Return to work in employees undergoing chemotherapy for cancer

- the role of physical activity and self-efficacy

PhD dissertation

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Health

Aarhus University

2019

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Financial support

DEFACTUM, Central Denmark Region
Aarhus University
The Danish Cancer Society
The Oticon Foundation

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The work of the present dissertation was conducted in collaboration with:

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Acknowledgements

The work presented in the present PhD dissertation was carried out between February 2016 and November 2019 at DEFACTUM, Central Denmark Region, Denmark and Department of Public Health, Aarhus University, Denmark in close collaboration with the Department of Oncology, Aarhus University Hospital, Denmark.

I'm greatly indebted to a number of people who made this project possible.

First of all, I would like to thank *all the men and women with cancer* who took their valuable time and energy to participate in the studies in the present PhD. Without you, the project would not have been possible. I'm very grateful.

I would also like to express my deepest gratitude to all my supervisors; Merete Labriola, Robert Zachariae, Dorte Gilså Hansen, Inger Højris and Claus Vinther Nielsen. It has been a privilege working with such brilliant people. I'm truly honored. In particular:
Merete Labriola: I own you my heartfelt thanks. Thank you for believing in me and in the project from the very beginning and for introducing me to the field of occupational rehabilitation. Thank you for your never-ending support, for your warmth and for your understanding of my personal life and life priorities and for letting me into your life, professionally and privately.

Robert Zachariae: You have been a huge inspiration for me since my time as a student at Department of Psychology and it has been a great honor working alongside you. Thank you for inspiring discussions and for challenging me. Also, thank you for hosting me at two inspiring research stays at EPoS and for inviting me to participate in projects alongside the PhD, in particular for the opportunity to contribute to the book "Livet efter kræft".

Dorte Gilså Hansen: You have been a dedicated supervisor from the very first day of the project. Thank you for your commitment, for constructive discussions and brilliant feedback when I was writing my scientific papers. I have learned so much from you. Finally, thank you for opening up your home in Middelfart for me to discuss the project.

Inger Højris: Without you, the project would not have been possible. Thank you for your emphatic support, for the time and effort you have spent on making this project possible at the hospital, and for always finding new ways when some doors closed. Thank you for many pleasant and enlightening conversations regarding the field of cancer and cancer treatment.

Claus Vinther Nielsen: I entered your office in the spring of 2014 with an idea of a future PhD project and a wish to collaborate with DEFACTUM in this project. Thank you for welcoming me and my ideas, for inviting me to be a part of the academic research environment at DEFACTUM, and for taking the project under your wings the last year of the project.

My sincere appreciations also go to *the management, the department nurses, and the nurses at the Department of Oncology, Aarhus University Hospital,* for making this project possible. Thank you for your enormous help in the process of including patients to the project and for always meeting me with a smile at my weekly visits during the inclusion period.

Also, a great thank you to the staff at *The Body and Cancer Units in Aarhus, Aalborg and Vejle* for great help including patients to the validation study in the present dissertation. It has been a pleasure working with you. I admire your professional dedication and commitment to your work. I'm grateful for your help within this project.

Furthermore, a special thanks to:
Thomas Maribo: For giving me an inspiring working environment at MarselisborgCentret

Inger Hornbech: For being a constant source of practical help, support and fun

Christina Malmose Stapelfeldt and Louise Lindholdt: For great help and introduction to the DREAM registry

Thomas Lund: For enlightening discussions regarding the statistical possibilities within this project and for your ever-present help with statistical analyses whenever I needed it.

Data and Documentation, DEFACTUM, and in particular Kristian Kyhl: For great help constructing the on-line questionnaire and for outstanding help and technical support throughout the project.

Mathias Tvilling Rasmussen: My savior within the world of STATA – thank you for always patiently helping me and for your huge contribution to the validation project in this dissertation.

The Clinical Trial Unit, Aarhus University Hospital: For great help in the process of including participants, and in particular, *Jeppe Neimann*, for developing a system to identify eligible patients.

My research assistants; Ida Ejdrup Larsen, Jeanette Lauridsen, Ditte Kuhlmann, and Mette Zacher: Your conscientious work has been of great value for the project and to me - Thank you all.

My dear colleagues at MarselisborgCentret: For creating an inspiring academic working environment and for making my work life so much fun. You have all added professional and personal value to my life. I will miss you all.

Irene Dyhrberg Andersen and Hanne Olsson, Body and Cancer, Department of Oncology, Aarhus University Hospital. My deepest gratitude to the two of you. Thank you for believing in my ideas from the very beginning and for your dedication, inspiration and guidance in the development of the project. The present PhD was literally born in your office at a meeting in the fall 2013. Thank you for your always warm welcomes of me at the Body and Cancer unit in the years to follow.

Also, a special thanks to *all my close friends:* For always being there, supporting me and my children. Each and every one of you is special to me and has added value and joy to my life.

My deepest gratitude also goes to *my parents and the rest of my family*: Thank you for your endless love and support and for always helping me in every possible way. I love you all.

Finally, *my children Camille, Julie and Kasper:* You are the greatest joy of my life. Thank you for bringing meaning and joy to my life every single day – I love you.

In loving memory of Kristian Melgaard – my husband and dearest friend (1976-2012)

I dedicate this PhD dissertation to you - Your way of fighting the cancer has been the greatest source of inspiration in the development of this project.

.

I will always love you.

List of scientific papers

The PhD dissertation is based on the following three studies:

1. **Validation of the Return To Work Self-Efficacy questionnaire in a population of employees undergoing treatment for cancer**

   Rosbjerg, R., Hansen, D.G., Zachariae, R., Stapelfeldt, C.M., Hoejris, I., Rasmussen, M.T., Drysdale, S.W., Labriola, M.
   Submitted: Journal of Occupational Rehabilitation, 22 July 2019 (under review)

2. **The predictive value of return to work self-efficacy for return to work among employees with cancer undergoing chemotherapy**

   Rosbjerg, R., Hansen, D.G., Zachariae, R., Hoejris, I., Lund, T., Labriola, M.
   Submitted: Journal of Occupational Rehabilitation, 18 November 2019

3. **Physical activity, return to work self-efficacy, and work status among employees undergoing chemotherapy for cancer - a prospective study with 12 months follow-up**

   Rosbjerg, R., Zachariae, R., Hansen, D.G., Hoejris, I., Duijts, S., Gehr, N.L., Andersen, I.D., Labriola, M.
   Submitted: Journal of Occupational Rehabilitation, 19 November 2019 (under review)

Abbreviations

BDI: Beck's Depression Inventory
CBI: Cancer Behavior Inventory
CI: Confidence Interval
COSMIN: The COnsensus-based Standards for the selection of health Measurement INstruments
DREAM: Danish Register for Evaluation of Marginalization
FACIT-F: The Functional Assessment of Chronic Illness Therapy-Fatigue
GPC-Q: Global Perceived Change question
HADS: Hospital Anxiety and Depression Scale
HR: Hazard Ratio
ICC: Intraclass Correlation Coefficient
ICF: International Classification of Functioning
IQR: Interquartile range
LOA: Limits of agreement
OR: Odds Ratio
PA: Physical activity
RTW: Return to work
RTWSE: Return to work self-efficacy
RTWSE-19: The 19-item RTWSE questionnaire
SD: Standard Deviation
SDC: Smallest Detectable Change
SE: Self-efficacy
SEM: Standard Error of Measurement
STROBE: STrengthening the Reporting of OBservational studies in Epidemiology
WAI: Work Ability Index
WHO: World Health Organization

Concepts used in this dissertation

Cancer rehabilitation refers to *"a goal-oriented, collaborative process between a patient with cancer, relatives and professionals. The purpose is to help the patient, who experiences or is likely to experience significant disabilities in his or her physical, mental and / or social functioning, to attain an independent and meaningful life. Rehabilitation is based on the patient's entire life situation and decisions and consists of coordinated, coherent and knowledge-based efforts"* (1) *(*my translation). This definition is used by the Danish Health Authority in Cancer Plan II (1) and it originates from the definition of rehabilitation in the Danish whitepaper on the concept of rehabilitation – Rehabilitation in Denmark ("Hvidbog om rehabiliteringsbegrebet - Rehabilitering i Danmark ") from 2004 (2).

Cancer survivor: In the present dissertation the term "cancer survivor" will be defined as: *"Anyone who has been diagnosed with cancer, from the time of diagnosis to the end of life"* (3). "Cancer survivor" as a concept was introduced by Mullan (4) to capture both current patients with ongoing illness and patients cured for cancer. He argued that the concept of cured used in relation to other diseases did not realistically describe the experience of people having had cancer. As a result, he proposed the concept "survivor" to define both those being cured and those still living with the disease (4).

COSMIN refers to *"The COnsensus-based Standards for the selection of health Measurement INstruments"*(5). COSMIN is based on an international Delphi study including 50 experts with backgrounds in psychometrics, epidemiology, statistics, and clinical medicine, aiming at achieving consensus regarding standards for measurement tools (Figure 1). COSMIN has been used as a guideline in the development and the conduction of the validation study (Study I) in the present dissertation.

Figure 1 The COnsensus-based Standards for the selection of health Measurement INstruments

Fatigue is defined as "*a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Compared with the fatigue experienced by healthy individuals, CRF is more severe, more distressing, and less likely to be relieved by rest*" (6).

Internal consistency refers to the interrelatedness of the items in a questionnaire (7,8).

Occupational rehabilitation is defined as *"a timely, planned process with clear goals and tools, where several actors work together to provide the necessary assistance to help the citizen to achieve the best possible functioning, independence and participation in working life and society"*(9)(my translation).

Physical activity refers to *"Any bodily movement produced by skeletal muscles that requires energy expenditure"*(10) as defined by the World Health Organization (WHO). Within this definition it is further implied that: *"The term "physical activity" should not be mistaken with "exercise". Exercise, is a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective. Physical activity includes exercise as well as other activities which involve bodily movement and are done as part of playing, working, active transportation, house chores and recreational activities"* (10)(WHO). The tools for measuring physical activity were chosen based on this understanding of physical activity.

Reliability refers *"to the extent to which scores for patients who have not changed are the same for repeated measurements"* and are free of measurement errors (7).

Responsiveness refers to the ability of an instrument to detect change over time in the construct being measured as described by the COSMIN group (7,8).

Return to work can be referred to as a process or an outcome (11). When referred to as a process, return to work is understood as *"a health-related behavior involving elements of motivation and self-management, influenced by physical, psychological, and social factors"* (12). When return to work is used as an outcome, the operationalization of it will be described in the relevant methods section.

Self-efficacy is rooted in social cognitive theory. The concept was introduced by Albert Bandura and refers to *"beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments"* (13). According to Bandura, self-efficacy plays a key role in human agency by influencing the choices and persistence of actions of the individual (13).

STROBE refers to guidelines aiming at STrengthening the Reporting of OBservational studies in Epidemiology (14), developed in an international collaboration between epidemiologists, methodologists, statisticians, researchers and journal editors. The STROBE guidelines guided the development and dissemination of the observational studies in the present dissertation.

Symptom burden refers to long-term and late effects of cancer treatment (15).

Validity refers to *"the degree to which an instrument truly measures the construct(s) it purports to measure"*(7).

Work disability is defined as occurring "*when a worker is unable to stay at work or return to work because of an injury or disease"*(16).

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1.0 Point of departure

"People have always striven to control the events that affect their lives"

Albert Bandura

These words are the opening lines in the book "Self-efficacy – the exercise of control" by Albert Bandura (13). *People have always striven to control the events that affect their lives;* however, when diagnosed with cancer, most people are faced with the ultimate uncontrollability and unpredictability. A cancer diagnosis *per se* as well as the treatment-induced side-effects are known to contribute to feelings of helplessness and loss of control (17-20).

In his book, Bandura further states: *"The inability to exert influence over things that adversely affect one's life breeds apprehension, apathy and despair"*(13) - hence, the inability to control has fundamental and negative consequences for the individual. Similarly, low level of self-efficacy (SE) in cancer survivors has been shown to be associated with poor psychological health, reduced quality of life and increased levels of anxiety and depression (13,21-26). Low level of SE is also associated with passive coping styles, whereas high level of SE is associated with active adjustment style and "fighting spirit" (13,25). In other words, a sense of control or an expectation of being able to do something, despite the cancer disease, is of great importance to the psychological well-being of cancer survivors.

How can this knowledge be used within the field of cancer rehabilitation? How do we increase the level of SE in cancer survivors – and which positive effects might this have? These questions came to my mind in 2013 and were the first thoughts for a future PhD project.

Briefly, I ended up conducting a validity study of 68 employees with cancer, participating in the Body and Cancer program, a six-week group-based exercise program, at three hospitals in Denmark (Aarhus, Aalborg, and Vejle). In this study, I validated the Danish version of the 19-item Return To Work SE questionnaire (RTWSE-19) (27) among employees undergoing treatment for cancer (Study I). Furthermore, I conducted a survey study of 217 employees with cancer initiating chemotherapy at Aarhus University Hospital between November 2016 and May 2018, where the participants filled out questionnaires three times during a period of 12 months. Based on the survey study and with additional data from patient records and Danish national registers, I conducted two follow-up studies examining the predictive value of RTWSE on actual return to work (RTW) (Study II), and the association between physical activity and work status and the mediating role of RTWSE in this association (Study III).

2.0 Background

2.1 Cancer epidemiology

In Denmark, approximately 43,000 individuals are diagnosed with cancer annually (28). The most frequent cancers are breast, lung, prostate, and colon cancer with incidences of 4,872, 4,780, 4,362, and 3,745 cases, respectively, in 2017 (28). The incidence of cancer has been steadily increasing for the last decades with an increase of 19% among men and an increase of 13% among women during the last 10 years (28). Steadily increasing incidence combined with substantial improvements in treatment have led to an increase in the number of individuals living with a cancer diagnosis (28-31). In Denmark, the one-year survival rates are 80% for men and 82% for women diagnosed with cancer between 2014 and 2016, while the five-year survival rates are reported to be 62% for men and 65% for women (28). In 2017, the prevalence of cancer in Denmark counted 324,649 individuals (28), which corresponds to an increase of 3.6% compared to 2016. Similar increases in incidence and prevalence of cancer are observed internationally. In Europe, the incidence and prevalence of cancer in 2018 was 4.2 million and 12.1 million, respectively (29). Approximately 50% of those diagnosed with cancer are of working age (30,32).

2.2 The meaning of work

To most people, work plays an essential role in life. In Denmark, the employment rate is 75% among people between 16 and 64 years of age (33), which is equal to the majority of the adult population. Besides providing an income (34), several additional positive benefits of employment have been supported by research. First, having a job structures everyday life (35) and facilitates an active social life outside the family, thereby contributing to social networks, social roles and social status (34,35). Work is furthermore a central part of most people's identity (34,35). While a specific profession gives a specific professional identity, being an active member of the work force provides an identity of contributing and thereby being a valued member of society (35). Moreover, employment has been shown to be positively associated with quality of life, self-esteem, as well as physical and mental health (34,35). Due to these multiple benefits, work is considered just as important for a good health as diet and exercise from a public health perspective (16). It should, however, be kept in mind that some jobs can be prejudicial to health due to job insecurity, negative working environments, and job strain (34). Yet, in the present dissertation, work is considered a positive outcome.

According to Abraham Maslow, people are motivated by needs – needs of deficiency and needs of growth (36,37). Within Maslow's terminology, motivation for work can be explained by the fulfillment of a hierarchy of needs (36-38)(Figure 2). By generating economic resources and thereby ensuring means for accommodation and daily living, employment contributes to fulfillment of the physiological and the safety needs, which are part of the two levels in the bottom of the hierarchy. Additionally, by facilitating social networks and by contributing to social roles as well as positive self-images, self-esteem and identity, work also contributes to fulfillment of the three top-level needs. Thus, work is a way to fulfill not just the need for food and accommodation, but also the needs for personal growth.

Figure 2 Maslow' hierarchy of needs

The theory of needs by Maslow has been criticized over the years for being gender biased and culture centered, but evidence of the existence of the needs and their internal relationship has been found as well (39). However, it is not within the scope of this dissertation to discuss the validity of the theory and the hierarchy, solely to illustrate the huge contribution of work in the fulfillment of many aspects of human life and needs. The motivation for work and Maslow's hierarchy of needs will furthermore be used as a theoretical perspective in the discussion of the findings of this dissertation.

2.2.1 Cancer and the meaning of work

Facing a potential life-threatening disease such as cancer, on might ask how important work is? However, qualitative findings suggest, that work continues to be a vital aspect of life to many cancer survivors (40-45) as it represents:

- a distraction from their disease (41-44)
- normality; working equals having a normal life (43-46)
- a way of obtaining satisfaction and meaning in daily life despite the disease (44,45)
- a social network and support outside the family (42,44,45)
- a marker of health and well-being (44,45)
- a source of control (41,44)
- a source of hope (41,44)

Work thus seems to continue to play a pivotal and positive role for many cancer survivors during and after the disease. In other words, despite a cancer disease work still seems to fulfill the needs of belonging, esteem and self-actualization, and staying at work or returning to work is reported as a great wish of many cancer survivors (45).

On the other hand, it should also be mentioned that work may also be a source of distress for cancer survivors (43). Concerns about the financial situation of the family, the future work- and earning possibilities and the fear of getting fired are also reported by cancer survivors (40,43,44). Furthermore, it is well known that cancer, being potentially life-threatening, encourages many cancer survivors to reprioritize core values, which may result in work becoming less important (40-44). Similar perspectives are reported in people with work disability across various diagnoses (47).

2.3 Cancer and work disability

Cancer and the treatment-induced side effects may lead to work disability for a shorter or longer time (32,48,49). Work disability is defined as occurring "*when a worker is unable to stay at work or return to work because of an injury or disease*" (16). Since cancer disease and cancer treatment often lead to both physical and psychological side effects (32,50-53), cancer survivors often experience difficulties in sustaining work or in returning to work during and after treatment (32). The most common side and long-term effect of cancer and treatment is fatigue (54-56). Fatigue in cancer survivors has repeatedly been shown to be associated with later RTW, lower productivity, increased absenteeism, and reduced working hours (15,55,57,58).

An international meta-analysis of 36 studies showed that unemployment is 1.4 times more common in cancer survivors compared to cancer-free controls (30). In Denmark, an increased risk of unemployment among cancer survivors has also been reported (59); an increased risk of unemployment of 12% for female cancer survivors and of 6% for male cancer survivors compared to age- and gender-matched controls with no history of cancer, measured during 20 years of follow-up from time of diagnosis (59). Furthermore, cancer survivors have more sick days (46,48,49), reduced work ability (32,46,49), and are at higher risk of early retirement (60,61) compared to the general population or cancer-free controls.

Physical and psychological long-term effects of cancer and cancer treatment are reported by cancer survivors for more than 10 years after treatment cessation (31,56). A cohort study (62) including 1400 cancer survivors interviewed 1-5 years after diagnosis showed that, even though many cancer survivors did RTW within one year or had sustained their job throughout treatment, 11% stopped working in the following years for cancer-related reasons.

On average, 62% (range 30%-94%) of cancer survivors RTW within one or two years after the diagnosis (32,49). A recent systematic review regarding RTW of cancer survivors based on 12 studies from Central and Northwestern Europa reported that the median time between diagnosis and documented RTW was two years (0.2–23.4 years), and that RTW rates of cancer survivors in Europe ranged from 39% to 77% with an average of 64% (63). In Denmark, RTW rates of 62% and 49% have been reported among patients diagnosed with colorectal cancer (64) and haematological malignancies (65), respectively.

The societal financial burden of work disability due to cancer is high (66-68). In Denmark, the average annual costs of lost productivity (sick leave and disability pension) of the four most frequent cancers amounted to; DKK 575.4 million for breast cancer, DKK 341.3 million for lung cancer, DKK 289.4 million for colorectal cancer, and DKK 53.6 million for prostate cancer in the years 2010-2012 (66).

Considering the implications for quality of life among cancer survivors and their families, and the financial burden for society, improving the work ability and the process of RTW for cancer survivors is of major importance.

2.4 Work disability prevention within a biopsychosocial perspective

The present dissertation has been developed within a biopsychosocial perspective of the RTW process, thus acknowledging the importance of physical, psychological, and social factors in the RTW process in cancer survivors. The process of returning to work can thus be defined as *"a health-related behavior involving elements of motivation and self-management, influenced by physical, psychological, and social factors"* (12).

