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Quality of Life and Symptoms in Long-term Survivors of Colorectal Cancer: Results from NSABP Protocol LTS-01

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In the interests of transparency:

This is original work that has not been published elsewhere. Previous related works are as follows:

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Kunitake H, Zheng P, Yothers G, Land SR, Fehrenbacher L, Giguere JK, et al. Routine preventive care and cancer surveillance in long-term survivors (LTS) of colorectal cancer: Results from NSABP Protocol LTS-01. *J Clin Oncol.* 2010; 28:5274-79.

Kidwell KM, Yothers G, Ganz PA, Land SR, Ko CY, Cecchini RS, et al. Long-term neurotoxicity effects of oxaliplatin added to fluorouracil and leucovorin as adjuvant therapy for colon cancer: Results from National Surgical Adjuvant Breast and Bowel Project trials C-07 and LTS-01. *Cancer.* 2012; 118:5614-22.

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Abstract

Purpose—Little is known about health-related quality of life (HRQL) in long-term survivors (LTS) of colorectal cancer (CRC).

Methods—Long-term CRC survivors (> 5 years) treated in previous National Surgical Adjuvant Breast and Bowel Project trials were recruited from 60 sites. After obtaining consent, a telephone survey was administered, which included HRQL instruments to measure physical health (Instrumental Activities of Daily Living [IADL], SF-12 Physical Component Scale [PCS], SF-36 Vitality Scale), mental health (SF-12 Mental Component Scale [MCS], Life Orientation Test, and Impact of Cancer), and clinical symptoms (Fatigue Symptom Inventory [FSI], European Organisation for Research and Treatment of Cancer Colorectal Module [EORTC-CR38], and Brief Pain Inventory). A multivariable model identified predictors of overall quality of life (global health rating).

Results—Participants (N=708) had significantly higher HRQL compared with age group-matched non-cancer controls with higher mean scores on SF-12 PCS (49.5 vs. 43.7, $p < 0.05$), MCS (55.6 vs. 52.1, $p < 0.05$) and SF-36 Vitality scale (67.1 vs. 59.9, $p < 0.05$). Multivariable modeling has demonstrated that better overall physical and mental health (PCS and MCS), positive body image (EORTC-CR38 scale), and less fatigue (FSI), were strongly associated with overall quality of life as measured by the global health rating. Interestingly, ability to perform IADLs, experience of cancer, gastrointestinal complaints, and pain were not important predictors.

Conclusions—In long-term CRC survivors, overall physical and mental health were excellent compared with general population. Other disease-related symptoms did not detract from good overall health.

Keywords

Quality of life; Colorectal cancer; Survivors

Introduction

The high incidence of colorectal cancer (CRC), along with improving techniques in treatment, has led to a very large population of patients who have now transitioned from treatment to survivorship. CRC survivors today account for approximately 9% of the estimated 14.5 million cancer survivors in the United States [1]. As this population grows, the focus of health-care providers has now extended beyond the primary treatment to include improving cancer survivorship care and enhancing the health-related quality of life (HRQL) of long-term survivors.

One of the challenges inherent to studying the HRQL of long-term CRC survivors is the difficulty in identifying an appropriate cohort of patients. Potential recruitment sources previously included convenience samples from clinical practices or hospital tumor registries whose patients experienced varied treatments [2–4]. In contrast, recruitment of long-term

survivors from cancer clinical trials has the potential to identify patients with more uniform treatment exposures, allowing the evaluation of HRQL in a large group of survivors of similar treatment background. With this in mind, the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol Study LTS-01 was conceived. This study was designed to investigate important issues including preventive care and cancer surveillance, HRQL, functional outcomes, and clinical symptoms of these long-term survivors (defined as ≥ 5 year survival) of colon and rectal cancer [5]. Patients were recruited from five closed NSABP adjuvant therapy trials: three colon cancer trials (C-05, C-06, and C-07) and two rectal cancer trials (R-02 and R-03), which had accrued patients from 1987 to 2002. The results of the LTS-01 study concerning routine preventive care (e.g., flu shot), cancer screening (e.g., mammogram, Pap smear, or PSA test), and CRC surveillance (e.g., colonoscopy, computed tomography scan, or carcinoembryonic antigen test), as measured using survey items from the National Health Interview Survey, have been reported earlier [6]. In this study we report our findings on the HRQL of the long-term survivors in the LTS-01 study, focusing on three areas: physical health, mental health, and clinical symptoms.

