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Cancer, fatigue and the return of patients to work—a prospective cohort study

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Abstract

Fatigue is a highly prevalent and debilitating symptom in cancer survivors. The aim of this study was to assess the impact of fatigue and other cancer-related symptoms on the return to work of cancer survivors. A prospective inception cohort study with 12 months of follow-up was initiated. At 6 months following the first day of sick leave, levels of fatigue, depression, sleep problems, physical complaints, cognitive dysfunction and psychological distress were assessed, in addition to clinical, sociodemographic and work-related factors. Data were obtained from one academic hospital and two general hospitals in the Netherlands. 235 patients who had a primary diagnosis of cancer and underwent treatment with curative intent were included. The rate of return to work was measured at 6, 12 and18 months. Hazard ratios (HRs) for the duration of sick leave up to 18 months following the first day of sick leave were calculated. The rate of return to work increased from 24% at 6 months to 64% at 18 months following the first day of sick leave. Fatigue, diagnosis, treatment type, age, gender, depression, physical complaints and workload were all related to the time taken to return to work. Fatigue scores were also strongly related to diagnosis, physical complaints, and depression scores. Fatigue at 6 months predicted a longer sick leave with a hazard ratio of 0.71 (95% Confidence Interval (C.I.) 0.59–0.85), adjusted for diagnosis, treatment type, age and gender. In a multivariate Cox regression analysis, diagnosis, treatment, age, physical complaints and workload remained the only significant predictors of duration of the sick leave. 64% of cancer survivors returned to work within 18 months. Fatigue levels predicted the return to work. This was independent of the diagnosis and treatment, but not of other cancer-related symptoms. Better management of cancer-related symptoms is therefore needed to facilitate the return to work of cancer patients.

Keywords: Fatigue; QoL; Cancer patients; Return to work

1. Introduction

Cancer-related fatigue has been described as "the commonest and most debilitating symptom in patients with cancer" [1]. From an individual's point of view, not being able to return to work following an illness, frequently results in financial losses, social isolation and a reduction in self-esteem [2,3]. Conversely, returning to work can improve the quality of life of many cancer patients. Patients often see returning to work as proof of a complete recovery. Treating clinicians, as well as occupational physicians, may contribute to a successful return to work, and can thus enhance the quality of life of cancer patients [4]. The economic impact is considerable: 75% of patients and 40% of those who care for these patients change their employment status because of cancer-related fatigue [1]. From a societal point of view, it is therefore important to reduce avoidable work incapacity resulting in such economic loss [5].

Cancer is a collective name for a heterogeneous group of diagnoses whose treatment is far from uniform. There is some evidence that the consequences of the illness and

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its treatment, or cancer-related symptoms that are experienced by the patients, can affect the likelihood of resumption of work by cancer patients. For example, the relatively rapid return to work of patients with testis carcinoma is explained by the relative absence of cancer-related symptoms [6]. Although, concentrating on differences at the level of diagnosis bears the risk of generalisation: e.g. not *all* patients with testis carcinoma experience few problems following work resumption.

Cancer-related symptoms are in general independent of the cancer site and treatment. Fatigue is one of the best-known and best-researched symptoms. Other equally relevant cancer-related symptoms are depression, sleep problems, physical complaints, cognitive dysfunction and psychological distress [7–9]. Cancer-related fatigue can have psychological and physical causes and is as such associated with other cancer-related symptoms: e.g. sleep problems, depression and physical complaints [1].

Cancer-related symptoms are not only highly prevalent in cancer patients, irrespective of the cancer site, but they are also likely to have an impact in a wide variety of work settings and may thus hinder the resumption of work. In addition to cancer-related symptoms, the impact of clinical, work-related and subject-related variables [6] on the resumption of work needs to be considered, including diagnosis and treatment, physical workload [10], work stress, age, gender and work hours [6].

The aim of the present study was to examine the relationship between fatigue and other cancer-related symptoms and the return to work in cancer patients, taking into account the impact of clinical-, work- and subject-related factors (Fig. 1). The impact of the symptoms will be considered in a cohort of cancer survivors starting from 6 months following their first day of sick leave. The research question is: do the symptom scores at 6 months after the first day of sick leave predict the time taken to return to work and the rate of return to work at 12 months of follow-up?

