Original Article

Evidenced-Based Report on the Occurrence of Fatigue in Long-Term Cancer Survivors

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Key Words
Cancer survivor, fatigue, long-term sequela, quality of life

Abstract
Although some cancer survivors report persistent fatigue years after treatment, little is known about the prevalence of the symptom in this population as compared with the general population. This article examines current evidence for the occurrence of fatigue in long-term cancer survivors by reviewing published population-based studies that incorporated controls from the general population. Using the search criteria "fatigue AND cancer survivors" in PubMed, the authors identified 16 articles (based on 15 cross-sectional datasets) comparing fatigue severities in survivors of adult cancers with those in the general population. When data allowed, Hedges' g effect size calculations were generated. A total of 8096 cancer survivors were examined across datasets. Cancer survivor sample sizes ranged from 15 to 1933 per dataset. Most datasets focused on either breast cancer (7) or Hodgkin's disease survivors (6). Four studies did not clearly exclude patients undergoing active treatment. Nine articles (based on 8 datasets) showed statistically significant ($P < .05$) differences among groups; 4 articles showed negative results; and 3 showed both positive and negative results depending on fatigue dimension measured. Among the studies that reported scores for the fatigue subscale of the European Organization for Research and Treatment of Cancer Core Questionnaire for Quality of Life (most studies), mean fatigue levels in cancer survivors ranged from 28.7 to 36.5 out of an overall score of 100, and mean fatigue levels in matched general population controls ranged from 20 to 30 out of 100. No associations between instruments and results were apparent. Although the small numbers of studies prevented comparisons among cancer subtypes, equal positive and negative studies were seen in breast cancer survivors and, notably, no negative studies were seen involving Hodgkin's disease survivors. Most effect sizes calculated were small. Fatigue was a burden to both cancer survivors and members of the general population. While evidence for greater fatigue severity in cancer survivors was mixed, most studies reported greater fatigue in cancer survivors as compared with controls. The magnitude of this effect was generally small. Inferences from the data were limited by variability in both the definition of survivor and the fatigue assessments used, as well as by the cross-sectional design of the studies. Prospective longitudinal studies are needed to determine causal relationships between excessive fatigue and surviving cancer. (*JNCCN* 2008;6:347–354)

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As the number of cancer survivors increases, the long-term sequelae of cancer and its treatment, such as fatigue, will also grow in importance. Fatigue can not only be a subjectively distressing symptom but can also impact negatively on a person's ability to perform activities of daily living, participate in interpersonal relationships, and return to work.[1] Although as many as 75% of people with active cancer are estimated to experience fatigue,[2] less is known about the occurrence of this symptom in long-term cancer survivors.

Over the past decade, as researchers have begun to estimate the extent of fatigue in cancer survivors, several challenges have emerged. A central difficulty has been the failure to identify robust and consistent physiologic correlates of cancer-related fatigue. For instance, no definitive cardiac, pulmonary, immunologic, or endocrine dysfunctions have been linked with fatigue in cancer patients long after the active phase of their treatments.[3] Even studies comparing levels of exercise tolerance between cancer patients with fatigue and general population controls have not shown significant differences.[4]

As a result, cancer-related fatigue remains a fully patient-reported outcome. Although several instruments have been developed and validated for measuring this symptom, they serve to quantify severity of fatigue much more than its cancer-relatedness. The years that intervene between cancer diagnosis and long-term survival et al. expose these individuals to various competing causes for fatigue, including medical comorbidities and the effects of aging. These factors must be accounted for to accurately estimate rates of cancer-related fatigue in long-term survivors.

One research approach that addresses some of these concerns is a population-based survey of cancer survivors that includes a general population control group. If properly conducted, such a study could estimate the additional fatigue risk conferred by being a long-term survivor of cancer above and beyond what a similar person without cancer might experience. The authors examined current evidence for the existence of cancer-related fatigue in long-term cancer survivors by reviewing published population-based studies that included controls from the general population.

