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**AFFILIATION TO THE LABOUR
MARKET AFTER DIAGNOSIS AND
TREATMENT FOR BREAST CANCER –
THE IMPACT OF PSYCHOLOGICAL
VULNERABILITY**

**BY
LAURA SANDHOLDT SCHÄRFE JENSEN**

DISSERTATION SUBMITTED 2017



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AFFILIATION TO THE LABOUR MARKET AFTER DIAGNOSIS AND TREATMENT FOR BREAST CANCER – THE IMPACT OF PSYCHOLOGICAL VULNERABILITY

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Dissertation submitted 2017



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Laura Schärfe Jensen, March 2016

LIST OF PUBLICATIONS

This PhD thesis is based on the following studies that were carried out during my research fellowship in the Department of Social Medicine, Aalborg University Hospital in the period 2014-2017.

1. *Jensen LS, Overgaard C, Garne JP, Bøggild H & Fonager K.* The impact of a history of psychiatric medical treatment on return to work after a diagnosis of breast cancer: a registry based study. Manuscript in review. *Scandinavian Journal of Public Health.*
2. *Jensen LS, Overgaard C, Bøggild H, Garne JP, Lund T, Overvad K & Fonager K.* Long-term consequences of breast cancer on personal income: a registry based cohort study among Danish females. Manuscript in review. *BMC Public Health.*
3. *Jensen LS, Overgaard C, Garne JP, Carlsen K, Bøggild H & Fonager, K.* Can register data be used as a proxy for perceived stress? A cross sectional study. Published in *Annals of Epidemiology* 26 (2016), 493-499.

ENGLISH SUMMARY

In Denmark, nearly 5,000 women are diagnosed with breast cancer every year, and more than 60,000 women are living with a history of breast cancer. Surviving breast cancer does not mean surviving without consequences, which may be numerous and affect life in one way or another. One of the aspect of life affected by breast cancer is the affiliation to the labour market. Breast cancer is positively associated with unemployment, early retirement and disability pension, and for most women the diagnosis of breast cancer entail a temporary leave from work. Returning to work following sickness absence caused by breast cancer is important for the individual women, their families and for society in general. A variety of factors are demonstrated to affect the return to work rate and affiliation to the labour market in the following years among women diagnosed with breast cancer. One of the factors are prior and present mental health problems, which are known to affect labour market affiliation also when cancer is not present.

Throughout this dissertation the term “psychological vulnerability” will be used as a term including mental health problems, psychiatric disorders, stress and it will be measured through the use of psychiatric medical treatment (antidepressants, anxiolytics, and antipsychotics). In study III will consultations with psychologists or psychiatrists also be included.

The aim was to examine short-term and long-term consequences of breast cancer and psychological vulnerability on different aspects of affiliation to the labour market: return to work, employment rates and income changes, up to 10 years of follow-up. The study focused on women being self-supporting prior to the diagnosis of breast cancer and women being able to participate in the work force through follow-up. A further purpose was to examine whether register data on psychiatric treatment could be used as a proxy for perceived stress.

Study I explored whether psychiatric medical treatment received 2, 3 or 4 years prior to a diagnosis of breast cancer influenced return to work one year later. The study found, that among women, who had received psychiatric medical treatment prior to the diagnosis of breast cancer, a reduced percentage of individuals had returned to work one year later (63% versus 69%), and the likelihood for returning to was (RR=0.91 (95% CI 0.87-0.94)). The influence of psychiatric medical treatment on return to work after sickness absence caused by breast cancer was strongest among the youngest age-group, and among women with a high income.

Supplemental analyses for the dissertation addressed the long-term consequences of both breast cancer and psychological vulnerability according to employment rates

among Danish women. Both breast cancer and psychological vulnerability prior to a diagnosis of breast cancer decrease the percentage of women being self-supporting.

Study II investigated income changes in the years following a diagnosis of breast cancer. Women diagnosed with breast cancer had – compared to a breast cancer-free cohort - a higher mean annual income one year prior to a diagnosis of breast cancer and for all 10 years of follow-up. However, it took women diagnosed with breast cancer between seven (stage IA) and nine years (stage IB-IV) to achieved the same percent-wise change in income as cancer-free women. Having a history of psychological vulnerability prior to a diagnosis of breast cancer did not negatively affect the long-term income changes for participating in the work force.

Study III examined whether registry data on prescribed psychiatric medical treatment and information on consultation with psychologists or psychiatrists could be used as a proxy for perceived stress. The study found, that despite a positive association between prescribed psychiatric medical treatment/ consultations with psychologists or psychiatrist and perceived stress, registry data could not be used as a proxy for perceived stress, because of low positive predictive values.

This thesis, with focus on psychological vulnerability prior diagnosis of breast cancer, contributes with new knowledge about short- and long-term consequences of breast cancer among a sub-group of women diagnosed with breast cancer. It is the first Danish study examining the long-term consequences of breast cancer on personal income, compared to a cancer-free cohort. Furthermore, the thesis found that registry data on psychiatric medical treatment and consultations with psychologists or psychiatrists could not be a valid proxy for perceived stress.

DANSK RESUME

I Danmark rammes næsten 5.000 kvinder hvert år med brystkræft og mere end 60.000 kvinder lever med en tidligere brystkræft diagnose. Ofte er der følgevirkninger som påvirker livet i en eller anden grad. Et af de aspekter som ofte påvirkes af brystkræft er tilknytningen til arbejdsmarkedet. Brystkræft er positivt associeret med arbejdsløshed, efterløn og førtidspension, og for de fleste kvinder betyder det, at diagnosticeres med brystkræft en midlertidig pause fra arbejde. Tilbagevenden til arbejdsmarkedet efter sygefravær forårsaget af brystkræft er vigtigt for den enkelte kvinde, deres familier, og for samfundet i almindelighed. Forskellige faktorer har vist sig at have betydning for tilbagevenden til arbejdsmarkedet, og for den fremtidige tilknytning til arbejdsmarkedet hos kvinder diagnosticeret med brystkræft. En af disse faktorer er det at have psykiske vanskeligheder – både tidligere og aktuelle. Psykiske vanskeligheder i sig selv påvirker også tilknytningen til arbejdsmarkedet.

I denne afhandling bruges ordet ”psykisk sårbarhed” som et bredere begreb, der dækker psykiske vanskeligheder, psykiske sygdomme og stress. Det vil blive målt som forbruget af medicin udskrevet for psykiske lidelser (antidepressiv-, angstdæmpende-, og antipsykotisk medicin). I studie III vil konsultationer hos psykolog og psykiater blive inkluderet.

Formålet med denne afhandling er at undersøge både kort- og lang tids konsekvenser af brystkræft og kombinationen af brystkræft sammen med psykisk sårbarhed i forhold til forskellige aspekter af arbejdsmarkedstilknytningen: tilbagevenden til arbejde efter et år, det at være selvforsørgende i de efterfølgende år og indkomstændringer over en ti års periode. Studiet fokuserer på kvinder der er selvforsørgende forud for diagnosetidspunktet og kvinder der er en del af arbejdsstyrken i de efterfølgende år. Endvidere er formålet det undersøges om register data på forskellige former for psykiatrisk behandling kan bruges som et mål for selv vurderet stress.

Studie I undersøgte hvorvidt behandling mod psykiske lidelser 2, 3 eller 4 år før diagnosticering af brystkræft påvirkede tilbagevenden til arbejdsmarkedet efter et år. Studiet viste, at tidligere behandling for psykiske lidelser reducerede procentdelen af kvinder, der var tilbage på arbejdsmarkedet fra 69% til 63%. Sandsynligheden for at være tilbage i arbejde blev også reduceret (RR=0.91 (0.87-0.94)). Den negative betydning af behandling for psykiske lidelser før diagnosticering af brystkræft var mest udtalt for yngre kvinder, og hos kvinder med en høj indtægt.

Supplerende analyser - lavet specielt til denne afhandling - undersøgte hvorvidt betydningen af brystkræft og psykisk sårbarhed i forhold til at være selvforsørgende i de følgende år. Både brystkræft og psykisk sårbarhed forud for diagnosticering af

brystkræft reducerede procentdelen af kvinder der var selvforsørgende i de efterfølgende år.

Studie II undersøgte eventuelle indkomstændringer i årene efter diagnosticering hos brystkræft. Kvinder, der var diagnosticeret med brystkræft havde – sammenlignet med kvinder uden brystkræft - en højere gennemsnitlig årlig indkomst et år før diagnosetidspunktet samt for alle de efterfølgende 10 års. Til trods for dette tog det kvinderne, der var diagnosticeret med brystkræft, henholdsvis 7 år (stadie IA) og 9 år (stadie IB-IV) at nå den samme procentvise ændring i indkomsten, som kvinder der ikke var diagnosticeret med brystkræft. Dét, at have modtaget medicinsk behandling for psykiske lidelser forud for diagnosetidspunktet havde ikke en negativ påvirkning på de langsigtede indkomstændringer for de kvinder der var en del af arbejdsstyrken.

Studie III undersøgte hvorvidt register data på udskrevet medicinsk behandling for psykiske lidelser samt konsultationer hos psykolog eller psykiater 2, 3, eller 4 år forud for diagnosticering af brystkræft kunne bruges som en mål for selvvrurderet stress. Det blev vist, at selv om der var en positiv association mellem udskrevet medicin for psykiske lidelser og konsultationer hos psykolog eller psykiater og selvvrurderet stress, så kunne register data ikke bruges som et mål for selvvrurderet stress på grund af lave prediktive værdier.

Denne afhandling med fokus på psykisk sårbarhed forud for diagnosticering af brystkræft bidrager med ny viden om kort- og lang tids konsekvenserne af brystkræft hos en undergruppe af kvinder diagnosticeret med brystkræft. Det er det første danske studie der undersøger langtids-konsekvenserne af brystkræft på personlig indkomst, og sammenligner med kvinder uden brystkræft. Endvidere finder afhandlingen at register data på psykiatrisk behandling ikke kan bruges som et mål for selvvrurderet stress.

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CHAPTER 1: INTRODUCTION

The major theme of this dissertation is affiliation to the labour market following a diagnosis of breast cancer, which is relevant since a large part of women diagnosed with breast cancer are of working age and thereby part of the work force prior to their diagnosis of breast cancer. Some patients experience problems in returning to work, but not all. Hence, it is important to identify those women with problems in returning to work and provide them with the appropriate support and counselling in order to help them return to work.

One potential group of women with a higher risk of lasting absence from work may be women with a psychological vulnerability existing prior to the diagnosis of breast cancer. Psychological vulnerability (measured as the use of psychiatric medical treatment in this dissertation) itself is found to affect the affiliation to the labour market. Furthermore, it is associated with an increased risk of getting breast cancer, and additionally, psychological vulnerability prior to a diagnosis of breast cancer is reported to increase the level of psychological vulnerability in the wake of breast cancer(1), which is associated with a prolonged period on sick leave afterwards and decrease the chance for return to work .

In addition, this dissertation focuses on methodological aspects, examining whether register data on prescriptions of psychiatric medical treatment together with data on consultations with psychologist or psychiatric can be used as a proxy for perceived stress. Stress is used in this part of the dissertation instead of psychological vulnerability, since no data on the latter were available. A correlation between psychological vulnerability and stress is demonstrated in the literature and will be described.

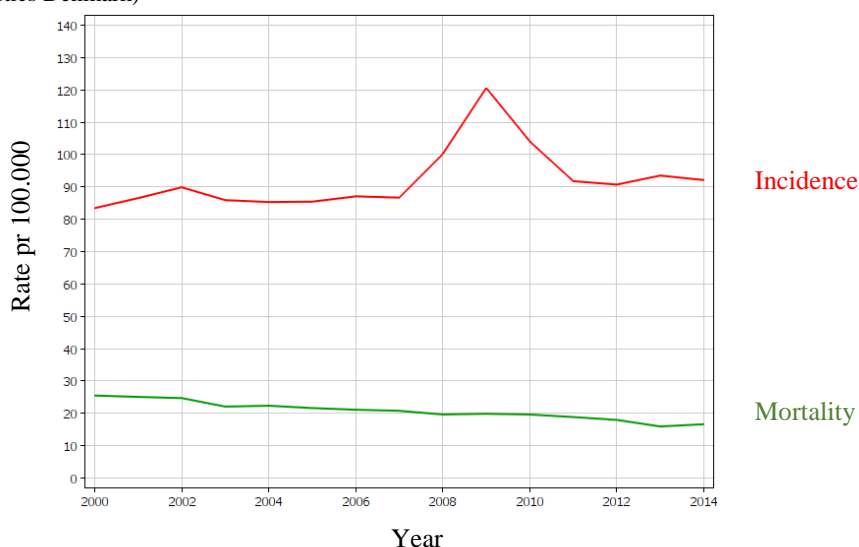
The first chapter provides a description of breast cancer epidemiology in Denmark, some of the consequences experienced by the individual woman and a description of existing knowledge on breast cancer and affiliation to the labour market including reimbursement of social benefits. A description of psychological vulnerability will follow as it is used in this dissertation, together with an introduction to Cohens Perceived Stress Score (PSS). Finally, the rationale for this dissertation will be given.

