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No excess fatigue in young adult survivors of childhood cancer

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Abstract

Clinical reports suggest that many survivors of childhood cancer experience fatigue as a long-term effect of their treatment. To investigate this issue further, we assessed the level of fatigue in young adult survivors of childhood cancer. We compared the results with a group of young adults with no history of cancer. The impact of demographic, medical and treatment factors and depressive symptoms on survivors' fatigue was studied. Participants were 416 long-term survivors of childhood cancer (age range 16–49 years, 48% of whom were female) who had completed treatment an average of 15 years previously and 1026 persons (age range 16–53 years, 55% female) with no history of cancer. All participants completed the Multidimensional Fatigue Inventory (MFI-20), a self-report instrument consisting of five scales (general fatigue, physical fatigue, mental fatigue, reduced activity, reduced motivation) and the Center for Epidemiologic Studies Depression Scale (CES-D). Small differences were found in the mean scores for the different dimensions of fatigue between the long-term survivors and controls (range effect sizes −0.34 to 0.34). Women experienced more fatigue than men. Logistic regression revealed that being female and unemployed were the only demographic characteristics explaining the various dimensions of fatigue. With regard to medical and treatment factors, diagnosis and severe late effects/health problems were associated with fatigue. Finally, depression was significantly associated with fatigue on all subscales. Our clinical practice suggests a difference in fatigue in young adult childhood cancer survivors and their peers. This could not be confirmed in this study using the MFI-20. The well known correlation between fatigue and depression was confirmed in our study. Further research is needed to clarify the undoubtedly complex somatic and psychological mechanisms responsible for the development, maintenance and treatment of fatigue in childhood cancer survivors.

Keywords: Childhood cancer; Young adult survivors; Fatigue; Depression

1. Introduction

Since the 1970s, the results from the treatment of children with cancer have significantly improved. Nowadays, the cure rate is approximately 70% and in countries with advanced medical care, 1 in every 1000 young adults are cured [1]. It is well recognised that treatment can be associated with significant adverse late effects, including second malignancies, endocrine abnormalities, cardiac dysfunction, pulmonary disease, hepatic, renal, and gastrointestinal dysfunction, neurocognitive dysfunction and psychological sequelae [2–4]. While these long-term effects are discussed extensively in the literature, there is limited discussion of fatigue as a symptom experienced by survivors of childhood cancer.

Among cancer patients fatigue is a common, debilitating and distressing symptom, due to their illness and/or their treatment [5–8]. While different definitions of cancer-related fatigue have been suggested, most include references to tiredness [9] or weariness, weakness, exhaustion and lack of energy [8,10]. Recent multidimensional conceptualisations of fatigue in adult cancer patients suggest that fatigue is a subjective experience with significant physical (e.g. weakness), behavioural (e.g. alterations in sleep patterns and activity level), cognitive, and affective (e.g. mood disturbance)

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components [7–9,11]. Fatigue can have serious adverse effects on quality of life [12,13], as well as a considerable impact on self-care activities [14].

It has also been reported that some patients experience significant degrees of fatigue long after the conclusion of cancer treatment, even if all known causes have been resolved and the patients are in remission [15–31]. These studies investigated patients treated for breast cancer, Hodgkin's disease, lymphoma patients and various types of cancer. The mean time elapsed since treatment varied from 9 months to 12 years and percentages of fatigue from 17 to 30% [32].

To our knowledge, no studies in the literature have specifically focused on fatigue in childhood cancer survivors. Wasserman and colleagues [33] reported "easy fatigability" in 5% of 40 survivors of childhood and adolescent Hodgkin's disease. In the study by Kanabar and colleagues [34], four out of 50 survivors who had completed treatment with chemotherapy and/or radiation therapy followed by autologous bone marrow rescue had problems related to a lack of energy. Moe and colleagues [35] found that the somatization score on the General Health Questionnaire with items closely related to fatigue demonstrated a significantly higher score for survivors of acute lymphoblastic leukaemia (ALL) than for the controls. Finally, Zeltzer and colleagues [36] reported no difference between the Profile of Moods State Fatigue subscale score of 552 survivors of childhood ALL and 394 sibling controls. Because no difference in fatigue was found in this population, a further evaluation of risk factors for fatigue was not performed. The above findings contrast to clinical observation and reports of former childhood cancer patients. Results from a former qualitative study performed by us, indicate that fatigue is a serious problem in a subgroup of young adult survivors of childhood cancer and that fatigue affects many aspects of quality of life [37].

However, the symptom of fatigue is not specific for cancer. Fatigue and lack of energy is a prevalent symptom in the general population, and prevalence estimates range from 11 to 45% [38,39]. Fatigue is also a major complaint among attenders of general practices [40,41], and it is a central symptom in many other diseases, for example, ischaemic heart disease [42] and depression [41]. To interpret the significance of results obtained in follow-up studies involving childhood cancer patients, a comparison should therefore be made with persons without a history of cancer. Some studies indicate that disease-free cancer patients report more fatigue than controls do [15,18,19,21,22]. However, in other studies no differences in fatigue scores were found between cancer patients, following treatment 22 and 9 months before, respectively, and healthy comparisons [17,20].

Little is known about the role of demographic, medical and former treatment modalities in predicting post-treatment fatigue. Some studies have found higher prevalences or higher mean scores in women [17,38,39,41,43,44], whereas others did not find such differences [45,46]. Servaes and colleagues [32] evaluated 16 studies in which the focus was on "off-treatment fatigue". Most studies found no relationships between present fatigue and former disease- and treatment variables. In two studies, the severity of posttreatment fatigue was related to the extent of treatment. In these studies, former chemotherapy patients (sometimes in combination with radiation therapy and/or hormonal therapy) reported higher levels of fatigue compared with those treated with radiation therapy alone [16,17,19,20,24].

