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Breast and Prostate Cancer: The Impact of Diagnosis and Treatment on Sick Leave and Work

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The cover page illustrates the estimated average number of days: (I) spent on sick leave immediately after robot-assisted radical prostatectomy, (II) spent on prostate cancer-specific sick leave in men on active surveillance during the first five years after diagnosis, (III) permanently lost from work due to stage I breast cancer in women aged 50 years at diagnosis, and (IV) spent on cancer-specific sick leave in women with stages I to III breast cancer during the first five years after diagnosis.

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Breast and Prostate Cancer: The Impact of Diagnosis and Treatment on Sick Leave and Work

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Abstract

Treatment for breast or prostate cancer can have negative consequences on working life. In addition to sick leave during treatment, women and men with breast or prostate cancer are at increased risk of permanent absence from work, although data on the underlying reasons for this are sparse. The overall aim of this thesis was to study the impact of breast and prostate cancer and their specific treatments on sick leave and work using population-based Swedish register data.

Studies I and II examined the influence of prostate cancer treatment on sick leave and receipt of disability pension. Two different types of surgery (robot-assisted and open retropubic radical prostatectomy) were studied in men with low-, intermediate- or high-risk prostate cancer, as were the treatment strategies (surgery, radiotherapy, or active surveillance) for men with low- or intermediate-risk prostate cancer. The studies included working-aged men diagnosed with prostate cancer from 2007 onward and matched prostate cancer-free men identified in the Prostate Cancer Data Base Sweden (PCBaSe). In 2,571 men with low-, intermediate- or high-risk prostate cancer (Study I), we found that robot-assisted surgery was associated with an earlier return to work compared with open surgery. Surgery type, however, had no influence on long-term rates of sick leave and disability pension receipt. In 8,699 men with low- or intermediate-risk prostate cancer (Study II), men on active surveillance spent less than half as many days on sick leave due to prostate cancer compared with those treated with primary radical prostatectomy or primary radiotherapy in the first 5 years after diagnosis. At year 5 after diagnosis, there were no major differences in the proportion of men on sick leave, disability pension, and death between treatment strategies.

Studies III and IV were based on working-aged women diagnosed with breast cancer from 1997 onward and matched breast cancer-free women identified in the Breast Cancer Data Base Sweden (BCBaSe). In Study III, we quantified the permanent loss of working time due to breast cancer diagnosis and treatment. Permanent loss was defined as disability pension receipt of at least 75%, early old-age retirement, or death. The study included 19,661 women with breast cancer and 81,303 breast cancer-free women. We estimated that women aged 50 at diagnosis on average lost between 0 years (for *in situ* and subgroups of stage I breast cancer)

and 8 years (for stage IV breast cancer) of their remaining working time due to breast cancer. Study IV examined the underlying causes of sick leave and disability pension receipt after a breast cancer diagnosis. In 16,603 women with stage I to stage III breast cancer, we found that cancer was the most commonly reported cause of sick leave and disability pension receipt, with cancer progression as the strongest determinant. In addition, sick leave and/or disability pension receipt due to lymphedema, fatigue-related conditions, mental disorders, cardiovascular diseases, and inflammatory diseases was more common in women with breast cancer compared with breast cancer-free women.

The results of this thesis show that prostate cancer treatment type has an impact on sick leave and work mainly in the first year of diagnosis. Breast cancer may have a considerable impact on working life, although it is reassuring that many women with early-stage breast cancer are able to remain in the labor market. Disease progression is not the only reason for absence from work in women with breast cancer; our findings suggest that a wide range of physical and physiological conditions underlie the increased risk of permanent absence from work observed in both our studies and others. As a whole, the findings of this thesis can be used to improve the management and rehabilitation of breast and prostate cancer diagnosed in working-aged women and men.

List of scientific papers

I. Plym A, Chiesa F, Voss M, Holmberg L, Johansson E, Stattin P, Lambe M. Work disability after robot-assisted or open radical prostatectomy: A nationwide, population-based study. European Urology. 2016;70(1):64–71.

II. Plym A, Clements M, Voss M, Holmberg L, Stattin P, Lambe M. Sick leave and disability pension after active surveillance, surgery, or radiotherapy in men with localized prostate cancer in Sweden. (*Manuscript*)

III. Plym A, Bower H, Fredriksson I, Holmberg L, Lambert PC, Lambe M. Loss in working years after a breast cancer diagnosis. British Journal of Cancer. 2018;118(5):738–743.

IV. Plym A, Johansson ALV, Bower H, Voss M, Holmberg L, Fredriksson I, Lambe M. Causes of sick leave, disability pension, and death following a breast cancer diagnosis in women of working age. (*Submitted*)

Svensk sammanfattning

Varje år drabbas över 7 000 svenska kvinnor och män i arbetsför ålder av bröst- eller prostatacancer. Utredning och behandling av cancer kan ha både psykologiska och fysiska konsekvenser, som i sin tur påverkar möjligheten att arbeta. För många individer är arbete en viktig del av livet, som utöver ekonomisk trygghet erbjuder ett socialt sammanhang och en känsla av att bidra till samhället. Efter en cancerdiagnos kan möjligheten att arbeta vara särskilt viktig, då återgången till arbetet kan betraktas som en normalisering av livet och ett tecken på återvunnen hälsa.

Trots detta har bara ett fåtal studier undersökt långtidskonsekvenserna av bröst- och prostatacancer på arbetslivet. De studier som finns pekar på att individer som drabbats av cancer har en högre risk att vara sjukskrivna och få sjukersättning, även så långt som fem år efter diagnos. Det är till viss del oklart varför kvinnor och män med bröst- eller prostatacancer försvinner ut ur arbetslivet tidigare. Denna avhandling syftade till att studera hur diagnos och behandling av bröst- eller prostatacancer påverkar sjukskrivning och arbete baserat på data från kvalitetsregister för cancer som länkats mot information från bland annat Försäkringskassan.

I avhandlingens första två delarbeten studerade vi hur behandlingsstrategin för prostatacancer påverkar sjukskrivning och sjukersättning upp till fem år efter diagnos. Vi observerade att typ av behandling till stor grad påverkade sjukskrivning under det första året efter diagnos. I en jämförelse av typ av kirurgi för prostatacancer fann vi att män som opererats med robot-assisterad kirurgi hade en kortare sjukskrivningsperiod än män som opererats med öppen kirurgi. På lång sikt fanns dock inga skillnader i sjukskrivning och sjukersättning mellan de två operationsteknikerna. I delarbete två jämfördes aktiv monitorering, kirurgi och bestrålning bland män med låg- och intermediärrisk prostatacancer. Vi fann att aktiv monitorering hade lägst påverkan på arbetslivet: Män som hade aktiv monitorering som primär behandlingsstrategi hade mindre än hälften så många dagar med sjukskrivning på grund av prostatacancer de första fem åren efter diagnos än män som opererats eller bestrålats. Fem år efter diagnos var dock över

90% av männen, oavsett behandlingsstrategi, i arbete eller stod till arbetsmarknadens förfogande.

I avhandlingens tredje och fjärde delarbete beräknade vi hur många arbetsår som förloras på grund av en bröstcancerdiagnosis samt studerade de underliggande medicinska orsakerna till sjukskrivning och sjukersättning hos kvinnor med bröstcancer. I jämförelse med bröstcancerfria kvinnor fann vi att 50-åriga kvinnor i snitt förlorade upp till 8 år av förväntad kvarvarande arbetstid som en konsekvens av sin bröstcancersjukdom. Kvinnor med *in situ* bröstcancer och vissa kvinnor med gynnsamma prognostiska faktorer förlorade inga arbetsår. Bland de underliggande orsakerna till sjukskrivning och sjukersättning hos kvinnor med bröstcancer återfanns förutom cancer även flera andra sjukdomstillstånd. Jämfört med bröstcancerfria kvinnor var det en större andel kvinnor med bröstcancer som inte kunde arbeta på grund av lymfödem, trötthet och smärtrelaterade besvär, depression, stress och ångest, samt kardiovaskulära och inflammatoriska sjukdomar.

Sammantaget visar resultaten i denna avhandling på att behandling för bröst- och prostatacancer kan ha en stor påverkan på arbetslivet. Resultaten kan användas för att förbättra vården och utveckla program och arbetsplatsinsatser för kvinnor och män som drabbats av cancer i arbetsför ålder.

Contents

List of abbreviations

ADT	Androgen Deprivation Therapy
AIC	Akaike Information Criterion
ALND	Axillary Lymph Node Dissection
AS	Active Surveillance
BCBaSe	Breast Cancer Data Base Sweden
CI	Confidence Interval
CIF	Cumulative Incidence Function
ER	Estrogen Receptor
GEE	Generalized Estimating Equations
GGG	Gleason Grade Group
GnRH	Gonadotropin Releasing Hormone
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
ICD	International Classification of Diseases
ISCO	International Standard Classification of Occupations
IQR	Interquartile Range
LISA	The Longitudinal Integration Database for Health Insurance and Labor Market Studies
MiDAS	Micro Data for Analysis of Social Insurance Database
NOCWO	Nordic Study on Cancer and Work
NPCR	National Prostate Cancer Register
PCa	Prostate Cancer
PCBaSe	Prostate Cancer Data Base Sweden
PR	Progesterone Receptor
PSA	Prostate-specific Antigen
RARP	Robot-assisted Radical Prostatectomy
RP	Radical Prostatectomy
RRP	Retropubic Radical Prostatectomy
RT	Radiotherapy
SNB	Sentinel Node Biopsy
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4 trial
TNM	Classification system used for staging of breast cancers

1 Introduction

Cancer is often considered a disease of the elderly. However, around one-third of all cancers in Sweden are diagnosed in individuals under the age of 65. Many of these individuals are in the midst of their working lives, which are often put on hold because of the cancer diagnosis. As well as the treatment itself, treatment-related adverse events may affect the ability to continue working. In addition to its impact on lifetime earnings, not being able to work can also influence psychological wellbeing. Work is an important aspect of life, offering a sense of belonging and providing structure for daily life.

Breast and prostate cancer are the most common cancer diagnoses in working-aged women and men. Women with breast cancer usually follow an intense treatment protocol, with post-diagnostic sick-leave periods of up to a year. Prostate cancer may also require more intensive treatment, but curative treatment can often be postponed until signs of progression appear. Few previous studies have researched the long-term influence of specific treatments for breast and prostate cancer on sick leave and work. Such information is relevant in order to improve quality of life for working-aged women and men diagnosed with cancer.

In the present thesis, we aimed to study the impact of diagnosis and treatment of breast or prostate cancer on sick leave and work. In this work we also focused on applying statistical methods that quantify this impact in absolute terms so as to increase our understanding of how cancer influences working life.

Throughout this thesis, the term "working-aged" refers to individuals under the age of 65, the standard retirement age in Sweden. Breast and prostate cancer are rarely diagnosed in individuals under the age of 30.

2 Background

2.1 Breast and prostate cancer in working-aged women and men

In 2016, approximately 50% of all breast cancers and 30% of all prostate cancers in Sweden were diagnosed in working-aged people [1]. Over 7,000 working-aged women and men received a diagnosis of breast or prostate cancer, which accounted for 30% to 40% of all cancers in this age group. For people under the age of 65, the cumulative risk of being diagnosed with breast cancer is 6%, and with prostate cancer 5%.

The incidence of breast and prostate cancer in working-aged women and men has increased in Sweden since the 1970s (Figure 2.1) [2]. Factors believed to explain the rise in breast cancer incidence include changes in lifestyle factors and the introduction of organized mammography screening programs [3]. The rise in prostate cancer incidence most likely reflects the widespread use of prostate-specific antigen (PSA) testing. This increased focus on early diagnosis, along with more effective treatment [4], has led to reductions in both breast and prostate cancer mortality (Figure 2.1) [5]. Today, more than 30,000 working-aged women and 13,000 working-aged men live with a diagnosis of breast or prostate cancer in Sweden.

In comparison with outcomes for many other types of cancer, survival rates for breast and prostate cancer are high. In women diagnosed with breast cancer at the age of 50 to 59, the most recent estimates of 5 and 10-year relative survival are 94% and 88%, respectively [5]. In men diagnosed with prostate cancer, the corresponding estimates are 96% and 92%.

The prognosis is strongly dependent on disease stage and other tumor characteristics at diagnosis. For example, in an analysis of studies from the Early Breast Cancer Trialist's Collaborative Group on women with estrogen receptor-positive breast cancer diagnosed before the age of 75, the 10-year cumulative risk of breast cancer-specific death was 8% in women with no lymph node involvement at diagnosis, compared with 29% in women with 4 to 9 involved lymph nodes [6]. Based on data from the National Prostate Cancer Register of Sweden, the 10-year cumulative risk of prostate cancer-specific death in men with localized disease aged 60 at diagnosis was 1% in men in the lowest risk category, compared with 12% in the highest risk category [7].

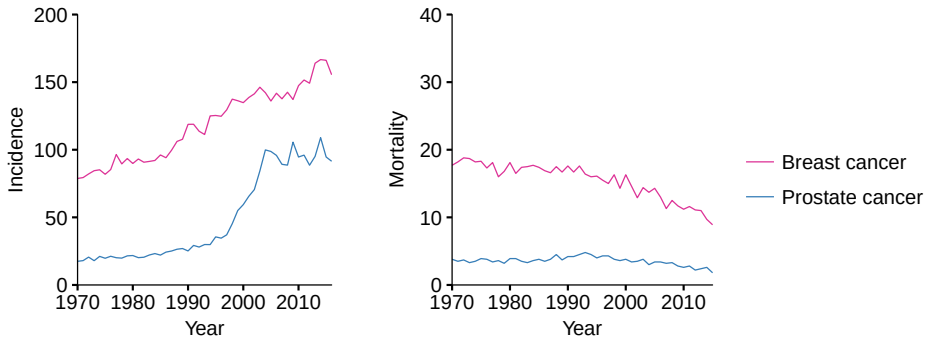

Figure 2.1: Age-standardized incidence and mortality (per 100,000) of breast and prostate cancer in women and men aged less than 65 years at diagnosis

2.2 Prostate cancer: diagnosis, classification, and treatment

2.2.1 Diagnosis and classification

Symptoms of prostate cancer generally only occur during more advanced stages of the disease, and include frequent urination, weak urine flow, and difficulty starting or stopping urine flow. The number of men diagnosed with asymptomatic prostate cancer has increased in Sweden since PSA testing became available. From 2004 to 2016, the proportion of tumors detected during health checkups increased from 29% to 53% [8]. This resulted in a steep decrease in the median age at diagnosis, from 74 years in 1996 to 70 years in 2005 [9].

The diagnosis of prostate cancer is confirmed through biopsy. Prostate cancer is classified histologically according to the Gleason grading system [10]. By characterizing and assigning a grade to the most prevalent and the second-most prevalent tumor growth patterns, a summary score is calculated and assigned using the Gleason grade grouping system (GGG) (Table 2.1); the higher the assigned GGG, the worse the prognosis.

Table 2.1: Gleason Grade Group

Gleason Grade Group	Gleason Score	Gleason Pattern
1	≤ 6	$\leq 3 + 3$
2	7	3 + 4
3	7	4 + 3
4	8	4 + 4
5	9–10	4 + 5, 5 + 4, 5 + 5

Localized prostate cancer can be classified into 4 risk categories: very low-, low-, intermediate- and high-risk disease (Table 2.2) [11]. Based on data from the National Prostate Cancer Register [12], in 2017, 41% of men under the age of 65 were diagnosed with low-risk disease, 37% with intermediate-risk disease, 11% with high-risk disease, 3% with regionally metastasized disease, and 5% with metastatic disease.