1.1 BREAST CANCER IN DENMARK

Incidence and mortality

Breast cancer is a common disease in Denmark with 4,761 new cases in 2014 (2) (See Figure 1), which is the second highest incidence rate of breast cancer in the world (3). In 2014, 60,197 Danish women were living with a history of breast cancer (4), and this number is expected to increase due to increasing life expectancy, improved surgical and medical therapies and early detection.

Figure 1: Incidence rate and mortality rate of breast cancer in Denmark, 2000-2014 (Ref. Statistics Denmark)



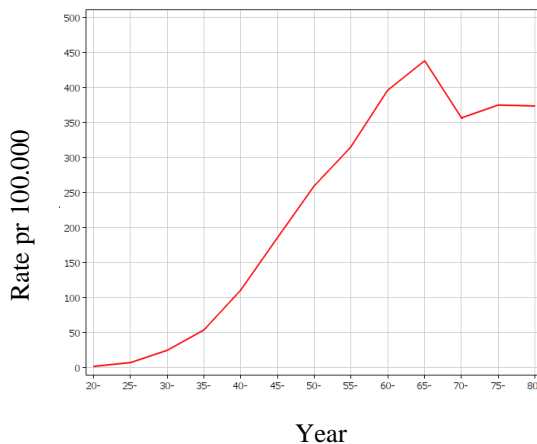
Danish studies (5,6) have demonstrated that the incidence of breast cancer increase with increasing social advantage, which is consistent with other European studies amassed in a review from 2016 (7). A meta-analysis (including 4 studies) conducted in the review showed significantly higher breast cancer incidence among women with higher socioeconomic status, which may be explained by reproductive factors, mammography screening, hormone replacement therapy, and lifestyle factors (high Body Mass Index and alcohol consumption). In relation to mortality, the results were more ambiguous. The review reported (based on another meta-analysis also including four studies) a significantly increased mortality among women with a higher socioeconomic status, while no association was found in another study (8).

In addition to higher socioeconomic status, the incidence of breast cancer may be increased in female subjects with schizophrenia or depression (5,9–11). A review

from 2009 reported (10), that the increase in incidence might be a result of reduced parity among women admitted for psychiatric disorders, since after adjusting for this factor no increase in incidence of breast cancer was demonstrated (11). Reproductive factors are thereby found to be an explanatory factor of the increased incidence of breast cancer - both in relation to socioeconomic status and psychiatric disorders.

The incidence of breast cancer is demonstrated to increase with increasing age, and is at the highest at 65 years of age. Despite the fact that a large part of women are diagnosed at an age above working age, it still affects a lot of women in the labour market (Figure 2).

Figure 2: Incidence rate of breast cancer in Denmark in relation to age, 2000-2014 (Ref. Nordscan).



1.2 CONSEQUENCES OF BREAST CANCER

Surviving breast cancer does not mean surviving without consequences, some of which may be short-term, long-term or even permanent. In tune with this, Bradley and Bednarek say that:

“certain types of cancer are no longer perceived as terminal illnesses, but instead, chronic diseases that require regular monitoring (e.g. mammograms, blood tests), treatment (e.g. tamoxifen), and life style modifications (e.g. smoking cessation, diet, exercise)” (12)

The consequences of being diagnosed with breast cancer and accomplish the recommended treatment are numerous and by no means uniform (5). The impact for the individual women is unique, and it is difficult to make generalizations, although tendencies may be seen. One life-long consequence striking women diagnosed with

breast cancer is the fear of recurrence and dying (13). Treatment is comprehensive and includes for the majority of women a combination of different treatment modalities: surgery, radiotherapy, chemotherapy and endocrine treatment, which lead to various side effects. Some of the most cited are fatigue (14,15), sleep disturbances (16), lymphedema (17), cognitive dysfunction (18), pain (19) and diverse mental health problems (anxiety, depression) (20–22) which all, in one way or another, affect life after ended treatment, and thereby also - for the majority of women at working age - future affiliation to the labour market.

1.3 RETURN TO WORK

Returning to work after sickness absence caused by breast cancer is one of the crucial factors in the process of trying to return to life as it was prior to the diagnosis of breast cancer, when being at working age. Return to work has important implications for:

- 1) The individual women: return to work is seen as an important milestone in the transition from illness to normality (23,24), a transition desired by many women, although it can be hard to achieve. Work may be related to quality of life (25), and may be crucial for the women's economic, social and psychological health (26).
- 2) The family: return to work for the mother/ wife/ partner means normalization in the internal relations changes with the diagnosis of breast cancer. For mothers to depending children, the key factors that influence the decisions to continue in/ return to/ or leave paid work include: a change in perspective regarding what is important in their lives; level of support from the workplace and home; the extent to which participation in paid work is a financial necessity; the extent to which their identity is connected to paid work, and; ongoing level of pain and fatigue (27).
- 3) Society: return to work is desired from a socio-economic point of view. An increase in the employment rate means an increase in taxes, together with a decrease in the rates of reimbursement of various social benefits (26).

Women diagnosed with breast cancer are found to have a high “return to work” rate compared to women diagnosed with other types of cancer (28), which may be explained by less severe functional limitations following successful treatment among women diagnosed with breast cancer compared to other cancer patients (29). However, studies have found that the period until return to work is prolonged among women diagnosed with breast cancer compared to other types of cancer (30), and that the period on sick leave has prolonged during the last decades (31). These findings may reflect the extensive treatment for breast cancer and the changes in treatment

during the last decades, and may argue for the use of more long-term follow-up studies in future research.

1.4 FACTORS AFFECTING RETURN TO WORK

Return to work after diagnosis and treatment of breast cancer is a process influenced by a variety of factors related to different aspects of life. In the following table (Table 1), some of the factors found in existing literature will be listed. The factors are found in studies identified through a systematic literature search, and the factors have been critically considered. The construction of the table is inspired by the model of chronic cancer survivorship and return to work (Cancer & work model) presented by Feuerstein and colleagues in 2010 (32). The model is constructed on basis of a systematic review including 45 papers on cancer and return to work. Seven broad categories of variables (health and well-being, symptoms, function, work environment, work demands, cancer survivor characteristic and policies, procedures, & economic factors) associated with four work outcomes (return to work, work ability, work performance, and sustainability) are included in the model. For Table 1 in this thesis, the 7 categories are condensed to five (symptoms and function has been added together, as have work environment and work demands). The policies, procedures, and economic factors have been renamed societal and cultural factors to broaden up this category.

Table 1: Factors associated with return to work following a breast cancer diagnosis and treatment divided into five broader categories (red=barriers; blue=facilitators; and green=can operate as both a barrier and a facilitator, or found to be of no importance):

Categories	Barriers, facilitators, or both/ none	Factors
Symptoms and function	Barriers	Tumor stage (33–37), lymph node involment (37), Her2 status (37), fatigue (34,35,38–43), exhaustion (42), nausea (38), pain (40,43), lymphedema (36,40,44), hair loss (24), febrile neutropenia (38), depression and anxiety (39,43,45), emotional distress (44), the scale of the operation (34,38), axillary lymph node dissection (46), endocrine therapy (35), cognitive changes/ ability (40,47), new cancer event (48).
	Both	Chemotherapy (33,35,37,40–42,46,49–54), chemotherapy and radiotherapy (40,55); radiotherapy (37,56), axillary node dissection (52).

Health and well-being	Barriers	Comorbidity (34,36,51,57), low satisfaction with vocational situation (52).
	Facilitators	Gain a sense of normality (23,24,42,45,58), re-assessment of work life balance (23), sense of belonging (59,60), higher life satisfaction with life as a whole (46,52), willingness/ self-motivation (42,45), good self-rated health (46), strong wish to stay in the labour market (60), sense of meaning (61).
	Both	Health in general (33).
Work environment and work demands	Barriers	Employer discrimination (33), employers negative attitude (45), high demands at job (43,46,52,57), anxiety for letting down employer (24), anxiety for being less competent (24), heavy lifting (33), reduced work related abilities (34,39), reduced working hours (34,35), manual work (51), job is too difficult (48), discouraging work environment (42), public sector (62).
	Facilitators	Relationship with employers (23), moral support and adjustments from employer/ colleagues (36,39,40,43,47,58,60,63,64), workplace accommodations (33,65), hours worked prior diagnosis of breast cancer (30), white collar job (50), self-employed (36), missing workplace (42).
Individual characteristics	Barriers	View on work changed (60), changes in priority (63,66).
	Facilitators	Distraction from breast cancer (63), no children living at home (51), good self-assessed workability 6 months after the first day of sick leave (67).
	Both	Age (33–35,40,50,52,55), income (33,34,39,50,55), education (33–35,39,40,52), marital status (34,40,52), financial issues (23,24,43,45,61).
Societal and culture factors	Barriers	Missing advice from health professionals (24,38,47,57,68,69), black race (33), no health insurance (48), over protective family (43), disrespectful attitude of social insurance officers (64).
	Facilitators	Union membership (48,50,55), social support (40,45,51,57,58,64,65), family history of breast cancer (58).

Table 1 shows, that barriers against return to work are mainly related to severity of breast cancer and side-effects following treatment, factors related to unfavourable working conditions, and missing support from colleagues and employees. Facilitators are related to general well-being, getting social support and experiencing a sense of belonging and normality. Several of the treatment modalities are found to have divergent results depending on different studies and various time frames. One

example is chemotherapy. It is shown, that chemotherapy is associated with prolonged sick leave after 6 month by Johnson et al, 2011 (52), while no effect of chemotherapy on sick leave was reported after 12 and 18 months by Bouknight et al, 2006 (33). Bushunow et al. (70) described – in 1995 – that return to work after 3, 6, 9, and 12 months were not affected by chemotherapy. Common to all the studies are a low number of participants (n= 102 (52), 145 (70) and 416 (33)). Other factors with divergent results are demographic- and socioeconomic factors. Educational level is demonstrated to have divergent results on return to work after diagnosis of breast cancer (33–35,39,40,52), and a Danish study found that the effect of educational level changes according to whether the individual women were employed in the public sector or the private sector (62).

Table 1 included both quantitative and qualitative studies, and different study designs were used. The majority of the quantitative studies are cohort studies.

The reduced affiliation to the labour market as a consequence of breast cancer, may induce changes in income for the majority of women being self-supporting prior to the diagnosis of breast cancer.

1.5 CHANGES IN INCOME AFTER BREAST CANCER

Studies on income after a diagnosis of cancer/ breast cancer, have been performed in different countries all over the world. In this, and the following sections, the focus will be on studies performed in the Nordic countries, because the Nordic countries are associated with a special model of welfare policy characterised by a general, solidaristic, and universal nature of social legislation: the state redistribution welfare system (71), which makes comparison between studies more reasonable. Table 2 gives an overview and a critical assessment of studies on income changes following a diagnosis of breast cancer conducted in the Nordic countries. The studies were identified through a systematic literature search.

Most of the studies described a negative association between breast cancer income changes in the years following the diagnosis of breast cancer. The preponderance of studies had a follow-up period between one and five years, and demonstrated that the negative effect of breast cancer persisted throughout the study period (56,72–74). In a Danish study, conducted by Rayce et al. (74), almost ¼ of women diagnosed with breast cancer experienced a loss in annual income in the first year following diagnosis. No information was given in relation to the definition of income, but comparing to the results in some of the other studies in Table 2, the income variable is assumed not to include social benefits or other transfer benefits, since a decrease is seen.

Table 2: Studies on income changes after cancer/ breast cancer (BC=breast cancer) ordered by publication year.

