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PANORAMA OF DISEASES ASSOCIATED WITH BREAST CANCER

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PANORAMA OF DISEASES ASSOCIATED WITH BREAST CANCER
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Breast cancer is the most common cancer in women. Although the incidence of breast cancer has increased over time, so too has patient survival. Given these trends, the prevalence of breast cancer has steadily increased in recent decades, exposing these women to other associated diseases which can influence carcinogenesis, prognosis, and treatment. This thesis uses Swedish register data, combined with data from the Libro-1 and Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) cohorts, to study other diseases associated with breast cancer in women. Specifically, this thesis investigates how diseases in early adulthood influence the risk of breast cancer, and how overall health is affected by breast cancer treatment.

In Study I, the risk of breast cancer in women with and without preeclampsia was studied using data from the Swedish Medical Birth Register and KARMA cohort. Women diagnosed with preeclampsia had a decreased risk of breast cancer and lower mammographic density. In addition, sisters of breast cancer patients and women with a high genetic predisposition to breast cancer had a lower risk of preeclampsia. This suggests that inherited factors may contribute to the inverse association between preeclampsia and breast cancer.

In Study II and Study III, the risk of mental disorders and psoriasis were compared between a Swedish nationwide cohort of breast cancer patients and the general population. Women with invasive breast cancer had an increased risk of depression, anxiety, stress-related disorders, and psoriasis. This increased risk was greatest shortly after cancer diagnosis and remained over the subsequent five years. Patients with in-situ breast cancer only experienced an increased risk of stress-related disorders during the first six months after cancer diagnosis. With regard to risk predictors, the Libro-1 cohort of Stockholm-Gotland breast cancer patients showed that younger age at diagnosis, higher tumor grade, lymph node positive tumors, comorbidity, and chemotherapy were independently associated with an increased risk of depression and anxiety. The effect of tumor grade and chemotherapy was mainly limited to the first two years after diagnosis, while comorbidity contributed to long term risk. Younger age at diagnosis was the only risk factor identified for stress-related disorders; while for psoriasis, radiotherapy and mastectomy were associated with increased disease risk. Aside from these treatment-specific predictors, genetic predisposition, obesity and smoking were also risk factors for psoriasis in breast cancer patients.

Study IV used a matched cohort design to describe a wide spectrum of diseases after breast cancer diagnosis. In a Swedish nationwide breast cancer cohort, breast cancer patients had an increased risk of infection and several non-communicable diseases, compared to matched healthy individuals. Diseases with the highest hazard ratios - lymphedema, radiodermatitis, and neutropenia - correspond to the side effects of surgery, radiotherapy, and chemotherapy. Despite an increased incidence of many diseases, increased mortality risk among breast cancer patients was only due to other solid cancers. A higher risk of other solid cancers could be

predicted by menopausal disorders, indicating the need for gynecological surveillance of breast cancer patients.

In conclusion, our results suggest that inherited factors contribute to an inverse association between preeclampsia and breast cancer, given that the inverse association was also found between preeclampsia and women with a high genetic predisposition to breast cancer. This thesis identifies an increased risk of several diseases after breast cancer diagnosis, including menopausal disorders, mental disorders, and psoriasis. Such diseases are related to cancer treatment, and suggest that a multidisciplinary perspective on post-cancer care is required for breast cancer patients.

LIST OF SCIENTIFIC PAPERS

I. **Yang, H.**, He, W., Eriksson, M., Li, J., Holowko, N., Chiesa, F., Hall, P. & Czene, K. (2018). Inherited factors contribute to an inverse association between preeclampsia and breast cancer. Breast Cancer Research, 20(1), 6.

II. **Yang, H.**, Brand, J. S., Fang, F., Chiesa, F., Johansson, A. L., Hall, P., & Czene, K. (2017). Time-dependent risk of depression, anxiety, and stress-related disorders in patients with invasive and in situ breast cancer. International Journal of Cancer, 140(4), 841-852.

III. **Yang, H.**, Brand, J. S., Li, J., Ludvigsson, J. F., Ugalde-Morales, E., Chiesa, F., Hall, P. & Czene, K. (2017). Risk and predictors of psoriasis in patients with breast cancer: a Swedish population-based cohort study. BMC Medicine, 15(1), 154.

IV. **Yang, H.**, Pawitan, Y., He, W., Eriksson, L., Holowko, N., Hall, P. & Czene, K. Disease trajectories and mortality among women diagnosed with breast cancer. (Submitted)

CONTENTS

LIST OF ABBREVIATIONS

AIs	Aromatase inhibitors
BMI	Body mass index
CCI	Charlson comorbidity index
CI	Confidence interval
ER	Estrogen receptor
GWAS	Genome Wide Association Study
hCG	human Chorionic Gonadotropin
HER-2	Human epidermal growth factor receptor 2
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IGF-1	Insulin-like growth factor-1
IGFBPs	Insulin-like growth factor binding proteins
INCA	Information Network for Cancer treatment
IRR	Incidence rate ratio
KARMA	KARolinska MAmmography project for Risk Prediction of Breast Cancer
Libro-1	The Linne bröst 1
OR	Odds ratio
PheWAS	Phenome-Wide Association Study
PIN	Personal identity number
PR	Progesterone receptor
PRS	Polygenic risk score
SIR	Standardized incidence ratio
SNPs	Single Nucleotide Polymorphisms
VTE	Venous thromboembolism

1 INTRODUCTION

Breast cancer is the most prevalent cancer among women worldwide, and the number of breast cancer patients is increasing in both developed and developing countries [1]. Several factors have contributed to this increasing trend, such as lifestyle transitions, the coverage of screening programs, and improvements in treatment, which led to a large number of women living with a history of breast cancer disease. This prolonged survival time after breast cancer diagnosis also makes it possible to investigate the occurrence of other diseases among breast cancer patients. These diseases might not only influence treatment decisions and patient prognosis but also quality of life and social welfare. In Sweden, the well-established health care registers that cover the entire nation provide an opportunity to study these diseases, and the results we observe in Sweden may shed light on clinical practice in other countries.

There are several reasons for other diseases to be associated with breast cancer. The pleiotropic effect of genetic variants and certain unhealthy lifestyle factors may affect the risk of many diseases, including breast cancer. In this thesis, we wanted to investigate how diseases in early adulthood influence a woman's risk of breast cancer and whether genetic variants contribute to the association. Considering the roles of hormones in breast tumor carcinogenesis, several hormone-related diseases have been studied to test their association with breast cancer risk, including preeclampsia.

Treatments for breast cancer might be toxic for other organ systems and increase the risk of other diseases. A diagnosis of cancer per se is a stressful life event, which can impair patient mental health. In this thesis, we also tried to reveal the effect of cancer diagnosis and treatment on the risk of other diseases after breast cancer diagnosis, with a focus on mental disorders and psoriasis, considering their impact on patient quality of life and welfare.

In addition to diseases with a known association with breast cancer, many other diseases have not been studied in these patients. Therefore, we screened across a wide spectrum of diseases among breast cancer patients to discover unknown associations. We also attempted to link the sequential pattern of disease incidence to the mortality of patients. These efforts may help to identify key diagnostic indicators to aid in early detection and treatment of life-threatening outcomes later in life.

2 BACKGROUND

2.1 EPIDEMIOLOGY OF BREAST CANCER

Breast cancer is one of the most common cancers diagnosed worldwide. It has been reported that one in ten women will be diagnosed with breast cancer in their lifetime in developed countries. In 2016, approximately 1.7 million women are diagnosed with breast cancer, which represents 22% of all female cancers [1]. Generally, breast cancer is a female cancer, and less than 1% of patients are male [2]. The annual incidence of new cases is higher in more developed regions than in less developed regions of the world (1.06 and 0.64 million cases in 2016, respectively), as well as the incidence rate of breast cancer (88.1 per 100,000 person-years compared to 18.8 per 100,000 person-years). Geographically, women from North America and Western European countries suffer from a higher incidence of breast cancer [1] (Figure 2.1).

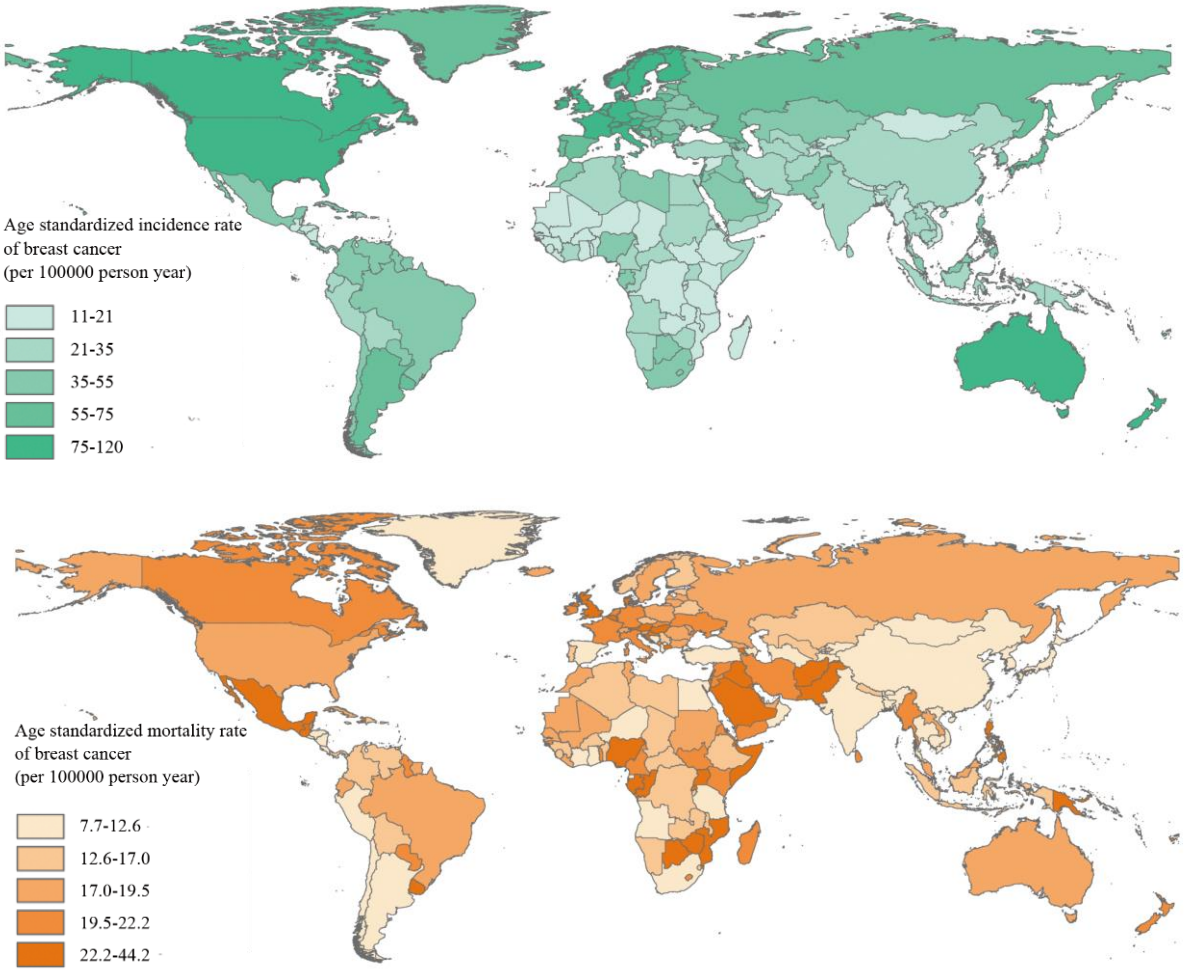

Figure 2.1 *Geographic view of breast cancer incidence and mortality in 2016.*

Data obtained from a publication of Global Burden of Disease Cancer Collaboration [1].

Breast cancer ranks as the first cause of death for women among all cancer types and the fifth cause of death among all diseases worldwide [3]. Different from the large disparity in breast cancer incidence throughout the world, the mortality rate of breast cancer is not quite different

in more developed and less developed regions (15.5 and 7.4 per 100,000 person-years, respectively), possibly because of better screening and treatment in more developed regions.

In Sweden, breast cancer accounts for 29.2% of all female cancers and 13.0% of cancer mortality, with an annual incidence of 7,558 and mortality of 1,391 patients in 2016 [4]. The incidence rate of breast cancer has nearly doubled from 72.5 per 100,000 person-years in 1965 to 150.5 per 100,000 person-years in 2015 [5]. Despite the increasing incidence of breast cancer over time, more patients currently survive the disease. Thanks to the nationwide mammographic screening program and improved treatments, the five-year survival rate of Swedish breast cancer patients has increased from 82% in 1990-1994 to 92% in 2016 [4, 5]. Due to these trends in incidence and survival, the number of prevalent breast cancer cases has increased steadily over the past decades. In 2016, there are approximately 108,000 breast cancer patients in Sweden.

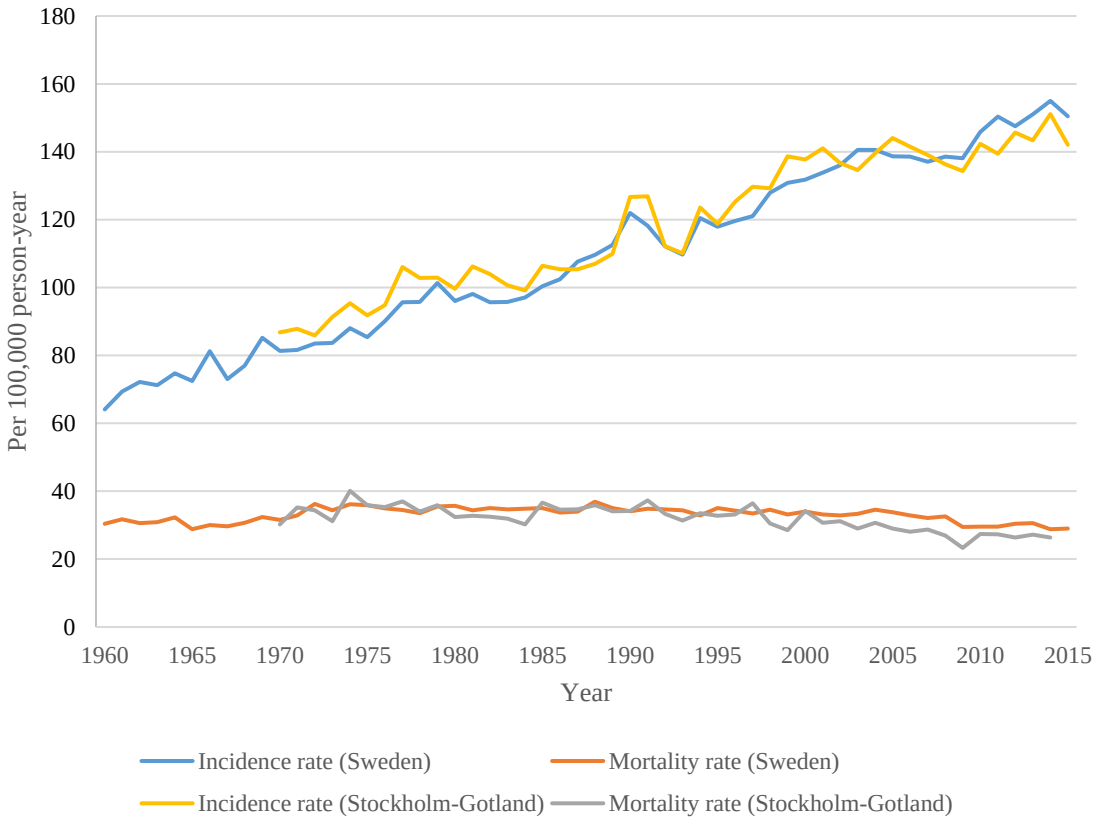

Figure 2.2 *Incidence and mortality rates of breast cancer in Sweden*

Data obtained from NORDCAN [5].

