Fatigue in Cancer Patients Compared with Fatigue in the General United States Population

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BACKGROUND. Although fatigue is a common symptom among cancer patients, it is also a common experience in the general, healthy population. Its universality has made it difficult to appreciate whether the fatigue experienced by patients with cancer is distinguishable from the fatigue experienced by the general population. Because the etiology of fatigue is multifactorial, it also has been difficult to appreciate fully the relative contribution of anemia to cancer-related fatigue.

METHODS. To address this issue, responses to a brief, standardized set of 13 questions from the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System were compared across three groups: anemic cancer patients (n = 2369 patients), nonanemic cancer patients (n = 113 patients), and the general United States population (n = 1010 persons).

RESULTS. Fatigue scores of the anemic cancer patients (at both baseline and upon completion of anemia therapy) were significantly worse compared with the scores of nonanemic cancer patients that, in turn, were worse compared with the scores of the general United States population ($P < 0.001$). Score distributions were quite distinct for these three groups. Within the group of anemic cancer patients, the degree of anemia (mild, moderate, or severe) also was predictive of the degree of fatigue ($P < 0.001$), although the distributions were not dramatically distinct.

CONCLUSIONS. Although anemia is clearly a factor that contributes to the severity of disease-related fatigue among cancer patients, hemoglobin levels explain only part of the difference compared with fatigue among the general United States population. The distinct distributions of fatigue scores of anemic cancer patients compared with the general United States population and the substantial sample sizes of these two groups enabled a discriminant analysis approach that allowed the differentiation of anemic cancer patients from the general population with high sensitivity (0.92) and reasonable specificity (0.69). Thus, although fatigue is a symptom most anyone can relate to, the fatigue of cancer patients, particularly those who are anemic, is decidedly worse. Interventions targeting this common and life-disrupting symptom likely would be of considerable value to patients with cancer. ***Cancer* 2002;94:528–38.** *© 2002 American Cancer Society.*

KEYWORDS: fatigue, cancer-related fatigue, anemia, quality of life.

Fatigue is the most common unrelieved symptom of cancer.[1–6] Fatigue, as a symptom, is a subjective sensation of weakness, lack of energy, or tiredness[7] and, as a syndrome, has been defined as an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work.[8] We previously proposed diagnostic criteria for cancer-related fatigue (CRF).[2] These criteria include diminished energy and mental capacity and increased need to rest that is disproportionate to any recent change in activity level and is evident nearly every day during any 2-week period in the past month. CRF has a profound, negative impact on daily activities, social activ-

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ities, and overall quality of life.[1,2,9–11] Therefore, aggressive treatments are needed to restore normal functioning. Although CRF is pervasive, its cause and severity are less well understood. One of many causes of CRF is the anemia that accompanies the disease (*anemia of chronic disease*) and its treatment. Although it is not the only cause of CRF, anemia is the easiest to document using standard complete blood count hemoglobin (Hgb) levels for mild (10.00–11.99 g/dL), moderate (8.00–9.90 g/dL), and severe ($<$ 8.00 g/dL) anemia. These clinical definitions allow us to establish *criterion groups* of anemic cancer patients who can be tested for levels of self-reported fatigue and its impact on function.

One of the challenges in appreciating the impact of fatigue on the life of the person with cancer is the fact that fatigue occurs commonly in the general population. Approximately 20% of men and 30% of women in the general population complain of frequent tiredness.[12] Labeling it *healthy fatigue*, Glaus[13] found that 55% of healthy individuals identified a physical sensation of fatigue/tiredness, 21% identified an affective sensation of fatigue, and 24% identified cognitive fatigue. The pervasiveness of fatigue in everyday life, on the one hand, may help professionals be empathic to cancer patients with fatigue. However, if the fatigue experienced by cancer patients, as patients suggest, is different and more extreme than that experienced by healthy individuals, then it is possible that the existence of healthy fatigue is a barrier to full appreciation of the impact of CRF. Clinicians may not want to treat everyday, reversible fatigue, because it will improve spontaneously with proper sleep hygiene. However, if CRF has a different etiology, severity, and course than everyday fatigue, then *usual* methods of reversing it are likely to fall short.

An initial step toward a better understanding of CRF is to differentiate the fatigue experienced by cancer patients from that experienced in the general population. This can be furthered by evaluating the extent to which one objective, measurable contributor to CRF (i.e., anemia) can account for differences between cancer patients and the general population. This strategy can help one appreciate the magnitude of the difference in the impact fatigue has on daily life in anemic cancer patients compared with nonanemic cancer patients and, more importantly, compared with the general population. If this is assessed using the same measuring instrument, then these direct comparisons can be made. In this study, the fatigue experienced by the general population was compared with that reported by anemic and nonanemic cancer patients using a simple, 13-item questionnaire to measure self-reported fatigue.

The objective of this study was to examine how cancer patients, anemic and nonanemic, compared with the general population on a fatigue questionnaire: The Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue).[14] The FACIT-Fatigue asks about the intensity of fatigue as well as its impact on daily life. We asked three research questions: 1) Do cancer patients, both anemic and nonanemic, report more fatigue on the FACIT-Fatigue than people in the general United States population? 2) Do gender and age play roles in the severity or impact of self-reported fatigue? 3) Assuming differences exist between anemic cancer patients and the general population, can useful *cut-off scores* be derived to differentiate a distinct population of those with fatigue?