Author (year)	Title	Design	Aim	Study population	Exposure	Outcome	Definition income	Results	Comments
Rayce et al. (2008)	Economic consequences of incident disease: The effect of loss of annual income.	Register-based cohort study.	To estimate the effect of BC on loss of annual income on an individual level, to analyse whether loss of job mediates the effect on loss of annual income, and to analyse whether an association is modified by socio-economic position (occupational level and income in the year prior to diagnosis).	The setting was a 10% random sample of all individuals living in Denmark and aged 43-60 years in 1996-1999. The study (333 women diagnosed with BC).	First-time BC.	Moving one decile or more down the income distribution of the whole population (corresponding to 25,000 DKK in the year following diagnosis of BC compared to the average income of the two years prior BC.	Not stated.	22.5% experienced a loss in annual income ≥ 1 decile) in the year following diagnosis. $OR_{sexes} = 1.37$ for moving down a decile in income distribution. No mediating effect of employment was found.	No definition on income. Relative old study – changes in legislation has been made since then. Complicated study selection. Short follow-up.
Syve et al. (2008)	Cancer's impact on employment and earnings – a population-based study from Norway.	Register-based cohort study.	To explore the extent to which Norwegian cancer survivors stay affiliated to working life compared to the cancer-free population, and to quantify declines in earnings associated with cancer.	Women, born in Norway, alive and residents throughout 2001, 549,258 women were included (22,206 cancer survivors and 7,871 = BC).	Diagnosis of different types of cancer.	Percentwise decline in earnings compared to earnings of women employed in 2001, 40-44 years old with elementary school education (\$25,500).	Gross labour earnings (Sickness benefits are included in the earnings variable, but not compensations e.g. disability pension and capital gains).	BC=an overall 13.9% decline in earnings. Education = modifying factor in relation to all cancer types incl. BC.	For cancer in general calculations for different time periods are performed. For each cancer-type only one result is stated (the mean for all years).
Eaker et al. (2011)	Breast Cancer, Sickness Absence, Income and Marital Status. A Study on Life Situation 1 Year Prior Diagnosis Compared to	Matched cohort study.	To examine the possible influence of a BC diagnosis on subsequent working, and marital status, sickness absence and income.	4,761 women aged 40-59 years of age and registered with primary BC in Sweden during 1992-2003 matched to 23,805 women without BC.	Diagnosis of BC.	10% or 20% increase in income among women diagnosed with BC compared to cancer-free women.	Personal income from all sources minus taxation.	3 and 5 years after diagnosis of BC: RR for income increase with 10% or 20% was respectively 0.99/0.98 among cases compared to controls.	The majority of studies on income report decrease in income – this study examine increase. In congruence in relation to age: 20-59 or 40-59.

Author (Year)	Title	Design	Aim	Study population	Exposure	Outcome	Definition income	Results	Comments
Haugland et al (2012)	3 and 5 Years after Diagnosis. A cohort study of permanently reduced work ability in breast cancer patients.	Cohort study.	To explore various aspects of employment and the risk of receiving disability pension over time since primary diagnosis in BC patients compared to cancer-free women.	1,548 women diagnosed with BC (all stages) between 1992 and 1996 at the age of 45-54 years and 1,548 cancer-free women matched on age, marital status and municipality, Norway.	Diagnosis of BC.	Income reduction > 10% (€ 2,000).	Personal income excluding transfers and social benefits.	Income year-1 was significantly higher among BC compared to cancer-free (when working at time of diagnosis). BC increased the risk for negative changes in income >10%. The negative effect of BC on income was temporary (strongest for the first 2 years. No significantly difference after 5 years).	Rough measure for income changes (>10%) Relative old study Only 1-1 matching – may increase the risk for selection bias. Long follow-up.
Syse et al (2012)	Cancer's unequal impact on incomes in Norway.	Cohort study.	To explore the extent to which cancer survivors' sociodemographic features influence their incomes given cancer and stage, from one to eight years post-diagnosis. To explore how cancer survivors' current incomes depend upon their age, educational attainment, prior income, number of children and marital status.	502,500 Norwegian women of which 4,908 were diagnosed with BC between 2000 and 2007, aged 40-39 years. Having an income in 2008.	Diagnosis of different types of cancer.	Percent-wise reduction in income in 2008 referring to 336,100, which is the estimated income in 2008 of childless, unmarried women 45-49 years old with a partial college degree and labour earnings below \$10,000 in 1999.	Labour earnings and any compensatory welfare benefits.	Women diagnosed with BC experienced a 5.7% decline in income compared to earnings of childless, unmarried women 45-49 years old with a partial college degree and labour earnings below \$10,000 in 1999 (\$36,100). The effect of BC was most severe for those with a low educational level and/or low prior earnings and became more pronounced with increasing age. No effect modification of marital status.	The outcome measure is very specific, but in relation to the separated analyses (education, prior income, age and children) it give sense.
Heinesen et al (2013)	Effects of breast and colorectal cancer on labour market	Longitudinal study	To estimate causal effects of breast and colorectal cancer on labour market	5,683 women diagnosed with BC and 157,137 cancer-free	Diagnosis of BC	In accordance to income changes in DKK from 2 years before diagnosis of	Three definitions: a = earnings; b = total	Significant, negative effect of BC on earnings and total income 1-3 years later. Restricting the	Outcome not clearly stated

Author (year)	Title	Design	Aim	Study population	Exposure	Outcome	Definition income	Results	Comments
	outcomes – Average effects and educational gradients.		outcomes 1-3 years after the diagnosis.	controls, age = 30-60 years; 2000-2004; Denmark.		breast cancer to three years after.	personal income before taxes (including transfer income); and ϵ = total income after taxes.	analyses to persons who are employees (most of the year). Only a small negative effect is found on earnings, marginally significant for women diagnosed with breast cancer.	
Bemh et al. (2013)	A controlled study of income development for breast cancer survivors in Norway.	Cohort study.	Seeks to assess the impact of BC on survivors' annual income at 1 to 13 years of follow-up.	4,020 (2,010 cases and 2,010 matched cancer-free controls) between 45-54 years of age. Matched for age, marital status, and municipality of residence. Cases were diagnosed between 1992-1996.	Diagnosis of first time BC.	Changes in income each year of follow-up compared to income one year prior to diagnosis of BC.	Personal income excluding transfers and social benefits.	Cases: income reduced immediately after diagnosis. After 1 year the income between cases and controls = significantly different, a pattern that remained persistent for the rest of the follow-up period. Increasing stage = differences became more pronounced through not always statistically significant.	Outcome not clearly stated.
Andersen et al. (2015)	The effect of breast cancer on personal income three years after diagnosis by cancer stage and education: a register-based cohort study among Danish females.	Cohort study.	To investigate whether there is an association between stage of incident BC and personal income three years after diagnosis.	7,372 women aged 30-60 years diagnosed with BC were compared to 213,276 controls.	Diagnosis of incident BC.	Income three years after diagnosis of BC.	Gross income including social benefits and other transfers.	Three years after diagnosis of BC, controls experienced an increase in income, while BC patients experienced a decrease in income compared to pre-cancer income (2.5% if BC is localised and 3.7% if BC is metastatic). No statistically significant educational gradient in the effect of cancer stage on income was found.	Control group not comparable to cases in relation to age. Large sample size

If that is the case, then the follow-up period should be longer to create new knowledge, because it is known that earnings are reduced immediately after a diagnosis of breast cancer since a large part of the women diagnosed with breast cancer are absent from work in order to receive treatment. Income is still affected three to five years after the diagnosis of breast cancer, which ask for more long-term studies.

Three of the studies included longer follow-up periods and reported divergent results (75–77). Syse et al. demonstrated, that women diagnosed with breast cancer in the period 2000 through 2007, in 2008 (follow-up between 1 and 8 years) experienced an overall 5.7% reduction in income compared to a cancer-free reference category (75). Only a part of the study population was women diagnosed with breast cancer and the study did not examine the yearly changes for each type of cancer. Examining the different cancer sites together the study illustrated that the negative impact of cancer was most pronounced one to two years after diagnosis. Benth et al. (77) and Hauglann et al. (76) examined only women diagnosed with breast cancer and proposed a negative effect of breast cancer on income, but while Benth et al. found the effect to be persistent for all 13 years of follow-up, Hauglann et al. reported only a temporary negative effect of breast cancer on income; a strong effect for the first two years after diagnosis and no significant effect after 5 years of follow-up. The income variable in the two latter studies included only earnings, but while Hauglann et al. only examined women participating in the work force, Benth et al. included all women in the study populations also those receiving temporary and permanent benefits, which may explain the discrepancy in the results.

Two of the studies indicated that the decrease in income was associated with severity of breast cancer (73,77); the higher stage of breast cancer, the more pronounced effect on income. In relation to educational level, the results were divergent: according to Syse et al. (75) the effect of breast cancer on income was more pronounced among low-educated women, while no educational modification was demonstrated by Rayce et al. (74). Due to the Danish welfare system (71) with reimbursement independent of educational level, no differences would be expected after one year of follow-up as in the study conducted by Rayce et al.. Marital status seemed to have no influence on changes in income (75).

According to existing literature, breast cancer is proposed to have a temporarily negative effect on income in the years following breast cancer among women being part of the work force. The long-term consequences of breast cancer on income in a Danish setting have not been examined, nor has the effect of severity of disease or modifying socio-economic factors.

1.6 THE ASSOCIATION BETWEEN BREAST CANCER AND SOCIAL BENEFITS IN THE NORDIC COUNTRIES AND FACTORS WITH IMPACT ON THIS ASSOCIATION

Studies of return to work show that not all women diagnosed with breast cancer manage to be self-supporting in the following years. A positive association between breast cancer and different types of social benefits is described, which may contribute to the decrease in income described in the previous section. The next section will describe existing knowledge about breast cancer and the combination of breast cancer and psychological vulnerability in relation to sickness benefits, unemployment benefits, early retirement pension and disability pension.

Sickness benefits

Diagnosis of breast cancer is associated with a prolonged period on sick leave compared to other cancer diagnosis (30,78) and the sick leave period has increased through the last decades among this group of patients (41). A Danish study found, that after one year 31% of women diagnosed with breast cancer were on sick leave (79).

Other studies reported an increase in the risk for receiving sickness benefits in the years following a diagnosis of breast cancer. After three years the relative risk (RR) was 1.49 (95%, CI 1.40-1.58) and after five years RR=1.24 (95% CI 1.15-1.33) (56). Torp et al. (80) demonstrated concomitant, that the odds for receiving sickness benefits was 1.79 (95% CI 1.46-2.19) after five years for women diagnosed with breast cancer.

The severity of breast cancer, together with treatment related variables, were found to affect the period on sick leave. Eaker et al. (56) and Kvillemo et al. (81) demonstrated that after three years 40% of women diagnosed with stage III-IV breast cancer received sickness benefits, while it was 25% of those with stage I breast cancer (56). The odds for receiving sickness benefits for women diagnosed with stage III-IV breast cancer compared to women with stage I breast cancer were 4.29 (95% CI 2.84-6.30) (81). After five years the percentages had equalized, although Kvillemo et al. reported that the odds for receiving sickness benefits were 4.76 (95% CI 2.73-8.31) if diagnosed with stage III-IV breast cancer. Both studies found, that the reduction in sickness benefits were replaced by an increase in disability pension. The odds for being on long-term sick leave for women with combined treatment (at least two modalities: surgery, radiation, chemotherapeutics, or endocrine treatment) were 5.98

(95% CI 4.43-8.09) compared to breast cancer patients only receiving one type of treatment (78).

Anxiety and depression were both demonstrated to increase the risk for sick leave in connection to breast cancer. Furthermore, anxiety and depression were associated with long-term sick leave independent of breast cancer or other disorders (82,83). Depressive symptoms were highly prevalent in the working population, and Duijts, Spelten and Verbeek described, that based on the results of the two above-mentioned studies, return to work of patients with depression seemed as difficult, if not more, when compared to cancer patients (84). Since depression and anxiety both were associated with sick leave and were highly prevalent in the working population, then mental health problems might also affect sickness absence in combination with breast cancer.

Unemployment benefits

A Danish study described in 2014 (79), that one year after a diagnosis of breast cancer 92% were part of the work force, but of those seven percent were unemployed. After two years the figures were: 81% were part of the work force, and 10% were unemployed. Unemployment before diagnosis of breast cancer was the most important determinant of unemployment in the following years, although low socioeconomic status and demography also was a part of the explanation. Adjuvant treatment did not increase the risk for unemployment (79). A study examining unemployment among Canadian women reported, that after three years 21% of women diagnosed with breast cancer were unemployed vs 15% of cancer-free women. The risk for being unemployed was 1.29 (95% CI 1.05-1.59) (48).

In Norway, no effect of breast cancer was demonstrated in relation to unemployment (56). It almost seemed like breast cancer had a protective impact, although the results were not statistically significant.

As with sickness benefits, the risk for being unemployed was also affected by psychiatric comorbidity (depression and schizophrenia) – both among women diagnosed with breast cancer and among women without breast cancer (79,85).

Early retirement pension

This section will only include findings from two Danish studies, since early retirement is a Danish concept, and not a straightforward concept to use comparing to other countries. According to Oorschoot and Jensen (86), a broad interpretation of early retirement is used in the different countries, which focuses primarily on different

transitions of older workers (mostly 50+, or 55+) into inactivity. These transitions may be the result of opting for an entitlement to an early retirement scheme, but also of taking up a disability benefits for health reasons, becoming unemployed, or leaving the labour market for other reasons. In Denmark, to take early retirement, one must have paid to the scheme for at least 30 years, and have a maximum of five years reaching the age for old age pension (87).

An increased risk for taking early retirement is found associated with a diagnosis of breast cancer, although the association is not as strong as for other cancer types, neither as long-lasting (88). The rate for women taking early retirement was higher for women with somatic comorbidity, previous depression or having received sickness benefits in the year before the diagnosis of breast cancer (89).