Table 2.2: Risk categories for localized prostate cancer

Risk category	
Very low	T1c (detection through needle biopsy), PSA density < 0.15 μg/l/cm^3, $\leq$ 8 mm total cancer length in $\leq$ 4 biopsy cores
Low	T1 (not palpable) - T2a (involves one-half of 1 lobe or less), GGG 1, PSA < 10 μg/l
Intermediate	T2b (involves more than half of 1 lobe), GGG 2-3, and/or PSA 10 to < 20 μg/l
High	T2c (involves both lobes) - T3 (extends through the prostatic capsule), GGG 4-5 (or extensive 3), and/or PSA $\geq$ 20 μg/l

2.2.2 Treatment

Men with localized prostate cancer have several treatment options: radical prostatectomy, radiotherapy, hormone therapy, active surveillance, and watchful waiting. Treatment decisions are based upon tumor characteristics, life expectancy, and individual preferences. Since 2007, Swedish guidelines have recommended active surveillance as the first-choice treatment for men with low-risk prostate cancer [11]. Active surveillance is a strategy that delays curative

treatment until signs of disease progression appear, and includes blood tests every 3 to 6 months, rectal examinations every 6 to 12 months, and a biopsy every second to third year.

In 2017, the percentage of men aged 64 or younger managed using active surveillance was 93% in the very-low-risk group, 71% in the low-risk group, and 16% in the intermediate-risk group [12]. Watchful waiting is another strategy for men with a life expectancy of less than 10 to 15 years for whom subsequent curative treatment is not an option. Typically, these men receive hormone therapy starting from the time of symptomatic progression.

Radical prostatectomy and radiotherapy are commonly used to treat intermediate- and high-risk prostate cancer. Radical prostatectomy is a surgical procedure to remove the whole prostate gland, with or without surrounding lymph nodes. It can either be performed as an open procedure (retropubic radical prostatectomy) or with traditional or robot-assisted laparoscopic techniques. The advantages of robot-assisted radical prostatectomy over open surgery are decreased bleeding and shorter hospital stays [13], but previous studies have found no major differences in functional outcomes [14, 15].

External beam radiotherapy is another standard option for treatment of prostate cancer, especially for larger tumors with possible growth outside the prostate gland. This technique has the advantage of not requiring anesthesia and hospital stays, but its disadvantage is a small risk of secondary cancers [16]. Radiotherapy is usually given for up to 8 weeks and can be combined with hormone therapy. Brachytherapy is a further option in which radioactive seeds are placed in the prostate. In a randomized trial comparing radical prostatectomy, external beam radiotherapy, and active surveillance for the treatment of localized prostate cancer (the ProtecT trial), the 10-year prostate cancer-specific mortality rate was similar across all treatment groups [17].

Recurrence is not uncommon after treatment for prostate cancer: A study based on the National Prostate Cancer Register of Sweden found that around one-fifth of men with localized prostate cancer treated with radical prostatectomy experienced disease progression within the first 10 years [18]. For these men, possible treatment options include salvage radiotherapy, hormone therapy, or watchful waiting. Hormone therapy—also called androgen deprivation therapy (ADT)—is the first-choice treatment for localized high-risk, recurrent, or metastatic prostate cancer. Hormone therapy is aimed at lowering testosterone

levels through either surgical (orchiectomy) or medical castration. The most frequently used agents for medical castration are gonadotropin-releasing hormone (GnRH) agonists and anti-androgens.

2.2.3 Treatment-related adverse events and quality of life

Due to the location of the prostate, the most common adverse events after radical prostatectomy and radiotherapy involve erectile, urinary, and bowel functions. In the ProtecT trial, 67% of men had an erection firm enough for intercourse at baseline [19]. Six months later, this proportion had fallen to 12% in the prostatectomy group, 22% in the radiotherapy group, and 52% in the active surveillance group. Long-term data on erectile function are available from a follow-up study performed within the National Prostate Cancer Register of Sweden (NPCR follow-up study) [20]. After a median follow-up of 12 years after diagnosis, normal erectile function was reported in 11% of men treated with prostatectomy, 16% of men treated with radiotherapy, and 20% of men with active surveillance as the primary management strategy, compared with 35% of age-matched prostate cancer-free men.

Men treated with radical prostatectomy are at a particularly high risk of urinary incontinence. In the ProtecT trial, 46% of men in the prostatectomy group used absorbent pads at 6 months, compared with 5% in the radiotherapy group, and 4% in the surveillance group [19]. In the NPCR follow-up study, 21% of men treated with prostatectomy, 9% of men treated with radiotherapy, and 8% of men on active surveillance used pads [20]. Bowel dysfunction is primarily a concern after radiotherapy. In the ProtecT trial, the proportion of men in the radiotherapy group reporting blood in stools increased from 1.6% at baseline to 3.8% at 6 months [19]. In the NPCR follow-up study, men treated with radiotherapy had a 2-fold increased risk of bowel dysfunction compared with prostate cancer-free men [20].

Men under multimodal treatment, especially combinations that include hormone therapy, generally have the highest risk of adverse events [20, 21]. Hormone therapy is associated with an increased risk of a range of adverse events including erectile dysfunction, enlarged breasts, hot flashes, cognitive impairment, depression, osteoporosis, and cardiovascular and other metabolic diseases [22]. For example, a recent meta-analysis of 18 studies found that use of hormone

therapy in men with prostate cancer was associated with a 1.4-fold increased risk of depression [23].

Prostate cancer has been reported to have an impact on general well-being. In the Scandinavian Prostate Cancer Group Study Number 4 trial (SPCG-4), in which radical prostatectomy was compared to watchful waiting with additional data on a population-based control group, 35% of men in the prostatectomy group, 34% of men in the watchful waiting group and 45% of control men reported a high quality of life after a median follow-up of 12 years [24]. A recent Dutch study also reported poorer quality of life in men with prostate cancer compared with population-based control men [25].

Problems related to mental health are of particular concern after a prostate cancer diagnosis. In the Dutch study, 14% of men with prostate cancer had clinically relevant mental health problems 5 years or more after diagnosis, compared with 6% in control men [25], which is largely consistent with results from an earlier meta-analysis [26]. More urinary issues and decreased sexual satisfaction were significant predictors of poorer mental health [25]. In a Swedish study based on data from the National Prostate Cancer Register of Sweden, men in all risk categories were at increased risk of use of antidepressant medication [27].

2.3 Breast cancer: diagnosis, classification, and treatment

2.3.1 Diagnosis and classification

Approximately 65% of all breast cancer in Sweden is detected by mammography screening, which is offered to women aged 40 to 74 years within an invitational screening program [28]. The remaining tumors are detected by clinical signs and symptoms reported by the woman herself, the most common of these being a lump. The median age at diagnosis in Sweden in 2017 was 65 years, with an interquartile range of 54 to 73 years.

Diagnosis of breast cancer is based on clinical examination, imaging, and biopsy. Breast cancer is broadly categorized into *in situ* and invasive cancer, of which ductal and lobular are the most common subtypes. Invasive breast cancer is further classified by expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and the cellular proliferation marker Ki-67. Four molecular subtypes of breast cancer have been

defined accordingly, each with distinct clinical and prognostic features (Table 2.3) [29].

Table 2.3: Molecular subtypes of breast cancer

Subtype	
Luminal A	ER and/or PR positive, HER2 negative, low Ki-67
Luminal B	ER and/or PR positive, HER2 negative, high Ki-67
HER2-positive	HER2 positive
Triple-negative/basal-like	ER and PR negative, HER2 negative

The most commonly used staging system for breast cancer is the American Joint Committee on Cancer TNM system (Table 2.4) [10]. In 2017, the majority of Swedish women diagnosed at under the age of 65 had luminal A or B breast cancer (71%), no lymph node involvement (85%), and no distant metastasis at diagnosis (98%) [28].

Table 2.4: TNM classification of breast cancer

Stage	T-stage	N-stage	M-stage
0	*In situ*	N0	M0
IA	T1 ($\leq$ 20 mm)	N0	M0
IB	T0–T1 ($\leq$ 20 mm)	N1 (micrometastases)	M0
IIA	T0–T1 ($\leq$ 20 mm)	N1 (1–3 axillary lymph nodes)	M0
	T2 ($>$ 20 to $\leq$ 50 mm)	N0	M0
IIB	T2 ($>$ 20 to $\leq$ 50 mm)	N1 (1–3 axillary lymph nodes)	M0
	T3 ($>$ 50 mm)	N0	M0
IIIA	T0–T2 ($\leq$ 50 mm)	N2 (4–9 axillary lymph nodes)	M0
	T3 ($>$ 50 mm)	N1-N2 (1–9 axillary lymph nodes)	M0
IIIB	T4	N0-N2 ($\leq$ 9 axillary lymph nodes)	M0
IIIC	Any T	N3 ($\geq$ 10 axillary lymph nodes)	M0
IV	Any T	Any N	M1

2.3.2 Treatment

Surgery removing parts of the breast (partial mastectomy/breast-conserving surgery) or the whole breast (mastectomy) is often the first line of treatment in women with breast cancer [29]. Mastectomy is indicated when breast-conserving

surgery is not possible due to tumor size or multifocal tumor growth, or because of aesthetic concerns or patient preferences. Breast-conserving surgery with post-operative radiotherapy is not associated with a survival disadvantage compared with mastectomy [30, 31].

Staging of the axillary lymph nodes is usually performed at the same time as breast cancer surgery. Axillary lymph node dissection, removing some or all of the lymph nodes, was the standard procedure until the early 2000s. Today, the primary method for axillary staging is sentinel lymph node biopsy, in which only the first lymph node that drains the tumor is examined. In case of a positive sentinel node biopsy, axillary lymph node dissection of at least 10 lymph nodes is recommended. Randomized trials comparing sentinel node biopsy to axillary lymph node dissection have found similar overall survival rates for the two strategies, but with a considerably lower risk of adverse effects such as lymphedema after sentinel node biopsy [32].

Post-operative radiotherapy is standard treatment following breast-conserving surgery, and may be administered after mastectomy in cases with large tumors or lymph node involvement. Radiotherapy is usually given 5 days per week during 5 weeks, sometimes followed by a supplemental boost of radiation. Adjuvant chemotherapy can further reduce the risk of recurrence, and is recommended for women with ER-negative tumors, women with lymph node involvement, or women without lymph node involvement but with a high risk of recurrence [29]. Chemotherapy is typically given every third week for 6 cycles, and the most common types chemotherapy used are anthracyclines and taxans, either alone or in combination, or a combination of cyclophosphamide, methotrexate, and fluorouracil. Around 50% of Swedish women aged 65 years or under at diagnosis received chemotherapy in 2017 [28].

Women with HER2-positive tumors—about 15% of all breast cancers—benefit from chemotherapy combined with HER2-targeted therapy (Trastuzumab). For women with ER-positive tumors, additional endocrine treatment is recommended. The selective estrogen receptor modulator Tamoxifen is indicated in pre-menopausal women, whereas aromatase inhibitors are recommended for post-menopausal women. Radiotherapy and chemotherapy are usually completed within 4 to 6 months after surgery, while HER2-targeted therapy is given for 1 year and endocrine treatment is recommended for 5, or sometimes 10 years.

2.3.3 Treatment-related adverse events and quality of life

Adverse events such as pain, fatigue, and lymphedema are common after treatment for breast cancer. In a meta-analysis of 23 studies, nearly 40% of women were reported to suffer from persistent pain after breast cancer surgery, with axillary lymph node dissection as the strongest risk factor [33]. A meta-analysis of 27 studies reported that approximately 25% of women treated for breast cancer develop severe fatigue [34] that may persist for 10 years after diagnosis [35]. Chemotherapy is one of the most important risk factors for fatigue: 80% to 96% of women undergoing chemotherapy experience fatigue during the treatment phase [36]. However, the association between chemotherapy and persistent long-term fatigue is weaker [37]. Lymphedema is another adverse event affecting around 20% of all women treated with axillary lymph node dissection [38].

Several other conditions have been associated with treatment for breast cancer, such as cardiovascular disease (which has been linked to anthracyclines, trastuzumab, and radiotherapy); osteoporosis (linked to aromatase inhibitors); infertility and menopausal symptoms (linked to chemotherapy and tamoxifen); joint symptoms (linked to aromatase inhibitors); and secondary cancers (linked to chemotherapy, radiotherapy, and tamoxifen) [39, 40]. Breast cancer has also been associated with an increased risk of depression, anxiety, and stress-related disorders, especially during the first years after diagnosis [41, 42]. The highest risk of depression has been observed in young women, women with nodal involvement, and women with comorbidities [42].

In a Danish study of long-term breast cancer survivors, around 20% reported that their daily activities were limited by treatment sequelae [43]. The proportion was highest in working-aged women, among whom up to 30% reported limited daily activities. Although breast cancer is associated with a high morbidity burden, the overall quality of life in women with breast cancer has been found to be similar to, or sometimes better than, that reported by women of the same age in the general population with the exception of the initial period after diagnosis [44–46] and women diagnosed with breast cancer before the age of 50 [45, 47].

2.4 Work after cancer

2.4.1 Presumptions and definitions

For many women and men, work is a central part of life that can provide a sense of belonging, a structure for the day, and a feeling of contributing [48]. Previous research has found that cancer patients often have a desire and need to re-engage in paid work, not only to meet financial needs, but also to regain a sense of normality [49, 50]. Returning to work can be a sign of recovery, marking the transition from disease to regained health. Being able to work is also an important factor associated with good quality of life after treatment for cancer [51, 52].

Diagnosis and treatment for cancer can affect working life in many different ways, and a broad range of work-related outcomes has been investigated in previous studies. In the cancer and work model initially proposed by Feuerstein et al., 4 major types of outcomes were recognized (Table 2.5) [53].

Table 2.5: Different types of work-related outcomes

Outcomes	Definition
Return to work	Return to full-time work after diagnosis or treatment
Work ability	Refers to "an individual's psychological, physical, and social means to engage in work" [53, p. 432]
Work performance	Includes, for example, absenteeism from work due to sick leave, work productivity, and perceived impairments while at work
Sustainability	Remaining employed or remaining in the work force

Feuerstein et al. also identified factors influencing these outcomes, and categorized them into factors related to health (e.g., comorbidities), symptoms of treatment (e.g., fatigue), functional abilities (e.g., strength), work demands (e.g., number of clients), work environment (e.g., flexibility), and legal and economic factors (e.g., possibility of obtaining disability benefits).

Another commonly used term is work disability, defined "as occurring when a worker is unable to stay at work or return to work because of an injury or disease" [54, p. ix]. Temporary work disability is generally labeled sickness absence or sick leave, whereas permanent work disability refers to a permanent reduction (part or full-time) in work time, often accompanied by the receipt of a disability pension.

Inherently, the inability to work is related to the demands at work. Therefore, work disability is not necessarily a measure of morbidity, and can be regarded as an "integrated measure of functioning" [55, p. 129].

2.4.2 Swedish legislation

As a part of the Swedish welfare system, all residents with a minimum income from work or unemployment benefits are eligible for sickness benefits in the event of work incapacity of at least 25% due to disease or injury [56]. The first 14 days of a sick-leave period are paid by the employer, with the first day being a qualifying day with no benefits paid. For sick-leave periods longer than 14 days, sickness benefits are paid by the Swedish Social Insurance Agency, with benefits corresponding to about 80% of an individual's income up to a certain ceiling. Special rules apply for the unemployed and self-employed, for whom the Swedish Social Insurance Agency also compensates the first days that are paid by the employer in other situations. In addition, those who are self-employed can choose to have longer qualifying periods (up to 90 days). In case of permanent work incapacity, the Swedish Social Insurance Agency can grant disability pensions to persons aged 30 to 64 years living in Sweden. A person can receive part or full-time sickness benefit.