MATERIALS AND METHODS

Data Collection

The purpose of this report was to demonstrate the differences in self-reported fatigue between people with cancer and the general population, paying special attention to cancer patients known to have anemia. To determine differences among cancer patients attributable to Hgb levels, we combined data from several relevant sources, all of which included responses to the FACIT-Fatigue Scale. This is a 13-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue.[1,14] The questionnaire is presented in Figure 1.

We distinguished three groups of respondents: anemic cancer patients, nonanemic cancer patients, and people from the general population. The general population sample was not screened for current or past medical conditions. The anemic cancer patients had recently been entered onto an open-label clinical trial of recombinant-human Epoetin α therapy for reversal of chemotherapy-related anemia.[15] The inclusion criteria for these patients were as follows: They had to have a nonmyeloid malignancy and a Hgb level $\leq$ 11.0 g/dL, and they had to be receiving concomitant chemotherapy, have a life expectancy $\geq$ 6 months, and be able to understand and give informed consent. Patients were not included in the study if they had uncontrolled hypertension, known hypersensitivity to mammalian cell-derived products, anemia due to factors other than cancer/chemotherapy, or prior Epoetin α therapy or if they were candidates for bone marrow transplantation who were receiving peripheral blood progenitor cell therapy. Patients had primarily mild anemia (30%) and moderate anemia (61%). Details of the trial were published by Demetri et al.[15] Although the trial called for three assessments,

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless ("washed out")	0	1	2	3	4
I feel tired	0	1	2	3	4
I have trouble starting things because I am tired	0	1	2	3	4
I have trouble finishing things because I am tired	0	1	2	3	4
I have energy	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat	0	1	2	3	4
I need help doing my usual activities	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
I have to limit my social activity because I am tired	0	1	2	3	4

FIGURE 1. The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Questionnaire.

fatigue scores for the purpose of this analysis were drawn only from the baseline assessment. We selected the baseline assessment, because this would ensure, by virtue of eligibility for the trial, that all patients were anemic at the time of testing. Because the purpose of this article was not to evaluate the impact of treatment for anemia, we did not focus on the trial data after baseline. However, available fatigue scores at the time of completion (n = 1439 patients) were included, not to evaluate the effectiveness of Epoetin α but to appreciate better the distribution of fatigue among a group of Epoetin α-treated chemotherapy patients relative to that of patients about to initiate erythropoetin therapy. The mean time to completion for patients was 89 days (standard deviation [SD], 37 days).

We drew data on the nonanemic cancer patients from two available data bases that included both Hgb level and FACIT-Fatigue scores collected at the same time. One of these data sets has been published.[1,14] The exclusion criteria of the patients were as follows: 1) they received cytotoxic chemotherapy or underwent surgery either within the past week or expected to within 1 week; 2) they currently were receiving radiation therapy; 3) they had received either a blood transfusion or growth factor injection 3 days prior to data collection; 4) they were anticipating transfusion or a growth factor injection 1 week after the collection of baseline data; 5) they had brain metastasis; or 6) they were pregnant. The other nonanemic cancer patient data source was from a longitudinal descriptive study of the economic and quality-of-life impact of fatigue on people with cancer. To be eligible, patients had to have a cancer diagnosis and no prior chemotherapy or radiation therapy within the previous 6 months. All baseline assessments were conducted on the first day of chemotherapy. Only 113 of 131 patients with baseline Hgb levels > 12 g/dL were included. Because some of these patients were expected to develop anemia over the course of the longitudinal follow-up, and this group was selected explicitly for this report as a nonanemic comparison group, only baseline data are presented.

The general United States population data were collected by an independent survey research organization through telephone interviews using random-

TABLE 1
Sample Demographics

Characteristic	General population	Cancer patients: Nonanemic	Cancer patients: Anemic
No. of patients	1010	113	2369
Gender (%)			
Female	51.7	64.6	60.8
Male	48.3	35.4	39.2
Age (yrs)	45.7 ± 16.8	54.8 ± 13.6	63.4 ± 12.8
Race (%)			
White	79.5	90.2	78.2
Black	9.5	6.2	11.7
Hispanic	3.7	1.8	5.4
Other	7.3	1.8	4.7
Hemoglobin (g/dL)[a]	Not assessed	Mean, 13.5 ± 1.2; range, 7.3 (12.0–19.3)	Mean, 9.3 ± 1.0; range, 6.4 (4.6–11.0) (9.8% severe anemia, 60.8% moderate anemia, 29.5% mild anemia)

[a] Severe anemia: hemoglobin (Hgb) <8 g/dL; moderate anemia: Hgb 8–9.99 g dL; mild anemia: Hgb 10–12 g dL.

digit dialing.[16] Quotas were set for gender and region to ensure representativeness. Of the telephone numbers generated, 75% were valid numbers. The response rate was 53%. These survey results had a margin of error equal to ± 3.0%.[16,17] Among the general population participants, 7% had a history of cancer, 7% had a history of diabetes, 8.3% had a history of heart disease, and 25.3% had a history of hypertension.