Design and Methods

Patient selection

Sixty-five NSABP study sites that had previously participated in the colon and rectal cancer adjuvant treatment trials (C-05, C-06, C-07, R-02, R-03) were invited to participate and 60 were able to obtain Institutional Review Board approval to enroll patients in the LTS-01 study. (See Ganz et al. 2009 [5] for a complete description of the institutional and patient recruitment process). The NSABP adjuvant therapy trials spanned a 20-year period with the two rectal cancer protocols being the oldest of the five studies included. The R-02 trial compared adjuvant MeCCNU, vincristine, and fluorouracil (FU) with and without radiotherapy with adjuvant leucovorin and FU with and without radiotherapy in patients with Dukes' B and C rectal cancer. Accrual to the R-02 study began in August 1987 and closed in December 1992 [7]. The R-03 trial compared preoperative multimodality therapy (FU + leucovorin + radiotherapy) with the same regimen administered postoperatively and accrued patients from June 1993 to June 1999 [8]. Of the three colon cancer protocols, the C-05 trial compared FU plus leucovorin with FU plus leucovorin plus interferon alfa 2a and accrued patients from October 1991 to February 1994 [9]. The C-06 treatment trial compared oral uracil/ftorafur plus leucovorin with FU plus leucovorin and accrued patients from February 1997 to March 1999 [10]. The C-07 trial compared intravenous FU plus leucovorin with FU plus leucovorin plus oxaliplatin and accrued patients from February 2000 to November 2002 [11]. Patients who had participated in these five protocols at one of the 60 NSABP sites and were long-term survivors (≥ 5 years) were identified by the NSABP Biostatistical Center and were invited to participate in the LTS-01 study.

Patients who agreed and provided informed consent received a computer-assisted telephone interview using a battery of survey instruments including standardized measures of HRQL, functional outcomes, and clinical symptoms. Telephone interviews were conducted in English between 2007 and 2009 using trained interviewers.

Survey instruments and variables

The LTS-01 study included instruments to investigate both the health behaviors and HRQL of long-term CRC survivors. A more detailed description of the questions related specifically to health behaviors including cancer screening, cancer surveillance, and use of health care services has been previously presented [6]. To evaluate HRQL, including both physical and mental health, and clinical symptoms, the LTS-01 survey included several previously validated HRQL instruments, including: the Instrumental Activities of Daily Living scale (IADL) [12], the 12-Item Short-Form Health Survey (SF-12) [13,14], the Short-Form-36 (SF-36) Vitality Scale [15], the European Organisation for Research and Treatment of Cancer-Colorectal survey (EORTC-CR38) [16], the Brief Pain Inventory (BPI) [17], the Fatigue Symptom Inventory (FSI) [18,19], the Life Orientation Test (LOT) [20,21], and the Impact of Cancer Instrument version 1 (IOC) [22]. Finally, a Global Health Rating (GHR) question was included, which asked the participants to score their overall quality of life (QoL) for the past 7 days on a 10-point scale where zero represented death and 10 represented perfect health. The GHR score was used as the dependent variable in the multivariable regression to determine factors associated with better global health. These instruments were administered to the entire cohort, whereas selected instruments were used in patients treated on specific trials, and are not reported here [23].

Statistical analysis

The LTS-01 cohort scores for each HRQL scale were compared with historical published norms using Fisher's Exact Tests [12,14,15,18,21,22]. Multivariable regression utilizing a linear model was used to determine predictors of better GHR and included not only demographic variables (age, gender, marital status, education, insurance status, and retirement status) but also HRQL instrument scores (IADL [total score], SF-12 [Mental Component Summary (MCS) and Physical Component Summary (PCS)], EORTC-CR38 [Body Image score and Gastrointestinal Tract Problem score], BPI [total score], FSI [Total Average Fatigued during the past week], and IOC [positive score and negative score]). All statistical analyses were performed using Statistical Analysis Software (SAS; version 9.1 for Windows, SAS Institute, Cary, NC). This study was approved by the Institutional Review Board at the University of California, Los Angeles, the University of Pittsburgh, and at each participating NSABP Study Protocol LTS-01 study site. Informed written consent was required.