The Swedish Social Insurance system has undergone several changes [57]. During certain periods, the initial period of sick leave paid by the employer was longer (28 days between January 1997 and March 1998, and 21 days between July 2003 and December 2004). In 2003, the insurance for disability pensions was transferred from the public pension system to the public sickness insurance system. The method for calculating disability benefits changed, but the eligibility criterion—reduced work capacity due to a health problem—remained the same. In 2008, the rules for sick leave and disability pension receipt became stricter. A time limit for sick leave was introduced, restricting the ability to obtaining sick leave for more than a year. A stricter assessment of work ability was also imposed, with fixed time-points for assessment at 90 and 180 days after the start of the sick-leave period. To obtain a disability pension, work capacity has to be permanently reduced for the foreseeable future, and the assessment must be made against the labor market as a whole.

2.4.3 Swedish guidelines on sick leave

Several stakeholders are involved in the sick-leave process. The physician is responsible for diagnosis and treatment decisions, assessing work capacity, and for determining the duration of the sick leave, all the while respecting individual needs. The Social Insurance Agency makes the final decision based on the information provided by the physician. The guidelines in Table 2.6 were introduced by the National Board of Health and Welfare in 2007 to help both physicians and insurance officers with the process, although every decision must be based on individual circumstances [58].

Table 2.6: Cancer-specific guidelines for sick leave

Type of cancer/treatment	Recommended sick leave
Breast cancer	
Partial mastectomy with minor axillary surgery	Up to 3 weeks
Mastectomy and/or extensive axillary surgery	Up to 6 weeks
Adjuvant chemotherapy	Often requires full-time sick leave
Radiotherapy	Sick leave can be indicated because of practical reasons or adverse events from previous treatments
Endocrine or HER2-targeted therapy	Usually allows for at least part-time work
Prostate cancer	
Radical prostatectomy	Up to 6 weeks
Radiotherapy	Can require up to 8 weeks sick leave during the latter part of the treatment due to adverse events
Metastatic breast or prostate cancer	Extended sick leave can be required, often 1 year or longer

2.4.4 Previous research on work after prostate cancer

Return to work

Time to return to work after surgery for prostate cancer has been examined in a few previous studies [59–65]. Two studies from the United States reported a median absence of 25 days or less after radical prostatectomy [59, 61], whereas European

studies generally report longer absences from work. Two German studies found a median time to return to work after radical prostatectomy of 42 and 56 days, respectively [62, 63]. In a Swedish/Danish study, a median of 55 days of sick leave was reported for men treated with open radical prostatectomy, compared with 26 days for men treated with robot-assisted radical prostatectomy [60].

Return to work after other types of treatment for prostate cancer has been less thoroughly studied. In one of the US-based studies, hormone treatment and/or radiotherapy was associated with a median of only 3 days of absence from work in the first 6 months after diagnosis [59]. A Danish study examined the duration of sick leave after radiotherapy and hormone therapy and found a median duration of 9 weeks in the first year after the start of treatment [66].

Over 80% of men with prostate cancer are able to return to work within the first year of diagnosis [63, 67]. In addition to treatment type, factors associated with a delayed return to work in men with prostate cancer are high tumor stage [60, 63], high physical workload or manual work [60–62, 65], young age [61, 63, 65], and low income or education [60, 62, 65].

Work-related aspects beyond return to work

Treatment for prostate cancer can also have a long-term impact on working life, although only a limited number of studies on this aspect have been published. A Norwegian study examined sick leave after prostate and other cancers and found that men with prostate cancer had a 1.6-fold increased risk of sick leave 5 years after diagnosis compared with a control population (Figure 2.2) [68]. In two Danish studies with up to 20 years of follow-up, it was reported that men with prostate cancer had a 4-fold increased risk of early retirement pension before the age of 60 [69], but no increased risk of unemployment [70]. A Finnish study also found that prostate cancer was associated with a small increased risk of retirement, but not with unemployment [71]. In the Nordic Study on Cancer and Work (NOCWO), men with prostate cancer had an increased risk of non-employment, which included unemployment, disability pension receipt, and retirement [72].

Self-reported work ability has been examined in men with prostate cancer. In the NOCWO study, men with prostate cancer reported a lower ability to work than control men [73]. Another study found that while most men are able to continue

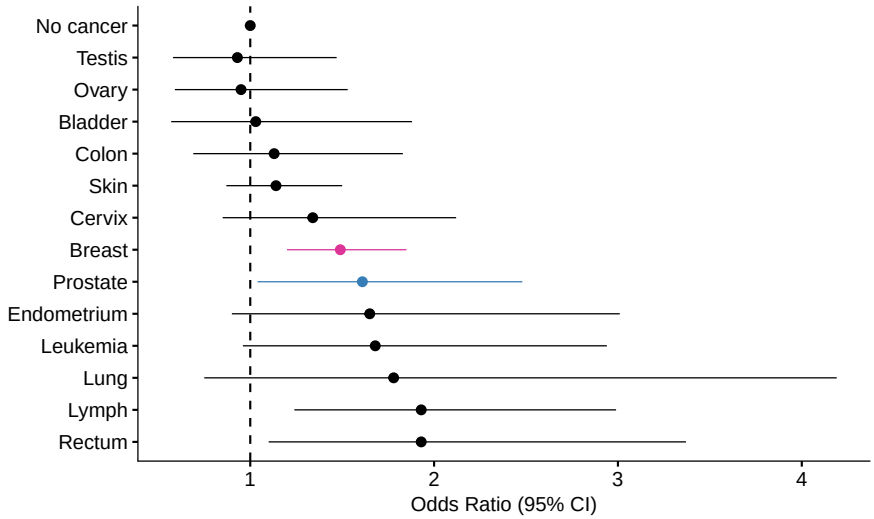

Figure 2.2: Odds ratio of sick leave five years after diagnosis

to work after radical prostatectomy, the cancer diagnosis has a negative impact on working life 3 years after the surgery in 34% of the men still working [74]. In an extended analysis partly based on the same cohort of men, 24% reported a moderate or poor ability to work during a period of up to 6 years after surgery [75]. Men who underwent surgery less than 3 years ago and men with additional hormone therapy and/or radiotherapy were at the highest risk for moderate or poor ability to work.

In a recently published study from the United Kingdom, the treatment type for prostate cancer influenced the transition from employment to unemployment 18 to 42 months after diagnosis [76]. A larger proportion of men receiving radiotherapy and/or hormone therapy moved to unemployment compared with men treated with surgery only or men on active surveillance or watchful waiting.

Underlying medical reasons for absence from work

Treatment-related symptoms can negatively influence employment and work. In a Norwegian study of men who had undergone radical prostatectomy, a reduction in physical functioning was associated with reduced work status 3 months after surgery [65]. In two other studies from the same research group, fatigue and

urinary leakage were factors that were strongly related to perceived work ability up to 6 years after surgery [74, 75]. In the study from the United Kingdom, moderate or severe urinary and bowel symptoms were associated with a 2-fold increased risk of becoming unemployed [76].

2.4.5 Previous research on work after breast cancer

Return to work

The majority of women diagnosed with breast cancer are able to return to work within 1 year after diagnosis. In one Swedish study, 83% of women with early-stage breast cancer had returned to work 10 months after diagnosis [77]. The proportion was lower in women treated with chemotherapy (63%), and higher in women not treated with chemotherapy (91%). Four other Swedish studies [50, 78–80] and several studies from other European countries [81–83] have reported similar estimates of return-to-work, ranging from 68% to 79% at 11 to 12 months after diagnosis.

Time to return to work—usually measured as the duration of sick leave—after a breast cancer diagnosis has been examined in a few previous studies [59, 84, 85]. In a French study, the median duration of sick leave was 11 months [85]. Chemotherapy was associated with longer sick leave (15 months), as was mastectomy (13 months), axillary lymph node dissection (13 months), and radiotherapy (12 months). Similar durations of absence from work were observed in a study from the Netherlands [84], whereas considerably shorter absences (less than 2 months) were reported in a study from the United States [59]. Other studies have examined the number of days on sick leave in the first year after diagnosis [86–90]. For example, in a nationwide Swedish study, Kvillemo et al. observed that women diagnosed with all stages of breast cancer had a mean of 185 days of sick leave or disability pension receipt in the first year after diagnosis, compared with less than 80 days in matched control women [86].

In a systematic review including 26 studies, chemotherapy was reported to be one of the major factors negatively influencing time to return to work after a breast cancer diagnosis [91]. Other treatment-related factors frequently reported to delay return to work were mastectomy and axillary lymph node dissection. Among the work-related factors, workplace support from employers and colleagues was reported to be the key factor for facilitating return to work.

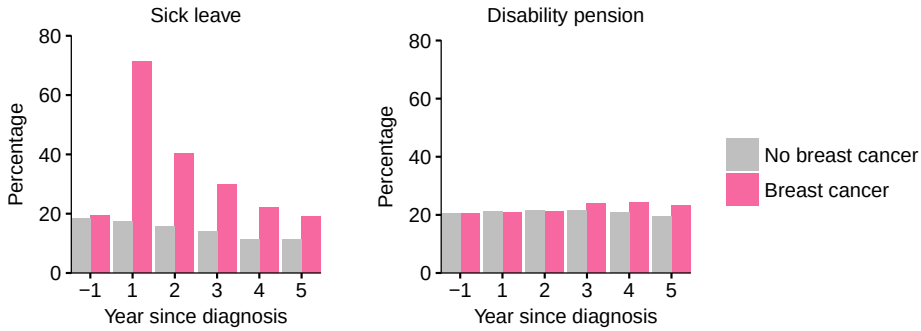

Figure 2.3: Percentage of women on sick leave and disability pension by year since diagnosis

Several sociodemographic factors were also reported to facilitate return to work, including high income, high educational level, and social support from family and friends.

Work-related aspects beyond return to work

Breast cancer can also have negative consequences on work and employment beyond the first year after diagnosis. Three Swedish register-based studies have examined the risk of sick leave and disability pension receipt in women with breast cancer during the first 5 years after diagnosis in comparison with matched breast cancer-free control women [86, 89, 92]. Eaker et al. observed that breast cancer was associated with a 1.2-fold increased risk of sick leave and a 1.5-fold increased risk of disability pension receipt 5 years after diagnosis [92]. An increased risk was found across all disease stages. The two other Swedish studies also found evidence of an increased risk of sick leave in women with breast cancer 3 years [89] and 5 years after diagnosis [86]. In the study by Kvillemo et al., 19% of women with breast cancer and 11% of control women had at least 1 period of sick leave in the fifth year after diagnosis, after excluding those no longer at risk (Figure 2.3) [86]. Receipt of disability pension benefits was reported in 23% of women with breast cancer and 20% of control women.

The long-term risk of sick leave and disability pension receipt has also been examined in studies from other European countries. Two Norwegian studies reported a 1.5-fold increased risk of sick leave in year 5 after diagnosis (Figure

2.2) [68] and a 2.7-fold increased risk of disability pension receipt during a period of up to 14 years after diagnosis [93]. In a Danish study it was observed that women with breast cancer was the only group of cancer survivors that still had a significantly increased risk of early retirement pension before the age of 60 after 12 years of follow-up [69]. In a Dutch study by Paalman et al., the 10-year cumulative incidence of disability pension receipt was 33% in women with breast cancer, compared with 14% in control women [94].

Other studies have assessed rates of unemployment or non-employment, which is a mixture of different types of absences, in the years following a breast cancer diagnosis. In a recently published cohort study of women with early-stage breast cancer in the Unites States, 56% of women with breast cancer and 63% of control women were still employed 2 years after diagnosis [95]. Another research group from the United States reported that women who remained free from recurrence did not, on average, spend much more time away from work in the third year after diagnosis (2.1 months) compared with control women (1.9 months) [90]. However, the duration of absence was considerably higher in women with new cancer events (4.1 months). In the study by Paalman et al., women with breast cancer were at increased risk of unemployment [94], whereas no increased risk was found in an older Finish study [71].

Self-reported work ability has also been examined in a few studies. Danish women living with breast cancer for at least 5 years reported lower work ability than control women [96], and similar findings were reported in two other studies [73, 97]. In a recent study from Singapore, approximately 40% of employed women with breast cancer had poor or moderate work ability 1 year or more after diagnosis [98]. While a Norwegian study reported poorer work capacity in women with breast cancer who had returned to work compared with control women, breast cancer had no impact on working hours or the proportion of full-time workers [99].

In addition to the adverse influence of a more advanced disease stage at diagnosis, most previous studies with data on tumor and treatment characteristics have reported an impact of treatment type on long-term absence from work: For example, in the study by Eaker et al., mastectomy, axillary lymph node dissection, chemotherapy, and hormonal therapy were independently associated with an increased risk of sick leave and disability pension receipt 3 years after diagnosis, with somewhat weaker associations in year 5 [92]. Paalman et al. also observed an increased risk of disability pension receipt after axillary lymph node dissection

up to 10 years after diagnosis, but not after mastectomy alone or hormonal therapy [94]. Chemotherapy was associated with an increased risk only in the first 5 years after diagnosis. In a cohort of women from the United States with early-stage breast cancer, chemotherapy, but not mastectomy, was also associated with an increased risk of unemployment 4 years after diagnosis [100]. In contrast to these studies, two Danish studies found no evidence that chemotherapy increased the risk of unemployment 2 years after diagnosis [101] or early retirement during a mean follow-up of 3 years [102].

Underlying medical reasons for absence from work

During the first year following diagnosis, women with breast cancer are absent from work in order to undergo treatment; treatment modality is a major determinant of time to return to work. Treatment-related adverse events such as pain in the breast, arm and shoulder function impairments, and lymphedema have been noted to delay return to work [84, 85, 103]. In a small Swedish study of 14 women who remained on sick leave 8 months after diagnosis, reasons for sick leave on the medical certificate were related to systemic adverse events [79].

The medical reasons for sick leave and other types of absence from work beyond the first year have rarely been studied. Kvillemo et al. included medical diagnoses for sick leave in their analysis, and observed that breast cancer was the reported cause in 42% of days on sick leave and 12% of days on disability pension in year 5 after diagnosis [86]. The corresponding numbers for the remaining causes were not presented. A few other studies have examined whether certain symptoms are related to absence from work following diagnosis. Fatigue and pain have been associated with an increased risk of not being employed [95, 104]. Sleep disturbances have also been identified as a mediating factor for absence from work, accounting for 8% of missed work days in women and men with breast or prostate cancer [105].

A number of studies have examined factors affecting work ability in the years following a breast cancer diagnosis. Fatigue has been identified as a major factor explaining work ability and work limitations in women with breast cancer [106, 107]. In the Danish study of self-reported work ability in women with breast cancer, fatigue was associated with an 11-fold increased risk of impaired work ability [96]. After fatigue, the strongest associations were observed for anxiety,

low income, and little support from supervisors, which were associated with a 2-fold increased risk of impaired work ability.

Breast and arm symptoms have also been reported to reduce work ability and work capacity in women with breast cancer [98, 108]. In a study of Canadian women with breast cancer, those with arm pain had an 8-fold increased risk of reduced work capacity compared with those with no arm pain [108]. In a recent systematic review including both quantitative and qualitative studies, physical impairments were consistently described as negatively influencing work ability and return to work, whereas findings regarding cognitive functioning conflicted [109].

2.4.6 Methods used in previous studies on work and cancer

Study designs

Most previous quantitative studies on work and cancer have had a cross-sectional or prospective cohort design [91, 110–112]. In a systematic review of employment after different types of cancer, 23 out of 64 studies (36%) included a comparison group [111]. In another review, it was observed that only 7 out of 28 cohort studies (25%) were population-based [112]. Several authors have pointed out that there is a lack of high-quality prospective studies investigating the medium and long-term impact of cancer on employment and work [110–112].

Ways of measuring absence from work

In addition to the many different types of work-related outcomes that have been studied, there are also differences between studies in how outcomes have been measured. Already in the 1960s, a study identified 41 different ways of measuring absence from work [113]. The topic has been discussed in later reviews, and reflects that multiple scientific disciplines are involved [114, 115]. Furthermore, to understand and delineate the complete picture of absence from work, several measures may be needed.