2.2 RISK FACTORS FOR BREAST CANCER

Breast cancer is a hormone-related cancer with a heritability of 31%. Common environmental and individual environmental factors explain the other 16% and 53% of the disease liability [6]. An overview of the major risk factors for breast cancer is presented in Figure 2.3, showing genetic, hormone and other lifestyle factors.

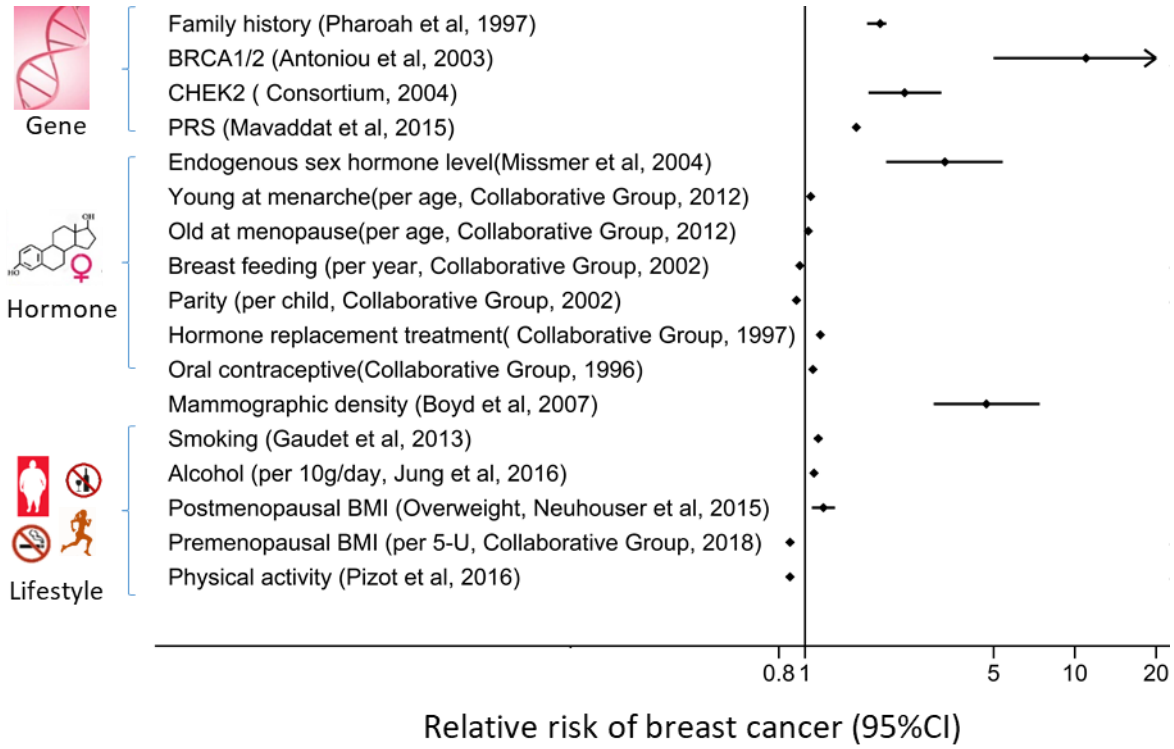

Figure 2.3 *Relative risk of breast cancer according to gene, hormone and lifestyle factors*

2.2.1 Family history and genetic factors

An increased risk of breast cancer has been shown in women with a family history of breast cancer. Women with any affected first-degree relatives have a twice increased risk of breast cancer, and the affected second-degree relatives are associated with a 50% increased risk [7]. Compared to women with no affected relatives, the risk of breast cancer is increased by 80%, twice and three times in women with one, two and more than two affected relatives, respectively [8].

The strong effect of family history is partly explained by inherited genetic mutations, with the famous BRCA1 and BRCA2 genes accounting for 16% of the familial risk and other genes, such as PTEN, P53, STK11 and CDH1, accounting for approximately 5% [9]. The rare moderate-penetrance breast cancer susceptibility genes, including CHEK2, ATM, BRIP1 and PALB2, contribute to a much lower proportion of familial risk (approximately 2.3%). Thus, the majority of the family history effect is hypothesized to be originated from common polygenic variance. Figure 2.4 illustrates the liability of breast cancer by these genetic variants.

With the development of high throughput genotyping technology, various Genome-Wide Association Studies (GWAS) have been performed to harvest new Single Nucleotide Polymorphisms (SNPs) for breast cancer. An SNP is a single allele alteration in the DNA chain with a frequency of more than 1% in the population and therefore is viewed as a common genetic variance. Current efforts by a consortium of researchers have discovered 172 breast cancer-associated loci, explaining approximately 18% of the familial risk of breast cancer [10]. The significant SNPs can be summed up to a polygenic risk score (PRS) for breast cancer risk prediction. Women with the highest 1.5% PRS experience a three-fold increased risk of breast

cancer compared with the remaining population [11]. Adding the PRS into the common breast cancer prediction tools also increases the precision of prediction [12].

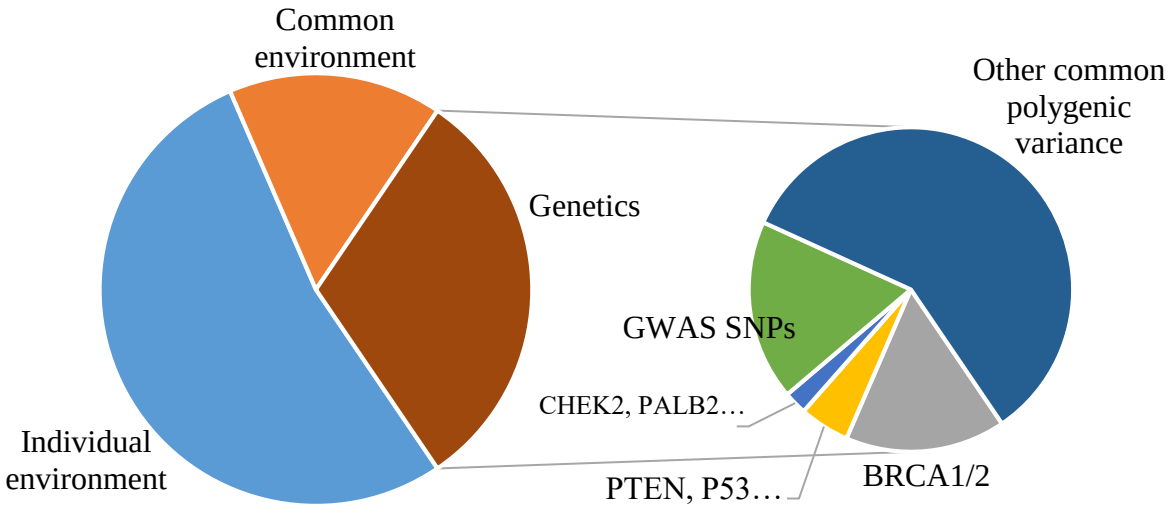

Figure 2.4 *Breast cancer disease liability by gene and environment factors*

2.2.2 Hormone-related factors

Breast tissue is sensitive to hormones, especially estrogen and progesterone. Approximately 75% of breast tumors express estrogen receptor alpha [13]. In postmenopausal women, a higher level of total circulating estrogen is strongly associated with an increased risk of breast cancer [14]. An excess serum level of androgen also contributes to higher breast cancer risk in these women [15], probably through aromatase activity in fat tissues. For premenopausal women, the estrogen level fluctuates across the menstrual cycle and thus is difficult to compare. However, studies still suggest a positive association between circulating estrogen level and breast cancer risk in premenopausal women [16].

The duration of exposure to estrogen is also important, because the lifelong exposure to estrogen depends on both the level of estrogen and duration of exposure. Reproductive factors indicating a longer period of ovarian activity, such as early menarche, late menopause and more menstrual cycles, increase the risk of breast cancer [17]. However, breastfeeding, early age at first pregnancy and multiple pregnancies may influence the differentiation of mammary gland cells and consequently protect women from breast cancer [18]. In addition, pregnancy characteristics and related diseases, including placenta weight and preeclampsia also affect breast cancer risk in later life [19, 20].

In addition to endogenous hormones, exogenous hormones also increase breast cancer risk. Hormone replacement therapy has been used to maintain the serum estrogen level and relieve menopausal syndromes (hot flushes, osteoporosis, psychological change, etc.) [21]. Current and recent users of hormone replacement therapy have an approximately 14% increased risk of breast cancer [22], which is mainly due to the continuous combined estrogen plus progestin therapy [23]. Similar to hormone replacement therapy, oral contraceptive users have an

increased breast cancer risk; however, this increased risk diminishes beyond 10 years after drug cessation [24].

2.2.3 Mammographic density

Mammographic density refers to the sum of pixels in the mammogram, which corresponds to dense breast tissues. The pixels are generated by X-rays that permeate different types of breast tissues differently, with dark areas referring to fat tissues and white pixels referring to epithelial and stromal tissues [25]. Mammographic density is often analyzed by comparison with the entire breast area, resulting in a percent density. Mammograms showing the mediolateral oblique view were usually measured, and in our group, the full automated software STRATUS was used to measure area-based mammographic density (absolute dense area and percent density). The STRATUS software can measure both raw and processed mammogram images regardless of the vendor of the mammography machine and allows comparison of mammographic density at the population level [26]. An illustration of the mammograms is shown in Figure 2.5. A higher percent density is a strong risk factor for breast cancer [27], and inclusion of mammographic density in the breast cancer risk prediction models increases the discriminatory accuracy [28].

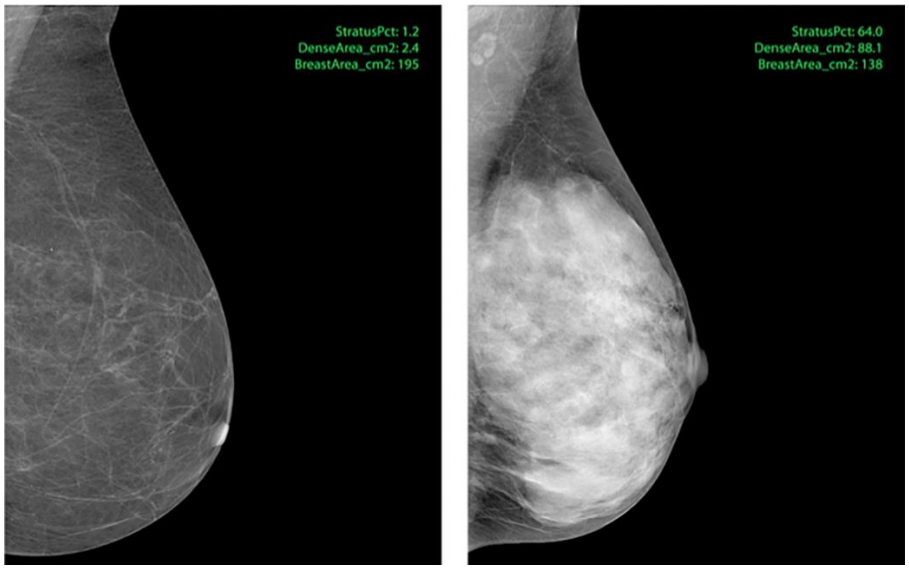

Figure 2.5 *Illustration of mammograms measured by our group [29].*
Left: mammogram with low percent density; right: mammogram with high percent density.

2.2.4 Other lifestyle factors

Similar to other cancers, lifestyle factors play an important role in breast cancer development. Cigarette smoking has been shown to increase breast cancer risk by 20%, especially for women who initiate smoking before their first delivery [30]. Likewise, alcohol consumption is positively associated with the risk of both ER-positive and ER-negative breast cancer [31], and even a moderate dosage can increase the risk [32]. Body mass index (BMI), as an indicator of body fat distribution, slightly decreases the risk of breast cancer in premenopausal women but elevates breast cancer risk in postmenopausal women [33, 34]. This disparity is probably due to a change in the main source of endogenous estrogen, from the ovary to adipose cells after

menopause. Independent of BMI, women who exert a higher level of physical activity experience a reduction in breast cancer risk compared with less active individuals [35].

2.3 DIAGNOSIS OF BREAST CANCER

2.3.1 Current approaches to diagnosis

In the 1990s, Sweden started the nationwide breast cancer screening program, and according to the detection mode, breast cancer can be divided into screening-detected cancers and interval cancers. If the radiologists find a suspicious image in the screening mammogram, the patients will be recalled for an additional mammogram or ultrasound, as well as a fine needle aspiration, to confirm whether there is a tumor. Patients diagnosed with interval cancers typically have some symptoms in the breast.

The most common symptom of breast cancer is a lump in the breast. Other possible symptoms include redness of the breast skin, clear or bloody fluid from the nipple, and dimpled or puckered breast skin (orange-like skin). In Sweden, women with these suspicious symptoms are referred to a standardized care process and first tested using the three major diagnostic approaches for breast cancer: clinical examination, imaging and biopsy (Figure 2.6) [36].

