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Return to work of cancer patients after a multidisciplinary intervention including occupational counselling and physical exercise in cancer patients: a prospective study

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Abstract

Objectives:

To support return to work among cancer patients, a multidisciplinary rehabilitation program was developed which combined occupational counselling with a supervised physical exercise program during chemotherapy. Aim was to investigate return to work (RTW) rates of cancer patients and to evaluate changes in work-related, quality of life and physical outcomes.

Design: Longitudinal prospective intervention study using a one-group design.

Setting: Two hospitals in the Netherlands.

Participants: 93 Patients with a primary diagnosis of cancer receiving chemotherapy and on sick leave were included. Patients completed questionnaires on RTW, importance of work, work ability (WAI), RTW self-efficacy, fatigue (MFI), and quality of life (EORTC QLQ C-30) at baseline and 6, 12 and 18 months follow-up. Before and after the exercise program 1RM muscle strength and cardiorespiratory fitness (VO_2 peak) were assessed.

Results: Six months after start of a multidisciplinary rehabilitation program that combined occupational counselling with a supervised physical exercise program, 59% of the cancer patients returned to work, 86% at 12 months and 83% at 18 months. In addition, significant improvements ($p<0.05$) in importance of work, work ability, RTW self-efficacy, and quality of life were observed, whereas fatigue levels were significantly reduced. After completing the exercise program, 1RM muscle strength was significantly increased but there was no improvement in VO_2 peak level.

Conclusions: Return to work rates of cancer patients were high after completion of the multidisciplinary rehabilitation program. A multidisciplinary rehabilitation program which combines occupational counselling with a supervised physical exercise program is likely to result in return to work, reduced fatigue and increased importance of work, work ability, and quality of life.

Keywords: Employment, Occupational status, Neoplasms, Exercise

Article summary: strengths and limitations of the study:

- First study to combine a physical training program with occupational counselling in a multidisciplinary rehabilitation program.
- Validated questionnaires were used to assess work ability, work limitations, self-efficacy, fatigue, and quality of life.
- Because of the lack of a control group, there is no direct proof of the effects of our multidisciplinary program.
- Possible bias in the selection of participants with respect to the type of cancer.
- The cancer patients who were included were highly motivated to participate while those who did not participate might have been less motivated and more likely to have a different lifestyle.

Introduction

Survival rates of cancer have been rising over previous decades, due to early detection and improved treatment. On the other hand treatment for cancer may have detrimental effects, as many cancer survivors experience long-term negative physical and/or psychological effects from cancer or cancer-related treatment. A large proportion of cancer patients stop working after diagnosis [1] because of the intensity of treatment regimen or prognosis [2]. When treatment has ended, the majority of cancer survivors will attempt to return to work, as being employed is synonymous with a normal life [3] and is regarded as a marker of complete recovery [4]. Moreover, employment provides a sense of structure, income and identity, and a revival of social contacts [5,6].

However, cancer survivors experience RTW difficulties. Eighteen months after diagnosis, a third of all cancer survivors did not succeed in returning to work [7] and overall cancer survivors have 1.4 times higher risk of being unemployed compared to healthy controls [8]. When work was resumed, working hours, work ability, and work functioning may be affected as well [7,9]. Therefore, it is important to provide employed cancer patients with interventions or rehabilitation programs to support their work resumption.

Interventions to enhance work resumption should intervene multiple factors because rehabilitation strategies that target both health-related and work-related factors may be effective in enhancing work resumption and subsequent work performance [10]. This was shown in a Cochrane review reporting modest evidence for the effectiveness of multidisciplinary interventions which incorporated physical, psychological and vocational components [11].

A physical exercise program may attenuate the side effects of chemotherapy such as reduced muscle strength and cardiorespiratory fitness, fatigue, and physical limitations. Findings from previous reviews and meta-analyses show that physical exercise of moderate to high intensity has beneficial effects on cardiorespiratory fitness, muscle strength, cancer-related fatigue, and quality of life, both during and following treatment [12-14]. Moreover, the improvement of physical functioning and the reduction of fatigue may facilitate RTW. Cancer survivors perceived that participating in a physical exercise program improved their fitness and confidence in physical abilities, and provided them with renewed energy that led to less fatigue and being more physically active in daily life [15]. According to the interviewed survivors, these effects may have facilitated their RTW. Moreover, controlled effect studies found a beneficial effect of an exercise intervention on RTW rates and number of working hours [14,16].

Rehabilitation that focuses on work may enhance return to work in cancer survivors as well. Work-related factors such as diminished work demands and provision of accommodations at the workplace significantly improve work outcomes in this population [17, 18]. Adequate vocational guidance by an occupational physician (OP) might be another strategy to facilitate RTW of cancer patients [19, 20]. An OP can provide advice to counteract perceived barriers and limitations in work, for instance by making adjustments in work tasks and / or work hours, by recruiting social support from the workplace, and by setting up gradual work resumption [21]. Additional to this practical support, an OP may help to improve the attitude towards (return to) work or address misconceptions about work ability. Negative expectations about illness, future work capacity and RTW are associated with slower RTW in patients with different types of chronic disorders [22,23]. Also, personal factors such as self-assessed work ability [24] or motivational factors such as the intention to RTW or meaning of work [7], that may affect RTW can be addressed by an OP.

Advice and guidance provided by an OP, given at an early stage, combined with a physical exercise program, may increase the likelihood of a timely and enduring RTW in cancer patients. Hence, a multidisciplinary rehabilitation program was developed to provide support regarding RTW early in the treatment process consisting of both exercise training and specialized occupational counselling [21]. In this multidisciplinary rehabilitation, counselling was provided by an oncological occupational physician (OOP), who is an OP specialized in supporting patients with cancer experiencing work-related problems and who works within the clinical setting.

The aim of this study is to investigate RTW for cancer patients who completed this multidisciplinary rehabilitation program and to evaluate changes in work ability, self-efficacy, work limitations, muscle strength, physical fitness, fatigue levels and quality of life before and after program completion.

Methods

Study design and population

This prospective study using a one-group design was conducted between August 2011 and February 2015 in Haaglanden Medical Center (HMC) in The Hague and Isala in Zwolle, two large medical centers in the Netherlands. Eligible patients were aged between 18 and 60 years, had a primary diagnosis of cancer and were being treated with chemotherapy with curative intent. In addition, they had been in paid employment at the time of diagnosis and were absent from work or intended to report sick before the start of treatment, and were able to complete a questionnaire in Dutch. Patients with severe mental disabilities or those who were physically unable to perform exercise training were excluded from participation, as were patients with testicular cancer, as the latter experience relatively few problems upon RTW [8, 25,26].

Procedure

Patients from these hospitals were invited by their treating oncologist and were consecutively assigned to the multidisciplinary intervention if they met eligibility criteria for the study. Informed consent was obtained from all individual participants included in the study. The intervention started immediately after inclusion and had a duration of approximately 4 months.

Participants received four questionnaires; at entry into the program, and 6 (T1), 12 (T2) and 18 months (T3) later to obtain information on their RTW, sickness leave duration, importance of work, work ability, work limitations, fatigue level, quality of life, self-efficacy concerning RTW, and physical activity level. Data on sociodemographics, cancer-related and work-related factors were collected at baseline. The study protocol was approved by the hospitals' medical ethics committees (ref no 2011_099).

Multidisciplinary rehabilitation program

The multidisciplinary rehabilitation program consisted of personal counselling on work-related issues by an oncological occupational physician (OOP) and supervised physical exercise in a clinical setting during curative treatment. The intervention protocol has been described in detail in a previous paper [21].

Before the exercise program started, participants underwent a sports medical assessment by a sports physician in order to 1) assess their cardio-respiratory fitness by measuring peak oxygen consumption (VO_2 peak) during an incremental exercise test (ramp) on a bicycle until exhaustion and 2) trace possible physical contra-indications for training. The moderate-to-vigorous intensity exercise program was supervised by a trained physiotherapist and included interval training on a cycle ergometer and resistance exercises of the large muscle groups. The intensity of the exercises was set individually and expressed as a percentage of the maximal workload, assessed by a steep-ramp test in the case of interval training [27], or as a percentage of the 1-repetition maximum (1-RM) for strength exercises [12]. Exercises were performed ranging from 2 series of 8 repetitions to 3 series of 12 repetitions with increasing weight. Four muscle groups were tested with strength equipment that was also used for the resistance training, performing leg press, chest press, lateral pulley and deltoid pulley. After completion of the exercise program, muscle strength and VO_2 peak were tested again.

Alongside the exercise program, participants received one to three individual counselling sessions conducted by an OOP. Following a structured protocol, various work-related topics were discussed. The OOP

provided advice on gradual work resumption taking into account a patient's job type, medical situation, own opinions, and work ability. All participants had a first counselling session scheduled early during the intervention program. Depending on the patient's preferences and the extent to which he or she was experiencing barriers to work, a second and third counselling session was planned.

Outcome measurements

Sociodemographic, clinical characteristics and work-related factors

The sociodemographic variables measured at baseline included age and gender of participants, their education level and marital status. Clinical characteristics were diagnosis (categorized into breast cancer, colorectal cancer or non-Hodgkin lymphoma), treatment modalities additional to chemotherapy (surgery, radiotherapy and/or hormonal treatment) and time since diagnosis. Work-related factors assessed in the baseline questionnaire were working hours, type of contract (permanent, temporary or self-employed), job tenure in years in current position, breadwinner status (sole, shared or no), shift work (no shift work, irregular service, shift work), company size (small (1-10), medium (10-100), large (>100)), and date of sick leave.

Return to work

Primary outcome return to work is defined as any work resumption, irrespective of the number of hours a participant worked prior to diagnosis. Participants were asked at 6, 12, and 18 months follow-up whether they had returned to work, and if so on which date. In addition, time to RTW after sick leave was calculated as the number of days between the first date of sick leave and the first day of work resumption.

Secondary outcome measures

Secondary outcomes included perceptions regarding work, such as the importance of work, work ability, self-efficacy regarding RTW and work limitations; physical factors, such as muscle strength, cardiorespiratory fitness, physical activity level and fatigue; and quality of life.

Importance of work was measured by rating the perceived importance of work in one's current situation on a visual analogue scale (VAS) ranging from 0 to 10, with higher scores indicating higher importance of work. Work ability was assessed with the first item of the Work Ability Index (WAI) [28], which measured current work ability compared with the lifetime best on a scale from 0 to 10 (higher is better). Self-efficacy regarding RTW was measured using the 11-item self-efficacy scale developed by Lagerveld et al. [29] with higher scores indicating higher self-efficacy. Work limitations were assessed using the Work Limitations Questionnaire (WLQ) [30]. The WLQ asks participants to rate their difficulty to perform 25 specific job demands in the last 2 weeks and contains four work limitation scales that report the degree to which health problems interfere with job demands, expressed as a percentage of time (0% limited none of the time – 100% limited all of the time).