The relationship between depression and fatigue experienced by cancer survivors has not been systematically studied *per se*; however, most of the data suggests a positive relationship between depressive symptoms and fatigue [15,17–20,31]. The relationship between these two constructs is clearly complex. Fatigue may be the result of a depressed mood [47]. However, the person who continuously perceives his or her energy as insufficient may become depressed. To complicate matters, in cancer, depression and fatigue may co-occur without having a causal relationship, because they can both originate from the same pathology [48].

The aim of the present study was to assess the level of fatigue in young adult survivors of childhood cancer. The severity was compared with that observed in a group of young adults with no history of cancer. Furthermore, the impact of demographic, medical and treatment factors and depressive symptoms on the survivor's fatigue was studied.

2. Patients and methods

2.1. Study group

Data were collected from two samples: young adult survivors of childhood cancer (hereafter referred to as the 'survivors' group) and a reference group of persons with no history of cancer (hereafter referred to as the 'comparison' group).

2.1.1. Survivors group

Patients eligible for participation in the study were those attending the long-term follow-up clinic at The Emma Kinderziekenhuis/Academic Medical Center, Amsterdam for their annual evaluation between January 1997 and July 1999. The long-term follow-up clinic was established in 1996 to monitor long-term sequelae of childhood cancer and its treatment. Patients become eligible for transfer from active-treatment clinics to the follow-up clinic when they had successfully completed their cancer treatment at least 5 years earlier. Survivors are evaluated annually in the clinic by a paediatric

oncologist (persons aged <18 years) or internist-oncologist (persons aged >18 years) for late medical effects, as well as a research nurse or psychologist for psychosocial effects. Study participants had to be aged 16 years or older, have had a pathological confirmation of malignancy and their cancer had to have been diagnosed before the patients were 19 years of age. Within the study period, a total of 459 patients were offered appointments to attend the follow-up clinic. Of these patients, 11 attended, but were not included in this study (1 person was schizophrenic, 8 were developmentally delayed and 2 were deemed ineligible because of a current health problem causing emotional upset). A further 32 patients did not attend, representing a failed attendance rate over this period of 7%. Survivors who did attend were significantly younger than survivors who did not attend (mean = 24 versus 26 years; $P<0.05$), but there were no differences with regard to sex or type of diagnosis. A total of 416 patients were approached to take part in this study during their visit to the follow-up clinic and all agreed to participate. After their informed consent, the survivors were individually asked to complete a questionnaire by one of the authors. The investigator was present to make sure that the questionnaire was clearly understood. Most survivors had no difficulty in completing the questionnaire, only 2 subjects needed some assistance.

2.1.2. Comparison group

Participants were recruited with the help of the survivors' general practitioners (GPs). Letters with response cards were sent to the GPs of the potential survivor group ($n=540$) explaining the purpose of the study and asking for their help in selecting an age-matched control group. Three hundred and thirty GPs responded (61% response rate), of which 151 stated that they could not participate because of a lack of time: thus, 179 of the notified GPs agreed to take part in the study. These GPs were asked to select 10 subjects from their patients registry lists (starting with a given letter from the alphabet) with a given sex and age range. Those with (a prior history of) cancer were to be excluded. The GPs had to send to those who were eligible a packet containing the questionnaire, a stamped return address envelope and a cover letter. Two weeks after the original mailing date, the GPs had to send another packet with the same content and a reminder letter. Of 1790 questionnaires mailed, 23 were returned because the subjects had moved and their address could not be traced. 24 refused to participate for various reasons (lack of time $n=5$; not able to understand Dutch $n=4$; perceived invasion of privacy $n=7$; other reasons $n=8$). Of the remaining 1743 questionnaires, 1096 completed questionnaires were returned (response rate 63%). Four responses were excluded afterwards because the respondents did not met the inclusion criteria (too young $n=3$; too old $n=1$) and an additional 66 questionnaires lacked responses in many items. Thus, complete data were obtained from 1026 of those eligible. No significant differences were found with respect to age, sex, educational and marital status in a Chi-square analysis to test for differences between the controls who provided complete data and the 66 controls who did not.

2.2. Measures

Data were collected on sociodemographic characteristics in terms of age at follow-up, gender, marital status (single, living together/married), educational level (low = less than high school, high = high school or advanced degree), and employment status (unemployed, student/homemaker, employed). In addition, a paediatrician, who had experience regarding the long-term effects of childhood cancer, reviewed the medical record prior to the visit to obtain information about survivor's cancer history and these data were recorded onto structured data coding sheets. Age at diagnosis, time since completion of therapy and duration of treatment were assessed. Diagnoses were categorised into: leukaemia/non-Hodgkin's lymphoma with or without cranial radiation therapy (CRT), solid tumours, and brain/central nervous system (CNS) tumours. Treatment was aggregated into three categories: chemotherapy (with or without surgery), radiation therapy (with or without surgery), and combination therapy (chemotherapy and radiation therapy with or without surgery). Finally, late effects and health problems were scored on an adapted version of the Greenberg, Meadows & Kazak's Scale for Medical Limitations [49] by two paediatric oncologists and a paediatric oncology nurse, who were blinded to the survivors' identity. Patients were categorised into the following three groups according to their most serious medical limitation: 1 (mild) = no limitations of activity. This group included children with one kidney and second benign neoplasms, and no cosmetic or organ dysfunction; 2 (moderate) = no serious restriction of daily life. This group included children with hypoplasia or asymmetry of soft tissue, mild scoliosis and other mild orthopaedic problems, moderate obesity, abnormally short stature, mild hearing loss, cataract, hypothyroidism, delayed sexual maturation, learning delay, enucleation of one eye, small testis, elevated follicle stimulating hormone/luteinising hormone (FSH/LH), alopecia, hypertension, pulmonary diffusion disturbances; 3 (severe) = significant restriction on daily activity or severe cosmetic changes. This group included children with learning delay requiring special education, soft-tissue or bone changes that alter appearance, severe asymmetry, absent limb, dental reconstruction, gonadal failure, azoospermia, known sterility, blindness, organ damage that limits activity, second malignant neoplasms,

hemipareses, fatigue that affect daily and social activities. Sixteen percent (n = 68) of survivors were categorised as mild, 45% (n = 189) as moderate, and 38% (n = 159) as severe.