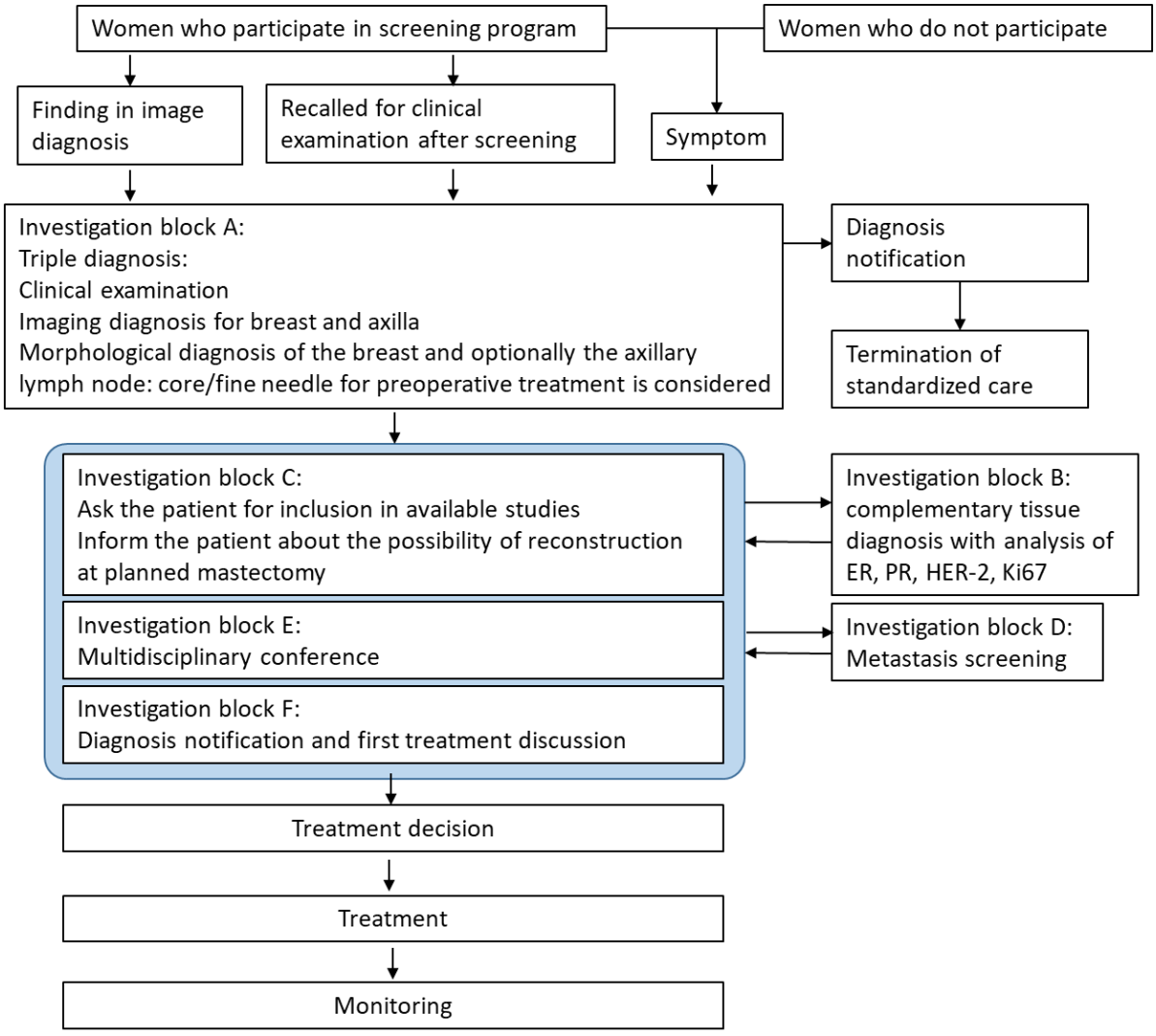

Figure 2.6 *Standardized diagnostic care for breast cancer in Sweden*

The clinical examination usually includes a review of family history, menstrual status, previous breast surgery, endocrine treatment and previous symptoms. The clinician should also perform a physical examination by palpation of both the breast and regional lymph nodes and inspection of the breast and overlying skin.

Mammography is the primary imaging technique for breast cancer diagnosis. However, if the woman is pregnant, breastfeeding or younger than 30 years old, ultrasound is the first choice. For women with dense breast tissue or a family history of breast cancer, MRI may also be offered due to its greater sensitivity. In a mammogram, fat tissues absorb fewer X-rays and appear as dark areas, while fibro-glandular tissues and tumors are dense areas with bright pixels [25]. Mammography is used not only in clinical diagnosis of breast cancer but also in screening programs in Sweden due to its low cost and high efficiency.

Although clinical examination and imaging help in diagnosing a breast tumor, cytology and tissue biopsy are the definitive approaches for breast cancer diagnosis. For preoperative tissue tests, focal point fine needle aspiration is generally sufficient if the patient is primarily operable and the clinical and diagnostic findings are clear. However, it is not possible to determine the invasiveness of a tumor by cytology, and a core needle tissue biopsy is therefore needed, which can also provide a better measurement of the tumor characteristics (will be described in 2.3.2). In a biopsy test, if cancer cells are proliferating within the basal epithelial membrane, the tumor is usually called an in situ cancer. However, cancer growing beyond the epithelial membrane and invading into the stromal cells is called invasive cancer. At the time of diagnosis, in situ cancer accounts for approximately 10% of all the breast cancers diagnosed in Sweden and is usually associated with better survival [37, 38].

2.3.2 Tumor characteristics

At the time of breast cancer diagnosis, several tumor characteristics are measured to investigate the aggressiveness of the tumor, including tumor size, lymph node involvement, hormone receptors, and histological grade. These tumor characteristics are usually measured by the pathologist using several techniques, such as immunohistochemistry and in situ hybridization.

Tumor size, lymph node and distant metastasis

Tumor size is a traditional measurement for breast cancer and a fundamental characteristic for predicting clinical outcomes after cancer [39]. However, the correlation between tumor size and breast cancer survival seems to only be significant in luminal (ER+/HER-2−) breast cancers and not in other molecular subtypes (will be introduced later), suggesting the limitation of tumor size as a prognostic indicator and the unpredictability of a receptor-negative cancer [40].

Axillary lymph node metastasis is the most important prognostic indicator for primary breast cancer, especially for patients with four or more involved lymph nodes [41]. In current clinical practice, a sentinel-node biopsy is performed to detect whether metastasis to the lymph node has occurred [42]. The sentinel node is identified with a radioactive isotope and a blue dye

injected into the tumor. Lymph node-positive patients usually receive a complete axillary dissection along with chemotherapy.

Distant metastasis is an indicator of breast cancer with a worse prognosis because the tumor cells are already disseminated to other sites in the body. Approximately 5-10% of breast cancers are metastatic at diagnosis, and only 20% of these patients will survive for more than 5 years [43]. Because the majority of metastatic breast cancer patients are incurable, the primary strategy for them is palliative care, with the aim of improving their quality of life and extending their survival time.

A summation of these three tumor characteristics is the TNM classification system, which was developed in the 1970s and was recently updated to the 8th version in 2017 [44]. The details of TNM classification are summarized in Table 2.1. According to the TNM classification, tumor grade, hormone receptor status and gene panels, breast cancer can be categorized into four stages. When breast cancer is diagnosed, approximately 60% of the patients have stage 0-I cancer, 30% have stage II-III cancer and less than 10% have stage IV cancer. Stage 0-III breast cancer patients usually have an approximately 90% five-year survival rate, while for stage IV cancer patients, the five-year survival rate is approximately 20-30% [45].

Table 2.1 *American Joint Committee on Cancer Definition of TNM*

Category	**Criteria**
Tumor size (T)	
Tx	Tumor size can not be assessed
T0	No evidence of tumor
Tis	Carcinoma in situ
T1	Tumor size ≤ 20 mm in the greatest dimension
T2	Tumor size >20 mm but ≤50 mm in the greatest dimension
T3	Tumor size >50 mm in the greatest dimension
T4	Tumor of any size with invasion into the chest wall or the skin
Regional lymph nodes (N)	
Nx	Regional lymph nodes can not be assessed
N0	No metastasis to lymph node
N1	Metastases to ipsilateral level I and II axillary lymph node(s), and are still movable
N2	Metastases in ipsilateral level I and II axillary lymph nodes, but are clinically fixed or matted or Metastases in ipsilateral internal mammary lymph nodes without evidence of axillary lymph node metastasis
N3	Metastases in ipsilateral infraclavicular lymph nodes (level III), with or without level I and II axillary lymph node involvement, or Metastases in ipsilateral internal mammary lymph nodes and also in the level I and II axillary lymph node, or Metastasis in ipsilateral supraclavicular lymph nodes, regardless of axillary or internal mammary lymph node metastasis
Distant metastasis (M)	
M0	Not any evidence of distant metastasis
cM0(i+)	No clinical or radiographic evidence of distant metastasis, but evidence of tumor cells in circulating blood, bone marrow, or other non-regional lymph nodal tissue; with metastasis tumor size ≤ 0.2 mm and without any symptoms of metastasis
M1	Clinical or radiographic evidence of distant metastasis, with/without histologically proven, metastatic tumor size >0.2 mm

Histologic grade

Another classification approach for breast cancer is based on the histologic grade, which represents the potential aggressiveness of the tumor. The Nottingham (Elston-Ellis) modification of the Scarff-Bloom-Richardson grading system is recommended for grading breast cancer [46]. According to mammary gland cell formation (or differentiation), the nuclear features (or pleomorphism) and the mitotic activity, breast tumors are classified as Grade I, II or III. Grade II tumors are classified with the lowest degree of concordance among different pathologists and therefore need to be sub-classified according to molecular profiling [46].

Molecular classification

Breast cancer can be classified according to molecular receptor status, namely, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER-2) status, and Ki-67 index.

Estrogen receptors are a group of proteins expressed in several human tissues and are activated by estrogen [47]. In breast cancer, the majority of ERs are ER-α, which is overexpressed by approximately 75% of breast cancer tumors [13]. The ER expression level is tested via immunohistochemical staining assay, and the cancer is categorized as ER positive when more than 10% of the cancer cells express ER. In 2010, this cut-off of 10% was changed to 1% [48], although patients with 1-9% of the cancer cells expressing ER still have worse survival than those with >10% of ER+ cancer cells [49]. A higher ER level is associated with improved survival after the patients are treated with endocrine therapy [50], while ER-negative cancer patients usually have a poor survival [51].

Another female hormone receptor, PR, also plays an important role in breast cancer development and prognosis. PR expression is strongly dependent on ER expression. PR is also tested using an immunohistochemical staining assay with a recommended cut-off of 1% [48]. Although a previous observational study showed better overall survival for PR+ and ER+ patients [52], a recent meta-analysis suggested that ER is the sole factor predicting endocrine treatment response without contribution from PR [53]. The function of PR in clinical prognosis prediction is still uncertain.

HER-2 is expressed in many types of cancer [54]. HER-2 is a membrane tyrosine kinase that is associated with cell proliferation, survival, and apoptosis. Overexpression of HER-2 can be detected in 15-20% of breast cancer patients, and HER-2-positive patients are more likely to relapse and have poor survival [55]. HER-2 expression is also tested using an immunohistochemical staining assay, with tumors exhibiting HER-2 expression in >30% of cells categorized as HER-2 positive and those with <10% of cells expressing HER-2 as HER-2 negative. For tumors with 10-30% cell staining, in situ hybridization assay is used to confirm the categorization [56].

Ki-67 is a nuclear non-histone protein showing proliferative activity of the tumor. The Ki-67 level is measured as the percentage of tumor cells with positively stained nuclei. Currently, there is still no standard cut-off point for the Ki-67 level, although a 14% cut-off has been used

to differentiate Luminal A and B cancer [57]. A higher level of Ki-67 staining indicates a worse overall survival [58]. However, additional role of Ki-67 in breast cancer treatment and prognosis apart from other biomarkers is still uncertain [59].

***Table 2.2**. Molecular subtypes of breast cancer*

Molecular subtype	Characteristics
Luminal A	ER and/or PR positive, HER-2 negative, Ki-67<14%
Luminal B	ER and/or PR positive, HER-2 negative, Ki-67 ≥14%
	Or: ER and/or PR positive, any Ki-67, HER-2 overexpressed or amplified
Basal-like (triple negative)	ER and PR negative, HER-2 negative
HER-2-enriched	HER-2 overexpressed or amplified, ER and PR negative

Based on the genes that a tumor expresses, breast cancer can be divided into four molecular subtypes: Luminal A, Luminal B, HER-2-enriched, and basal-like cancer. Characteristics of these molecular subtypes are listed in Table 2.2 [60]. Among all breast cancer patients, 74% of cases are luminal A, 10% are luminal B, 12% are triple negative and 4% are HER-2-enriched [45]. Luminal A cancer is associated with better survival 5 years after diagnosis, albeit this effect attenuates over time [61].

2.4 TREATMENT OF BREAST CANCER

Treatment for breast cancer patients can be divided into i) local treatment to remove the tumor and stop its spreading, and ii) systemic treatment to kill micro site tumors and metastasis. Figure 2.7 shows standard treatment options for early stage breast cancer patients.