In 1998, Hensing et al. suggested some basic measures to be used in studies examining sick leave related to (1) number of sick-leave spells or episodes, (2) number of days on sick leave, or (3) number of individuals who are sick-listed [114]. The choice of denominator is crucial: the researcher must decide if

denominator should include all sick leave-insured individuals (i.e., all individuals at risk) or individuals on sick leave only. A further issue is that the degree of sick leave can vary; should part-time sick leave be handled the same way as full-time sick leave? Some previous studies have examined the net number of days on sick leave by multiplying the number of days on sick leave by the degree of compensation [86, 88, 89].

Another issue is self-reported sick leave versus register-based sick leave. Most of the Swedish studies reporting on sick leave after breast and prostate cancer have used register-based data, which are considered more reliable than self-reported data [115].

Commonly used statistical methods and their limitations

In most previous studies examining sick leave and disability pension receipt, the data have been analyzed either with a count model such as Poisson regression or standard survival analysis using Cox proportional hazards regression [116]. In a Poisson model, the outcome variable is a count or a rate of, for example, the total number of days on sick leave and disability pension during a defined follow-up period. The underlying assumption of a Poisson model that the variance should be equal to the mean is often violated in sick-leave data. In many settings, most individuals have zero days of sick leave whereas those with sick leave are absent for long periods. This means that the data is heavily skewed, and the variance is larger than the mean. If the variance is larger than expected under the Poisson distribution, the data are considered to be overdispersed. Ignoring overdispersion leads to too-small standard errors and too-narrow confidence intervals. Some previous studies have used (zero-inflated) negative binomial regression [117] or linear regression with non-parametric bootstrap to obtain confidence intervals [118]. Authors of other studies have categorized sick leave into a binary variable and performed a logistic regression [86, 92].

In a Cox model, the time until the occurrence of an event is of interest. In a standard Cox regression, only the first occurrence of an event is considered, which is usually appropriate for studies of disability pension receipt or return to work. However, this is a potential problem in studies on sick leave, since sick leave can occur repeatedly. Although seldom used, survival analysis for recurrent events is generally more suitable for sick-leave data [119]. Furthermore, many previous studies have failed to consider competing events. Competing events are

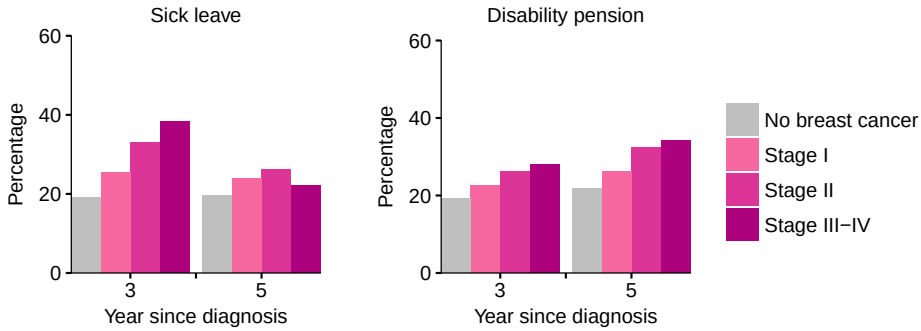

Figure 2.4: Percentage of women on sick leave by year since diagnosis

present if an individual is at risk of more than one mutually exclusive event, and the occurrence of one event will prevent the other event from happening.

In studies of sick leave in cancer patients, two obvious competing risks are receipt of disability pension and death. An illustrative example of this is presented in the study by Eaker et al., in which the proportion of women on sick leave in years 3 and 5 after diagnosis was presented stratified by disease stage [92]. In year 3, the proportion of women taking sick leave was 38% in women with stage III–IV disease, and 25% in women with stage I disease (Figure 2.4). In year 5, the relationship was reversed: only 22% of women with stage III–IV and 24% of women with stage I disease took sick leave. Instead, over 30% of women with advanced stage disease who were still alive had moved on to disability pension, whereas 36% of women who were initially part of the study population had died. Not considering or presenting estimates of competing events can therefore lead to erroneous conclusions regarding absence from work.

3 Aims

The overarching aim of this thesis was to study the impact of the diagnosis and treatment of breast and prostate cancer on sick leave and work.

The specific research questions were:

Study I: Do men with prostate cancer treated with robot-assisted radical prostatectomy return to work earlier and experience lower rates of long-term work disability than men treated with retropubic radical prostatectomy?

Study II: How much time is lost from work due to sick leave and disability pension receipt in men with prostate cancer on active surveillance as compared with men undergoing primary radical prostatectomy or primary radiotherapy?

Study III: How many working years can women expect to lose due to the diagnosis and treatment of breast cancer?

Study IV: Which medical causes underlie the increased risk of sick leave and disability pension receipt in women with breast cancer?

4 Material and methods

4.1 Study design and data material

This thesis includes 4 population-based cohort studies based on data from the Prostate Cancer Data Base Sweden (PCBaSe) or the Breast Cancer Data Base Sweden (BCBaSe). PCBaSe and BCBaSe are research databases that have been created using individual level record-linkage between quality registers for breast and prostate cancer and several national demographic and health care registers, which are described below. PCBaSe includes all men registered in the National Prostate Cancer Register of Sweden (NPCR), which has nationwide coverage. BCBaSe includes all women registered in the Breast Cancer Quality Registers of Stockholm-Gotland, Uppsala-Örebro and the northern regions of Sweden, with a combined coverage of about 60% of the Swedish population.

Comparison cohorts of cancer-free women and men have also been added to both the PCBaSe and BCBaSe at a ratio of 1:5. In the PCBaSe, controls were randomly selected from the Total Population Register using incidence density sampling, individually matched according to birth year and region of residence. In the BCBaSe, controls who were breast cancer-free in the year of which the index case was diagnosed were randomly selected from the Total Population Register, and individually matched according to sex, birth year, and region of residence. All controls could later become a case.

4.1.1 Data sources

The National Prostate Cancer Register of Sweden (NPCR)

Since 1998, newly registered cases of prostate cancer from all 6 health care regions in Sweden have been reported to the NPCR. Beginning in 2008, reporting was performed using the nationally uniform INCA platform. The completeness of the NPCR is high, including more than 98% of all men reported to the Swedish Cancer Register; reporting to the Swedish Cancer Register is mandated by law [120, 121].

The NPCR includes data on prostate adenocarcinomas. The variables registered include date of diagnosis, birth date, serum PSA, Gleason pattern, clinical stage, and primary treatment strategy, including surgery type, type of radiotherapy, type of conservative treatment (active surveillance or watchful waiting), and type of

hormone therapy [122]. Some information is available for all years, while others as surgery type and type of conservative treatment is only available from 2007 onward. In the NPCR, only treatment initiated within 6 months after the date of diagnosis is recorded. Data on subsequent treatment have also been obtained through additional data collections and linkages with other registers [123].

An evaluation of data quality of 48 variables in the NPCR was performed in 2015 by comparing data in the NPCR to data from medical charts and from other Swedish registers [121]. The overall agreement was high. For example, it was observed that for 95% of men with prostate cancer, the information on surgery type in the NPCR was in exact agreement with data extracted from medical charts. It was also observed that only 1% of radical prostatectomies recorded in the patient register were not recorded in the NPCR.

The Breast Cancer Quality Register

The Breast Cancer Quality Register is a population-based register that collects clinical data on newly diagnosed breast cancer cases. This thesis includes register data from 3 of the 6 health care regions in Sweden. Since 2008, breast cancer cases from all 6 regions have been registered through the INCA platform. Similar to the NPCR, the completeness of the National Breast Cancer Quality Register is high: 98% of all women with breast cancer registered in the Swedish Cancer Register are captured by the the National Breast Cancer Quality Register [28].

The Breast Cancer Quality Register includes data on invasive and *in situ* breast cancer diagnosed in both women and men. The information collected includes date of diagnosis, birth date, pre- or postmenopausal status, laterality, clinical stage, tumor size, tumor grade, ER status, PR status, HER2 status, level of Ki67, surgery type, and planned adjuvant treatment such as radiotherapy, chemotherapy, hormone therapy, and HER2-targeted therapy. Before 2008, the set of variables collected differed between health care regions.

The agreement between planned adjuvant treatments as registered in the National Breast Cancer Quality Register and initiated adjuvant treatments extracted from medical charts has been examined in a previous study of 970 women [124]. It was observed that in 94% to 96% of cases, planned adjuvant treatment corresponded to initiated treatment. In the same study, reasons for discontinuation of initiated treatment were also examined. For example, 10% of

women who initiated chemotherapy did not complete the treatment as planned, with toxicity being the main reason.

The Micro Data for Analysis of Social Insurance Database (MiDAS)

The Micro Data for Analysis of Social Insurance (MiDAS) database is managed by the Swedish Social Insurance Agency. It contains data on all periods of sick leave and disability pension compensated by the Social Insurance Agency since 1994 [125]. The variables included are start and end dates, type of compensation, degree of compensation (25%, 50%, 75%, or 100%,) and the main and secondary underlying diagnosis reported by the certifying physician according to the International Classification of Diseases (ICD) version 9 or 10. For data on sick leave, information on diagnosis is only considered to be satisfactorily recorded starting in 2005, and there is no information on the secondary diagnosis. Since days 2 to 14 of a sick leave period are usually paid by the employer, the database contains little to no information on sick leave periods 14 days or shorter.

While no published studies to date have examined the quality of data in MiDAS, data based on payments are generally considered accurate. In the early 1990s, a Swedish study assessed the quality of diagnoses for sick leave in a regional sick-leave register [126]. In that study, it was observed that for 50% of the cases, the diagnosis code in the register corresponded exactly to the diagnosis code input by a general practitioner after review of the medical records. When the whole group of diseases to which the diagnosis belonged was considered instead, the match increased to 80%.

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) is a database kept at Statistics Sweden. Since 1990, it has integrated administrative data from the labor market, and the educational and social sectors [127]. It includes information on marital status, education level, socioeconomic index, vocational code, employment status, welfare benefits, and income for all individuals in Sweden aged 16 and older. The data in LISA are generally for a specific calendar year.

The Income and Taxation Register

The Income and Taxation Register, kept by Statistics Sweden, also contains information on income [128]. In addition to income from work, other types of allowances are also registered, such as old-age pension.

The Total Population Register

The Total Population Register was established in 1968 and is kept by Statistics Sweden. It includes data on place of residence and in- and out-migration from Sweden. There is a concern about over-coverage in this register, since not all individuals report emigration. The over-coverage has been estimated to be 0.25% to 0.5% of the Swedish population [129].

The Patient Register

The Patient Register is administered by the National Board of Health and Welfare [130]. Since 1987, it has contained records of inpatient care with hospital discharge diagnoses from all hospitals in Sweden. One main discharge diagnosis and up to 8 additional diagnoses are recorded according to the ICD. Around 1% of all records lack information as to the main medical diagnosis, and up to 2% lack information on patient identity. A large number of studies validating the information in the patient register have been performed, most reporting that 85% to 95% of diagnoses in the patient register correspond to diagnoses in medical charts [131]. Since 2001, the Patient Register has also included records of specialized outpatient care. During the first years, up to 25% to 30% of all records lacked information on the primary diagnosis, a figure that was reduced to 4% by 2016 [130]. Almost all public health care providers report to the outpatient register, but not all private providers. The register's geographical coverage has been estimated to be around 80% [131].

The Swedish Prescribed Drug Register

Since July 2005, the Swedish Prescribed Drug Register, kept by the National Board of Health and Welfare, has collected individual-level information on all prescriptions dispensed in Swedish pharmacies [132]. The register includes information such as drug name, amount, dose, and prescription and dispensing

dates. Less than 0.3% of all dispensed prescriptions lack information on patient identity. Drugs dispensed for inpatient hospital care and non-prescribed drugs are not included in the register.

The Cause of Death Register

The Cause of Death Register is kept by the National Board of Health and Welfare and includes information on date and cause of death as reported by a physician on the medical death certificate [133]. The register is virtually complete with respect to number of deaths, and information on the specific cause of death is available for 96% of all deaths.

4.1.2 Ethical considerations using register data

The use of register-based data is regulated in Swedish law by the Public Access and Secrecy Act (Offentlighets- och sekretesslagen), the General Data Protection Regulation (Dataskyddsförordningen and Dataskyddslagen), and the Ethical Review Act (Etikprövningslagen). Health-related data are considered sensitive, and may only be used in certain circumstances. They may be used for research purposes if data protection principles—for example, by approval from an Ethical Review Board—are met. All studies in this thesis have been approved by the Ethical Review Board in Umeå or Stockholm. An exception to the requirement of informed consent was granted due to the large number of involved study participants. Other measures taken to protect the confidentiality of study participants were secure databases, de-identification of data for analyses, and presentation of results only on an aggregated level without possibility to backtrace.

4.2 Study populations

Studies I and II were based on men identified in the PCBaSe and studies III and IV on women identified in the BCBaSe. All studies included a matched comparison cohort of breast and prostate cancer-free women and men.

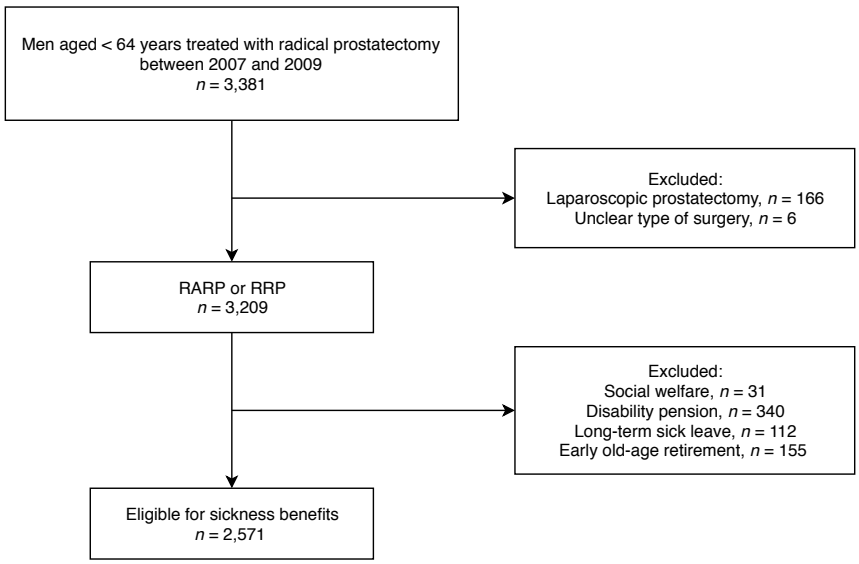

Figure 4.1: Flowchart Study I

4.2.1 Study I

Study I included all men diagnosed with non-metastatic prostate cancer (T1–T3, N0, M0, and PSA < 50 μg/l) under the age of 64 years treated with retropubic or robot-assisted radical prostatectomy between January 1, 2007 and December 31, 2009. Exclusion criteria were being on long-term sick leave at the time of surgery (beginning 2 months or more prior to surgery), receipt of disability pension prior to surgery, and receipt of old-age pension benefits or social welfare in the year prior to surgery. After applying these exclusion criteria to both men with and men without prostate cancer, the study population consisted of 2,571 men with prostate cancer (Figure 4.1) and 9,483 matched prostate cancer-free men.