Fatigue was measured with the Multidimensional Fatigue Inventory (MFI-20), which is a self-report instrument consisting of 20 statements that can be rated on a five-point scale ranging from 'yes, that is true' to 'no, that is not true'. Items are combined to form five scales, including general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation [50,51]. General fatigue refers to fatigue expressed by people in terms of statements like "I feel tired" and "I feel rested". Physical fatigue refers to physical sensations related to the feelings of tiredness. Mental fatigue refers to deficits in cognitive functioning, such as having difficulties concentrating. Finally, reduced activity covers not doing any useful activities and reduced motivation covers lack of motivation to initiate such activities. Higher scores indicate higher levels of fatigue. The MFI-20 has well-established levels of reliability and validity among cancer patients [17]. The reliability (i.e. internal consistency) in our study, as measured by Cronbach's alpha coefficient, ranged from 0.74 for the reduced motivation scale to 0.90 for the general fatigue scale.

Depression was measured with a part of the Center for Epidemiologic Studies Depression scale (CES-D) [52], which is a 20-item self-reporting scale, developed to measure depressive symptomatology in the general population. Respondents rate the degree to which they have experienced each depressive symptom during the past week on a four-point frequency scale (0 = rarely or none of the time; 3 = most or all of the time). To avoid any overlap in symptomatology with the MFI-20, we used this scale without the items of the domain 'somatic and retarded activity' (n = 7) [48]. In this paper, we refer to the questionnaire as the mood component of depression. Scores on this mood component could range from 0 to 39, with higher scores indicative of greater depressive symptomatology. In our study, Cronbach's alpha coefficient for this scale was 0.88.

2.3. Statistical analysis

The Statistical Package for Social Sciences (SPSS) Windows version 9.01 was used for all statistical analyses. Descriptive statistics were performed for all of the variables. Differences in demographic characteristics between survivors and the comparison group were analysed with Chi-square tests or Student's t-tests. Differences between the mean MFI-20 subscale scores of the survivors and the comparison group were tested with the Student's t-test. To examine the magnitude of these differences, effect sizes were calculated by dividing the difference between a given mean score of the survivor group and the mean score in the comparison group by the standard deviation of scores in the comparison group. An effect size of 0.20 is considered small, whereas effect sizes about 0.50 and 0.80 or greater are moderate and large, respectively [53].

Univariate relationships between survivors' MFI-20 scores and the mood component of the CES-D were assessed by Pearsons correlation coefficients. To investigate which variables predict survivors' fatigue, all variables were stepwise presented to a multiple regression model to assess their independent prognostic value. For three variables (employment status, diagnosis and treatment), we created dummy variables and took the first category (unemployment, leukaemia/non-Hodgkin's lymphoma without CRT, and chemotherapy with or without surgery) as a reference for the analysis. First (Step 1), survivors' demographic characteristics were presented to the model. Second (Step 2), medical and treatment characteristics were entered, followed by the mood component of the CES-D (Step 3). Finally, the demographic, medical and treatment characteristics and the mood component of the CES-D were entered in the regression together (Step 4). With this strategy, the contribution of the separate steps show which variables in particular contribute to fatigue. Every model was repeated five times, for every fatigue subscale (general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation) separately. For each regression, the explained variance (R^2) was determined.

3. Results

3.1. Characteristics of survivors and comparison group

Information about the demographic and medical characteristics of the survivor group and the comparison group is listed in Table 1. The survivors' age at diagnosis ranged from 0 to 18 years (median 8), the range of the time since completion of therapy was 5 to 33 years (median 15). The median duration of treatment was 16 months (range 0–170 months). The survivors were treated for a variety of cancers. The most frequent diagnoses were leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease and Wilms' tumour. We compared the distribution of cancer diagnoses of our study population with the distribution of diagnoses of the survivors, who were known to be alive, but were not yet seen in the follow-up clinic. We found an over-representation of leukaemias and lymphomas in our study group. For logistic considerations many survivors with these diagnoses were seen in the follow-up clinic during the first few years after the clinic was set up.

The median age at follow-up of the survivors was 24 years (range 16–49 years), this was slightly younger than that of the comparison group (median 26; range 16–53

years). There were more male than female survivors, whereas the reverse was true for the comparison group. Furthermore, a Chi-square analysis showed that survivors and controls differed in terms of marital status and educational level. More survivors had never married compared with controls and more survivors had a lower educational level than the controls. However, because these could be typical features of the survivor group, univariate analysis of variance was performed to examine the influence of age at follow-up, sex, subject status, marital status, educational level, and the interaction of these variables on the different domains of fatigue. We found no significant effects of subject status and marital status and subject status and educational level on any of the dependent variables. Therefore, the influence of marital status and educational level on the dependent variables were not further accounted for.