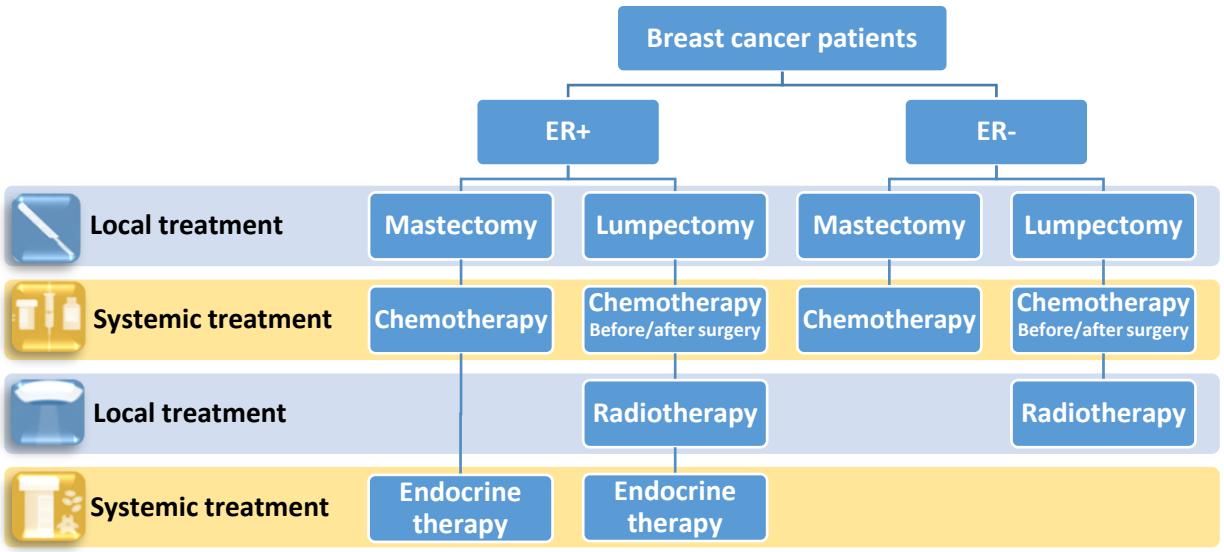

Figure 2.7 *Standard treatment options and procedures for early stage breast cancer patients*

2.4.1 Local treatment

Removing the tumor through surgery has been the primary treatment for breast cancer for about two centuries [62]. Mastectomy (removal of the entire breast) and lumpectomy (breast-conserving surgery) are the two major surgical treatments for breast cancer. Mastectomy is aimed to excise invasive or non-invasive breast tumors with clear margins together with the whole breast, while in a lumpectomy, only a portion of the breast is excised. Recent studies have shown that patients treated with a lumpectomy followed by radiotherapy have the same survival outcome as those that underwent a mastectomy [63]. However, if the tumor is too large or there are multiple tumor sites, a mastectomy is still recommended [64]. The primary complications after breast surgery include pain, infection, and bleeding [65, 66]. Breast surgery is sometimes accompanied by an axillary lymph node dissection, which causes side effects such as lymphedema, pain and numbness of the upper limb [67]. The number of dissected lymph nodes is associated with a higher risk of infection and lymphedema in breast cancer patients and consequently impairs overall survival [68, 69]. To reduce these side effects and the hospital stay, the current technology of sentinel lymph node biopsy spares node-negative women from axillary lymph node dissection [70], and a maximum of 2 metastatic sentinel lymph nodes can be considered safe to avoid axillary dissection [71].

In Sweden, radiotherapy is recommended for almost all early-stage breast cancer patients to prevent local recurrence in case tumor cells remain after surgery. Irradiation is usually applied to the remaining breast tissues and areas around the surgical margin, with a total dosage of 50 grays. Radiotherapy after lumpectomy has been reported to reduce the risk of breast cancer recurrence by approximately 15% [72, 73]. Even for women with mastectomy, radiotherapy still reduces the risk of recurrence and mortality [74]. Although the irradiation is focused on the tumor site (or around the tumor site), currently, radiation-associated skin side effects still exist, such as dermatitis and psoriasis [75, 76]. Some long-term side effects, mainly lung cancer and ischemic heart disease, may occur 10-20 years after the treatment [77, 78].

2.4.2 Systemic treatment

In the case of micro-metastasis to other sites in the body, chemotherapy is recommended after surgery to interrupt cancer cell proliferation and induce apoptosis. Breast cancer patients with lymph node involvement or ER-negative or HER-2-positive tumors are usually recommended for chemotherapy [79]. In Sweden, chemotherapy medicines for breast cancer primarily include 5-fluorouracil+epirubicin+cyclophosphamide (FEC), cyclophosphamide+ methotrexate+fluorouracil (CMF), and taxane-containing regimens (added when the tumor has metastasized to lymph nodes) [80, 81]. Anthracycline-based chemotherapy contributes to a one-third breast cancer mortality reduction in ten years after cancer diagnosis, and adding taxanes additionally reduces the mortality by 10% [82]. Chemotherapy agents indiscriminately interrupt cell proliferation, and thus, other cells with high proliferative activity are also damaged during the treatment period, causing a variety of side effects, including infection, neutropenia, anemia, nausea, diarrhea, malnutrition, and venous thromboembolism (VTE). [83]. In addition to these short-term side effects, chemotherapy also has long-term effects of

cardiac toxicity and neurotoxicity, potentially leading to heart failure and cognitive impairment later in life [84].

Considering the high level of ER expression in breast cancer cells, endocrine therapy has been developed to prevent receptor activation and consequently to restrict tumor cell proliferation. There are two main medications for endocrine therapy: selective estrogen receptor modulators for all ER-positive patients and aromatase inhibitors (AIs) for postmenopausal ER-positive patients. Launched in 1975, tamoxifen is a selective estrogen receptor modulator that acts as an ER antagonist in breast tissue. Tamoxifen is usually prescribed to ER-positive patients for five years after cancer diagnosis and reduces breast cancer mortality by 30% [53]. The current international guideline suggests an extension of tamoxifen use for 10 years or switching to AIs for another 5 years [85]. AIs inhibit the aromatase enzyme in adipose tissues to prevent the conversion of androgens into estrogen. They reduce breast cancer recurrence and mortality by another 15% compared with the effect of tamoxifen [86]. These two types of medicines share certain side effects, such as hot flashes, weight gain, insomnia and fatigue. However, tamoxifen is an agonist that maintains endometrial polyp production and bone mineral density, and thus, more endometrial cancers and fewer bone fracture cases are observed in tamoxifen users [87, 88].

In addition to chemotherapy and endocrine therapy, targeted therapy for breast cancer is aimed at blocking specific tumor development receptors or pathways. The most famous targeted drug for breast cancer, trastuzumab (or Herceptin), is a monoclonal antibody that targets HER-2. It is usually given to HER-2-positive breast cancer patients after chemotherapy for 1 year and improves the overall survival of these patients by 30% [89]. The major side effect of trastuzumab is cardiac toxicity; however, this is primarily a short-term effect [90]. Other drugs, which target VEGF, PARPs and immune checkpoints, are still in clinical trials to treat triple negative breast cancer [91].

2.5 PROGNOSIS OF BREAST CANCER

As a result of the universal coverage of screening programs and therapy development, the five-year survival rate for breast cancer patients has improved in the past three decades from 75% to 90% (Figure 2.8) [5]. Despite the improvement in prognosis, breast cancer patients still suffer from a decreased life expectancy after diagnosis compared with women of the same age [92, 93]. The cancer-associated factors for poor survival include stage, grade, hormone receptor status and HER-2 status, while accessibility to high-quality health care and socioeconomic status may also influence patient survival [94, 95].

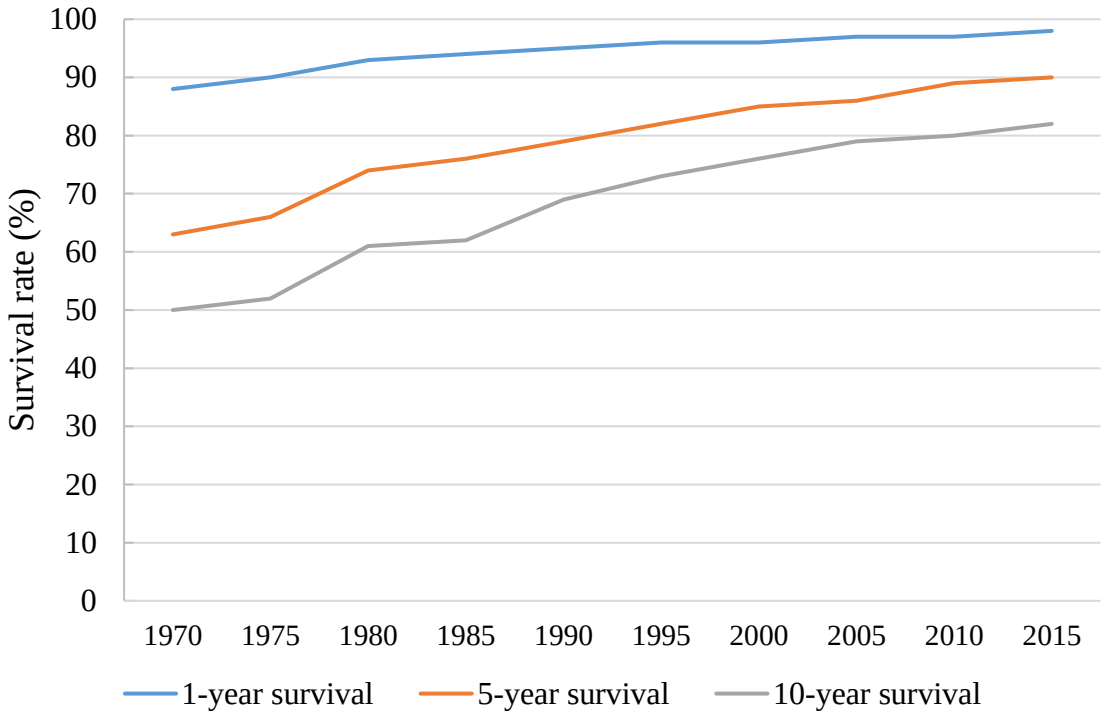

Figure 2.8 *Survival rate of breast cancer in Sweden (1970-2015)*

Data obtained from NORDCAN [5]

In breast cancer patients, the 30-year cumulative mortality rate for breast cancer is 27%, while that for causes other than breast cancer is 48% [37]. Other important causes of mortality include cerebrovascular disease, cardiac disease, dementia and other cancers [96]. The probability of dying from breast cancer is quite high shortly after diagnosis, but the impact diminishes beyond 1 year after cancer diagnosis [97]. Five-year survivors of breast cancer have a risk of dying from other diseases similar to that of the general female population [98].

2.6 OTHER DISEASES ASSOCIATED WITH BREAST CANCER

Due to the common genetic or environmental risk factors, as well as the side effects of treatment, breast cancer is associated with many other diseases. Some of the diseases are listed in Figure 2.9. These diseases are usually associated with poor overall survival, poor overall quality of life and higher health care cost for breast cancer patients [99-101]. Therefore, it is important to understand the panorama of diseases associated with breast cancer, i.e., how diseases in early adulthood influence the risk of breast cancer and how breast cancer treatments affect the overall health status of patients.

2.6.1 Overview of diseases associated with breast cancer

One third of breast cancer patients are comorbid with other chronic diseases at the time of their cancer diagnosis [102]. Among the five-year survivors of breast cancer patients, the proportion of patients comorbid with other diseases increases to 50%, and approximately 20% of these patients have more than two other diseases [98]. The most frequent diseases diagnosed in breast cancer patients include hypertension, cardiac disease, diabetes, and lung diseases [102]. Among the associated diseases before breast cancer diagnosis, benign breast disorders, diabetes and

other tumors are associated with an increased risk of breast cancer [103, 104], while preeclampsia and celiac disease are associated with a decreased risk [105, 106]. However, the risk of many other diseases increases after breast cancer diagnosis, including heart failure, bone fracture, infection, and coronary artery disease. Many of these diseases are caused by breast cancer treatment, for example, trastuzumab increases the risk of heart failure, while AIs increase the risk of bone fracture [88, 90].

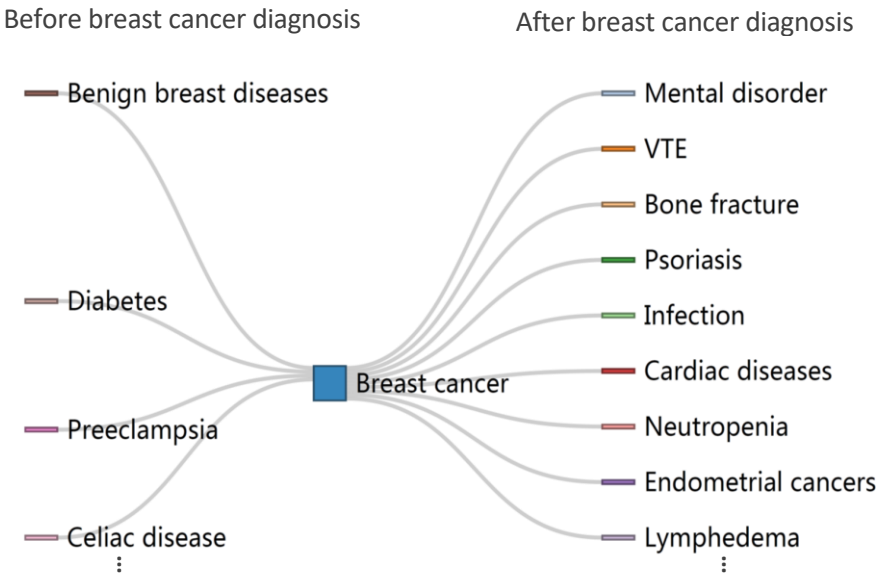

Figure 2.9 *Selected diseases associated with breast cancer.*

The majority of studies in this field focus on specific diseases associated with cancer treatment. However, the effect of breast cancer treatment is sometimes systemic, and chronic diseases usually occur together because they share many risk factors. Consequently, many breast cancer patients have several other diseases. A current approach to studying a series of diseases in breast cancer patients is to use the Charlson comorbidity index (CCI), which includes 14 diseases [107]. Nonetheless, these diseases are not specifically selected for breast cancer, and the acute effects of treatment, such as infection, neutropenia and VTE, are not included in the CCI. Therefore, it is important to have a comprehensive view of diseases associated with breast cancer, including both acute and chronic conditions. It would also be interesting to study the sequential association between treatment side effects and later life-threatening outcomes, which may help to identify key diagnoses to mitigate future poor outcomes.