Methods

Population-based studies of fatigue in cancer survivors were identified in PubMed using the search strategy "fatigue AND cancer survivors." Papers were selected for further review if their citations and abstracts contained information that met several requirements, such as being published in or before January, 2007; explicitly stating the use of a fatigue measure or an instrument with a fatigue domain; and including a general population control group. Studies of fatigue in survivors of childhood cancers were excluded. Studies that used siblings as controls were also excluded because of possible differences between siblings of cancer survivors and the general population. When ambiguities were encountered, inclusion was determined through author consensus. Data from studies meeting the review criteria were extracted and presented in a summary table. Hedges' g effect sizes were calculated whenever studies presented means with either variances or confidence intervals.[5]

Results

Studies

The initial search strategy yielded 178 citations for fatigue in cancer survivors. Of those, 16 were population-based studies from 15 unique datasets (summarized in Table 1). No longitudinal studies comparing cancer survivors with the general population were identified.

The study surveyed 8096 survivors, with sample sizes ranging from 15 to 1933. Most articles reported on survivors of either breast cancer (7 studies, N = 5071) or Hodgkin's disease (7 studies, N = 1879, including one study with 33 cases of mixed non-Hodgkin and Hodgkin's lymphoma).

Nine different instruments, summarized in Table 2, were used to assess fatigue in the studies. These instruments ranged in length from 1 to 36 items, and included quality-of-life instruments with fatigue subscales and instruments specifically designed to measure fatigue.

All Cancers

Both survivors and controls reported fatigue to some degree. Eight datasets showed statistically significant ($P < .05$) differences between the cancer survivor group and the general population.[6,8,10,12,15–18,20] Four reported negative or no results,[7,9,13,14] and 3 reported both positive and negative results, depending on the dimension measured.[3,11,19] Differences between the groups did not seem to be associated with the instrument selected to assess fatigue.

Five studies presented scores for the fatigue subscale of the European Organization for Research and Treatment of Cancer Core Questionnaire for Quality of Life (EORTC QLQ-C30), a quality-of-life measure that assessed global fatigue with three 100-point questions that were then averaged.[6,12,13,16,20] In those 5 studies, mean fatigue levels in cancer survivors ranged from 28.7 to 36.5 out of an overall score of 100 (0 = not fatigued at all, 100 = most fatigued), and mean fatigue levels in controls ranged from 20 to 30 out of 100. Another 4 studies used the Fatigue Questionnaire, an instrument composed of 11 items measuring global, mental, and physical fatigue, each assessed on a 3-point scale and then summed.[8,11,17,29] Out of an overall score of 33, fatigue levels in those studies ranged, in survivors, from 12.7 to 17.9 and in controls, 11.9 to 12.3.

Of the 11 datasets in which effect size could be evaluated, most indicated that the effect of having survived cancer on average fatigue level was small. Eight datasets evidenced effect sizes of 0.3 or less; 2 evidenced effect sizes between 0.5 and 0.65; and 1 dataset produced effect sizes ranging from 0.35 to 0.89, depending on the metric evaluated. Effect size measurements did not seem to differ according to type of cancer or instrument used to measure fatigue.

Table 1 Level of Fatigue in Cancer Survivors Compared with Levels of Fatigue Among General Population Controls