Table 1 shows the demographic information of anemic cancer patients, nonanemic cancer patients, and the general population. All three groups had similar race distribution. However, cancer patients were older and were represented more heavily by women than the general population sample.

Data Analysis

To provide some assurance that the selected general population sample was reasonably representative of Americans in the surveyed age group, the 12-item short form of the Medical Outcomes Study (MOS SF-12) also was administered. Most participants (84.4%) claimed that they had good, very good, or excellent health, whereas 15.6% said that their health status was fair or poor. The mean ± SD scores for the Physical Component Summary (PCS) and the Mental Component Summary (MCS) in our sample were 48.41 ± 9.95 and 51.67 ± 9.59, respectively, and 50.12 ± 10.00 and 50.04 ± 9.59, respectively, in the report by Ware et al.[18] The 25th, 50th, and 75th percentiles of the PCS were 43.76, 51.68, and 55.50, respectively, in our sample and 46.53, 53.55, and 56.49, respectively, in the report by Ware et al.; and the respective 25th, 50th, and 75th percentiles of the MCS were 47.72, 55.03, and 57.89 in our sample and 45.13, 52.85, and 57.30 in the report by Ware et al. The close agreement of descriptive statistics in the two samples suggests that our general population sample was as representative as the sample used by Ware et al.

Before the 13-item response data from the FACIT-Fatigue were analyzed, all negatively worded items were reversed, as instructed in the manual.[19] Therefore, consistent with all FACIT scales, higher scores represent better health (in this case, less fatigue), and lower scores represents worse health or more fatigue. All raw scores also were transformed into interval measures ranging from 0 to 100 using a probabilistic logistic regression model (i.e., Rasch measurement model). The purpose of this transformation was to create an interval metric for more accurate comparison of anemic cancer patients and the general population across the full range of fatigue. Using data from the anemic cancer patients, a conversion table to traverse from individual raw scores to interval measures was then created. Raw and transformed scores for each of the three groups were then compared using a one-way analysis of variance with multiple post-hoc group comparisons and using Tukey honestly significant difference (HSD) tests.

RESULTS

Score Transformation

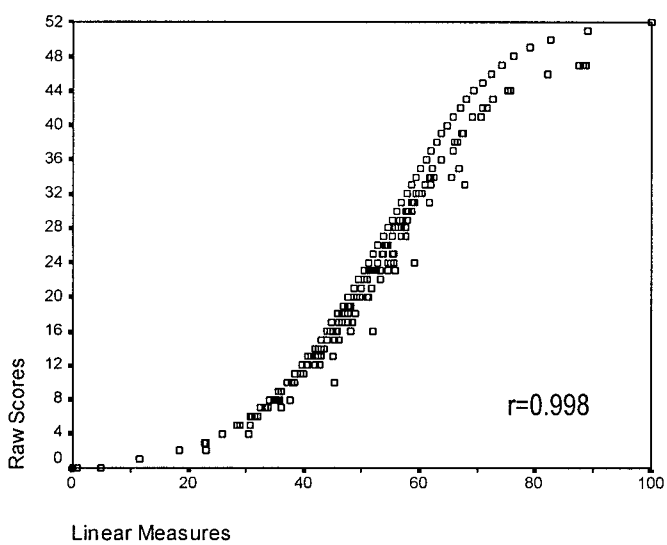
Using the WINSTEPS computer program,[20] we conducted a log-linear transformation of raw scores into

TABLE 2
Raw Score to Interval Measure Conversion Table (Based on 2292 anemic cancer patients and 1010 general population)[a]

Raw score	Interval measure	S.E.	Raw score	Interval measure	S.E.	Raw score	Interval Measure	S.E.
0	0	17.0	18	46	3.0	36	61	2.8
1	11	9.5	19	47	2.9	37	62	2.9
2	18	6.9	20	48	2.9	38	63	2.9
3	23	5.8	21	49	2.9	39	64	3.0
4	26	5.1	22	49	2.8	40	65	3.1
5	28	4.6	23	50	2.8	41	66	3.1
6	31	4.3	24	51	2.8	42	67	3.2
7	32	4.0	25	52	2.8	43	68	3.4
8	34	3.8	26	53	2.8	44	69	3.5
9	36	3.7	27	54	2.8	45	71	3.7
10	37	3.5	28	54	2.7	46	72	3.9
11	38	3.4	29	55	2.7	47	74	4.2
12	40	3.3	30	56	2.7	48	76	4.7
13	41	3.2	31	57	2.8	49	79	5.4
14	42	3.2	32	58	2.8	50	83	6.5
15	43	3.1	33	59	2.8	51	89	9.2
16	44	3.0	34	59	2.8	52	100	16.8
17	45	3.0	35	60	2.8	—	—	—

S.E.: standard error.

[a] Because of the nonlinearity of the conversion and nonnormality of score distributions, individual, not group, scores can be converted. Interval measures were created by log-linear transformation with a Rasch analysis.