2.6.2 Preeclampsia

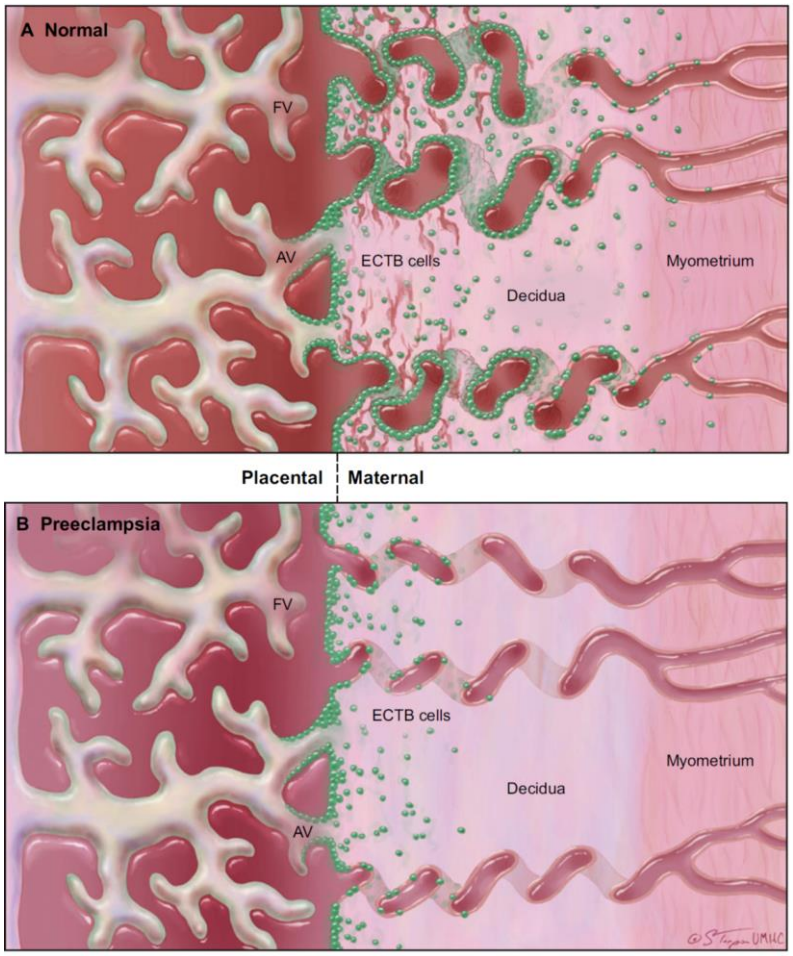

Figure 2.10 *Disruption of vascular remodeling in preeclampsia*
In a normal placenta (A), the vessel is compliant and blood flow from maternal side to placental spaces is enough, while in placenta of preeclampsia patients (B), the vessel walls remain stiff and the blood flow is limited. This figure is adopted from a publication of Pennington K., et., al [108]. FV, floating villi; AV, anchoring villi; ECTB, extravillous cytotrophoblast.

Preeclampsia is a main course of maternal mortality and is characterized by hypertension and proteinuria [109]. Preeclampsia occurs in 3-5% of pregnant women and causes stroke, eclampsia, placental abruption and renal failure during pregnancy [110]. Pathophysiology of preeclampsia is characterized by disruption of vascular remodeling and systemic anti-angiogenic response [108]. Evidence for the inverse association between preeclampsia and breast cancer has continuously been demonstrated since the 1980s [20, 106, 111, 112], but the mechanism of this association is still under discussion [113].

Some common risk factors may contribute to the inverse association between breast cancer and preeclampsia. A lower level of estrogen is observed in preeclampsia patients [114], indicating a lower level of exposure to endogenous hormones for the breast tissues. A high level of placental human chorionic gonadotropin (hCG) is also observed in preeclampsia patients[115]. In breast tissues, hCG has been shown to provoke mammary gland cell differentiation and inhibit breast cancer development [116, 117]. In addition, hCG could also induce insulin-like growth factor binding proteins (IGFBPs) and reduce the level of insulin-like growth factor-1 (IGF-1) [118]. A low level of IGF-1 and a high level of IGFBPs are observed in preeclampsia

patients [119], while a higher level of IGF-1 is found in premenopausal breast cancer patients and in women with high mammographic density[120, 121].

Placental ischemia is the key event in preeclampsia and is associated with a high level of soluble fms-like tyrosine kinase-1 [122]. A recent GWAS found an SNP near the FLT1 gene associated with preeclampsia risk, which is also associated with breast cancer risk [123, 124]. Candidate gene approach revealed approximately 70 genes that might be associated with preeclampsia, and several of the genes overlap with breast cancer risk genes, such as ACE, IGF1 and FLT1 [123, 125-127]. However, the results from different studies have been inconsistent, and thus, no universally acceptable risk gene has been defined for preeclampsia [128].

2.6.3 Mental disorders

Breast cancer patients are at increased risk of developing several mental disorders, including mainly depression, anxiety, and stress-related disorders [129]. These disorders do not only affect patients' psychological well-being but might also influence work performance [130], treatment adherence [131, 132], and overall quality of life [133].

The increased risk of mental disorders in breast cancer patients is to some extent a consequence of coping with the severe and stressful life event of cancer diagnosis. The hypothalamic-pituitary-adrenal axis and sympathetic nervous system are considered to be the main players involved in the biological mechanism of the stress response, which releases hormones, such as corticotrophin-releasing hormone, adrenocorticotropic hormone and glucocorticoids [134]. A previous study showed associations between depression and adrenocorticotropic hormone and cortisol levels in breast cancer patients, supporting this potential pathway [135]. Late-stage and lymph node-positive tumors may result in a higher risk of mental disorders [136-138], suggesting a dosage effect of this stress response. Previous studies have shown a 70% increased risk of depression and anxiety in breast cancer patients [138-141]. However, the risk by time since diagnosis has rarely been described, despite the fact that the effect of the diagnosis may diminish over time, while treatments for cancer are given at different time points after diagnosis.

Chemotherapy is the main treatment approach studied for the association between breast cancer and mental disorders. The side effects of chemotherapy (e.g., alopecia, nausea and vomiting) may be sufficiently stressful to increase the risk of depression and anxiety [142, 143]. However, some population-based studies did not find an impact of chemotherapy on depression and anxiety [138], likely because of the time-dependent effect of chemotherapy, which should be detectable only during and shortly after active treatment.

2.6.4 Psoriasis

The risk of skin disorders, such as dermatitis and skin infection, is increased in breast cancer patients [68, 75]. However, the risk of psoriasis is less well studied, and previous analyses were mainly based on case reports [76, 144, 145]. Common symptoms of psoriasis include erythema and silver scaly plaques on the skin, but the severe subtype, arthropathic psoriasis, may result in joint deformation and disability. Psoriasis patients usually report a poor health-related quality of life and suffer from significant social stigma [146-148].

Psoriasis cases after breast cancer are mostly attributed to skin trauma induced by cancer treatments (surgery and radiotherapy) [76, 149]. Skin trauma (burns, scratches, bruises, cuts, etc.) has been reported to trigger approximately 43-76% of psoriasis cases [150], and an abnormal trauma healing process (keratinocyte differentiation and hyperproliferation) could contribute to the disease onset [151]. Moreover, as stressful life event is a risk factor for psoriasis [152], the increased risk of psoriasis in breast cancer patients might be the result of a psychological response to cancer diagnosis and treatment decisions.

In addition to skin injury and psychological stress, psoriasis has some lifestyle risk factors, such as smoking, alcohol consumption and high BMI [153-155]. Streptococci infection and certain medications, such as lithium, beta-blockers and nonsteroidal anti-inflammatory drugs, may also increase psoriasis risk [156, 157].

2.6.5 Other important diseases associated with breast cancer treatment

Adjuvant chemotherapy is very effective in reducing the risk of metastasis and mortality in breast cancer patients but also causes serious side effects, including neutropenia, infection, VTE, and cardiac disease [83]. Neutropenia in cancer patients is characterized as a temperature >38.5°C and an absolute neutrophil count of <500 cells/ml [158]. Approximately 5.5-30.6% of breast cancer patients develop neutropenia after chemotherapy [83, 159], and chemotherapy regimens (especially taxane) are considered the main risk factor for neutropenia [160]. Other risk factors include age, comorbidity, BMI, baseline neutrophil count and genetic factors [161]. Preventive measures for neutropenia include maintenance of hygiene status and prophylactic use of antimicrobials (only recommended for high-risk patients) and Granulocyte colony stimulating factor [162, 163].

Infection is a common complication in breast cancer patients. In addition to infection caused by the immunosuppressive effect of chemotherapy, skin infection is also common in breast cancer patients due to radiotherapy and lymphedema after axillary surgery [68]. Older age, comorbidities, and advanced cancer stage are independent risk factors for infection. Infection overall is associated with poor survival in cancer patients, especially for breast cancer patients with respiratory infection and sepsis [68].

VTE is a common outcome in cancer patients. The 1-year cumulative incidence of VTE is 0.84% in breast cancer patients [164], and the risk increase persists for 10 years after cancer diagnosis [165]. There are several hypotheses for the incidence of VTE in cancer patients. The

development of a systemic hypercoagulable state is considered a key pathogenic process in VTE, and tumor production of procoagulants, fibrinolytic agents and pro-angiogenic cytokines could interact with vessels and blood cells to promote this process [166]. Apart from the tumor itself, surgery, endocrine therapy and chemotherapy are also associated with VTE risk in breast cancer patients [167].

Cardiotoxicity is one of the long-term side effects of chemotherapy, likely because of the free radical-mediated myocyte damage caused by anthracyclines [168]. Radiotherapy for breast cancer usually causes some degree of incidental exposure of the heart to ionized radiation, consequently increasing ischemic heart disease risk [78, 169]. In addition, trastuzumab is also associated with an increased risk of cardiac disease and has a synergistic effect when combined with chemotherapy [170]. However, the risk does not outweigh the benefit of treatment [90], although cardiac disease is already the leading cause of mortality in breast cancer patients aside from the cancer itself [96].

Endocrine therapy is given to breast cancer patients for at least 5 years and could cause diseases such as endometrial cancer and bone fracture. Long-term users of tamoxifen are at a higher risk of endometrial cancer, with a more advanced endometrial tumor type and worse survival [171]. Bone fracture is more frequently observed in patients treated with AIs because the peripheral antagonist action of AIs inhibits the formation of estrogen after menopause [88]. Older patients with more comorbid diseases are at increased risk of bone fracture [172]. Consequently, drugs such as bisphosphonates are prescribed to patients together with AIs to prevent bone loss and fracture [173].

3 AIMS

The overall aim of this thesis project was to describe the panorama of diseases associated with breast cancer and examine how these associations are influenced by genetic, patient, tumor and treatment characteristics. To reach the overall aim, four study goals were developed:

1) To investigate the association between preeclampsia and breast cancer;
2) To assess the time-dependent risk of depression, anxiety and stress-related disorders in breast cancer patients;
3) To examine the risk and predictors of psoriasis in breast cancer patients;
4) To investigate disease trajectories and mortality in breast cancer patients.

4 STUDY MATERIALS

4.1 SWEDISH POPULATION AND HEALTH REGISTERS

Sweden has a long history of collecting and registering population statistics since the 16th century, when the church started to keep information on local parish members. The first publication of population statistics was in 1749, and this publication became regular after the establishment of Statistic Sweden in 1858 [174]. From 1947 onwards, a personal identity number (PIN) has been used for every individual resident in Sweden, and this PIN contains information regarding an individual's birth date and 4 additional digital numbers [175]. Currently, the National Tax Board holds full responsibility for creating the PIN and delivering the notifications to other administrations, including Statistic Sweden and National Board of Health and Welfare (Socialstyrelsen). These two agencies hold the majority of the population and health-related registers, and the PIN makes it possible to link these registers together to conduct nationwide population-based medical studies. Figure 4.1 shows the time line of different registers and two cohorts used in this thesis.

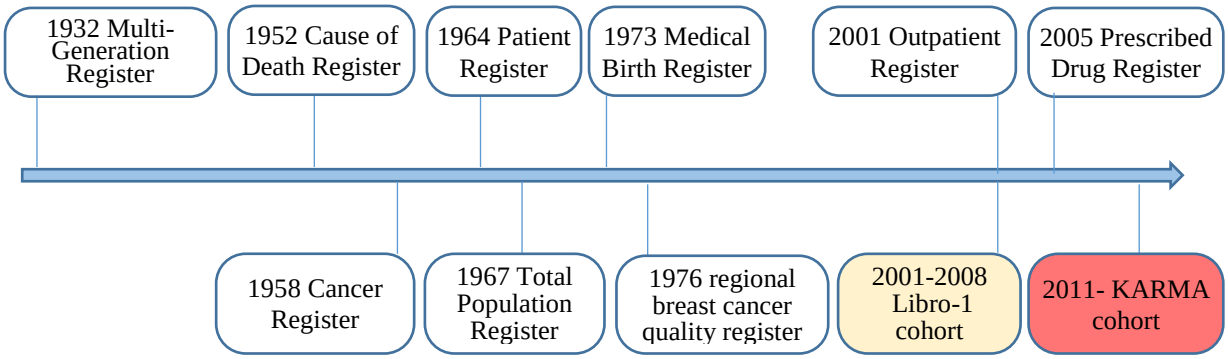

Figure 4.1 *Time line of the Swedish registers and the Libro-1 and KARMA cohorts*

The Total Population Register and the National Census

The Total Population Register was constructed by Statistic Sweden in 1967 when it started collecting data from the local population registers. In 1991, Statistic Sweden handed the responsibility for the Total Population Register to the National Tax Board. The Total Population Register includes an individual's date and place of birth, socioeconomic status, and address, among other information. In addition to the Total Population Register, the Swedish government also conducted a national population and housing census every decade (every five years since 1960) from 1860 to 1990. In 1995, the Swedish Parliament decided to change the census method by using a completely register-based approach, while previously, the general public needed to answer questionnaires [176]. The general population in this thesis were people who participated in the 1990 national census.

The Swedish Multi-Generation Register

Since 1961, a Multi-Generation Register was created to record child-parent (biological and adoptive) relationships in Sweden. As the personal record and PIN system was initiated in 1947

and a child's parents were recorded in their personal record if the child was 15 years old or younger, only people who were born in 1932 or later are included in the Multi-Generation Register. The Swedish government used the 1960 census data as the basis of Multi-Generation Register, and people who were alive, born or immigrated to Sweden from 1961 onward were registered [177]. The Multi-Generation Register mainly contains the PIN and country of birth for the indexed person and their parents; the information on mothers has 97% coverage, while the information on fathers is 95%. Using the parental information, siblings of the index person can be found in the register and were used for Study I in this thesis.

The Swedish Cause of Death Register

The first attempt to collect mortality data at a population level in Sweden dates back to 1751. Before 1911, only certain important causes of death were included in the register, such as maternal mortality and suicide. From 1952 on, the Cause of Death Register became electronically available, and the underlying cause of death was coded according to the World Health Organization standards, the International Statistical Classification of Diseases and Related Health Problems (ICD). The Cause of Death Register has an almost 100% completeness, and only 0.9% of the underlying cause of death information is missing [178]. However, the overall concordance between the disease registered on the death certificate registration and the medical record for hospital-based mortality is approximately 77%, but is quite high for cancer (92%) [179].