Several biopsychosocial conceptual models of work disability have been developed (69). *The case-management ecological model*, developed by Loisel et al. (69,70), is known for providing the most complete visual overview of the complexity of factors influencing work participation and the RTW process in a work disabled individual (Appendix 4). The model illustrates the individual worker surrounded by four different arenas of significance in the management of work disability; the personal system, the health care system, the workplace system, and the legislative and insurance systems. The overall social context, including culture and politics, is also presented in the model (69,70). Another influential and widely used biopsychosocial model within the area of rehabilitation is the *International Classification of Functioning* (ICF)(69,71), developed by the World Health Organization (WHO). In this model, the functioning of an individual is dependent on a complex dynamic interaction between the individual's health condition and personal/psychological and societal/environmental factors. ICF was originally developed to improve the communication among healthcare professionals (69). Yet, the model has been applied within occupational rehabilitation as well, as described in a recent scoping review (72).

Both models have served as an inspiration for the work within this dissertation. However, Feuerstein et al. have developed the *Cancer and Work model*, which is based on a review of existing research within the area of cancer and RTW (48)(Figure 3). This model also represents a biopsychosocial view of the RTW process. Being evidence-based and cancer-specific, the Cancer and Work model was chosen as the primary conceptual framework for the studies in this dissertation.

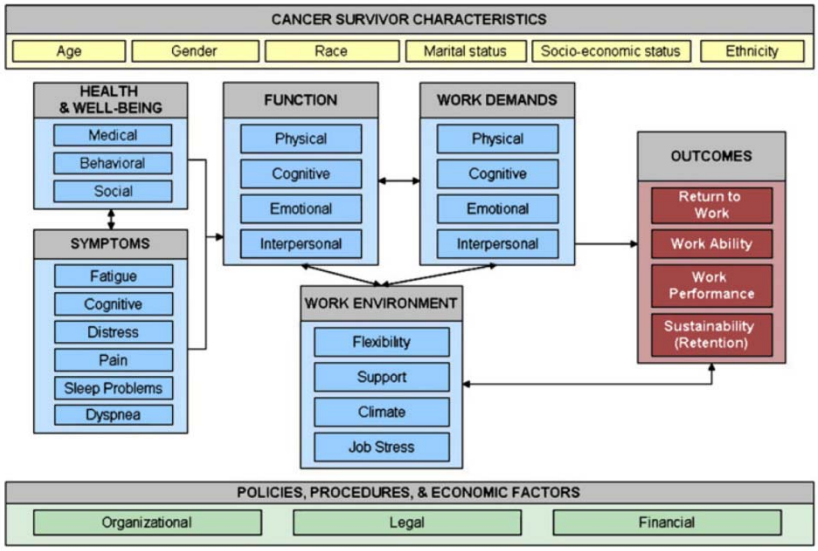

Figure 3 The Cancer and Work model

As in the case-management ecological model (70), the multifactorial nature and the complexity of the RTW process is acknowledged in the Cancer and Work model.

To improve the work ability and the process of RTW for cancer survivors, it is necessary to obtain a better understanding of the RTW process of this group. Focusing on *physical activity* and *SE*, the perspective of the present dissertation primarily lies within the *function* of the individual in accordance with the terminology of Feuerstein et al. (48). The importance of the other categories is recognized as well by including factors from these categories as covariates in the studies.

2.5 Physical activity

Numerous studies underline the benefits of physical activity on health and well-being in cancer survivors (73-75). Besides increasing physical functioning (73,76,77), physical activity during and after cancer treatment is associated with increased psychological well-being (78), quality of life (75,76), and reduced fatigue (77,79). Being physically active during treatment has also been shown to increase cancer survivor's sense of control (80-83). Moreover, it is also associated with lower risk of death, relapse, and comorbidity in cancer survivors (54,84-86). The amount of evidence on the physical and psychological benefits of physical activity for cancer survivors has been steadily accumulating during the last two decades (75,87,88). As a result, physical activity has become an integral part of international (89) as well as national guidelines regarding cancer rehabilitation (90,91).

However, the possible effects of physical activity on the work lives of cancer survivors have received less attention (87,92,93). Research in work-related interventions for cancer survivors is generally sparse (94,95), especially concerning work-related interventions including physical activity (92,93).

In a systematic review from 2017 (94), 138 studies within occupational therapy and cancer rehabilitation were identified. Of these, only three studies addressed RTW, and only one of these focused on the effect of physical training in the RTW process (96). This study found that cancer survivors participating in a high-intensity exercise program minimized their decrease in work ability after their cancer diagnosis (-5.0 hours/week vs. -10.8 hours/week), measured at follow-up three years after diagnosis, compared to an age-matched control group from two other hospitals receiving usual care ($p = 0.40$)(96).

In a systematic Cochrane review from 2015 (92) focusing on interventions to increase RTW for cancer patients, 15 randomized controlled trials (RCT) were identified of which only one involved physical activity. Based on this one study (97) with low quality evidence, it was concluded, that physical training did not appear to be more effective than usual care in improving RTW (92). Similar conclusion was made in a systematic Campbell review (93), also published in 2015, regarding work-related interventions for cancer survivors. Here, three RCT studies (98-100), investigating the effect of physical activity intervention programs, were identified. They found no effect in relation to number of sick days or employment status. However, methodological shortcomings of the included studies were identified, and the quality of the evidence was rated as limited (93).

Subsequently, support for the hypothesis of a positive effect of physical activity on RTW has been reported in two observational studies (101,102) and in three RCT studies (77,103,104), in which RTW was measured as secondary variables.

Summing up, evidence is strong regarding the general benefits of physical activity on the health and well-being of cancer survivors, but results regarding the effect of physical activity on RTW remain limited, of low quality, and lack consistency. Thus, further research is needed.

Moreover, the mechanisms involved in the possible association between physical activity and work; i.e., how physical activity may affect work, are also scarcely investigated (105). Investigating mediating variables can help explain *how* or *why* one factor affects another (106), in the present dissertation, how or why physical activity may affect work. Understanding the underlying mechanisms between the independent and dependent variables provides an opportunity of moving outside "the black box" by answering some of the how and why–questions, which may be beneficial when designing future intervention programs (106). SE may be a mediator between physical activity and work.

2.6 Self-efficacy

SE is theoretically rooted in social cognitive theory. According to social cognitive theory, human behavior is determined by reciprocal determinism, in which behavioral, internal personal, and environmental factors operate as determinants of each other (13,107)(Figure 4).

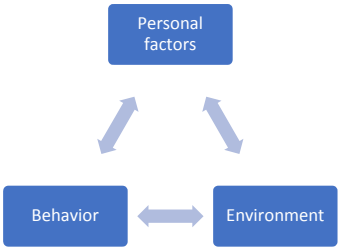

Figure 4 The relationship between the three major classes of determinants in triadic reciprocal determinism: *Behavior*, the internal *personal factors* in the form of cognitive, affective, and biological events, and the external *environment* (13)

Internal personal factors in form of cognitive, affective and biological factors influence how the individual recognizes, perceives and reacts to external stimuli (13,107). According to Bandura (13), the most central and pervasive mechanism of agency is the belief in personal efficacy, or SE. SE is defined as *"beliefs in one's capabilities to organize and execute the courses of action required to produce certain attainments"*(13). SE plays a central role in human agency by influencing the choices and persistence of actions of the individual (13,108). If people believe that they have the capabilities to produce a desired result, they will try to make things happen. On the other hand, if they do not believe they have the capabilities, they are more likely not to try at all. SE has been shown to be positively associated with mental health, health promoting behaviors (exercise, smoking cessation, healthy eating and drinking habits etc.), career development, and other desirable outcomes (13).

2.6.1 Return to work self-efficacy

Along the line of desirable outcomes positively associated with high SE is RTW (109,110). In numerous studies, return to work-SE (RTWSE) has been shown to be positively associated with work ability and work status among employees on sick leave due to both physical and mental conditions; moreover, it has been shown to be predictive of actual RTW (12,27,110-114). In samples of long-term sick-listed employees with all-cause sickness absence, those with high RTWSE had a significantly shorter time to RTW than those with low RTWSE (27,114). Similar findings have been found in employees on sick leave due to both mental (111,113) and musculoskeletal disorders (110,112).

Based on the observed positive associations with both work/RTW and physical activity behaviors (13,115,116), SE may be a mediator in the possible association between physical activity and work. Support of this hypothesis is found in two qualitative studies in which "increase in self-confidence" (117) and "increase in the confidence in physical abilities" (105) were reported as the positive influences of physical activity on RTW. To the best of my knowledge, the mediating role of RTWSE in the possible association between physical activity and work has not yet been examined.

2.6.2 Return to work self-efficacy in cancer populations

In general, little attention has been given to the significance of SE in relation to work life variables in cancer survivors (118,119). While the predictive value of RTWSE has been confirmed repeatedly in populations of employees on sick leave due to mental disorders (111,113), musculoskeletal disorders

(110,112) and all-cause sickness absence (27,114), the predictive value of RTWSE among cancer survivors has only been examined in one study with limited generalizability (120). Hence, further research regarding the predictive value of RTWSE in a cancer population is needed.

In the present dissertation, the Danish version of the 19-item RTWSE questionnaire (RTWSE-19) (27,110) was chosen as the measurement tool of RTWSE. The RTWSE-19 was translated and culturally adapted into Danish in 2016 (27). Originally, the questionnaire was developed and validated in a population of patients with low-back pain (110). Several RTWSE questionnaires have been developed and validated in various populations (12,110,113) but none yet in a cancer population. The psychometric properties of a measurement tool may change if applied to individuals with more or less severe diseases than the population for which the tool was developed (7). Applying the RTWSE questionnaire in future research or clinical practice concerning the RTW of cancer survivors would require a validation of the questionnaire in this specific population. Moreover, as RTWSE was one of the primary variables of interest in this dissertation, a reliable measure of the concept within the population of interest is important. Thus, a validation of the RTWSE-19 questionnaire among cancer survivors is needed.

2.7 The societal and legislative context

As presented in the Cancer and Work model (48), the findings in the present dissertation should be analyzed and interpreted in the light of the overall societal and legislative context in which the studies have been conducted. In this section, a short introduction to the Danish sick leave policy and to cancer rehabilitation in Denmark will be presented.

2.7.1 The Danish sick leave policy

According to current Danish laws (121), all citizens who are unable to work, regardless of the reason why they are unable to work, are entitled to receive public transfer payments, e.g. sickness absence compensation, early retirement, etc. In case of sickness absence, the expenses for the first four weeks are covered by the employer. After the four weeks, it is possible for all members of the work force to receive sickness absence compensation from the municipality for 22 weeks. If the sickness absentee receives wages as usual while being on sick leave, the employer is entitled to receive a sickness absence compensation, thus reducing the employer's expenses. For citizens with a severe, life-threatening illness, an extension of the sickness absence compensation period is possible for up to an additional 26 weeks. For many cancer survivors, an extension of the sickness absence is thus possible.

2.7.2 Cancer rehabilitation in Denmark

In Denmark, cancer rehabilitation is a part of the Danish healthcare system and is thus available and free to all cancer survivors (90). Cancer rehabilitation takes place in the municipalities and typically includes

elements of physical activity, psychosocial interventions and occupational advice (90,122). Based on assessments of individual needs, cancer survivors are referred to municipal cancer rehabilitation by the hospitals or the general practitioner. Parallel interventions and programs may be offered at the hospitals while the cancer survivor is undergoing treatment (90). An example of an in-hospital parallel intervention program in Denmark is the Body and Cancer program (88), which is a six-week group-based exercise program offered to cancer survivors undergoing chemotherapy. The Body and Cancer program was originally a project initiated at Rigshospitalet in Copenhagen in 2001, but due to positive physical and psychological effects (88), the Body and Cancer program is now established in the cities Aarhus, Herning, Esbjerg, Aalborg, Vejle, Sønderborg and Odense as well. Rehabilitative initiatives have traditionally been initiated after the end of the treatment. However, initiating rehabilitation at the time of diagnosis is now recommended, as this is believed to reduce the symptom burden (90,122,123).

With the primary aim of improving cancer treatment and cancer rehabilitation in Denmark, national guidelines and policy recommendations have been developed:

- National Cancer Plans I-IV (124)(in Danish: "Nationale Kræft Planer"), issued by the Danish Health Authority and published in 2000, 2005, 2010 and 2016, respectively, including guidelines and policy recommendations regarding cancer treatment and cancer rehabilitation
- The "Cancer-packages" (91)(in Danish: "Kræftpakker"), which describe standardized pathways from suspected disease until diagnosis, treatment, rehabilitation, and/or palliation. These packages have been established for a number of selected cancer diseases to increase and ensure the quality of cancer treatment and rehabilitation in Denmark. The development of these cancer packages was based on objectives in Cancer Plan II.
- The "Disease management program for rehabilitation and palliation in cancer"(90) (in Danish: Forløbsprogram for rehabilitering og palliation i forbindelse med kræft), based on objectives in Cancer Plan III, was developed in 2012 and revised in 2018. The primary objective of this program is to describe the rehabilitative and palliative interventions in Denmark and the primary aim is to ensure the overall quality and coherence of the interventions.

3.0 Aims

The overall aim of the present dissertation was to contribute with new knowledge regarding the role of SE and physical activity within the area of occupational rehabilitation of cancer survivors.

The specific aims were:

1) To evaluate the psychometric properties of the 19-item RTWSE questionnaire in employees with cancer on sick leave in relation to reliability, validity and responsiveness (Study I).

2) To examine the predictive value of RTWSE on RTW during 15 months of follow-up in a sample of sick-listed employees undergoing chemotherapy for various cancers and furthermore, to examine the relative contribution of RTWSE as predictor variable compared to personal, health-, illness-, treatment-, and work-related factors (Study II).

3) To examine the association between physical activity and work status in employees undergoing treatment for cancer, and furthermore, to examine the mediating role of RTWSE in this association (Study III).

4.0 Methods

In this section, the methods of the three studies will be presented. An overview of the study designs is presented in Table 1. The three studies were based on two different study populations. Study I (light grey, Table 1) was based on a sample of cancer survivors recruited from the Body and Cancer programs at Aarhus University Hospital, Aalborg University Hospital and Vejle Hospital, Denmark, between September 2017 and August 2018. Studies II and III (dark grey, Table 1) were based on a population of cancer survivors initiating chemotherapy at Department of Oncology, Aarhus University Hospital, Denmark, between November 2016 and May 2018.

Table 1 Overview of designs, study populations, sample sizes, primary variables, and statistical analyses

Study	Design	Study population	N	Primary dependent variable	Primary independent variable	Statistical analyses
I	Validation study	Cancer survivors participating in the Body and Cancer programs in Aarhus, Aalborg and Vejle, September 2017 – August 2018	68	Return to work self-efficacy total scale and three subscales: "Meeting job demands", "Modifying tasks", and "Communicating needs".		Reliability: Cronbach's alpha, Intraclass Correlation Coefficient (ICC), Standard Error of Measurement (SEM) Bland-Altman plot, Limits of Agreement (LOA) Construct validity: Spearman's correlation analyses Responsiveness: Spearman's correlation analyses, Smallest Detectable Change (SDC)
II	Prediction study	Cancer survivors initiating chemotherapy at Aarhus University Hospital, November 2016 - May 2018	114	Return to work during 15 months of follow-up from baseline	Return to work self-efficacy	Cox proportional hazards regression analyses (Unadjusted and multivariate analyses) Cumulative incidence curves (Aalen Johansen)
III	Prospective observational study	Cancer survivors initiating chemotherapy at Aarhus University Hospital, November 2016 - May 2018	217	Work status, measured at 12 months after baseline	Physical activity	Logistic regression analyses (unadjusted and multivariate analyses) The Sobel Goodmann test

As the study populations and data sources were distinctive for Study I compared to the studies II and III, which were based on the same survey study, the methods of the studies will be presented according to the study populations. Initially, aim, methods, variables of interest and statistics of Study I will be presented followed by a description of methods, variables of interest, aims and statistics of Study II and Study III within the same section. Finally, ethical approvals of the studies will be presented.

4.1 Study I: The validation study

4.1.1 Aim

To evaluate the psychometric properties of the 19-item RTWSE questionnaire in employees with cancer on sick leave in relation to reliability, validity and responsiveness.

4.1.2 Methods

Design and setting

The validation study was based on a sample of 68 cancer survivors, participating in the Body and Cancer programs at Aarhus University Hospital, Aalborg University Hospital or Vejle Hospital, Denmark, between September 2017 and August 2018. The Body and Cancer program is a six-week group-based exercise program which is offered to cancer survivors as a supplement to chemotherapy. In the present study, the participants were followed for three months, completing questionnaires at the initiation of the program (baseline, t1), after one week (t2) and after three months (t3).

Inclusion criteria and procedure

The Body and Cancer program is an existing program at the three hospitals. Participation in the program requires a referral from the treating oncologist using the following inclusion criteria: I) undergoing chemotherapy, II) >18 years of age, III) good performance status (WHO: 0-1)(125), and IV) able to understand Danish. Exclusion criteria: brain tumors, brain and bone metastases, and acute coronary syndrome (88). Participants of the Body and Cancer program were eligible for Study I if they were employed and on full time sick leave at time of inclusion.

At initiation of the Body and Cancer program, the program staff, consisting of nurses and physiotherapists, identified and invited eligible cancer survivors to participate in the study by a short oral introduction and a written information folder (see information folder in appendix 5).

Based on guidelines regarding validation studies (7), a sample size of >50 participants was the predefined aim. In total, 69 cancer survivors were included in the study of whom 68 completed the baseline questionnaire. Hence, the study sample thus consisted of 68 cancer survivors (60 women and eight men) undergoing chemotherapy. The completion of the questionnaires at t1 and t2 was managed by the program staff of the Body og Cancer program at the training facilities during the first (t1) and second

week (t2) of the program. At t3, questionnaires were sent by regular mail to the participants together with a prepaid return envelope. A reminder e-mail was sent after 14 days in case of no response.

4.1.3 Variables of interest

Table 2 gives an overview of the variables of interest in the validation study.

Table 2 Variables of interest in the validation study

Data source	Variables of interest	Data
Questionnaire	Return to work self-efficacy	The 19-item Return-To-Work Self-Efficacy questionnaire (RTWSE-19)(27,110), measuring an individual's expectation regarding own ability to RTW. Each item is scored on an 11-point scale (0 = not at all certain, 10 = completely certain). The questionnaire includes a total scale and three subscales: "Meeting job demands" (7 items), "Modifying tasks" (7 items), and "Communicating needs" (5 items). Mean scores are calculated by dividing the total sum of the scale by the number of completed items. Total mean scores range from 0 to 10. RTWSE scores are considered as low (<5), moderate (5-7.5) or high (> 7.5). The questionnaire showed high internal consistencies (Cronbach's alpha) in a Danish population: 0.93 ("Communicating needs"), 0.94 ("Modifying tasks"), and 0.97 (total scale and "Meeting job demands") (27). In case of >20% missing values, total and subscale scores were defined as missing (7)
	Cancer-related self-efficacy	The Cancer Behavior Inventory (CBI) (126-128), a 14-items questionnaire measuring an individual's expectation of being able to handle the cancer disease and the treatment-related side-effects. Each item is scored on a 9-point numerical rating scale (1 = not at all certain, 9 = completely certain). Higher total sum score indicates higher cancer-related SE. Acceptable Cronbach's alpha coefficients ranging from 0.84 to 0.88 has been shown in a population of patients with various cancer diagnoses (126). Missing items were handled using the method of mean imputation, but only in cases with high internal consistency (Cronbach's alpha >0.70) for the total scale(129).
	Psychological distress	The Hospital Anxiety and Depression Scale (HADS) (130,131), a two subscale questionnaire with seven items measuring anxiety and seven items measuring depression. Each item is scored 0-3. According to guidelines, sum scores were categorized as: none (0-7), mild (8-10) or severe (11-21) anxiety or depression, respectively. In a population of women with breast cancer, the HADS anxiety scale and the HADS depression scale have shown Cronbach's alpha values of 0.79 and 0.87, respectively (132).
	Work ability	The Work Ability Index (WAI)(133,134), a questionnaire with three single items, measuring 1) general work ability on a scale ranging from 0 (not able to work) to 10 (the best work ability ever), 2) physical work ability on a scale ranging from 1 (very bad) to 5 (very good), and 3) mental work ability on a scale ranging from 1 (very bad) to 5 (very good).
	Global Perceived Change question	A single item measuring perceived change since baseline regarding expected ability to RTW, with options of response ranging from –6 (much worse) to +6 (much better) and with 0 indicating no change (7). Stable expectations of RTW were defined by the research team as scores of -1, 0, and +1.
	Sociodemographic variables	
	Age	Years
	Gender	Male, female
	Primary and secondary education	7th grade, 8th-9th grade, 10th grade, lower secondary education, upper secondary education
	Professional education	No vocational education, < 3 years vocational education, vocational education, short-/medium-cycle higher education (3-4 years), bachelor's degree (3-4 years), long-cycle higher education/PhD (>4 years)
	Work type	Physical, sedentary, mixed
	Sick leave	On full time sick leave, not on sick leave, part time sick leave
	Illness- and treatment-related variables	
	Diagnosis	Breast cancer, other cancer diagnoses
	Treatment modalities	Chemotherapy, surgery, radiotherapy

All variables were included in the questionnaire at t1 and t3. At t2, only the RTWSE-19 and the Global Perceived Change question were included (see questionnaire I, II and III in appendix 5).