Muscle strength and cardiorespiratory fitness were assessed during measurements before and after the exercise program as the results of 1-RM tests for muscle strength, and exercise testing using both the steep ramp test (expressed as Watt) and VO_2 peak test [12, 31]. Fatigue was measured with the Multidimensional Fatigue Inventory (MFI), a 20-item instrument designed to measure fatigue in five dimensions [32]. The corresponding subscales range from 4 to 20, in which higher scores indicate more fatigue. Physical activity level was obtained

by calculating the average amount of hours a participant had performed activities of moderate to high intensity in work, household, leisure time, or sports using questions from the short questionnaire to enhance health enhancing physical activity (SQUASH) [33].

Health-related quality of life was assessed using the EORTC-QLQ-C30, specifically designed for cancer patients [34]. This 30-item list incorporates five functional scales (physical, role, emotional, cognitive an social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), six single items on symptoms and one overall quality of life scale. Scales and items ranged from 0 to 100; higher scores on the functional scales indicated better quality of life, whereas higher scores on the symptom scales and items represented worse quality of life. Scores on all different scales were calculated according to their published scoring algorithms. For scales containing missing values, the half-scale imputation rule was applied which is the most used procedure in the published scoring algorithms.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 22, and R software (R Foundation 2008, from http://www.R-project.org). Descriptive statistics were used to characterise the study population and to display outcomes measured at baseline and follow-up measurements.

The rate of return to work over time was evaluated using generalized estimating equation analyses with identity covariance structure and using a binomial distribution with a logit link. Time was included in the model as a fixed effect, and a random effect for subject was incorporated. This analysis adjusts for the non-independence of observations over time and handles missing values. The median time until RTW was analysed with a Kaplan-Meier survival analyses.

The secondary outcomes measured at 6, 12 and 18 months after inclusion into the study were analyzed with Skillings-Mack test to examine any change in scores over time. This Skillings-Mack test is an adaptation of the non-parametric Friedman test, that can be used to test repeated measurements in case of non-normal distributed data, which handles missing data that were acquired in the data due to non-response. In case of a statistically significant main effect of time, post hoc analyses with Bonferroni corrections were performed by exact Wilcoxon signed rank tests. To avoid performing multiple comparisons, these analyses were performed for both the difference between baseline and T1, to assess changes during rehabilitation, and between T1 and T3 to assess changes over the remaining follow-up period.

Muscle strength and cardiorespiratory fitness were measured before and after program completion. Differences between those measurements were assessed by a paired Student's t-test. Of all pairwise comparisons, mean differences including 95% confidence interval (CI) were calculated. A p-value of <0.05 was considered statistically significant.

Results

Study population

Of the 95 included patients that had completed the rehabilitation program, 93 had returned their baseline questionnaires. The second questionnaire at 6 months follow-up was completed by 82 of the 93 participating patients (response rate of 88%). At 12 months of follow-up, the questionnaire was returned by 72 of the 93 participants (77%) and at 18 months of follow-up, 68 of the 93 participants returned the questionnaire (73%).

The baseline sociodemographics, work- and disease related characteristics of the study population are presented in table 1. Participants had a mean age of 48 years and 90% was female. The majority of the participants had breast cancer (84%); other cancer diagnoses were colorectal cancer and non-Hodgkin lymphoma. Approximately 89% underwent surgery, 76% received radiotherapy and/or hormonal treatment. Before diagnosis and treatment, participants worked on average 28 hours per week. The majority of participants worked at a large company of more than 100 employees, was (shared) breadwinner and did perform any shift work.

Return to work

Primary outcome was the rate of RTW: the percentage of participants who returned to work at T1, T2 and T3. The rate of RTW increased significantly over time ($F=8.51$, $p<0.001$). Six months after inclusion in the study, 49 participants (59%) had, at least partially, returned to work. The rate of RTW increased to 86% of the study population at 12 months follow up, and this percentage was maintained at 18 months follow-up (83%). Median time to RTW was 292 days (95% CI; 259 - 325) in this study population.

Perceptions regarding work, work ability and work limitations

Data on different perceptions about work are shown in table 2. There was a significant increase in the perceived importance of work over time ($p<0.001$); the rating of 5.4 at baseline significantly improved to 6.4 at T1 and showed further improvement to 7.1 at T3.

The overall work ability ($p<0.001$) and self-efficacy regarding RTW ($p<0.001$) also showed a significant effect over time. Both the scores were not significantly better at T1 compared to baseline. At 18 months follow-up (T3) the participants showed a significant increase as compared to baseline in both overall WAI (difference was 1.8; 95% CI: 1.2 – 2.5) and self-efficacy (difference was 0.5; 95% CI: 0.3 – 0.7).

Perceived work limitations could only be assessed in those participants reported to have returned to work. Overall, a significant effect of time was seen in all WLQ subscales. Post hoc analysis showed that there was a significant increase in percentage of time workers experienced limitations in meeting job demands regarding time management (19.3 at T1), physical tasks (7.1 at T1) and production (13.5 at T1). Although scores were lower when measured at T3, the reductions in perceived work limitations, of -6, -1 and -7 respectively, were not significant.

Fatigue and physical activity level

Participants showed reducing fatigue levels over time ($p<0.001$), with a change in total score of -4.8 after program completion (T1) and -8.3 at T3 on a scale of 20-100 (table 3). Considering the different subscales,

scores at T1 show significantly less physical (-1.6; 95% CI -2.6 to -0.6) and general fatigue (-1.3; 95% CI -2.2 to -0.3), less reduced (improved) activity (-1.6; 95% CI -2.6 to -0.6) and less reduced (improved) motivation (-1.1; 95% CI -1.9 to -0.3). At T3 scores of all subscales were reduced further compared to fatigue levels obtained at T1 (physical fatigue: -1.9; 95% CI -3.2.to -0.5, general fatigue: -1.5; 95% CI -2.7 to -0.2, reduced activity: -2.0; 95% CI -3.3 to -0.7, and reduced motivation -0.9; 95% CI -1.7 to -0.1).

Physical activity levels, measured in average hours a week performing moderate activity in work, leisure time, household and sports significantly changed over time. At T1 there was a significant reduction in activity level; 27 (±22) hours versus 40 (±13) hours of physical activity at baseline. Activity level was regained at T3, as this timeframe showed a significant increase of 13.8 hours, to 38 hours (±16) per week.

Cardiorespiratory fitness and muscle strength

Cardiorespiratory fitness as well as muscle strength were measured at the start and completion of the physical exercise program. Paired t-tests results showed that there was a significant improvement of muscle strength (table 4). After training, all 1-RM results increased significantly, ranging from an improvement of 5 kg (95% CI: 4 to 7) for the lateral pulley to an improvement of 44 kg (95% CI 36 to 51) obtained for leg press.

At baseline, cardiorespiratory fitness measured as VO_2 peak was 28.0 ml/min/kg (±7.1) on average. After the training program this value was significantly decreased to an average of 26.6 ml/min/kg (±7.2). Maximal workload obtained in this VO_2 peak test at baseline of 171 Watt (±43) did not change significantly (173 Watt (±50) after program completion). The maximal short exercise capacity, obtained with the steep ramp test, was significantly increased after completing the training program from 190 (±54) to 220 (±52) Watt.

Health-related quality of life (HRQoL)

HRQoL was measured multidimensionally and included global health, physical, role, cognitive, emotional and role functioning as well as symptoms such as fatigue, pain and nausea which are presented in table 5. All these HRQoL scales showed a significant change over time, except for cognitive functioning (p=0.108) and pain (p=0.055). Fatigue scores decreased over the total timeframe as the score at T1 (mean score 32 (±22)) and at T3 (mean score 24 (±21)) were significantly lower than measured at baseline (mean score 43 (±25)) and T1 respectively. A similar pattern was seen for role functioning which continued to increase significantly between follow-up measurements from 60 (±28) at baseline to 73 (±25) at T1 and 85 (±26) at T3. Physical functioning (mean difference 4; 95% CI 1 to 7), social functioning (mean difference 12; 95% CI 6 to 18) and global health status (mean difference 9; 95% CI 5 to 13) showed an increase between T1 and T3, whereas the nausea scale showed a significant reduction in symptoms between baseline and T1 (mean difference -6; 95% CI -12 to -1).

Discussion

Six months after start of a multidisciplinary rehabilitation program that combined occupational counselling with a supervised physical exercise program, 59% of the cancer patients returned to work, 86% at 12 months and 83% at 18 months. In addition, significant improvements in importance of work, work ability, RTW self-efficacy, muscle strength and quality of life were observed, whereas fatigue levels were significantly reduced.

Interpretation of the findings

The RTW rates found in this study were higher as compared to those found in the article of Mehnert [7] concerning a review of the literature. This pattern was shown at all three follow-up moments: at 6 months follow-up 59% versus an average of 40% in the literature, at 12 months 86% versus 62% and at 18 months follow-up 83% versus 73%.

The recent controlled effect study from van Waart and colleagues [14] which was aimed at cancer patients undergoing chemotherapy as well and focused on RTW as secondary outcome, showed similar RTW rates compared to the current study. After receiving either a home-based low-intensity self-managed physical activity program the RTW (yes/no regardless of number of hours) was 83% at the end of follow-up, which was 6 months after the end of chemotherapy. After a moderate- to high exercise program supervised by a physical therapist the RTW was 79%. However, in the study of van Waart and colleagues the home-based exercises were repeated on a daily basis while in our study, the moderate exercise program was performed twice a week. On the other hand our study included the occupational counselling of an occupational physician specialized in cancer-related problems with RTW which is expected to have a positive effect on RTW. Both interventions produced good RTW rates but because our current study was not a controlled study it is not possible to draw strong conclusions on the effect of the addition of occupational counselling.

Results show that work became increasingly important to the cancer patients in our study during and after completion of the intervention. Their perceived work ability and perceived self-efficacy with respect to work increased over the course of the intervention and during the year of follow-up as well. Interestingly, the experienced importance of work of cancer patients in our study increased first, during the intervention and shortly after, while perceived work ability and self-efficacy for RTW showed larger improvements later, during the year of follow-up. A possible explanation could be that during the intervention, the consultations with the OOP might have affected the patient's perceived importance of work. At the same time, the adverse effects from the treatments including chemotherapy would have been present and recovery would still have been in progress, which could have negatively affected the patients' physical and cognitive work abilities and self-efficacy for RTW. An earlier study of Tamminga and colleagues showed as well that during the initial RTW phase, physical or psychological side-effects hampered work resumption [35]. After the intervention and during the year of follow-up, the effects of the chemotherapy would have ceased and thus the perceived work ability and self-efficacy for RTW improved.