Results

Demographics

Sixty-five institutions across the United States were invited to participate and 60 (92.3%) were able to obtain Institutional Review Board approval to take part in the LTS-01 protocol study. From these institutions, 744 long-term survivors consented to participate and 708 (95.2%) completed the LTS-01 interview. The majority were white (93.1%) with mean age 66.2 years (SD=10.6 years). Fifty-seven percent were male and median survival from surgery was 8.2 years (range 5–19.5 years). Most were from the colon cancer trials: 147 (21%) from C-05, 180 (25%) from C-06, and 354 (50%) from C-07. A smaller number were from the rectal cancer trials: 15 (2%) from R-02 and 12 (2%) from R-03. Overall, 75.9%

were married and most (93.8%) had a high school diploma or higher education level. Nearly all (97.3%) had health care coverage with private insurance and/or Medicare. (Table 1)

Health-related quality of life

Physical Health—LTS-01 participants had statistically significant higher physical HRQL as compared with age- group matched non-cancer controls, as demonstrated by statistically significant higher mean scores on the SF-12 PCS and SF-36 Vitality scale. LTS-01 participants were also able to accomplish nearly all IADLs (mean 7.9), whereas the mean IADL score for the reference population was 4.2. (Table 2)

Mental Health—LTS-01 participants had significantly better mental health compared with age group-matched non-cancer controls as demonstrated by a statistically significant higher mean score on the SF-12. However, LTS-01 participants were less optimistic than the comparison non-cancer cohort, which was reflected in a lower score on the Life Orientation Test: Optimism. Comparison of the LTS-01 cohort with a smaller group (n=39) of long-term (5–10 year) survivors of CRC demonstrated no significant difference in the scores on the IOC: Positive Impact Scale and Negative Impact Scale [22].

Clinical Symptoms—LTS-01 participants had statistically significantly more average fatigue than the non-cancer comparison cohort. They reported being fatigued an average of 3.1 days (SD 2.5d) during the past week with the worst fatigue rated as 4.9 (SD 2.7) on a scale of 0–10 (0: not at all fatigued, 10: as fatigued as I could be). Surprisingly, participants on average stated that they were bothered by gastrointestinal issues such as abdominal pain and bloating not at all or a little bit (EORTC-CR38 Gastrointestinal score mean 88.5, SD 12.5). Most participants felt that their disease and treatment affected their body image and masculinity/femininity not at all or a little bit (EORTC-CR38 Body image score mean 84.5, SD 151). Of the 708 participants in the LTS-01 study, 428 (60.5%) reported no pain in the previous 4 weeks.

Factors associated with better overall health

The median GHR was 9 (range 0–10). A comparison of demographic, physical health, mental health, and clinical symptom variables for participants with GHR less than median and greater than or equal to the median was performed (Table 3). There were statistically significant differences between these two groups with respect to marital status, education, retirement status and all measures of HRQL with the exception of the Impact of Cancer, Positive Impact Scale. Multivariable modeling utilizing a linear model controlling for demographic factors demonstrated that better overall physical and mental health (SF-12 PCS and MCS, SF-36 Vitality Scale), a positive body image (EORTC-CR38: Body Image), and less fatigue (FSI: Total Average Fatigued) were strongly associated with better overall health (Table 4). The presence of pain (BPI: Total score), gastrointestinal complaints (EORTC-CR38: Gastrointestinal), the experience of cancer (IOC: Positive and Negative Impact Scales), and the ability to perform IADLs were not important predictors of overall HRQL. In addition, there was a negative relationship between education and better overall health.

Discussion

There is an increasing awareness of and interest in the HRQL of the growing population of long-term CRC survivors in the United States. In light of the difficulty in identifying and studying this group, the LTS-01 protocol was developed to overcome some of the barriers in recruiting this specific patient population by focusing on long-term survivors of completed adjuvant therapy trials for colon and rectal cancer. The LTS-01 cohort was recruited from 60 participating NSABP sites, resulting in a nationally representative sample of CRC survivors who participated in clinical trials and whose care and experience is representative of cancer clinical trial patients across the country.