Disability pension

A positive association between breast cancer and receiving disability pension (56,72,76,90) is described. In a Norwegian study, the risk for receiving a disability pension after three and five years was unchanged: 1.47 (95% CI 1.37-1.58) (56). A high stage of breast cancer was found to increase the proportion of women having disability pension (56), and to shorten the time from diagnosis to disability pension (90). Hauglann et al. (90) reported, that compared to cancer-free women the hazard rate for having disability was 2.4 times higher for women diagnosed with breast cancer (95% CI 2.1-2.7) over a 13 year period. Socioeconomics were not found to increase the risk for having disability pension, but the time from diagnosis to disability pension was shorter among survivors with low income and low educational level (90).

Two studies used early retirement as a measure for, what in Denmark would be included in the disability pension term. In a German study, Singer et al. (91) defined patients as “early retired” if they received a full health-related early retirement pension, while Lindbohm et al. (92) included both disability-based and non-disability-based retirement into the early retired category. Both described studies proposed a positive association between a diagnosis of breast cancer and being retired. Furthermore, they both found that psychiatric comorbidity increased the risk for taking early retirement. Singer et al.(91) demonstrated, that having had a depression increased the risk for taking early retirement to 3.6 (95% CI 1.1-11.6) but only for high income women. For anxiety and adjustment disorders an increase in the risk as seen among low income women.

1.7 PSYCHOLOGICAL VULNERABILITY

Mental health problems (depression, anxiety and schizophrenia) are found to affect the affiliation to the labour market – both in combination with breast cancer (79,85,89) and standing alone (93). In combination with breast cancer the risk of receiving sickness benefits is increased, and the period on sick leave is found to be prolonged (82,83). Likewise is the risk of being unemployed (79) or taking early retirement (89). Most of the conducted studies focus on mental health problems as a result of breast cancer and not as being present prior to the diagnosis of breast cancer. Due to the high prevalence of mental health problems (94) it must be assumed that a certain percentage of women being diagnosis with breast cancer are experiencing mental health problems prior to the diagnosis of breast cancer, which means that they to a greater extent might be defined as being psychological vulnerable, according to the severity of mental health problems and whether the mental health problems are present or previous.

Definition of psychological vulnerability

Psychological vulnerability is often implicit and rarely explicit defined. Researchers working from multiple theoretical perspectives (95,96) have argued that psychological development progresses over the life-course along two primary dimensions, and disturbances in either of them contribute to psychological vulnerability and increase the possibility of psychopathology. The two dimensions are: (a) *self-definition* (the development of a well differentiated, integrated, realistic and, essentially, positive identity); and (b) *interpersonal relatedness* (the development of intimate, mutually satisfying, reciprocal interpersonal relationships). The relationship between the two dimensions is described by Blatt and Luyten (97):

“Throughout life, meaningful interpersonal experiences contribute to a fuller articulation, differentiation, and integration of the sense of self that, in turn, facilitates the establishment of more mature forms of interpersonal relatedness. Although the relative balance between these two developmental dimensions and the specific life experiences that contribute to the development of a sense of self and the capacity for interpersonal relatedness varies across individuals and across cultures these two fundamental dimensions essentially evolve through a basic synergistic developmental process.” (Page 799 (97)).

Both concerns with self-definition and interpersonal relatedness, and thereby also psychological vulnerability, is found to be positively associated with anxiety, depression and schizophrenia (97).

Interrelation between psychological vulnerability and stress – and an introduction to Cohens Perceived Stress Score (PSS)

As described above, defining psychological vulnerability is complex, but besides containing concerns with self-definition and interpersonal relatedness, the concept is also having a relation to stress. According to Sheldon Cohen stress is seen as the product of two constructs; impinging demands and comprised resources, which conjoin to produce somatic and mental changes that put people at risk for pathology (98).

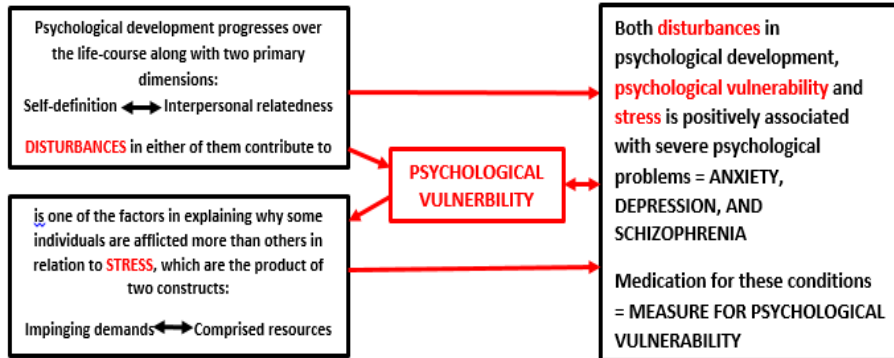
Another description of stress and the correlation to illness is described by a Malaysian psychiatrist Salleh Mohd Razali (born 1953) (99):

”Stress affects everyone, young and old, rich and poor. Life is full of stress. Stress is an every fact of life that we must all deal with. It comes in all shapes and sizes; even our thoughts can cause us stress and make the human body more susceptible to illness” ((99) Page 9).

All persons are exposed to stress and stressful events at some time in their life. Most persons are resilient to such events and continue to function normally, but for a subset of individuals, experiencing stressful events contribute to the development of more severe psychological problems (100), and one of the pathways from stressful events to more severe psychological problems include psychological vulnerability. The relationship between stress and illness is complex and the susceptibility to stress varies from person to person. One of the factors found to explain the difference in why some individuals are afflicted more than others in relation to stress is a genetic vulnerability (99), which constitute a certain part of the more generalised term: psychological vulnerability.

The correlation between psychological vulnerability, stress, psychiatric disorders and psychiatric medical treatment is attempted illustrated in Figure 2, explaining why psychiatric medical treatment may be used as a measure for psychological vulnerability. On one hand is psychological vulnerability in a person found to be a result of disturbances in on of the two primary dimensions in psychological development, and on the other hand psychological vulnerability is found to be one of the reasons that some individuals are affected more than others of stress. Both are found to be positively correlated with severe psychological problems, which include anxiety, depression and schizophrenia.

Figure 2: The correlation between psychological vulnerability, stress, and psychiatric disorders.



Sheldon Cohen is born in the United States in 1947, and became in 1982 Professor of Psychology at Carnegie Mellon University in Pittsburgh. In 1983 Cohen together with his colleagues developed the The Perceived Stress Scale (101). According to Cohen et al.(101), the Perceived Stress Score measures general stress and is thus relatively free of content that is specific to any particular population, which may have contributed to the fact, that Cohens Perceived Stress Score has become one of the most widely used psychological instruments for measuring nonspecific perceived stress. The score is used in Study III in this dissertation. Different versions of the Perceived Stress Score is developed, and in Study III the version consisting of ten items is used. Each item scores between 0 and 4, which gives a total score between 0 and 40. The higher score, the higher level of perceived stress. The scale measures the degree to which respondents felt they were unable to control important things in their life, their confidence in their ability to handle personal problems, how often they felt they could not cope with all the things they need to do, and how often difficulties were overwhelming within the past month.

1.8 RATIONALE FOR THIS RESEARCH

Study I and Study II

As described in section 1.6 psychological vulnerability is associated with an increased risk of not being self-supporting. When women, despite psychological vulnerability, manage to be self-supporting, it may be assumed that they are closer to exclusion from the labour market and marginalisation than other women when diagnosed with breast cancer.

Existing literature has revealed other correlations between psychological vulnerability and breast cancer, but no studies have examined the relation of psychological vulnerability prior to diagnosis of breast cancer among self-supporting women. The topic is relevant since the combination of psychological vulnerability and breast cancer is seen in a greater part of women, due to an increasing incidence of both breast cancer and mental health problems, and in order to examine whether psychological vulnerability could be one of the explanations for why some women have problems with returning to work after sick leave caused by breast cancer, although they are cured.

In a Nordic setting a diagnosis of breast cancer induce changes in income in the following years for many women. The majority of studies examining this topic, have focused on the first (up to) five years of follow-up, while the more long-term consequences to a lesser extent has been examined, and since the preponderant of studies with short follow-up time reported ongoing discrepancies between women diagnosed with breast cancer and cancer-free women, it may be interesting to examine whether the differences are temporary or more permanent. Furthermore, no studies have focused on the combination of breast cancer and prior psychiatric medical treatment in relation to income changes. Receiving psychiatric medical treatment itself may cause changes in income, which might be enhanced in combination with breast cancer.

Study III

Using different types of data, means different advantages and disadvantages. Data on perceived stress is often collected through study-specific questionnaires, and/ or health surveys, which is time consuming and costly (102,103). Using registry-based data instead of questionnaires would make research in relation to stress – in the countries where registry data are available – fast and inexpensive. Studies have found divergent results when comparing registry-based data with survey data. Only one study was the association between perceived stress and psychiatric treatment, and in that study another perceived stress scale was used (104).

CHAPTER 2: AIMS OF THE THESIS

The overall topic of this thesis is breast cancer and the affiliation to the labour market in the following years. The general objective was to investigate short - and long-term consequences of breast cancer in relation to future affiliation to the labour market, and to examine whether the presence of psychological vulnerability prior to the diagnosis of breast cancer affects these consequences. In addition, the dissertation examines methodological issues according to the use of registry data as a proxy for perceived stress. The general objective will be examined through three independent studies, and the specific aims of the three different studies were:

- 1) To explore whether prescription of psychiatric medical treatment prior to a diagnosis of breast cancer influence return to work one year later among women being self-supporting prior to the diagnosis of breast cancer.
- 2) To investigate whether a diagnosis and treatment of breast cancer affects future income among Danish women, being self-supporting at time of diagnosis. In addition, to study if potential changes in income differs according to marital status, the use of psychiatric medical treatment prior to the diagnosis of breast cancer, and educational level.
- 3) To examine whether registry data on prescribed psychiatric medical treatment (anxiolytic/ antidepressants/ antipsychotics) and consultations with psychologists or psychiatrist can be used as a proxy for survey data on perceived stress.

CHAPTER 3: MATERIALS AND METHODS

3.1 STUDY DESIGN AND STUDY SETTINGS

All three studies included in this thesis were conducted in the field of clinical epidemiology, and while the first two studies were nationwide cohort studies using Danish national administrative registries (from 2000 to respectively, 2012 in Study I and 2012 in Study II) examining short-term and long-term consequences of two outcomes (psychiatric medical treatment prior diagnosis of breast cancer and breast cancer), while Study III was a cross-sectional study linking register data from 2009-2011 with survey data from the North Denmark Region Health Survey 2010 (105) to allow for comparison of a register based and a self-reported measure for psychological vulnerability.

3.2 STUDY POPULATIONS

For each of the three studies – and for some supplemental analyses - different study populations were defined. The interrelation between the study populations are illustrated in Figure 3 (page 36).

General study population: Study I and Study II

The base study population for Study I and Study II including the supplemental analyses was identified through The Danish Breast Cancer Cooperative database and consisted of Danish women diagnosed with incident breast cancer, in a 12-year period from January 2000 to December 2012.