In the current study participants showed decreased physical activity levels during and after chemotherapy which were regained through time while fatigue levels diminished over time. This could be an effect of time because the treatment with chemotherapy was coming to an end. However, Van Waart and colleagues showed that moderate- to high-intensity exercise during which patients were receiving chemotherapy, had a beneficial effect on cardiorespiratory fitness as well as fatigue [14]. Courneya and colleagues found a

significant improvement in fatigue among breast cancer patients who received an aerobic exercise training or a resistance exercise training during chemotherapy, compared to patients that did not receive any training [36]. Based on the outcomes of the present study, as well the outcomes of the studies of van Waart and colleagues Courneya and colleagues, physical rehabilitation interventions seem to reduce fatigue during chemotherapy.

The results of the present study imply that muscle strength had increased after completion of the program. There was no increase in VO_2 peak as was expected based on the studies of Backer and colleagues and van Waart and colleagues [12,14]. However, the training program in this study was more aimed at improving muscle strength than on aerobic exercise because that is an important first step in (work) functioning. This could be an explanation for the lack of effect on VO_2 peak.

HRQoL significantly increased on all domains except on the domains of cognitive functioning and pain. Several mechanisms might explain this increase. First, after the end of treatment and during follow-up, improvement of HRQoL EORTC scores is shown in most RCTs involving cancer patients [37] and it is likely that the same course applied to the patients in our study. Second, at follow-up the large majority of our patients had returned to their work. Earlier studies have shown that RTW is positively related to HRQOL [38] and therefore it is plausible that the patients in our study showed improved quality of life scores because they had returned to work.

Strengths and limitations

An important strength of the present study is that to our knowledge it is the first to combine a physical training program with occupational counselling in a multidisciplinary rehabilitation program. Thereby RTW of cancer patients was supported through multiple strategies which were shown to be effective on RTW in a Cochrane review [11]. The training program was supervised by trained physiotherapists and sport physicians. Validated measures were utilized to assess fitness and muscle strength and validated questionnaires were used to assess work ability, work limitations, self-efficacy, fatigue, and quality of life. As a result, the results obtained in this study are reliable. However, there are also limitations to this study. In the first place, we did not randomize patients because we based the study on a real life situation and patients who met the inclusion criteria were invited to participate. Because of the lack of a control group, there is no direct proof of the effects of our multidisciplinary program. However, the controlled effect studies showed to a large extent comparable findings [14,16,36]. Another limitation of our study design is the possible bias in the selection of participants with respect to the type of cancer and the motivation to participate in a physical exercise program. We mainly included female patients with breast cancer and we cannot be sure if the results could be generated to male patients and other types of cancer. Furthermore, the cancer patients who were included were highly motivated to participate. Those who did not participate might have been less motivated and more likely to have a different lifestyle. At the same time the intervention might have been most beneficial for the latter group but we could not reach them. It is also not yet clear whether this type of intervention should be offered to all cancer patients or whether it is better to "personalize" the intervention to certain subgroups of patients.

Based on the present study, it is recommended to offer cancer patients a multidisciplinary intervention, including occupational counseling and an exercise program. An implication for research is to study the effects of this multidisciplinary intervention and the added value of an OOP in a RCT and in other hospitals in order to

assess the feasibility of the intervention more broadly and to identify subgroups of patients in need of differentiated approaches.

Conclusion

A multidisciplinary rehabilitation program, combining specialized occupational counselling with a physical exercise program supervised by a sports physician and a physiotherapist, is likely to support RTW among cancer patients. The program also seems to improve self-reported fatigue levels and physical activity, perceived importance of work, work ability, RTW, self-efficacy, quality of life, muscle strength and work perceptions. It can be considered a promising intervention to support cancer patients in resuming their work.

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Competing interests statement.

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Author's contribution.

- ML: Acquisition, analysis, and interpretation of data for the work; Drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- IG: Acquisition, analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- IH: Acquisition, analysis, and interpretation of data for the work; drafting and revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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- SB: Acquisition, analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- AS: Acquisition, analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- WH: Conception and design of the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- MF: Conception and design of the work; analysis, and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- AB: Conception and design of the work; Acquisition, analysis, and interpretation of data for the work; Drafting the work and revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

[1] Petersson LM, Wennman-Larsen A, Nilsson M, et al. Work situation and sickness absence in the initial period after breast cancer surgery. *Acta Oncol* 2011;50:282-8.

[2] Nachreiner NM, Ghebre RG, Virnig BA, et al. Early work patterns for gynaecological cancer survivors in the USA. *Occup Med* 2012;62:23-8.

[3] Saunders SL, Nedelec B. What work means to people with work disability: a scoping review. *J Occup Rehabil* 2014;24:100-10.

[4] Stergiou-Kita M, Grigorovich A, Tseung V, et al. Meta-synthesis of survivors' work experiences and the development of strategies to facilitate return to work. *J Cancer Surviv* 2014;8:657-70.

[5] Isaksson J, Wilms T, Laurell G, et al. Meaning of work and the process of returning after head and neck cancer. *Support Care Cancer* 2016;24:205-13.

[6] Banning M. Employment and breast cancer: a meta-ethnography. *Eur J Cancer Care* 2011;20:708-19.

[7] Mehnert A. Employment and work-related issues in cancer survivors. *Crit Rev Oncol Hematol* 2011;77:109-30.

[8] de Boer AG, Taskila T, Ojajarvi A, et al. Cancer survivors and unemployment: a meta-analysis and meta-regression. *JAMA* 2009;301:753-62.

[9] Lee MK, Yun YH. Working situation of cancer survivors versus the general population. *J Cancer Surviv* 2015;9: 349-60.

[10] Silver JK, Baima J, Newman R, et al. Cancer rehabilitation may improve function in survivors and decrease the economic burden of cancer to individuals and society. *Work* 2013;46: 455-72.

[11] de Boer AG, Taskila T, Tamminga S J, et al. Interventions to enhance return-to-work for cancer patients. *Cochrane Database of Systematic Reviews* 2015;25:CD007569.

[12] de Backer IC, Vreugdenhil G, Nijziel MR, et al. Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life. *Br J Cancer* 2008;99:30-6.

[13] Mishra SI, Scherer RW, Snyder C, et al. The effectiveness of exercise interventions for improving health-related quality of life from diagnosis through active cancer treatment. *Oncol Nurs Forum* 2015;42:E33-53.

[14] van Waart H, Stuiver MM, van Harten WH, et al. Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial. *J Clin Oncol* 2015;33:1918-27.

[15] Groeneveld IF, de Boer AG, Frings-Dresen M H. Physical exercise and return to work: cancer survivors' experiences. *J Cancer Surviv* 2013; 7: 237-46.

[16] Thijs KM, de Boer AG, Vreugdenhil G, et al. Rehabilitation using high-intensity physical training and long-term return-to-work in cancer survivors. *J Occupat Rehabil* 2012;22: 220-9.

[17] Feuerstein M, Todd BL, Moskowitz MC, et al. Work in cancer survivors: a model for practice and research. *J Cancer Surv* 2010; 4:415-37.

[18] Mehnert A, de Boer A, Feuerstein M. Employment challenges for cancer survivors. *Cancer* 2013;119 Supp 11:2151-9.

[19] Verbeek J, Spelten E, Kammeijer M, et al. (2003) Return to work of cancer survivors: a prospective cohort study into the quality of rehabilitation by occupational physicians. *Occup Environ Med* 2003;60:352-7.

[20] Taskila T, Lindbohm ML. Factors affecting cancer survivors' employment and work ability. *Acta Oncol* 2007;46:446-51.

[21] Groeneveld IF, de Boer AG, Frings-Dresen MH. A multidisciplinary intervention to facilitate return to work in cancer patients: intervention protocol and design of a feasibility study. *BMJ Open* 2012;2, pii: e001321.

[22] Heijbel B, Josephson M, Jensen I, et al. Return to work expectation predicts work in chronic musculoskeletal and behavioral health disorders: prospective study with clinical implications. *J Occup Rehabil* 2006;16:173-84.

[23] Ekbladh E, Thorell LH, Haglund L. Perceptions of the work environment among people with experience of long term sick leave. *Work* 2010;35:125-36.

[24] de Boer AG, Verbeek JH, Spelten ER, et al. Work ability and return-to-work in cancer patients.*Br J Cancer* 2008;98:1342-7.

[25] Roelen CA, Koopmans PC, Schellart AJ, et al. Resuming Work After Cancer: A Prospective Study of Occupational Register Data. *J Occup Rehabil* 2010; 21:431-40.

[26] Roelen CA, Koopmans PC, Groothoff JW, et al. Return to work after cancer diagnosed in 2002, 2005 and 2008. *J Occup Rehabil* 2011;21:335-41.

[27] de Backer IC, Schep G, Hoogeveen A, et al. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. *Arch Phys Med Rehabil* 2007; 88:610-6.

[28] Tuomi K, Ilmarinen J, Jahkola A. Work Ability Index. Helsinki: Finnish Institute of Occupational Health 1998; 2nd revised ed.

[29] Lagerveld SE, Blonk RWB, Brenninkmeijer V, et al. Return to work among employees with mental health problems: Development and validation of a self-efficacy questionnaire. *Work & Stress* 2010;24: 359-75.

[30] Lerner D, Amick BC, Rogers WH, et al. The Work Limitations Questionnaire. *Med Care* 2001;39:72–85.

[31] de Backer, I C, Schep, G, Backx, F J, et al. Resistance training in cancer survivors: a systematic review. *Int J Sports Med* 2009;30: 703-12.

[32] Smets E, Garssen G, Bonke B, et al. The Multidimensional Fatigue Inventory, psychometric qualities of an instrument to assess fatigue. *J Psychometric Res* 1995;39:315–25.

[33] Wendel-Vos GC, Schuit AJ, Saris WHM, et al. Reproducibility and relative validity of the Short Questionnaire to Assess Health-enhancing physical activity. *J Clin Epidemiol* 2003;56:1163-69.

[34] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-76.

[35] Tamminga SJ, de Boer AG, Verbeek JH, et al. Breast cancer survivors' views of factors that influence the return-to-work process--a qualitative study. *Scand J Work Environ Health* 2012;38:144-54.

[36] Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol* 2007;25:4396-404.

[37] Zikos E, Coens C, Quinten C, et al. The Added Value of Analyzing Pooled Health-Related Quality of Life Data: A Review of the EORTC PROBE Initiative. *J Natl Cancer Inst* 2015;108(5): pii: djv391.

[38] Mellon S, Northouse LL, Weiss LK. A population-based study of the quality of life of cancer survivors and their family caregivers. *Cancer Nurs* 2006;29:120-131.