* interval measures were created by loglinear transformation via Rasch analysis

FIGURE 2. Relation between interval measures (range, 0–100) and raw scores (range, 0–52).

interval measures by setting the lowest possible raw score (0) at 0 and setting the highest possible raw score (52) at 100. Table 2 shows the raw scores and their corresponding interval measures, and Figure 2 depicts the correlation (i.e., an ogive curve) between raw scores and interval measures. The very high correlation (Spearman rho [R^2] = 0.998; $P < 0.001$) suggests the compatibility between raw scores and interval measures; however, the ogive correlation implies that the raw-to-interval measure ratio is not consistent across the full range of the construct (fatigue) being measured. A linear relationship between raw scores and interval measures in the middle part of the curve was found, whereas the raw scores were not as sensitive as interval measures at the two extreme ends. For example, a 1-unit raw score interval at the lowest

TABLE 3
Comparing Fatigue in Anemic Cancer Patients with Fatigue in the General Population

		Range		Mean[a]		Median	
Group	No.	Raw score	Interval Measure	Raw score	Interval measure	Raw score	Interval measure
Anemic cancer patients	2292[b]	0–52	0–100	23.9 ± 12.6	50.2 ± 13.7	23	50.3
Nonanemic cancer patients	113	9–52	33–100	40.0 ± 9.8	68.4 ± 14.9	42	66.8
General population	1010	2–52	18–100	43.6 ± 9.4	74.7 ± 15.0	47	74.0

[a] The means of anemic cancer patient, nonanemic cancer patients, and the general population were significantly different from each other for both raw scores ($F_{(2, 3414)}$ = 1071.8; $P < 0.001$) and interval measures ($F_{(2, 3414)}$ = 1087.5; $P < 0.001$). Tukey HSD post-hoc comparisons revealed that each group was significantly different from all others ($P < 0.001$).
[b] Of 2369 anemic cancer patients, 2292 patients (97%) completed the baseline questionnaire.

end and the highest end (from score 0 to score 1 and from score 51 to score 52, respectively) = 11 transformed (interval) units, from 0 to 11 and from 89 to 100, respectively. Conversely, between raw scores of 6 and 46 (most of the scale), the ratio between the raw score and the interval measure is essentially one-to-one.

Comparison between Anemic Cancer Patients and the General Population

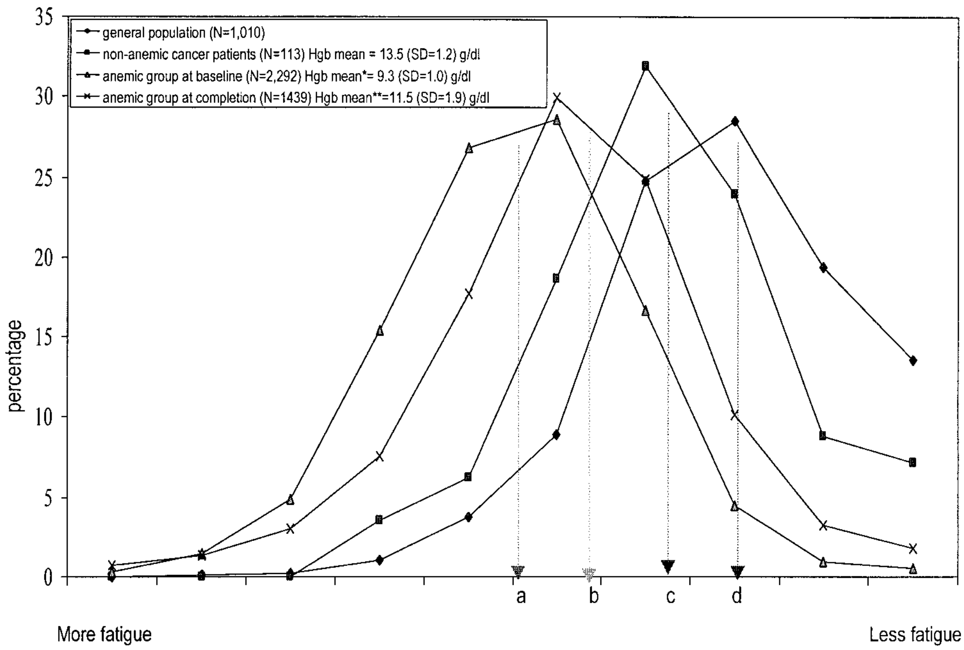
Table 3 compares all cancer patients (anemic and nonanemic) with the general population on their fatigue scores. To help the interpretability of the 0–100 interval scale, both raw scores and interval measures are reported and then compared. On both raw scores and interval measures, the general population showed significantly less fatigue (higher scores) than anemic cancer patients ($P < 0.001$) and nonanemic cancer patients ($P < 0.001$). Tukey HSD tests comparing all three groups were significant ($P < 0.001$). Median scores also are provided, because not all distributions were normal. The general population group had a higher median value (raw score, 47; interval measure, 74.0) than anemic cancer patients (raw score, 23; interval measure, 50.0). For the remainder of this article, primarily interval measures will be reported; however, these can be converted using Table 2. It is noteworthy that Table 2 can be used only when the raw score was based on complete individual data (based on all 13 questions) or if the raw score was prorated to adjust for missing responses, as described in the FACIT manual.[19]