Study I

The exposure was prescription of psychiatric medical treatment in year 2, 3 or 4 prior to a diagnosis of breast cancer as a surrogate measure of psychological vulnerability. Psychiatric medical treatment was defined according to the Anatomical Therapeutic Chemical (ATC) classification system from WHO Collaborating Centre for Drug Statistics Methodology (106). The drugs used in this study were: antidepressants (N06A), anxiolytics (N05B) or antipsychotics (N05A). The outcome of Study I was return to work 52 weeks after diagnosis of breast cancer. Examining return to work after diagnosis of breast cancer only makes sense if the

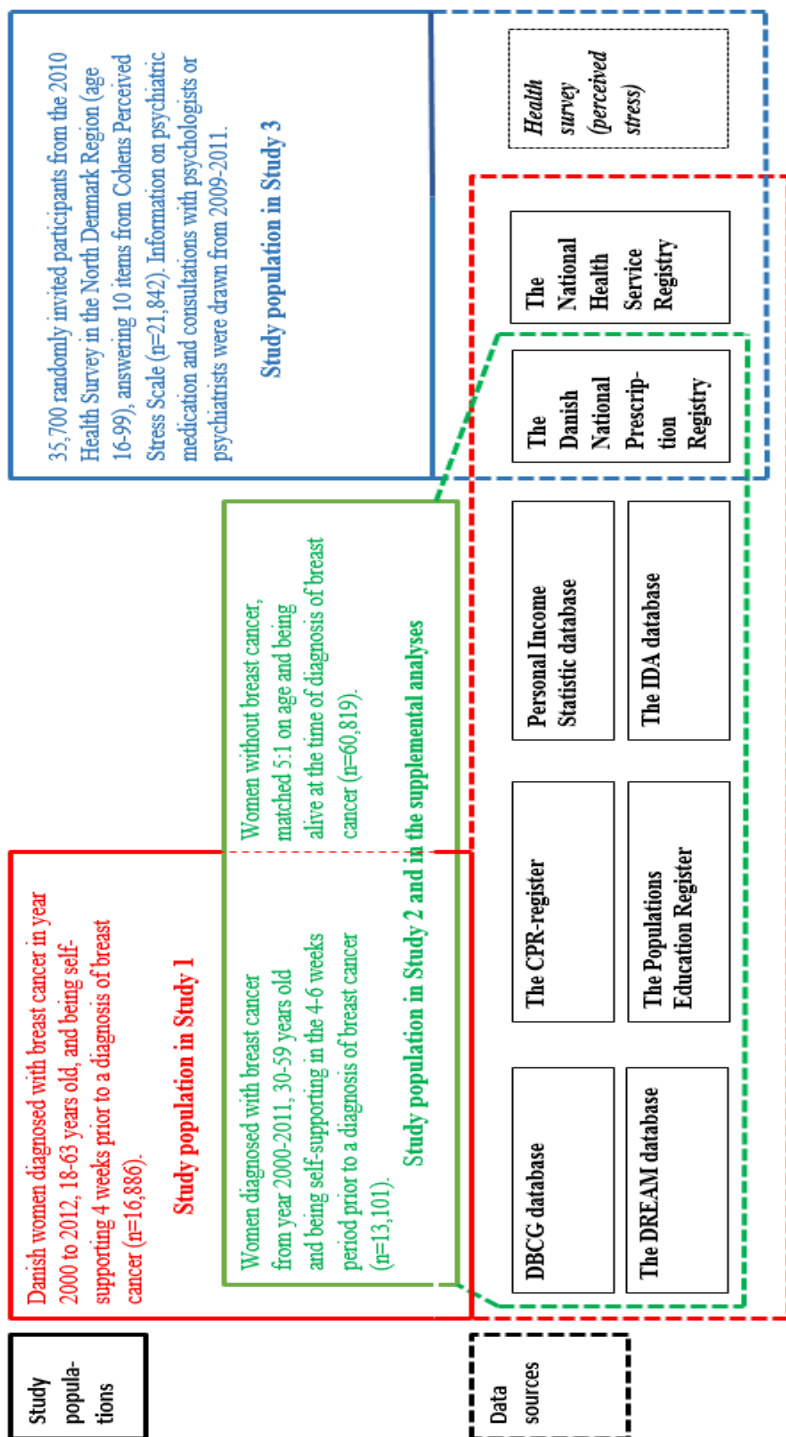


Figure 3: The three study populations and the data sources used in each study.

women in the study population are in work at time of diagnosis. Therefore, the study population consisted of women of working age, with at least one year left on the labour market (18-63 years of age), and being self-supporting four weeks prior to the diagnosis of breast cancer. Individuals receiving permanent benefits, temporary labour-market related benefits, and temporary health related benefits, four weeks prior to the diagnosis of breast cancer were excluded. Furthermore, women not resident in Denmark or women appearing with missing values were excluded. The final study population comprised a total of 16,866 women, who were followed 52 weeks from the time of diagnosis. Women diagnosed with breast cancer were divided into two groups according to whether they had received any prescriptions for psychiatric medical treatment in year 2, 3 or 4 prior to the diagnosis of breast cancer (14,231 of the women diagnosed with breast cancer had not received any prescriptions, while 2,655 had received at least one prescription).

A supplemental analysis for the thesis

Supplemental analyses were conducted in order to contribute with additional knowledge about the long-term consequences of psychiatric medical treatment and breast cancer in relation to participation in the labour market, which are not clarified in the papers included in this thesis. The outcome was being self-supporting. The exposure was breast cancer and psychiatric medical treatment prior to a diagnosis of breast cancer. The study population examined in the analysis was the study population from Study II. The follow-up period was 10 years.

Study II

The exposure was diagnosis of breast cancer, while the outcome was changes in incomes until one of the following events: death, emigration, early retirement, age pension or end of the observation period (31 December 2013). The study included two cohorts: 1) an exposed group of women between 30 and 59 years of age diagnosed with incident breast cancer in 2000-2011; and 2) an unexposed group that comprised women without breast cancer. This group included five unexposed subjects age-matched to each patient with breast cancer. Unexposed women had to be alive on the date the matched patient was diagnosed with breast cancer. We excluded women that did not reside in Denmark and women that received any kind of permanent or temporary labour market benefits or health-related benefits in a 4- to 6-week period prior to diagnosis. Finally, women with missing values on one of the variables were excluded. The final study population consisted of an exposed cohort of 13,104 women diagnosed with breast cancer and an unexposed reference cohort of 60,870 breast cancer-free subjects. The follow-up period varied between two and ten years.

Study III

The third study was based on data from the North Denmark Region Health Survey 2010 conducted in February 2010. In North Denmark Region, a total of 35,700 randomly selected persons (age > 16 years) received a questionnaire; 23,392 (65.5%) returned the questionnaire and 21,842 had completed the 10 questions constituting Cohens Perceived Stress Score (PSS). Using the unique civil registration number, data from the survey were linked to two different administrative data sources containing information on prescribed psychiatric medical treatment and consultations with psychologists or psychiatrists.

3.3 DATA SOURCES

For the studies included in the dissertation eight different registers were used, together with information from a survey. The data sources are described in Table 3.

Table 3: Description of the data sources and which studies each data source is used in.

The registers (existed since)	Used in study I, 2 or 3	The register was used for:
The Danish National Prescription Registry (1994) (107)	Study I-III	Information on psychiatric medical treatment (ATC codes: N05A, N05B, and N06A).
The National Health Service Registry (108,109)	Study I and III	The number of consultations with either psychologists or psychiatrists for each individual from 2005-2012.
The Danish Breast Cancer Cooperative Group (DBCG) database (1976) (110)	Study I and II	Identify women diagnosed with incident breast cancer from 2000 to respectively 2012 (Study I) and 2011 (Study II). Information on clinical factors (and age in Study II).
The Danish DREAM database (1991) (111)	Study I and II	The various types of benefits reimbursed to study participants weekly.
The Population's Educational Register (112)	Study I and II	The maximal educational attainment of the study cohorts.
Personal Income Statistics database (113)	Study I and II	Personal income in DKK (Danish kroner) and deflated according to its 2009 valuation.

Integrated Database for Labour Market Research (IDA) (1980) (114)	Study I and II	Marital status (and age in Study II).
The Danish civil registration system (1968) (115,116)	Study I-III	Individual-level linkage between the other registers used in the studies.
	Study II	The register is used in creating the cancer-free group of women.
The North Denmark Region Health Survey 2010	Study III	35,700 randomly selected persons received a questionnaire. 23,392 (65.5%) returned the questionnaire and 21,842 completed all the Perceived Stress Score Items.

3.4. STATISTICAL ANALYSES

Study I

Baseline characteristics between women with a diagnosis of breast cancer that had received at least one prescription for psychiatric medical treatment 2, 3, or 4 years prior to their diagnosis of breast cancer and those who had not received any prescription, were evaluated using Chi² test. Weekly distributions of social benefits were calculated for individuals with and without prior psychiatric medical treatment. A modified Poisson regression model (117) was used to examine the impact of psychiatric medical treatment received prior to the diagnosis of breast cancer on return to work 52 weeks later. The estimates were adjusted for potential confounders and four models were generated, each adding one group of potential confounders (demographic factors, clinical variables, and socioeconomic factors). Separate analyses for different age-groups were performed, together with an interaction test for income and psychiatric medical treatment prior to a diagnosis of breast cancer.

Three sub-analyses were conducted. The first included individuals who had received prescriptions for psychiatric medical treatment in at least two out of three years in order to examine whether long-term treatment influenced return to work more than short-term treatment. The second sub-analysis used separate analyses for each type of medication (N05A, N05B, and N06A) to examine if there were any discrepancies between the different types of medication. In the latest sub-analysis, consultations with psychologists or psychiatrists were included in the exposure in order to study the robustness of the exposure.

Supplemental analysis for the thesis

The percentages of women being self-supporting were calculated for all years in follow-up (1-10 years) and this percentage represents the employment rate among these women. The study population was divided into four groups according to breast cancer status and whether the women were psychologically vulnerable before the diagnosis of breast cancer: Group 1: diagnosed with breast cancer and having a history of psychological vulnerability; Group 2: diagnosed with breast cancer; Group 3: having a history of psychological vulnerability, and Group 4) none of the conditions. Two analyses for each group were conducted: the first examining all women being alive and living in Denmark in the certain year; and the second analysis only including women participating in the work force (excluding women receiving disability pension or taking early retirement)..

Study II

Frequencies and percentages were calculated for all co-variables included in the study. The mean annual income (and the percentage-wise changes in income compared to the year before diagnosis of breast cancer) was calculated for each year of follow-up. The exposed women were divided into two groups according to severity of disease (1: stage IA and 2: stage IB-IV).

In order to take changes in income among the general population into account, a calendar year and age specific expected change in real income was estimated. The income change for exposed and unexposed women were dichotomized according to whether their changes in income were above or below the expected change in income among the Danish female population. We examined the impact of breast cancer on income in each year of follow-up by applying a logistic regression model. The analyses were only conducted on individuals participating in the work force in each year.

Stratified analyses were conducted according to age, educational level and psychiatric medical treatment received 2, 3, or 4 years prior to the diagnosis of breast cancer.

Study III

Percentages and medians were used to describe the distribution of prescribed psychiatric medical treatment and consultations with psychologists or psychiatrists in the different PSS score groups divided into three age groups (< 40 years, 40-65 years, and > 65 years).

Logistic regression models were used in order to determine the association between psychiatric treatment and PSS scores. The regression models were adjusted for

potential confounding factors: age and gender. Separate analyses on data from each year were conducted in order to examine whether the association between psychiatric treatment and PSS scores change depending on whether register data were collected before or after perceived stress was measured.

Different statistical methods were used in order to describe the agreement between the PSS score and psychiatric treatment: sensitivity, specificity, and positive agreement using PSS score as a gold standard, and positive and negative agreement, and finally, kappa measure. Analyses with different combination of numbers of prescriptions and referrals were conducted to test whether some combinations were better predictors than others.

Software

Data management in Study I and Study II was conducted with SAS version 9.4 (Cary) and statistical analyses in all three studies (Study I-3) were performed using STATA version 11 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.v) and STATA version 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

3.5. ETICHS STATEMENT

All studies were approved by the Danish Data Protection Agency (Ref. 2008-58-0028). All data were linked and stored in computers held by Statistics Denmark and made available with de-identified personal information to ensure that individuals could not be identified. In accordance with Danish legislation, only aggregated statistical analyses and results were published (118). Anonymized register-based studies do not require obtained written informed consent.

CHAPTER 4: RESULTS

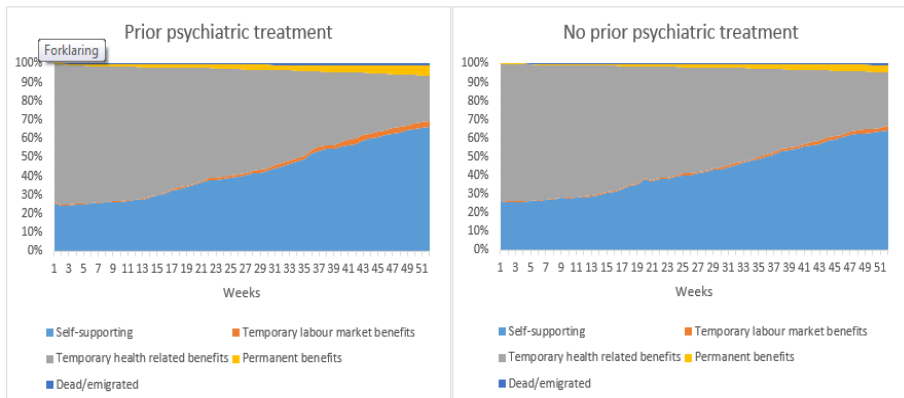
4.1 SHORT-TERM CONSEQUENCES OF BREAST CANCER AND PSYCHOLOGICAL VULNERABILITY ON RETURN TO WORK (STUDY I)

In Study I, we included 16,866 women diagnosed with breast cancer, and fifteen percent of those had received psychiatric medical treatment in year 2, 3, or 4 prior to their diagnosis of breast cancer. The distribution of the different types was as follows: 1% had received anxiolytics, 9% had received antidepressants, while 10% had received anxiolytics.

After 52 weeks 63% of individuals who had received psychiatric medical treatment prior to the diagnosis of breast cancer had returned to work, while the figure was 69% for those not having received psychiatric medical treatment. Almost one-fifth (16%) of the women were self-supporting throughout all 52 weeks (Figure 3).

The use of psychiatric medical treatment prior to a diagnosis of breast cancer reduced the likelihood for having returned to work ($RR_{\text{crude}}=0.91$ (95% CI 0.87-0.94)) 52 weeks later. Adjusting for demographic, clinical, and socioeconomic variables did not significantly change the association ($RR_{\text{adjusted}}=0.90$ (95% CI 0.87-0.93)).