The Swedish Patient Register

The advantage of performing medical research in Sweden is partly due to the good coverage of the Patient Register, which allows complete follow-up of individuals to detect disease incidence. The Swedish Patient Register started in 1964/1965 and reached complete coverage in 1987. Since 2001, outpatient hospital visits are also recorded in the Patient Register, which has a coverage of approximately 80% (visits to public hospitals have almost 100% coverage). Primary and contributory diagnoses for patients are coded according to the Swedish Version of ICD codes (1964-1968: ICD-7; 1969-1986: ICD-8; 1987-1996: ICD-9; 1997 to present: ICD-10). Overall, primary diagnosis is found in 99% of all the hospital discharges, and the positive predictive values for the diagnosis codes are 85- 95% based on the 3-digit codes [180].

The Swedish Prescribed Drug Register

The Prescribed Drug Register was recently established in July 2005 and covers all counties in Sweden [181]. It is an automatic register containing information on prescribed drugs dispensed at the pharmacy, including the prescribed date, pick-up date, drug name, and the dosage and amount of drug. The drug names are coded according to the anatomical therapeutic chemical classification system. Of note, drugs used in the inpatient ward and over-the-counter drugs are not recorded in this register.

The Swedish Medical Birth Register

Since 1973, information on maternal deliveries and newborn infants has been recorded in the Medical Birth Register held by the National Board of Health and Welfare, which has a coverage of 99% of the births in Sweden [182]. Starting from 1982, the information has been collected through copies of antenatal, obstetric and pediatric medical records. The antenatal record is collected by the midwife from the first antenatal visit (at approximately 8-12 weeks gestation) and includes height, weight, smoking status and previous reproductive history. The obstetric and pediatric records are reported by the clinician when the mother is discharged from the hospital after delivery and include complications and mode of delivery, as well as the gestational age, birth weight, Apgar score and infant diagnosis for the child. Complications during pregnancy and delivery are also coded according to the Swedish version of the ICD, and the quality of the antenatal and obstetric records is considered high [183].

The Swedish Cancer Register

To monitor cancer incidence in Sweden, the Swedish Cancer Register was established in 1958 to collect information on cancer diagnosis and tumor stage (from 2004). Swedish physicians and pathologists are obliged to report the information to the Cancer Register when they diagnose a cancer, regardless of whether the tumor is benign or malignant. The completeness of the Cancer Register is considered to be 100% [184]. The Cancer Register is tumor-based, and thus, bilateral breast tumors are entered into the register separately. The completeness and correctness of invasive breast cancer information in the Cancer Register are considered to be 99% and 96%, respectively, while those for in situ cancer are 95% and 96% from the assessment in the 1990s [185].

The breast cancer quality register

Although the Swedish Cancer Register provides a good record of all sites of cancer in Sweden, detailed information for specific cancer types is not included. Since 1970s, the six regions of Sweden started to establish their own breast cancer quality registers [186], and in 2007, all these quality registers were combined into a national breast cancer quality register (Information Network for Cancer treatment, INCA). Since the studied breast cancer patients cover both periods, INCA and the breast cancer quality register in Stockholm and Gotland Regional Cancer Center are used in this thesis. The accuracy (concordance) of tumor characteristics (especially ER and PR status) and recommended treatment information in the breast cancer quality register is considered to be 92-96% [187, 188].

In addition to these registers, we also used information from some population registers, such as the Education Register and Migration Register, to retrieve information on education level and to censor the follow-up of individuals at emigration.

4.2 THE LIBRO-1 COHORT

The Linne bröst 1 (Libro-1) cohort consists of all the breast cancer patients diagnosed in the Stockholm-Gotland region between 2001 and 2008 according to the regional breast cancer quality register. For those patients with an available address and alive in 2009, an invitation to participate in the study was sent by letter, and 61% of them consented to be involved. For the entire Libro-1 cohort in the quality register, we linked the patients to the Swedish Cause of Death, Patient, Migration, Prescription and Cancer Registers. For those who consented to participate, we also sent a questionnaire seeking information about various breast cancer risk factors, such as family history, lifestyle and reproductive factors. At the time of invitation, two EDTA-buffered blood-sampling tubes and transportation kits were also provided, and the participants were asked to go to the local clinic for blood collection. The blood samples were sent to UK for genotyping by use of an Illumina iSelect SNP Array (iCOGS, comprising 211,155 SNPs) [189]. The missing genotypes were imputed using the 1000 Genomes Project March 2012 release as a reference.

4.3 THE KARMA COHORT

The KARolinska MAmmography project for Risk Prediction of Breast Cancer (KARMA) is a screening-based cohort formed through an invitation to all women participating in a mammographic screening or clinical mammography in four hospitals in Sweden (Stockholm South Hospital, Helsingborg Hospital, Skåne University Hospital and Landskrona Hospital) between January 2011 and March 2013 [29]. During the recruitment period, 70,877 women consented to join the study, and 97% of them completed a web-based questionnaire containing approximately 250 questions related to breast cancer, such as family history, lifestyle, diet, and quality of life questions. Mammograms of the participants were collected continuously each time they underwent mammography in these hospitals from the baseline. All the KARMA participants donated their blood in the hospital after they consented. Approximately 2700 breast cancer patients and 6400 controls in the KARMA cohort were genotyped with an Illumina Infinium OncoArray assay, comprising 499,170 SNPs[10], while more than 5000 other controls were genotyped using iCOGS (selected as controls for the genotyped breast cancer patients in the Libro-1 cohort) [189]. The missing genotypes were also imputed using the 1000 Genomes Project March 2012 release as a reference.

5 STUDY DESIGNS AND METHODS

5.1 OVERVIEW OF THE DESIGNS AND METHODS USED IN THE THESIS

To investigate the association between other diseases and breast cancer, we used several study designs and methods. An overview of these methods is presented in Table 5.1.

Table 5.1 *Overview of the study designs and methods*

	Study I	Study II	Study III	Study IV
Sources	Medical Birth Register (nationwide cohort) and KARMA cohort, linked with Cancer, Cause of Death, Multi-Generation, Education and Migration registers	Swedish Cancer Register (nationwide cohort) and Libro-1 (regional cohort), linked with Patient, Cause of Death, Prescribed Drug, and Migration registers and the 1990 national census		
Cohort	Pregnant women in Sweden	Breast cancer patients in Sweden		
Inclusion period	Nationwide cohort: first delivery 1973-2005 KARMA cohort: first delivery after 1958	Nationwide cohort: 2001-2009 Libro-1: 2001-2008	Nationwide cohort: 2001-2011 Libro-1: 2001-2008	Nationwide cohort: 2001-2011
Follow-up period	Nationwide cohort: 1973 to 2011 KARMA cohort: 1958 to 2015	Nationwide cohort: 2001 to 2010 Libro-1: 2001 to 2013	Nationwide cohort: 2001 to 2012 Libro-1: 2001 to 2013	Nationwide cohort: 2001 to 2012
Outcomes	Breast cancer incidence, preeclampsia and mammographic density	Depression, anxiety and stress related disorders	Psoriasis	Disease incidence and mortality
Explanatory variables (covariates)	Age, calendar period, life-style factors, preeclampsia diagnosis, genetic predisposition to breast cancer and several reproductive factors.	Age at diagnosis, calendar period, place of residence, comorbidity, tumor characteristics, and treatment.	Age at diagnosis, calendar period, place of residence, socioeconomic status, life-style and treatment factors.	Age at diagnosis, calendar period, place of residence, socioeconomic status
Main statistical models	Poisson regression Logistic regression Linear regression	SIR Flexible parametric survival model	Stratified Cox regression Ordinary Cox regression	Stratified Cox regression Conditional logistic regression

5.2 STATISTICAL METHODS USED IN THE THESIS

5.2.1 Survival analysis and models

Survival analysis is usually performed for the time-to-event outcomes in a cohort. Two main variables should be measured in the survival analysis: one is the duration from study entry to the end of event occurrence, and the other is the event indicator to show the outcome status. If the individual drops out or cannot be followed or the specific event does not occur when the study ends, the event is right censored, and the indicator is considered 0. In this thesis, we used different survival analysis models to test the association between breast cancer and other diseases.

Kaplan-Meier estimator and cumulative incidence

The central concept of survival analysis is based on the survival function S(t), the probability of survival until time t. There are several parametric and nonparametric approaches to estimate the survival function. The Kaplan-Meier method is one of the most common nonparametric approaches and calculates the probability of survival each time the event occurs and multiplies these probabilities.

The cumulative incidence is defined as the probability of an event occurring within a given time and can be calculated as 1-S(t). Hence, the Kaplan-Meier method can be extended to calculate cumulative incidence.

Standardized incidence ratio

To measure the risk of disease occurrence, an incidence rate or incidence density is usually calculated by dividing the number of events by the person-times at risk. A ratio of the incidence rates can then be interpreted as the effect of exposure on the disease occurrence, compared with the control group. Sometimes, if there is no control group for analysis or the comparison group is the general population, a standardized incidence ratio (SIR) could be an alternate parameter to assess the effect of exposure. The SIR divides the observed number of events by the expected number of events. The expected number of events is calculated by multiplying the number of person-time observed in specific strata of the exposure group by the incidence rates of the disease outcomes in the corresponding strata of the general population. In this thesis, we have the national census data, and the incidence rates of diseases were therefore directly calculated from the registers. Calculation of the confidence interval (CI) is based on the Poisson distribution.

Poisson regression model

The Poisson regression model is a type of generalized linear model that assumes the log rate of event incidence to be linearly related to the explanatory variable. When used in survival analysis, Poisson regression estimates the baseline incidence rates and calculates the incidence rate ratio (IRR) for comparison of different groups. Poisson regression can also address the multiple time scales problem in the survival analysis by splitting the record according to

different time-scale intervals. Follow-up time splitting can also be used to analyze time-varying effect of the exposure by splitting the record at the exposed time point and the exposed person-time was counted from this time point.

Cox regression model

The Cox proportional hazard model is the most frequently used survival model in medical research. It compares the hazard of an event in the exposed group to the hazard in the unexposed group, and a hazard ratio (HR) is estimated to assess the effect of exposure on the event occurrence. Cox regression assumes the hazard to be proportional over time, which should be checked using tests, such as the Schoenfeld residuals test. For matched cohort data, an extension of the Cox model, stratified Cox regression, is recommended to condition the matching variables and to address the presence of potential confounders as well as the imbalances in matching scheme caused by censoring [190, 191]. It is a conditional model for ordinary Cox regression, similar to the conditional logistic regression for the ordinary logistic regression model.

Flexible parametric model

The flexible parametric model is a restricted cubic spline-based model for survival analysis [192]. It is fitted according to the cumulative hazard function (a negative logarithm for the survival function) in the log scale using a cubic spline. In the model, the cubic spline is restricted to be linear outside the first and the last splining knots. For a large-scale dataset (e.g., the population-based studies in this thesis), five to six knots are recommended to put into the model. At this step, the flexible parametric model is similar to the Cox model, in which the proportionality of hazard is still assumed, and provides an overall estimation of the HR. In a further step, an interaction term between covariate (x) and time using a second spline function can be added into the model, and the effect of covariate x is then dependent on time. The number of knots in the second spline function should be less than the knots used in the first spline, and the number is recommended to be 3 to 4. This technique allows us to analyze the time-dependent risk profile of specific exposure when the proportional hazard assumption does not hold.

5.2.2 Logistic regression model

The logistic regression model is commonly used when dealing with binary outcomes in medical research. The model uses a logarithm transformation for the odds of outcome events and fits a linear model to the explanatory variables. Estimation of the coefficient is performed with a maximum likelihood approach, and the exponential of the coefficient is the odds ratio (OR), interpreted as the odds of being a case in the exposed group compared with the unexposed group. The logistic regression model is usually used in studies with case-control design.

In the special occasion of an individually matched case-control design, the conditional logistic regression model is used to estimate the OR. This model assumes a constant OR across the matched strata and controls the matching variables by conditioning.

5.2.3 Linear regression model

A linear regression model is used to assess the effect of exposure on continuous outcomes, while the exposure could be continuous or categorized. An ordinary least square approach is usually used to estimate the best fitted linear function ($Y=\beta_0+\sum\beta_i x_i+\varepsilon$) describing the change in outcome by one unit change in the exposure. The linear regression model has four major assumptions (LINE): (i) Linearity between the exposure and the outcome; (ii) Independence between the error variable ε and exposure x_i, and the mean of ε should be zero; (iii) Normal distribution of Y for any exposure x_i; and (iv) Equal variance (homoscedasticity) for the errors in outcome variables, given different values of exposure variable.

If the normality and homoscedasticity assumptions do not hold, the ordinary least square estimation for the standard error of β will be problematic. In this scenario, a sandwich variance estimator could be used to release these two assumptions.

5.3 SPECIFIC DESIGN FOR EACH STUDY

5.3.1 Association between preeclampsia and breast cancer

To assess the risk of breast cancer in women diagnosed with preeclampsia, we included two cohorts: a Swedish nationwide cohort of pregnant women and women with a child in the KARMA cohort (Aim 1 in Figure 5.1). The nationwide cohort was retrieved from the Swedish Medical Birth Register and included all women who delivered their first child between 1973 and 2005 (n=1,337,934). Pregnancy characteristics, such as BMI, smoking status, maternal age and previous reproductive history, as well as preeclampsia diagnosis, are included in the register. The preeclampsia diagnosis was recorded according to ICD codes as follows: ICD-10: O14 and O15; ICD-9: 642E, 642F and 642G; and ICD-8: 63703, 63704, 63709, 63710 and 63799. For the KARMA cohort, information on preeclampsia diagnosis was asked in the questionnaire. In this study, we only included women who had delivered their first child after 1958 and completely answered the questionnaire (n=55,044). Follow-up for both of the cohorts started from the birth date of each woman's first child and ended on the date of the first breast cancer diagnosis, emigration date, date of death or end of follow-up (December 31, 2011 for the nationwide cohort and February 28, 2015 for the KARMA cohort), whichever came first. Information on breast cancer diagnosis, emigration, and death was obtained by linking these two cohorts to the Swedish Cancer Register, Swedish Migration Register and Swedish Cause of Death Register.

The Poisson regression model was used to calculate the IRR of breast cancer in women diagnosed with preeclampsia compared with women without preeclampsia. The underlying time scale for this analysis was attained age. We constructed two models to test the effect of preeclampsia diagnosis on breast cancer risk: a basic model adjusting for calendar period and a multivariable model additionally adjusting for the number of births, age at first birth, BMI categories, and educational level in the nationwide cohort. For the KARMA cohort, the multivariable model was also adjusted for alcohol use, age at menarche, physical activity at 18

years old, body shape at 18, and irregular menstrual cycles in adult life. We also estimate the risk of ER+ and ER- breast cancer separately in the KARMA cohort.