In the LTS-01 study, participants rated their overall physical and mental health even higher than historical non-cancer comparison cohorts as evidenced by higher scores on the SF-12 PCS and MCS and the SF-36 Vitality Scale. This was also seen in several other studies of long-term CRC survivors [2,3]. In those studies, participants had a high functional status and relatively few symptoms, which appeared to be the case for LTS-01 participants as well. As a group, LTS-01 participants had good functional capacity with 98% able to perform all of the IADL activities. Although they reported more severe fatigue than their non-cancer counterparts, on average they experienced fatigue for 3.1 days (SD 2.5 days) per week, similar to the healthy comparison cohort (3.1 days, SD 2.2 days), and suffered from relatively minor gastrointestinal issues such as mild abdominal pain and bloating. Importantly, the majority of patients (60.5%) reported no pain in the previous 4 weeks.

Using multivariable modeling and controlling for demographic factors, better overall physical and mental health, as well as a positive body image and less fatigue were strongly associated with better overall health. Interestingly, cancer-specific issues such as pain, gastrointestinal complaints, the impact of cancer, as well as performance of IADLs, were not statistically significant predictors of overall HRQL. The IOC positive impact scale score, which correlates strongly with post-traumatic growth, was near statistically significant in the model (parameter estimate 0.148, $p=0.055$). In a previous study,[24] overall health rating scales were more often associated with physical health and did not include psychological wellbeing. However in our model, mental health as measured by the SF-12 MCS was also independently associated with overall health, while adjusting for other demographic and physical health factors. This is an important finding because the LTS-01 study not only demonstrates higher MCS than historical published norms but we have also shown that, in this cohort of long-term survivors of CRC, mental health is associated with better GHRs.

In a study of 1,608 CRC patients in the NSABP adjuvant trial C-06, Kopec et al [25]. demonstrated that FACT-C scores and SF-36 Vitality scores did not change appreciably from baseline to week 15/16. Despite an increase in symptoms associated with chemotherapy treatments during that time period, QoL improved. Both the Kopec study and the LTS-01 study suggest that patient-perceived QoL is not based solely on the presence or absence of clinical symptoms but involves a complex mixture of physical and psychological factors.

In our earlier study of the health behaviors of long-term cancer survivors in the LTS-01 protocol [6], we found that LTS-01 participants were statistically significantly more likely to

have a usual source of health care and were more likely to have received a flu shot in the past 12 months than a non-cancer cohort case-matched by age, sex, race, and education from the general United States population. In addition, LTS-01 participants had a 10–14% higher absolute rate of receiving routine cancer screening tests with Pap smear, mammogram, and prostate-specific antigen test than the comparison non-cancer cohort. For cancer surveillance, almost all LTS-01 participants (96.5%) met the minimum surveillance guideline of having a colonoscopy every 5 years. Overall, these long-term CRC survivors were successful in receiving necessary health care and were diligent in pursuing recommended cancer screening and surveillance.

Good health behaviors do not necessarily correlate with a good QoL. However, in this highly-select population of CRC survivors who participated in clinical trials and the even more highly-select group of survivors who agreed to participate in the LTS-01 study, we identified a population of patients who were doing well in terms of self-reported physical health, mental health, and clinical symptoms as long-term CRC survivors and felt their QoL was high. A potential factor that could be intervened upon to improve overall health is attention to fatigue. A previous study by Husson et al [26], which evaluated fatigue in 6,011 long-term cancer survivors, found that levels of fatigue were related to cancer type, age, gender, time since diagnosis, receipt of chemotherapy, number of medical comorbidities, education, and absence of a partner. Interventions to address fatigue in these long-term CRC survivors, including education regarding fatigue as an anticipated side effect of cancer treatment or physical exercise training, might improve overall health ratings. In addition, the American Society of Clinical Oncology recently published a clinical practice guideline [27] on screening, assessment, and management of fatigue in adult survivors of cancer, which highlights the importance of addressing this common problem in cancer survivors.

The finding that higher education was negatively associated with QoL in our multivariable model was unexpected. Further investigation using frequency distributions by GHR demonstrated that LTS-01 participants had lower percentages of college and post-graduate education in the GHR less than median group compared to the greater than or equal to the median group. To our knowledge, this is the first study to demonstrate this negative association between higher education and lower QoL in long-term CRC survivors. Potential reasons for this relationship could be due to increased understanding of risk of cancer recurrence, decreased income or ability to work related to cancer treatment, or this could merely be a chance finding that needs further exploration in other studies.

