFA model was fit to both samples combined.

To determine whether case definition items exhibited DIF for SSc versus cancer, the multiple indicator multiple cause (MIMIC) model was used. The base MIMIC model consists of the CFA factor model with the direct effect of group (SSc vs cancer) on the latent factor added. This serves to control for group differences on fatigue level. The MIMIC model also allows for adjustment for variables that may differ between comparison groups by adding a direct effect on the latent factors. We controlled for differences in age.

Each item was regressed separately on the grouping variable to assess potential DIF. DIF was represented by a statistically significant ($p < 0.05$) link of group with the item, controlling for differences in the overall level of the latent factor. If there was DIF for 1 or more items, the item with the largest magnitude of DIF was considered to have DIF, and the association between group and that item was included in the model. This procedure was repeated until no remaining items showed significant DIF. Once all items with significant DIF were identified, the magnitude of DIF items collectively was evaluated by comparing the difference on the latent factor between groups in the baseline model and after controlling for DIF. The magnitude of this difference was interpreted following Cohen effect sizes, with ≤ 0.20 SD indicating small, 0.50 SD = moderate, and 0.80 SD = large differences[39]. Hommel correction for multiple testing was applied[40].

A logistic regression procedure was used to assess whether Criterion B exhibited significant DIF[13]. Thus, we assessed whether the Criterion B response (yes/no) was associated with group membership (SSc vs cancer) after controlling for differences in the level of fatigue (symptoms A2–A10). In step 1, the total scale score for each patient was entered in the equation, following by the grouping variable to assess uniform DIF (step 2). Significant DIF was defined as the presence of a significant difference (1-df chi-square test, $p < 0.05$) for the difference in chi-squared for the logistic regression between step 1 and step 2; and an effect size of at least 0.13, defined as the difference in Nagelkerke R^2 between steps 1 and 2[13].

An exploratory analysis was conducted to assess the effect of eliminating items with DIF on the prevalence of fatigue caseness in the SSc and cancer samples. The congruency of results using these alternative criteria and the original criteria was assessed.

CFA and MIMIC analyses were conducted using Mplus 7[31] and all other analyses were conducted using IBM SPSS Statistics 20.

RESULTS

Sample characteristics. Demographic and disease characteristics are displayed in Table 1.

SSc sample. In total, 345 patients with SSc were contacted for an interview and 344 completed the cancer-related fatigue interview, including 301 women. Of the 301 women, 10 were diagnosed with current MDD and not included in the present analysis. Thus, the SSc sample consisted of 291 female patients with a mean age of 58.1 years (SD 11.5) and mean time since diagnosis of 10.5 years (SD 8.5). Most patients (n = 219, 75.5%) were diagnosed with limited (n = 211, 72.8%) or sine SSc (n = 8, 2.8%). Seven patients (2.4%) reported cancer comorbidity, and 45 (15.4%) used immunosuppressant medication at the time of the interview. In total, 102 female patients (35.1%) met the criteria for chronic illness-related fatigue. The number of women who endorsed Criterion A and B items are displayed in Table 2.

Cancer sample. No women were excluded based on Criterion C. Thus, the cancer sample consisted of 278 female patients without psychiatric disorder with a mean age of 57.9 years (SD 11.4) and a mean time post-treatment of 11.1 months (SD 6.6). Of these patients, 188 (67.6%) had a negative lymph node status, and 90 (32.4%) were positive. The majority (n = 155, 56.5%) underwent mastectomy, 123 (43.5%) received conserving surgery, and 145 (52.5%) received chemotherapy. Of the 278 women, 105 (37.8%) met criteria for cancer-related fatigue. The number of women who endorsed Criterion A and B items are displayed in Table 2.

Confirmatory factor analysis. A single-factor structure showed good fit in both samples [SSc: chi-square (27) = 38.8, p = 0.07, CFI = 0.94, TLI = 0.92, RMSEA = 0.06; cancer: chi-square (27) = 28.1, p = 0.41, CFI = 1.00, TLI = 1.00,

Table 1. Demographic and disease characteristics for women with SSc and cancer. Values are n (%) unless otherwise specified.