The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN)(5,7,8) guided the design of the study. The study included examination of the reliability, the validity and the responsiveness of the RTWSE-19 questionnaire.

4.1.4 Statistics

Floor and ceiling effects of the RTWSE-19 were analyzed based on the percentage of participants achieving the lowest (i.e., 0) or the highest (i.e., 10) possible score on the total as well as the subscales. Floor and ceiling effects were found if >15% achieved the lowest or the highest score, respectively

Reliability

Reliability was examined by internal consistency and by test-retest reliability. Internal consistency, referring to the interrelatedness of the items in a questionnaire, was examined by Cronbach's alpha (7,135). According to guidelines, a Cronbach's alpha value between 0.70 – 0.95 indicated good internal consistency (7).

In examining the test-retest reliability, the time between test and retest was one week (t1-t2). According to the definition of reliability as *"the extent to which scores for patients who have not changed are the same for repeated measurements"* (7), only the participants who rated themselves as stable regarding their expectations of RTW at t2 (i.e., ratings of -1, 0 or +1 on the Global Perceived Change question) were included in the test-retest reliability analyses. The test-retest reliability was measured by Intraclass Correlation Coefficient (ICC) and by Standard Error of Measurement (SEM) (7). According to guidelines (7), ICC values >0.90 indicated excellent intraclass correlation.

The $ICC_{agreement}$ and the $SEM_{agreement}$ were used as they include the systematic differences in the measurement errors. $IIC_{agreement}$ and $SEM_{agreement}$ are defined as:

$$ICC_{agreement} = \frac{\sigma_p^2}{\sigma_p^2 + \sigma_o^2 + \sigma_{recidual}^2} \qquad SEM_{agreement} = \sqrt{\left(\sigma_o^2 + \sigma_{recidual}^2\right)}$$

By use of Bland-Altman plots, the test-retest reliability was further illustrated by showing the differences in RTWSE-19 scores between t1 and t2 (t2-t1) plotted against the mean RTWSE-19 scores of t1 and t2. In the Bland-Altman plots, the 95% limits of agreement (LOA) were also estimated and illustrated.

Validity

The construct validity of the RTWSE-19 was assessed by testing predefined hypotheses regarding correlations between RTWSE-19 scores and scores of other questionnaires measuring constructs, which were hypothesized to be associated with RTWSE. Correlation coefficients were considered small (0.1 - 0.2), medium (0.3 - 0.4), or large (>0.5)(136).

The following hypotheses of correlations were defined based on a theoretical background of RTWSE (13) and previous research (for a thorough argumentation for the hypotheses, see Study I, appendix 1):

1. A large positive correlation (>0.5) between RTWSE-19 and cancer-related SE (13,113,137)
2. A large positive correlation (>0.5) between RTWSE-19 and Mental Work Ability

(13,109,110,112,114)

3. A medium positive correlation (>0.3) between RTWSE-19 and General Work Ability (13,109,110,112,114)
4. A medium positive correlation (>0.3) between RTWSE-19 and Physical Work Ability (13,109,110,112,114)
5. A medium negative correlation (>-0.3) between RTWSE-19 and depression (12,13,113)
6. A medium negative correlation (>-0.3) between RTWSE-19 and anxiety (12,13,113)
7. No correlation (<0.1) between RTWSE-19 and the test date.

Responsiveness

Responsiveness, referring to the ability of an instrument to detect change over time in the construct being measured (7), was assessed by means of the criterion approach, the Smallest Detectable Change (SDC), and the construct approach.

The criterion approach refers to an anchor-based method in which a global rating scale, in the present case a Global Perceived Change question, is used as a golden standard for change (7). According to the personal Global Perceived Change ratings at t3, the participants were categorized in groups (13 groups in total, from -6 till +6); all participants with a Global Perceived Change rating of -6 in one group, of -5 in another group etc.. Subsequently, the mean change score of the RTWSE-19 total scale between t1 and t3 of the participants in each group was calculated. The more positive expectations regarding RTW on the Global Perceived Change question, the higher positive RTWSE-19 change scores were anticipated, and likewise, the more negative expectations regarding RTW on the Global Perceived Change question, the higher negative RTWSE-19 change scores were anticipated.

The SDC referring to the change beyond measurement error (7), was assessed by identifying the values for the 95% LOA in the Bland-Altman plots in the test-retest analyses, as scores outside the LOA are likely to refer to real change. The SDC refers to changes larger than: $d \pm 1.96 \times SD_{difference}$ where d refers to the systematic error and $1.96 \times SD_{difference}$ to the random error.

As responsiveness is considered an aspect of validity (7), the construct approach was used to evaluate the validity of the change scores of the RTWSE-19. Predefined hypotheses regarding correlations between change scores in RTWSE-19 from t1 to t3 and change scores in cancer-related SE (CBI) and work ability (WAI), respectively, from t1 to t3 were investigated. The following hypotheses were defined based on a theoretical background of RTWSE (13) and previous research (for a thorough argumentation of the hypotheses, see Study I, appendix 1):

8. A large positive correlation (>0.5) between change scores in RTWSE-19 from t1 to t3 (t3-t1) and change scores in cancer-related SE from t1 to t3 (t3-t1) (13,83,138).
9. A large positive correlation (>0.5) between change scores in RTWSE-19 from t1 to t3 (t3-t1) and

change scores in Mental Work Ability from t1 to t3 (t3-t1) (12,13,83,110,114,119).

10. A medium positive correlation (>0.3) between change scores in RTWSE-19 from t1 to t3 (t3-t1) and change scores in General Work Ability from t1 to t3 (t3-t1) (12,13,83,110,114,119).
11. A medium positive correlation (>0.3) between change scores in RTWSE-19 from t1 to t3 (t3-t1) and change scores in Physical Work Ability from t1 till t3 (t3-t1) (12,13,83,110,114,119).

4.2 Studies II and III: The prediction study and the prospective observational study

Studies II and III were both prospective observational studies based on the same study population and the same data set, including data from patient questionnaires, patient records and Danish national registers. Initially, the study population and the complete data set will be presented, followed by the specific designs and variables of interest for Study II and Study III, respectively.

4.2.1 Methods

Design and setting

Studies II and III were based on a population of employees with various cancers, initiating chemotherapy at Aarhus University Hospital, Denmark, between November 2016 and May 2018, and invited to participate in a prospective, observational study regarding physical activity and work life. Participants were followed for 12 (Study III) and 15 (Study II) months, respectively, combining data from patient outcome questionnaires, patient records and Danish national registers. The participants were asked to complete questionnaires at baseline, at three months, six months, and 12 months.

Inclusion criteria

Patients were considered eligible based on the following inclusion criteria: I) 18-62 years of age, II.a) initiating chemotherapy for a newly diagnosed cancer disease, or II.b) due to relapse, if the patient had not initiated chemotherapy for a previous or current cancer during the last 24 months, III) all treatment intentions (i.e., curative, palliative, adjuvant and neo-adjuvant), IV) employed at the time of inclusion (working, on full, or on part time sick leave), and V) ability to read and understand Danish.

Procedure

A stepwise inclusion procedure was followed. First, the Clinical Trial Unit at Aarhus University Hospital identified eligible patients with regard to age and history of cancer. At the initiation of the first chemotherapy cycle, a clinical nurse gave eligible patients a short oral introduction to the study and a package including a study information folder (see appendix 6), a contact sheet (including two options of which the patient had to mark one; either a consent for receiving a phone call from a research assistant to learn more about the study or a decline to participate in the study), and a written informed consent (final consent for participating in the study). If the nurses during the first chemotherapy session considered an eligible patient to be incapable of receiving additional information beyond treatment-

related information, they postponed the introduction until second or third treatment session. Eligible patients who were interested in learning more about the project signed the contact sheet allowing a research assistant to contact the patient by telephone. On the phone, the research assistant screened the patients regarding employment status and provided additional information about the project. Written informed consent was retrieved from those who were eligible and wanted to participate. Subsequently, a baseline questionnaire was send by e-mail or regular mail in accordance with the patient's preference. Finally, after having returned the baseline questionnaire, the patients were included. At three, six, and 12 months, a similar questionnaire without the demographic items was distributed. In case of no response, two reminder e-mails were sent after five and ten days, respectively.

Population

As shown in the flowchart of inclusion (Figure 5), a total of 4,105 cancer survivors initiated chemotherapy at Aarhus University Hospital during the inclusion period. Initial exclusion due to age and history of cancer treatment and secondary exclusion by hospital staff resulted in a total of 816 patients eligible to receive an invitation to participate in the study. Of these, 312 (38%) accepted to be contacted by phone; 29 were unreachable by phone and 57 were excluded due to being unemployed at the time of inclusion (n=55) and being withdrawn from chemotherapy (n=2). A total of 228 cancer survivors agreed to participate. Among these, 11 did not respond to the questionnaire, leading to a baseline population of 217 cancer survivors completing the baseline questionnaire.

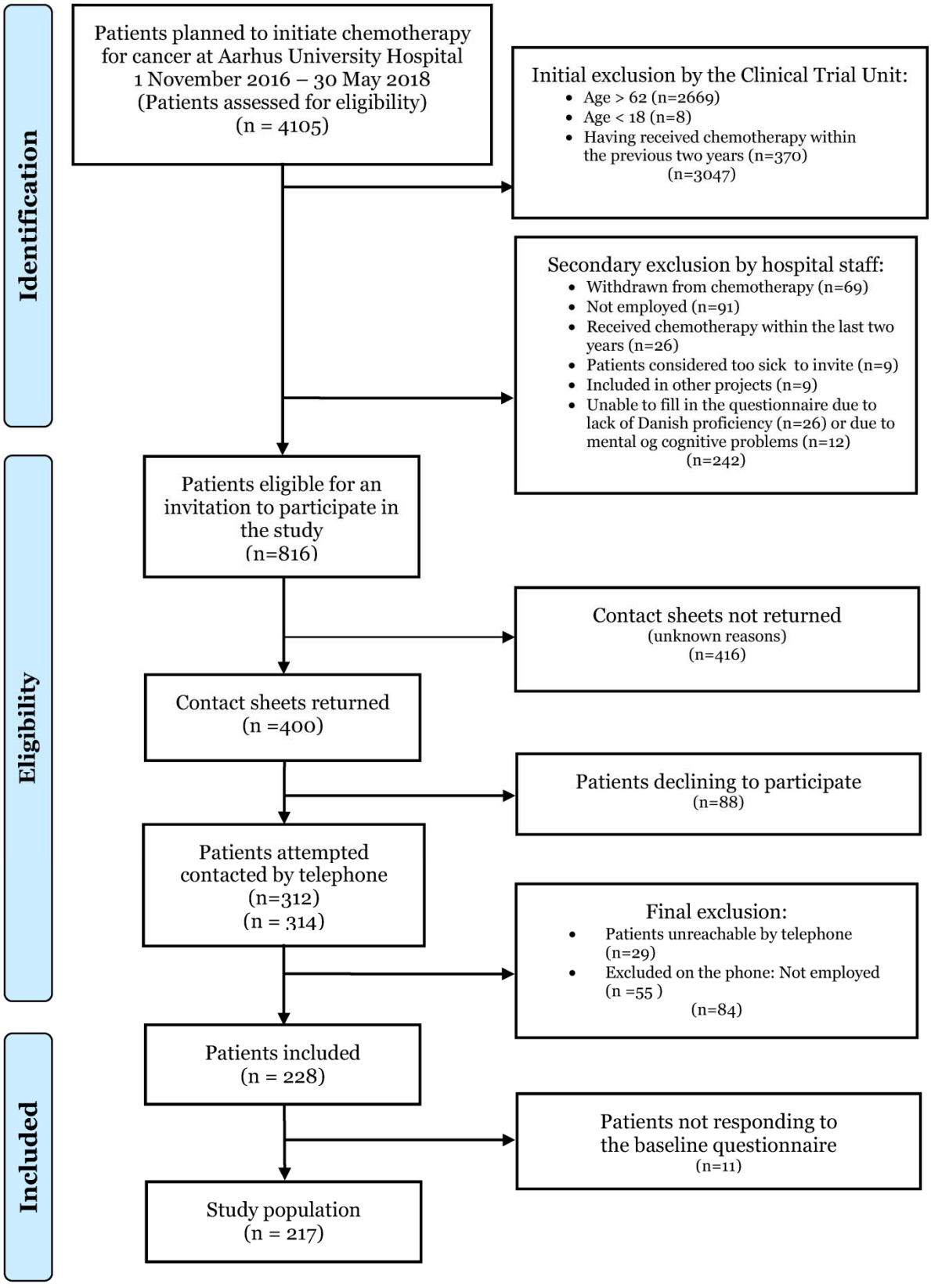

Figure 5 Flow chart of inclusion

4.2.2 Data sources

An overview of the complete data set is presented in Table 3. The complete questionnaire is accessible in appendix 6.

Table 3 Overview of the full data set: Data sources, variables of interest and data used in studies II and III

Data source	Variables of interest	Data	Study
DREAM register	Return to work / work status	Data regarding RTW and work status was obtained from the "Danish Register for Evaluation of Marginalization" (DREAM), containing information on all public transfer payments to adult Danish citizens since august 1991(139,140). The public transfer payments are registered on a weekly basis by means of three-digit codes describing if any kind of public transfer payment is granted. In case of no registration, the citizen is categorized as being self-supporting. Using data from DREAM has proven valid for research of sickness absence and RTW (141).	II and III
The Danish Education Register of Statistics Denmark	Education	Four levels based on the highest level of completed education; I) none: <10 years of education, II) short: 10-12 years of education, III) moderate: 13-15 years of education, and IV) long: >15 years of education (142).	II and III
Questionnaire	Pre-illness level of physical activity in the leisure time	The pre-illness level of physical activity refers to the level of leisure time physical activity one year prior to the cancer diagnosis and was measured by the The Saltin-Grimby Physical Activity Level Scale (143). This scale was originally a four-level self-assessment scale of leisure time physical activity. However, based on recommendations by Grimby (144), the original level III "low intensity physical activity >4 hours/week or vigorous physical activity for 2–4 hours/week" was spilt into two levels, level III and IV. Thus, in the present study the scale consisted of a five level self-assessment scale, in which the participants, based on their leisure time physical activity level over the past 12 months, were asked to categorize themselves according to one of five levels: I) sedentary or < 2 hours low intensity physical activity/week, II) low intensity physical activity 2-4 hours/week, III) low intensity physical activity >4 hours/week, IV) vigorous physical activity for 2–4 hours/week, or V) vigorous physical activity >4 hours/week. The scale has been shown to have good concurrent validity (144), including in Denmark (145).	III
	Current level of physical activity in the leisure time	The Saltin-Grimby Physical Activity Level Scale (143) was used to measure the current level of physical activity in the leisure time, using the same five categories as mentioned above.	III
	Current level of daily physical activity	The International Physical Activity Questionnaire, long version (IPAQ-long) (146), a 15-item questionnaire measuring physical activity in four domains: Work, transportation, housework/gardening and leisure time. Duration (hours and minutes) and frequency (number of days) of physical activity during the past seven days are reported for all four domains and within each domain at three different levels (low, moderate and high). The amount of physical activity reported is subsequently converted into MET (Metabolic Equivalent of Task) minutes/week and further into categories of total physical activity at either low (below 600 MET minutes/week), moderate (600-3000 MET minutes/week) or high (at least 3000 MET minutes/week) level; 600 MET minutes/week equals on average 30 minutes physical activity daily and hence, the recommended level of physical activity across health boards (146). The questionnaire is found reliable and valid across countries (147), including Denmark (148).	III
	Return to work self-efficacy	As in Study I, RTWSE was measured by means of the RTWSE-19 questionnaire (109,110). For a description of the questionnaire, see section 4.1.3.	II and III
	Depression	Beck's Depression Inventory (BDI) (149), consisting of 21 items, was used to measure depression. According to guidelines, the total sum score of 63 is categorized into; no depression (0-13), mild depression (14-19), moderate depression (20-28), or high depression (29-63). The BDI is a valid measure of depression (150) with a Cronbach's alpha value of 0.90 shown in a cancer population (52).	II
	Fatigue	Fatigue was measured by the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), version 4. A five point scale ranging from 0 (not at all) to 5 (very much) is used to score each item. The total sum score is between 0 - 52 with higher scores referring to higher levels of fatigue (151). Good validity and reliability in cancer populations has been shown with Cronbach's alpha values >0.93 (152,153).	II

Data source	Variables of interest	Data	Study
	Performance status	Performance status was measured by the 1-item performance scale, developed by the Eastern Cooperative Oncology Group (ECOG)(125). Participants categorized themselves in one of five levels: 0) fully active, able to carry on all pre-disease performance without restriction; I) restricted in strenuous activity but able to carry out work of a light nature; II) capable of all self-care but unable to carry out any work activity, up and about for >50% of the time; III) capable of only limited self-care, in bed for >50% of the time, or IV) cannot carry out any self-care, totally confined to bed or chair.	II and III
	Cancer-related self-efficacy	As in Study I, Cancer-related self-efficacy was measured by means of the Cancer Behavior Inventory (CBI) (126-128). For a description of the questionnaire, see section 4.1.3.	-
	Health-related quality of life	Health-related quality of life was measured by the widely used EQ-5D-3L (154), a five single items questionnaire covering five areas: Mobility, self-care, usual activities, pain/discomfort, anxiety/depression, in which the respondent rate their own health status according to three levels of severity (154,155). The scale has been found valid and reliable in cancer populations (156).	-
	Sociodemographic variables		
	Age	Years (obtained by the individual's civil registration number)	II and III
	Gender	Male, female (obtained by the individual's civil registration number)	II and III
	Ethnicity	Danish, other	III
	Marital status	Living alone, married, living with parents, widower, divorced, has always lived alone	III
	Children living at home	Number of children living at home	III
	Level of education	No vocational education, < 3 years vocational education, vocational education, short-/ medium-cycle higher education (3-4 years), bachelor's degree (3-4 years), long-cycle higher education/PhD (>4 years)	II and III
	Job type	Physical, sedentary, mixed	II and III
	Leaderships tasks	Yes, no	III
	Self-employed	Yes, no	III
	Perceived support from the workplace	A 10-point rating scale with 10 indicating the highest level of perceived support	II and III
Patient records	Illness- and treatment-related variables		
	Type of cancer	Female reproductive system, breast, lung incl. mesotheliomas, urological incl. male reproductive system, upper gastrointestinal, colorectal, cerebral and the central nervous system, other	II and III
	Treatment intention	Curative, palliative, adjuvant, neo-adjuvant	II and III
	Treatment modalities besides chemotherapy	Chemotherapy, Chemotherapy and one additional treatment modality, Chemotherapy and two additional treatment modalities	II and III
	Time since diagnosis	Days	II and III
	Time since initiation of chemotherapy	Days	II and III

Data from patient questionnaires and patient records were obtained at baseline, three months, six months and 12 months, except for the sociodemographic variables and the pre-illness level of physical activity which were only obtained at baseline.