Figure 5: The weekly distribution (through 52 weeks of follow-up) of women being self-supporting or, receiving different types of social benefits, together with the percentage of women who died or emigrated, divided according to whether the women have received prior psychiatric medical treatment or not.



When stratifying for age the relative risk between psychiatric medical treatment prior to a diagnosis of breast cancer and being self-supporting 52 weeks later increased with increasing age. An age in excess of 50 years, or being in receipt of a high income, both significantly increased the probability of returning to work. No interaction between income and psychiatric medical treatment prior to a diagnosis of breast cancer was identified.

Including consultations with psychologists or psychiatrists into exposure did not change the likelihood for having returned to work one year later significantly (RR=0.94 (95% CI 0.94 (0.90-0.98)); neither did separating the exposure into each type of medication (anxiolytics: RR=0.93 (95% CI 0.90-0.97); antidepressants: RR=0.90 (95% CI 0.86-0.94); and antipsychotics: RR=0.92 (95% CI 0.83-1.02)). Using a combined measure of either consultations with psychologists or psychiatrists or psychiatric medical treatment RR=0.89 (95% CI 0.86-0.93) were estimated vs. RR=0.90 (95% CI 0.87-0.94) when using psychiatric medical treatment alone.

4.2 LONG-TERM CONSEQUENCES OF BREAST CANCER AND PSYCHOLOGICAL VULNERABILITY ON AFFILIATION TO THE LABOUR MARKET (SUPPLEMENTAL ANALYSES)

The results from the supplemental analysis are illustrated in figure 6 (page 45). The figure shows the percentage of women being self-supporting each year of follow-up and thereby reflect the employment rate. The women were divided into four groups according to whether they were diagnosed with breast cancer and/ or having a history of psychological vulnerability.

From study I it is known that almost 70% of women diagnosed with breast cancer were self-supporting after one year if they did not have a history of psychological vulnerability, and that the figure was 65% if they had a history of psychological vulnerability. Compared to breast cancer-free women these percentages were low, since more than 90% of the cancer-free women were self-supporting. Breast cancer – standing alone – was found to affect the percentage of self-supporting women for the entire period of follow-up. After ten years the percentage of self-supporting women diagnosed with breast cancer reached the percentage of self-supporting cancer-free women, if the women were participating in the work force. Otherwise, breast cancer induced a decrease in the percentage of women being self-supporting and after ten years only 75% of all women diagnosed with breast cancer were self-supporting. On

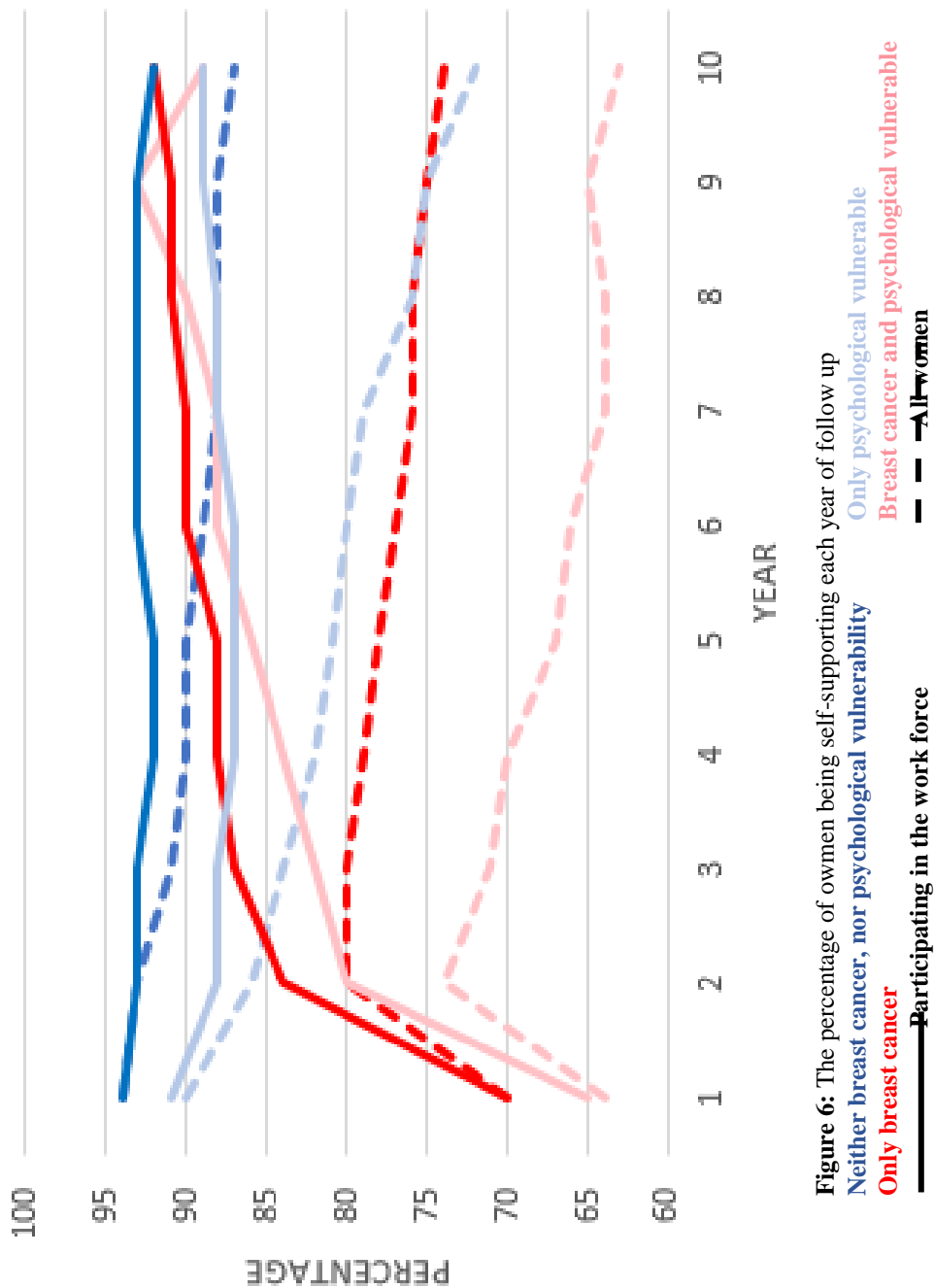


Figure 6: The percentage of owmen being self-supporting each year of follow up
 Neither breast cancer, nor psychological vulnerable Only psychological vulnerable
 Only breast cancer Breast cancer and psychological vulnerable
 — Participating in the work force - - - All women

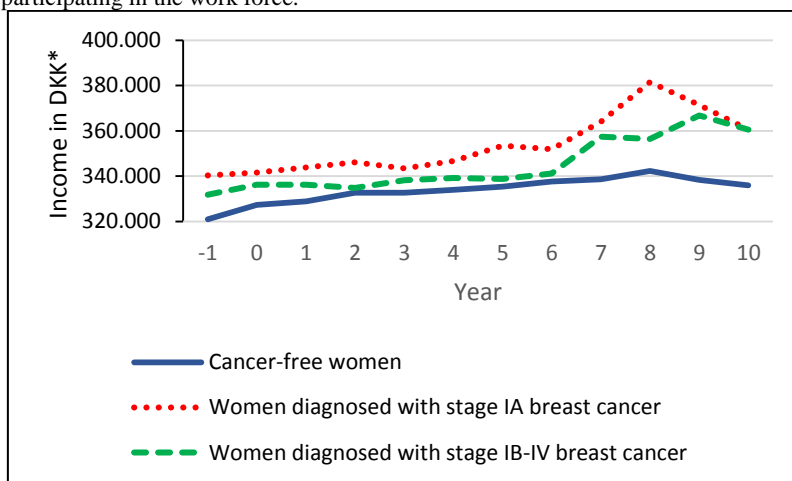
the basis of the results displayed in figure 6, this percentage was similar to the percentage of self-supporting women without breast cancer, but with a history of psychological vulnerability. The combination of breast cancer and having a history of psychological vulnerability seemed to have the greatest impact on the employment rate. If the women manage to participate in the work force almost 90% were self-supporting after ten years, but if they did not manage to participate only 63% were self-supporting.

The gap between the solid and the dashed lines in each colour illustrate the increased risk for receiving permanent benefits.

4.3 LONG-TERM CONSEQUENCES OF BREAST CANCER ON CHANGES IN INCOME (STUDY II)

Unexposed women had the lowest mean annual income compared to the two exposed groups of women (stage IA and stage IB-IV) through all years of follow-up, when participating in the work force (Figure 7).

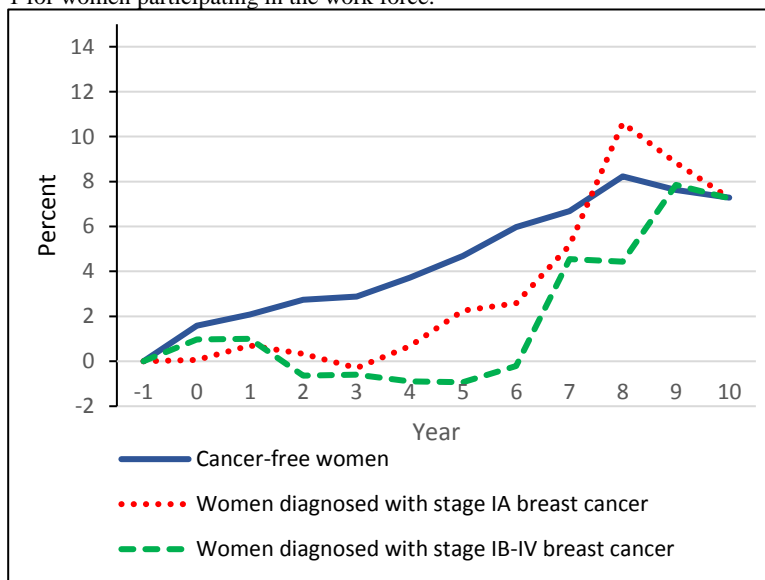
Figure 7: Mean annual income for Danish women (aged 30-59) diagnosed with breast cancer (2000-2011) and breast cancer-free women for each year in a 10 years period for women participating in the work force.



The percent-wise change in income among exposed women were negative compared to the unexposed women until seven years of follow-up (for women diagnosed with stage IA) and nine years of follow-up (for women diagnosed with stage IB-IV) (Figure 8).

Logistic regression analyses were used to compare the odds for attaining an increase in income change above that expected in the general population among women diagnosed with breast cancer compared to breast cancer-free women. There was no significant difference between the two cohorts during the first year. At three years of follow-up the two cohorts differed most (OR=0.81 (95% CI 0.77-0.84)). Thereafter, the difference narrowed and after seven years no significant differences were observed.

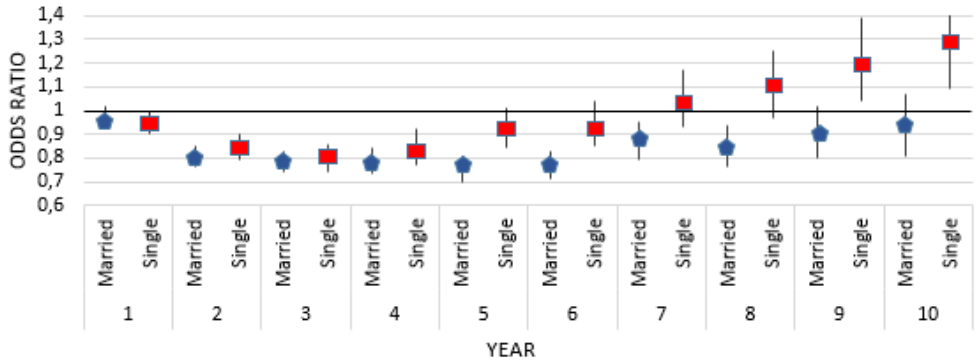
Figure 8: Percent-wise changes in income for Danish women (aged 30-59) diagnosed with breast cancer (2000-2011) and breast cancer-free women (matched 5:1 on age and alive at time of diagnosis). The change in income for each of 10 follow-up years is compared to income year-1 for women participating in the work force.