Table 1. Baseline characteristics of included participants who completed the rehabilitation program

Characteristic		Participants (n=93)
Sociodemographics		
Gender (% female, (n))		90.3% (84)
Age (years; mean (±sd))		47.9 (7.4)
Education level (% (n))	low	14.0% (13)
	intermediate	33.3% (31)
	high	52.7% (49)
Marital status (% (n))	Single	19.4% (18)
	Not living with partner	9.7% (9)
	Living with partner	71.0% (66)
Disease-related variables		
Cancer type (% (n)) *	Mamma	83.9% (78)
	Colorectal	8.6% (8)
	Non-Hodgkin Lymphoma	5.4% (5)
	Other	2.2% (2)
Days since diagnosis (mean (±sd))		61.9 (44.3)
Type of chemotherapy (% adjuvant (n))		87.1% (81)
Treatment additional to chemotherapy (% (n))*	Surgery	89.2% (83)
	Radiotherapy	30.1% (28)
	Hormone treatment	12.9% (12)
	Radiotherapy + hormone treatment	33.3% (31)
Type of contract (% (n))	Permanent employment	78.5% (73)
	Temporary employment	5.4% (5)
	Self-employed	11.8% (11)
Work-related variables		
Weekly working hours (mean (±sd))		28.3 (10.3)
Years in current employment		10.8 (8.4)
Years in paid employment *		22.9 (9.6)
Company size	Large (> 100)	62.5% (55)
	Medium (10-99)	22.7% (20)
	Small (1-9)	9.1% (8)
Shift work	No shiftwork	81.3% (74)
	Irregular service	16.5% (15)
	Shift work	2.2% (2)
Breadwinner status	Sole	34.8% (32)
	Shared	45.7% (42)
	Partner	19.6% (18)

Table 2. Changes in perceptions regarding work and work limitations of included participants who completed the rehabilitation program (n=93)

Measure	Baseline	T1	T2	T3	Time effect		Difference between baseline - T1			Difference between T1 - T3		
	mean (sd)	mean (sd)	mean (sd)	mean (sd)	p		mean	95% CI	p	mean	95% CI	p
Importance of work	5.4 (2.2)	6.4 (1.9)	7.0 (1.6)	7.1 (1.7)	0.000		**1.0**	**0.6 - 1.5**	**<0.001**	**0.8**	**0.2 - 1.3**	**0.005**
Overall work ability	5.2 (2.0)	5.8 (2.2)	7.2 (1.8)	7.5 (2.1)	0.000		0.5	-0.1 - 0.9	0.072	**1.8**	**1.2 - 2.5**	**<0.001**
RTW SE	3.5 (0.7)	3.7 (0.8)	4.0 (0.7)	4.2 (0.6)	0.000		0.2	-0.3 - 0.4	0.061	**0.5**	**0.3 - 0.7**	**<0.001**
WLQ, time management	11.7 (14.0)	29.3 (24.1)	17.6 (19.6)	21.0 (20.8)	0.000		**19.3**	**11.9 - 26.7**	**<0.001**	-6.1	-15.4 - 3.2	0.23
WLQ, physical demands	6.1 (11.1)	12.9 (13.7)	9.3 (12.0)	11.4 (14.7)	0.008		**7.1**	**3.0 - 11.1**	**0.001**	-1.4	-5.5 - 8.16	0.88
WLQ, mental-interpersonal demands	11.1 (10.4)	27.4 (20.1)	18.9 (19.3)	18.5 (16.4)	0.000		16.8	11.0 - 22.6	0.054	-6.8	-5.5 - 1.1	0.06
WLQ, production demands	15.5 (12.9)	28.9 (23.4)	19.8 (21.2)	23.1 (20.2)	0.013		**13.5**	**6.6 - 20.3**	**<0.001**	-7.0	-31.2 - 2.6	0.09

RTW SE: Return To Work Self-Efficacy; WLQ: Work Limitations Questionnaire; sd: standard deviation; CI: Confidence Interval

Table 3. Changes in fatigue and physical activity of included participants who completed the rehabilitation program (n=93)

Measure	baseline	T1	T2	T3	Time effect		Difference between baseline - T1			Difference between T1 - T3		
	mean (sd)	mean (sd)	mean (sd)	mean (sd)	p		mean	95% CI	p	mean	95% CI	p
MFI, General fatigue	13.0 (4.9)	11.4 (4.9)	9.8 (4.4)	9.8 (4.7)	0.000		**-1.3**	**-2.2 - -0.3**	**0.007**	**-1.5**	**-2.7 - -0.2**	**0.019**
MFI, Physical fatigue	12.1 (4.7)	10.1 (5.0)	8.2 (4.2)	8.3 (4.4)	0.000		**-1.6**	**-2.6 - -0.6**	**0.003**	**-1.9**	**-3.2 - -0.5**	**0.003**
MFI, Reduced motivation	9.7 (3.6)	8.3 (3.4)	7.4 (3.3)	7.2 (3.1)	0.000		**-1.1**	**-1.9 - -0.2**	**0.019**	**-0.9**	**-1.7 - -0.1**	**0.040**
MFI, Reduced activity	12.3 (4.8)	10.2 (4.6)	8.3 (3.9)	8.4 (4.5)	0.000		**-1.6**	**2.6 - -0.6**	**0.002**	**-2.0**	**-3.3 - -0.7**	**0.002**
MFI, Mental fatigue	11.2 (4.2)	11.6 (4.6)	10.1 (4.3)	9.4 (4.5)	0.045		0.8	-0.4 - 2.0	0.226	**-2.1**	**-3.3 - -0.8**	**0.002**
MFI, Total score	58.2 (18.4)	51.6 (18.8)	43.7 (16.4)	43.2 (18.1)	0.000		**-4.8**	**-8.6 - -1.0**	**0.009**	**-8.3**	**-13.3 - -3.4**	**0.001**
Physical activity	40.4 (12.9)	28.6 (21.9)	42.9 (17.5)	38.1 (15.5)	0.000		**-11.2**	**-19.0 - -3.5**	**<0.001**	**13.8**	**7.4 - 20.2**	**<0.001**

MFI: Multidimensional Fatigue Inventory; sd: standard deviation; CI: Confidence Interval

Table 4. Changes in muscle strength and cardiorespiratory fitness of included participants who completed the rehabilitation program (n=93)

Measure	Mean (sd) Baseline	Mean (sd) after completion	Mean difference	95% CI	p
VO2 peak (ml/min/kg)	28.0 (7.1)	26.6 (7.2)	-1.9	-2.9 to -0.9	<0.001
Maximal workload (Watt)	171.1 (43.1)	173.6 (50.3)	0.8	-4.9 to 6.6	0.771
1RM leg press (kg)	141.9 (42.0)	187.1 (52.7)	43.6	36.4 to 50.7	<0.001
1RM lateral pulley (kg)	22.5 (17.5)	26.1 (17.7)	5.4	3.7 to 7.2	<0.001
1RM chest press (kg)	16.7 (12.4)	25.1 (15.8)	8.5	6.9 to 10.0	<0.001
1RM deltiod pulley (kg)	23.3 (24.7)	31.1 (12.6)	101	8.3 to 11.8	<0.001
Maximal short exercise capacity (steep ramp test) (Watt)	190.1 (53.7)	220.1 (51.8)	27.5	20.6 to 34.4	<0.001

Table 5. Changes in health-related quality of life and symptom burden of included participants who completed the rehabilitation program (n=93)

EORCTC QLQ-C30 QoL measure	baseline	T1	T2	T3	Time effect		Difference between baseline and T1			Difference between T1 and T3		
	mean (sd)	mean (sd)	mean (sd)	mean (sd)	p		mean	95% CI	p	mean	95% CI	p
Physical functioning	84.4 (16.4)	85.5 (15.9)	91.2 (12.5)	88.9 (13.4)	**0.001**		0.9	-2.4 to 4.2	0.876	**4.2**	**1.0 to 7.3**	**0.012**
Role functioning	60.6 (27.9)	73.3 (25.4)	83.1 (23.5)	84.8 (25.7)	**0.000**		**9.7**	**3.6 to 15.9**	**0.005**	**11.5**	**4.3 to 18.8**	**0.003**
Cognitive functioning	80.5 (16.8)	74.7 (22.5)	78.7 (21.3)	78.9 (22.4)	0.108		**-6.9**	**-12.0 to -1.8**	**0.005**	3.3	-3.0 to 9.7	0.38
Emotional functioning	74.1 (19.7)	79.4 (19.6)	83.6 (18.0)	83.2 (20.3)	**0.002**		3.3	-1.7 to 8.3	0.062	2.8	-2.4 to 8.0	0.57
Social functioning	73.1 (23.1)	76.5 (22.9)	82.9 (22.0)	88.5 (20.8)	**0.003**		1.9	-2.9 to 6.8	0.434	**11.5**	**5.5 to 17.6**	**0.001**
Fatigue	42.7 (25.3)	31.8 (21.9)	23.6 (19.9)	24.3 (20.8)	**0.000**		**-9.2**	**-15.1 to -3.4**	**0.005**	**-7.8**	**-13.7 to -1.9**	**0.015**
Nausea	11.4 (19.8)	4.9 (16.1)	1.4 (4.6)	2.7 (8.9)	**0.012**		**-6.1**	**-11.5 to -0.6**	**0.011**	-3.3	-7.9 to 1.2	0.31
Pain	21.8 (25.4)	17.1 (22.5)	10.9 (18.4)	13.0 (17.5)	0.055		-3.9	-9.9 to 2.1	0.172	-4.4	-9.9 to 1.2	0.19
Global health	66.8 (21.8)	74.7 (18.5)	83.3 (16.2)	82.4 (17.3)	**0.000**		5.5	0.1 to 10.9	0.138	**8.8**	**4.5 to 13.2**	**<0.001**

QOL: Quality Of Life; sd: standard deviation; CI: Confidence Interval

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Return to work of cancer patients after a multidisciplinary intervention including occupational counselling and physical exercise in cancer patients: a prospective study in the Netherlands

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Abstract

Objectives:

To support return to work among cancer patients, a multidisciplinary rehabilitation program was developed which combined occupational counselling with a supervised physical exercise program during chemotherapy. Aim was to investigate return to work (RTW) rates of cancer patients and to evaluate changes in work-related, quality of life and physical outcomes.

Design: Longitudinal prospective intervention study using a one-group design.

Setting: Two hospitals in the Netherlands.

Participants: Of the eligible patients, 56% participated. 93 Patients with a primary diagnosis of cancer receiving chemotherapy and on sick leave were included. Patients completed questionnaires on RTW, importance of work, work ability (WAI), RTW self-efficacy, fatigue (MFI), and quality of life (EORTC QLQ C-30) at baseline and 6, 12 and 18 months follow-up. Before and after the exercise program 1RM muscle strength and cardiorespiratory fitness (VO_2 peak) were assessed.