4.3 Study II: The prediction study

4.3.1 Aim

To examine the predictive value of RTWSE on RTW during 15 months of follow-up in a sample of sick-listed employees undergoing chemotherapy for various cancers and furthermore, to examine the relative contribution of RTWSE as predictor variable compared to personal, health-, illness-, treatment-, and work-related factors.

4.3.2 Methods

Design

In an observational prospective design, the participants were followed for 15 months combining data from patient questionnaires and patient records obtained at baseline and data from Danish national registers obtained during 15 months of follow-up.

Population

The total baseline population in the survey study was 217 cancer survivors (see Figure 5). Two additional inclusion criteria were added in the present study (see Figure 6); on full time sick leave at baseline and time of follow-up ≥15 months. Thus, 82 were excluded due to working at baseline, 18 patients were excluded due to incomplete follow-up time (<15 months), and three participants were excluded due to missing data on the primary independent variable, RTWSE. The final study population in Study II thus consisted of 114 participants (N=114).

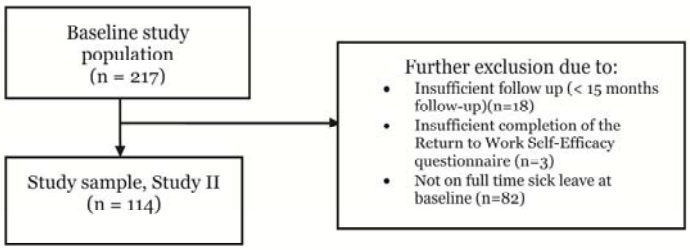

Figure 6 Flow chart of inclusion

Variables of interest

The dependent variable

Return to work

The primary independent variable in Study II was RTW during 15-months of follow-up defined as the first week of at least four successive weeks of financial self-support according to DREAM. Thus, in the present study, four successive weeks of being self-supported was regarded as having returned to work. Defining RTW as *four successive* weeks of self support was chosen I) to ensure that the RTW was without relapse for at least four weeks, i.e., sustainable RTW, and II) to ensure comparability with previous

studies investigating the predictive value of RTWSE (111,114). Death and permanent exit from the labor market (retirement and disability pension) were treated as competing risks during follow-up.

Independent variables

The following independent variables were included:

- *RTWSE* (dichotomized at the highest tertile, i.e., 7.5, originally reported by Shaw (110). Participants with a total mean score ≤7.5 were thus considered low in RTWSE and participants with a total mean score >7.5 as high in RTWSE)
- The following health-related variables: *depression, fatigue, and performance status*
- The following illness- and treatment-related variables: *type of cancer, treatment intention, number of treatment modalities in addition to chemotherapy, time since diagnosis, time since initiation of chemotherapy*
- The following work-related variables: *job type* and *perceived support from the workplace*
- The following sociodemographic variables: *age, gender, and level of education.*

Only the baseline measurements of the independent variables were used. RTWSE was the primary independent variable, and the remaining were used as covariates in the statistical analyses.

4.3.3 Statistics

Average numbers of days until full RTW and cumulative incidence curves for full RTW during 15 months of follow-up were calculated for the low RTWSE group and the high RTWSE group, respectively.

To compare rates of RTW in the two groups, unadjusted and adjusted hazard ratios (HR) were calculated by means of Cox proportional hazards regressions with RTWSE as the independent variable and weeks to full RTW as the dependent variable. HR values >1 indicated shorter time to RTW. Evaluation of the assumption of proportional hazards was made by means of log-minus-log survival curves and by observed and fitted survival curves (results not shown).

The Cox proportional hazards regression analyses were completed stepwise. Initially, the unadjusted model was calculated followed by bivariate Cox proportional hazards regression analyses examining the associations between each of the covariates and RTW. Covariates showing statistically significance at $p<0.20$ in the bivariate analyses, were subsequently added as covariates in the multivariate Cox proportional hazards regression models according to the following plan: in model 2, the sociodemographic variables were added; in model 3, the illness- and treatment-related variables were further added; and in model 4, the health- and work-related variables were further added.

A significance level of p<0.20 in the bivariate Cox regression analyses was in line with existing research (111,114) and chosen to ensure inclusion of all relevant covariates in the following multivariate models. A lower threshold might have resulted in exclusion of potential predictor variables. The predictor variables finally included in the multivariate model were checked for multicollinearity using the variance inflation factor (VIF); VIF values >5 indicated multicollinearity (157). In the multiple Cox regression models, the level of statistical significance was 5%. During follow up, permanent exit from the labor market and death were considered competing risks.

4.4 Study III: The prospective observational study

4.4.1 Aim

To examine the association between physical activity and work status in employees undergoing chemotherapy for cancer, and furthermore, to examine the mediating role of RTWSE in this association.

This was investigated by examining the following three objectives:

1. the association between physical activity and work status at baseline
2. the association between physical activity reported at baseline, and work status at 12 months after baseline
3. the mediating role of RTWSE, measured at three months, in the possible association between physical activity reported at baseline, and work status at 12 months after baseline

4.4.2 Methods

Design

In Study III, the participants were followed for 12 months combining data from patient questionnaires completed at baseline and at three months, data from patient records obtained at baseline, and data from Danish national registers obtained at baseline and at 12 months.

Population

In Study III, the entire baseline population of the survey study were included, i.e., 217 cancer survivors (Figure 5).

Variables of interest

Dependent variable

Work status

The primary dependent variable was work status as recorded in the DREAM register. Data regarding work status was obtained at baseline and at 12 months and defined as either: I) "at work" or II) "not at work". "At work" included those with no registration in DREAM (the self-supported).

Thus, in the present study, being self-supported was regarded as working. At baseline, "not at work" included those receiving any kind of sickness absence compensation. At 12 months follow-up, "not at work" included receiving any kind of sickness absence compensation, permanent exit from the labor market (retirement and disability pension), and death.

Independent variables

The following independent variables were included:

- Physical activity, measured by three variables: *The pre-illness level of leisure time* physical activity (pre-illness $PA_{leisure}$), *the current level of leisure time physical activity* (current $PA_{leisure}$) and *the current level of daily physical activity* (current PA_{daily})
- *RTWSE* (dichotomized at the highest tertile, i.e., 7.5, originally reported by Shaw (110). Participants with a total mean score ≤7.5 were thus considered low in RTWSE and participants with a total mean score >7.5 as high in RTWSE)
- *Performance status*
- The following sociodemographic variables: *age, gender, ethnicity, level of education, marital status, children living at home, job type, having leadership tasks, being self-employed, and perceived support from the workplace*
- The following illness- and treatment-related variables: *type of cancer, time since diagnosis, time since initiation of chemotherapy, number of treatment modalities in addition to chemotherapy, and treatment intention.*

The independent variables were obtained at baseline and at three months.

4.4.3 Statistics

Statistics are presented according to the three objectives of the study:

Objective 1: Associations between physical activity and work status at baseline

Using logistic regression, the Odds Ratios (ORs) for the associations of pre-illness and current level of PA, respectively, with work status at baseline were estimated. An unadjusted analysis was conducted in model 1. Subsequently, the multivariate analyses were performed according to the following predefined plan: In model 2, the following sociodemographic variables were added: gender, age, and educational level; in model 3, the following illness- and treatment-related variable was added: treatment intention; and in model 4, the functional variable performance status was added.

In order to minimize the number of variables in the multiple models, the following categorical covariates were dichotomized: educational level (none/short versus moderate/long), treatment intention (palliative versus curative/adjuvant/neo adjuvant), and performance status (level 0 versus ≥1).

Objective II: Associations between physical activity at baseline and work status at 12 months
Using logistic regression, the ORs for the associations of pre-illness and current level of physical activity with work status at 12 months were estimated. An unadjusted analysis was conducted in model 1. Subsequently, the multivariate analyses were performed according to the following predefined plan: In model 2, the following sociodemographic variables were added: gender, age, educational level, and baseline work status; in model 3, the following illness- and treatment-related variable was added: treatment intention; and in model 4 the functional variable performance status was added. Baseline work status was added as a covariate in model 2, as previous sick leave has shown to be negatively associated with work status (158). As in objective I, the categorical covariates were dichotomized.

Objective III: The mediating role of RTWSE
The mediating role of RTWSE, measured at three months, was investigated by means of the Sobel Goodmann test but only in the cases of significant associations between physical activity measured at baseline and work status at 12 months (objective II). Before conducting the Sobel Goodmann test, essential preconditions were tested: In order for RTWSE to be a mediator, significant associations between RTWSE (the potential mediator) and a) the independent variable (physical activity, baseline) and b) the dependent variable (work status, 12 months), respectively, were required. Only when the significance of these associations were confirmed, the Sobel Goodmann test was carried out.

4.5 Ethical approvals

Oral and written informed consent was obtained from all participating cancer survivors in the studies. The studies were approved by the Danish Data Protection Agency (j.no.1-16-02-729-17 (Study I) and j. no. 1-16-02-45-16 (studies II and III)). The studies did not include biological material or biomedical treatments and hence, approval from the Central Denmark Region Committee on Health Research Ethics was not relevant according to current Danish law (request no. 143/2017 (Study I) and request no. 82/2016 (studies II and III)).

5.0 Results

The present section provides a summary of the results of studies I, II and III.

5.1 Results: Study I, The validation study

The study sample included 60 women and eight men. Table 4 presents baseline sociodemographic and clinical characteristics of the participants.

Table 4 Sociodemographic and clinical characteristics of the participants in a three-months follow-up study validating the Danish version of the Return To Work Self-Efficacy questionnaire (RTWSE-19)

	Mean (SD), range
Sociodemographics	
Age (years)	47 (9,69), 26-68
Missing	0
	N (%)
Gender	
Female	60 (88)
Male	8 (12)
Educational Level	
Low	15 (22)
Middle	31 (46)
High	22 (32)
Work Type	
Manual	11 (16)
Non-manual	32 (47)
Mixed	22 (32)
Missing	3 (5)
Clinical characteristics	
Diagnosis	
Breast	41 (60)
Other	26 (38)
Missing	1 (2)
Treatment	
Chemotherapy	30 (44)
Chemotherapy, surgery	25 (37)
Chemotherapy, surgery, radiotherapy	13 (19)
Place of treatment	
Aarhus University Hospital	31 (46)
Aalborg University Hospital	23 (34)
VejleHospital	14 (20)

SD: Standard Deviation

5.1.1 Descriptive statistics

The means and standard deviations (SD) of the total scale and the three subscales are presented in Table 5. In the "Communicating needs" subscale, a ceiling effect occurred as 20.59% (95%CI: 11.74-32.12) of the participants had the highest possible score. No other ceiling or floor effects were found.

Table 5 Baseline scores with analysis of internal consistency and floor and ceiling effects of the Return To Work-Self-Efficacy-19^{DK} questionnaire. The table shows mean, SD, median, interquartile range, Cronbach's alpha and % of participants achieving the lowest and highest score, respectively. Confidence Intervals (CI) are shown in parentheses.

Scales	N	Mean (95% CI)	SD_{mean}	Median (95% CI)	IQR	Cronbach's alpha	Floor effect (97.5% CI)* (% of participants achieving the lowest score)	Ceiling effect (95% CI) (% of participants achieving the highest score)
Total scale	68	7.25 (6.74-7.76)	2.10	7.47 (6.99-8.66)	3.32	0.97	0 (0-5.28)	5.88 (1.63-14.38)
Meeting job demands	67	6.60 (5.95-7.24)	2.64	7.57 (6.14-8.00)	4.43	0.97	0 (0-5.36)	7.46 (2.47-16.56)
Modifying tasks	68	7.06 (6.50-7.62)	2.32	7.43 (6.71-8.33)	3.07	0.92	0 (0-5.28)	5.88 (1.63-14.38)
Communicating needs	68	8.44 (8.02-8.87)	1.75	9.00 (8.48-9.40)	2.00	0.90	0 (0-5.28)	20.59 (11.74-32.12)

SD: Standard deviation
IQR: Interquartile range
CI: Confidence Interval
* One-sided, i.e. 97.5 % CI

Table 6 Test and retest reliability of the Return To Work Self-Efficacy-19^{DK} questionnaire (RTWSE-19 ^{DK}) with a mean time between test and retest of 8.88 days (SD = 3.71). The table shows means and SD of scores at t1 and t2, differences of means with SD, Intraclass Correlation Coefficients (ICC), and Standard Error of Measurement (SEM). Confidence Intervals (CI) are shown in parentheses

Scales	N	Time 1 (t1) Mean (SD)	Time 2 (t2) Mean (SD)	Difference between t1 & t2 Mean (95% CI)	$SD_{difference}$	ICC (95% CI)	SEM
Total scale	49	7.11 (2.09)	6.84 (2.09)	0.27 (0.01 – 0.53)	0.89	0.90 (0.85-0.95)	0.65
Meeting job demands	48	6.38 (2.75)	6.18 (2.62)	0.21 (-0.14 – 0.55)	1.19	0.90 (0.85-0.95)	0.85
Modifying tasks	48	6.86 (2.36)	6.66 (2.28)	0.19 (-0.15 – 0.54)	1.18	0.87 (0.80-0.94)	0.83
Communicating needs	49	8.46 (1.63)	8.13 (1.79)	0.34 (0.07 – 0.60)	0.91	0.84 (0.76-0.92)	0.68

t1 = time 1 (baseline), t2 = time 2 (one week)
SD: Standard deviation
CI: Confidence Interval
ICC: Intraclass Correlation Coefficient
SEM: Standard Error of Measurement

5.1.2 Internal consistency

As seen in Table 5, Cronbach's alpha values ranged from 0.90 ("Communicating needs") to 0.97 ("The total scale" and "Meeting job demands"). Hence, the total scale as well as the three subscales all showed good internal consistencies.

5.1.3Test-retest reliability

Of the initial 68 participants at baseline, 67 (99%) returned the questionnaire at one week (t2). Yet, five questionnaires were incomplete (>20% missing values in the total scale of the RTWSE-19 questionnaire (n=2) or missing on the Global Perceived Change question (n=3)) and thus excluded. Additional 13 participants were excluded due to too high or too low ratings on the Global Perceived Change question at t2 (≤-2 or ≥+2) (Table 8). The final test-retest sample included 49 (72%) participants. The mean time between the test and the retest was 8.88 days (SD = 3.71) with a range of 6-20 days.

As shown in Table 6, the ICC values ranged from 0.84 (95% CI 0.76-0.92) ("Communicating needs") to 0.90 (95% CI 0.85-0.95) ("the total scale" and "Meeting job demands"), indicating high test-retest reliability on the total scale as well as the subscales. SEM values are also shown in Table 6.

Figure 7 shows the Bland-Altman plots, including the 95% LOA for the total scale as well as for the three subscales.

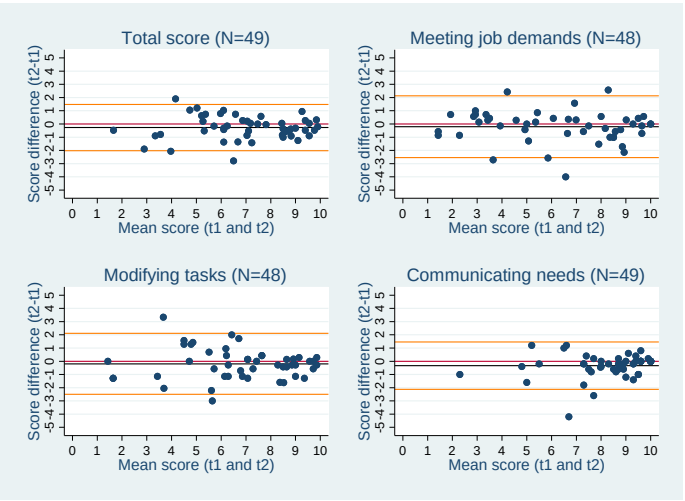

Figure 7 *Bland-Altman plot of score differences (t2-t1) of the total score and subscales (i.e. "Meeting job demands", "Modifying tasks" and "Communicating needs") of the Return To Work Self-Efficacy-19 against the mean scores (t1 and t2) in employees undergoing treatment for cancer. The black horizontal line correspond to the mean difference and the yellow horizontal lines to the 95% limits of agreement (LOA).*

Time 1 (t1)= Baseline, Time 2 (t2)= one week after baseline

5.1.4 Construct validity

Table 7 shows the correlation coefficients between the baseline scores of the RTWSE-19 total scale and scores of cancer-related SE, work ability, psychological distress and test date, respectively. The hypotheses regarding cancer-related SE (hypothesis 1), Mental Work Ability (hypothesis 2), General Work Ability (hypothesis 3) and test date (hypothesis7) were confirmed whereas hypotheses 4, 5, and 6

regarding correlations with Physical Work Ability and psychological distress (i.e., HADS depression and HADS anxiety), respectively, were not confirmed.

Table 7 Correlation between total scores at t1 and change scores at t3 (t3-t1), respectively, of the Return To Work Self-Efficacy-19 questionnaire (RTWSE-19) and cancer-related self-efficacy, work ability, depression, anxiety and test date, respectively.

	Return To Work Self-Efficacy-19			
	N	**Total score (t1) Rho**	**N**	**Change score (t3-t1) Rho**
Cancer Behavior Inventory (CBI), total score				
Cancer-related self-efficacy	68	0.54***	47	0.19
Work Ability Index (WAI)				
General Work Ability	68	0.35**	45	0.33*
Physical Work Ability	68	0.26*	48	0.35*
Mental Work Ability	68	0.51***	48	0.50***
Hospital Anxiety and Depression Scale (HADS)				
Depression score	68	-0.08	-	-
Anxiety score	68	-0.10	-	-
Test date (date of month)	68	0.03	-	-

*= p< 0.05, **= p< 0.01, *** = p<0.001
t1 = time 1 (baseline), t3 = time 3 (three months)

5.1.5 Responsiveness

Of the initial sample of 68 participants at baseline, 52 (76%) returned the questionnaire at three months (t3). However, four questionnaires were incomplete (>20% missing values in the total scale of the RTWSE-19 questionnaire) and were excluded, resulting in a sample of 48 participants (71%) at t3. The mean time from t1-t3 was 109 days (SD: 27.32, range: 86–207).

Table 8 Mean change between baseline (t1) and t2 and t3, respectively, of the Return To Work Self-Efficay-19^{DK} (RTWSE-19) total score categorized according to change in expectation of returning to work (GPC) at t2 and t3

Global Perceived Change (GPC) score	N	Mean change in the RTWSE-19 total scores Time 2 (N=62)	SD	N	Mean change in the RTWSE-19 total scores Time 3 (N=48)	SD
Low expectation						
-6	0	-	-	1	-2.00	0
-5	0	-	-	0	-	-
-4	0	-	-	0	-	-
-3	0	-	-	1	-3.89	0
-2	2	-0.94	0.07	3	-0.28	1.69
-1	5	0.16	1.02	5	-1.12	0.70
No difference	41	-0.32	0.90	19	0.07	1.29
1	3	-0.25	0.40	4	0.07	1.69
2	5	-0.68	0.41	5	-0.24	1.57
3	1	-0.16	0	3	2.04	3.48
4	2	-0.11	0.45	3	1.49	1.25
5	2	0.11	0.52	3	0.97	0.86
6	1	5.95	0	1	0.95	0
High expectation						

t1 = time 1 (baseline), t2 = time 2 (one week), t3 = time 3 (three months)
SD = Standard Deviation, RTWSE-19 : Return To Work Self-Efficacy-19

The criterion approach: Table 8 shows the mean change scores between t1-t3 of the RTWSE-19 total scale, categorized according to the participants' scores at the Global Perceived Change question at t3.

SDC: The values of the SDC were calculated by the LOA in the Bland Altman plot of the test-retest (Figure 7). The LOA ranged between -2.02 – 1.48 (the total scale), -2.54 – 2.13 ("Meeting job demands"), -2.50 - 2.11 ("Modifying tasks"), and -2.12 - 1.45 ("Communicating needs)". Change scores beyond +/- 3.5 (i.e., the range from -2.02-1.48) at t3 were thus indicative of SDC of the total scale. As seen in Table 8, only one respondent had a mean change score beyond SDC, i.e., a score of -3.89 (SD: 0).