Study	Disease	Fatigue Instrument	Cancer Survivors	General Population	Mean Fatigue Scores; SD or CI	*P* Value(s) for CS vs. GP*
Joly et al.,[6] France	Hodgkin's disease	EORTC† QLQ-C30†	N = 93 YSD_{mean} = 10 [range: 4, 17] Chemo + Rad = 62% No active treatment	N = 186 (age, gender, residency)‡ [marriage, education]§	CS = 28.7 (26.9) GP = 22.2 (21.5)	*P* < .025 ES = 0.28
Ganz et al.,[7] USA	Breast	SF-36†	N = 864 YSD = 1–5 Chemo + Rad = N/A No active treatment	N not provided (age, gender)‡	Vitality score CS > GP	*P* = N/A ES = N/A
Loge et al.,[8] Norway	Hodgkin's disease	FQ†	N = 459 YSD_{mean} = 12 (SD, 5.5) Chemo + Rad = 47% +/− active treatment	N = 2214 (age, sex, marriage, education)‡	CS = 14.3 (4.9) GP = 12.2 (3.9)	*P* < .001 ES = 0.51
Bower et al.,[9] USA	Breast	SF-36†	N = 1957 YSD = 1−5 Chemo + Rad > 50% No active treatment	N = 1953 (age, gender)‡	Vitality Score CS = 60.0 GP = 58.5	*P* < .009 ES = N/A
Knobel et al.,[3] USA	Non-specific lymphoma	EORTC-C30 FQ†	N_W = 15 N_M = 18 YST = 6 [range: 4, 10] 100% received ABMT No active treatment	N_W = 921 N_M = 874 (age, gender)‡	Women CS = 17.9, 95% CI, 14.4−21.5 GP = 12.3, 95% CI, 12.1−12.6 Men CS = 15.1, 95% CI, 12.9−17.4 GP = 12.0, 95% CI, 11.8–12.2	P_W < .001 P_M > .05 ES_W = 1.19 ES_M = 1.01
Servaes et al.,[10] Norway	Breast	CIS-fatigue†	N = 150 YSD_{mean} = 2.42 [range: 0.5, 5.8] Chemo + Rad = 44% No active treatment	N = 78 (age, gender)‡	CS = 28.5 (13.6) GP = 9.4 (11.0)	*P* < .001 ES = 0.71
Fossa et al.,[11] Norway	Testicular; Hodgkin's disease	FQ†	$N_{testicular}$ = 791 $YST_{testicular}$ > 4 N_{HD} = 249 YST_{HD} unknown Chemo + Rad = 21% +/− active treatment	N = 1083 (gender)‡	Measuring CF: TCS = 12.7 (4.2) HDS = 14.1 (4.5) GP = 11.9 (3.9)	For TCS > 30 y: *P* > .05 For TCS ≤ 30 y: *P* < .01 ES = .20
Ruffer et al.,[12] Germany	Hodgkin's disease	EORTC† QLQ-C30† MFI*	N = 818 YST_{median} = 5.2 Chemo + Rad = 51% +/− active treatment	N = 935 (age, gender, residency)‡	MFI CS = 37.6 (29.1) GP = 30.9 (23.2) QLQ-C30 CS = 36.5 (29.0) GP = 30 (24.7)	P_{MFI} < .001 $P_{QLQ-C30}$ < .001 ES_{MFI} = .26 $ES_{QLQ-C30}$ = 0.24
Arndt et al.,[13] Germany	Colorectal	EORTC† QLQ-C30†	N = 305 YSD > 1 Chemo + Rad = unknown +/− active treatment	N = 2028 (age)‡	CS = 35.4 GP = 23.8	*P* = N/A ES = N/A
Carpenter et al.,[14] USA	Breast	POMS-SF†	N = 15 YST > .08 Chemo + Rad = 40% No active treatment	N = 15 (age, gender, race, menopause)‡	CS = 8.60 (5.04) GP = 7.80 (4.43)	*P* < .65 ES = .16

Table 1 Continued

Study	Disease	Fatigue Instrument	Cancer Survivors	General Population	Mean Fatigue Scores; SD or CI	*P* Value(s) for CS vs. GP*
Curran et al.,[15] USA	Breast	5-day diaries with 10-point Likert scales†	N = 25 YST = 15.3 (7.1) Chemo + Rad = 24% No active treatment	N = 25 (age, gender)‡	CS_{rising} = 3.8 (2.3) CS_{10AM} = 2.9 (1.8) CS_{2PM} = 3.4 (1.8) CS_{9PM} = 4.6 (1.7) GP_{rising} = 3.1 (1.5) GP_{10AM} = 2.0 (1.0) GP_{2PM} = 2.3 (0.9) GP_{9PM} = 3.1 (1.6)	$P_{rising} > .05$ $P_{10} < .05$ $P_2 < .05$ $P_9 < .05$ $ES_{rising} = .35$ $ES_{10} = .61$ $ES_2 = .76$ $ES_9 = .89$
Jephcott et al.,[16] England	Anal Carcinoma	EORTC QLQ-C30†	N = 50 YST nor YSD provided Chemo + Rad = 100% No active treatment	N = 50 (age, gender)‡	CS = 36 (30) GP = 20 (21)	*P* < .002 ES = .61
Hjermstad et al.,[17,18] Norway	Hodgkin's Disease	FQ† SF-36	N = 476 YSD_{median} = 16.3 Chemo + Rad = 55% No active treatment	N = 3500 (age, gender, education) ‡	CS = 14.6, 95% CI, 14.1 to 15.7 GP = 12.1, 95% CI, 11.9−12.4	*P* < .001 ES = .26
Robb et al.,[19] USA	Breast	MFSI-SF† SF-36†	N = 127 YSD ≥ 1 Chemo + Rad = unknown +/− active disease	N = 87 (age, gender)‡	WF score : CS = 4.74 (2.79) GP = 4.34 (2.66) FD: CS = 11.14 (11.16) GP = 8.78 (11.27) VS: CS = ~57 GP = ~69	$P_{WF} > .05$ $P_{FD} > .05$ $P_{VS} < .001$ $ES_{WF} = .15$ $ES_{FD} = .23$ ES_{VS} = N/A
Ahn et al.,[20] Korea	Breast	EORTC† QLQ-C30† BFI	N = 1933 YSD ≥ 1 Chemo + Rad = unknown No active treatment	N = 500 (gender) ‡ [age, marriage, education, religion, employment] §	Least-squares mean score CS = 78.3 GP = 81.6	*P* < .001 ES = N/A