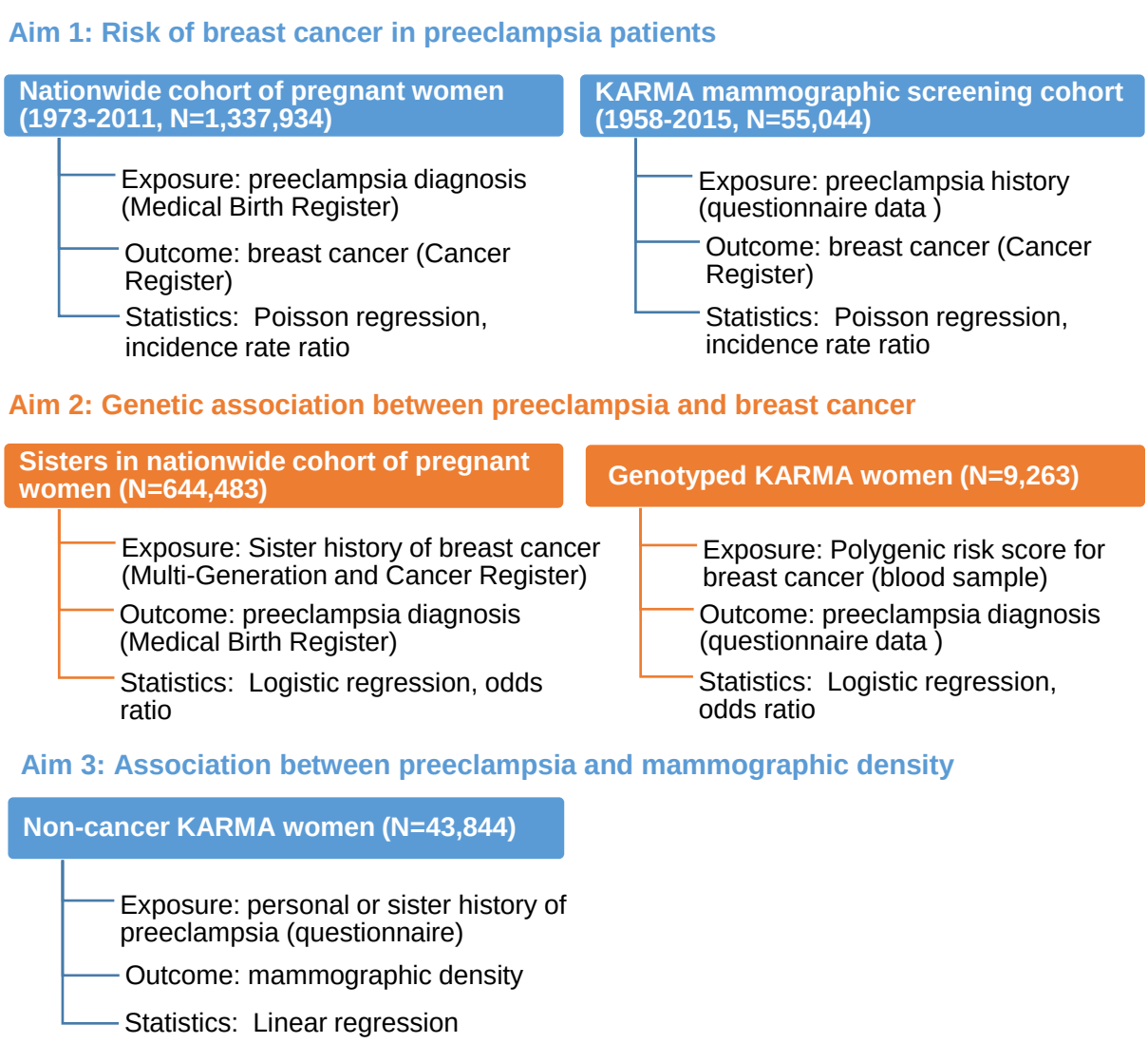

Figure 5.1 *Materials and methods used in the study for preeclampsia and breast cancer*

To identify the genetic association between preeclampsia and breast cancer, we linked both cohorts to the Swedish Multi-Generation Register and retrieved information regarding the women's sisters (Aim 2 in Figure 5.1). In the nationwide cohort, we used the logistic regression model to calculate the ORs of preeclampsia among cancer-free sisters of the breast cancer patients compared with cancer-free women without breast cancer sisters. In the KARMA cohort, blood samples from a subset of 9263 women without breast cancer were genotyped, and we selected 171 genome-wide significant SNPs to construct a PRS [10]. The PRS was calculated as follows: PRS = $\beta_1 x_1 + \beta_2 x_2 + \ldots . \beta_k x_k + \beta_n x_n$, where β is the per-allele log OR of a breast cancer-associated risk allele for SNP $_k$, x_k is the number of alleles for the same SNP (0, 1, 2), and $_n$ is the total number of the disease SNPs included in the profile. In this analysis, we calculated the OR of preeclampsia by different percentiles of the PRS (0-40%, 40-60%, 60-80%, 80-90% and 90-100%). For both of the analyses, we adjusted for number of births, age at first birth, BMI categories, smoking status and education in a multivariable model.

Considering mammographic density as an intermediate phenotype of breast cancer, we also tested the association between percentage density and previous preeclampsia diagnosis in the KARMA cohort (Aim 3 in Figure 5.1). In this analysis, women with any previous cancer or any breast surgery were excluded, leaving 43,844 women. We used the linear regression model with a robust sandwich estimator for the standard error. We adjusted for age at mammogram, BMI categories, age at menarche, number of births, age at first birth, menopausal status at mammogram, irregular menstrual cycle, physical activity at 18, body shape at 18, education level, smoking status, and alcohol consumption. We also tested the genetic association between preeclampsia and mammographic density by selecting the women in the cohort who have a sister (n=3500) and investigating the difference in mammographic density in sisters of patients with preeclampsia compared with women without a preeclamptic sister.

5.3.2 Time-dependent risk of mental disorders in breast cancer patients

To assess the risk of depression, anxiety and stress-related disorders in breast cancer patients, we used the Swedish Cancer Register to identify all the women diagnosed with primary invasive or in-situ breast cancer at an age range of 20-80 between 2001 and 2009 (n=50,652). We linked the cohort to the Swedish Patient Register to obtain information on main diagnoses of mental disorders according to ICD-10 codes: depression (F32 and F33), anxiety (F40 and F41) and stress-related disorders (F43) (Figure 5.2). We also excluded patients who had a history of mental disorders [ICD-10: F0-F4; ICD-9: 290-300, 303-306, and 308-311; and ICD-8: 290-300, 303-305, 307, and 309] to ensure an analysis focusing on the new-onset cases, leaving 40,849 patients with invasive and 4402 patients with in-situ breast cancer in the cohort. Follow-up of this cohort started from the date of breast cancer diagnosis and ended on the date of the first mental disorder, death, emigration, a new cancer diagnosis or end of follow-up (December 31, 2010). Information on death and emigration was obtained through linking the cohort to the Swedish Cause of Death and Migration Register. We compared the risk of depression, anxiety and stress-related disorders in invasive and in-situ breast cancer patients to that in the general population by calculating SIRs, overall and stratified by time since cancer diagnosis. Standardization was performed according to the age, calendar period and region of residence of the individuals.

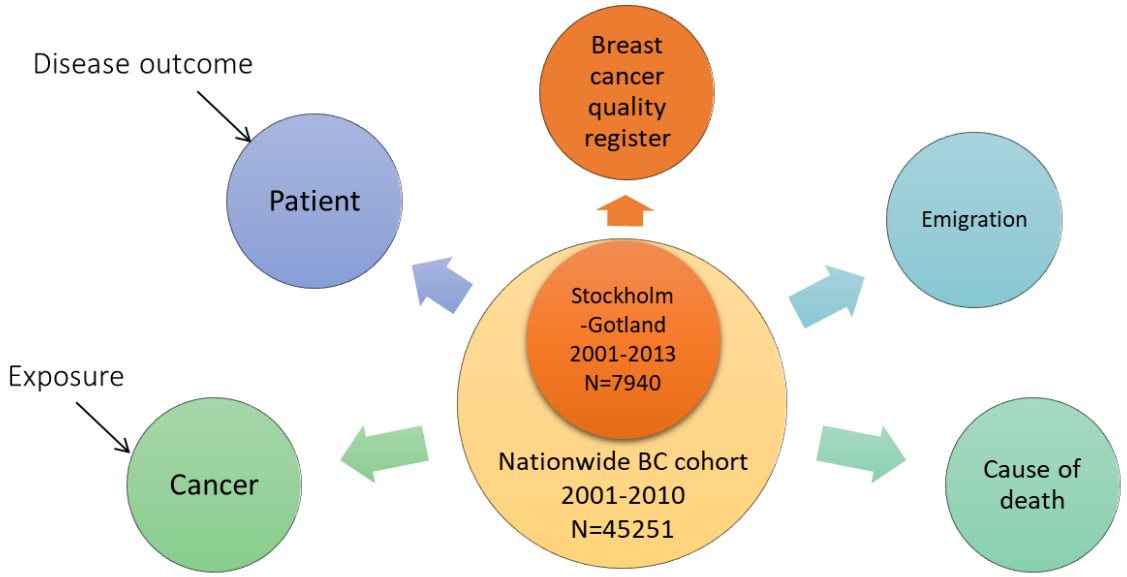

Figure 5.2 *Linkage of registers to obtain exposures and outcomes for mental disorder study*

To identify the risk factors for mental disorders in breast cancer patients, we constructed a Stockholm-Gotland regional cohort of invasive breast cancer patients (n=7,940, 2001-2008, at age 20-80), using the Libro-1 cohort. Patient, tumor and treatment characteristics of the breast cancer patients were extracted from the breast cancer quality register, including age at diagnosis, tumor size, histological grade, ER status, axillary lymph node involvement, distant metastasis, chemotherapy, endocrine therapy, radiotherapy and surgery. Information on comorbidities before breast cancer diagnosis was assessed by the CCI [107] using hospital discharge diagnoses from the Swedish Inpatient Register. Follow-up for this regional cohort was similar to that for the nationwide cohort, except for an extension of follow-up to December 31, 2013. The flexible parametric model was used to estimate the effect of these patient, tumor and treatment characteristics on the risk of mental disorders by calculating HRs. The proportional hazards assumption was tested using a likelihood ratio test, adding the time by covariate interaction term. In the case of non-proportionality, the time by covariate interaction term was kept in the model, and the effect of this covariate was reported at different time points since diagnosis. The underlying time scale for these analyses was time since diagnosis and a multivariable model including all these covariates was used.

5.3.3 Predictors of psoriasis in breast cancer patients

Since previous studies suggested a possible increased risk of psoriasis in breast cancer patients, we constructed a nationwide cohort of invasive breast cancer patients diagnosed between 2001 and 2011 to test this hypothesis (n=56,235). These patients were retrieved from the Swedish Cancer Register, and patients with a psoriasis diagnosis prior to cancer diagnosis were excluded. For risk comparison, we matched these patients with up to 5 non-cancer individuals from the general population according to age, county of residence and social-economic status (obtained from the 1990 national census). These reference individuals were free of cancer and psoriasis on the date of the matched patients' date of breast cancer diagnosis (the index date). In total,

we matched 280,852 reference individuals for these breast cancer patients. For both cohorts, the psoriasis diagnosis was obtained by linking the cohorts to the Swedish Patient Register and was identified by the main diagnosis using ICD codes: 706 (ICD-7), 696 (ICD-8 & 9) and L40 (ICD-10). The first psoriasis diagnosis was further sub-grouped into psoriasis vulgaris (L40.0), palmoplantar pustulosis (L40.3), arthropathic psoriasis (L40.5) and others (L40.1, L40.2, L40.4, L40.8, L40.9). Follow-up of both the cohorts started from the index date and ended on December 31, 2012, date of death, date of emigration, date of a secondary cancer diagnosis or date of psoriasis diagnosis, whichever came first. We used stratified Cox regression models to calculate HRs for psoriasis in breast cancer patients compared with the matched reference individuals, overall and by time since diagnosis.

To identify the risk factors for psoriasis in breast cancer patients, we again used the Libro-1 cohort as a regional breast cancer patient cohort, similar to the cohort for the mental disorder analysis in Study II, with the same follow-up scheme. In addition to the patient, tumor and treatment characteristics obtained from the breast cancer quality register, a subset of 4365 patients were alive in 2009 and consented to participate in the questionnaire survey and blood donation. Information on smoking status, BMI, alcohol consumption and physical activity prior to diagnosis was obtained from the questionnaire. Genotyping of the blood samples was performed and we selected 35 GWAS significant SNPs for psoriasis to construct a PRS [193]. The PRS calculation procedure was similar to the calculation for the breast cancer PRS in Study I, and the PRS was grouped into tertiles. An ordinary Cox regression model was used to test the association between cancer treatment and psoriasis risk, adjusting for age at cancer diagnosis, calendar period, and all the treatment characteristics. The effect of genetic predisposition and lifestyle factors were also tested in a model adjusting for age, calendar period and significant treatment risk factors in addition to the genetic and lifestyle factors. The proportional hazard assumption was tested using Schoenfeld residuals.

5.3.4 Disease trajectories and mortality in breast cancer patients

To study the disease trajectory (a sequential association of disease occurrences) and mortality among breast cancer patients, we identified 57,501 patients diagnosed with primary invasive breast cancer between 2001 and 2011, aged 20-80 years, from the Swedish Cancer Register (Figure 5.3). To compare the incidence and mortality of other diseases, we randomly sampled up to 10 women from the Swedish population as controls. The matching criteria included age, county of residence and social economic status. Each control individual was alive and free of breast cancer two months after the matched patient's cancer diagnosis (the index date), resulting in 564,703 matched controls. Disease incidence and mortality were coded according to the ICD codes. All diseases in this study were defined based on the 3-digit ICD-10 codes (A00 to N99) obtained from the primary and contributory diagnoses in Patient Register. We additionally combined several ICD codes considering their biological and clinical similarity (e.g., combining F40 and F41 for anxiety). Other cancer diagnoses were obtained from Swedish Cancer Register. Only those diseases with more than 100 cases among breast cancer patients

were included for analysis. The same range of diseases was tested for the mortality risk using only the underlying cause of mortality from Cause of Death Register.