The construct approach: Table 7 shows the correlations coefficients between changes scores from t1-t3 in the RTWSE-19 total scale and change scores from t-t3 in cancer-related SE, General Work Ability, Physical Work Ability and Mental Work Ability, respectively. A large positive correlation was found with Mental Work Ability change scores (hypothesis 9), and medium positive correlations were found with General Work Ability change scores (hypothesis 10) and Physical Work Ability change scores (hypotheses 11). The hypothesis regarding cancer-related SE was not confirmed (hypothesis 8). Three hypotheses (75%) were thus confirmed.

5.2 Results: Study II, The prediction study

The study sample in the prediction study included 114 employees with various cancers on sick leave at initiation of chemotherapy. Table 9 presents baseline sociodemographic, health-related, illness- and treatment-related, as well as work-related characteristics of the sample.

For the complete sample, the median time to RTW was 43.50 weeks (IQR: 27-65). During the follow-up period of 15 months, 34 participants (30%) remained on sick leave, 63 (55%) returned to work, seven (6%) retired early, and 10 (9%) died. Total follow-up time for the 114 participants was 5492 weeks.

5.2.1 The predictive value of RTWSE on full RTW

As shown in Table 9, 63 participants (55%) were categorized as low RTWSE while 51 participants (45%) were categorized as high RTWSE at baseline. The median time to full RTW was 45 weeks (IQR=29-65) for the participants in the low RTWSE group and 40 weeks (IQR=23-60) in the high RTWSE group. The difference did not reach statistical significance (p=0.058). In Figure 8, cumulative incidence curves of full RTW during 15 months are shown for the low and the high RTWSE groups, respectively.

Table 9 Baseline sociodemographic, health-related, illness- and treatment-related, and work-related characteristics of a population of 114 sickness absent employees initiating chemotherapy for cancer. Frequency, percentage and range, mean and standard deviation or median and interquartile range

	N	
Age (years) (mean and SD, range)	114	51 (7.47), 25-62
Gender (n and %)	114	
Female		87 (76)
Man		27 (24)
Education level (n and %)	112	
None		11 (10)
Short		44 (39)
Medium		42 (38)
Long		15 (13)
Work type (n and %)	112	
Physical		31 (28)
Sedentary		47 (42)
Mixed		34 (30)
Perceived support from the work place (mean and SD)	107	8.50 (2.38)
Type of cancer (n and %)	114	
Female reproductive system		8 (7)
Breast		56 (49)
Lung incl. mesotheliomas		10 (9)
Urological incl. male reproductive system		5 (4)
Upper gastrointestinal		11 (10)
Colorectal		13 (12)
Cerebral and the central nervous system		5 (4)
Other		6 (5)
Treatment intention (n and %)	114	
Curative		8 (7)
Adjuvant		62 (54)
Neo-adjuvant		18 (16)
Palliative		26 (23)
Treatment modalities (n and %)	114	
Chemotherapy		90 (79)
Chemotherapy and one additional treatment modality		21 (18)
Chemotherapy and two additional treatment modalities		3 (3)
Time since diagnosis (days) (medium and IQR, range)	114	69.50 (49-94), 20-1132
Time since initiation of chemotherapy (days) (mean and SD, range)	114	33 (19.91), 0-84
Return to work self-efficacy (n and %)	114	
Low RTWSE		63 (55)
High RTWSE		51 (45)
Depression (n and %)	113	
No depression		80 (71)
Mild depression		24 (21)
Moderate depression		9 (8)
Severe depression		0 (0)
Fatigue (mean and SD)	113	19.03 (SD: 8.20)
Performance status (n and %)	113	
Level 0: Fully active, able to carry on all pre-disease performance without restriction		26 (23)
Level I: Restricted in strenuous activity but able to carry out work of a light nature		67 (59)
Level II: Capable of all self-care but unable to carry out any work activity		17 (15)
Level III: Capable of only limited self-care, in bed for more than 50% of the time		3 (3)
Level IV: Cannot carry out any self-care, totally confined to bed or chair		0 (0)

SD: Standard Deviation. Iqr: Interquartile range

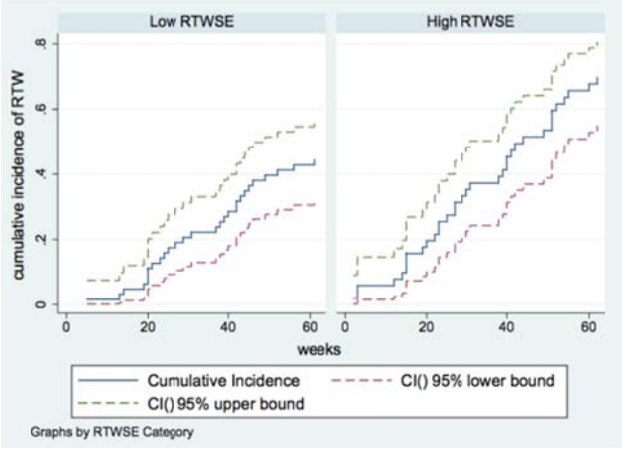

Figure 8 Aalen-Johansen cumulative incidence curves of full return to work for the low RTWSE group and the high RTWSE group

RTWSE: Return to work self-efficacy, RTW: Return to work, CI: Confidence Interval

In the unadjusted Cox proportional hazards regression model, high RTWSE was significantly associated with shorter time until full RTW (HR: 1.84, 95% CI: 1.12-3.03). By means of bivariate analyses (Table 10), four variables were associated with weeks until full RTW at a significance level of p<0.20: gender, treatment intention, depression, and perceived support from the work place. These were subsequently included in the multiple Cox proportional hazards regression analyses as covariates.

Table 10 Bivariate associations between sociodemographic, health-related, illness- and treatment-related and work-related characteristics at baseline and weeks until full RTW during 15 months of follow-up in a population of 114 sickness absent employees initiating chemotherapy for cancer. Hazards ratios, confidence intervals and p-values of the bivariate Cox proportional hazards regression analyses

Variable	N	HR	95% CI	P-value
RTWSE	114	1.84	1.12-3.03	**0.016***
Gender				
Men	27	1	-	-
Women	87	0.58	0.32-1.02	**0.059***
Age (years)	114	1.01	0.98-1.05	0.484
Educational level				
None	11	1	-	-
Short	44	1.20	0.50-2.92	0.680
Medium	42	0.76	0.31-1.89	0.556
Long	15	1.09	0.39-3.06	0.873
Work type				
Sedentary	47	1	-	-
Physical /mixed	65	1.33	0.80-2.23	0.274
Perceived support from work place (scale score)	107	1.14	0.99-1.30	**0.061***
Type of cancer				
Breast	56	1	-	-
Other	58	1.28	0.78-2.12	0.326
Treatment intention				
Curative, adjuvant, neo-adjuvant	26	1	-	-
Palliative	88	0.31	0.13-0.78	**0.013***
Treatment modalities				
Chemotherapy and no additional treatments	90	1	-	-
Chemotherapy + 1 or 2 additional treatments	24	1.22	0.68-2.22	0.506
Time since chemotherapy initiation (days)	114	1.00	0.99-1.02	0.567
Time since diagnosis (days)	114	1.00	0.99-1.00	0.273
Depression				
No depression	80	1	-	-
Symptoms of depression	33	0.58	0.32-1.07	**0.082***
Fatigue (sum score)	113	1.00	0.97-1.03	0.985
Performance status				
Fully active without restrictions (Level 0)	26	1	-	-
Restricted in some way (level ≥I)	87	0.85	0.48-1.51	0.584

*=significant at p<0.20

HR: Hazard Ratio

CI: Confidence Interval

Table 11 presents the multivariate Cox proportional hazards regression analyses. High RTWSE did not remain significantly associated with shorter time to full RTW after adding the illness- and treatment-related (model 3), and the health- and work-related (model 4) variables. Only gender and treatment intention were significantly associated with RTW in the multivariate model, showing that female gender and palliative treatment were significantly associated with later RTW.

Table 11 Hazard ratios for returning to work during 15 months of follow-up associated with the baseline level of Return To Work Self-Efficacy in a population of 114 employees undergoing treatment for cancer, including the Hazard Ratios for the covariates (gender, treatment intension, depression, and perceived support form work place). Hazards Ratios, confidence intervals and p-values of the unadjusted and the multivariate cox proportional hazards regression models

	Model 1 (unadjusted) (N=114)			Model 2[a] (N=114)			Model 3[b] (N=114)			Model 4[c] (N=107)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Low Return To Work Self-Efficacy	1	-	-	1	-	-	1	-	-	1	-	-
High Return To Work Self-Efficacy	1.84	1.12-3.03	**0.016**	1.75	1.06-2.89	**0.030**	1.58	0.95-2.65	0.079	1.12	0.62-2.02	0.711
Gender												
Male				1	-	-	1	-	-	1	-	-
Female				0.63	0.36-1.13	0.124	0.36	0.19-0.68	**0.001**	0.30	0.15-0.60	**0.001**
Treatment intention												
Curative, adjuvant, neo-adjuvant							1	-	-	1	-	-
Palliative							0.20	0.07-0.52	**0.001**	0.15	0.05-0.44	**0.001**
Depression												
No sign of depression										1	-	-
Symptoms of depression										0.89	0.46-1.74	0.742
Perceived support from the work place												
Scale score*										1.13	0.98-1.30	0.085

HR: Hazard Ratio
CI: Confidence interval
[a] Adjusted for gender
[b] Adjusted for gender and treatment intention
[c] Adjusted for gender, treatment intention, depression, and perceived support from the work place
* scale score with higher scores referring to higher levels of perceived support

With VIF values ranging from 1.14 to 1.27, no multicollinearity was found regarding the five independent variables (RTWSE, gender, treatment intention, depression and perceived support from the work place).

5.3 Results: Study III, The prospective observational study

The study sample included 217 employees undergoing chemotherapy for cancer. Table 12 shows the baseline sociodemographic and illness- and treatment-related characteristics of the working and the full time sickness absent participants, respectively.

Table 12 Baseline sociodemographic and illness- and treatment-related characteristics of a sample of employees undergoing chemotherapy for cancer, working/at part time sick leave or at full time sick leave at baseline. Mean and standard deviation, median and interquartile range, 95% confidence interval, frequency and percentage, and p-values

	Working / at part time sick leave (N=82)	At full time sick leave (N=135)	
	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)	P-value
Age (years), mean (SD)	52 (7.10)	50 (7.34)	0.063
Missing	0	0	
Time since diagnosis (days), median (IQR)	71.50 (48-98)	72.00 (49-96)	0.900
Missing	0	0	
Time since initiation of chemotherapy (days), mean (SD)	32 (18.71)	34 (19.55)	0.536
Missing	0	0	
Perceived support from the work place [a], mean (SD)	9.23 (1.73)	8.57 (2.31)	0.051
Missing	20	11	
	N (%)	N (%)	
Gender			0.056
Female	52 (63)	102 (76)	
Man	30 (37)	33 (24)	
Missing	0 (0)	0 (0)	
Ethnicity			0.203
Danish	76 (93)	125 (93)	
Other	0 (0)	4 (3)	
Missing	6 (7)	6 (4)	
Educational level			0.425
None	7 (8)	12 (9)	
Short	40 (49)	53 (39)	
Medium	21 (26)	48 (36)	
Long	10 (12)	19 (14)	
Missing	4 (5)	3 (2)	
Work type			0.130
Physical	14 (17)	35 (26)	
Sedentary	42 (51)	53 (39)	
Mixed	20 (25)	41 (30)	
Missing	6 (7)	6 (5)	
Self-employed			**0.002**
Yes	13 (16)	5 (4)	
No	63 (77)	124 (92)	
Missing	6 (7)	6 (4)	
Leadership			**0.024**
Yes	21 (26)	19 (14)	
No	55 (67)	110 (82)	
Missing	6 (7)	6 (4)	

Marital status			0.851
Married	60 (73)	106 (79)	
Living with parents	0 (0)	0 (0)	
Widower	1 (1)	1 (1)	
Divorced	12 (15)	19 (14)	
Have always lived alone	3 (4)	3 (2)	
Missing	6 (7)	6 (4)	
Children living at home			0.569
No	41 (50)	59 (44)	
Yes	35 (43)	68 (50)	
Missing	6 (7)	8 (6)	
Type of cancer			0.645
Female reproductive system	3 (4)	8 (6)	
Breast	42 (51)	69 (51)	
Lung incl. mesotheliomas	5 (6)	11 (8)	
Urological incl. male reproductive system	8 (10)	5 (4)	
Upper gastrointestinal	8 (10)	13 (10)	
Colorectal	7 (8)	17 (12)	
Cerebral and the central nervous system	5 (6)	5 (4)	
Other	4 (5)	7 (5)	
Missing	0 (0)	0 (0)	
Treatment intention			0.749
Curative	4 (5)	10 (7)	
Adjuvant	44 (54)	75 (56)	
Neo-adjuvant	11 (13)	20 (15)	
Palliative	23 (28)	30 (22)	
Missing	0 (0)	0 (0)	
Treatment modalities			0.864
Chemotherapy	64 (78)	109 (81)	
Chemotherapy and one additional treatment modality	16 (20)	22 (16)	
Chemotherapy and two additional treatments modalities	2 (2)	4 (3)	
Missing	0 (0)	0 (0)	

SD = standard deviation
IQR = interquartile range
[a] = measured on a 10-item rating scale with 10 indicating high level of perceived support

Table 13 shows the baseline measures of RTWSE, physical activity, and performance status of the working and the full time sickness absent participants, respectively.

Table 13 Baseline measures of return to work self-efficacy, physical activity, and performance status in a sample of employees undergoing chemotherapy for cancer, working / at part time sick leave or at full time sick leave at baseline. Median and interquartile range, 95% confidence interval, frequency and percentage, and p-values

	N	Working / at part time sick leave	N	At full time sick leave	P-value
		Median (IQR), 95% CI		Median (IQR), 95% CI	
Return to work self-efficacy total scale	76	8.29 (6,92-9.39), 7.63-8.90	131	6.95 (4.89-8.58), 5.89-7.72	**p<.001**
		N (%)		N (%)	
Pre-illness leisure time physical activity	82		135		0.592
Sedentary		6 (7)		11 (8)	
Light activity 2-4 hours/week		13 (16)		30 (22)	
Light activity >4 hours/week		28 (34)		38 (28)	
Vigorous activity 2-4 hours/week		30 (37)		43 (32)	
Vigorous activity >4 hours/week		5 (6)		13 (10)	
Current leisure time physical activity	82		135		0.068
Sedentary		11 (13)		36 (27)	
Light activity 2-4 hours/week		35 (43)		50 (37)	
Light activity >4 hours/week		22 (27)		31 (23)	
Vigorous activity 2-4 hours/week		13 (16)		12 (9)	
Vigorous activity >4 hours/week		1 (1)		6 (4)	
Current daily physical activity	79		130		**p<.001**
Low		3 (4)		23 (18)	
Moderate		22 (28)		51 (39)	
High		54 (68)		56 (43)	
Performance status	75		130		0.499
Level 0: Fully active		22 (29)		31 (24)	
Level 1: Restricted in strenuous activity		44 (59)		75 (58)	
Level 2: Capable of all self-care		9 (12)		21 (16)	
Level 3: Capable of only limited self-care		0 (0)		3 (2)	
Level 4: Totally confined to bed or chair		0 (0)		0 (0)	

IQR: Interquartile range

CI: Confidence Interval

At baseline, 82 (38%) worked and 135 (62%) were on full time sick leave. At 12 months follow-up, 154 (71%) worked, 35 (16%) were on full time sick leave, eight (4%) had retired early and 20 (9%) had died. Of the 135 full time sickness absent participants at baseline, 85 (63%) had returned to work at 12 months.

5.3.1 Associations between physical activity & work status at baseline (Objective I)

Employees reporting a moderate (>30 minutes/day on average) or a high level (>150 minutes/day on average) of current daily physical activity at baseline, were more likely to be working at baseline, compared to sedentary employees. This association remained significant in the multivariate models ($p<0.007$) (Table 14).

Table 14 Associations between baseline levels of physical activity and working at baseline in a population of employees undergoing chemotherapy for cancer. Odds Ratios, 95% confidence intervals, and p-values of the unadjusted and the multivariate logistic regression models

	Model 1 (unadjusted)				Model 2[a]				Model 3[b]				Model 4[c]			
Variable	N	OR	95% CI	P value	N	OR	95% CI	P value	N	OR	95% CI	P value	N	OR	95% CI	P value
Pre-illness level of leisure time physical activity	217			0.582	210			0.194	210			0.268	202			0.241
Sedentary		1.00	-			1.00	-			1.00	-			1.00	-	
Light activity 2-4 hours/week		0.79	0.24-2.61			0.87	0.25-2.98			0.87	0.25-3.01			0.91	0.26-3.22	
Light activity >4 hours/week		1.35	0.45-4.09			1.46	0.46-4.62			1.47	0.46-4.64			1.40	0.44-4.47	
Vigorous activity 2-4 hours/week		1.28	0.43-3.84			1.42	0.46-4.39			1.44	0.46-4.51			1.32	0.42-4.18	
Vigorous activity >4 hours/week		0.71	0.17-2.96			0.62	0.14-2.77			0.63	0.14-2.91			0.43	0.09-2.14	
Current level of leisure time physical activity	217			0.058	210			**0.014**	210			**0,024**	202			0.066
Sedentary		1.00	-			1.00	-			1.00	-			1.00	-	
Light activity 2-4 hours/week		2.29	1.03-5.11			2.98	1.25-7.09			2.98	1.25-7.08			2.61	1.08-6.29	
Light activity >4 hours/week		2.32	0.97-5.54			3.13	1.24-7.92			3.13	1.24-7.91			2.87	1.11-7.43	
Vigorous activity 2-4 hours/week		3.55	1.26-9.98			4.45	1.45-13.63			4.44	1.45-13.59			3.42	1.02-11.49	
Vigorous activity >4 hours/week		0.55	0.06-5.03			0.75	0.08-7.37			0.76	0.08-7.52			0.62	0.06-6.48	
Daily physical activity	209			**<0.001**	202			**0.002**	202			**0.004**	194			**0.010**
Low		1.00	-	-		1.00	-	-		1.00	-	-		1.00		
Moderate		3.31	0.90-12.17			3.39	0.90-12.73			3.35	0.88-12.69			2.83	0.73-10.96	
High		7.39	2.10-26.06			6.99	1.95-25.11			6.93	1.92-25.00			6.13	1.68-22.40	

OR: Odds Ratio
CI: Confidence Interval
[a] Adjusted for gender, age, and educational level
[b] Adjusted for gender, age, educational level, and treatment intention
[c] Adjusted for gender, age, educational level, treatment intention, and performance status

Table 15 Associations between baseline levels of physical activity and working at 12 months in a population of employees undergoing chemotherapy for cancer. Odds Ratios, 95% confidence intervals, and p-values of the unadjusted and the multivariate logistic regression models

	Model 1 (unadjusted)				Model 2[a]				Model 3[b]				Model 4[c]			
Variable	N	OR	95% CI	P value	N	OR	95% CI	P value	N	OR	95% CI	P value	N	OR	95% CI	P value
Previous level of leisure time physical activity	217			0.253	210			**<0.001**	210			**<0,001**	202			**<0.001**
Sedentary		1.00	-			1.00	-			1.00	-			1.00	-	
Light activity 2-4 hours/week		2.06	0.60-7.10			2.57	0.68-9.68			3.67	0.84-16.02			3.87	0.84-17.74	
Light activity >4 hours/week		1.35	0.44-4.17			1.65	0.49-5.60			1.66	0.44-6.30			1.67	0.44-6.41	
Vigorous activity 2-4 hours/week		1.45	0.47-4.43			1.31	0.40-4.30			2.33	0.62-8.79			2.42	0.63-9.24	
Vigorous activity >4 hours/week		0.55	0.14-2.12			0.82	0.18-3.75			1.71	0.31-9.47			1.74	0.31-9.85	
Current level of leisure time physical activity	217			**0.024**	210			**<0.001**	210			**<0.001**	202			**<0.001**
Sedentary		1.00	-			1.00				1.00				1.00	-	
Light activity2-4 hours/week		2.26	1.06-4.83			1.81	0.78-4.23			2.09	0.79-5.57			1.87	0.68-5.12	
Light activity>4 hours/week		1.88	0.82-4.31			1.32	0.53-3.30			1.28	0.44-3.68			1.20	0.40-3.61	
Vigorous activity 2-4 hours/week		5.43	1.43-20.70			5.06	0.99-25.78			5.58	0.92-33.79			5.39	0.78-37.32	
Vigorous activity >4 hours/week		0.56	0.11-2.76			0.43	0.08-2.49			0.55	0.07-4.38			0.54	0.07-4.54	
Daily physical activity	209			**0.001**	202			**<0.001**	202			**<0.001**	194			**<0.001**
Low		1.00	-			1.00	-			1.00	-			1.00	-	
Moderate		4.89	1.89-12.67			4.30	1.55-11.95			3.74	1.23-11.38			3.90	1.19-12.77	
High		4.92	2.00-12.12			3.98	1.48-10.67			3.52	1.21-10.22			3.43	1.12-10.51	

OR: Odds ratio
CI: Confidence Interval
[a] Adjusted for gender, age, educational level, and baseline work status
[b] Adjusted for gender, age, educational level, baseline work status, and treatment intention
[c] Adjusted for gender, age, educational level, baseline work status, treatment intention, and performance status

5.3.2 Associations between physical activity at baseline & work status at 12 months (Objective II)

Table 15 shows the associations between physical activity at baseline and work status at 12 months. Compared to sedentary employees, employees with a moderate (>30 minutes/day on average) or a high level (>150 minutes/day on average) of current daily physical activity at baseline, were more likely to be working at 12 months. Furthermore, employees who were physically active in their leisure time for more than two hours weekly were more likely to be working at 12 months compared to sedentary employees.