Discriminating Anemic Cancer Patients from the General Population

Figures 3–5 present FACIT-Fatigue score distributions by plotting the frequency in each of ten score deciles (0–10, 10–20, etc.). Figure 3 shows score distributions in anemic cancer patients at baseline, in anemic cancer patients at completion, in nonanemic cancer patients, and in the general population. We included anemic cancer patients at completion, not to evaluate the treatment they received, but to display a distribution of community-based outpatients at completion of Epoetin α treatment. Anemic cancer patients at baseline demonstrated a nearly perfectly normal distribution on this questionnaire, with a mean ± SD score of 50.2 ± 13.7 and a median score of 50.0, whereas a left-skewed distribution with median score of 74.0 was found for the general population. Each of the groups was significantly distinct from the other ($P < 0.001$), with the distribution of scores for anemic cancer patients at baseline approaching perfect normality. None of the nonanemic patients or the people from the general population produced the lowest possible score; of the anemic cancer patients at baseline, 8 of 2292 patients (0.35%) had the lowest possible score; of the anemic cancer patients at completion, 10 of 1439 patients (0.7%) had the lowest possible scores, and 26 of 1439 patients (1.8%) had the highest possible scores. In contrast, although there were virtually no anemic cancer patients at the measurement ceiling (0.5%), increasing numbers of nonanemic patients (7.1%) and general population participants (13.6%) reported the highest possible scores.

Anemic cancer patients at completion had a (bell-shaped) distribution pattern similar to that at baseline, although it was shifted to the right (less fatigued direction). Anemic cancer patients at completion were less fatigued than at baseline (mean ± SD score, 56.6 ± 15.5; median score, 58.0).

The results summarized in Table 3 and Figure 3 led to questions about the role of degree of anemia within the group of anemic patients and to the possible competing roles of gender and age on the differences noted. Substantial sample sizes in the anemic cancer patient and general population groups lent themselves to breaking down these samples by these



Note: Vertical dotted lines reflect medians of each group. Means of each group are also given below. Significant mean differences across groups were found, $F_{(2,3394)}=1082.1$, $P<0.0001$ (for group a vs. c vs. d) and $F_{(2,2574)}=422.7$, $P<0.0001$ (for group b vs. c vs. d at completion)***

a. anemic cancer patient group at baseline: median=50.0 (raw score = 23) mean=50.2 (SD=13.7)
b. anemic cancer patient group at completion: median=58.0 (raw score = 32) mean=56.6 (SD=15.5)
c. non-anemic cancer patients: median=67.0 (raw score = 42) mean=68.4 (SD=14.8)
d. general population: median=74.1 (raw score =47) mean=74.7 (SD=15.0).

* mean was based on 2220 patients who had valid fatigue scores and valid Hgb values
** mean was based on 1400 patients who had valid fatigue scores and valid Hgb values
*** Because the anemic cancer group at baseline and completion were not independent, we conducted two separate three-group analyses: group a vs c vs d, and group b vs c vs d

FIGURE 3. Distribution of fatigue among anemic cancer patients at baseline (a), anemic cancer patients at completion of study (b), nonanemic cancer patients (c), and the general United States population (d). Hgb: hemoglobin; SD: standard deviation.

important variables to assess their relative contributions. Figure 4 provides a further breakdown of distributions of anemic cancer patients by severity of anemia: mild (Hgb levels, 10.00–11.99 g/dL), moderate (Hgb levels, 8.00–9.99 g/dL), and severe (Hgb levels < 8.00 g/dL). Although the distributions are similar visually, with median fatigue scores comparable for moderate and severe anemia, mean raw score differences between adjacent levels of anemia are in the 2–3 point range and are significantly different from one another, with P values ranging from 0.01 (moderate to severe comparison) to 0.001 (both compared with mild anemia; see Fig. 4).

Because the anemic cancer patients had more women and were older than the general population sample, we also compared sample distributions (anemic cancer patients vs. general population), controlling for age ($<$ 50 years and $\geq$ 50 years) and gender (men and women). Across both groups, women age $\geq$ 50 years reported more fatigue than men age $\geq$ 50 years (F[degrees of freedom (df) = 1,3,274] = 20.7; $P < 0.05$). However, whereas older people in the general population reported more fatigue than their younger counterparts, there was no age effect in the cancer sample (F[df = 1,3,274] = 0).