Results: Six months after start of a multidisciplinary rehabilitation program that combined occupational counselling with a supervised physical exercise program, 59% of the cancer patients returned to work, 86% at 12 months and 83% at 18 months. In addition, significant improvements ($p<0.05$) in importance of work, work ability, RTW self-efficacy, and quality of life were observed, whereas fatigue levels were significantly reduced. After completing the exercise program, 1RM muscle strength was significantly increased but there was no improvement in VO_2 peak level.

Conclusions: Return to work rates of cancer patients were high after completion of the multidisciplinary rehabilitation program. A multidisciplinary rehabilitation program which combines occupational counselling with a supervised physical exercise program is likely to result in return to work, reduced fatigue and increased importance of work, work ability, and quality of life.

Keywords: Employment, Occupational status, Neoplasms, Exercise

Article summary: strengths and limitations of the study:

- First study to combine a physical training program with occupational counselling in a multidisciplinary rehabilitation program.
- Validated questionnaires were used to assess work ability, work limitations, self-efficacy, fatigue, and quality of life.
- Because of the lack of a control group, there is no direct proof of the effects of our multidisciplinary program.
- Possible biases are in the selection of participants with respect to the type of cancer, the high number of females (84%) and the relatively high level of education.
- The cancer patients who were included were highly motivated to participate while those who did not participate might have been less motivated and more likely to have a different lifestyle.

Introduction

Survival rates of cancer have been rising over previous decades, due to early detection and improved treatment. On the other hand treatment for cancer may have detrimental effects, as many cancer survivors experience long-term negative physical and/or psychological effects from cancer or cancer-related treatment. A large proportion of cancer patients stop working after diagnosis [1] because of the intensity of treatment regimen or prognosis [2]. When treatment has ended, the majority of cancer survivors will attempt to return to work, as being employed is synonymous with a normal life [3] and is regarded as a marker of complete recovery [4]. Moreover, employment provides a sense of structure, income and identity, and a revival of social contacts [5,6].

However, cancer survivors experience RTW difficulties. Eighteen months after diagnosis, a third of all cancer survivors did not succeed in returning to work [7] and overall cancer survivors have 1.4 times higher risk of being unemployed compared to healthy controls [8]. When work was resumed, working hours, work ability, and work functioning may be affected as well [7,9]. Therefore, it is important to provide employed cancer patients with interventions or rehabilitation programs to support their work resumption.

Interventions to enhance work resumption should intervene multiple factors because rehabilitation strategies that target both health-related and work-related factors may be effective in enhancing work resumption and subsequent work performance [10]. This was shown in a Cochrane review reporting modest evidence for the effectiveness of multidisciplinary interventions which incorporated physical, psychological and vocational components [11].

A physical exercise program may attenuate the side effects of chemotherapy such as reduced muscle strength and cardiorespiratory fitness, fatigue, and physical limitations. Findings from previous reviews and meta-analyses show that physical exercise of moderate to high intensity has beneficial effects on cardiorespiratory fitness, muscle strength, cancer-related fatigue, and quality of life, both during and following treatment [12-14]. Moreover, the improvement of physical functioning and the reduction of fatigue may facilitate RTW. Cancer survivors perceived that participating in a physical exercise program improved their fitness and confidence in physical abilities, and provided them with renewed energy that led to less fatigue and being more physically active in daily life [15]. According to the interviewed survivors, these effects may have facilitated their RTW. Moreover, controlled effect studies found a beneficial effect of an exercise intervention on RTW rates and number of working hours [14,16].

Rehabilitation that focuses on work may enhance return to work in cancer survivors as well. Work-related factors such as diminished work demands and provision of accommodations at the workplace significantly improve work outcomes in this population [17, 18]. Adequate vocational guidance by an occupational physician (OP) might be another strategy to facilitate RTW of cancer patients [19, 20]. An OP can provide advice to counteract perceived barriers and limitations in work, for instance by making adjustments in work tasks and / or work hours, by recruiting social support from the workplace, and by setting up gradual work resumption [21]. Additional to this practical support, an OP may help to improve the attitude towards (return to) work or address misconceptions about work ability. Negative expectations about illness, future work capacity and RTW are associated with slower RTW in patients with different types of chronic disorders [22,23]. Also, personal factors such as self-assessed work ability [24] or motivational factors such as the intention to RTW or meaning of work [7], that may affect RTW can be addressed by an OP.

Advice and guidance provided by an OP, given at an early stage, combined with a physical exercise program, may increase the likelihood of a timely and enduring RTW in cancer patients. Hence, a multidisciplinary rehabilitation program was developed to provide support regarding RTW early in the treatment process consisting of both exercise training and specialized occupational counselling [21]. In this multidisciplinary rehabilitation, counselling was provided by an oncological occupational physician (OOP), who is an OP specialized in supporting patients with cancer experiencing work-related problems and who works within the clinical setting.

The aim of this study is to investigate RTW for cancer patients who completed this multidisciplinary rehabilitation program and to evaluate changes in work ability, self-efficacy, work limitations, muscle strength, physical fitness, fatigue levels and quality of life before and after program completion.

Methods

Study design and population

This prospective study using a one-group design was conducted between August 2011 and February 2015 in Haaglanden Medical Center (HMC) in The Hague and Isala in Zwolle, two large medical centers in the Netherlands. Eligible patients were aged between 18 and 60 years, had a primary diagnosis of cancer and were being treated with chemotherapy with curative intent. In addition, they had been in paid employment at the time of diagnosis and were absent from work or intended to report sick before the start of treatment, and were able to complete a questionnaire in Dutch. Patients with severe mental disabilities or those who were physically unable to perform exercise training were excluded from participation, as were patients with testicular cancer, as the latter experience relatively few problems upon RTW [8, 25,26].

Procedure

Patients from these hospitals were invited by their treating oncologist and were consecutively assigned to the multidisciplinary intervention if they met eligibility criteria for the study. During the first four months of our study registration records on the eligibility of newly-diagnosed patients, their willingness to participate and reasons for non-participation were completed by oncologists and oncology nurses.

Informed consent was obtained from all individual participants included in the study. The intervention started immediately after inclusion and had a duration of approximately 4 months.

Participants received four questionnaires; at entry into the program, and 6 (T1), 12 (T2) and 18 months (T3) later to obtain information on their RTW, sickness leave duration, importance of work, work ability, work limitations, fatigue level, quality of life, self-efficacy concerning RTW, and physical activity level. Data on sociodemographics, cancer-related and work-related factors were collected at baseline. The study protocol was approved by the hospitals' medical ethics committees (ref no 2011_099).

Multidisciplinary rehabilitation program

The multidisciplinary rehabilitation program consisted of personal counselling on work-related issues by an oncological occupational physician (OOP) and supervised physical exercise in a clinical setting during curative treatment. The intervention protocol has been described in detail in a previous paper [21].

Before the exercise program started, participants underwent a sports medical assessment by a sports physician in order to 1) assess their cardio-respiratory fitness by measuring peak oxygen consumption (VO_2 peak) during an incremental exercise test (ramp) on a bicycle until exhaustion and 2) trace possible physical contra-indications for training. Within two weeks of the sports medical assessment, participants embarked on a 12-week, twice-weekly physical training program, supervised by a trained physiotherapist. The moderate-to-vigorous intensity exercise sessions lasted 1 hour and included interval training on a cycle ergometer and resistance exercises of the large muscle groups. The intensity of the exercises was set individually and expressed as a percentage of the maximal workload, assessed by a steep-ramp test in the case of interval training [27], or as a percentage of the 1-repetition maximum (1-RM) for strength exercises [12]. Exercises were performed ranging from 2 series of 8 repetitions to 3 series of 12 repetitions with increasing weight. Four muscle groups were tested with strength equipment that was also used for the resistance training, performing leg press, chest press, lateral

pulley and deltoid pulley. After completion of the exercise program, muscle strength and VO_2 peak were tested again.

Alongside the exercise program, participants received one to three individual counselling sessions conducted by an OOP. Following a structured protocol, various work-related topics were discussed. The OOP provided advice on gradual work resumption taking into account a patient's job type, medical situation, own opinions, and work ability. All participants had a first counselling session scheduled early during the intervention program. Depending on the patient's preferences and the extent to which he or she was experiencing barriers to work, a second and third counselling session was planned.

Measurements

Sociodemographic, clinical characteristics and work-related factors

The sociodemographic variables measured at baseline included age and gender of participants, their education level and marital status. Clinical characteristics were diagnosis (categorized into breast cancer, colorectal cancer or non-Hodgkin lymphoma), treatment modalities additional to chemotherapy (surgery, radiotherapy and/or hormonal treatment) and time since diagnosis. Work-related factors assessed in the baseline questionnaire were working hours, type of contract (permanent, temporary or self-employed), job tenure in years in current position, breadwinner status (sole, shared or no), shift work (no shift work, irregular service, shift work), company size (small (1-10), medium (10-100), large (>100)), and date of sick leave.

Return to work outcome measures

Primary outcome return to work is defined as any work resumption, irrespective of the number of hours a participant worked prior to diagnosis. Participants were asked at 6, 12, and 18 months follow-up whether they had returned to work, and if so on which date. In addition, time to RTW after sick leave was calculated as the number of days between the first date of sick leave and the first day of work resumption.

Secondary outcome measures

Secondary outcomes included perceptions regarding work, such as the importance of work, work ability, self-efficacy regarding RTW and work limitations; physical factors, such as muscle strength, cardiorespiratory fitness, physical activity level and fatigue; and quality of life.

Importance of work was measured by rating the perceived importance of work in one's current situation on a visual analogue scale (VAS) ranging from 0 to 10, with higher scores indicating higher importance of work. This measure gains insight into the meaning of work as experienced by the cancer patients at the time of measurement. Work ability was assessed with the first item of the Work Ability Index (WAI) [28], which measured current work ability compared with the lifetime best on a scale from 0 to 10 (higher is better). Self-efficacy regarding RTW was measured using the 11-item self-efficacy scale developed by Lagerveld et al. [29] with higher scores indicating higher self-efficacy. Work limitations were assessed using the Work Limitations Questionnaire (WLQ) [30]. The WLQ asks participants to rate their difficulty to perform 25 specific job demands in the last 2 weeks and contains four work limitation scales that report the degree to which health

problems interfere with job demands, expressed as a percentage of time (0% limited none of the time – 100% limited all of the time).

Muscle strength and cardiorespiratory fitness were assessed during measurements before and after the exercise program as the results of 1-RM tests for muscle strength, and exercise testing using both the steep ramp test (expressed as Watt) and VO_2 peak test [12, 31]. Fatigue was measured with the Multidimensional Fatigue Inventory (MFI), a 20-item instrument designed to measure fatigue in five dimensions [32]. The corresponding subscales range from 4 to 20, in which higher scores indicate more fatigue. Physical activity level was obtained by calculating the average amount of hours a participant had performed activities of moderate to high intensity in work, household, leisure time, or sports using questions from the short questionnaire to enhance health enhancing physical activity (SQUASH) [33].