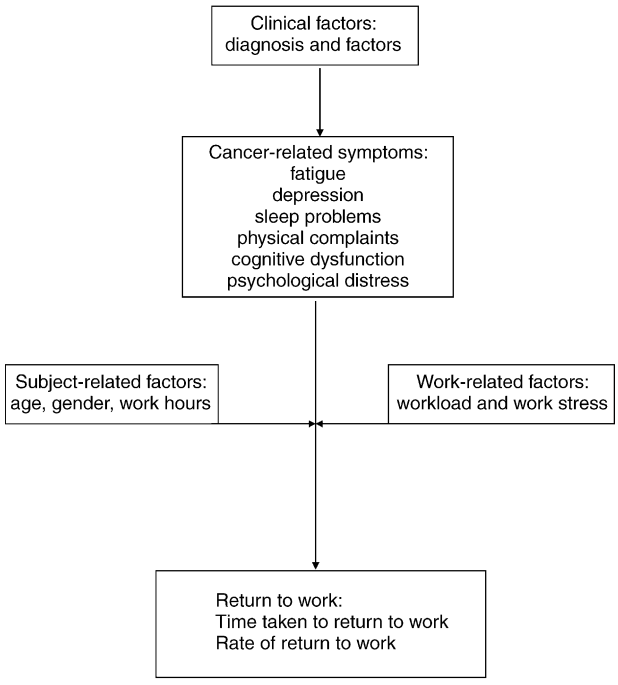

Fig. 1. Model of the impact of cancer-related symptoms on the return to work of cancer patients, controlling for clinical factors, person-related factors and subject-related factors.

2. Patients and methods

2.1. Subjects

In this prospective-cohort study, patients who had a primary diagnosis of cancer were consecutively included in the study. Recruitment occurred in three hospitals in The Netherlands: the Academic Medical Centre and the Onze Lieve Vrouwe Gasthuis, both in Amsterdam, and in the hospital De Heel in Zaandam. The following departments were also included in the study: Gynaecology, Haematology, Oncology, Surgery, Radiotherapy, and Urology. The attending physician obtained the patient's informed consent. Eligible patients were aged between 18 and 60 years, had a primary diagnosis of cancer, were in paid employment at the time of diagnosis and had to be within 4–6 months following their first day of sick leave. In addition, they should have had treatment with curative intent and be able to complete a questionnaire in Dutch.

Patients were asked three times about their cancer-related symptoms and their return to work. In order for results to be comparable, distribution of the questionnaires was conducted relative to the start of sick leave. Patients completed the first questionnaire on average at 6 months after their first day of sick leave, the second at 12 months and the third at 18 months. Information was collected on clinical-, subject-related, and work-related factors. The results of the first questionnaire were used to predict outcome at 12 months of follow-up.

2.2. Measures

2.2.1. Outcome measures

The patients return to work was investigated with the use of two outcome measures: time taken to return to work and rate of return to work at a specific point in time. Time to return to work at 12 months follow-up was calculated as the number of days between the first day of sick leave and the first day the patient returned to work. Any kind of work resumption qualified as a return to work, irrespective of the number of hours that the patients worked prior to their diagnosis. In addition, patients were asked to indicate if they were still on sick leave (yes/no) at 6, 12 and 18 months following their first day of sick leave.

This allowed for a description of consecutive rates of return to work for the three points in time.

2.2.2. Cancer related-symptoms

Fatigue was measured with a four-item sub-scale of the Multidimensional Fatigue Index (MFI [11]) that focuses on complaints related to general fatigue. Scores range from 4 to 20, with higher scores indicating more fatigue. Cronbach's alpha coefficient was 0.89 at the first assessment.

Depression was measured with the frequently used 20-item Center for Epidemiological Studies Depression Scale (CES-D [12]). Scores range from 0 to 60, with higher scores indicating higher levels of depressive feelings. A score of 16 or higher is indicative of serious depression. The internal reliability coefficient was 0.70 at the initial survey.

The Pittsburgh Sleep Quality Index [13] was used to measure sleep quality. Scores range from 0 to 21, where a higher score indicates poorer sleep quality. The Cronbach's alpha coefficient was 0.74 at the initial survey.

Physical complaints were measured with the physical distress sub-scale of the Rotterdam Symptom Check List (RSCL [14]). The score ranges from 23 to 92, with higher scores indicating more physical complaints. The internal reliability coefficient was 0.87 at the initial survey.

The Cognitive Failures Questionnaire, a measure of self-reported failures in perception, memory and motor function was used to map cognitive dysfunction [15]. The total sum-score ranges from 0 to 100. Higher scores point to more cognitive problems. Cronbach's alpha coefficient was 0.90 at the first assessment.

Psychological distress was measured with a sub-scale of the RSCL [14]. The score ranges from 7 to 28, where higher scores indicate more psychological distress. The internal reliability coefficient was 0.89 at the initial survey.