3.2. Fatigue in survivors versus comparison group

Survivors scored significantly lower (i.e. reflecting less fatigue) for general fatigue ($P < 0.05$, effect size −0.14) and reduced motivation ($P < 0.05$, effect size −0.19), but statistically higher (i.e. reflecting worse fatigue) for mental fatigue ($P < 0.05$, effect size 0.15) than controls. In Table 2, the mean scores and standard deviations for the different dimensions of fatigue are presented for the survivors and the comparison group in relation to sex and age at follow-up. In general, females experienced higher levels of fatigue on all subscales than men. Male survivors had significantly lower scores on general fatigue, reduced activity and reduced motivation than their peers (effect sizes −0.34, −0.25 and −0.34, respectively). Female survivors reported significantly more fatigue on the scales physical fatigue (effect size 0.21) and mental

Table 1
Demographic and medical characteristics of the study group

Variable	Survivors ($n = 416$)	Comparison group ($n = 1026$)	P value
Age at follow-up (years)			
Mean±S.D.	24±5.2	26±5.1	<0.001[a]
Sex %			
Men	52	45	
Women	48	55	0.02[b]
Marital status %			
Single	72	46	
Living together/married	28	54	<0.001[b]
Educational status %			
Lower level	67	57	
Higher level	33	43	<0.001[b]
Age at diagnosis (years)			
Mean±S.D.	8±4.7		
Time since completion of therapy (years)			
Mean±S.D.	15±5.9		
Duration of treatment (months)			
Mean±S.D.	16±20.4		
Diagnosis	*N* (%)		
Leukaemia/non-Hodgkin's lymphoma without CRT	116 (28)		
Leukaemia/non-Hodgkin's lymphoma with CRT	87 (21)		
Solid tumour	183 (44)		
Brain/CNS tumour	30 (7)		
Treatment			
Chemotherapy (with or without surgery)	197 (47)		
Radiation therapy (with or without surgery)	29 (7)		
Combination therapy (chemotherapy and radiation therapy with or without surgery)	190 (46)		
Medical limitations	*N* (%)		
None/mild	68 (16)		
Moderate	189 (45)		
Severe	159 (38)		

S.D., standard deviation; CRT, cranial radiation therapy; CNS, central nervous system.
[a] *t*-Test.
[b] Chi-square.

Table 2
Mean (S.D.) scores for the MFI-20 for the survivors and the comparison group in relation to sex and age at follow-up (higher scores indicates more fatigue)

Scale	Males		Females		⩽25 years		26–30 years		⩾31 years	
	Survivors ($n=216$)	Controls ($n=463$)	Survivors ($n=200$)	Controls ($n=563$)	Survivors ($n=290$)	Controls ($n=497$)	Survivors ($n=80$)	Controls ($n=458$)	Survivors ($n=46$)	Controls ($n=71$)
General fatigue	7.5 (4.3)**	8.8 (3.8)**	10.9 (5.2)	10.5 (4.5)	8.8 (4.9)*	9.6 (4.2)*	10.0 (5.3)	10.0 (4.4)	9.9 (5.6)	9.8 (4.8)
Physical fatigue	6.9 (3.8)	7.1 (3.2)	9.7 (4.7)*	8.8 (4.3)*	7.7 (4.1)	8.0 (3.9)	9.4 (4.8)*	8.1 (3.9)*	9.7 (5.4)	8.3 (4.0)
Mental fatigue	7.9 (4.5)	8.0 (3.7)	10.1 (4.9)**	8.7 (4.1)**	8.9 (4.8)	8.6 (3.9)	8.9 (4.6)	8.1 (3.9)	9.3 (5.2)	8.5 (3.9)
Reduced activity	6.9 (3.6)*	7.7 (3.2)*	8.6 (4.2)	8.0 (3.6)	7.4 (3.7)	7.8 (3.3)	8.6 (4.7)	8.0 (3.4)	8.3 (4.3)	7.9 (3.9)
Reduced motivation	6.1 (2.8)**	7.1 (2.9)**	7.3 (3.5)	7.3 (3.1)	6.4 (3.1)*	7.0 (2.9)*	7.1 (3.2)	7.4 (3.1)	7.6 (3.8)	7.9 (3.3)

*Statistically significant difference ($P<0.05$) in means by t-tests; **statistically significant difference ($P<0.001$) in means by t-tests.

fatigue (effect size 0.34) in comparison with their female peers. Within the age groups, survivors 25 years old or younger scored significantly lower for general fatigue and reduced motivation (effect sizes −0.19 and −0.21, respectively). Survivors 26–30 years old reported more physical fatigue than controls (effect size 0.33).

3.3. Association between survivors' fatigue and depression

Prior to the simultaneous regression analysis, Pearson product moment correlation's for fatigue and depression were performed (see Table 3). Significant correlation's are shown between CES-D mood scores and the MFI-20 subscale scores.

3.4. Prediction of survivors' fatigue by demographic, medical and treatment characteristics and depression

Table 4 presents the results of predictors of fatigue identified by multivariate regression analysis at each step. With regard to the demographic variables (Step 1), female gender was the strongest prognostic factor of fatigue on all subscales. Physical fatigue and reduced motivation were explained by an older age at follow-up. General fatigue, physical fatigue and reduced activity were associated with unemployment.

With regard to the medical and treatment characteristics (Step 2), severe late effects/health problems were associated with fatigue on all of the subscales. Physical fatigue showed a negative association with diagnosis, meaning that survivors with leukaemia/non-Hodgkin's lymphoma without CRT suffered from more fatigue than survivors with leukaemia/non-Hodgkin's lymphoma with CRT. Physical fatigue was also explained by treatment (radiation therapy with or without surgery).

In Step 3, depression was associated with fatigue on all subscales. After entering both demographic, medical and treatment characteristics and the mood component of the CES-D into the model (Step 4), the results showed that depression was the strongest predictor of fatigue on all subscales. Both general fatigue and physical fatigue were further associated with females, unemployment, survivors who have had leukaemia/non-Hodgkin's lymphoma without CRT, and severe late effects/health problems. Mental fatigue was associated with severe late effects/health problems as well as depression. Reduced activity was associated with a higher educational level, unemployment and severe late effects/health problems. The selected characteristics explained only a moderate proportion of the variability (R^2) of the fatigue scores: 29–46%.