Health-related quality of life was assessed using the EORTC-QLQ-C30, specifically designed for cancer patients [34]. This 30-item list incorporates five functional scales (physical, role, emotional, cognitive an social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), six single items on symptoms and one overall quality of life scale. Scales and items ranged from 0 to 100; higher scores on the functional scales indicated better quality of life, whereas higher scores on the symptom scales and items represented worse quality of life. Scores on all different scales were calculated according to their published scoring algorithms. For scales containing missing values, the half-scale imputation rule was applied which is the most used procedure in the published scoring algorithms.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 22, and R software (R Foundation 2008, from http://www.R-project.org). Descriptive statistics were used to characterise the study population and to display outcomes measured at baseline and follow-up measurements. Data on eligibility and willingness to participate from the first four months of the study were extrapolated to the total study period. To assess the association between adherence to the physical exercise program and the number of counselling session, we assessed a Spearman's rho correlation, The rate of return to work over time was evaluated using generalized estimating equation analyses with identity covariance structure and using a binomial distribution with a logit link. Time was included in the model as a fixed effect, and a random effect for subject was incorporated. This analysis adjusts for the non-independence of observations over time and handles missing values. The median time until RTW was analysed with a Kaplan-Meier survival analyses.

The secondary outcomes measured at 6, 12 and 18 months after inclusion into the study were analyzed with Skillings-Mack test to examine any change in scores over time. This Skillings-Mack test is an adaptation of the non-parametric Friedman test, that can be used to test repeated measurements in case of non-normal distributed data, which handles missing data that were acquired in the data due to non-response. In case of a statistically significant main effect of time, post hoc analyses with Bonferroni corrections for multiple comparisons were performed by exact Wilcoxon signed rank tests. To avoid performing a great range of comparisons, these analyses were performed for both the difference between baseline and T1, to assess changes during rehabilitation, and between T1 and T3 to assess changes over the remaining follow-up period.

Muscle strength and cardiorespiratory fitness were measured before and after program completion. Differences between those measurements were assessed by a paired Student's t-test. Of all pairwise

comparisons, mean differences including 95% confidence interval (CI) were calculated. A p-value of <0.05 was considered statistically significant.

Results

Study population

Of the patients treated at the oncology departments of the participating hospitals, 49% were not eligible for participation, the majority of whom because they were older than 60 years. Regarding the eligible patients, 56% were willing to participate in this study . There was no difference between participants and non-participants in gender and age at baseline Of the 95 included patients that had completed the rehabilitation program two participants did not return a baseline questionnaire and were excluded. This finally resulted in a study population of 93 patients.. The second questionnaire at 6 months follow-up was completed by 82 of the 93 participating patients (response rate of 88%). At 12 months of follow-up, the questionnaire was returned by 72 of the 93 participants (77%) and at 18 months of follow-up, 68 of the 93 participants returned the questionnaire (73%). The adherence rate to the exercise program was 86% and on average participants attended 20.5 of the 24 planned exercise sessions. Regarding the occupational counseling sessions, 94% of the participants attended the first protocoled session, 35% attended the optional second sessions and 8% had a third session with the OOP. Reasons for not attending the second or third included already returned to work (n=27), receiving good support from the company's occupational physician (n=25), receiving good support from their employer (n=18), and not considering further support necessary (n=10).
The Spearman correlation between the adherence to the exercise program and the number of counselling sessions was 0.22.

The baseline sociodemographics, work- and disease related characteristics of the study population are presented in table 1. Participants had a mean age of 48 years and 90% was female. The majority of the participants had breast cancer (84%); other cancer diagnoses were colorectal cancer and non-Hodgkin lymphoma. Approximately 89% underwent surgery, 76% received radiotherapy and/or hormonal treatment. Before diagnosis and treatment, participants worked on average 28 hours per week. The majority of participants worked at a large company of more than 100 employees, was (shared) breadwinner and did perform any shift work.

Return to work

Primary outcome was the rate of RTW: the percentage of participants who returned to work at T1, T2 and T3. The rate of RTW increased significantly over time ($F=8.51$, $p<0.001$). Six months after inclusion in the study, 49 participants (59%) had, at least partially, returned to work. The rate of RTW increased to 86% of the study population at 12 months follow up, and this percentage was maintained at 18 months follow-up (83%). Median time to RTW was 292 days (95% CI; 259 - 325) in this study population.

Perceptions regarding work, work ability and work limitations

Data on different perceptions about work are shown in table 2. There was a significant increase in the perceived importance of work over time ($p<0.001$); the rating of 5.4 at baseline significantly improved to 6.4 at T1 and showed further improvement to 7.1 at T3.

The overall work ability ($p<0.001$) and self-efficacy regarding RTW ($p<0.001$) also showed a significant effect over time. Both the scores were not significantly better at T1 compared to baseline. At 18

months follow-up (T3) the participants showed a significant increase as compared to baseline in both overall WAI (difference was 1.8; 95% CI: 1.2 – 2.5) and self-efficacy (difference was 0.5; 95% CI: 0.3 – 0.7).

Perceived work limitations could only be assessed in those participants reported to have returned to work. Overall, a significant effect of time was seen in all WLQ subscales. Post hoc analysis showed that there was a significant increase in percentage of time workers experienced limitations in meeting job demands regarding time management (19.3 at T1), physical tasks (7.1 at T1) and production (13.5 at T1). Although scores were lower when measured at T3, the reductions in perceived work limitations, of -6, -1 and -7 respectively, were not significant.

Fatigue and physical activity level

Participants showed reducing fatigue levels over time ($p<0.001$), with a change in total score of -4.8 after program completion (T1) and -8.3 at T3 on a scale of 20-100 (table 3). Considering the different subscales, scores at T1 show significantly less physical (-1.6; 95% CI -2.6 to -0.6) and general fatigue (-1.3; 95% CI -2.2 to -0.3), less reduced (improved) activity (-1.6; 95% CI -2.6 to -0.6) and less reduced (improved) motivation (-1.1; 95% CI -1.9 to -0.3). At T3 scores of all subscales were reduced further compared to fatigue levels obtained at T1 (physical fatigue: -1.9; 95% CI -3.2.to -0.5, general fatigue: -1.5; 95% CI -2.7 to -0.2, reduced activity: -2.0; 95% CI -3.3 to -0.7, and reduced motivation -0.9; 95% CI -1.7 to -0.1).

Physical activity levels, measured in average hours a week performing moderate activity in work, leisure time, household and sports significantly changed over time. At T1 there was a significant reduction in activity level; 27 (±22) hours versus 40 (±13) hours of physical activity at baseline. Activity level was regained at T3, as this timeframe showed a significant increase of 13.8 hours, to 38 hours (±16) per week.

Cardiorespiratory fitness and muscle strength

Cardiorespiratory fitness as well as muscle strength were measured at the start and completion of the physical exercise program. Paired t-tests results showed that there was a significant improvement of muscle strength (table 4). After training, all 1-RM results increased significantly, ranging from an improvement of 5 kg (95% CI: 4 to 7) for the lateral pulley to an improvement of 44 kg (95% CI 36 to 51) obtained for leg press.

At baseline, cardiorespiratory fitness measured as VO_2 peak was 28.0 ml/min/kg (±7.1) on average. After the training program this value was significantly decreased to an average of 26.6 ml/min/kg (±7.2). Maximal workload obtained in this VO_2 peak test at baseline of 171 Watt (±43) did not change significantly (173 Watt (±50) after program completion). The maximal short exercise capacity, obtained with the steep ramp test, was significantly increased after completing the training program from 190 (±54) to 220 (±52) Watt.

Health-related quality of life (HRQoL)

HRQoL was measured multidimensionally and included global health, physical, role, cognitive, emotional and role functioning as well as symptoms such as fatigue, pain and nausea which are presented in table 5. All these HRQoL scales showed a significant change over time, except for cognitive functioning ($p=0.108$) and pain ($p=0.055$). Fatigue scores decreased over the total timeframe as the score at T1 (mean score 32 (±22)) and at T3 (mean score 24 (±21)) were significantly lower than measured at baseline (mean score 43 (±25)) and T1 respectively. A similar pattern was seen for role functioning which continued to increase significantly between

follow-up measurements from 60 (±28) at baseline to 73 (±25) at T1 and 85 (±26) at T3. Physical functioning (mean difference 4; 95% CI 1 to 7), social functioning (mean difference 12; 95% CI 6 to 18) and global health status (mean difference 9; 95% CI 5 to 13) showed an increase between T1 and T3, whereas the nausea scale showed a significant reduction in symptoms between baseline and T1 (mean difference -6; 95% CI -12 to -1).

Discussion

Six months after start of a multidisciplinary rehabilitation program that combined occupational counselling with a supervised physical exercise program, 59% of the cancer patients returned to work, 86% at 12 months and 83% at 18 months. In addition, significant improvements in importance of work, work ability, RTW self-efficacy, muscle strength and quality of life were observed, whereas fatigue levels were significantly reduced.

Interpretation of the findings

The RTW rates found in this study were higher as compared to those found in the review of the literature of Mehnert [7] . This pattern was shown at all three follow-up moments: at 6 months follow-up 59% versus an average of 40% in the literature, at 12 months 86% versus 62% and at 18 months follow-up 83% versus 73%. As these findings were based on 64 different studies, we cannot assess whether the baseline characteristics of our study population is representative of those reviewed by Mehnert [7]. However, we do know that our participants are representative of the Dutch workforce in terms of working hours, type of contract and company size. We did have, nevertheless, an overrepresentation of highly educated women caused by the inclusion of a high percentage of breast cancer patients. Hence we also compared RTW rates to those of Dutch breast cancer patients only. Most recent findings were 70-71% for partial RTW 12 and 24 months after diagnosis [25,26], which are lower than our findings as well.

The recent controlled effect study from van Waart and colleagues [14] which was aimed at cancer patients undergoing chemotherapy as well and focused on RTW as secondary outcome, showed similar RTW rates compared to the current study in both intervention groups. RTW was assessed as yes or no, regardless the number of hours at the end of follow-up, which was 6 months after the end of chemotherapy. The RTW rate observed in their control group was 61%.. After receiving either a home-based low-intensity self-managed physical activity program the RTW was 79% . After a moderate- to high exercise program supervised by a physical therapist the RTW was 83%. However, in the study of van Waart and colleagues the home-based exercises were repeated on a daily basis while in our study, the moderate exercise program was performed twice a week for an average of 4.5 months. On the other hand our study included the occupational counselling of an occupational physician specialized in cancer-related problems with RTW which is expected to have a positive effect on RTW. Both interventions produced good RTW rates but because our current study was not a controlled study it is not possible to draw strong conclusions on the effect of the addition of occupational counselling.