5.3.3 The mediating role of RTWSE (Objective III)

The preconditions of RTWSE being a mediator in the observed associations between current daily physical activity and work status at 12 months and current leisure time physical activity and work status at 12 months, respectively (Objective II) were not fulfilled. This is illustrated in Figure 9. Solely the association between RTWSE and work status in the model regarding current leisure time physical activity reached statistical significance (model 1, Figure 9). Examinations of the mediating role of RTWSE in these associations were thus not conducted.

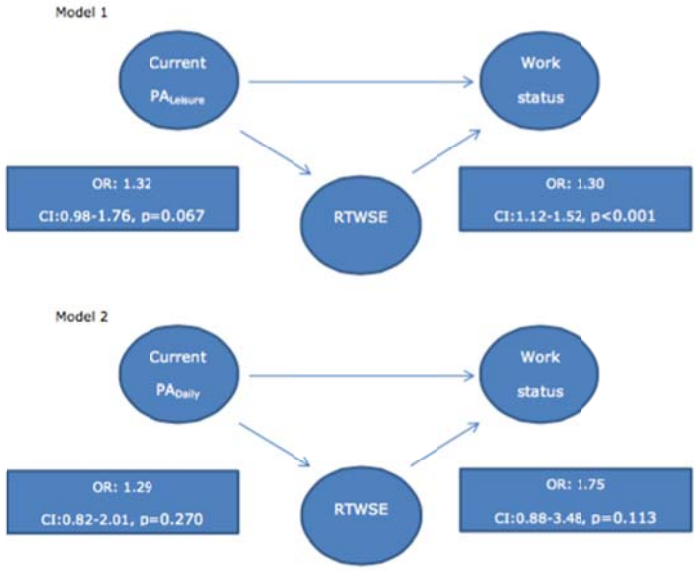

Figure 9 Associations between Current leisure time physical activity, measured at baseline, and Return to work self-efficacy, measured at three months and between Return to work self-efficacy, measured at three months, and work status at 12 months (model 1) and associations between Current daily physical activity, measured at baseline, and Return to work self-efficacy, measured at three months, and between Return to work self-efficacy, measured at three months, and work status at 12 months (model 2).

PA: Physical activity. RTWSE: Return to work self-efficacy. OR: Odds Ratio. CI: Confidence Interval

6.0 Discussion

6.1 Main findings

The primary aim of the present dissertation was to contribute with new knowledge regarding the role of SE and physical activity within the area of occupational rehabilitation of cancer survivors.

Study I and Study II contribute with new knowledge regarding the role of RTWSE in cancer populations. The main finding of Study I was that the psychometric properties of the RTWSE-19 questionnaire (27) were adequate when applied to employees undergoing chemotherapy for cancer, showing good reliability, adequate validity and moderate responsiveness. Study II contributes with further knowledge regarding the role of RTWSE in cancer populations by finding that RTWSE does not seem to be predictive compared to other variables (gender and treatment intention) when measured in a cancer population. Study III contributes with knowledge regarding the role of physical activity by finding that employees who were physically active at initiation of chemotherapy were more likely to be working at baseline and at 12 months follow-up, respectively. The results of Study III furthermore indicate that RTWSE does not seem to be a mediator between physical activity and work status as hypothesized.

6.2 Discussion of methods

This section will initially provide a discussion of methods in the three studies followed by considerations regarding external validity and public involvement.

6.2.1 Discussion of methods, Study I

The design of the validation study was guided by COSMIN (5) and is thus assumed to be adequate for validation studies. However, some methodological considerations regarding timing of test, retest and responsiveness in the validation study should be discussed in light of the results.

According to guidelines, test-retest refers to repeated measurements for persons "who have not changed" (7). As it was expected that the participants would be most stable during the first week of the Body and Cancer program as compared to subsequent weeks, the baseline questionnaires were completed within the first week of the program. This decision was made in collaboration with the Body and Cancer program staff in Aarhus.

As presented in the method section (section 4.1.4), the test-retest group in the present validation study was not defined based on a predefined time interval between test and retest but instead by the respondents' own indication of stability as reflected in their responses to the Global Perceived Change question at t2. The time-interval between test and retest was one week. The standard time interval between test and retest in validation studies is two weeks(7). However, the appropriate time interval depend on the construct measured: *"If the characteristic under study is stable, a longer time interval can be allowed, but if it changes rapidly the length of time between two tests should be as short as*

justified" (7). Keeping in mind that the participants in Study I were cancer survivors in risk of rapidly changing illness characteristics and side effects, two weeks were considered too long. Moreover, the participants were initiating the Body and Cancer program which might affect them as well (7,88). The choice of a one-week time interval was thus a compromise between the risk of change due to the illness and/or initiating a group intervention program and the fear of the participants remembering their previous answers. Subsequently, results showed that the mean time between the test and the retest in the test-retest group was 8.88 days, ranging from six to 20 days, indicating that perceived stability was reported by participants even in cases with a time-interval longer than two weeks. Similarly, perceived instability (ratings ≤-2 and ≥2 on the Global Perceived Change question) was reported by participants with a time-interval less than two weeks. Thus, a short time interval did not equal stability in the present sample. Defining the retest-group based on the participants own perception of stability therefore seems to be the appropriate decision in the present study.

Recommendations of a specific time interval in the responsiveness analyses is not defined by guidelines. The follow-up can be short or long depending on the concept of interest. The important aspect is that change is expected to occur within the given time frame (7). The choice of three months in Study I was inspired by the design of the previous Danish test of responsiveness of the RTWSE-19 (27). However, of the total responsiveness sample at t3 (n=48), results showed that only one participant (2%) reached a change in RTWSE beyond SDC. It could be speculated that the time period in the responsiveness test should have been longer to increase the likelihood of more participants having changed (positively or negatively) regarding RTWSE.

It must be considered a limitation of Study I, that the study sample in the follow-up was below the recommended number of 50 (7); 49 and 48 at t2 and t3, respectively. However, as it is only one and two participants below the recommended level, respectively, it is not assumed to have affected the results.

6.2.2 Discussion of methods, Study II and Study III

In epidemiological studies two types of error must be considered: random errors and systematic errors. Random error is referred to as "chance" and can be reduced by increasing the study sample. Systematic error refers to bias and can be divided into three major categories: selection bias, information bias, and confounding (159-161). The risk of selection bias, information bias, confounding and random error will be discussed in relation to the observed associations in Study II and Study III.

Selection bias

Selection bias is defined as a systematic over- or underestimating of an observed association due to distorted selection (161). It may occur when participation or follow-up in a study is not complete, if the participants who are included in the study differ from those who are not included but eligible (160,161). If the selection is associated with both the independent and the dependent variable, selection bias may

cause biased estimates (differentiated selection). On the contrary, if the selection is not assumed to be associated with neither the independent nor the dependent variable, or with the independent *or* the dependent variable, biased estimates do not usually occur (non-differentiated selection).

As participation in the survey study, on which Study II and Study III are based, was not complete at baseline, selection bias at study entry must be considered. According to inclusion procedure, all eligible cancer survivors were to be invited by the nurses at the Department of Oncology at Aarhus University Hospital during the inclusion period and further, to return a contact sheet with contact information or with a decline to participate. However, a large amount of the contact sheets (n=416) were not returned to the research team and of the 400 cancer survivors, who did return the contact sheet, 88 declined to participate (Figure 5). Data on these groups of non-responders were not accessible but could have informed us about selection bias.

In an attempt to gain knowledge regarding the 416 non-responders who did not return the contact sheet, we conducted a short written survey among the nurses, asking them about the possible reasons for the non-responses/the missing contact sheets according to their lived experiences during the inclusion period (see appendix 6). According to the nurses, the non-responses/the missing contact sheets appeared to be a result of:

- The nurses being too busy to/forgetting to invite an eligible cancer survivor
- The nurses intentionally avoided inviting an eligible cancer survivor if they considered the individual to be too ill/too frail to participate or the study to be irrelevant for this person
- Non-response of eligible cancer survivors who were invited but did not respond to the invitation.

Due to missing knowledge regarding sociodemographic and illness- and treatment-related variables of the non-responders, comparison between the non-responders and the responders was not possible. But considering a) the potential exclusion of the less resourceful patients by the nurses, b) knowledge from previous research reporting social inequality in study participation in general (159,162), and c) previous research showing that non-responders of cancer studies tend to have a lower education than participants (101,104), the inclusion in the present survey study is assumed to be prone to selection bias.

Furthermore, 71% of the baseline study population were women. The gender distribution among the non-responders is not known. Yet, statistics from the Clinical Trial Unit at Aarhus University Hospital show that 49.70% of all the cancer survivors, who initiated chemotherapy at Aarhus University Hospital in the inclusion period, eligible to study participation based on age and history of cancer treatment, were women. Selection bias regarding gender thus seems likely, which is supported by previous research reporting male gender to be associated with non-response (159).

The potential selection based on gender is assumed to be non-differentiated, as gender has been shown

not to be associated with the independent variables (RTWSE (110)(Study II) and physical activity (163)(Study III)) in neither of the studies. The estimates of the studies are thus not expected to be biased due to the distorted distribution of gender.

As education level has been shown to be negatively associated with RTWSE (110) and to be a prognostic factor of RTW in cancer survivors (46,49,164), the selection appears to be differentiated in Study II, and consequently, the observed estimates in the study may be biased. However, as the association between RTWSE and RTW is not likely to be different in the sample of non-responders compared to the responders, the biased selection is not expected to have affected the observed estimates.

Similar conclusions can be drawn in relation to Study III. Here the selection is also assumed to be differentiated, as educational level has been shown to be associated with both physical activity (165,166) and with work status among cancer survivors (46,49,164). The estimates of Study III may thus be over- or under-estimated. However, again there is no reason to expect the association between physical activity and work status to be different in the group of non-responders compared to the responders. Hence, the differentiated selection is not assumed to have affected the estimates of Study III considerably.

Attrition bias

Selection bias may also occur during follow-up, if the participants who drop out are different from those completing follow-up. In studies II and III, data concerning the primary dependent variables, RTW and work status, respectively, were obtained from the DREAM register, resulting in 100% complete cases and thus elimination of the risk of attrition bias. However, in Study III, the three-month measurement of RTWSE was used to examine the mediating role of RTWSE. A loss to follow-up of 14% (n=30) was found regarding the three-month measurement of RTWSE due to non-response. Comparing the responders and the non-responders showed no differences between the two groups with regard to sociodemographic and illness- and treatment-related characteristics, except for ethnicity; significantly more participants with non-Danish compared to Danish ethnicity were lost to follow-up. As the number of participants with a non-Danish ethnicity was only four individuals (2%), this selection is not assumed to have led to biased estimates in the examination of the mediating role of RTWSE in Study III.

Information bias

Information bias refers to systematic over- or under-estimation of an estimate due to misclassification of the dependent or independent variables (160,161). Two types of misclassifications are to be considered: differentiated and non-differentiated misclassification. The risk of differentiated misclassification is assumed to be low in Study II and Study III, since the exposures were measured prior to the outcomes due to the prospective designs. Yet, the risk of non-differentiated misclassification must be considered.

One of the major strengths in studies II and III was the use of register-based data for the dependent variables. The DREAM register has been found to be a valid tool for use in research regarding RTW and

sick leave (141). A high degree of correspondence (96.7% (95% CI: 95.6-97.6) between DREAM data on sickness absence benefits and workplace-registered sick leave of sick leave ≥ 15 days has been reported, along with a reported specificity close to 100% (95% CI: 98.3-100)(167). Hence, the risk of non-differentiated misclassification regarding the main outcomes in studies II and III is assumed to be low.

Likewise, the risk of non-differential misclassification regarding the illness- and treatment-related variables obtained from patient records in Studies II and III is assumed to be low, as data were obtained by two oncologists based on a predefined procedure which was initially tested in 50 participants to check for correspondence in data obtained by the two oncologists.

However, the risk of information bias due to non-differentiated misclassification in the self-ported data in studies II and III must be evaluated. As discussed in Study III, one of the limitations of this study was the self-reported measurement of physical activity. As exercise is a socially desirable behavior, the risk of overestimating the level of physical activity is highly present (168). Thus, the risk of misclassification is present. It is, however, assumed to be non-differentiated, as assumed to be the same in the groups compared in the study. Non-differentiated misclassification may lead to under-estimation of an actual association, not over-estimation. Hence, the significant associations found in Study III between physical activity and work status are not likely to be explained by the potential non-differentiated misclassification. However, if non-differentiated misclassification occurs regarding an independent variable including various degrees of exposure, it may have consequences for the conclusions drawn upon these results (161). An overestimation of the level of physical activity by the participants will thus interfere with the interpretation of the observed ORs. The observed OR (the chance of working) linked to a specific physical activity level is likely to be under-estimated, i.e., it is assumed that the positive effect of physical activity starts at a higher level than might actually be the case. This aspect must be considered when interpreting the results.

The risk of information bias due to misclassification in the remaining self-reported data in the survey study is assumed to be low due to the use of validated measurements tools and no expectation of under- or over-estimation of the participants when completing the questionnaires.

Confounding

An important limitation of the observational design is the risk of confounding, which must be considered as the observed associations between physical activity and work status in Study III may be explained by confounding factors and not actual causation, i.e., a misinterpretation of effects (160,161). Confounding was not an issue in Study II as the objective was prediction and not identification of risk factors. Hence, the covariates were included as potential predictor variables and not as confounders. In this section, the risk of confounding will thus only be discussed regarding Study III.

There are several ways to control for confounding. Common methods in study design are restriction,

randomization or matching. In analyses, regression analyses enable control for several potential confounders within the same analysis (160,161). Hence, adjusting for predefined independent variables in the logistic regression models was a way of minimizing the risk of potential confounders in Study III (160). The choice of included covariates was based on the Cancer and Work model (48) as presented in the background section (Figure 3). We included covariates from all areas of significance as presented in the model. However, the number of participants in the study did not allow for adjustment of all relevant confounders in the statistical models. If the number of covariates is high and the sample size small, there is a risk that the resulting estimates are unstable (161). The number of covariates were reduced to five (age, gender, level of education, treatment intention, and performance status) as a result of the final sample size. Initially, the intention was to adjust for diagnosis, depression, fatigue, and job type as well, which would have been relevant according to previous research (48). However, the following five covariates were chosen as they were considered the most important. First of all, age, gender, and educational level were considered the most important sociodemographic variables as they have all repeatedly been shown to be associated with RTW of cancer survivors (48,49,169). In collaboration with an oncologist, treatment intention was chosen to be the most important illness-and treatment-related variable. Finally, performance status was assumed to be the most important variable compared to depression, fatigue, and work type, when considering that the independent variable was physical activity. Another way of reducing the number of covariates would have been dichotomization of the physical activity scales. However, we considered that too much information would have been lost.

Despite the reduction of covariates, the risk of over-fitting is, however, still present in the statistical models in Study III. The total sample included 217 employees but the number of events in the smallest group at baseline was 82 and at 12 months it was 63. According to the general rule of thumb, logistic regression models should be used only with a minimum of 10 events per predictor parameter (170) thus allowing only eight and six predictor variables, respectively, in the present study (Study III). The multiple regression models in Study III regarding *leisure time* physical activity violated this rule by including nine covariates in the multivariate analysis at the cross-sectional baseline analyses and ten covariates in multivariate analysis in the follow-up analyses, resulting in only nine and six events per predictor variable, respectively. The number for the analyses regarding the *daily level* of physical activity is a bit higher as this variable does not contain as many levels. Here, the multivariate model at baseline included seven covariates and the multivariate model in the follow-up analysis included eight covariates, resulting in 11 and eight events per predictor variable. However, based on multiple analyses, Vittinghoff et al.(171) suggest that the number of minimum events per explanatory parameter can be reduced to 5 to 9 events without enhancing the risk of misinterpretation of the results considerably and conclude that *"systematic discounting of results, in particular statistically significant associations, from any model with 5–9 events per predictor variable does not appear to be justified"*. In line with this, the findings in the multivariate models generally seemed to be robust to confounder adjustments, as the estimates were

only slightly affected when adding additional confounding variables. Nevertheless, the results of this study should be interpreted with caution.

Random error

The level of random error reflects the statistical precision (159,160). In the present dissertation, the statistical precision has been evaluated by use of 95% CIs for all estimates. The CIs in the multivariate models of studies II and III are generally large, indicating lack of precision in the estimates. This can be explained by the relatively small sample sizes in studies II and III. Increasing the sample size is a way of increasing precision. A significance level of 5% was used, indicating 5% risk of type I error (160,161).

Summary: internal validity

The main strength of the epidemiological studies (Study II and Study III) is the use of register-based data for the primary outcomes (RTW and work status, respectively), thus ensuring 100% follow-up and thereby minimizing the risk of attrition bias. An additional strength is the prospective observational design in both studies as it reduced the risk of differentiated misclassification.

As the selection at study entry was differentiated, risk of selection bias is present in Study II and Study III, but is not expected to have a considerable impact on the observed estimates. However, non-differentiated misclassification is a concern in Study III, as the positive effects of lower levels of physical activity may be underestimated. Furthermore, confounding is a concern in Study III. Despite controlling for five known covariates in the analyses, confounding may still exist as the small sample size did not allow for adjustment of all relevant covariates. Finally, the risk of unknown confounders is also present. Thus, the greatest concern regarding the internal validity of the epidemiological studies is confounding, which should be kept in mind when interpreting the results of Study III.

6.2.3 External validity

External validity refers to the generalizability of the results of a study in other populations, in other settings, and in another time period (161). Conducting the validation study (Study I) at Body and Cancer units may have consequences for the generalizability of the results to other cancer populations. Due to referral rules, the participants in these programs do not resemble the general cancer population. Moreover, cancer survivors voluntarily participating in psychical activity programs have been shown to have higher levels of SE than cancer survivors who do not participate in these programs(115,116). However, conducting a test-retest requires completion of questionnaires at two time points with a predefined short time interval (7). Administrating this in a hospital ward, in this case Department of Oncology, Aarhus University Hospital, would be difficult. On the contrary, participants in the Body and Cancer programs were easily accessible, as they engaged in the program four out of five weekdays for six weeks. The conduction of the test-retest was thus possible to administer in this setting. As a result, the present validation of the RTWSE-19 questionnaire might not be generalizable to all cancer survivors.

In Study II and Study III, selection bias at study entry regarding level of education and gender was identified above. The external validity may thus be limited as the results may not be generalizable to the less resourceful and less educated employees with cancer. Generalizability of the findings of Study II and III to other countries may be limited as well as the findings in these studies must be interpreted in the light of the Danish health care system and laws on sickness absence (121).

6.2.4 Public involvement

Public involvement in research refers to "*research being carried out with or by members of the public rather than to, about, or for them*" (172). The over-all aim of the present dissertation, especially the hypotheses regarding RTWSE being a mediator between physical activity and work, is developed in close collaboration with the staff at the Body and Cancer program in Aarhus based on their lived experiences (2013/2014). This involvement is expected to have increased the relevance of the study for practice.