*Based on the Fatigue Instrument marked with †.
†Instrument used for SD or CI.
‡Matching criteria.
§Regression covariates.
Abbreviations: ABMT, autologous bone marrow transplantation; BFI, Brief Fatigue Inventory; CF, chronic fatigue (as defined by published cut-offs); CI, confidence interval; CIS-fatigue, Checklist Individual Strength-fatigue severity subscale; CS, cancer survivors; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Questionnaire for Quality of Life; ES, effect size; FD, fatigue disruption; FQ, fatigue questionnaire; GP, general public; HDS, Hodgkin's disease survivors; M, men; MFI, Multidimensional Fatigue Inventory; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; N/A, unknown; POMS-SF, Profile of Mood States-Short Form; SD, standard deviation; SF-36, Medical Outcomes Study Short Form 36; TCS, testicular cancer survivors; VS, vitality score; W, women; WF, "Worst" Fatigue; YSD, years since diagnosis; YST, years since treatment.

Breast Cancer

Seven articles compared fatigue severity in a total of 5071 breast cancer survivors with those in the general population.[7,9,10,14,15,19,20] Of these articles, 3 showed no differences between survivors and controls in level of fatigue[7,9,14] and 3 showed significant differences.[10,15,20] Another study[19] yielded mixed results: significant differences between groups in the domain of vitality but not "worst fatigue" or "fatigue disruption" (i.e., the extent that exhaustion interferes with functioning). Unlike the other breast cancer studies, this study did not clearly exclude patients undergoing active treatment.

The studies of breast cancer survivors varied along several dimensions: number of subjects, type of fatigue instrument, degree of controlling for potential confounders, and extent of cancer treatment. However, findings did not seem to be influenced by differences in sample sizes, instruments, degree of matching, or extent of cancer treatment. Survivor sample sizes ranged

Table 2 Fatigue Instruments Used in Population-Based Comparisons

Fatigue Instrument	Aim	Fatigue Dimensions Measured	Recall Timeframe	# Total Items; (# Fatigue-Specific Items)	Cronbach's Coefficient	Notes
BFI	Fatigue	Global, severity, interference in functioning	24 h	9 (9)	0.95-0.96[21]	
CIS-fatigue	Fatigue	Global, concentration, activity, motivation	2 wk	20 (20)	0.90[22]	Developed for chronic fatigue syndrome
Daily diary	Fatigue	Global	Present	1 (1)	None	
EORTC QLQ-C30	QOL, with fatigue subscale	Global	1 wk	30 (3)	<.70[23]	Developed for cancer
FQ	Fatigue	Global, mental, physical	1 mo	11 (11)	0.86[24]	Developed for primary care
MFI	Fatigue	Global, mental, physical, activity, motivation	24 h	20 (20)	Average: 0.84[25]	
MFSI-SF	Fatigue	Gobal, mental, physical, emotional, vigor	1 wk	30 (30)	0.85-0.96[26]	Developed for cancer, but with aim to not be "disease specific"
POMS-SF	QOL with fatigue and vigor subscales	Fatigue, vigor	2 wk	37 (5)	0.78-0.91[27]	
SF-36	QOL with vitality subscale	Vitality	1 mo	36 (4)	0.85[28]	

Abbreviations: BFI, Brief Fatigue Inventory; CIS-fatigue, Checklist Individual Strength-fatigue severity subscale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Questionnaire for Quality of Life; FQ, fatigue questionnaire; MFI, Multidimensional Fatigue Inventory; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; POMS-SF, Profile of Mood States-Short Form; QOL, quality of life; SF-36, Medical Outcomes Study Short Form 36.