2.2.3. Moderating factors

Clinical factors included diagnosis and the three most common types of treatment: surgery, radiotherapy and chemotherapy as reported by the patients. These clinical data were compared with data of the patients as registered in the Dutch Cancer Registry. No adjustments needed to be made as a result of this comparison. Twenty-two different diagnoses were grouped according to cancer site into gastrointestinal cancer, carcinoma of the breast, cancer of the female genitals, cancer of the male genitals and urological cancer, haematology/oncology, and other types of cancer. Treatment was grouped into single surgical treatment, surgery combined with radiotherapy, surgery combined with chemotherapy, and any other combination of treatment. We decided not to include a classification based on staging because most patients had a relatively good prognosis and were treated with curative intent. Sociodemographic factors encompassed age, gender and hours worked per week prior to diagnosis.

Two subscales of the Dutch Questionnaire on Experience and Judgement of Work (VBBA) [16] were included to measure physical workload and work stress. Patients were asked to assess their levels of workload and work stress for the work situation prior to diagnosis. Physical workload was measured with a seven-item scale, work stress with an 11-item scale. The scores range from 0 to 100, with higher scores indicating a higher level of physical work and more work stress, respectively. Internal reliability coefficients were 0.86 for workload and 0.90 for work stress.

2.3. Statistical analysis

Analyses were conducted with the Statistical Package for the Social Sciences (SPSS) for windows version 10. Pearson correlations were calculated to examine the relationship among the predictors at the initial survey at 6 months, e.g. between fatigue and sleep problems. Following the recommendations of Cohen, a correlation was considered to be high if $r > 0.50$. The relationship between categorical variables such as diagnosis and fatigue was assessed by means of ANOVA. To make the scores on predictor variables comparable, all scores were converted to a 0–100 scale. Changes in scores on predictor variables over time were assessed with a multivariate repeated measures analysis.

Kaplan–Meier curves and the log-rank test were used to assess the bi-variate relationship between time taken to return to work and the predictive factors: fatigue, depression, sleep problems, physical complaints, cognitive dysfunction, psychological distress, age, gender, workload, work stress and the clinical factors diagnosis and treatment type (Fig. 1). In a multivariate Cox regression analysis, we analysed the impact of fatigue in addition to personal and clinical factors. Next, we entered all variables for which the log-rank test returned a P value $\leqslant 0.10$ into a Cox regression analysis with forward selection of variables. Since this is a survival analysis, Hazard Ratios (HRs) indicate the risk of a shorter survival time, which in our case is a shorter time to return to work. Therefore, a HR smaller than one indicates the risk of a longer time taken to return to work.

3. Results

3.1. Sample characteristics

235 of the 264 patients who were eligible and were approached, completed the first questionnaire (response rate of 89%). Of the 29 patients who declined participation in the study; 12 were not interested, 13 were too ill, 2 participated in a concurrent study and 2 declined for other reasons. Hospital directions prohibited us to

collect additional information on the patients who did not participate. The follow-up questionnaire at 18 months following the first day of sick leave was completed by 195 patients (follow-up rate of 83%). 24 patients refused to complete the questionnaire for various reasons; 13 patients had died, two questionnaires were lost in the mail, and one patient could not be reached.

The sociodemographic and clinical characteristics, and the work-related factors are summarised in Table 1. The largest group constituted cancer of the female genitals, followed by patients with cancer of the male genitals/urological cancer or women with breast cancer. Surgery and a combination of surgery and radiotherapy accounted for 55% of all treatments. 77 patients (40%) still received treatment at 18 months following the first day of sick leave. Scores on workload and work stress were comparable to the general population scores.

3.2. Cancer related symptoms

The mean scores (standard deviation (S.D.)) for the cancer-related symptoms at the initial survey were comparable to those found in other studies of cancer patients (Table 1). The level of fatigue decreased from 50.6±30.0 (m±S.D.) at baseline to 44.1±30.1 at 12 months of follow-up (F (2.194) = 4.54 P = 0.011), the level of physical complaints decreased from 16.5±12.6 to 12.3±10.0 (F (2.191) = 17.56 P = 0.0001) and psychological distress from 22.2±20.5 to 13.0±17.7 (F (2.191) = 5.9 P = 0.003). There was no significant decrease for depression, sleep problems or cognitive problems.

Fatigue at the first assessment was related to depression (r = 0.54), physical complaints (r = 0.61), sleep problems (r = 0.33), emotional distress (r = 0.32), diagnosis (F = 2.834 P = 0.02), but not to treatment type (F = 1.843 P = 0.14). Physical complaints were related to depression and sleep (r > 0.50) and in addition, depression was related to psychological distress (r > 0.50).