Table 3
Pearson's correlation of the MFI-20 scores and the mood component of the CES-D for the survivors

MFI-20	CES-D mood
General fatigue	0.61**
Physical fatigue	0.58**
Mental fatigue	0.51**
Reduced activity	0.57**
Reduced motivation	0.61**

**Statistically significant differences ($P<0.001$).

4. Discussion

In this study, the level of fatigue among young adult survivors of childhood cancer was compared with a sample of young adults with no history of cancer. In addition, the relationship between the demographic, medical and treatment factors and depression on the survivor's fatigue were examined. The following discussion summarises the main findings, considers the clinical implications, and identifies several directions for future research.

The survivors and the comparison group differed in some aspects that possibly affected the comparisons. Significant differences were observed with regard to marital status and educational level. However, it is doubtful that these differences were influential because fatigue was not significantly related to marital status and educational level. The response rate among the

Table 4
Simultaneous regressions (Beta) for survivors' fatigue[a]

	GF	PF	MF	RA	RM
Step 1					
Demographic characteristics					
Sex (female)	0.34**	0.32**	0.22**	0.21**	0.19**
Age at follow-up (years)	0.08	0.22**	0.04	0.11	0.16*
Marital status (married)	0.01	−0.03	−0.09	−0.02	−0.04
Educational level (higher level)	0.01	0.04	−0.08	0.06	−0.02
Employment status[c]					
Student/homemaker	−0.24*	−0.23*	−0.13	−0.18*	−0.11
Employed	−0.18*	−0.13	−0.15	−0.06	−0.23
Total R^2[b]	15%	16%	7%	7%	6%
Step 2					
Medical and treatment characteristics					
Age at diagnosis (years)	−0.04	0.02	−0.11	−0.09	−0.01
Diagnosis[d]					
Leukaemia/non-Hodgkin's lymphoma with CRT	−0.12	−0.19*	0.03	−0.10	−0.04
Solid tumour	−0.03	−0.07	0.03	0.01	−0.05
Brain/CNS tumour	−0.09	−0.10	0.03	0.01	0.04
Duration of treatment (months)	0.05	0.05	−0.01	0.04	0.02
Years since completion of therapy	−0.02	0.06	−0.08	−0.01	0.05
Late effects/health problems	0.26**	0.25**	0.20**	0.23**	0.20**
Treatment[e]					
Radiation therapy (with or without surgery)	0.12	0.18*	0.12	0.04	0.07
Combination therapy (with or without surgery)	0.05	0.10	0.06	0.05	0.01
Total R^2[b]	9%	13%	7%	7%	7%
Step 3					
Mood component of the CES-D					
Depression	0.61**	0.58**	0.51**	0.58**	0.61**
Total R^2[b]	37%	34%	26%	33%	38%
Step 4					
Demographic, medical and treatment characteristics and depression					
Sex (female)	0.19**	0.18**	0.08	0.04	0.00
Age at follow-up (years)	0.01	0.25	−0.24	0.33	−0.30
Marital status (married)	0.04	−0.01	−0.04	0.01	0.01
Educational level (higher level)	0.03	0.06	−0.04	0.09*	0.04
Employment status[c]					
Student/homemaker	−0.12	−0.08	−0.09	−0.01	0.03
Employed	−0.20*	−0.18*	−0.08	−0.14*	−0.06
Age at diagnosis (years)	0.06	−0.08	0.21	−0.25	0.38
Diagnosis[d]					
Leukaemia/non-Hodgkin's lymphoma with CRT	−0.16*	−0.22**	0.01	−0.10	−0.04
Solid tumour	0.02	−0.06	0.05	0.04	−0.01
Brain/CNS tumour	−0.08	−0.09	0.01	0.02	0.04
Duration of treatment (months)	0.02	0.02	−0.03	−0.02	0.01
Years since completion of therapy	0.02	−0.15	0.23	−0.29	0.45
Late effects/health problems	0.14*	−0.14*	0.10*	0.11*	0.08
Treatment[e]					
Radiation therapy (with or without surgery)	0.01	0.08	0.06	−0.04	0.01
Combination therapy (with or without surgery)	0.04	0.09	0.06	0.06	0.01
Depression	0.54**	0.51**	0.46**	0.56**	0.59**
Total R^2[b]	46%	45%	29%	39%	40%

Abbreviations: GF: general fatigue, PF: physical fatigue, MF: mental fatigue, RA: reduced activity, RM: reduced motivation, CRT: cranial radiation therapy, CNS: central nervous system. *Statistically significant differences ($P < 0.05$); ** statistically significant differences ($P < 0.001$).

[a] Within each step, variables are presented in order of selection, see also Methods section.

[b] R is the percentage of the total variation of the dependent variable score that is explained by the independent variables together.

[c] Reference group = unemployment.

[d] Reference group = leukaemia/non-Hodgkin's lymphoma without CRT.

[e] Reference group = chemotherapy (with or without surgery).

controls was highly satisfactory for a mailed survey. Nonetheless, there are several limitations to the study. First, as with all survey studies, the likelihood of respondents being those particularly interested in the topic is high. Second, the respondents may be those who suffered from physical problems and were motivated to respond. Third, the findings of this study are limited by the heterogeneous patient groups with regard to the cancers involved, treatment regimens and the crude assessment categories used.