Results show that work became increasingly important to the cancer patients in our study during and after completion of the intervention. Their perceived work ability and perceived self-efficacy with respect to work increased over the course of the intervention and during the year of follow-up as well. Interestingly, the experienced importance of work of cancer patients in our study increased first, during the intervention and shortly after, while perceived work ability and self-efficacy for RTW showed larger improvements later, during the year of follow-up. A possible explanation could be that during the intervention, the consultations with the OOP might have affected the patient's perceived importance of work. At the same time, the adverse effects from the treatments including chemotherapy would have been present and recovery would still have been in progress, which could have negatively affected the patients' physical and cognitive work abilities and self-efficacy for RTW. An earlier study of Tamminga and colleagues showed as well that during the initial RTW phase, physical or psychological side-effects hampered work resumption [35]. After the intervention and during the year of

follow-up, the effects of the chemotherapy would have ceased and thus the perceived work ability and self-efficacy for RTW improved.

In the current study participants showed decreased physical activity levels during and after chemotherapy which were regained through time while fatigue levels diminished over time. This could be an effect of time because the treatment with chemotherapy was coming to an end. However, Van Waart and colleagues showed that moderate- to high-intensity exercise during which patients were receiving chemotherapy, had a beneficial effect on cardiorespiratory fitness as well as fatigue [14]. Courneya and colleagues found a significant improvement in fatigue among breast cancer patients who received an aerobic exercise training or a resistance exercise training during chemotherapy, compared to patients that did not receive any training [36]. Based on the outcomes of the present study, as well the outcomes of the studies of van Waart and colleagues Courneya and colleagues, physical rehabilitation interventions seem to reduce fatigue during chemotherapy.

The results of the present study imply that muscle strength had increased after completion of the program. There was no increase in VO_2 peak as was expected based on the studies of Backer and colleagues and van Waart and colleagues [12,14]. However, the training program in this study was more aimed at improving muscle strength than on aerobic exercise because that is an important first step in (work) functioning. This could be an explanation for the lack of effect on VO_2 peak.

HRQoL significantly increased on all domains except on the domains of cognitive functioning and pain. Several mechanisms might explain this increase. First, after the end of treatment and during follow-up, improvement of HRQoL EORTC scores is shown in most RCTs involving cancer patients [37] and it is likely that the same course applied to the patients in our study. Second, at follow-up the large majority of our patients had returned to their work. Earlier studies have shown that RTW is positively related to HRQOL [38] and therefore it is plausible that the patients in our study showed improved quality of life scores because they had returned to work.

Strengths and limitations

An important strength of the present study is that to our knowledge it is the first to combine a physical training program with occupational counselling in a multidisciplinary rehabilitation program. Thereby RTW of cancer patients was supported through multiple strategies which were shown to be effective on RTW in a Cochrane review [11]. The training program was supervised by trained physiotherapists and sport physicians. Validated measures were utilized to assess fitness and muscle strength and validated questionnaires were used to assess work ability, work limitations, self-efficacy, fatigue, and quality of life. As a result, the results obtained in this study are reliable. However, there are also limitations to this study. In the first place, we did not randomize patients because we based the study on a real life situation and patients who met the inclusion criteria were invited to participate. Because of the lack of a control group, there is no direct proof of the effects of our multidisciplinary program. However, the controlled effect studies showed to a large extent comparable findings [14,16,36]. Another limitation of our study design is the possible bias in the selection of participants with respect to the type of cancer and the motivation to participate in a physical exercise program. We mainly included female patients with breast cancer with a relatively high level of education and we cannot be sure if the results could be generated to male patients, people with lower levels of education and other types of cancer. Furthermore, the cancer patients who were included were highly motivated to participate. Those who did not

participate might have been less motivated and more likely to have a different lifestyle. At the same time the intervention might have been most beneficial for the latter group but we could not reach them. It is also not yet clear whether this type of intervention should be offered to all cancer patients or whether it is better to "personalize" the intervention to certain subgroups of patients.

Based on the present study, it is recommended to further investigate the effects of this multidisciplinary intervention, including occupational counseling and an exercise program in a controlled study. An implication for research is to study the added value of an OOP in a RCT and in other hospitals in order to assess the feasibility of the intervention more broadly and to identify subgroups of patients in need of differentiated approaches.

Conclusion

A multidisciplinary rehabilitation program, combining specialized occupational counselling with a physical exercise program supervised by a sports physician and a physiotherapist, is likely to support RTW among cancer patients. The program also seems to improve self-reported fatigue levels and physical activity, perceived importance of work, work ability, RTW, self-efficacy, quality of life, muscle strength and work perceptions. It can be considered a promising intervention to support cancer patients in resuming their work.

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Competing interests statement.

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Data sharing

No additional data

Author's contribution.

- ML: Acquisition, analysis, and interpretation of data for the work; Drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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- AB: Conception and design of the work; Acquisition, analysis, and interpretation of data for the work; Drafting the work and revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

[1] Petersson LM, Wennman-Larsen A, Nilsson M, et al. Work situation and sickness absence in the initial period after breast cancer surgery. *Acta Oncol* 2011;50:282-8.

[2] Nachreiner NM, Ghebre RG, Virnig BA, et al. Early work patterns for gynaecological cancer survivors in the USA. *Occup Med* 2012;62:23-8.

[3] Saunders SL, Nedelec B. What work means to people with work disability: a scoping review. *J Occup Rehabil* 2014;24:100-10.

[4] Stergiou-Kita M, Grigorovich A, Tseung V, et al. Meta-synthesis of survivors' work experiences and the development of strategies to facilitate return to work. *J Cancer Surviv* 2014;8:657-70.

[5] Isaksson J, Wilms T, Laurell G, et al. Meaning of work and the process of returning after head and neck cancer. *Support Care Cancer* 2016;24:205-13.

[6] Banning M. Employment and breast cancer: a meta-ethnography. *Eur J Cancer Care* 2011;20:708-19.

[7] Mehnert A. Employment and work-related issues in cancer survivors. *Crit Rev Oncol Hematol* 2011;77:109-30.

[8] de Boer AG, Taskila T, Ojajarvi A, et al. Cancer survivors and unemployment: a meta-analysis and meta-regression. *JAMA* 2009;301:753-62.

[9] Lee MK, Yun YH. Working situation of cancer survivors versus the general population. *J Cancer Surviv* 2015;9: 349-60.

[10] Silver JK, Baima J, Newman R, et al. Cancer rehabilitation may improve function in survivors and decrease the economic burden of cancer to individuals and society. *Work* 2013;46: 455-72.

[11] de Boer AG, Taskila T, Tamminga S J, et al. Interventions to enhance return-to-work for cancer patients. *Cochrane Database of Systematic Reviews* 2015;25:CD007569.

[12] de Backer IC, Vreugdenhil G, Nijziel MR, et al. Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life. *Br J Cancer* 2008;99:30-6.

[13] Mishra SI, Scherer RW, Snyder C, et al. The effectiveness of exercise interventions for improving health-related quality of life from diagnosis through active cancer treatment. *Oncol Nurs Forum* 2015;42:E33-53.

[14] van Waart H, Stuiver MM, van Harten WH, et al. Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial. *J Clin Oncol* 2015;33:1918-27.

[15] Groeneveld IF, de Boer AG, Frings-Dresen M H. Physical exercise and return to work: cancer survivors' experiences. *J Cancer Surviv* 2013; 7: 237-46.

[16] Thijs KM, de Boer AG, Vreugdenhil G, et al. Rehabilitation using high-intensity physical training and long-term return-to-work in cancer survivors. *J Occupat Rehabil* 2012;22: 220-9.

[17] Feuerstein M, Todd BL, Moskowitz MC, et al. Work in cancer survivors: a model for practice and research. *J Cancer Surv* 2010; 4:415-37.

[18] Mehnert A, de Boer A, Feuerstein M. Employment challenges for cancer survivors. *Cancer* 2013;119 Supp 11:2151-9.

[19] Verbeek J, Spelten E, Kammeijer M, et al. (2003) Return to work of cancer survivors: a prospective cohort study into the quality of rehabilitation by occupational physicians. *Occup Environ Med* 2003;60:352-7.

[20] Taskila T, Lindbohm ML. Factors affecting cancer survivors' employment and work ability. *Acta Oncol* 2007;46:446-51.

[21] Groeneveld IF, de Boer AG, Frings-Dresen MH. A multidisciplinary intervention to facilitate return to work in cancer patients: intervention protocol and design of a feasibility study. *BMJ Open* 2012;2, pii: e001321.

[22] Heijbel B, Josephson M, Jensen I, et al. Return to work expectation predicts work in chronic musculoskeletal and behavioral health disorders: prospective study with clinical implications. *J Occup Rehabil* 2006;16:173-84.

[23] Ekbladh E, Thorell LH, Haglund L. Perceptions of the work environment among people with experience of long term sick leave. *Work* 2010;35:125-36.

[24] de Boer AG, Verbeek JH, Spelten ER, et al. Work ability and return-to-work in cancer patients.*Br J Cancer* 2008;98:1342-7.

[25] Roelen CA, Koopmans PC, Schellart AJ, et al. Resuming Work After Cancer: A Prospective Study of Occupational Register Data. *J Occup Rehabil* 2010; 21:431-40.

[26] Roelen CA, Koopmans PC, Groothoff JW, et al. Return to work after cancer diagnosed in 2002, 2005 and 2008. *J Occup Rehabil* 2011;21:335-41.

[27] de Backer IC, Schep G, Hoogeveen A, et al. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. *Arch Phys Med Rehabil* 2007; 88:610-6.

[28] Tuomi K, Ilmarinen J, Jahkola A. Work Ability Index. Helsinki: Finnish Institute of Occupational Health 1998; 2nd revised ed.

[29] Lagerveld SE, Blonk RWB, Brenninkmeijer V, et al. Return to work among employees with mental health problems: Development and validation of a self-efficacy questionnaire. *Work & Stress* 2010;24: 359-75.

[30] Lerner D, Amick BC, Rogers WH, et al. The Work Limitations Questionnaire. *Med Care* 2001;39:72–85.

[31] de Backer, I C, Schep, G, Backx, F J, et al. Resistance training in cancer survivors: a systematic review. *Int J Sports Med* 2009;30: 703-12.

[32] Smets E, Garssen G, Bonke B, et al. The Multidimensional Fatigue Inventory, psychometric qualities of an instrument to assess fatigue. *J Psychometric Res* 1995;39:315–25.

[33] Wendel-Vos GC, Schuit AJ, Saris WHM, et al. Reproducibility and relative validity of the Short Questionnaire to Assess Health-enhancing physical activity. *J Clin Epidemiol* 2003;56:1163-69.

[34] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-76.

[35] Tamminga SJ, de Boer AG, Verbeek JH, et al. Breast cancer survivors' views of factors that influence the return-to-work process--a qualitative study. *Scand J Work Environ Health* 2012;38:144-54.