4.2.2 Study II

Study II included men diagnosed with localized low-risk (T1—T2, GGG 1, and PSA < 10 μg/l) or intermediate-risk (T1—T2, GGG 2 or 3, and/or PSA 10 to < 20 μg/l) prostate cancer under the age of 64 years. Men diagnosed between January 1, 2007 and December 31, 2012 and treated with either active surveillance, radical prostatectomy or radiotherapy were included. Exclusion criteria were being on sick leave 1 month prior to diagnosis, receipt of disability pension prior to diagnosis,

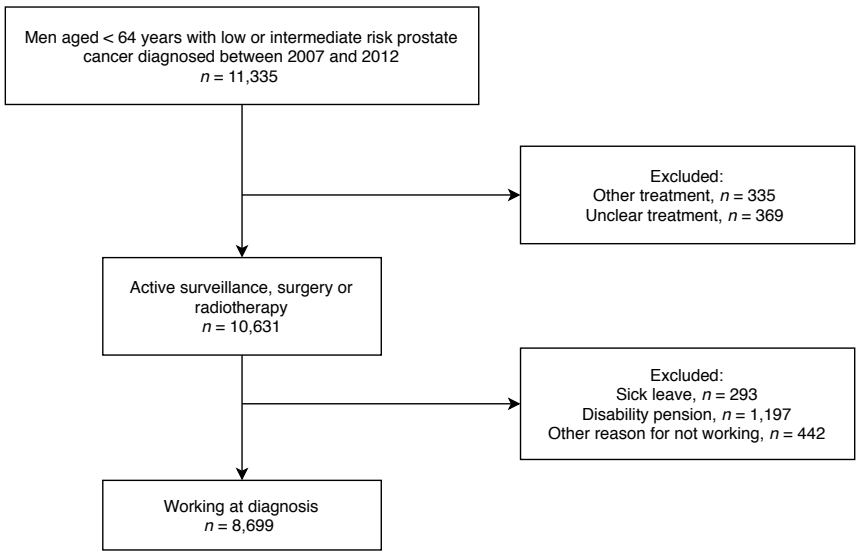

Figure 4.2: Flowchart Study II

and not working (i.e. no gainful employment) in the year prior to diagnosis. The final study population consisted of 8,699 men with prostate cancer (Figure 4.2) and 34,189 matched prostate cancer-free men.

4.2.3 Study III

Study III included women with *in situ* and invasive breast cancer of all stages diagnosed between January 1, 1997 and December 31, 2012 and aged 60 years or younger at diagnosis. Because data on old-age pension (which can be obtained starting at age 61) was only available beginning in 2003, women aged 56–60 years were only included if they were diagnosed between January 1, 2003 and December 31, 2012. Exclusion criteria were receipt of disability pension ($\geq$ 75%) prior to diagnosis, no income from work in the year prior to diagnosis, and receipt of old-age pension in the year of diagnosis. The final population consisted of 19,661 women with breast cancer (Figure 4.3) and 81,303 breast cancer-free women.

4.2.4 Study IV

Study IV included women with stage I to stage III breast cancer aged 30 to 64 years at diagnosis who were diagnosed between January 1, 2000 and December 31,

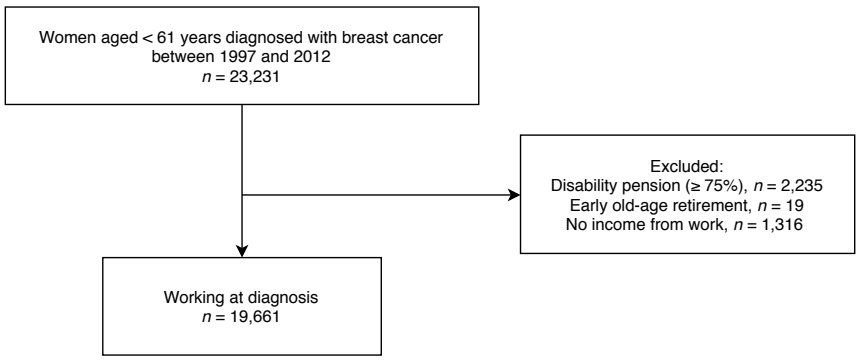

Figure 4.3: Flowchart Study III

2012. Analyses of sick leave were restricted to women diagnosed in 2005 or later. Women with stage IV breast cancer were not included due to strong competing events for some of the outcomes under study. Exclusion criteria were being on sick leave 1 month prior to diagnosis and receipt of disability pension prior to diagnosis. The final study population consisted of 16,603 women with breast cancer (Figure 4.4) and 63,773 breast cancer-free women.

4.3 Exposures

In all studies, the exposures were related to diagnosis and treatment of breast or prostate cancer.

4.3.1 Studies I and II

In Studies I and II, the exposure was type of radical prostatectomy (retropubic or robot-assisted radical prostatectomy) or type of treatment strategy (active surveillance, radical prostatectomy, or radiotherapy), extracted primarily from the NPCR. In Study I, information in the Patient Register was used to identify surgeries performed 6 months or later after diagnosis (which are not reported to the NPCR), or if information on surgery type was missing (7 out of 36 hospitals started to report surgery type starting in 2008). In one hospital (Karolinska University Hospital), all surgeries with missing information were coded as robot-assisted, which was the procedure used for 99% of men in this age group during the study period.

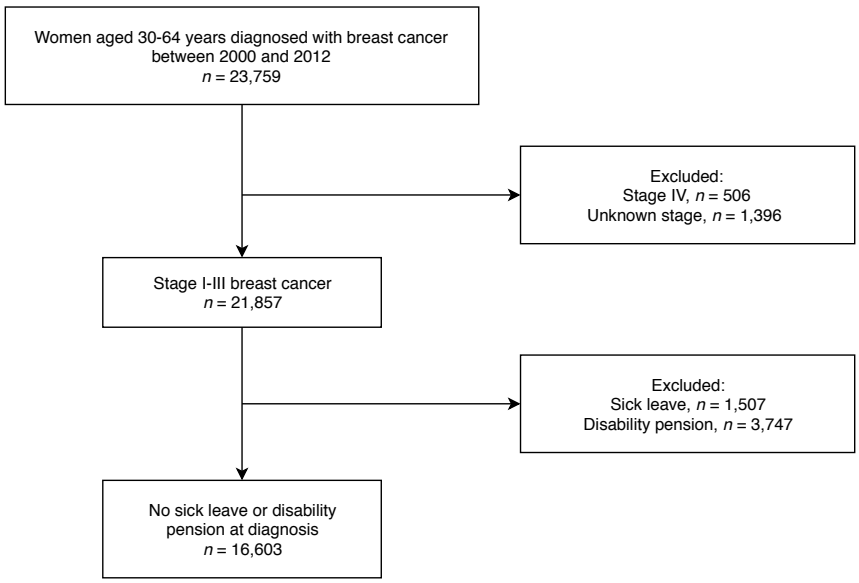

Figure 4.4: Flowchart Study IV

4.3.2 Studies III and IV

In Studies III and IV, the exposures of primary interest was breast cancer and stage of breast cancer, extracted from the Breast Cancer Quality Registers. Disease stage was defined according to the 7th edition of the American Joint Committee on Cancer TNM classification [134]. The T-stage and N-stage were extracted from information based on the pathology report when no neo-adjuvant treatment was given; otherwise, information from clinical examination was used. The clinical N-stage was also used if it was higher than the pathological N-stage.

4.4 Outcomes and follow-up

The primary outcomes in all studies are related to sick leave and disability pension receipt as granted by the Swedish Social Insurance Agency. Since the employer usually compensates the first 2 to 14 days of a sick leave period, only sick leave periods longer than 14 days are included in this thesis. However, the date of the first day of sick leave is available in MiDAS, and this date has been defined as the start date of sick leave in all studies. All types and degrees of sick leave and disability pension receipt were included, unless otherwise stated. Disability

pension receipt was considered to be a permanent absence from the labor market [135].

4.4.1 Study I

In Study I, we defined two outcomes: 1) time to return to work after surgery (duration of sick leave) and 2) days lost from work due to sick leave and disability pension receipt after return to work. Return to work was defined as the last date of the sick leave period that was ongoing or started within 30 days after the date of surgery. Sick-leave periods that started within 5 days after the end date of a previous sick leave period were considered a continuation of the previous period.

In the analysis of the second outcome, men were followed from the date of return to work after surgery until age 65, death, emigration, or end of follow-up (31 December 2012). Men with no registered sick leave were followed from the date of surgery. Prostate cancer-free comparison men were at risk from the date of return to work of their matched case. Men who did not return to work (n = 10) were not included in the analysis of the second outcome.

4.4.2 Study II

In Study II, the outcomes were sick leave and disability pension receipt. The competing event *death* was also included in the analysis. All-cause and cause-specific sick leave, disability pension receipt, and death were studied; causes of interest were prostate cancer (ICD-10 code C61), and depression, anxiety, and stress-related conditions (F32–F34, F38–F43, F45, F48). Periods with sick leave that ended within one month of a new event were not considered return to work. Men were followed from the date of diagnosis until age 65, death, emigration, or end of follow-up (31 December 2014).

4.4.3 Study III

In Study III, the outcome was permanent exit from the labor market, defined as receipt of disability pension ($\geq$ 75%), old-age retirement, or death. Since we did not have information on the exact time-point of old-age retirement, it was defined as the year when the annual income from the old-age pension obtained starting at age 61 exceeded the annual income from pensionable earnings. Women were

followed from diagnosis until permanent exit from the labor market, reaching age 65, emigration, or end of follow-up (31 December 2012). In a sensitivity analysis, we examined another definition of permanent exit from the labor market, defined as the year when the annual income from labor earnings decreased to zero. A separate analysis examining net number of days on sick leave in the first 3 years after diagnosis was also conducted.

4.4.4 Study IV

In Study IV, the outcomes were sick leave and disability pension receipt attributed to the following causes: cancer, mental disorders (i.e., depression, anxiety, and stress-related disorders), musculoskeletal disease, cardiovascular disease, inflammatory disease, fatigue, pain or insomnia, and lymphedema-related diagnoses (ICD-codes are listed in Supplementary Table 1 of Study IV). The competing event *death* was also included. Periods with sick leave that ended within one month of a new event were not considered return to work. Women were followed from diagnosis to age 65, death, emigration, or end of follow-up (December 31, 2013).

4.5 Covariates

In all 4 studies, included covariates belong to 3 broad categories: demographic and sociodemographic characteristics, health-related characteristics, and tumor and treatment characteristics. Covariates were mainly treated as confounders, and in studies II and IV some were also considered to be mediators. Confounders were measured before diagnosis and treated as time-constant, whereas mediators were measured after diagnosis and treated as time-varying. Depending on the aim and the method used in the study, we included some or all of the covariates listed below.

The demographic and sociodemographic variables included were age at diagnosis or surgery, calendar year of diagnosis, region of residence, highest level of education, disposable income, employment status, and occupation. Occupations were classified by skill levels according to the International Standard Classification of Occupations 2008 (ISCO-08) [136]. Age was included either as a categorical variable or as a continuous variable using restricted cubic splines.

Health-related variables prior to diagnosis or surgery were sick leave and comorbidities, the latter of which was based on hospitalizations in the Patient Register and further classified using the Charlson Comorbidity Index [137]. The Patient Register was also used to obtain information on cause-specific medical events after diagnosis, which were treated as mediators in Study IV.

In the studies of prostate cancer, tumor and treatment-related variables were risk category, lymph node dissection, type of hospital, and secondary treatment (secondary treatment was treated as a mediator in Study II). In the studies of breast cancer, variables included were tumor size, ER status, lymph node involvement, surgery type, type of axillary surgery, radiotherapy, chemotherapy, and endocrine treatment.

4.6 Statistical methods and measures

Survival analysis or, more generally, time-to-event analysis was the main statistical method in all 4 studies. An overview of the statistical methods used in this thesis is presented in Table 4.1.

Table 4.1: Statistical analyses used in this thesis

Study	Statistical analysis
I	Cox proportional hazards regression, Generalized Estimating Equations (GEE) Poisson regression
II	Non-parametric multi-state modeling
III	Flexible parametric survival analysis
IV	Non-parametric and flexible parametric multi-state modeling

4.6.1 Generalized Estimating Equations (GEE) Poisson regression

In Study I, we used Generalized Estimating Equations (GEE) Poisson regression to model days lost from work due to sick leave and disability pension receipt. GEE makes no assumption about the underlying distribution and uses robust standard errors (which do not assume equal variance across observations) to obtain confidence intervals. It is a common method for analyzing clustered data (the data in Study I were not treated as clustered). We included an over-dispersion parameter and an offset variable in the analysis, taking into account that not all

individuals were followed for the same period of time. Days lost from work were modeled as a rate, i.e., number of days lost per person-year.

4.6.2 The Cox proportional hazards model

In Study I, Cox proportional hazards regression was used to examine the association between return to work and surgery type for prostate cancer, with time since surgery as the underlying time scale. As with most other time-to-event methods, this is a model for the hazard rate, which is the instantaneous rate of having the event at time t. The effect measure obtained is the hazard ratio. In a Cox model, it is assumed that the hazard ratio remains constant over time, although this assumption can be relaxed by splitting follow-up time and including interaction terms, as was done in Study I. As with other time-to-event methods, unequal follow-up time is accounted for by censoring. Right censoring is the most common type of censoring, and occurs if, for example, a study participant is followed for the whole study period without experiencing the event. Cox models are semi-parametric, meaning no assumptions are made regarding the shape of the baseline hazard rate.

4.6.3 Flexible parametric survival analysis

In contrast to the semi-parametric Cox model, fully parametric models estimate the baseline hazard rate. The advantage of this is that measures of absolute effects can be obtained and time-dependent effects are more easily modeled. Flexible parametric models are, as the name implies, more flexible in capturing the shape of the baseline hazard than standard parametric models such as the Weibull model [138]. The flexibility is attained through the use of restricted cubic splines, with the number of join points or knots specified by the researcher. The number of knots, or rather the degrees of freedom (the number of knots minus 1), are chosen both for modeling of the baseline hazard function and for modeling of time-dependent effects. In Study III, the baseline hazard function was modeled with 5 degrees of freedom and the time-dependent effect of age at diagnosis and disease stage with 2 degrees of freedom. In Study IV, the Akaike Information Criterion (AIC) guided the choice of degrees of freedom [139], which was from 3 to 5 for the baseline hazard function and 1 to 3 for the time-dependent effect of breast cancer.

4.6.4 Competing risks

In the presence of competing events, cause-specific hazard ratios can be estimated using standard survival analysis as described above, and directly interpreted as long as the competing event is censored for. However, to account for competing risks rather than censoring them, the cause-specific cumulative incidence function (CIF) must be used [140]. The cause-specific CIF is the proportion of individuals who have experienced an event as a function of time, taking into account that it is impossible to experience an event if a competing event happened first. The probability of having any event is the sum of all cause-specific CIFs at a certain time. The CIF can be computed non-parametrically or after fitting a regression model for survival data [141, 142], as was done in Study III.

4.6.5 Multi-state survival analysis

Multi-state models are an extension of standard survival analysis, and allow for the inclusion of both recurrent events and related, possibly competing events in the same framework. The standard survival analysis can be viewed as a multi-state model with two states: alive (initial state) and dead (absorbing state); the change from alive to dead is called a transition. Survival analysis with competing risk is also a type of multi-state model, with two or more absorbing states. Further states and transitions can be added, including intermediate states. Figure 4.5 illustrates the multi-state models used in this thesis, with arrows representing possible transitions. In Studies II and III, we studied cause-specific sick leave, disability pension receipt, and death, as illustrated in Figure 4.6. In Study II, we further extended the multi-state model to include separate sick leave states for being on initial treatment strategy as opposed to having received secondary therapy (Figure 4.7).