from 25 to 1933 in the 3 articles that reported significant differences between cancer survivors and controls. In articles that reported no significant differences, sample sizes ranged from 15 to 1953. The instrument measuring fatigue included the Medical Outcomes Study Short Form 36 (SF-36), Fatigue Severity Subscale of the Checklist Individual Strength (CIS fatigue), Profile of Mood States-Short Form, daily diaries, Multidimensional Fatigue Symptom Inventory-Short Form, and EORTC QLQ-C30. The degree to which potential confounders were controlled for (through matching of controls with patients with breast cancer or through regression analysis) varied from controlling for age and gender alone in many studies to controlling for age, gender, marriage, education, religion, and employment.[20] Finally, analyzing differences in the nature and extent of cancer treatments in patients across studies was particularly challenging. Two articles[19,20] did not report on treatment histories. Among the 5 that did, great variation in the way treatments were reported limited the authors' ability to make comparisons. As a rough indictor of extent of treatment, the percentage of patients in each study who underwent both radiation and chemotherapy is also reported in Table 1. Among studies in patients with breast cancer, rates ranged from 24%[15] to 62%,[6] with most studies reporting rates of approximately 40%. Findings of studies that varied according to this measure of treatment did not seem to differ.

Lymphoma

Five datasets compared fatigue in a total of 1879 Hodgkin's disease survivors with fatigue in the general population.[6,8,11,12,17,18] Another study,[11] which had as its primary focus testicular cancer survivors, presented fatigue data on 249 Hodgkin's disease survivors and general population controls but did not directly compare controls and cancer survivors, and therefore has no value for comparing fatigue measures between survivors and the general population. Of the

5 applicable datasets, 4 showed clear differences between groups. Among these 4 studies, cancer survivor sample sizes ranged from 93 to 818. The degree to which potential confounders were controlled for varied from controlling for age and gender alone to controlling for age, gender, residency, marriage, and education.[6] The percentage of patients having undergone both chemotherapy and radiation varied from 47%[8] to 62%.[6] A final study presented data on a heterogeneous group of 33 lymphoma survivors who had all completed high-dose chemotherapy supported with autologous bone marrow transplantation.[3] This study showed significant differences in fatigue severity ($P < .001$) between female lymphoma survivors and age-matched controls but not between male lymphoma survivors and age-matched controls. Fatigue instruments used across studies included the EORTC QLQ-C30, fatigue questionnaire, Multidimensional Fatigue Inventory, and SF-36. Positive and negative outcomes in lymphoma survivors did not seem to be associated with sample size, degree to which confounders were controlled for, extent of cancer treatment, or fatigue instrument used. However, the methods of 2 of the 4 studies that reported positive results did not clearly state that data from patients undergoing active treatment had been excluded.[8,12]

Other Cancers

Three studies investigated fatigue in survivors of cancers other than breast or Hodgkin's disease. Two studies examined a total of 355 survivors of colorectal and anal cancers[13,16] and one study (mentioned among the Hodgkin's disease studies) included 791 testicular cancer survivors.[11] Although the first study in patients with colorectal cancer reported a difference greater than 10.5 points between cancer survivors and controls on the EORTC QLQ-C30, it unfortunately did not report a test of statistical significance on this difference. The second, a study in patients with anal carcinoma treated with nonsurgical means, reported a significant 16-point difference between groups on the EORTC QLQ-C30. Data on fatigue in the study of testicular cancer survivors were presented as patients who met criteria for chronic fatigue (based on previously published cutoffs) rather than according to fatigue severity levels. In that study, rates of chronic fatigue did not differ among cancer survivors and controls for most age groups but were significantly different for survivors aged 30 years or younger ($P < .001$).