The current study does have several limitations, which may impact the interpretation of the results. First, there is the issue of selection or response bias because there were 2,540 potentially eligible survivors available for recruitment but contact was made with only 976 patients (41% of eligible pool). Data was available for 914 of these patients to compare the characteristics between those who participated in LTS-01 and those who did not, and participating patients were younger, more likely to be married, and more likely to have been treated more recently [5]. However, it should be noted that we designed the LTS-01 protocol to capture the survival experience of long-term survivors of a wide range of survival length because self-reported HRQL has been shown in the past to vary over length of survivorship [28]. Future studies may include further analyses of LTS-01 HRQL by years of survivorship

to more precisely characterize the factors associated over time with CRC survivor QoL. Second, the patients participating in these colorectal cancer clinical trials may not be representative of the overall population of patients with colorectal cancer. In addition, the survivors participating in LTS-01 likely represent an even more select group of patients who were not only willing to participate in the trial but may have other unmeasured factors that impacted their long-term QoL. Third, the GHR outcome (used as a measure of overall quality of life) may not be sensitive to side effects of the treatments experienced by long-term CRC survivors. However, we attempted to comprehensively measure HRQL through assessments of physical health, mental health, and clinical symptoms, and to discern which of these domains were associated with the GHR. Fourth, it is also possible that other unmeasured variables such as psychological behaviors or exercise may have contributed to improved long-term QoL. Previous research has demonstrated that exercise, personality traits, and both internal and external resources are associated with improved HRQL in CRC survivors.[29–33] Fifth, these five NSABP trials enrolled patients over a 15-year time period (1987–2002) and there were likely simultaneous changes in cancer detection, perioperative care, and surgical approach, which may have impacted not only oncology outcomes but also QoL. Despite these limitations, the current study also has numerous strengths including a large sample size of long-term CRC survivors which has not been previously described in the literature, use of validated questionnaires, and standardization of treatments within each of the five included clinical trials.

In summary, long-term CRC survivors in the LTS-01 study had statistically significant higher overall HRQL and functional capacity compared with age group-matched non-cancer controls as demonstrated by higher mean scores on multiple QoL instruments. Multivariable modeling controlling for demographic factors demonstrated that better overall physical and mental health, positive body image, and less fatigue were strongly associated with better self-rated health. Other disease-related symptoms did not detract from overall QoL.

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Implications for Cancer Survivors

LTS of CRC within the setting of a clinical trial have higher HRQL than the general population and treatment regimens do not appear to be associated with any significant late effects on quality of life.

Table 1

Patient demographics: NSABP LTS-01

Characteristic	N=708
Mean age $\pm$ SD (yr)	66.19 $\pm$ 10.63
Male	57.1%
Race	
White	93.1%
Black	2.7%
Other	4.1%
Unknown	0.1%
Married	75.9%
Retired	56.2%
Education	
Less than high school	6.2%
High school graduate	53.5%
College	21.8%
Post graduate	18.5%
Health insurance	
Private and/or Medicare	97.3%
Government	1.8%
Uninsured	0.9%
Median survival time since surgery	8.2 yrs (range 5–19.5 yrs)

Table 2

Health-related quality of life: NSABP LTS-01

Instrument	LTS-01 (Mean [SD])	Reference (Mean [SD])
Physical Health ^b		
SF-12 Summary Physical Component Scale (PCS) ^a	49.5 (9.9)	43.7 (11.0)
SF-36 Vitality Scale ^a	67.1 (20.7)	59.9 (22.1)
Fatigue Symptom Inventory: ^a Average Fatigue	2.7 (2.2)	2.3 (1.8)
Instrumental Activities of Daily Living (IADL)	7.9 (0.8)	4.2 (range 0–8)
Mental Health ^c		
SF-12 Summary Mental Component Scale (MCS) ^a	55.6 (7.7)	52.1 (9.5)
Life Orientation Test: Optimism ^a	18.9 (4.6)	21.2 (4.3)
Impact of Cancer (IOC): Positive Impact Scale	3.7 (0.5)	3.6 (0.7)
Impact of Cancer (IOC): Negative Impact Scale	2.3 (0.6)	2.5 (0.7)