A multiple-regression analysis helped demonstrate the overall association between fatigue and gender, age, and Hgb level. Two analyses were conducted: one with Hgb as a continuous variable and the other with Hgb as a categoric variable (categories: severe anemia, moderate anemia, mild anemia, and nonanemic). Results showed that Hgb was the only significant predictor (standardized $\beta = 0.275$; $P < 0.001$). About 8% ($R^2 = 0.079$) of fatigue score variance was explained by Hgb as a continuous variable, and 6.5% of fatigue score variance was explained when Hgb was analyzed as a categoric variable. The distinctions between men versus women and older age versus younger age were negligible in the context of comparing diagnostic groups (anemic cancer patients vs. general population). Using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL), we also predicted group membership (i.e., either anemic cancer patient or general population) with a Discriminant

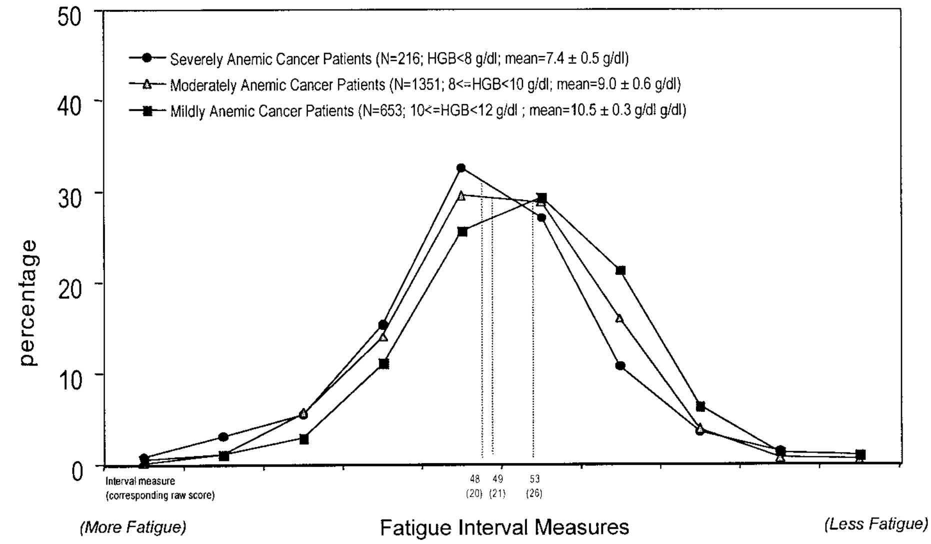


FIGURE 4. Distributions of fatigue level by degree of anemia. HGB/Hgb: hemoglobin; Tukey HSD: Tukey honestly significant difference test.

Note: Vertical dotted lines reflect medians of each group. Seventy-two subjects did not have valid Hgb values. For those who had valid Hgb values (N=2,220), means of each group were as follows: severe anemia 46.6, moderate anemia 49.6, and mild anemia 52.6, $F_{(2,2219)}$=19.2,$\underline{P}$< 0.0001. All three groups differed from each other in post-hoc (Tukey HSD) comparisons.

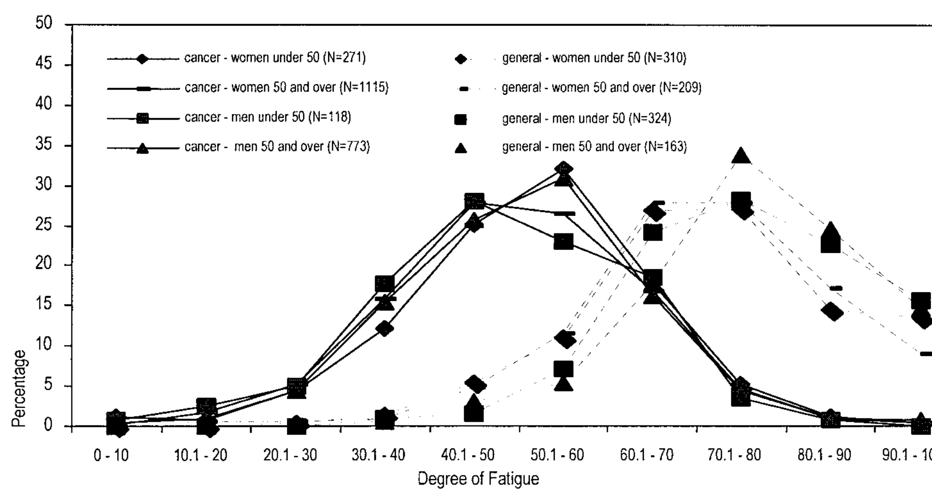


FIGURE 5. Age and gender stratified distributions of fatigue among anemic cancer patients compared with the general United States population.

Function Analysis (DFA). DFA searches for a linear discriminant function to maximize group differences and thereby predict group membership. Results showed that the discriminant function on fatigue scores was significant ($P < 0.001$; Canonical correlation, 0.625). This suggests that 39% (0.625^2) of group membership can be explained solely by fatigue score. Using this function, most people (84% of the total sample) were classified correctly. Specifically, 93% of anemic cancer patients were classified correctly, whereas 66% of people in the general population were classified correctly. The DFA also suggests that a cut-off interval measure of 68 (corresponding raw score, 43) best distinguishes anemic cancer patients from the general population. Specifically, anemic cancer patients are predicted to report fatigue levels associated with an interval measure of 68 or lower (or a raw score of 43), whereas people in the general population are expected to have fatigue scores higher than this cut-off score. Based on the receiver operating characteristic curve derived from the DFA, classification sensitivity at this score was 0.92, and the specificity was 0.68 (see Fig. 6).