Moreover, patients, healthcare professionals and researchers were involved in a pilot testing of the final questionnaire conducted among the following groups in June 2016 and August 2016: cancer survivors participating in the Body and Cancer program at Aarhus University Hospital (n=8), health professionals at the Body and Cancer program unit at Aarhus University Hospital (n=2), research professionals within the area of occupational rehabilitation and cancer rehabilitation (n=6) and one "naive" tester from the general population with no relation to research and cancer. The pilot test was conducted in order to evaluate the comprehensibility of the questionnaire including the introductions to each scale. The participants provided their feedback in writing and the written answers were used to determine the clarity of the instructions and identify deficiencies and errors in the text. Proposals to changes in the instructions were discussed with the main supervisor and based on a joint decision corrected in the final version of the questionnaire. Proposals to the wording of the questionnaires were not followed as the questionnaires were all validated scales and hence, making changes in these were not allowed. The pilot testing is considered to have increased the readability of the questionnaire.

6.3 Discussion of results

The main results will be discussed in the light of previous research, theoretical perspectives, and within the framework of the Cancer and Work model (Figure 3). Initially, the results regarding the role of SE in the RTW process of cancer survivors will be discussed (Study I and Study II), followed by a discussion of the results regarding the role of physical activity (Study III).

6.3.1 The role of SE in the RTW process of cancer survivors

The validity of the RTWSE-19 Questionnaire in a cancer population

In Study I, it was found, that the psychometric properties of the RTWSE-19 were adequate when applied to employees with cancer. No previous studies have validated a RTWSE questionnaire in a population of

employees with cancer. As mentioned in the background section, several RTWSE questionnaires have been developed (12,110,113), and so far they have been validated in populations of employees with musculoskeletal disorders (12), mental health problems (113), low back pain (110), and all-cause sickness absence (27). The RTWSE-19 questionnaire (109,110) was translated, culturally adapted and validated in Denmark in 2016 among sickness absentees on all-cause sick leave (27). In the present validation, the following psychometrical properties of the questionnaire have been confirmed in a cancer population:

- A ceiling effect of 20% on the subscale "Communicating needs", which resembles findings in the previous Danish validation of the questionnaire among all-cause sickness absentees of a ceiling effect of 20% on the same subscale (27)
- Good internal consistency of the scale and sub-scales with Cronbach's alpha values ≥0.90, which is in line with previous reported Cronbach's alpha values of this scale. Shaw (110) originally reported Cronbach's alpha values between 0.95 and 0.97 for the total scale and 0.98, 0.92 and 0.91 for the three subscales, respectively. The Danish validation showed Cronbach's alpha values ranging from 0.93 to 0.97 on both the total and the sub-scales (27)
- Good test-retest reliability, as all ICC estimates were above 0.70 and SEM values were low. The ICC values in the present validation were higher than those reported in the previous Danish validation of the questionnaire (27). This indicates that RTWSE has equally good reliability in employees on sick leave due to cancer compared to the general population of sickness absentees
- Adequate construct validity as positive correlations (r>0.5) with cancer-related SE and Mental Work Ability, a medium correlation (r>0.3) with General Work Ability, and no correlation with test date (r=0.03) were found. Four out of seven hypotheses (57%) were thus confirmed. In the original validation of the scale, 60% of the predefined hypotheses were confirmed showing correlations coefficients with pain measures between 0.17 and 0.31 (110). Construct validity was not measured in the previous Danish validation (27). The results of Study I are thus in line with previous research. Based on the associations with cancer-related SE, Mental and General Work Ability and the resemblance to results in the original validation by Shaw (110), the construct validity is assumed acceptable even though the confirmation rate of the hypotheses did not reach 75% as recommended(135), but only 57%
- Moderate responsiveness; the results regarding responsiveness showed the expected tendencies towards negative mean change scores on the RTWSE among participants with low RTW expectations at the Global Perceived Change question and positive mean change scores on the RTWSE for the optimistic participants (i.e., the criterion approach). Based on LOA, the SDC was defined as +/- 3.5 scale points. Additionally, the validation of the change scores (i.e., the construct approach) was confirmed in 75% of the hypotheses, which reaches the acceptable level (135). Inclusion of the criterion approach, the identification of the SDC values, and the construct approach in the examination of responsiveness has not previously been done in validation studies

of the RTWSE. However, the results regarding responsiveness should be interpreted with caution due to low number of participants at t3, as mentioned previously.

In summary, the psychometric properties of the RTWSE-19 questionnaire in a cancer population have been shown to be adequate and furthermore, to resemble the psychometric properties reported on RTWSE-19 in other sickness absence populations.

The predictive value of RTWSE in a cancer population

As mentioned in the background section, the predictive value of RTWSE has been documented in various sickness absence populations; all-cause sickness absence (27,114), mental (111,113), and musculoskeletal disorders (110,112), and once in a cancer population (120). The results of Study II were not in line with these previous results, as the predictive value of RTWSE was not confirmed.

The surprising results of Study II will be discussed within the framework of the Cancer and Work model (Figure 10). For the purpose of clarity, the model is presented in the present section in a modified version. First, the results of Study II will be discussed in relation to *personal factors* (cancer survivor characteristics, health, symptoms and function), followed by the *work-related factors* (work demands and work environment) and the *societal factors* (policies, procedures, and economic factors), and finally the *outcome-related factors* (outcomes).

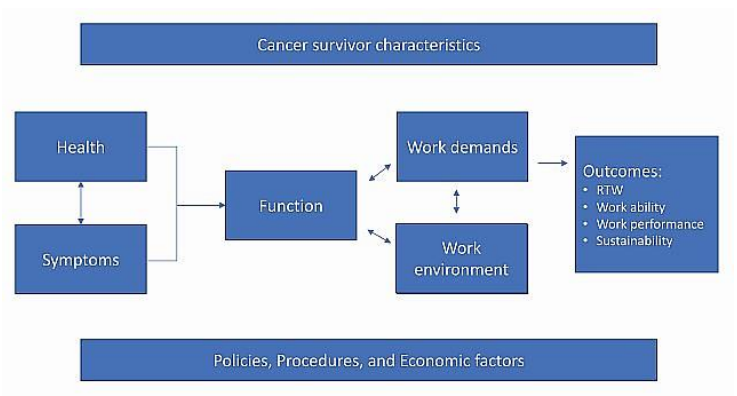

Figure 10 A modified version of the Cancer and Work model

Personal factors

The differences between previous results (27,110-114) and the results of Study II may first and foremost be explained by the diagnostic differences between the study samples. Being on sick leave due to cancer may be significantly different from being on sick leave due to various other illnesses, and the role of RTWSE as a strong determinant of RTW might be overruled by other factors when examined in employees with cancer. Based on the results of Study II, female gender and palliative treatment appears to be more predictive of RTW that RTWSE. The important role of gender and treatment-related factors has previously been reported in systematic reviews (43,46,48,49,169).

Unlike Study II, Wolvers et al. (120) found RTWSE to be predictive in a cancer population, consisting of

81 cancer survivors (87% breast cancer) and with a follow-up time of 18 months. Once again differences in population characteristics may contribute to understanding the divergent result of Study II. The participants in the study of Wolver's et al.(120) were all undergoing curative chemotherapy and participated in an intervention program including physical exercise, aiming at increasing RTW. It is possible to assume that RTWSE is more likely to have a predictive value in a population of cancer survivors undergoing curative treatment and who are motivated for RTW, than in a cancer population with a wider range of treatment intentions and potentially a wider range of motivation for RTW. As described in the background section, getting diagnosed with cancer may lead to reassessment of life priorities (40-42,44) and it is possible that some of the participants in Study II would have had an expectation of *being able* to work but *chose not* to work. Fifty percent of the sample in Study II were women with breast cancer. Post-hoc calculations have shown that the median age of the sub-sample of women with breast cancer was significantly lower than the median age of the remaining sample (breast cancer; 50 year of age, IQR=10, other cancers: 54 years of age, IQR 11, $p<0.01$). It is possible that these younger women with breast cancer were more likely to prioritize the family due to children living at home, thereby being more prone to stay home during treatment. Taking care of household tasks and/or children has been reported as barriers to RTW (40). This may also be the explanation for female gender being a predictor of late RTW in the present study. Changed priorities may also have caused some of the employees undergoing treatment with palliative intention to prioritize other things in life than work (40,44). Thus, differences in population characteristics regarding motivation for RTW and treatment intention might explain why RTWSE was shown to be predictive in the study by Wolvers et al. (120) but not in Study II.

Thus, motivation for RTW seems to be a likely mediator between RTWSE and actual RTW and a possible explanation for the divergent results of Study II. The role of motivation in the RTW process among cancer survivors has been underlined in a meta-synthesis of qualitative studies (44). In the definition of the RTW process motivation is emphasized as well: RTW is *"a health-related behavior involving elements of motivation and self-management, influenced by physical, psychological, and social factors"*(12). This dissertation aimed to focus on RTWSE, but the aspect of motivation appears to be pivotal as well when trying to understand the association between RTWSE and RTW.

According to social cognitive theory, SE and motivation are tightly connected. Motivation is defined as *"a general construct that encompasses a system of self-regulatory mechanisms" (Bandura 1997)* and consists of three main features: *"Selection, activation, and sustained direction of behavior towards certain goals"*(13). These goals can also be called outcome expectancies and in cooperation with SE they play a key role in human behavior (13). Motivation directs behavior towards goals but SE will still be the major basis for action; if the individual does not believe that he or she can attain the desired outcome, he/she will not engage in trying. So, if RTW is a desired outcome, and the individual believes that he or she can attain it, then the individual is likely to engage in trying. This is likely to be the case in the study

of Wolvers et al. (120) in which all the participants participated in an intervention program aiming at RTW. On the contrary, if work is not a desired goal, the individual will not engage in a behavior that leads towards that goal, irrespective of their RTWSE. This may explain the divergence between the results of Study II and the study of Wolvers et al. (120).

These perspectives can further be linked to Maslow's hierarchy of needs (36,37) (Figure 2). According to Maslow, the need for belongingness is based on a need for *"affectionate relations with people"*(36) and the need for esteem is based on *"achievement and respect from others"* (36). When faced with cancer, for some people, the most important aspects may be the belonging within the family and the achievements as a parent/a spouse, compared to the aspects offered by a workplace. Furthermore, a life-threatening illness is a potential threat to the safety need (36). Acknowledging the theory's hierarchical structure of the needs, it is thus likely that a cancer diagnosis, especially if treated with palliative intention, for some cancer survivors may threaten the safety need in such a way the upper levels becomes less important.

Work-related factors

In Study II, the work-related factors were represented by the covariates job type and perceived support from the workplace. Previous research has found non-manual jobs (32,43,169) and support from the workplace, e.g., flexible working conditions, emotional support from employer and colleagues, and continuous contact with the employer (46,49,169,173), to be positively associated with RTW. In the present sample, job type and perceived support from the workplace did not predict RTW, indicating that alternative covariates were stronger predictors. However, remembering the pivotal role of motivation, as hypothesized above, the work-related factors may still have had an impact, as these factors most likely will affect the individual's motivation regarding RTW (173).

Societal factors

As described in the background section, in Denmark, many cancer survivors are entitled to receive sickness absence compensation for 52 weeks. Had the study been conducted in another country, the results might have been different. In the United States, RTW rate after breast cancer is 93% at 12 months after the diagnosis, whereas the same rate is 43% in the Netherlands (174). In the Netherlands, the employees are entitled to sick leave for 2 years, which can explain the low RTW rate at 12 months compared to the United States (174) and to the average RTW rate across countries of 62% (32). These numbers illustrate the significance of the contextual factors. However, different health care systems are not likely to explain the difference in results between Study II and the study of Wolvers et al. (120), as this study was conducted in the Netherlands, where employees as mentioned are entitled to sickness benefit for an even longer period of time than in Denmark.

Outcome-related factors

Different measures of RTW may result in different results (11). The operationalization of the RTW

outcome measure varies across the studies within this area between time to event measures (111,114) and dichotomous measures at the end of follow-up (RTW: yes/no)(27,110,112,113). In Study II, time to event measures of RTW was used, as in Volker (114) and Nieuwenhuijsen (111), in which the predictive value was confirmed. Operationalization of RTW as time to event does not seem to be the reason for the non-significant results in the present study.

To sum up, differences in personal factors regarding treatment intention and motivation for RTW most likely explain the divergent results of Study II.

6.3.2 The role of physical activity in the RTW process of cancer survivors

To evaluate the knowledge within this area, an in-depth review of the studies within this area was made. The studies are discussed in relation to the findings of Study III and within the framework of the Cancer and Work model (Figure 10).

As reviewed in the background section, previous empirical evidence regarding the association between physical activity and the work lives of cancer survivors is scarce, inconsistent and of limited quality (92,93,95). Support for the hypothesis of a positive effect of physical activity on work life of cancer patients has been found in two previous observational studies, one study with a matched case-control design and in three RCTs, illustrated with green in Table 16 (appendix 7). However, the risk of confounding is present in the observational designs by Lee et al. (101) and by Leensen et al. (102), making it impossible to infer causation. In the case-control design by Thijs et al. (96), the baseline characteristics of the cases and the controls were similar, but the risk of unknown confounders remains as the control group consisted of patients from two other hospitals and hence other work places, which might be important for the outcome variable. The three RCT's found beneficial effects of physical intervention programs on RTW (77,103) and work ability (103,104), but in all three RCTs, RTW/work was measured as a secondary outcome measure among a range of other secondary variables, thus increasing the risk of type I error. Rejection of the hypothesis of a positive effect of physical activity on work in cancer survivors has been reported in four RCTs (97-100) of which one was a pilot study (97), one was a feasibility study (99) and two studies included light physical activity programs, relaxation training, and dance as a part of broader intervention programs (98,100), illustrated with blue in Table 16 (appendix 7).

Personal factors

Within the perspective of the Cancer and Work model, the divergent results within this area may be attributed to differences in population characteristics. However, a closer look at the study samples reveals that the study populations exclusively (77,97-99,101,103) or primarily (i.e., 80% (100), 84% (102), 71% (96), 65% (104), 51% (175), respectively) included women with breast cancer. Differences in population characteristics may still exist but can hardly explain the different results within this area.

Work-related factors

The employer is identified as one of the main stakeholders to facilitate RTW of cancer survivors as they are in a position to support the individual during RTW by providing the optimal settings for the individual to RTW (173,176). For the majority of previous studies, work-related factors were not included in the interventions or in the designs of the studies (for instance as covariates) (77,96-98,101,103,104). In two intervention studies personal or group-based counseling regarding work were included in the intervention; Leensen et al. (102) and Berglund et al. (100). Only one study, the study of Hubbard et al. (99), involved the workplace; in one case out of the seven cases in the intervention group, a meeting including the participation of the patient's Human Resources (HR) advisor at work was part of the intervention. Including the employer/the work place is recommended in RTW interventions across different health and injury conditions (158,177) and in RTW interventions for cancer survivors (95,177).

In study III, no work-related factors were included. Due to sample size, the work-related covariates were not included as potential confounders, which must be considered a limitation of study III. Similarly, the limited inclusion of the employers in the intervention studies within the field in general must be considered a limitation.

To conclude, the involvement of the workplace or of work-related factors is very limited in the studies within this area. Of the two intervention studies including work-related counseling, one found effect of the intervention (102) and one did not (100). Differences in the involvement of work-related factors do therefore not seem to explain the divergent result within this area.

Societal factors

The contradictory results within this field may be attributed to differences regarding the context of the intervention programs (e.g., intervention characteristics, different follow-up times etc.). The four RCTs rejecting the hypothesis of a positive effect of physical activity on work included two pilot/feasibility studies (97,99) with limited sample size, which increases the risk of type 2 error, and two studies including intervention programs with only limited content of physical activity. In the study of Berglund et al.(100), physical activity sessions were once a week during seven weeks, and in the study of Björneklett et al. (98), the intervention was a seven-day program, including dance and relaxation. Of the four RCT studies confirming the hypothesis of a positive effect of physical activity on work status, three included high intensity psychical activity (77,96,103) and one low-moderate intensity(104). Furthermore, the studies were conducted in different societal contexts; i.e., the Netherlands(96,102-104), Korea (101), Sweden (77,98,100), Canada (97), the United Kingdom (99), and Denmark(175). Complex interventions conducted in different contexts can be difficult to evaluate and compare (178), however, it is assumed that differences in intervention characteristics are likely to play a role in the contradictory results.

Outcome-related factors

Different measures of RTW/work status may lead to different results (11). Following outcome variables were used in the reviewed studies: work status (77,98,100-103,175), time to RTW (102), work ability (96), number of sick days (97-100), and perceived problems at work (104). The four studies reporting none-significant results were the only ones to define the work-related outcome as "number of sick days" during follow-up. Whether this is part of the reason for the different results within the area is difficult to conclude upon but it is possible.

Summing up, different intervention characteristics and different definitions of the work outcome measures in the studies may contribute to an understanding of the conflicting results within this area. The need of RTW to be more clearly and uniformly defined in future research is emphasized in a recent review of RTW for cancer survivors by Lamore et al. (95).

The contribution of Study III

Study III contributes to the existing knowledge by supporting the hypothesis of a positive association between physical activity and work in cancer survivors. To increase the scientific evidence within this area, high quality RCTs are needed (92,93,95). However, despite the non-randomized design, Study III is assumed to contribute with new knowledge within this area. A key difference between Study III and the previous studies within the field is the measurement of physical activity as the *daily* physical activity level and not as exercise or physical activity as part of an intervention study (RCT). Physical activity was measured by the International Physical Activity Questionnaire (IPAQ)(146), measuring physical activity in four different domains covering all activities within the day (146). This corresponds to the definition of physical activity by WHO as: *"any bodily movement produced by skeletal muscles that requires energy expenditure… Physical activity includes exercise as well as other activities which involve bodily movement and are done as part of playing, working, active transportation, house chores and recreational activities"* (10). As discussed in Study III, when the effects of physical activity on RTW and work status are measured by means of a RCT design including an intervention program, the specific effects of physical activity are difficult to distinguish. The above mentioned controlled studies confirming the positive effect of physical activity on RTW/work status included intervention programs consisting of exercise sessions supervised by physical therapists (77,96,103,104) and in some cases including individual coaching during and/or after the program (77,104). The reported effects in these studies may not be attributed to the physical activity *per se* but rather to participation in an intervention program, including socialization, and receiving supervision and coaching. Study III thus adds to existing evidence that the effect of physical activity on work status seems independent of participation in an intervention program, in other words, that the positive effect is related to being physical active *per se*.

Due to the risk of misclassification regarding self-reported physical activity (148,168), a risk of under-estimating the positive effects of lower level physical activity is present, as described in the discussion of

methods. Yet, the low precision of the estimates prevents us from concluding upon specific estimates of physical activity. Though, there seems to be tendencies to dose-response associations; the positive effect increases, the more physical activity increases. However, these interpretations must be seen in the light of the observational design. Causation cannot be inferred as the risk of confounding exists.

The underlying mechanism between physical activity and work

Investigating the underlying mechanisms in the association between physical activity and work was a specific aim in the present study. Based on previous research and theoretical background of SE, RTWSE was hypothesized to be a potential link between physical activity and work, but according to the findings of Study III, RTWSE does not seem to be a mediator in the observed associations. Keeping the results of Study II in mind, RTWSE does not appear to play the expected role in this cancer population, which might explain the results of Study III. To establish mediation, significant associations must be found between the independent variable (physical activity) and the mediator (RTWSE), and between the mediator (RTWSE) and the dependent variable (work status) (179). As RTWSE did not seem to predict work in the present cancer population (study II), the conditions to establish mediation were not present either. As discussed, RTWSE might be predictive of RTW in some cancer populations (i.e., in cancer survivors motivated for RTW). Consequently, the role of RTWSE as a mediator might also be different in other cancer populations.

Testing RTWSE as a mediator was an attempt to gain knowledge of how or why physical activity might affect work. However, we did not succeed in opening the black box, as RTWSE did not seem to be the mediator. Thus, opening that box is an objective for future research.