3.3. Return to work

For 14 respondents, data was missing for time taken to return to work, leaving a total of 221 respondents to be included in the analysis of the time taken to return to work. The median number of days on sick leave at 12 months of follow-up was 278 (IQ 355) days, ranging from 3 to 652 days.

For the assessment of the rate of return to work, 195 patients could be included in the analysis. At 6 months following the first day of sick leave, 24% had returned to work, at 12 months, this percentage had increased to 50%, and at 18 months to 64%.

Table 1
Sociodemographic, work-related and clinical characteristics of a cohort of cancer survivors (numbers vary from 195 to 221 due to missing values), measured on average 6 months after the first day of sick leave.

Sociodemographic factors	
Age (years)	42 (S.D. 9.3), range 19–58
Work hours per week, prediagnosis	34.3 (S.D. 13.1) range 3.5–80
Gender: female	60%
Children in household	43%
Breadwinner (sole or shared)	72%
Married/living with a partner	82%
Clinical factors	*n* (%)
Diagnosis	
Gastro-intestinal cancer	24 (11%)
Breast carcinoma	52 (24%)
Cancer of the female genitals	56 (25%)
Cancer of the male genitals/ urological cancer	51 (23%)
Haematology/Oncology	24 (11%)
Other	14 (6%)
Treatment	*n* (%)
Surgery	44 (20%)
Surgery and radiotherapy	76 (35%)
Surgery and chemotherapy	34 (15%)
All other combinations of treatment	67 (30%)
Cancer-related symptoms[a]	Mean (S.D.)
Fatigue	50.6 (30.0)
Depression	17.7 (13.7)
Sleep problems	30.0 (19.1)
Physical complaints	16.5 (12.6)
Cognitive dysfunction	28.2 (13.7)
Psychological distress	21.9 (20.5)
Work-related factors[a]	Mean (S.D.)
Physical workload pre-diagnosis	28.3 (26.5)
Work stress pre-diagnosis	45.6 (17.0)

S.D., standard deviation.
[a] On a 0–100 scale. A higher score indicates more problems.

3.4. Relationship between cancer-related symptoms and the patients return to work

In the univariate analysis using Kaplan–Meier curves and log-rank tests diagnosis, treatment, gender, age, depression, workload, work pressure, physical complaints and fatigue were related to the time to return to work at the P < 0.10 level. Sleep complaints, psychological distress and cognitive function were not related to the return to work.

In the Cox regression analysis on the number of days of sick leave until 18 months of follow-up, fatigue yielded a Hazard Ratio of 0.71 (95% CI 0.59–0.85) independent from diagnosis, treatment, age and gender (Fig. 2).

The HR for patients with a fatigue score in the lowest quartile compared with the highest quartile was 0.40. In other words, the risk of staying off work for a long time is 2.5 times greater for a cancer survivor who feels very tired after treatment for most of the time compared with a patient that does not experience any or only little

fatigue. This risk is adjusted for the influence of other predictive factors: tumour type, treatment type, age and gender.

In a Cox regression analysis, where we used a forward selection to select the strongest predictors of return to work, the final model only retained diagnosis, treatment, age, physical workload, physical complaints and depression. The high correlation between the cancer-related symptoms and fatigue removed fatigue from the statistical model (Table 2).

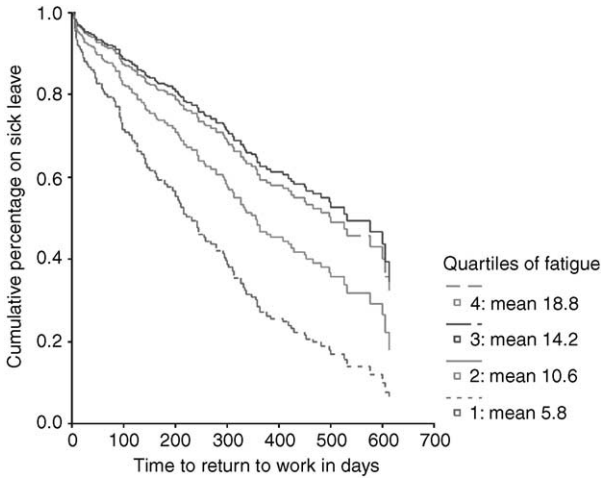

Fig. 2. Plot of fatigue scores in relation to time to return to work for cancer survivors after adjustment for diagnosis, treatment, age and gender ($N=214$).