In addition to an interval measure of 68 (raw score, 43), two other potentially useful cut-off scores are provided: 45 (raw score, 17) and 49 (raw score, 22). The measure of 45 corresponds to a score that is > 2 SD worse than normal, as defined by the general population distribution. This criterion (and others) can be evaluated to estimate the proportion of individuals in

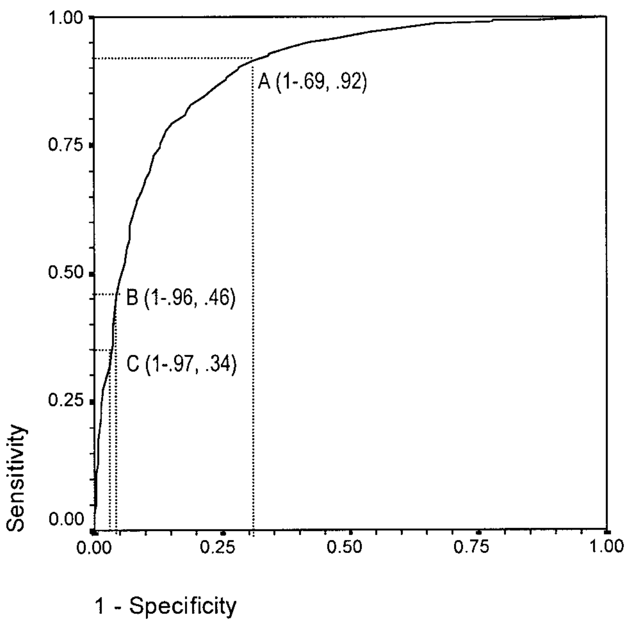


FIGURE 6. The receiver operating characteristic curve (ROC) was used to evaluate how well the Functional Assessment of Chronic Illness Therapy Fatigue Scale score discriminated cancer patients from the general United States population. The area under the curve was 0.892 (significantly different; $P < 0.0001$ from a null hypothesis; expected area under the nonparametric assumption, 0.5). The three criterion scores shown in Table 4 were plotted on the ROC curve. Point A (sensitivity, 0.92; specificity, 0.69) refers to a raw score of 43. Point B (sensitivity, 0.46; specificity, 0.96) refers to a raw score of 22. Point C (sensitivity, 0.34; specificity, 0.97) refers to a raw score of 17.

any cohort plotted in Figure 3. By summing the percentages of patients within a given cohort plotted to the left of any given x-axis score, one can approximate the proportion of individuals falling below that threshold. Thus, for example, because 45 is 2 SD below the general population mean of 74.7, this allows one to describe the proportion of anemic cancer patients who reported abnormally high fatigue (31.8%). Thus, whereas only 36 of 1010 respondents (3.6%) in the general population fell below 2 SD units of its average, the same was true of almost one-third of the cancer patients (see Fig. 3). The interval measure of 49 (i.e., below a raw score of 23) falls just below the average score of anemic cancer patients. Table 4 provides these three cut-off scores along with their respective sensitivity, specificity, and interpretive comments.

To appreciate further the differences between anemic cancer patients and the general population, we divided these two cohorts into four equal-sized quartiles (Q) based on their FACIT-Fatigue scores (see Fig. 7). Group 1 (Q1) included those who had the worst fatigue scores (0th to 25th percentile), whereas Group 4 (Q4) included those who had the least trouble with fatigue (75th to 100th percentile). Because the sample size of anemic cancer patients was almost twice that of the general population, we weighted each sample based on their proportion of the combined sample: For the general population, weight = 2292/(1010 + 2292); for anemic cancer patients, weight = 1010/(1010 + 2292). The percentage of anemic cancer patients within each quartile decreased significantly with each increasing (less fatigue) quartile, with a proportional increase of general population within each quartile increased (chi-square[1,3] = 174.84; $P < 0.001$; see Fig. 7). Individual chi-square analyses showed that the percentage of anemic cancer patients was significantly higher in the first and second quartiles ($P < 0.001$), whereas the percentage of general population was significantly higher in the fourth quartile ($P < 0.001$). No statistically significant different percentage was found in the third quartile.

DISCUSSION

Fatigue, the most common symptom reported by people with cancer, can be measured using a simple self-report instrument, such as the FACIT-Fatigue. Distributions of scores produced from assessment of cancer patients—both anemic and nonanemic—are significantly different from those produced from assessment of people in the general United States population. These differences are significant visually and statistically. Within the group anemic cancer patients, severity of anemia (using standard criteria for mild, moderate, and severe anemia) is associated with the degree of reported fatigue. However, although the presence and extent of anemia are associated with the degree of fatigue reported, it appears from the comparison of nonanemic cancer patients with the general population that anemia is not the only variable accounting for CRF. Several other possible causes of CRF have been suggested, including cytokine production, altered muscle metabolism, sleep deprivation, stress, and depression.[1,2,10,21–23] Nevertheless, the differences in fatigue attributable to the extent and degree of anemia are considerable. Furthermore, the distinctions between anemic cancer patients and the general population were sufficient to determine useful cut-off scores based on observed differences and discriminant analyses. These cut-off scores can provide useful interpretation of future group scores, differences over time, selection criteria for clinical studies, and criteria for the successful treatment of patients with CRF.