The results of the study suggest that young adult survivors of childhood cancer experience a level of fatigue that is more or less the same as that 'normally' experienced by persons of about the same age. We were, to put it mildly, somewhat surprised by the results because the survivor group was expected to be more fatigued. The present study was inspired by clinical reports from a subgroup of childhood cancer survivors who attended the long-term follow-up clinic in our hospital and complained about extreme fatigue which had a negative impact on their daily lives. Findings from a qualitative study done by our team, revealed that fatigue was a serious problem for some persons and affected many aspects of their daily life [37].

As described earlier, previous investigations that included a non-cancer comparison group also found comparable fatigue ratings between cancer patients and controls [17,20], and high rates of complaints of chronic fatigue are found in the general population and primary care studies as well. Therefore, on the basis of our results, we can not conclude that fatigue following treatment for childhood cancer is actually no more severe than 'normal' fatigue. Several factors have to be taken into account. First, the lack of differences between the survivors and controls may be due to the so-called 'response-shift'. Response shift refers to a theory that as a result of changes in a subject's health state, a person may undergo changes in internal standards, values or conceptualisations [54–56]. In our setting, it could imply that the experience of fatigue for a relatively long period could have changed a fatigued survivor's standard of measurement concerning fatigue and as a result fatigue has been underreported. Previous research has documented that response shift may adversely affect the results of self-reported outcomes in clinical trials and other longitudinal studies [57]. Second, in this study, we did not assess either the type of fatigue or intensity of activity nor the characteristics of fatigue. In our qualitative study [37], survivors gave many examples of how fatigue limited their activities or how they had to confine their activities to the essentials. Therefore, it is possible that fatigued survivors limit their activities to such a degree that as a result, their fatigue does not exceed the level found in the comparison group. Further work is needed to substantiate these findings. Future research should also address survivors' characteristics associated with fatigue. The results of some studies provide evidence that patients with cancer experience fatigue that is different from the fatigue experienced by a 'healthy' reference group [17,58–60]. For instance, a small exploratory study by Glaus and colleagues [59] compared patterns of fatigue in healthy workers and cancer patients. The healthy workers started the day without tiredness, remained fit until the late afternoon and were very fatigued in the evening. In the cancer patient group, the daily profile was different: fatigue was continuously present, patients already felt fatigued in the morning, and, to a certain degree, over the whole day. The authors proposed a circadian rhythm for fatigue in cancer patients. These findings partly correspond with the results in our qualitative study where most of our childhood cancer survivors reported that they already felt fatigued on waking up, even after sleeping many hours per night without sleeping impairments. Further work is needed between these and other correlates of fatigue, such as sleep disturbances and psychological distress. Third, we did not investigate the outcome of fatigue. If we want to demonstrate any difference in fatigue between cancer survivors and a comparison group the impact on quality of life, mobility, self-care, social isolation and role change needs to be explored in more detail.

When we examined the relationship between demographic, medical and treatment factors and depressive symptoms on survivors' fatigue we found that, among the demographic factors, female gender was significantly associated with severe fatigue on all of the subscales. This is in line with the outcomes of other studies [17,38,39,41,43,44]. As suggested by Akechi and colleagues [61], a possible explanation for the repeated finding of greater fatigue in women could be the gender difference in the perception of symptoms suggested by Gijsbers van Wijk and Kolk [62], who indicated that there are consistent sex differences in symptom reporting, with women having the higher rates. Unemployment was associated with higher levels of general and physical fatigue and reduced activity. It should be noted, however, that the unemployed group was small ($n = 42$) and more than half of these survivors were, partly or fully, officially declared unfit for work because of medical problems. It is not difficult to imagine that these persons have less energy and a decreased activity level. We found some relationship between medical factors and severe fatigue in this study. It is difficult to determine whether the present results are reliable because, to our knowledge, no prior study has addressed the associations between fatigue and these factors in childhood cancer survivors. It is unclear why survivors who have had leukaemia or non-Hodgkin's lymphoma without CRT were more likely to be generally and physically fatigued than survivors with other diagnoses. No satisfactory explanation is available for this finding.

It is not surprising that survivors with severe medical limitations had a higher risk of being fatigued than survivors with moderate and none/mild limitations, especially since survivors with severe medical limitations are more likely to have symptoms related to their disease. In one of the few multivariate studies of correlates of fatigue, Irvine and colleagues [58] found symptom burden to be an important independent predictor of fatigue levels. Another aspect that has to be taken into account is the fact that survivors suffering from fatigue that affected their daily and social activities were put into the severe medical limitation group. However, when we looked at the number of fatigued survivors in this category ($n = 66$), we found that more than half of these survivors ($n = 36$) were not put into this category because of their fatigue alone, but suffered from other severe medical limitations as well. No relationship was found between other medical and treatment factors and severe fatigue, such as age at diagnosis, duration of treatment and years since completion of therapy. This lack of association is in line with the results described in the majority of studies [32].

In accordance with results in the literature, depression was substantially related to fatigue. As noted before, the depression-fatigue association is a very complex one. Fatigue may result from a depressive mood [47], but depression could also be a result of persistent feelings of fatigue and this may especially be the case when the treatment for cancer has ended some time ago. Although an association between depression and fatigue cannot be ruled out as an explanation for fatigue experienced during and after treatment for cancer, it is clearly an incomplete description of the underlying process [32]. As stated by Smets and colleagues, it underlines that the role of depression should be taken into account when trying to alleviate fatigue [63] and that psychological support should form one aspect of a programme for the management of fatigue. Trijsburg and colleagues [64] reviewed 22 studies that explored the effectiveness of psychological treatment for patients with cancer. This review concluded that tailored 'counselling', where counselling and support were provided according to patients' needs, was effective not only in reducing distress and enhancing self-esteem, but also in reducing fatigue.