The multi-state models used in this thesis are Markov models, which are stochastic models describing the sequence of events [140, 143]. The underlying assumption is that the probability of transition to the next state is only dependent on the current state and time since origin, but not on the previous history of transitions. One situation in which the Markov assumption does not hold is when the length of stay in a state influences the transition to the next state; in such cases, semi-Markov models have been proposed, in which the time scale is time since

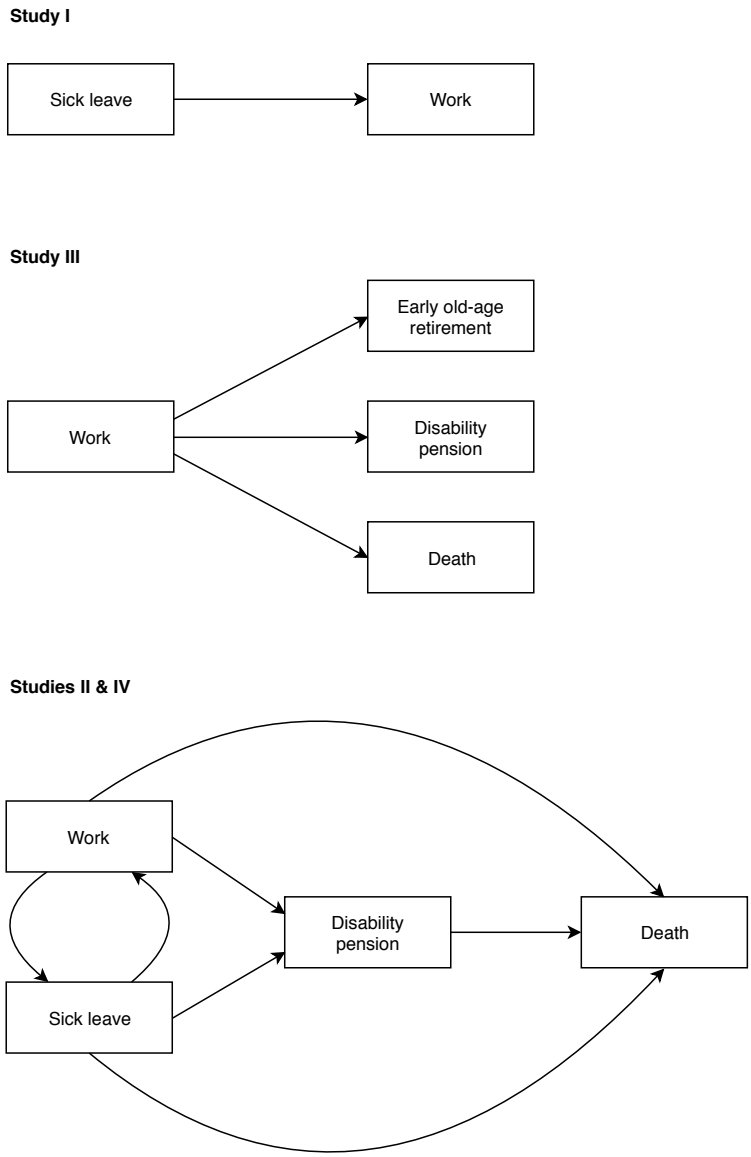

Figure 4.5: Multi-state models in this thesis

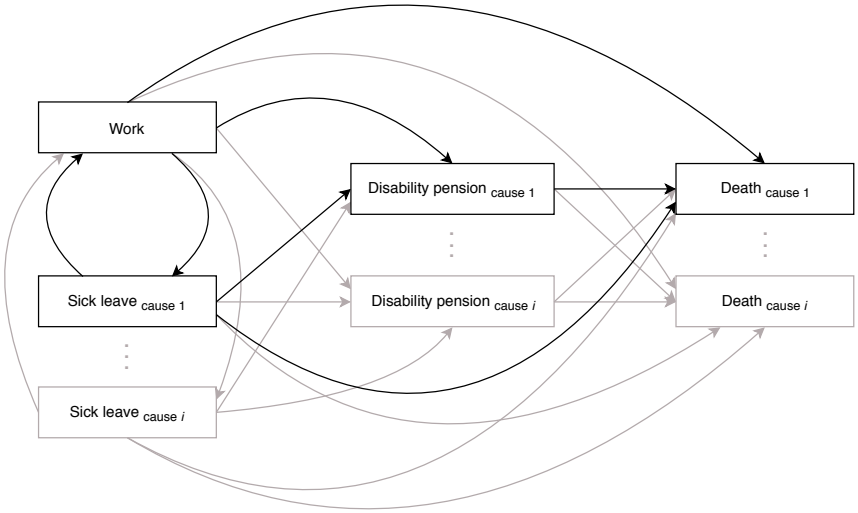

Figure 4.6: Cause-specific multi-state model (Studies II and IV)

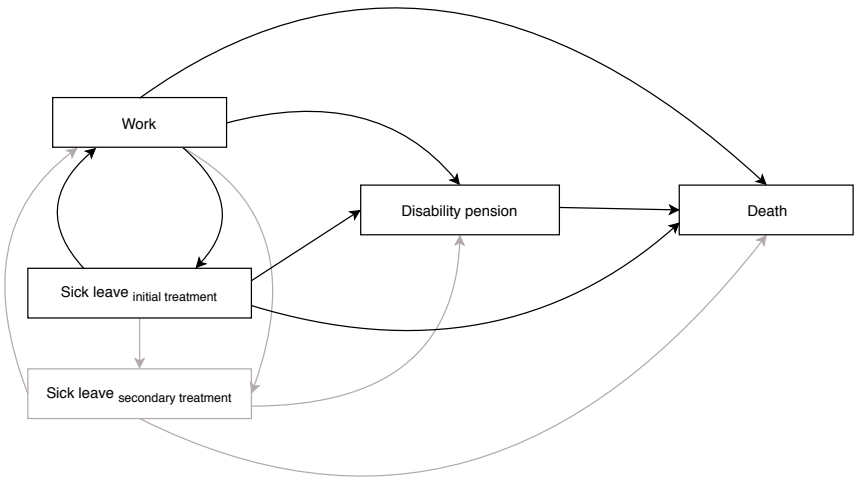

Figure 4.7: Multi-state model with different sick leave states according to treatment status (Study II)

entry into last state. Competing risk models are always Markovian (no previous history of events).

The Markov model is fully characterized by transition hazards (e.g., the instantaneous rate of entering state 2 from state 1 at time t) or by transition probabilities (e.g., the probability of entering state 2 at time t from state 1 at time s). A matrix of transition probabilities can be estimated non-parametrically using the Aalen-Johansen estimator, which is a matrix version of the Kaplan-Meier estimator [143]. From the matrix, transition probabilities and state occupancy probabilities can be obtained, the latter of which is the probability of being in a state at a certain time (equivalent to the transition probability if all individuals start in an initial state at time 0). In a competing risks model, transition probabilities are the same as the CIF. An important notion is that if the assumption of independent censoring holds, state occupancy probabilities obtained through the Aalen-Johansen estimator have also been found to be consistent estimators for non-Markov models [144].

In both Study II and Study IV, the Aalen-Johansen estimator was used to estimate and plot transition probabilities, with time since diagnosis as the underlying time scale. Other measures that can be obtained from a multi-state model are the probability of ever visiting a state and expected length of stay, which is the mean amount of time spent in a state between two time points. In Study II, length of stay was obtained by integration, whereas the probability of ever visiting a state was obtained by simulation, similar to the procedure described below. Confidence intervals were obtained by bootstrap resampling.

Since a multi-state model is characterized by a combination of transition-specific hazards, estimation can also be performed by fitting semi-parametric or fully parametric regression models. These regression models have the advantage that covariate-adjusted estimates can be obtained. Recently, a framework for flexible parametric multi-state modeling allowing for transition-specific distributions was presented by Crowther and Lambert [145]. Within this framework, which was used in Study IV, a model of choice is fitted for each transition in the multi-state model, including covariates and time-dependent effects as appropriate. Based on estimated coefficients from the fitted models, a simulated data set is then generated, from which transition probabilities and other measures can be calculated. Quantities of interest are either obtained for a specific covariate pattern or averaged (standardized) over the covariate distribution.

4.6.6 Work-life expectancy

Work-life expectancy is defined as the time spent working until retirement, given a certain age. The idea as such is not new, where economists have had an interest in work-life expectancy for a long time [146], but it has received only a small amount of attention in the field of public health and medicine [147]. Work-life expectancy is conceptually equivalent to life expectancy; the only difference is that life expectancy quantifies survival over the entire life span, whereas work-life expectancy is restricted to retirement (usually the age of 65). Restricted mean survival time is a more general term for work-life expectancy [148, 149].

Multi-state models are ideal models for estimating work life expectancies, where length of stay is an extension of restricted mean survival time [145]. For example, in the multi-state models illustrated in Figure 4.5, the work-life expectancy is the average time spent in the working state until retirement. We obtain loss of work-life expectancy (referred to as loss in working years in Study III) due to, for example, breast cancer, by calculating the difference in the time spent in the working state between women of the same age with and without breast cancer. This measure is a useful and easily interpretable summary measure from the often quite complex multi-state model. A measure of work-life expectancy has explicitly been used in Study III, but studies II and IV also include measures related to work-life expectancy (e.g., length of stay in work within the first 5 years after diagnosis).

5 Main results

5.1 Study I

Study I examined the influence of surgery type for prostate cancer on return to work and long-term work disability in 1,062 men treated with robot-assisted radical prostatectomy and 1,509 men treated with retropubic radical prostatectomy between 2007 and 2009. During this period, 9 out of 43 hospitals in Sweden performed robot-assisted radical prostatectomy (Figure 5.1).

Robot-assisted surgery was associated with an earlier return to work. Of men treated with robot-assisted surgery, 22% did not have a period of sick leave > 14 days after the surgery, compared with 12% of men treated with open surgery. The median time to return to work in men with sick leave > 14 days was 35 days (interquartile range [IQR], 8 to 52) after robot-assisted radical prostatectomy, compared with 48 days (IQR, 39 to 68) after retropubic radical prostatectomy. After adjustment for age, risk category, lymph node dissection, income, education, occupation, and prior sick leave, the overall hazard ratio of return to work comparing men who had undergone robot-assisted surgery with men treated with open surgery was 1.51 (95% CI, 1.38 to 1.66). Because the assumption of non-proportional hazards was not fulfilled, interval-specific hazard ratios were generated (Table 5.1).

Table 5.1: Hazard ratios and 95% confidence intervals of return to work

Surgery type	Time period	HR (95% CI)
Retropubic		1.00 (Ref.)
Robot-assisted	Overall	1.51 (1.38–1.66)
	Month 0–1	3.76 (3.04–4.66)
	Month 1–2	1.35 (1.19–1.53)
	Month 2–3	0.94 (0.73–1.20)
	Month 3–6	0.98 (0.68–1.42)
	Month 6–12	0.83 (0.47–1.48)

In addition to what is presented in the paper, we predicted the average time spent on sick leave from a flexible parametric survival model including the same confounders specified above. In that analysis, men treated with robot-assisted

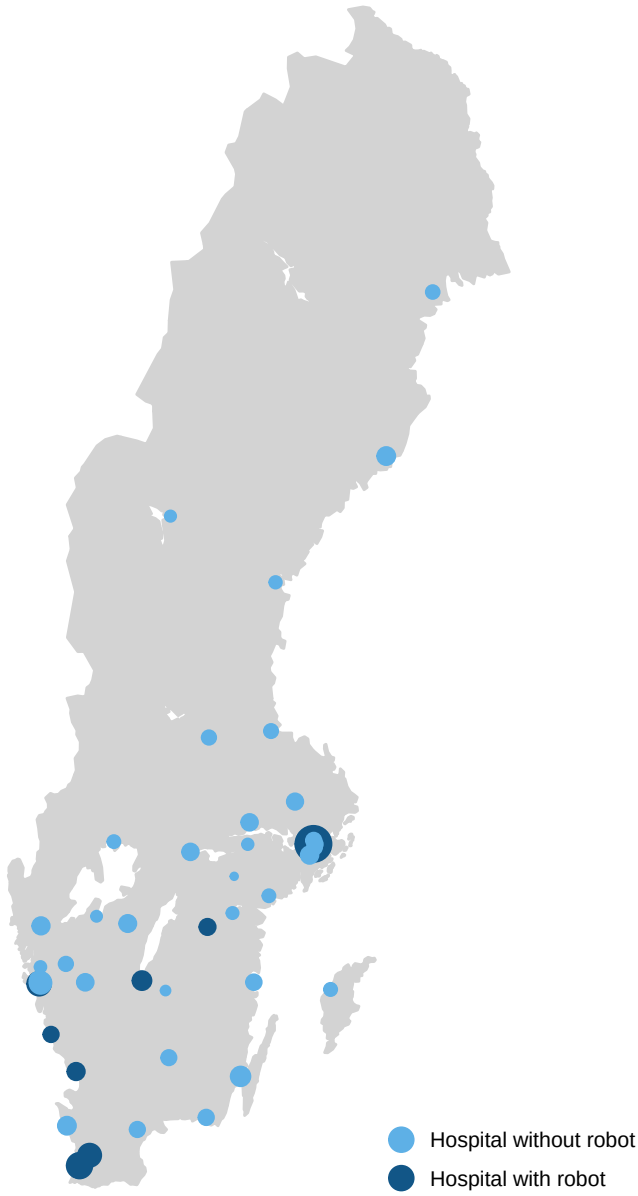

Figure 5.1: Hospitals performing radical prostatectomies in Sweden 2007–2009

surgery spent on average 37 days (95% CI, 34 to 40) on sick leave, as compared with 48 days (95% CI, 45 to 51) in men treated with open surgery.

We also examined the number of days lost from work due to sick leave and disability pension receipt after return to work. During a median follow-up of 3.6 years, men treated with robot-assisted surgery lost 12 days, and men with open surgery 15 days per person-year. After adjustment, surgery type was not associated with increased rates of sick leave and disability pension receipt (rate ratio 1.08; 95% CI, 0.82 to 1.42).

5.2 Study II

Study II examined the influence of choice of treatment modality for localized prostate cancer on days lost from work due to sick leave, disability pension receipt, and death in 8,699 men with low- or intermediate-risk prostate cancer diagnosed between 2007 and 2012, and 34,189 matched prostate cancer-free men. The percentage of men in each treatment strategy by year of diagnosis is presented in Table 5.2.

Table 5.2: Percentage of men in each treatment strategy by year of diagnosis

Treatment strategy	2007	2008	2009	2010	2011	2012
Active surveillance	20%	21%	24%	27%	31%	34%
Radical prostatectomy	67%	65%	63%	61%	60%	57%
Radiotherapy	13%	14%	13%	12%	10%	10%

The proportion of men on sick leave varied strongly by treatment strategy and time since diagnosis (Figure 5.2). In the group of men treated with surgery or radiotherapy, the proportion of men on sick leave was highest in the first year of diagnosis, with single-time point proportions of up to 30%. The probability of having at least 1 period with sick leave in the first year of diagnosis was 65% in men treated with surgery, and 45% in men who underwent radiotherapy. In men with active surveillance as the primary treatment strategy, the proportion of men on sick leave was low (2% to 5%) throughout the study period. Five years after diagnosis, the proportion of men free from sick leave, disability pension receipt and death was 95% in men on active surveillance, 93% in men treated with radical prostatectomy, and 92% in men treated with radiotherapy. The corresponding proportion in prostate cancer-free men was 94%.