These findings indicate that the 13-item FACIT-Fatigue questionnaire is a useful and simple self-report questionnaire that can distinguish anemic cancer patients from the general population. Scores on self-report questionnaires tend to be difficult for practitio-

TABLE 4
Suggested Cut-Off Scores for Clinical Use

Cut-off score				
Raw score	Interval measure	Sensitivity	Specificity	Interpretive comments
17	45	.34	0.97	Scores 17 and lower are statistically "deviant" from the mean of the general population
22	49	.46	0.96	Scores 22 or lower are below the mean of anemic cancer patients
43	68	.92	0.69	The cut-off score of 43 best divides anemic cancer patients and the general population, classifying people into groups with 84% overall accuracy

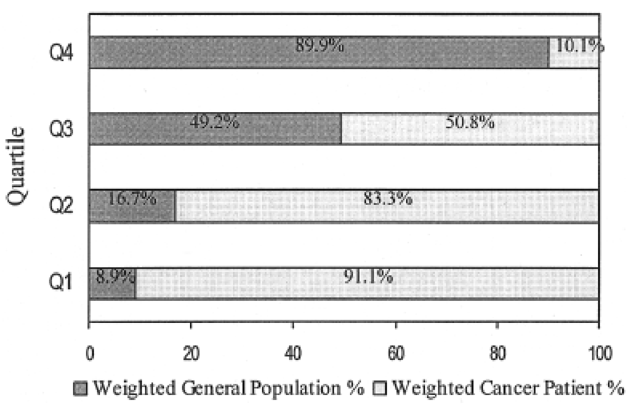


FIGURE 7. Interquartile proportions of anemic cancer patients compared with the general United States population.

ners and investigators to employ in meaningful ways; however, these scores can be shown to differ greatly, depending on whether the respondent is a cancer patient with anemia, a cancer patient without anemia, or from the general United States population. One barrier to successful clinical implementation has been the difficulty interpreting the scores obtained from cancer patients. Part of the challenge has been that fatigue is also part of normal functioning in the general population that does not require treatment. To effectively treat patients with CRF, it is necessary to differentiate it from everyday, reversible fatigue. Our results show that fatigue is clearly less severe and has a less negative impact on the general population than on cancer patients, particularly those with anemia. CRF appears to be significantly more disruptive than everyday fatigue. This study helps move toward better treatment of patients with CRF by illustrating the differences between cancer patients and the general population in terms of the impact of fatigue on daily living.

The FACIT-Fatigue score distributions of anemic cancer patients compared with the general population are distinct and are not attributable to age or gender. When gender, age, and diagnostic group (i.e., cancer patients and the general population) were taken into consideration, diagnostic group most dominantly affects distribution compared with the other two factors (see Fig. 5). The four cancer patient versus general population distributions shown in Figure 5 remain visually distinguishable, and there appears to be no major influence of gender or age on these distinctions.

The FACIT-Fatigue scale was created initially to assess anemia-related fatigue.[14] A normal distribution of fatigue scores obtained from anemic cancer patients supports the applicability of this scale to this population. In contrast, the general population distribution was skewed and showed some considerable ceiling effects, suggesting some room for improvement in differentiating people on the higher end of the health continuum. The conversion table that provides the corresponding 0–100 interval measures for every possible raw score (0–52) can be useful for the clinician or investigator seeking to enhance the interpretive potential of fatigue scores. An added advantage of interval measures is their compatibility with the use of parametric statistics in analysis of group differences or changes over time. A high correlation between the 0–100 interval measures and the raw scores suggests the compatibility of these two measurement approaches. The conversion table can serve further as a bridge between clinicians and patients in communicating their fatigue-related issues. A person who obtains a score $\leq$ 49 (raw score, 22) can be described as scoring below the average score of anemic cancer patients, defined as Hgb $\leq$ 11 g/dL. Although this score divides the anemic cancer sample in half, with 48.6% falling below it, only 5% of the general population had fatigue scores below this level.

Returning to the original cut-off score of 68 (raw score, 43), this is optimal for differentiating the groups with a sensitivity of 0.92 and a specificity of 0.69. This cut-off score has predicted 84% of results correctly. Ninety-two percent of anemic cancer patients, compared with 34.1% of the general population, were in this area. It is important to note that the conversion table (Table 2) is appropriate for individual or median scores but not for group mean (average) scores. This occurs because the raw-to-interval conversion is not linear, and not all distributions were normally distributed.

It is apparent from these data that CRF, as measured by the FACIT-Fatigue questionnaire, is of a considerably greater magnitude than the fatigue reported by the general population. Within the cancer patient cohort, the presence and degree of anemia was related significantly to the degree of reported fatigue. Clearly, although fatigue is a symptom experienced at some point or another by virtually all people, the degree and impact of fatigue reported by people with cancer are decidedly worse and deserving of clinical attention.

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