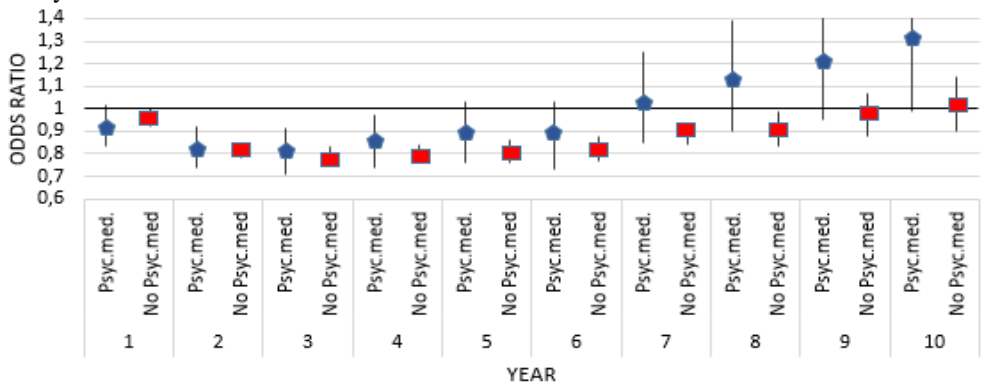
Stratified analyses (Figure 9) according to marital status, prior psychiatric medical treatment, and educational level found similar patterns in each strata for the first six years. For the following years, the associations between breast cancer and income changes tended to differ according to marital status and prior psychiatric medical treatment. We found positive associations with a single marital status (Figure 10a) and a history of psychiatric medical treatment (Figure 10b), although only the association with a single marital status were statistically significant. For women with a high educational level (Figure 10c) the impact of breast cancer on income tended to last longer than the impact among women with a low educational level.

Figure 9: Odds ratio (OR) for experiencing an increase in income in Danish women diagnosed with breast cancer compared to breast cancer-free women, matched on birth day and to be alive at time of diagnosis of breast cancer. The analyses are stratified according to a) marital status, b) psychiatric medical treatment prior to a diagnosis of breast cancer, and c) educational level

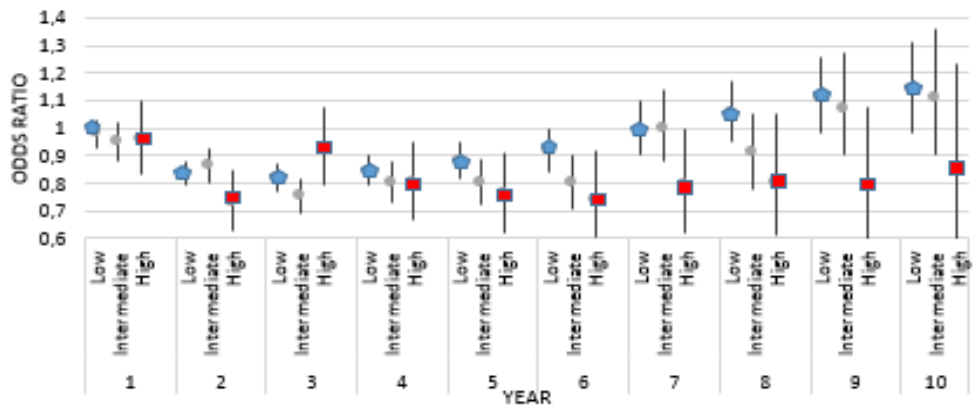
a: Marital status



b: Psychiatric treatment



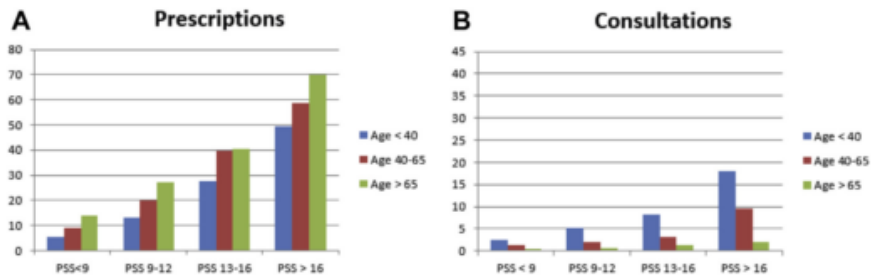
c: Educational level



4.4 THE CORRELATION BETWEEN REGISTER DATA AND COHEN'S PERCEIVED STRESS SCALE (STUDY III)

The completeness of answers to items on perceived stress among those who returned the questionnaire declined with age (<40 years, 95.5%; >65 years, 86.4%). Women had a higher mean PSS score than men (12.9 vs. 11.5). Overall, 0.6% redeemed prescriptions for anxiolytics, 3.5% for antipsychotics, and 12.1% for antidepressants, while 3.2% had consulted a psychologists and 1.0% has seen a psychiatrist. The division according to the different stress score groups and age groups can be seen in Figure 11.

Figure 11: Percentage of persons receiving prescriptions or consultations with psychologists or psychiatrists for the different age and stress score groups.



More in the older age group received psychiatric medical treatment, and fewer in the older age groups consulted psychologists or psychiatrists compared to the younger age group.

Individuals with a high PSS score was found to have an increased risk of being prescribed medication or consulting psychologists or psychiatrists compared with a low PSS score. See Table 3 (page 50). Using the lowest PSS score group as a reference, the odds for having received prescribed psychiatric medical treatment or consultations with psychologists or psychiatrists were: OR=1.5 (95% CI 1.4-1.7) for the second lowest PSS score group, OR=2.5 (95% CI 2.2-2.8) for the second highest PSS score group, and OR=7.3 (95% CI 6.5-8.1) for the highest PSS score group.

Sensitivity (8.7%-37.6%), specificity (88.5%-98.0%), positive predictive value (49.4%-56.8%), positive (16.2%-42.7%) and negative (85.5%-87.2%) agreement along with kappa coefficient (0.095-0.285) were estimated for different combinations of numbers of prescriptions and consultations with psychologists or psychiatrists.

Table 3: Odds of being prescribed medicine or consulting a psychologist or psychiatrist in the different PSS score groups from 2009-2011 (n=21,842)

The different stress score groups PSS score	Low <9	Second lowest 9-12		Second highest 13-16		Highest >16	
		OR (95% CI)	Adj. OR (95% CI) ^a	OR (95% CI)	Adj. OR (95% CI) ^a	OR (95% CI)	Adj. OR (95% CI) ^a
Prescribed anxiolytics	1	1.8 (0.8-3.7)	1.8 (0.9-3.8)	4.5 (2.4-8.6)	4.6 (2.4-8.8)	7.3 (3.9-13.7)	7.4 (4.0-13.8)
Prescribed antipsychotics	1	1.4 (1.1-1.8)	1.4 (1.1-1.8)	1.7 (1.3-2.2)	1.6 (1.2-2.0)	3.2 (2.6-3.9)	2.8 (2.2-3.4)
Prescribed antidepressants 1, 2, or 3	1	1.5 (1.3-1.7)	1.5 (1.3-1.7)	2.4 (2.1-2.8)	2.3 (2.0-2.7)	7.6 (6.7-8.3)	7.2 (6.3-8.2)
Consultations with psychologist	1	1.5 (1.3-1.7)	1.5 (1.3-1.7)	2.4 (2.1-2.7)	2.3 (2.0-2.6)	7.2 (6.4-8.1)	6.9 (6.1-7.7)
Consultations with psychiatrist	1	1.8 (1.4-2.4)	1.6 (1.2-2.1)	2.7 (2.0-3.5)	2.4 (1.8-3.2)	6.3 (4.9-8.0)	5.5 (4.3-7.0)
Consultations with 5 or 6	1	2.8 (1.4-5.6)	2.8 (1.4-5.4)	4.9 (2.6-9.3)	5.0 (2.6-9.4)	15.7 (8.7-28.4)	16.1 (8.9-29.2)
Either medicine or consultation	1	1.9 (1.5-2.5)	1.8 (1.4-2.3)	3.0 (2.3-3.8)	2.8 (2.2-3.6)	7.8 (6.2-9.7)	7.2 (5.7-9.0)
Either medicine or consultation	1	1.5 (1.4-1.7)	1.5 (1.3-1.7)	2.5 (2.2-2.8)	2.3 (2.1-2.6)	7.3 (6.5-8.1)	6.8 (6.1-7.6)

Adj. OR = adjusted odds ratio.

PSS < 9 = reference group.

^a Adjusted for age and gender.

CHAPTER 5 DISCUSSION IN RELATION TO EXISTING LITERATURE

5.1 THE SHORT-TERM CONSEQUENCES OF BREAST CANCER

Return to work and income

One year after diagnosis of breast cancer the studies included in this thesis demonstrated that almost 70% of women diagnosed with breast cancer had returned to work, if they had no history of psychological vulnerability. Having a history of psychological vulnerability lowered the risk for returning to work ($RR_{\text{crude}}=0.91$ (95% CI 0.87-0.94) and the percentage to around 65%. The figures were respectively 94% and 91% in the group of cancer-free women without and with a history of psychological vulnerability. The fact that both breast cancer and psychological vulnerability reduced the percentage of women being self-supporting was in line with the results from other studies (41,42,46,63). In relation to return to work 52 weeks after diagnosis and treatment for breast cancer a wide range of percentages were reported: from 43% (31) to 93% (119). This may be due to diverse study populations and different legislation in the countries included in the studies.

It has not been possible to find any studies examining the effect of psychological vulnerability prior to a diagnosis of breast cancer on return to work. The topic is relevant since the group of women with the combination of psychological vulnerability and breast cancer constitute a substantial group of women diagnosed with breast cancer (in study I 15%). Psychiatric comorbidity in the period following diagnosis of breast cancer is a significant issue for women with both early and advanced stages of breast cancer (120–123), and that having a history of depression or anxiety predict a greater depressive symptomatology following treatment for breast cancer (123), but the association to return to work is missing. Psychiatric comorbidity following diagnosis and treatment for breast cancer is furthermore, found to affect the following return to work process (39,43,60,68), and psychiatric disorders in itself is reported to reduce the likelihood for being self-supporting (124,125). This study contributes with new knowledge in this area, and demonstrate that having a history of psychological vulnerability before diagnosis with breast cancer has a significant, although limited negative effect on womens ability to return to work in in the first year after diagnosis of breast cancer.

Regardless of the influence of both breast cancer and psychological vulnerability prior to the diagnosis of breast cancer on return to work at one year of follow-up, no effect is found in relation to changes in income in Study II after one year. This may be explained by the welfare policy in the Nordic countries, with reimbursement of sickness benefits to all citizens. At one year of follow-up, five of the studies in Table 2 reported possible income changes after a diagnosis of breast cancer (72,75,77,76,126). The results were apparently divergent, but after taking the different definitions on income used in the studies into account, the results were concurrent. Including social benefits and reimbursement from insurance providers into the income variable, no changes were found after one year, while a significantly decline in income was reported in studies only including earnings in the income variable.

No social benefits in the first year

It was surprising that 16% of the study population in Study I did not receive any social benefits during the first year after a diagnosis of breast cancer. One explanation might be, that they were sick listed, but not long enough for the women to be registered in the DREAM database. The Danish legislation in that field has changed during the study period, and individuals had to be on sick leave for respectively 14, 15 and 21 days (the period changed in 2007 and 2008 (127)) before they were registered in the DREAM database. Due to the extensive treatment, it would have been assumed that almost all women were absent from work, when only including women being self-supporting prior to the diagnosis of breast cancer. Other reasons for women not to be registered in DREAM could be that they were financed by their spouses, or that employers failed to apply for reimbursement.

A Norwegian study, examining sick leave pattern among 5-year cancer survivors, reported that among women (40% diagnosed with breast cancer) 21% did not take sick leave within the first year after diagnosis (80), which is almost consistent with the results from this study. The small discrepancy may be explained by the fact that sick leave in Norway is registered when it exceed 16 days, while registration in Denmark takes up to three weeks.

A Canadian study demonstrated, that only 2% of women belonging to a union continued to work during the first three years after diagnosis of breast cancer. The figure was 15% of women not belonging to a union and 34% of self-employed workers (48). Membership in a union, means - among other - financial support in relation to sickness absence in countries without the same welfare-system as in the Nordic countries, and this financial support presumable made it possible for more women to be sicklisted from work when diagnosed with breast cancer.

5.2 THE LONG-TERM (1-10 YEARS) CONSEQUENCES OF BREAST CANCER

Employment rate and income

The employment rate in the years following a diagnosis of breast cancer increased continuously for women who managed to participate in the work force. After 9 years the employment rate for women diagnosed with breast cancer equalized the employment rate of breast cancer-free women. For both groups a similar pattern was seen in relation to income changes. The percent-wise increase in income reached the same level in the two groups after respectively seven years (stage IA breast cancer) and nine years (stage IB-IV breast cancer).

A Norwegian study reported that throughout a nine-year observation period, no significant differences in employment rates were found between women diagnosed with breast cancer and cancer-free women who worked at the time of diagnosis and who had not received disability pension or age pension at the end of each observed year (76). The result after nine years was consistent with the results from the present study, although the present study found differences in the intermediate years. One explanation might be, that the Norwegian study examined women diagnosed with breast cancer in the period 1992 to 1996 and only a few percent of the study population received chemotherapy. Chemotherapy are known to induce long-lasting side-effects, which might affect the employment rate more long term. A German study (63) examining whether breast cancer induced an increased drop-out of paid work (among 227 breast cancer patients and 647 random sample age-matched women), found that six years after surgery, the employment rates among breast cancer survivors were still only half as high as among controls. Contrary the Norwegian study, the German study included women receiving permanent benefits, which may explain a part of the discrepancy. Differences in legislation may be a part of the explanation. None of the above-mentioned studies included information related to psychological vulnerability. Differences in income between women diagnosed with breast cancer and cancer-free women were seen in the Norwegian study described above (76) until five years of follow-up. In the present study the negative effect of breast cancer on income were seen up until seven years, for women diagnosed with stage IA breast cancer, and nine years for stage IB-IV. Negative changes in income in the present study were measured as percent-wise changes, while Hauglann et al. only measured a change >10%. If that measure was used in the present study, no impact on income would have been found.