We also calculated length of stay on work, sick leave, disability pension receipt, and death in the first 5 years after diagnosis. In all treatment strategies, the majority of time was spent in the working state. The average time spent on prostate cancer-specific sick leave was lowest in men on active surveillance (16 days; 95% CI, 14 to 18), the vast majority of which was spent by men with subsequent conversion to radical therapy. The number of days on prostate cancer-specific sick leave was considerably higher in men treated with primary radical prostatectomy (48 days; 95% CI, 45 to 50) or primary radiotherapy (44 days; 95% CI, 37 to 50). The time

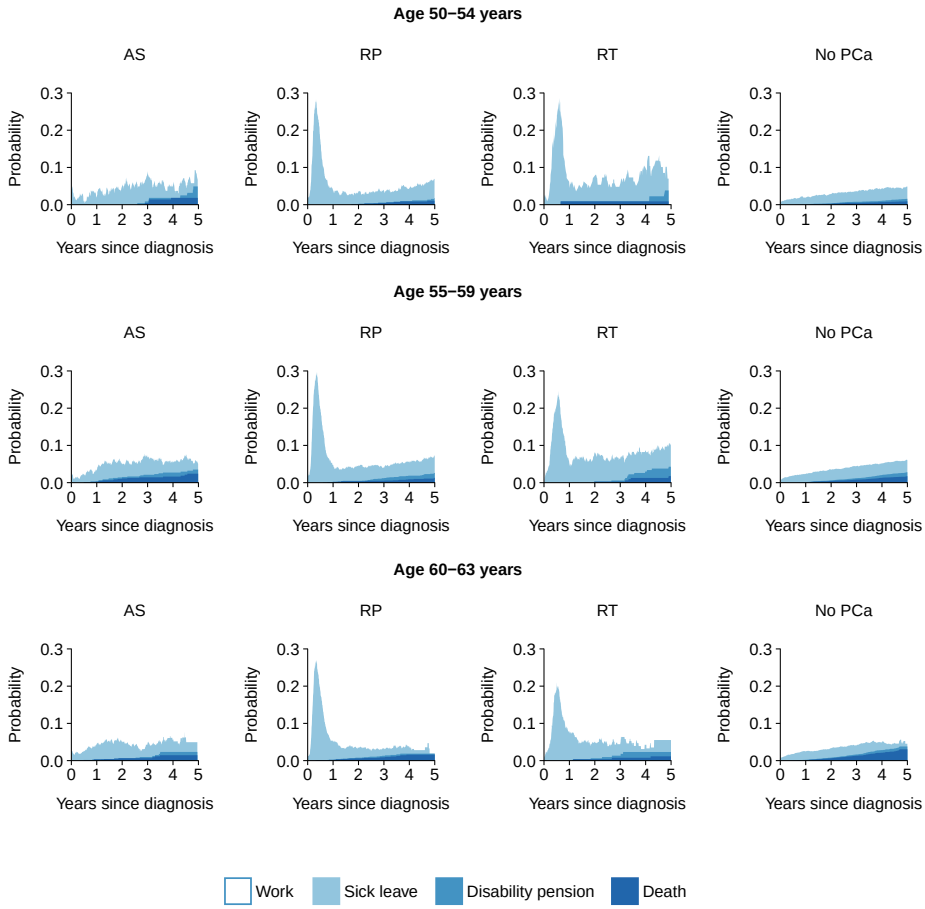

Figure 5.2: Proportion of men on sick leave, disability pension receipt, and death by initial treatment strategy. Abbreviations: AS, active surveillance; PCa, prostate cancer; RT, radiotherapy; RP, radical prostatectomy

spent on sick leave due to depression, anxiety, and stress was also lowest in men on active surveillance. When also taking other causes of sick leave, as well as disability pension receipt and death into account, men on active surveillance lost 21 days (95% CI, 20 to 21) from work compared with prostate cancer-free men. In men treated with radical prostatectomy, the corresponding loss was 45 days (95% CI, 45 to 46), and in men treated with radiotherapy, 72 days (95% CI, 71 to 73).

5.3 Study III

Study III examined the loss of work-life expectancy (loss in working years) due to breast cancer and associated treatments in 19,661 women diagnosed with breast cancer between 1997 and 2012, and 81,303 matched breast cancer-free women. Of the women included, 2,218 (11%) had *in situ*, 7,301 (37%) stage I, 6,535 (33%) stage II, 2,197 (11%) stage III, and 340 (2%) stage IV breast cancer. In 1,070 (5%) women, no information on disease stage was available.

The loss in working years due to disability pension receipt, early old-age retirement, and death varied by age at diagnosis, disease stage, and treatment type. It was highest in women with stage IV breast cancer, among whom women aged 50 years at diagnosis lost on average 8.1 years (2,967 days) (Table 5.3). In contrast, women with stage I breast cancer who where also aged 50 years at diagnosis lost on average 0.5 years (166 days).

Table 5.3: Loss in working years due to breast cancer in women aged 50 years at diagnosis

Stage	Loss in working years (95% CI)
In situ	-0.1 (-0.5 to 0.4)
Stage I	0.5 (0.2 to 0.7)
Stage II	0.9 (0.5 to 1.2)
Stage III	2.5 (1.9 to 3.1)
Stage IV	8.1 (6.5 to 9.7)

Some groups of women, including women with *in situ* breast cancer and women with stage I breast cancer treated with breast-conserving surgery, radiotherapy, chemotherapy, and endocrine therapy, had no loss in working years. Chemotherapy and mastectomy were generally not associated with a loss in working years, whereas axillary lymph node dissection was. Figure 5.3 illustrates the probability of exit from the labor market by primary reason for exit and treatment type in women aged 55 years at diagnosis with stage I breast cancer.

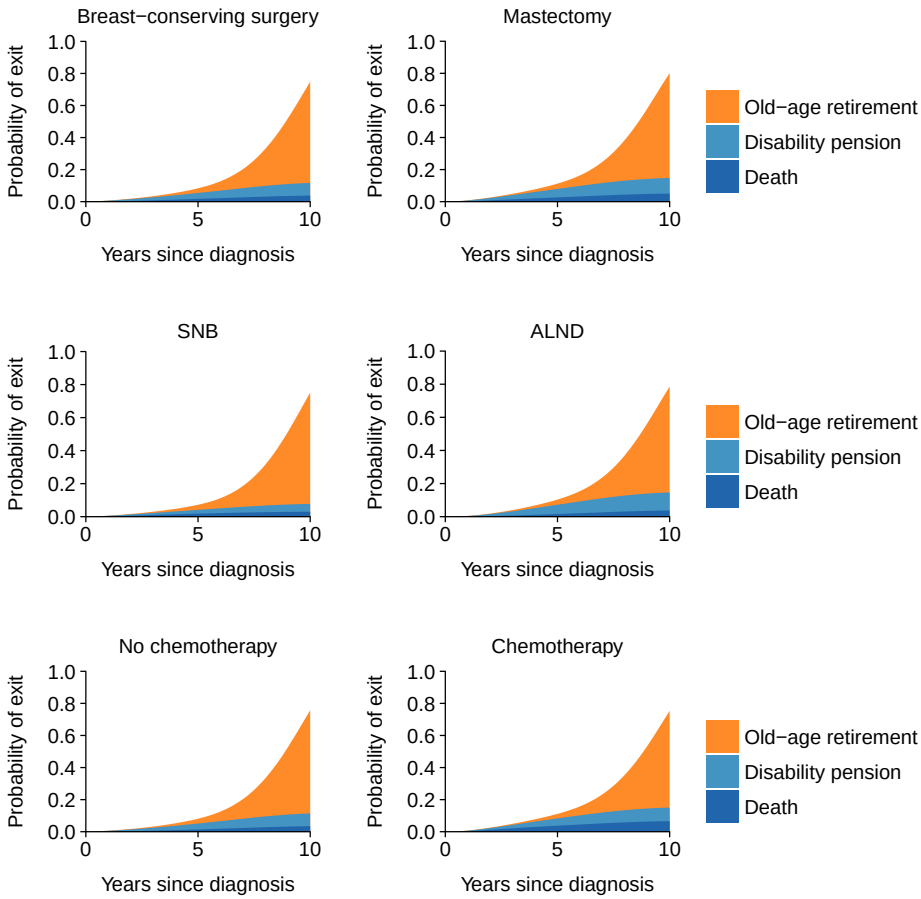

Figure 5.3: Probability of exit from the labor market by primary reason for exit and treatment type. Abbreviations: ALND, axillary lymph node dissection; SNB, sentinel node biopsy

5.4 Study IV

Study IV assessed the risk of cause-specific sick leave and disability pension receipt in women with breast cancer compared with breast cancer-free women. The study population was partly the same as in Study III, and included 16,603 women with stages I to III breast cancer diagnosed between 2000 and 2012, and 63,773 matched breast cancer-free women.

Cancer was the most commonly reported cause of both sick leave and disability pension receipt in women with breast cancer (Figure 5.4). In the first year of diagnosis, 80% of women had at least 1 period of sick leave attributed to cancer. One year after diagnosis, 26% of women were on sick leave because of cancer, and 3% due to other reasons. Five years after diagnosis, the proportion of women on sick leave due to cancer had decreased to 3%, similar to the proportion on sick leave due to other reasons (4%). The proportion of women on disability pension was low: less than 3% of women were on disability pension 5 years after diagnosis. The corresponding proportion at year 10 after diagnosis was 11%.

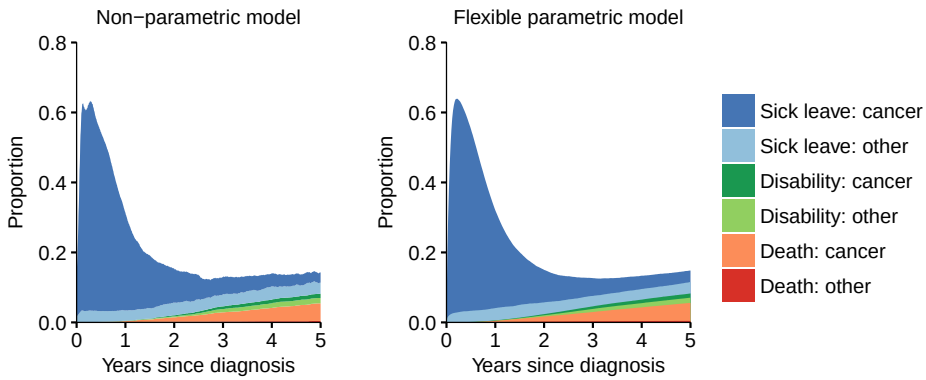

Figure 5.4: Proportion of women on sick leave, disability pension and death by type of modeling

Compared with breast cancer-free women, women with breast cancer had up to a 100-fold increased risk of sick leave and disability pension receipt due to cancer. Metastatic disease was a strong contributing factor, but other conditions, including mental disorders, were also identified as contributors. The most common

secondary diagnoses for disability pension attributed to breast cancer are presented in Table 5.4 (27% of women had a secondary cause registered).

Table 5.4: The 10 most common secondary causes of disability pension attributed to breast cancer

ICD-10 code	Disease	*n* (%)
F32	Depressive episode	15 (9)
I97	Postprocedural disorders of circulatory system, not elsewhere classified	14 (9)
C79	Secondary malignant neoplasm of other and unspecified sites	13 (8)
F43	Reaction to severe stress, and adjustment disorders	13 (8)
C78	Secondary malignant neoplasm of respiratory and digestive organs	9 (6)
M54	Dorsalgia	8 (5)
M25	Other joint disorders, not elsewhere classified	7 (4)
F41	Other anxiety disorders	5 (3)
M50	Cervical disc disorders	3 (2)
M53	Other dorsopathies, not elsewhere classified	4 (2)

Despite the strong competing risk of cancer-specific absence from work, we also observed an increased risk of both sick leave and disability pension receipt due to mental disorders (Table 5.5). The absolute risk increase, however, was low: In the first 5 years, women with breast cancer spent on average 17 days (95% CI, 14 to 18) on sick leave due to mental disorders, as compared with 16 days (95% CI, 14 to 17) in breast cancer-free women. Mastectomy was the only clinical factor significantly associated with an increased risk of disability pension receipt due to mental disorders. We also observed an increased risk of disability pension due to inflammatory and cardiovascular diseases.

Table 5.5: Adjusted hazard ratio of sick leave and disability pension receipt comparing women with breast cancer with breast cancer-free women

Disease group	$HR_{\text{Sick leave}}$ (95% CI)	$HR_{\text{Disability pension}}$ (95% CI)
Cancer	97.3 (90.6–104.5)	53.6 (40.6–70.7)
Mental disorders	1.24 (1.15–1.33)	1.54 (1.29–1.85)
Musculoskeletal diseases	0.86 (0.80–0.93)	1.13 (0.95–1.34)
Cardiovascular diseases	1.21 (0.97–1.49)	1.45 (0.98–2.15)
Inflammatory diseases	0.80 (0.63–1.02)	1.46 (1.05–2.03)

6 Discussion

6.1 Summary of findings

Our findings show that around 60% to 80% of men who underwent surgery for prostate cancer had at least 1 period of sick leave longer than 14 days after the procedure. The duration of absence was related to surgery type; we found that men treated with robot-assisted radical prostatectomy returned to work earlier than men treated with retropubic radical prostatectomy, also after adjusting for factors such as risk category, education, and income. In contrast to prostate cancer surgery, active surveillance had only a slight impact on sick leave. During the first 5 years after diagnosis, men with active surveillance as the primary treatment strategy had less than half as many days on prostate cancer-specific sick leave as men treated with radical prostatectomy or radiotherapy. The type of primary treatment strategy had little to no influence on long-term sick leave and disability pension receipt.

In women with breast cancer, 80% had at least one longer period with sick leave in the first year of diagnosis. The amount of time lost from work in subsequent years was strongly associated with disease stage at diagnosis. Women aged 50 years at diagnosis with stage I breast cancer lost on average half a year of their remaining working time, in contrast to women with stage IV disease, who lost over 8 years. Treatment type also had an influence, especially axillary lymph node dissection, which increased the risk of receiving disability pension both in all-cause and cause-specific analyses. Our findings from cause-specific analyses indicate that adverse events due to breast cancer treatment have an impact on permanent absence from work. Women with breast cancer had an increased risk of sick leave and/or disability pension receipt due to nearly all of the studied disease groups, including mental disorders, cardiovascular disease, inflammatory diseases, fatigue-related conditions, and lymphedema.

6.2 Methodological considerations

The findings presented in this thesis should be viewed in relation to possible sources of error. In epidemiological research, errors are broadly categorized into how individuals are selected (selection bias), how variables are measured

(measurement bias), the presence of common causes shared by exposure and outcome (confounding), and random variability [150].

6.2.1 Selection bias

The major strength of the studies in this thesis was the use of population-based, mostly national, demographic and health care registers with virtually complete geographical coverage, which minimizes the risk of selection bias. In addition, follow-up through nationwide registers reduces bias arising from differential loss to follow-up. Individuals who emigrate out of Sweden can be thought of as lost to follow-up, a proportion that was low (< 1%) in the included studies. Selection bias may also be caused by restricting the analysis to individuals with complete follow-up; for example, those who have not died [150]. In the present thesis, estimates of the competing event *death* are simultaneously reported to illustrate the overall impact of cancer on working life.

6.2.2 Measurement bias

The registers used to obtain data for the purpose of this thesis are considered to have high validity in terms of included variables, which reduces the risk of measurement bias. Because variables were recorded prospectively, any errors in the measurement of exposure are unrelated (nondifferential) to the outcomes under study. We had an issue with misclassification of the exposure in Study I: because surgery type was not available in the NPCR for all hospitals and all years, we had to rely on data from the Patient Register. While conducting the study, we discovered that some of the robot-assisted surgeries had been reported as open surgeries in the Patient Register. Although we were able to partly account for this, such a misclassification would bias the relative risk estimates toward the null hypothesis.

Measurement errors of the outcomes may be differential with respect to the exposure. For example, women with breast cancer may be more closely monitored than women without breast cancer, and physicians may record medical events in a different way. The increased contact with health care providers among women with breast cancer might also increase the likelihood of being sick-listed, although the underlying medical condition may be of equal severity compared with cancer-free women. We cannot rule this out as a contributing factor for the increased risk of

sick leave and disability pension receipt observed in women and men with cancer. However, cancer-specific sick leave and disability pension receipt should be less affected by such a bias, simply because we are more certain that the underlying cause is related to cancer and cancer treatment.