[36] Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol* 2007;25:4396-404.

[37] Zikos E, Coens C, Quinten C, et al. The Added Value of Analyzing Pooled Health-Related Quality of Life Data: A Review of the EORTC PROBE Initiative. *J Natl Cancer Inst* 2015;108(5): pii: djv391.

[38] Mellon S, Northouse LL, Weiss LK. A population-based study of the quality of life of cancer survivors and their family caregivers. *Cancer Nurs* 2006;29:120-131.

Table 1. Baseline characteristics of included participants who completed the rehabilitation program

Characteristic		Participants (n=93)
Sociodemographics		
Gender (% female, (n))		90.3% (84)
Age (years; mean (±sd))		47.9 (7.4)
Education level (% (n))	low	14.0% (13)
	intermediate	33.3% (31)
	high	52.7% (49)
Marital status (% (n))	Single	19.4% (18)
	Not living with partner	9.7% (9)
	Living with partner	71.0% (66)
Disease-related variables		
Cancer type (% (n)) *	Mamma	83.9% (78)
	Colorectal	8.6% (8)
	Non-Hodgkin Lymphoma	5.4% (5)
	Other	2.2% (2)
Days since diagnosis (mean (±sd))		61.9 (44.3)
Type of chemotherapy (% adjuvant (n))		87.1% (81)
Treatment additional to chemotherapy (% (n))*	Surgery	89.2% (83)
	Radiotherapy	30.1% (28)
	Hormone treatment	12.9% (12)
	Radiotherapy + hormone treatment	33.3% (31)
Type of contract (% (n))	Permanent employment	78.5% (73)
	Temporary employment	5.4% (5)
	Self-employed	11.8% (11)
Work-related variables		
Weekly working hours (mean (±sd))		28.3 (10.3)
Years in current employment		10.8 (8.4)
Years in paid employment *		22.9 (9.6)
Company size	Large (> 100)	62.5% (55)
	Medium (10-99)	22.7% (20)
	Small (1-9)	9.1% (8)
Shift work	No shiftwork	81.3% (74)
	Irregular service	16.5% (15)
	Shift work	2.2% (2)
Breadwinner status	Sole	34.8% (32)
	Shared	45.7% (42)
	Partner	19.6% (18)

Table 2. Changes in perceptions regarding work and work limitations of included participants who completed the rehabilitation program (n=93)

Measure	Baseline	T1	T2	T3	Time effect		Difference between baseline - T1			Difference between T1 - T3		
	mean (sd)	mean (sd)	mean (sd)	mean (sd)	p		mean	95% CI	p	mean	95% CI	p
Importance of work	5.4 (2.2)	6.4 (1.9)	7.0 (1.6)	7.1 (1.7)	0.000		**1.0**	**0.6 - 1.5**	**<0.001**	**0.8**	**0.2 - 1.3**	**0.005**
Overall work ability	5.2 (2.0)	5.8 (2.2)	7.2 (1.8)	7.5 (2.1)	0.000		0.5	-0.1 - 0.9	0.072	**1.8**	**1.2 - 2.5**	**<0.001**
RTW SE	3.5 (0.7)	3.7 (0.8)	4.0 (0.7)	4.2 (0.6)	0.000		0.2	-0.3 - 0.4	0.061	**0.5**	**0.3 - 0.7**	**<0.001**
WLQ, time management	11.7 (14.0)	29.3 (24.1)	17.6 (19.6)	21.0 (20.8)	0.000		**19.3**	**11.9 - 26.7**	**<0.001**	-6.1	-15.4 - 3.2	0.23
WLQ, physical demands	6.1 (11.1)	12.9 (13.7)	9.3 (12.0)	11.4 (14.7)	0.008		**7.1**	**3.0 - 11.1**	**0.001**	-1.4	-5.5 - 8.16	0.88
WLQ, mental-interpersonal demands	11.1 (10.4)	27.4 (20.1)	18.9 (19.3)	18.5 (16.4)	0.000		16.8	11.0 - 22.6	0.054	-6.8	-5.5 - 1.1	0.06
WLQ, production demands	15.5 (12.9)	28.9 (23.4)	19.8 (21.2)	23.1 (20.2)	0.013		**13.5**	**6.6 - 20.3**	**<0.001**	-7.0	-31.2 - 2.6	0.09

RTW SE: Return To Work Self-Efficacy; WLQ: Work Limitations Questionnaire; sd: standard deviation; CI: Confidence Interval

Table 3. Changes in fatigue and physical activity of included participants who completed the rehabilitation program (n=93)

Measure	baseline	T1	T2	T3	Time effect		Difference between baseline - T1			Difference between T1 - T3		
	mean (sd)	mean (sd)	mean (sd)	mean (sd)	p		mean	95% CI	p	mean	95% CI	p
MFI, General fatigue	13.0 (4.9)	11.4 (4.9)	9.8 (4.4)	9.8 (4.7)	0.000		**-1.3**	**-2.2 - -0.3**	**0.007**	**-1.5**	**-2.7 - -0.2**	**0.019**
MFI, Physical fatigue	12.1 (4.7)	10.1 (5.0)	8.2 (4.2)	8.3 (4.4)	0.000		**-1.6**	**-2.6 - -0.6**	**0.003**	**-1.9**	**-3.2 - -0.5**	**0.003**
MFI, Reduced motivation	9.7 (3.6)	8.3 (3.4)	7.4 (3.3)	7.2 (3.1)	0.000		**-1.1**	**-1.9 - -0.2**	**0.019**	**-0.9**	**-1.7 - -0.1**	**0.040**
MFI, Reduced activity	12.3 (4.8)	10.2 (4.6)	8.3 (3.9)	8.4 (4.5)	0.000		**-1.6**	**2.6 - -0.6**	**0.002**	**-2.0**	**-3.3 - -0.7**	**0.002**
MFI, Mental fatigue	11.2 (4.2)	11.6 (4.6)	10.1 (4.3)	9.4 (4.5)	0.045		0.8	-0.4 - 2.0	0.226	**-2.1**	**-3.3 - -0.8**	**0.002**
MFI, Total score	58.2 (18.4)	51.6 (18.8)	43.7 (16.4)	43.2 (18.1)	0.000		**-4.8**	**-8.6 - -1.0**	**0.009**	**-8.3**	**-13.3 - -3.4**	**0.001**
Physical activity	40.4 (12.9)	28.6 (21.9)	42.9 (17.5)	38.1 (15.5)	0.000		**-11.2**	**-19.0 - -3.5**	**<0.001**	**13.8**	**7.4 - 20.2**	**<0.001**

MFI: Multidimensional Fatigue Inventory; sd: standard deviation; CI: Confidence Interval

Table 4. Changes in muscle strength and cardiorespiratory fitness of included participants who completed the rehabilitation program (n=93)

Measure	Mean (sd) Baseline	Mean (sd) after completion	Mean difference	95% CI	p
VO2 peak (ml/min/kg)	28.0 (7.1)	26.6 (7.2)	-1.9	-2.9 to -0.9	<0.001
Maximal workload (Watt)	171.1 (43.1)	173.6 (50.3)	0.8	-4.9 to 6.6	0.771
1RM leg press (kg)	141.9 (42.0)	187.1 (52.7)	43.6	36.4 to 50.7	<0.001
1RM lateral pulley (kg)	22.5 (17.5)	26.1 (17.7)	5.4	3.7 to 7.2	<0.001
1RM chest press (kg)	16.7 (12.4)	25.1 (15.8)	8.5	6.9 to 10.0	<0.001
1RM deltiod pulley (kg)	23.3 (24.7)	31.1 (12.6)	101	8.3 to 11.8	<0.001
Maximal short exercise capacity (steep ramp test) (Watt)	190.1 (53.7)	220.1 (51.8)	27.5	20.6 to 34.4	<0.001

Table 5. Changes in health-related quality of life and symptom burden of included participants who completed the rehabilitation program (n=93)

EORCTC QLQ-C30 QoL measure	baseline	T1	T2	T3	Time effect		Difference between baseline and T1			Difference between T1 and T3		
	mean (sd)	mean (sd)	mean (sd)	mean (sd)	p		mean	95% CI	p	mean	95% CI	p
Physical functioning	84.4 (16.4)	85.5 (15.9)	91.2 (12.5)	88.9 (13.4)	**0.001**		0.9	-2.4 to 4.2	0.876	**4.2**	**1.0 to 7.3**	**0.012**
Role functioning	60.6 (27.9)	73.3 (25.4)	83.1 (23.5)	84.8 (25.7)	**0.000**		**9.7**	**3.6 to 15.9**	**0.005**	**11.5**	**4.3 to 18.8**	**0.003**
Cognitive functioning	80.5 (16.8)	74.7 (22.5)	78.7 (21.3)	78.9 (22.4)	0.108		**-6.9**	**-12.0 to -1.8**	**0.005**	3.3	-3.0 to 9.7	0.38
Emotional functioning	74.1 (19.7)	79.4 (19.6)	83.6 (18.0)	83.2 (20.3)	**0.002**		3.3	-1.7 to 8.3	0.062	2.8	-2.4 to 8.0	0.57
Social functioning	73.1 (23.1)	76.5 (22.9)	82.9 (22.0)	88.5 (20.8)	**0.003**		1.9	-2.9 to 6.8	0.434	**11.5**	**5.5 to 17.6**	**0.001**
Fatigue	42.7 (25.3)	31.8 (21.9)	23.6 (19.9)	24.3 (20.8)	**0.000**		**-9.2**	**-15.1 to -3.4**	**0.005**	**-7.8**	**-13.7 to -1.9**	**0.015**
Nausea	11.4 (19.8)	4.9 (16.1)	1.4 (4.6)	2.7 (8.9)	**0.012**		**-6.1**	**-11.5 to -0.6**	**0.011**	-3.3	-7.9 to 1.2	0.31
Pain	21.8 (25.4)	17.1 (22.5)	10.9 (18.4)	13.0 (17.5)	0.055		-3.9	-9.9 to 2.1	0.172	-4.4	-9.9 to 1.2	0.19
Global health	66.8 (21.8)	74.7 (18.5)	83.3 (16.2)	82.4 (17.3)	**0.000**		5.5	0.1 to 10.9	0.138	**8.8**	**4.5 to 13.2**	**<0.001**

QOL: Quality Of Life; sd: standard deviation; CI: Confidence Interval

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	6,7,8
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	7,8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,9, 19
		(b) Indicate number of participants with missing data for each variable of interest	6,9,10,19,20,21,22,23
		(c) Summarise follow-up time (eg, average and total amount)	6,9,10,19,20,21,22,23
Outcome data	15*	Report numbers of outcome events or summary measures over time	9,10,20,21,22,23
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,9,10,19,20,21,22,23
		(*b*) Report category boundaries when continuous variables were categorized	9,10,20,21,22,23
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13, 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.