In conclusion, this report represents the first evaluation of fatigue in childhood cancer survivors. The lack of difference in fatigue between the survivors and controls is noteworthy. However, in our opinion, one must be wary of concluding that survivors' fatigue is a trivial complaint. There is no doubt that many childhood cancer survivors face a multitude of overwhelming and de-energising problems and "I just don't have any energy" is one of them.

Presently, we are sorely limited in what we can offer patients who are fatigued after treatment for cancer. In our opinion, it is critical that health care providers acknowledge fatigue in order to grant it legitimacy. From clinical practice, we found that simply asking about our survivors' fatigue, listening, and taking the problem seriously helps them to cope and adjust to the problem. To be able to offer more than that, we need to understand more about the nature and mechanisms of cancer-related fatigue. There is a need for studies that use prospective longitudinal designs to yield more definitive information about the incidence and aetiology of fatigue.

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References

1. Dreyer ZE, Blatt J, Bleyer A. Late effects of childhood cancer and its treatment. In Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. Philadelphia, Lippincott Williams & Wilkins, 2001, 1431–1461.
2. Hobbie W, Ruccione K, Moore IK, Truesdell S. Late effects in long-term survivors. In Foley GV, Fochtman D, Mooney KH, eds. *Nursing Care of the Child with Cancer*. Orlando, FL, W.B. Saunders Company, 1993, 466–496.
3. Schwartz CL. Late effects of treatment in long-term survivors of cancer. *Cancer Treat Rev* 1995, **21**, 355–366.
4. Meister LA, Meadows AT. Late effects of childhood cancer therapy. *Curr Probl Pediatr* 1993, **23**, 102–131.
5. Oberst MT, Hughes SH, Chang AS, McCubbin MA. Self-care burden, stress appraisal, and mood among persons receiving radiotherapy. *Cancer Nurs* 1991, **14**, 71–78.
6. Irvine DM, Vincent L, Bubela N, Thompson L, Graydon J. A critical appraisal of the research literature investigating fatigue in the individual with cancer. *Cancer Nurs* 1991, **14**, 188–199.
7. Smets EM, Garssen B, Schuster-Uitterhoeve AL, de Haes JC. Fatigue in cancer patients. *Br J Cancer* 1993, **68**, 220–224.
8. Winningham ML, Nail LM, Burke MB, *et al*. Fatigue and the cancer experience: the state of the knowledge. *Oncol Nurs Forum* 1994, **21**, 23–36.
9. Piper BF, Lindsey AM, Dodd MJ. Fatigue mechanisms in cancer patients: developing nursing theory. *Oncol Nurs Forum* 1987, **14**, 17–23.
10. Aistars J. Fatigue in the cancer patient: a conceptual approach to a clinical problem. *Oncol Nurs Forum* 1987, **14**, 25–30.
11. Piper BF, Rieger PT, Brophy L, *et al*. Recent advances in the management of biotherapy-related side effects: fatigue. *Oncol Nurs Forum* 1989, **16**, 27–34.
12. Ferrell BR, Grant M, Dean GE, Funk B, Ly J. "Bone tired": the experience of fatigue and its impact on quality of life. *Oncol Nurs Forum* 1996, **23**, 1539–1547.
13. Irvine DM, Vincent L, Graydon JE, Bubela N. Fatigue in women with breast cancer receiving radiation therapy. *Cancer Nurs* 1998, **21**, 127–135.
14. Rhodes VA, Watson PM, Hanson BM. Patients' descriptions of the influence of tiredness and weakness on self-care abilities. *Cancer Nurs* 1988, **11**, 186–194.