^a p < 0.05^b Higher scores on the SF-12 Summary Physical Component Scale, SF-36 Vitality Scale, and IADL indicate better physical health. Higher scores on the Fatigue Symptom Inventory indicate increasing level of fatigue.^c Higher scores on the SF-12 Summary Mental Component Scale indicate better mental health. Higher scores on the Life Orientation Test: Optimism indicate more optimism. Higher scores on the IOC Positive Impact Scale and lower scores on the Negative Impact Scale indicate better mental health

Table 3

Demographic, physical health, mental health, and clinical symptom variables stratified by global health rating:
NSABP LTS-01

Variable	Global Health Rating < median n=328	Global Health Rating median n=380	P value*
Patient demographics (%)			
Age (years)			0.27
<50	7.0	7.6	
50–59	21.6	18.2	
60–69	28.7	35.0	
70	42.7	39.2	
Male gender	55.2	56.7	0.35
Race			0.48
White	94.8	93.4	
Black	2.4	4.0	
Other	2.4	2.6	
Unknown	0.3	0.0	
Married	70.1	80.8	<0.001
Education			0.01
Less than high school	7.6	5.0	
High school graduate	56.1	51.3	
College	21.0	22.4	
Postgraduate	15.3	21.3	
Health insurance	98.8	99.2	0.56
Retired			0.005
Yes	61.0	51.6	
No	38.1	48.4	
Unknown	0.9	-	
Physical health, Mean ± SD			
SF-12 PCS	44.3 ± 11.5	53.9 ± 5.0	<0.001
SF-36 Vitality Scale	54.3 ± 20.3	78.1 ± 13.5	<0.001
Independent Activities of Daily Living	7.8 ± 0.9	7.9 ± 0.7	<0.001
Mental health, Mean ± SD			
SF-12 MCS	52.5 ± 9.7	58.2 ± 3.8	<0.001

Variable	Global Health Rating < median n=328	Global Health Rating median n=380	P value *
Life Orientation Test	17.6 ± 4.9	20.0 ± 4.0	<0.001
Impact of Cancer, Positive Impact Scale	3.8 ± 0.5	3.7 ± 0.5	0.23
Impact of Cancer, Negative Impact Scale	2.6 ± 0.6	2.1 ± 0.5	<0.001
<i>Clinical symptoms, Mean ± SD</i>			
EORTC-CR38 Body Image Scale	78.0 ± 17.4	90.0 ± 10.0	<0.001
EORTC-CR38 Gastrointestinal Scale	84.8 ± 13.8	91.7 ± 10.3	<0.001
Brief Pain Inventory	79.9 ± 24.1	91.1 ± 16.7	<0.001
Fatigue Symptom Inventory	3.8 ± 2.3	1.9 ± 1.7	<0.001

PCS Physical Composite Score, MCS Mental Composite Score, EORTC European Organisation for Research and Treatment of Cancer

* Chi square test for categorical variables, Wilcoxon rank-sum test for continuous

Table 4

Factors associated with overall health: NSABP LTS-01

Variables ^a	Parameter Estimate	P value
<i>Patient demographics</i>		
Male Gender	−0.174	0.035
College Education or more	−0.095	0.041
<i>Physical health</i>		
SF-12 Summary Physical Component Scale (PCS)	0.055	<0.001
SF-36 Vitality Scale	0.017	<0.001
Instrumental Activities of Daily Living (IADL)	0.011	0.834
<i>Mental Health</i>		
SF-12 Summary Mental Component Scale (MCS)	0.059	<0.001
Life Orientation Test	0.010	0.313
IOC: Positive Impact Scale	0.116	0.136
IOC: Negative Impact Scale	−0.072	0.439
<i>Clinical symptoms</i>		
EORTC-CR38: Body Image	0.014	<0.001
EORTC-CR38: Gastrointestinal	0.001	0.776
BPI: Total score	0.001	0.700
FSI: Total Average Fatigued	−0.064	0.004

IOC Impact of Cancer, EORTC European Organization for Research and Treatment of Cancer, BPI Brief Pain Inventory, FSI Fatigue Symptom Inventory

^a Also included but not significant: age, race, marital status, health insurance, and retired