Table 2
Cox regression analysis on time taken by cancer survivors to return to work ($N=214$); forward stepwise regression, with fatigue, depression, physical complaints, age, gender, workload, diagnosis, treatment and gender entered as categorical variables

	Time to return to work	
	Hazard ratio	95% CI
Age, 10-year categories	0.76	0.62–0.93
Diagnosis		
Cancer of the male genitals/ urological cancer (*reference*)	1.00	
Breast cancer	0.45	0.24–0.86
Cancer of the female genitals	0.55	0.33–0.92
Gastrointestinal cancer	0.82	0.43–1.57
Haematology/oncology	0.24	0.10–0.61
Other types of cancer	0.35	0.14–0.84
Treatment		
Surgery only (*reference*)	1.00	
Surgery/radiotherapy	0.57	0.35–0.91
Surgery/chemotherapy	0.24	0.12–0.48
All other combinations	0.49	0.26–0.95
Physical workload, quartiles	0.81	0.68–0.96
Physical complaints	0.83	0.67–1.01
Depression, quartiles	0.81	0.66–0.99

95% CI, 95% Confidence Interval.

4. Discussion

In this study, 64% of the cancer patients had returned to work at 18 months following their first day of sick leave. Fatigue levels at 6 months after the start of sick leave predicted the return to work at 18 months following the first day of sick leave. This was independent of the diagnosis and treatment, but not of other cancer-related symptoms. Age and physical workload were also independently related to the return to work. The other potential predictive factors sleep problems, cognitive functioning, psychological distress and work pressure were not significantly related to the return to work.

To our knowledge, this is the first longitudinal study in which the impact of cancer-related symptoms on the resumption of the work has been investigated in a systematic way. We were able to follow the cohort for a sufficiently long and appropriate period in which an additional 40% returned to work. The loss of patients during the follow-up was small. We studied factors that were important in predicting the return to work, identified from previous research. Within the cohort, there was a wide variety of symptoms and cancer types which facilitates the generalisation of our results to cancer survivors in general. For all of the predictive factors, we used validated questionnaires.

The findings were in line with previous research that established the importance of fatigue and physical workload, in addition to diagnosis and treatment, but our study also showed that cancer-related symptoms are highly correlated.

Return to work is dependent on the nature of the social security system and many other social and cultural factors. This certainly influences the absolute rates of and time to return to work. In this study, the measures of association between the predictive factors and outcome measure are relative, comparing risks between subgroups of the cohort. This allows for a generalisation across countries.

The interrelated nature of the cancer-related symptoms makes it difficult to disentangle potential relationships with the outcome measure. Even though the correlation coefficients were all far below 0.90, beyond which there would be too much collinearity, the statistical model yielded different results when all cancer-related symptoms were entered at the same time [17]. We chose a stepwise regression analysis in the final model to decide which predictors were most strongly related to the time taken to return to work. Due to multicollinearity, this result is arbitrary for cancer-related symptoms. Since fatigue is a component of many cancer-related symptoms, we feel that to improve the return to work rates fatigue should still be an important focus of attention.

Our study was based on a theoretical model that hypothesised that apart from fatigue, more cancer-related symptoms would influence the return to work. This

turned out not to be the case for sleep problems, emotional distress and cognitive dysfunction. For cognitive dysfunction, studies are needed that focus on different types of chemotherapy resulting in specific cognitive dysfunction that may have remained obscured in our heterogeneous sample. Of the subject-related factors, this study only confirmed the previously found impact of age on the time taken to return to work.

To better predict problems encountered the resumption of work, we need more knowledge about the process of returning to work in general. Qualitative studies could yield more insight into the processes that take place. These processes may be cognitive, e.g. 'work will harm my health', may depend on social relations, e.g. 'my spouse thinks it is too early to go back to work', or be dependent on the advice of the treating clinicians, e.g. 'rest is the best cure for fatigue'.

In our review of the return to work of cancer patients, we found that the percentage of cancer survivors varied from 30 to 93%, with a mean rate of 62% across all of the studies [6]. The findings of our study compare favourably with these results. However, patients who were very ill, in particular, and those who died were lost to follow-up. We can not exclude that with the inclusion of some of these patients the rate of return to work would have been lower and the predictive value of the clinical factors could have been higher. This positive finding may also have been influenced by patients going back to work too soon. However, job satisfaction scores were relatively stable over time, with a score of 92.4 (S.D. 13.0) in the assessment taken prior to diagnosis, and a slightly, but not significantly, lower mean score of 89.7 (S.D. 17.5) for all of the survivors who had returned to work at 18 months following the first day of sick leave (range 0–100, where a higher score indicates more job satisfaction).

This study showed that cancer-related symptoms have an impact on social functioning with the important consequence of limiting the resumption of work, independent of other clinical and personal predictors. Curt recently advocated clear and well established guidelines for the management of fatigue by physicians [1]. The findings from our study underscore the need for such guidelines.

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