Variable	SSc, n = 291	Cancer, n = 278
Age, yrs, mean (SD)	58.1 (11.5)	57.9 (11.4)
Time since diagnosis, yrs, mean (SD)	10.5 (8.5)	N/A
Time since onset first non-Raynaud symptom, yrs, mean (SD)	13.6 (10.1)	N/A
Time post-treatment, mos, mean (SD)	N/A	11.1 (6.6)
Limited/sine disease	219 (75.5)*	N/A
Current immunosuppressant medication	45 (15.4)	N/A
Cancer comorbidity	7 (2.4)	N/A
Negative lymph node status	N/A	188 (67.6)
Mastectomy	N/A	155 (56.5)
Previous chemotherapy	N/A	145 (52.5)
Meeting criteria for fatigue	102 (35.1)	105 (37.8)

* Because of missing values: n = 290. SSc: systemic sclerosis; N/A: non-applicable.

Table 2. Number of patients who endorsed Criterion A and B items.

Fatigue Case Definition Items	SSc Sample		Cancer Sample		p
	Completed Item, n	Endorsed Item, n (%)	Completed Item, n	Endorsed Item, n (%)	
A1. Two weeks of fatigue in past month	291	145 (49.8)	278	144 (51.8)	0.68
A2. General weakness	145	107 (73.8)	144	94 (65.3)	0.13
A3. Trouble concentrating	145	81 (55.9)	143	97 (67.8)	0.04
A4. Decreased motivation	145	96 (66.2)	143	87 (60.8)	0.39
A5. Insomnia/hypersomnia	145	118 (81.4)	144	119 (82.6)	0.88
A6. Non-restorative sleep	145	111 (76.6)	144	120 (83.3)	0.19
A7. Having to push to do things	144	123 (85.4)	144	107 (74.3)	0.03
A8. Sadness or frustration	145	105 (72.4)	144	94 (65.3)	0.21
A9. Trouble completing daily tasks	145	109 (75.2)	144	99 (68.8)	0.24
A10. Short-term memory problems	145	87 (60.0)	141	104 (73.8)	0.02
B. Impairment in functioning	122	102 (83.6)	116	105 (89.7)	0.13

SSc: systemic sclerosis.

RMSEA = 0.02]. Inspection of modification indices indicated that freeing error terms to covary would not improve model fit substantially.

Symptoms (A2–A10). The single-factor model was fit to the combined SSc and cancer samples, including a direct effect of group on the latent fatigue factor, as well as a direct effect of age on the latent fatigue factor, and fit well [chi-square (43) = 74.5, p = 0.002, CFI = 0.94, TLI = 0.92, RMSEA = 0.05]. Prior to accounting for possible DIF, patients with SSc had 0.05 SD higher latent factor scores (more fatigue) than patients with cancer, although this difference was not statistically significant (95% CI –0.23–0.33, p = 0.71). As shown in Table 3, there were 2 items with statistically significant DIF. Item 10 (short-term memory, z = 3.18, p = 0.002) and item 3 (trouble concentrating, z = 3.45, p < 0.001) were significantly less often endorsed by women with SSc compared with women with cancer with similar latent fatigue factor levels.

As shown in Table 3, after correcting for DIF for items 3 and 10, compared with the base model, there was an increase of 0.22 SD on the latent fatigue factor in the difference between SSc and cancer. Thus, after correcting for DIF, women with SSc scored 0.27 SD higher on the latent fatigue factor (95% CI –0.03–0.57, p = 0.08) than women with breast cancer, a small to moderately higher level, although statistically nonsignificant.

As a sensitivity analysis, we ran the MIMIC model with only the 7 items that had no statistically significant DIF, which yielded virtually the same results as the 9-item model corrected for the 2 DIF items with a factor loading for group on the latent factor of 0.27 (95% CI –0.03–0.56, p = 0.08).

Criterion B. In step 1 of the logistic regression analysis (total score of symptoms A2–A10), Nagelkerke R^2 was 0.217. In step 2, when the group variable was added to the model, Nagelkerke R^2 increased to 0.229 ($\Delta R^2 = 0.012$), which was not significant (chi-square (1) = 1.78, p = 0.18), suggesting

Table 3. Factor loadings for the fatigue case definition criteria in the SSc versus cancer samples and influence on the overall estimates of fatigue latent factor scores.