In all studies, there was a risk of misclassification of outcomes due to lack of data. Sick-leave periods under 15 days are not recorded in the database kept by the Swedish Social Insurance Agency. As a result, presented proportions of sick leave are likely an underestimate of the true proportion of women and men on sick leave, and we have overestimated the proportion remaining in work. This is true for both the cancer and the comparison cohort. However, it is unclear whether the degree of underestimation is related to the diagnosis and treatment of cancer, and whether the estimates involving the comparison group are affected. In Studies I and III, we performed sensitivity analyses to examine the effect of potential misclassification of the outcomes, for which results in general were in agreement with results from main analyses.

With the exception of Study III, the studies did not include absence from work due to unemployment or old-age retirement before the age of 65 years. In our multi-state model, individuals who are unemployed or take early retirement pension are considered to be available for work, and remain in the working state unless they transition to sick leave, disability pension receipt, death, or are censored. Thus, the working state consists of both individuals who are truly working and individuals who are absent from work due to any other reasons than the one under study.

Another issue was the lack of data on all of the underlying medical diagnoses for sick leave and disability pension receipt. While we have no reason to question that the registered cause was an underlying reason for sick leave or disability pension receipt, we lacked information on contributing reasons, since MiDAS only contains 1 diagnosis for sick leave (up to 2 diagnoses are recorded for disability pension receipt). This is particularly problematic when the registered cause is "breast cancer" or "prostate cancer": is the underlying reason ongoing treatment for cancer, cancer progression, or a treatment-related adverse event? The registered reason "cancer" is therefore not very precise. In addition, the reporting of diagnoses might vary over time, and by certifying physicians. Depression is an example of a diagnosis that was commonly reported as a secondary cause for disability pension receipt in women with breast cancer. We cannot rule out that the proportion of women and men with cancer who were

absent from work due of mental disorders was underestimated, since such conditions were considered to be cancer-related and thus coded as cancer. This might attenuate the role of mental disorders in the risk of absence from work in cancer patients (i.e., the observed hazard ratio is closer to 1 than the causal hazard ratio). Similar reasoning applies to the other non-cancer causes.

An additional issue was that only the first diagnosis for the period of sick leave or disability pension receipt is recorded in MiDAS; any changes in diagnosis are not recorded. Based on a report by the Swedish Social Insurance Inspectorate, around 7% of all sick-leave diagnoses are later changed to a diagnosis within another diagnostic group [151]. This percentage is lower for diagnoses related to mental disorders (F00–F99), and higher for diagnoses related to signs and symptoms of disease (R00–R99).

6.2.3 Confounding

A potential limitation of the studies included in this thesis is residual confounding. For example, we lacked information on factors related to work load and work environment, which are important risk factors for sick leave and disability pension receipt. Other than the most severe medical conditions captured by the Patient Register, we also lacked information on general health status, another important risk factor. We further had little to no data on some prognosis and treatment-related factors, such as dose and duration of treatment. In our analysis, however, we were able to control for many other possible confounders, of which age at diagnosis, time since diagnosis, previous sick leave, and tumor stage were the most important.

In Study I, confounding was a concern, and analyses were adjusted for nearly all clinical and sociodemographic variables on which we had information. However, the relative risk estimates did not change substantially by, for example, adding income and type of occupation to a model that already included education. Furthermore, any unmeasured confounder would need to be strongly associated with the outcome to completely explain away the association between surgery type and return to work. However, it is still possible that the association could be explained by a priori beliefs of faster recovery after robot-assisted surgery, which might have influenced how the doctors prescribed sick leave. Likewise, men who needed to go back to work earlier may have actively chosen robot-assisted surgery.

A priori beliefs are less of an issue in the analysis of our second outcome, days lost from work after return to work.

In Study II, confounding by indication was the main concern: having a more aggressive tumor is both an indication for undergoing radical treatment and a risk factor for cancer progression, which in itself increased the risk of sick leave and disability pension receipt. To reduce confounding by indication, the analysis was stratified by risk category. To examine the influence of other possible confounders, we stratified the analysis by age at diagnosis, level of education, and prior sick leave. The pattern of prostate cancer-specific sick leave remained the same: men on active surveillance had less than half as many days on sick leave as men who underwent primary radical therapy within all subgroups.

In Studies III and IV, confounding by calendar period was a concern due to the long study period. Both the treatment of breast cancer and the likelihood of receiving disability benefits changed during the period under study. Calendar period was therefore either included as a covariate in the models, or accounted for by applying a period approach [152], which better reflects the experiences of women diagnosed in more recent years. In analyses comparing women with breast cancer to breast cancer-free women, unadjusted estimates (not controlling for any other factor than the matching factors and time since diagnosis) were in general similar to adjusted estimates.

6.2.4 Random variability

The impact of random error due to sampling variability was minimized by the use of large cohorts of women and men. However, some of our analyses were based on a small number of events, especially the cause-specific analyses in Study IV, which increases the risk of observing an association as a result of random error (i.e. chance finding).

6.3 Comparison with previous research

6.3.1 Studies on prostate cancer

At least three previous studies have compared time to return to work after robot-assisted or retropubic radical prostatectomy [60, 62, 64], two of which were published after our study had been performed (Table 6.1). The median time for

return to work after open surgery in our study was 48 days, which was similar to the previous studies. Time to return to work after robot-assisted surgery varied considerably more, from 26 to 42 days. Given the randomized design, the study by Yaxley et al. best reflects the impact of robot-assisted surgery on return to work, although some criticism has been directed at the 2-surgeon design of this trial [153]. Randomization overcomes the issue of confounding, which was a major limitation in both our study and the study by Hohwü et al. As in a previous study on Norwegian men [74], we found that the surgical technique did not have a long-term influence on work.

Table 6.1: Time to return to work after robot-assisted (RARP) and retropubic radical prostatectomy (RRP)

Author	Study Design	*n*	Median, days	
			RARP	RRP
Hohwü [60]	Cohort	274	26	55
Plym (Study I)	Cohort	2,571	35	48
Yaxley [64]	Randomized controlled	129	43	47
von Mechow [62]	Cohort	1,451	42	42

Only a handful of studies have examined the impact of other types of treatment for prostate cancer on absence from work [59, 66, 76]. The findings of our study are largely in agreement with those studies, although previous studies are restricted to the first 2 years after diagnosis. In the Danish study by Sveistrup et al., 91% of men treated with radiotherapy (in all risk categories) were free from sick leave, disability pension receipt and death 1 year after diagnosis [66]. This estimate is very close to our estimate of 94% at the same point in time, although our analysis was restricted to men with low- or intermediate-risk cancer. Bradley et al. examined the mean number of days lost from work in the first 6 months after diagnosis (all stages of prostate cancer were included) [59]. Similar to our study, men treated with surgery or radiotherapy lost more days from work (33 and 10 days, respectively) than men with no treatment, who on average lost 3 days. In both our study and others, direct comparisons of treatments are generally complicated, since cancer characteristics are more adverse in men receiving primary radical therapy compared with men on active surveillance.

Our study is the first to report that men who remained on active surveillance had nearly no sick leave related to prostate cancer; the majority of days recorded were accounted for by men with subsequent radical therapy. Our study is also the first to report on sick leave due to mental disorders such as depression, anxiety, and stress-related conditions. During the first 5 years after diagnosis, men on active surveillance had close to the same number of days on sick leave due to mental disorders as prostate cancer-free men (6 days). The number of days was slightly higher after primary radical prostatectomy (8 days) and after radiotherapy (12 days). Our results are in agreement with conclusions drawn from a systematic review in which active surveillance was generally not associated with reduced psychological well-being [154]. However, some criticism has been directed at the methodology used in previous studies, especially regarding the the lack of an appropriate control group [155].

6.3.2 Studies on breast cancer

In comparison with that for prostate cancer, the number of previous studies on sick leave and work in women with breast cancer is considerably larger. However, no previous study has presented estimates on work-life expectancy that combine different work-related outcomes and summarize the impact on work until retirement. Most earlier studies have included only 1 or 2 work-related outcomes and presented measures of effect at a specific point in time. A few studies report on time lost from work within a specific year [86, 89, 90]. Estimates of the amount of time lost due to death (loss in life expectancy) have been presented previously: women with breast cancer aged 50 years at diagnosis lost on average 7 years of life in comparison with population controls in an Australian study [156].

We also estimated how certain treatments influenced the loss of working time. In agreement with previous studies on the risk of receiving disability pension [92, 94], we observed that axillary lymph node dissection increased the amount of time lost from work. However, we found no evidence that mastectomy increased the loss of working time, which is in agreement with some [94, 100], but not all previous studies [92]. Chemotherapy was also not associated with an increased loss of working time, a finding that requires further consideration given that chemotherapy has been associated with an increased risk of disability pension receipt and other work-related outcomes in several previous studies [92, 94, 100]. In contrast to the other studies, our outcome is a combination of disability pension receipt, old-

age retirement, and death. Our findings might reflect that the survival benefit of receiving chemotherapy outweighs the increased risk of receiving disability benefits. Furthermore, our estimates should be viewed as restrictive estimates of the permanent loss of working time after a breast cancer diagnosis, since sick leave or part-time disability pension of less than 75% are not included.

Comparison with previous research is also complicated by country-specific settings. In studies performed in Northern European countries, chemotherapy has been associated with sick leave and disability pension receipt [92, 94], but not with unemployment [94, 101]. In contrast, chemotherapy was associated with unemployment in a US-based study [100]. Rather than contradicting each other, these contrasting findings may reflect differences in insurance systems and the protection of employees.

In agreement with previous research [95, 96, 98, 104–108], we found that fatigue-related conditions and lymphedema were underlying causes of absence from work in some women with breast cancer. We also observed that women with breast cancer had a higher risk of sick leave and disability pension receipt due to mental disorders compared with breast cancer-free women. This appears to contradict a conclusion in the study by Kvillemo et al., in which the authors stated that "the higher prevalence of sickness absence and disability pension was a result of breast cancer only, not because of mental or other somatic diagnoses" [86, p. 6]. This conclusion only relates to the absolute effect of breast cancer on disability pension due to mental disorders. In absolute terms, differences for causes other than cancer were small also in our study, reflecting the fact that it is relatively rare to be on disability pension due to, for example, depression. In addition, women with breast cancer have strong competing events, such as *death* and *disability pension receipt due to cancer*.

Women with breast cancer were also at increased risk of disability pension receipt due to cardiovascular and inflammatory diseases. Although this has not been studied previously, our findings are not unexpected considering that previous studies have found evidence of increased risks of both cardiovascular [157–159] and some types of inflammatory diseases [160, 161] after diagnosis and treatment for breast cancer. However, our study was not designed to study the underlying mechanism behind the association, which might be related to the treatment for breast cancer, but also to shared risk factors.

No previous studies are available for comparison on the impact of treatment on cause-specific disability pension receipt. Except for endocrine therapy, all of the treatment modalities studied increased the risk of disability pension receipt due to cancer. Mastectomy was the only factor that was significantly associated with an increased risk of disability pension receipt due to mental disorders. It has previously been suggested that mastectomy increases the risk of psychological distress in young women [162], although we cannot rule out residual confounding as an explanation. Axillary lymph node dissection was the only factor significantly associated with disability pension receipt due to musculoskeletal disorders, most likely reflecting morbidity related to arm and shoulder functioning.

6.4 Generalizability

Due to the population-based and partly nationwide study designs, most of our results can be generalized to working-aged women and men diagnosed with breast or prostate cancer in Sweden. However, the presented probabilities of sick leave and disability pension receipt are specific to the calendar period under study, and are expected to change if the treatment for cancer changes or if the legislation for social insurance undergoes major changes. For example, the rules for obtaining disability pension are much stricter now than in the early 2000s, and disability pension receipt has become less common.

Parts of our results can also be generalized to women and men in other countries with high labor force participation. It is reasonable to assume that the adverse event profile after treatment for breast or prostate cancer does not differ across countries, and the relative impact of a specific treatment strategy on working life is likely to be similar. An assuring example are the results in Study I, which had remarkably similar estimates of time to return to work after radical retropubic prostatectomy as studies performed in Germany and Australia [62, 64].

7 Conclusions and implications

As a whole, the results of the present thesis show that diagnosis and treatment of breast and prostate cancer have a considerable impact on sick leave and work, in particular during the first year following diagnosis. The only exception to this was men with prostate cancer remaining on active surveillance, who spent a similar amount of time on sick leave in the first 5 years after diagnosis as prostate cancer-free men. At year 5, the type of initial treatment strategy for prostate cancer had little or no influence on sick leave and disability pension receipt. With the exception of women with *in situ* breast cancer and subgroups of women with early-stage breast cancer, breast cancer had a considerable impact on amount of time lost from work until retirement. In addition to cancer progression, both psychological and physical morbidity secondary to breast cancer diagnosis and treatment were underlying causes of absence from work.

The implications of the results in this thesis are at least 5-fold: First, our results highlight that continuous follow-up and monitoring of adverse events following treatment for cancer is needed to reduce the impact on daily activities such as work. We have identified several medical reasons for absence from work, and intervening and mitigating some of these at an early stage may be possible.

Second, our findings can be used to improve and tailor vocational rehabilitation programs. Reintegration into work is an important aspect of quality of life, and whenever possible efforts should be made to facilitate this process. In this thesis, we have identified not only individuals at risk for leaving the labor market, but also studied the underlying reasons. This information is particularly useful because it helps identify the areas of expertise and content needed for rehabilitation programs. It also provides helpful information for employers by increasing the understanding of what type of work-place adaptations may be expected to be necessary.

Third, our findings can be used as additional guidance for treatment decisions for localized prostate cancer, which can be difficult because they involve a balance between potential harm and benefits. Although the type of treatment strategy had an influence on sick leave and work, our findings showed that the long-term impact on work was similar across treatment strategies. However, the studies included in this thesis were not randomized, and the findings must be viewed in conjunction with results from other studies.

Fourth, the absolute measures presented in this study are easy to understand for lay men, and can be used by the treating physician when communicating with patients about the possible implications of treatment on working life. Raising awareness of potential future health problems can help in mitigating the consequences on daily activities.

Fifth, our results are not only important for setting clinical guidelines, but also for developing cancer-specific policies for sick leave. Such policies should include procedures taking not only physical but also psychological consequences of a cancer diagnosis into account.

8 Future perspectives

With the number of women and men living with a history of breast, prostate, or other cancer expected to increase, issues related to sick leave and work will gain importance. Reintegration into work is not only important for the individual diagnosed with cancer, but also for employers and the society as a whole. Productivity losses due to sick leave and disability pension have been estimated to account for over 30% of the total cost of breast cancer in Sweden [163].

Future studies can provide results to improve reintegration into work in several ways. It is essential to improve our understanding of the underlying causes of absence from work in cancer patients, for example, by extracting more detailed information on reasons for sick leave from medical charts, or by surveying patients. Such investigations can also be used to validate the information available in MiDAS, which has not been done to date. To separate out the effects of cancer progression and the effects of adverse events resulting from treatment, future studies should, if possible, include information on local relapse. Furthermore, separately examining the underlying reasons for part and full-time sick leave and disability pension receipt is also likely to reveal new insights.

To better understand the effects of a specific treatment, detailed information not only on the treatment type, but also on the dosage and duration of treatment is needed. This information is partly available in the Cancer Quality Registers for women and men diagnosed in more recent years. Also, the ongoing development of real-time databases with prospective registration of oncological drugs, including information on reasons for discontinuation and side effects, will open up new possibilities. Due to the observational nature of such studies, methods from the field of causal inference would preferably be applied [164]. However, a randomized study represents the optimal design, and the importance of including work-related outcomes also in randomized trials has been recognized [64, 78].

It would also be of value to study what type of rehabilitation women and men diagnosed with breast or prostate cancer need in order to remain in the work force, ideally by performing a study examining the effect of an intervention on sick leave and work. It has recently been suggested that flexible sick leave (i.e., the patient decides on which days she or he feels well enough to work) can reduce the number of days on sick leave after a cancer diagnosis, with positive effects on psychological wellbeing [165].

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