Discussion

In addition to obvious heterogeneity regarding cancer subtype and previous treatment, the population-based studies varied in several other important aspects, including definitions of cancer survivor, instruments used to measure fatigue, the degree of controlling for potential confounders, and sample size. Differing definitions of survivorship greatly impact the makeup of a cancer survivor sample. The National Cancer Institute (NCI) offers a clinical definition of survivorship as "from diagnosis until end of life," and includes patients undergoing active treatment. NCI also offers a research definition of survivorship as "beyond the acute diagnosis and treatment phase," excluding patients undergoing active treatment.[30] Some studies (particularly in Hodgkin's disease survivors) seemed to include patients in the active phase of their treatment, rather than limiting samples to patients in the surveillance stage.[8,11–13,19] Although some studies evaluated patients as early as 1 year from diagnosis (when the effects of active treatment may not have fully resolved),[7,9,13,19,20] others screened patients a mean of 15.3 years after active treatment.[15]

As seen in Table 2, fatigue instruments also varied widely. Questionnaires ranged in scope (health-related quality of life vs. fatigue-specific), length (1–36 questions), conception of the variable of interest ("fatigue" vs. "vitality"), and recall timeframe (present vs. in the past month). This heterogeneity limited these investigators' abilities to aggregate data and to tease out true differences between cancer survivors and controls.

Finally, the studies varied in terms of power, a particularly important factor for those studies not reporting differences. Sample sizes ranged from 15 per group[14] to nearly 2000 per group,[8] greater than a 100-fold difference. An association between sample size and findings did not seem to be noted among the studies included in this review.

Despite the variability inherent in these studies, some inferences could be drawn from the data. First, fatigue is a symptom common to both cancer survivors and members of the general population. According to average scores on the EORTC QLQ-C30, which is 1 of 2 instruments used most frequently in the reviewed studies, levels of fatigue ranged from approximately 29% to 37% of the theoretical maximum among cancer survivors and from 20% to 30% of the theoretical maximum among general population controls.

Both populations showed substantial variability in fatigue severities.

Second, on average, cancer survivors seem to experience greater fatigue than the general population; however, the effect of having survived cancer on average fatigue severity tends to be small. Of the 15 datasets in this study, more than half (9/15) showed cancer survivors to be more tired than their general population counterparts, and 3 studies yielded mixed results. Even in studies with the most rigorous definitions of survivors (at least 2 years out from treatment), 3 of 4 showed clear differences among groups[6,15,19] and 1 reported positive results on some measures and negative results on others.[3] Most computed effect sizes were small, suggesting that the size of the observed differences in fatigue between cancer survivors and members of the general population were modest at best.

The fact that studies looked at survivors of particular cancer subtypes allows for comment on the differences among these subgroups. For instance, no strong evidence was seen for the occurrence of excessive fatigue among survivors of breast cancer. Equal numbers of positive and negative studies were included in this subgroup, a particularly surprising result, because most breast cancer survivors were women, who tended to complain of worse fatigue across studies.[3,8] In contrast, no published negative studies compared Hodgkin's disease survivors with general population controls. Although one might be tempted to conclude that Hodgkin's disease survivors are clearly more tired than members of the general public, confidence in the results must be tempered by lack of clear exclusion of patients undergoing active treatment in 2 of the positive studies. Too few studies in other cancer subtypes have been performed to draw conclusions.

Although these inferences are provocative, this review has several limitations. First, the studies focused on quantitative differences in fatigue levels between cancer survivors and members of the general population and did not explore qualitative differences in the experience of fatigue. Other important differences in the characteristics of fatigue may have been overlooked. Although the studies involved comparisons with the general population, all were cross-sectional and none collected data about fatigue onset and duration. The existence of fatigue after cancer treatment does not imply causality; in fact, some differences may have been present before cancer diagnosis and even before cancer onset. Furthermore, assessing cancer-related symptoms in cancer survivors may be subject to "response shift," the tendency over time for a person experiencing illness to alter internal values, standards, and definitions of life quality.[31] Through this cognitive process, individuals may report different fatigue ratings over time, not only because fatigue levels have changed but because the way they measure fatigue has changed. This trend toward reporting lower levels of symptoms over time may actually underestimate the extent of fatigue in cancer survivors. Lastly, the authors are unable to account for the possibility of publication bias, with a tendency for studies that have positive results to be published.

To address some of these limitations, and to begin to quantify fatigue incidence, prospective, longitudinal, population-based studies that begin at or before cancer diagnosis are needed; none seem to have been published. The collection of data on fatigue in terms of its onset, duration, and level, as well as on specifics of cancer treatments and comorbid medical illnesses may help develop a greater understanding of the mechanisms underlying differences in fatigue between cancer survivors and the general population (if they are still found to exist). Epidemiologic studies like these may ultimately guide experts to targeted interventions for cancer-related fatigue in survivors.

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