15. Hann DM, Jacobsen PB, Martin SC, *et al*. Fatigue in women treated with bone marrow transplantation for breast cancer: a comparison with women with no history of cancer. *Support Care Cancer* 1997, **5**, 44–52.
16. Woo B, Dibble SL, Piper BF, Keating SB, Weiss MC. Differences in fatigue by treatment methods in women with breast cancer. *Oncol Nurs Forum* 1998, **25**, 915–920.
17. Smets EMA, Visser MRM, Willems G, *et al*. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. *Br J Cancer* 1998, **78**, 907–912.
18. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med* 1998, **21**, 1–18.
19. Broeckel JA, Jacobsen PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1998, **16**, 1689–1696.
20. Hann DM, Jacobsen P, Martin S, Azzarello L, Greenberg H. Fatigue and quality of life following radiotherapy for breast cancer: a comparative study. *J Clin Psychiatry Med Sett* 1998, **1**, 19–33.
21. Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. *J Clin Oncol* 1999, **17**, 253–261.
22. Howell SJ, Radford JA, Smets EM, Shalet SM. Fatigue, sexual function and mood following treatment for haematological malignancy: the impact of mild Leydig cell dysfunction. *Br J Cancer* 2000, **82**, 789–793.
23. Knobel H, Loge JH, Nordoy T, *et al*. High level of fatigue in lymphoma patients treated with high dose therapy. *J Pain Symptom Manage* 2000, **19**, 446–456.
24. Bower JE, Ganz PA, Desmond KA, *et al*. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol* 2000, **18**, 743–753.
25. Okuyama T, Akechi T, Kugaya A, *et al*. Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale. *Support Care Cancer* 2000, **8**, 215–222.
26. Curt GA, Breitbart W, Cella D, *et al*. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist* 2000, **5**, 353–360.
27. Loge JH, Abrahamsen AF, Ekeberg, Kaasa S. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. *J Pain Symptom Manage* 2000, **19**, 91–99.
28. Servaes P, Van der Werf S, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with Chronic Fatigue Syndrome. *Support Care Cancer* 2001, **9**, 11–17.
29. Cella D, Davis K, Breitbart W, Curt G. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001, **19**, 3385–3391.
30. Knobel H, Harvard-Loge J, Brit-Lund M, Forfang K, Nome O, Kaasa S. Late medical complications and fatigue in Hodgkin's disease survivors. *J Clin Oncol* 2001, **19**, 3226–3233.
31. Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Spiegel D. Psychosocial problems among survivors of Hodgkin's disease. *J Clin Oncol* 1986, **4**, 805–814.
32. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer* 2002, **38**, 27–43.
33. Wasserman AL, Thompson EI, Wilimas JA, Fairclough DL. The psychological status of survivors of childhood/adolescent Hodgkin's disease. *AJDC* 1987, **141**, 626–631.
34. Kanabar DJ, Attard-Montalto S, Saha V, Kingston JE, Malpas JE, Eden OB. Quality of life in survivors of childhood cancer after megatherapy with autologous bone marrow rescue. *Ped Hemat Oncol* 1995, **12**, 29–36.
35. Moe PJ, Holen A, Glomstein A, *et al*. Long-term survival and quality of life in patients treated with a national all protocol 15–20 years earlier: IDM/HDM and late effects? *Ped Hemat Oncol* 1997, **14**, 513–524.
36. Zeltzer LK, Chen E, Weiss R, *et al*. Comparison of psychologic outcome in adult survivors of childhood acute lymphoblastic leukemia versus sibling controls: a cooperative Children's Cancer Group and National Institutes of Health study. *J Clin Oncol* 1997, **15**, 547–556.
37. Langeveld N, Ubbink M, Smets E. 'I don't have any energy': the experience of fatigue in young adult survivors of childhood cancer. *EJON* 2000, **4**, 20–28.
38. Chen MK. The epidemiology of self-perceived fatigue among adults. *Preventive Med* 1986, **15**, 74–81.
39. Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. *J Epidem Comm Health* 1992, **46**, 92–97.
40. Bates DW, Schmitt W, Buchwald D, *et al*. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. *Arch Intern Med* 1993, **153**, 2759–2765.
41. Fuhrer R, Wessely S. The epidemiology of fatigue and depression: a French primary-care study. *Psychol Med* 1995, **25**, 895–905.
42. Appels A, Mulder P. Fatigue and heart disease. The association between 'vital exhaustion' and past, present and future coronary heart disease. *J Psychosom Res* 1989, **33**, 727–738.
43. Pater JL, Zee B, Palmer M, Johnston D, Osoba D. Fatigue in patients with cancer: results with National Cancer Institute of Canada Clinical Trials Group studies employing the EORTC QLQ-C30. *Support Care Cancer* 1997, **5**, 410–413.
44. Kroenke K, Wood DR, Mangelsdorff D, Meier NJ, Powell JB. Chronic fatigue in primary care. Prevalence, patient characteristics, and outcome. *JAMA* 1988, **260**, 929–934.
45. Cathebras PJ, Robbins JM, Kirmayer LJ, Hayton BC. Fatigue in primary care: prevalence, psychiatric comorbidity, illness behavior, and outcome. *J Gen Intern Med* 1992, **7**, 276–286.
46. Wessely S, Chalder T, Hirsch S, Pawlikowska T, Wallace P, Wright DJM. Postinfectious fatigue: prospective cohort study in primary care. *Lancet* 1995, **345**, 1333–1338.
47. Mermelstein HT, Lesko L. Depression in patients with cancer. *Psychooncology* 1992, **1**, 199–215.
48. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? *Supp Care Cancer* 1998, **6**, 101–108.
49. Greenberg HS, Kazak AE, Meadows AT. Psychologic functioning in 8- to 16-year-old cancer survivors and their parents. *J Pediatr* 1989, **114**, 488–493.
50. Smets EM, Garssen B, Bonke B, de Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995, **39**, 315–325.
51. Smets EM, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer* 1996, **73**, 241–245.
52. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Measurement* 1977, **1**, 385–401.
53. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, Academic Press, 1977.
54. Breetvelt IS, Van Dam FSAM. Underreporting by cancer patients: the case of response-shift. *Soc Sci Med* 1991, **32**, 981–987.
55. Sprangers MA. Response-shift bias: a challenge to the assessment of patients' quality of life in cancer clinical trials. *Cancer Treat Rev* 1996, **22**, 55–62.
56. Schwartz CE, Feinberg RG, Jilinskaia E, Applegate JC. An evaluation of a psychosocial intervention for survivors of childhood cancer: paradoxical effects of response shift over time. *Psychooncology* 1999, **8**, 344–354.
57. Sprangers MA, Van Dam FS, Broersen J, *et al*. Revealing response shift in longitudinal research on fatigue-the use of the thentest approach. *Acta Oncol* 1999, **38**, 709–718.

58. Irvine D, Vincent L, Graydon JE, Bubela N, Thompson L. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with the fatigue experienced by healthy individuals. *Cancer Nurs* 1994, **17**, 367–378.
59. Glaus A. Assessment of fatigue in cancer and non-cancer patients and in healthy individuals. *Support Care Cancer* 1993, **1**, 305–315.
60. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. *Eur J Cancer Care* 1996, **5**, 8–23.
61. Akechi T, Kugaya A, Okamura H, Yamawaki S, Uchitomi Y. Fatigue and its associated factors in ambulatory cancer patients: a preliminary study. *J Pain Symptom Manage* 1999, **17**, 42–48.
62. Gijsbers van Wijk CMT, Kolk AM. Sex differences in physical symptoms: the contribution of symptom perception theory. *Soc Sci Med* 1997, **45**, 231–246.
63. Smets EMA. *Fatigue in Cancer Patients Undergoing Radiotherapy*. Thesis, University of Amsterdam, The Netherlands, 1997.
64. Trijsburg R, van Knippenberg F, Rijpma S. Effects of psychological treatment on cancer patients: a critical review. *Psychosom Med* 1992, **54**, 489–517.