Fatigue Case Definition Items	Base Model*		DIF Corrected Model**	
	Factor Loading	95% CI	Factor Loading	95% CI
A2. General weakness	0.51	0.36–0.65	0.51	0.36–0.66
A3. Trouble concentrating	0.73	0.60–0.85	0.73	0.61–0.85
A4. Decreased motivation	0.71	0.60–0.82	0.71	0.60–0.82
A5. Insomnia/hypersomnia	0.35	0.16–0.54	0.35	0.16–0.54
A6. Nonrestorative sleep	0.44	0.26–0.61	0.43	0.25–0.60
A7. Having to push to do things	0.77	0.64–0.90	0.77	0.64–0.90
A8. Sadness or frustration	0.70	0.59–0.82	0.70	0.59–0.82
A9. Trouble completing daily tasks	0.67	0.53–0.80	0.66	0.53–0.79
A10. Short-term memory problems	0.59	0.45–0.74	0.60	0.45–0.74
Direct effects on items attributable to group***				
Item 3			–0.51	–0.88 – –0.22
Item 10			–0.55	–0.85 – –0.24
Structural effect of group on latent factor***	0.05	–0.23–0.33	0.27	–0.03–0.57

* Not corrected for DIF. ** Corrected for DIF for items 3 and 10. *** Cancer sample is reference. SSc: systemic sclerosis; DIF: differential item functioning.

that there was not DIF for Criterion B for patients with SSc versus cancer.

Case definition with and without DIF items. As shown in Table 4, 97.5% of the cancer sample was categorized consistently as a case or non-case when comparing the diagnosis based on the standard 5 of 9 symptom criterion and the revised 4 of 7 criterion that excluded the 2 DIF items (Cohen $\kappa = 0.95$). The prevalence of cases of fatigue was similar in the SSc (35.1% vs 36.1%) and cancer samples (37.8% vs 37.4%) using the 2 different criteria (Table 5).

DISCUSSION

The main finding was that items 3 (concentrating) and 10 (short-term memory) of the cancer-related fatigue case definition were significantly more frequently endorsed by patients with breast cancer than women with SSc with similar levels of fatigue. If these 2 items, which appear to be metrically inequivalent across diseases, are omitted from the case definition, and the case definition is changed to Criterion A1 plus at least 4 out of the 7 remaining symptoms, the overall prevalence of cancer-related fatigue in the cancer sample (37.4%) was similar to the estimate when 5 of 9 symptoms were required (37.8%). Further, the status of individual patients changed for only 7 of 278 women (2.5%).

Both items 3 and 10 are related to cognitive symptoms. A recent study reported that cognitive fatigue was present in 29% of patients with cancer, and was less common than physical fatigue (57%) and emotional fatigue (37%)[41]. Cognitive fatigue could be related to cancer treatment, in particular chemotherapy, monoclonal antibody therapy, and radiotherapy[42]. A previous study in women successfully treated for breast cancer found that women meeting criteria for cancer-related fatigue performed worse on measures of verbal memory, sustained attention, and reaction time compared with women not meeting criteria[30]. Several centrally acting cytokines may contribute to this, specifically vascular endothelial growth factor and brain-derived neurotrophic factor, both of which were elevated in the group with cancer-related fatigue compared with non-cases[30]. These cytokines can disrupt the permeability of the blood-brain barrier and provide a plausible biological mechanism for the central fatigue effects in cancer from an indirect tumor effect or secondary to treatment[43].

Authors of a systematic review of the cancer-related fatigue criteria reported that it is unclear whether the current requirement of a minimum of 5 out of 9 symptoms versus using a case definition based on fewer symptoms discriminates better between persons with and without cancer-related fatigue, and recommended investigating further refinement of the criteria[44]. Based on our findings, items 3 and 10 do not add substantially to identifying cases among patients with breast cancer. Because these items appear to be more related to cancer-related fatigue specifically, eliminating these items from the interview would facilitate the use of these criteria more broadly to assess chronic illness-related fatigue in other diseases, including rheumatic diseases.

A unifying case definition of fatigue that can be applied broadly in medical populations would improve the comparability of results between diseases that would facilitate research on etiology and interventions to reduce fatigue, as well as communication about fatigue among health professionals and patients. Cochrane systematic reviews in cancer[45,46] and rheumatoid arthritis[47], for instance, have identified that physical exercise and psychosocial interventions are promising approaches to addressing fatigue in these diseases. These types of programs can be quite resource- and time-intensive, and should preferably be targeted to patients who may benefit most. Including patients with clinically significant fatigue, using the proposed case definition, could increase the potential for improvement. Further, coordinated efforts across investigations and diseases, including comparison and pooling of data, will strengthen the understanding and management of chronic illness-related fatigue.