Despite the negative impact of breast cancer reported in this study, breast cancer patients had a higher mean annual income compared to the cancer-free cohort through

all years. This might reflect the socioeconomic gradient in the incidence of breast cancer, which also is reported in the existing literature (76). In contrast to the results in this study, Benth et al (77) reported a persistent negative effect of breast cancer on income. The discrepancy between women diagnosed with breast cancer and cancer-free women were increasing through all 13 years of follow-up, although only significant for the first ten years.

Disability pension and early retirement

Examining all women in the supplemental analyses demonstrated that from two to ten years of follow-up, a ten percent difference was seen in the employment rate between women diagnosed with breast cancer and cancer-free women. Examining breast cancer with a history of psychological vulnerability further decreased the employment rate with another ten percent. These differences reflected the increased risk for receiving disability pension or taking early retirement.

Consistent with this study, existing studies have found a positive association between breast cancer and both early retirement (88,89) and disability pension (72,77,76,90). The association between breast cancer and early retirement is in several studies found to be affected by different aspects of psychological vulnerability (89,91,92). The studies have been conducted in different countries, which indicate that the association is independent of legislative conditions.

5.3 THE USE OF REGISTER BASED DATA AS A MEASURE FOR PERCEIVED STRESS

Study III demonstrated a significant association between Cohens PSS scores and register data on psychiatric medical treatment or consultations with psychologists or psychiatrist. The results were consistent with other studies, although other measures for perceived stress were used. A Swedish study found that a high level of perceived stress was associated with the use of psychotropic medicine, although it was based on registrations in a self-registered questionnaire. Furthermore, instead of using Cohens PSS, the study used a 30-item stress scale, indicating that the association between stress and psychiatric treatment was not depending on a specific measurement tool (104).

Because of low predictive values registry data on psychiatric medical treatment may not be used as a proxy for perceived stress. Stress and psychological vulnerability are according to existing literature related (100) and psychological vulnerability is described as one of the pathways leading from stressful events to more severe

psychological problems Likewise, is mental health problems and psychological vulnerability (97). Because of the relatedness between mental health problems and psychological vulnerability an association between psychiatric medical treatment and psychological vulnerability must be expected, but whether it is stronger or weaker compared to the results from study III is unclear.

CHAPTER 6: METHODOLOGICAL CONSIDERATIONS - STRENGTHS AND LIMITATIONS

All three studies were population-based studies with complete linkage between a clinical database and nationwide administrative registers (study I and II) and between a survey and regional administrative data (study III). Data were prospectively collected and retrospectively retrieved from databases with high quality (107–109,111,114,128). The study populations in the three studies were large (between 13,000 and 22,000 individuals) with complete follow-up for study I and II and up to 10 years of follow-up (study II).

There were however limitations to all three studies that need to be acknowledged. First of all, all three studies are observational in nature, meaning that any relationships found are merely associations and may not be causal.

Selection bias

One of the inclusions criteria in the two first studies were, that women should be self-supporting prior to the diagnosis of breast cancer, although it was defined differently in the studies. In Study I the women should be self-supporting in one week (week 4 prior to diagnosis), while the women should be self-supporting in three consecutive weeks (week 4-6 prior to diagnosis) in Study II. In both studies, it was decided that the period between measuring whether the women were self-supporting and the time for diagnosis should be four weeks, in order to minimize the risk of excluding women being on sick leave due to the diagnosis of breast cancer. During the study period the employer payment period for sick leave compensation changes from 14-15 days (2007) and 15-21 days (2008)(127). Women included in study I could therefore be different over time. However, the analyses in Study I were adjusted for calendar time and a subsequent analysis using the consecutive three-week period did not change the associations between psychiatric medical treatment and return to work.

Examining only women participating in the work force in Study II might underestimate the economic consequences for all women diagnosed with breast cancer since some of them were receiving disability pension or took early retirement. Women diagnosed with breast cancer were included over a long time period of time (11 years) with changes in treatment modalities over time. However, both calendar time and treatment was taken into account in the analyses. Still, the estimates for

patients with long term follow up was based on patients diagnosed early in the study period and the number of women included in the analyses were low.

In Study III the response rate for the survey was 65.5%, introducing the risk of selection bias. Non-response due to illness could underestimate the perceived stress level, while non-response from healthy individuals could overestimate the perceived stress level. Non-respondents in Danish health surveys had more unfavourable health behaviours than respondents (129), indicating that the perceived stress level could be underestimated. This was supported by discrepancies in the percentages of individuals having received prescribed psychiatric medical treatment in study I and III. Only 0.6% of individuals in the health survey (study III) had received anxiolytics, while it was 10% of the women in study II.

Information bias

The use of perceived psychiatric medical treatment as a measure for psychological vulnerability, may induce several limitations. First, in addition to psychiatric medical treatment, psychiatric treatment modalities consist of consultations with psychologists or psychiatrists and admissions to psychiatric hospitals and therefore, some patients with psychiatric disorders do not receive prescriptions for medications. Individuals with mild or moderate depressive symptom may be treated only with psychotherapy (130), and will be misclassified without a history of psychological vulnerability in study I and II. Secondly, psychiatric medical treatments are sometimes prescribed for other diagnoses, like pain and sleep disturbances (131,132). Studies have reported, that up to 20% of antidepressants are prescribed on other indications than depression. The Danish National Prescription Register does not include informations on indication; thus, women may be misclassified as psychologically vulnerable. Both types of misclassification might underestimate the effect of psychological vulnerability prior to a diagnosis of breast cancer in relation to aspects of the affiliation to the labour market. Third, using prescribed psychiatric medical treatment as a measure for psychological vulnerability entailed, that women with a varied group of mental health problems (with diverse prognosis) all were pronounced as psychologically vulnerable, without taking the severity of the disorder into consideration. The focus in the studies included in this dissertation, were not the mental health problems in themselves or the severity of these conditions. Psychological vulnerability was used to define a group of women, with a larger risk for being marginalized and excluded from the labour market, when diagnosed with breast cancer. Women not being self-supporting in week 4 or week 4-6 prior diagnosis of breast cancer were excluded from the studies, regardless of the reason. It is assumed, that women with severe psychiatric disorders therefore will be excluded.

The study period in Study II went from 2000-2011 and through these years the effective income changes from being positive to negative as a result of economic recession (133). In order to take these changes into account, a calendar year and age specific expected change in real income was estimated, based on informations from Statistics Denmark. The income change for women diagnosed with breast cancer and cancer-free women were dichotomized according to being above or below the expected change in income in the Danish female population. Both exposed and unexposed women in study II were self-supporting when included in the studies, and the majority of women would therefore experience a decrease in income if they became unemployed or were absent owing to illness. This could explain that only 42% of the unexposed women in Study II were classified as above the expected change in income among the Danish female population. Another explanation could be, as published in a report from The Federation of Danish Enterprise (134), that through the 1990's social benefits increased more in real income, than earnings. Only including self-supporting women in study II, means only including those with low changes in real income.

Cohens PSS examines the respondents stress level in the last month, which may introduce recall bias. Individuals receiving psychiatric treatment might report a lower stress score as a consequence of treatment, and overestimate the association between perceived stress and psychiatric treatment. However, the association might be underestimated due to the design with concomitant compilation of data. It may be argued whether a questionnaire survey containing Cohens PSS is the right data source in this context, and it may sow doubt about the use of the Cohens PSS as a gold standard as used in some of the analyses in Study III. Three approaches of stress assessment are adopted due to the absence of a gold standard measurement of stress; 1) the environmental approach, 2) the psychological approach, and 3) the biological approach (135). Different tools can measure psychological stress, and Cohens PSS are the most widely used. Despite the widely use of the score, it only measure a small part of stress as a concept.

Confounding

All studies were observational studies with the usual risk of confounding inherent in the study design. Although there was adjusted for potential confounding factors in the multivariate models there were unmeasured potential confounders, that were not controlled for in the regression models or taken into account. In Study I an unmeasured potential confounder could be comorbidity. Comorbidity is assumed to be associated with both the exposure (psychiatric medical treatment) and the outcome (return to work), and adjusting for comorbidity could have weakened the association

between the exposure and the outcome, since comorbidity are assumed to be more present among women having a history of psychiatric medical treatment.

In study II comorbidity could also be a confounder associated with both breast cancer and income, but with more women suffering from other disorders in the group of women without cancer compared to the women diagnosed with breast cancer, because of the socioeconomic gradient in breast cancer. Another possible confounder in study II could be the number of home living children, since women diagnosed with breast cancer have few children compared to the breast cancer-free group of women.

Missing

In study I and II missing observation were observed, mostly < 10%. Complete case analyses were used, and no specific measures were taken to address missing data further. In study II with separate analyses each year of follow-up, individuals with missing on income in one year were only excluded the certain year, and included in the other years until one of following events: death, emigration, early retirement, age pension, or the end of the observation period.

CHAPTER 7: CONCLUSION AND PERSPECTIVES

This research has made a contribution to the existing knowledge about the affiliation to labour market following a diagnosis of breast cancer among self-supporting Danish women. Furthermore, the research contribute with knowledge about more methodological aspects of the use of registry data as a measure for perceived stress.

A diagnosis of breast cancer has a negative effect on the employment rate and income changes in the following years, although the discrepancies between women diagnosed with breast cancer and cancer-free women evens out, when women are participating in the work force. Having a history of psychological vulnerability when being diagnosed with breast cancer enhance the negative effect of breast cancer on return to work after one year and the employment rate in the following years, but do not have a negative effect on income changes.

According to the methodological aspect of the use of registry data as a measure for perceived stress, this research found, that although a positive association is demonstrated between psychiatric treatment and perceived stress, psychiatric treatment may not be used as a proxy due to low predictive values.

Psychological vulnerability in study I and II was measured as prescribed psychiatric medical treatment. Other studies examining this topic have used the international classification of diseases (79), and questionnaires together with interviews (91) as a measure for mental health problems/ psychiatric disorders (both covered by the definition of psychological vulnerability used in this dissertation). This should be taken into account when interpreting the results from existing studies and when planning future studies.

Outcome in study I was return to work, measured as being self-supporting in week 52 after diagnosis: simple and easy to obtain and understand, but it could be argued that the outcome was to rough a measure. In order to receive more detailed informations about the affiliation to the labour market after sickness absence caused by a diagnosis of breast cancer, patterns in sick leave could be examined. Women included in study I and in the supplemental analyses were either registered as self-supporting or sick listed each week (no information on part-time sick leave or part-time work). This may have underestimated the number of women who returned to work, because it is assumed that some of the women resume work part-time.

In study II the outcome was income changes. Using registry data on annual income, this might be slightly underestimated, due to illegal work and tax evasion. It may be assumed that cancer-free women to a higher extent than women diagnosed with breast cancer take illegal work, both because breast cancer patients are struggling more with the affiliation to the labour market than cancer-free women in the years following diagnosis and treatment, but also because low-educated women might take illegal work to a higher degree than high-educated women. Examining household income instead of personal income or together with personal income could also contribute with more exhaustive knowledge, but since focus in the thesis was self-supporting women, personal income was used.

A diagnosis of breast cancer are found to have a negative effect on both the affiliation to labour market and income changes in the following years examining self-supporting Danish women. Even women diagnosed with stage IA breast cancer experience long lasting effects on income, also when they manage to participate in the work force. Having a history of psychological vulnerability prior to a diagnosis of breast cancer, decrease the return to work rate after one year and the employment rate for the following years for women participation in the work force. No changes in income is registered. Although, not all women manage to participate in the work force, and more women being psychological vulnerable when they are diagnosed with breast cancer do not manage to maintain the affiliation to the labour market. This could be one of the reasons for women struggling with return to work, although it is not the full explanation.

The consequences of breast cancer are long-lasting, and affects negatively both the employment rate as well as income changes – and psychological vulnerability prior to a diagnosis of breast cancer enhance the negative effect. A diagnosis of stage IA breast cancer caused a change in income compared to the cancer-free women, for the first seven years. Based on data from the studies in this dissertation it is not possible to explain this long lasting effect of breast cancer among women being self-supporting prior to diagnosis. Further research is required in order to better understand why women - cured for breast cancer - are struggling for years, even if they manage to participate in the work force. Using qualitative methods could help to clarify this.

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