6.4 The Cancer and Work model as a framework – does it work?

Applying the Cancer and Work model as a framework in the present PhD process has been helpful. The model is considered a helpful tool in understanding the complexity of interacting factors in the RTW process, in the development of the studies, in identifying important covariates, in understanding and discussing results, and finally, in identifying areas of importance not included in the studies. The Cancer and Work model includes more or less the same factors as the Case-management ecological model, but the stakeholders in the health care system and the legislative and insurance system (70) are illustrated in much more detail in the latter model (Appendix 4). Keeping in mind the definition of cancer rehabilitation as *"a goal-oriented, collaborative process between a cancer patient, relatives and professionals"* (i.e., the first line of the definition of cancer rehabilitation as applied in Cancer Plan II (1)), the stakeholders in that collaborative process appears more clearly depicted in the ecological model than in the Cancer and Work model. As we did not include any stakeholders from the systems around the cancer survivor in the present dissertation, the Cancer and Work model was overall appropriate as a framework of the complexity of interacting factors, whereas research regarding the RTW process of cancer survivors including stakeholders might benefit from a joint perspective of these two models.

7.0 Conclusion

7.0 Conclusion

Based on the results of the three studies, the main conclusions of the present dissertation are:

1. The RTWSE-19 questionnaire showed good reliability, adequate validity and moderate responsiveness when applied in a population of employees undergoing chemotherapy for cancer.

2. The predictive value of RTWSE on RTW was not confirmed in the present sample of employees undergoing treatment for cancer, whereas female gender and palliative treatment were the only significant predictors of RTW.

3. Physical activity was positively associated with work status in employees undergoing treatment for cancer in the 12 months period after initiating chemotherapy. The hypothesis of RTWSE being a mediator between physical activity and work was, however, not confirmed.

8.0 Perspectives

"People have always striven to control the events that affect their lives"

These words by Bandura (13) were the point of departure of the present PhD dissertation. Supported by previous evidence, being physically active is a way of gaining or regaining self-confidence (105,117) and a sense of control (81,83) when diagnosed with cancer. These positive effects of physical activity were hypothesized to affect the expectations of being able to work and thereby positively affect work status and RTW in cancer survivors. However, based on the findings of the present dissertation, RTWSE does not seem to be "the missing link" in the observed associations between physical activity and work. Still, some implications for practice and future research deserve consideration.

8.1 Implications for practice

Identifying predictive factors of RTW can be helpful for practice as they can be used to identify persons in risk of late or no RTW. Based on current knowledge, RTWSE cannot be recommended to be used as a predictor of RTW in cancer survivors in general. Analyzing the results of Study II in the light of previous research suggested that RTWSE might be predictive of RTW in cancer survivors for whom RTW is a desired goal. Motivation thus becomes pivotal when discussing the predictive value of RTWSE. Motivation is also emphasized in the national guidelines regarding cancer rehabilitation. In the "Disease management program for rehabilitation and palliation in cancer" (90) by the Danish Health Authority from 2015, it is stated that the needs assessment of the individual cancer survivor must be based on and should identify *"needs, motivation and resources"* of the individual cancer survivor. Previous studies have shown, that many cancer survivors are left alone with questions about work and express a need for guidance (180,181). Identifying these cancer survivors in need of guidance is of utmost importance. Including work-related issues in the early phase of the assessment of needs is already recommended in the national guidelines (90) but many health care professionals at the hospitals hesitate to bring up issues of work with cancer survivors; mentioning work early in the process is considered inappropriate by many (182,183). Nonetheless, 75% of the adult working age population in Denmark are part of the labor market and 50% of all newly diagnosed cancer survivors are of working age. Thus, to many cancer survivors, considerations regarding work will be present at time of diagnosis regardless of prognosis, as they have to make a decision whether or not to work during treatment. The present dissertation identified RTWSE-19 as a psychometrically valid tool among cancer survivors. Considering the general observed hesitation among health care professionals to bring up issues regarding work with cancer survivors, RTWSE might be a tool for healthcare professionals or other stakeholders to structure the conversations regarding work-related issues. Including the RTWSE-19 as a tool in the early needs assessment process might be beneficial as it is conceivable, that it could facilitate the conversation regarding work and be useful by identifying the most challenging aspects of RTW for the individual. Yet,

research is needed regarding the use of the RTWSE-19 questionnaire in clinical practice, but it is assumed to be a logical next step.

The findings of the present dissertation support the value of physical activity for the work lives of cancer survivors, thereby contributing to the existing knowledge regarding the benefits of physical activity for cancer survivors. However, cancer illness and cancer treatment have shown to have a negative impact on the level of physical activity (184,185), and many cancer survivors do not adhere to guidelines regarding the recommended level of physical activity (186,187). Based on the existing knowledge regarding positive effects of physical activity for cancer survivors, initiatives supporting cancer survivors to sustain or become physically active despite the illness and the treatment-related side-effects can be recommended. In Denmark, municipal cancer rehabilitation includes elements of physical activity (122), and the national guidelines regarding cancer rehabilitation (90) emphasize the importance of physical activity for cancer survivors. Still, it has been found that a significant number of cancer survivors are not referred to cancer rehabilitation (122,188). In these situations, cancer survivors are lost in the gap between treatment at the hospital and municipal rehabilitation (188). Considerable efforts should be made to reach all cancer survivors. Based on the findings of the present dissertation, the benefits of physical activity concerning work appear to be separated from the benefits of physical activity as a part of an intervention program. According to previous research, counseling alone regarding physical activity from a health care provider can improve physical activity behavior among cancer survivors (189-191). It is thus conceivable, that systematic counseling at the hospitals may be a way of reaching all cancer survivors at an early stage of the illness trajectory. The challenge is, though, to identify those in need of an intervention program to increase the level of physical activity from those for whom counseling is enough. Staying within the perspective of the social cognitive theory, according to Bandura, interventions aiming at increasing the level of physical activity must be tailored to the individual's level of perceived efficacy (13).

Recommending rehabilitation initiatives including physical activity tailored to the specific needs of the individual cancer survivor is not a new recommendation. It resembles the recommendations already presented in the Danish national guidelines (90,122). Yet, the perspectives are new in that sense that they are based on research regarding the work lives of cancer survivors. However, more research within this area is needed. Based on the work of the present dissertation, physical activity appears to have a positive effect on the work lives of cancer survivors, but the scientific evidence within this area is still scarce. Therefore, "work" is still not found on the long lists of positive effects of physical activity for cancer survivors stated in the research literature (93) and in guidelines regarding cancer rehabilitation (122). More high-quality research supporting the effect of physical activity on work among cancer survivors is needed in order for that to happen. If "work" ends up being added to these lists in the future, it could be a way of bringing attention to the possible cost-effectiveness of physical activity programs

(i.e., less lost productivity) and thereby potentially be important knowledge for decision-makers in their decisions regarding allocating resources in healthcare.

8.2 Implications for future research

Future research within the area of occupational rehabilitation of cancer survivors will benefit from applying RTWSE-19 as a validated and psychometrically sound tool for measuring RTWSE in cancer populations. On the other hand, the questionnaire should be used with caution regarding responsiveness until more research has been done. Responsiveness of the questionnaire should be examined in a bigger study population to allow for more participants having changed in their RTWSE score at three months. Furthermore, RTWSE was not found to be predictive of RTW in the present sample of employees with cancer. More research is needed to examine the predictive value of RTWSE in different cancer populations. Based on existing knowledge, motivation for RTW as an effect modifier in the association between RTWSE and RTW seems relevant to include in future research. Further attempts to identify the underlying mechanisms between physical activity and work are recommended as well, as it might help us understand why and how physical activity affects work.

In general, research regarding RTW interventions for cancer survivors is still needed as the results within this field are scarce and of low quality (95). Similar conclusion can be drawn regarding the effect of physical activity on the work lives of cancer survivors (92,93). The research area of physical activity and work is furthermore dominated by studies conducted among women with breast cancer. Studies within other populations of cancer survivors are recommended. Finally, the limited inclusion of employers as stakeholders in the RTW intervention studies must be considered another general limitation within this area. Including the employers and/or the workplaces when designing future intervention studies is recommended.

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10.0 English Summary

Background

People with current or previous cancers have more sick days, lower productivity, reduced working hours and are at increased risk of unemployment and early retirement, compared to the general population. Approximately 50% of those diagnosed with cancer are of working age. The steadily increasing number of people with cancer of working age has led to a stronger demand for occupational rehabilitation for employees with cancer. Numerous studies underline the benefits of physical activity for cancer survivors. Physical activity during cancer treatment is associated with increased psychological well-being, quality of life, and reduced fatigue. The possible effects of physical activity on the work lives of cancer survivors have received less attention. Furthermore, the underlying mechanisms in the possible association between physical activity and work are scarcely examined as well. Self-efficacy (SE) may be a mediating factor in this association. SE is a psychological factor of great importance in the RTW process. Return to work SE (RTWSE) has been found to be positively related to work status and work ability and has furthermore proven to be a strong predictor of actual RTW in employees on sick leave due to both psychological and physical disorders. However, little attention has been given to the significance of SE in relation to work life variables in populations of cancer survivors.

The aims of the present dissertation were: 1) To examine the psychometric properties of the 19-item RTWSE questionnaire (RTWSE-19) in sick-listed employees with cancer in relation to reliability, validity and responsiveness, 2) to examine the predictive value of RTWSE on RTW in a sample of sick-listed employees undergoing chemotherapy for various cancers, and 3) to examine the association between physical activity and work status in employees undergoing chemotherapy for various cancers, and furthermore, to examine the mediating role of RTWSE in this association.

Methods

Study I was a validation study based on a sample of 68 cancer survivors participating in the Body and Cancer programs at three hospitals in Denmark (Aarhus University Hospital, Aalborg University Hospital, and Vejle Hospital) from September 2017 to August 2018. The Danish RTWSE-19 questionnaire was completed at baseline, after one week, and after three months. Work ability, cancer-related SE, and psychological distress were also measured. Internal consistency, test-retest reliability, construct validity, and responsiveness were examined. Study II was a prediction study based on 114 employees undergoing chemotherapy for cancer at Aarhus University Hospital November 2016 – Mai 2018 and followed for 15 months. Data included patient questionnaires (RTWSE, depression, fatigue, performance status), patient records (illness- and treatment-related factors), and Danish national registers (RTW and education). Using Cox proportional hazards regression, associations between RTWSE at baseline and weeks until full RTW were analyzed. Study III was a prospective observational study in which data from patient questionnaires (physical activity, RTWSE, performance status), patient records (illness- and treatment-related factors), and Danish national registers (work status, education)

were gathered for 217 employees initiating chemotherapy for cancer at Aarhus University Hospital November 2016 – Mai 2018. By means of logistic regression analyses, the associations of physical activity at baseline with work status at baseline and at 12 months, respectively, were examined. The role of RTWSE as a potential mediator was investigated using the Sobel Goodmann test.

Results

In Study I, the RTWSE-19 questionnaire showed good internal consistency, good test-retest reliability, adequate construct validity and moderate responsiveness when applied in a cancer population. In Study II, it was found that high RTWSE was significantly associated with shorter time to RTW in the unadjusted statistical models. But the association did not remain significant in the full adjusted model. Only female gender and palliative treatment were predictive of later RTW. In Study III, positive associations between physical activity and work status were found; employees who rated their daily level of physical activity level as moderate (>30 minutes/day) or high (>150 minutes/day) at initiation of chemotherapy were more likely to be working at initiation of chemotherapy and at 12-month follow-up, compared to sedentary employees. Similarly, being physically active in the leisure time for more than two hours/week at initiation of chemotherapy were positively associated with work status at 12-month follow-up. The precondition of RTWSE being a mediator in the associations between physical activity at baseline and work status at 12 months were not fulfilled and the Sobel Goodman test was thus not conducted.

Conclusion

Firstly, the RTWSE-19 questionnaire showed good reliability, adequate validity and moderate responsiveness when applied in a cancer population. Secondly, RTWSE did not predict RTW among employees undergoing chemotherapy for cancer. The predictive value of RTWSE thus seems to be different when measured in a population of employees on sick leave due to cancer than in other sickness absence populations. The only significant predictors of RTW were gender and treatment intention; female gender and palliative treatment being significantly associated with later RTW. Thirdly, being physical active at initiation of chemotherapy seems to be positively associated with work status in the 12-month period after initiation of chemotherapy. However, RTWSE does not appear to be a mediator in the observed associations between physical activity and work.

11.0 Dansk resumé

Baggrund

Nuværende og tidligere kræftpatienter har flere sygedage, lavere produktivitet, øget behov for reduceret arbejdstid samt øget risiko for arbejdsløshed og førtidspension sammenlignet med den almene befolkning. Cirka 50 % af de, der bliver diagnosticeret med kræft, er i den erhvervsaktive alder. Det stadigt stigende antal kræftpatienter i den erhvervsaktive alder har medført et øget behov for arbejdsrettet rehabilitering til denne gruppe. Talrige undersøgelser understreger fordelene ved fysisk aktivitet for kræftpatienter. Fysisk aktivitet under kræftbehandling er forbundet med øget psykologisk velbefindende, øget livskvalitet og reduceret træthed. De mulige positive effekter af fysisk aktivitet for kræftpatienters tilbagevenden til arbejde (TTA) er dog kun sparsomt belyst. De underliggende mekanismer i den mulige sammenhæng mellem fysisk aktivitet og arbejde er ligeledes begrænset undersøgt. Self-efficacy (SE) kunne tænkes at være en medierende faktor i denne sammenhæng. SE er en psykologisk faktor, der har vist sig betydningsfuld for arbejdsfastholdelse og TTA hos sygemeldte. Niveauet af SE i forhold til TTA, såkaldt Return To Work SE (RTWSE), hos sygemeldte ser ud til at være positivt associeret til arbejdsfastholdelse og arbejdsevne og har endvidere vist sig at være en stærk prædiktor af TTA hos sygemeldte medarbejdere med både psykiske og fysiske lidelser. Betydningen af RTWSE i forhold til kræftpatienters arbejdsliv er dog kun sparsomt undersøgt.

Formålene med denne ph.d.-afhandling var: 1) at undersøge RTWSE-19 spørgeskemaets psykometriske egenskaber i anvendelsen blandt kræftpatienter med fokus på redskabets reproducerbarhed, validitet og evne til at måle forandring over tid, 2) at undersøge den prædiktive værdi af RTWSE-19 spørgeskemaet i relation til TTA i en population af sygemeldte medarbejdere med kræft, og 3) at undersøge sammenhængen mellem fysisk aktivitet og arbejdsmarkedsstatus hos en gruppe medarbejdere med kræft, samt at undersøge om RTWSE medierer denne sammenhæng.

Metode

Studie 1 var et valideringsstudie. Studie populationen bestod af 68 kræftpatienter, som deltog i Krop og Kræft på tre hospitaler i Danmark (Aarhus Universitets Hospital, Aalborg Universitets Hospital og Vejle Sygehus) i perioden fra september 2017 til august 2018. RTWSE spørgeskemaet blev udfyldt ved baseline, efter 1 uge og efter tre måneder. Følgende variable blev yderligere målt: arbejdsevne, kræft-relateret SE, angst og depression. Intern konsistens, test-retest reproducerbarhed, begrebsvaliditet, og evnen til at måle forandring over tid blev undersøgt. Studie II var et prædiktionsstudie. Studiepopulationen bestod af 114 sygemeldte medarbejdere, som modtog kemoterapi for kræft på Aarhus Universitets Hospital i perioden mellem november 2016 og maj 2018, og som blev fulgt i 15 måneder efter opstart af kemoterapi. Data inkluderede patientspørgeskemaer (RTWSE, depression, træthed og fysisk funktionsniveau), patient journaler (sygdoms- og behandlings-relaterede faktorer) og nationale registre (TTA og uddannelse). Sammenhængen mellem RTWSE ved baseline og uger til TTA undersøgtes ved hjælp af Cox regression. Studie III var et prospektivt observationelt studie, hvor data fra

spørgeskemaer (fysisk aktivitet, RTWSE og fysisk funktionsniveau), patient journaler (sygdoms- og behandlings-relaterede faktorer) og nationale registre (arbejdsmarkedsstatus og uddannelse) blev indsamlet på 217 medarbejdere, som modtog kemoterapi for kræft på Aarhus Universitets Hospital i perioden fra november 2016 til maj 2018. Ved hjælp af logistisk regression undersøgtes sammenhængen mellem fysisk aktivitet ved opstart af kemoterapi med arbejdsmarkedsstatus ved opstart af kemoterapi og ved 12 måneder efter opstart af kemoterapi. Den medierende rolle af RTWSE blev undersøgt ved hjælp af Sobel Goodmann testen.

Resultater

I studie I viste RTWSE spørgeskemaet sig at have god intern konsistens, god test-retest reproducerbarhed, tilpas begrebsvaliditet og moderat evne til at måle forandring over tid i anvendelsen blandt kræftpatienter. I studie II viste høj RTWSE sig at være signifikant associeret med kortere tid til TTA i de univariate statistiske modeller, men den signifikante sammenhænge forsvandt i de multivariate modeller. At være kvinde samt at modtage palliativ behandling viste sig at være prædiktive faktorer for senere TTA. I studie III fandtes en signifikant og positiv sammenhæng mellem fysisk aktivitet og arbejdsmarkedsstatus. Medarbejdere med kræft, som havde et moderat (>30 minutter/dag i gennemsnit) eller et højt (>150 minutter/dag i gennemsnit) niveau af fysisk aktivitet ved opstart af kemobehandling, havde signifikant større sandsynlighed for at være på arbejde ved opstart af kemoterapi samt 12 måneder efter opstart af kemoterapi sammenlignet med inaktive medarbejdere med kræft. I tråd med dette, viste det sig endvidere, at det at være fysisk aktiv i sin fritid i mere end 2 timer om ugen ved opstart af kemoterapi var positivt associeret med arbejdsmarkedsstatus 12 måneder efter opstart af kemoterapi sammenlignet med at være fysisk inaktiv i sin fritid. Forudsætningerne for RTWSE som medierende faktor mellem fysisk aktivitet ved opstart af kemoterapi og arbejdsmarkedsstatus efter 12 måneder blev ikke opfyldt, og Sobel Goodmann testen blev derfor ikke gennemført.

Konklusion

Anvendt i en kræftpopulation viste RTWSE spørgeskemaet god reproducerbarhed, passende validitet og moderat evne til at måle forandring over tid. RTWSE viste sig ikke at være en prædiktor for TTA blandt medarbejdere sygemeldte på grund af kræft. Den prædiktive værdi af RTWSE ser derved ud til at være anderledes, når den måles blandt kræftpatienter sammenlignet med andre populationer af sygemeldte. De eneste signifikante prædiktorvariable i forhold til TTA var køn og behandlingsintension, hvor det at være kvinde og det at modtage palliativ behandling ser ud til at være signifikant associeret med senere TTA. Slutteligt viste det sig, at fysisk aktivitet ved opstart af kemoterapi ser ud til at være positivt associeret med arbejdsmarkedsstatus 12 mdr. efter opstart af kemoterapi. RTWSE ser dog ikke ud til at være en medierende faktor i sammenhængen mellem fysisk aktivitet og arbejde.

12.0 Appendices

Appendix 1

Study I: Validation of the Return To Work Self-Efficacy questionnaire in a population of employees undergoing treatment for cancer

Rosbjerg, R., Hansen, D.G., Zachariae, R., Stapelfeldt, C.M., Hoejris, I., Rasmussen, M.T., Drysdale, S.W., Labriola, M.

Appendix 2

Study II: The predictive value of return to work self-efficacy for return to work among employees with cancer undergoing chemotherapy

Rosbjerg, R., Hansen, D.G., Zachariae, R., Hoejris, I., Lund, T., Labriola, M.

Appendix 3

Study III: Physical activity, return to work self-efficacy, and work status among employees undergoing chemotherapy for cancer - a prospective study with 12 months follow-up

Rosbjerg, R., Zachariae, R., Hansen, D.G., Hoejris, I., Duijts, S., Gehr, N.L., Andersen, I.D., Labriola, M.

Appendix 4

"The arena in work disability prevention": The case-management ecological model

Appendix 5

Study I:

The patient information folder

Questionnaires: baseline, one week and three months

Appendix 6

Studies II and III:

The patient information folder

The baseline questionnaire

Questionnaire for survey, conducted among the nurses at Department of Oncology, Aarhus University Hospital

Appendix 7

Table 16: Overview of studies regarding physical activity and work.