As far as we know, no other studies have assessed the measurement equivalence of fatigue measures across medical diseases, which is surprising given that common measures have been routinely used across illnesses, including rheumatic diseases[48]. Other measures of fatigue, in particular questionnaires that were initially designed for cancer-related fatigue and that include potentially cognitive fatigue items, may similarly have items that are less applicable and may

Table 4. Congruency between original and alternative case definitions in the cancer sample (n = 278). Values are n (%).

Case Based on ≥ 5 of 9 Symptoms + B	Case Based on ≥ 4 of 7 Symptoms + B*	
	No	Yes
No	170 (61.2)	3 (1.1)
Yes	4 (1.4)	101 (36.3)

* Criterion B was not administered to 3 patients in the cancer sample who did not meet the 5-symptom criterion in the original definition. For estimation purposes, it was assumed that it would have been met based on the 90% rate of meeting Criterion B in the cancer sample.

Table 5. Estimated prevalence of patients meeting criteria based on original and alternative requirements for number of symptoms in SSc (n = 291) and cancer (n = 278) samples. Values are n (%).

Definition Used	SSc Prevalence	Cancer Prevalence
A1 + ≥ 5 of 9 (A2–A10) + B	102 (35.1)	105 (37.8)
A1 + ≥ 4 of 7 (A2, A4–A9) + B	105 (36.1)*	104 (37.4)*

* Criterion B was not administered to 6 patients in the SSc sample and 3 patients in the cancer sample who did not meet the 5-symptom criterion in the original definition. For estimation purposes, it was assumed that it would have been met based on 84% and 90% rates of meeting Criterion B in SSc and cancer samples, respectively. SSc: systemic sclerosis.

distort results when used more broadly in patients with other chronic diseases because similar scores obtained across these diseases may not reflect similar levels of fatigue.

There are limitations that should be considered in interpreting the results of our study. First, both samples constituted convenience samples, and only women were included in our present study. Thus, our sample may not reflect the full spectrum of the SSc and breast cancer populations. Second, the SSc and cancer samples were derived from 2 different countries that may have led to differences in sociocultural factors that could have influenced our results. Third, in the SSc sample, a phone interview was conducted to assess fatigue criteria, whereas a face-to-face interview was conducted in cancer. There are many examples of studies that have demonstrated the equivalency between structured diagnostic interviews conducted per telephone versus face-to-face interviews, for example in depression[49,50], but this has not been established for the diagnostic fatigue interview. Fourth, although we excluded patients with depression, we did not exclude patients with SSc with other psychiatric disorders that could have influenced fatigue, such as anxiety. Fifth, the case definition items were developed by experts; however, it is possible that there are other items that may better reflect fatigue in chronic illness. In addition, although there are clear commonalities between fatigue in cancer and other (rheumatic) conditions, there may also be components of fatigue that are disease-specific and that may not be identified by these generic fatigue criteria. As yet, very little is known about the fatigue experience of patients with SSc; however, that would guide refinement of criteria for SSc. Additional research to better understand fatigue experiences of patients with SSc may facilitate work in this area. Finally, the assessment of DIF across the breast cancer and SSc samples is an important step in establishing the measurement properties of a generic chronic illness-related fatigue case definition. Future studies, however, should continue to examine other measurement properties, including aspects of reliability and validity, in SSc, across other rheumatic diseases and cancer, as well as examine DIF based on variables such as age, sex, and race/ethnicity.

The cancer-related fatigue criteria can be used equivalently as a chronic illness-related fatigue case definition in SSc if the cognitive fatigue symptoms are not included. If our results are replicated, in SSc and other populations, refining the cancer-related fatigue criteria, particularly eliminating items 3 and 10, would facilitate research and the evaluation of interventions for fatigue in chronic diseases. Harmonized definitions of fatigue and the use of instruments with demonstrated measurement invariance across diseases will advance research and development and implementation of interventions in rheumatic diseases and other conditions.

APPENDIX 1.

List of study collaborators. Canadian Scleroderma Research Group: M. Baron, Montreal, Quebec; M. Hudson, Montreal, Quebec; N. Khalidi, Hamilton, Ontario; E. Kaminska, Hamilton, Ontario; J.E. Pope, London, Ontario; J. Markland, Saskatoon, Saskatchewan; N. Jones, Edmonton, Alberta; P. Docherty, Moncton, New Brunswick; J.P. Mathieu, Montreal, Quebec.

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