Follow-up of the entire cohort started from the index date and ended on December 31st, 2012 (December 31st, 2011, for other cancer incidences), date of emigration, date of death, or date of the studied disease incidence (or mortality), whichever came first. Individuals with disease diagnosis before the index date were excluded when analyzing that specific disease. A phenome-wide association study (PheWAS) [194] was performed to assess disease incidence and mortality among breast cancer patients, compared with matched controls. PheWAS was previously used to reveal unknown associations between a specific gene and phenotypic features (e.g., electronic medical records) in a hypothesis-free approach. We extended this method to assess the association between breast cancer and a range of diseases after cancer diagnosis. For each disease, a matched-cohort analysis was performed using a stratified Cox regression model. The significant p-values were therefore identified according to Bonferroni correction.

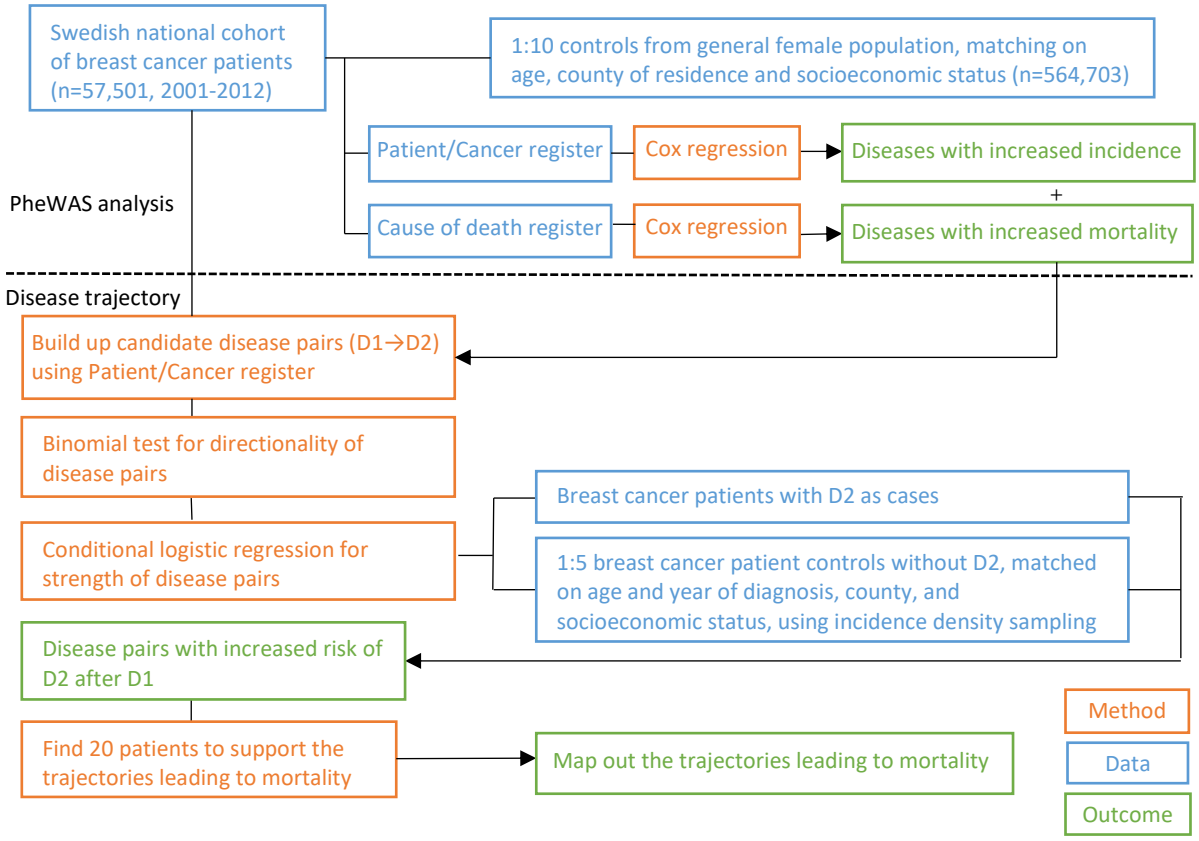

Figure 5.3 *Flow chart of the design and methods for disease trajectories and mortality analyses.*

Disease trajectories were studied using binomial tests to assess the sequential directionality for a pair of diseases (D1→D2) and ORs to measure the strength of the association [195]. Only diseases with significantly increased incidence after breast cancer diagnosis and disease pairs (D1→D2) with more than 50 cases of D2 after D1 were involved in the test. Patients with either D1 or D2 before the start of follow-up were excluded. We defined breast cancer patients with

D2 as cases and matched them with 5 patient controls using incidence density sampling. The matching criteria included age at breast cancer diagnosis, year of breast cancer diagnosis, county of residence and social economic status. The conditional logistic regression model was used to calculate the ORs, and the threshold of p-values was set according to Bonferroni correction. Significant disease pairs passing the directionality and association tests with OR>1 were combined into disease trajectories. Those disease pairs with more than 20 cases leading to mortality were valid and mapped separately according to the cause of mortality.

6 RESULTS

6.1 ASSOCIATION BETWEEN PREECLAMPSIA AND BREAST CANCER

In both the nationwide cohort of pregnant women and the KARMA cohort, approximately 5-6% of women had been diagnosed with preeclampsia, and older age at first birth, more parities, higher BMI and smoking were associated with preeclampsia in a univariate test. In the nationwide cohort, 27,626 women developed breast cancer during the follow-up, corresponding to an age-adjusted incidence rate of 1.5/1000 person-years, while in the KARMA cohort, 2496 women developed breast cancer at the end of follow-up, corresponding to an age-adjusted incidence rate of 3.0/1000 person-years.

We found a decreased risk of breast cancer after preeclampsia diagnosis in both the nationwide (IRR=0.90, 95% CI=0.85; 0.96) and KARMA cohort (IRR=0.75, 95% CI=0.61; 0.93). The reduced risk of breast cancer was even lower in women with two or more occurrences of preeclampsia (Table 6.1). However, the risks of ER+ and ER- breast cancer in the KARMA cohort were similar (IRR for ER+=0.80, 95% CI=0.61; 1.05 and IRR for ER-=0.76, 95% CI=0.36; 1.62), suggesting this association between preeclampsia and breast cancer did not differ according to ER status.

Table 6.1. *Association between preeclampsia and breast cancer among nationwide cohort and KARMA cohort*

Condition	No. of breast cancer cases	IRR (95%CI)	
		Model 1	Model 2
Nationwide cohort (N=1,337,934)			
Pre-eclampsia			
No	26447	1.00 (REF)	1.00 (REF)
Yes	1179	**0.88 (0.83;0.94)**	**0.90 (0.85;0.96)**
once	1082	**0.90 (0.84;0.95)**	**0.91 (0.86;0.97)**
multiple times	97	**0.76 (0.62;0.92)**	**0.81 (0.66;0.99)**
KARMA cohort (N= 55,044)			
Pre-eclampsia			
No	2410	1.00 (REF)	1.00 (REF)
Yes	86	**0.77 (0.62;0.95)**	**0.75 (0.61;0.93)***

Abbreviations: IRR=Incidence rate ratio; CI=Confidence interval. Model 1 adjusted for calendar period (10-year categories); Model 2 further adjusted for number of births, age at first birth, weight status categories, smoking status and education level. The underlying time scale was attained age.
* For Model 2 using the KARMA cohort, we additionally adjusted for alcohol use, age at menarche, body shape at age 18, physical activity at age 18, and irregular menstrual cycles in adult life.

To test whether inherited factors contributed to the inverse association between breast cancer and preeclampsia, we first investigated the familial aggregated association between these two diseases. In cancer-free sisters of the breast cancer patients in the nationwide cohort, the risk of preeclampsia was reduced by 11% (OR=0.89, 95% CI=0.83; 0.96). Another attempt to show genetic association in the KARMA cohort indicated that women with the highest 10% of PRS

for breast cancer were less likely to develop preeclampsia during their pregnancy (OR=0.56, 95% CI=0.36; 0.86. Figure 6.1).

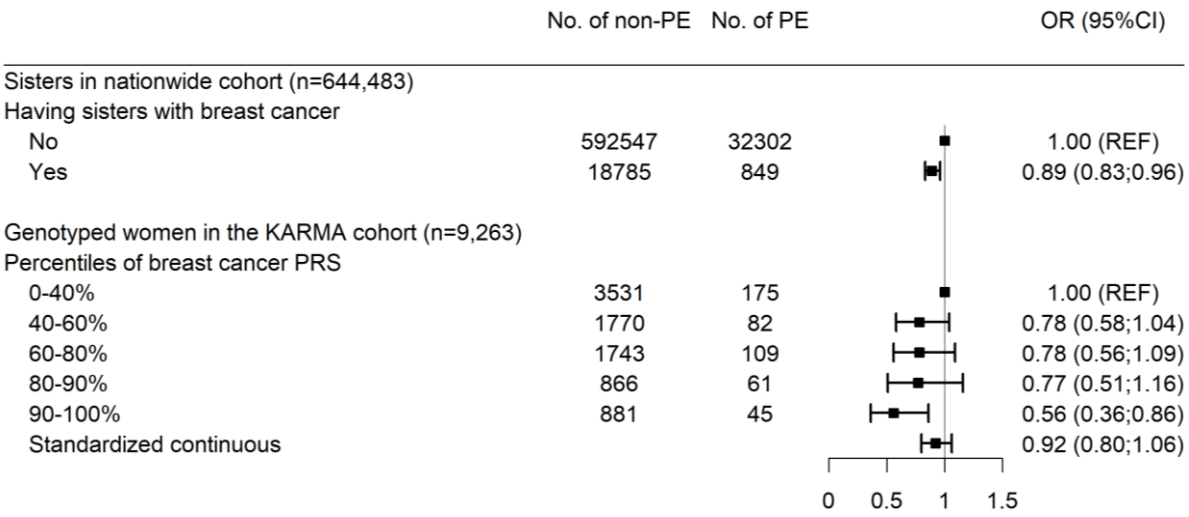

Figure 6.1. *Association between genetic predisposition to breast cancer and preeclampsia in women without breast cancer*

Abbreviations: No.=Number; PE=Preeclampsia; OR=Odds ratio; CI=Confidence interval; PRS=Polygenic risk score.

Considering mammographic density as a proxy of breast cancer, we also analyzed the association between preeclampsia and percentage mammographic density. In the 43,844 women available for density analysis, 2261 had a previous diagnosis of preeclampsia. These preeclampsia patients had a lower density (-2.04%, 95% CI=-2.65;-1.43) compared with women without preeclampsia in the multivariable adjusted model. When testing the familial aggregated association between preeclampsia and density among the 3500 women with available sister information in the cohort, sisters of the preeclampsia patients also had a lower mammographic density than women without a preeclampsia sister (-2.76%, 95% CI=-4.96; -0.56).

6.2 TIME-DEPENDENT RISK OF MENTAL DISORDERS IN BREAST CANCER PATIENTS

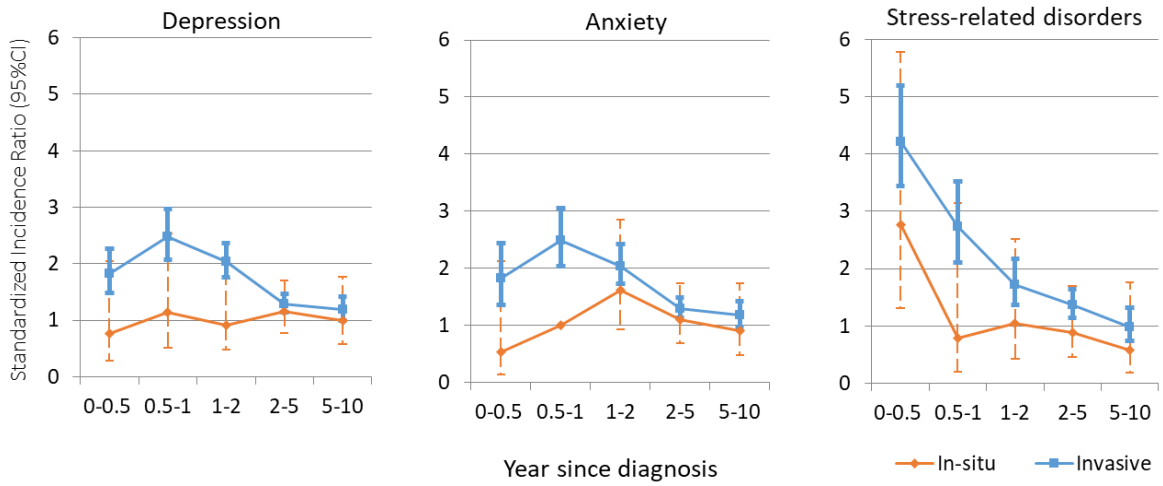

Figure 6.2 *Risk of depression, anxiety and stress-related disorders in the nationwide breast cancer cohort, compared with general female population*

In the nationwide cohort of breast cancer patients, the 5-year cumulative incidences of depression, anxiety and stress-related disorders in invasive cancer patients were 2.1, 1.5 and 1.1%, respectively, while those for in-situ patients were 1.4, 1.1 and 0.7%. Invasive cancer was associated with an increased risk of mental disorders compared with the risk in the general population, with similar SIRs for depression (SIR=1.57, 95% CI=1.46; 1.69), anxiety (SIR=1.55, 95% CI=1.43; 1.68) and stress-related disorders (SIR=1.77, 95% CI=1.60; 1.95). The increased risk of these mental disorders was highest in the first year after cancer diagnosis and remained increased for five years (Figure 6.2). However, the in-situ breast cancer patients did not experience an overall risk increase for mental disorders after cancer diagnosis, except for an increased risk of stress-related disorders during the first half year (SIR=2.76, 95% CI=1.31; 5.79).

Table 6.2 *Hazard ratios of depression, anxiety and stress-related disorders according to patient, tumor and treatment characteristics in the regional breast cancer cohort.*

	Total	Depression		Anxiety		Stress-related disorder	
	No.	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)
Patient characteristics							
Age at diagnosis							
23-44 years	1012	86	REF (1.00)	114	REF (1.00)	47	REF (1.00)
45-54 years	1913	115	0.77 (0.58; 1.03)	109	**0.53 (0.41; 0.69)**	64	0.70 (0.48; 1.03)
55-64 years	2629	80	**0.40 (0.30; 0.55)**	86	**0.32 (0.24; 0.43)**	26	**0.20 (0.12; 0.33)**
65-80 years	2386	54	**0.33 (0.23; 0.47)**	53	**0.22 (0.16; 0.32)**	10	**0.09 (0.04; 0.18)**
Comorbidities †							
No	6797	287	REF (1.00)	304	REF (1.00)	128	REF (1.00)
Yes	1143	48	**1.44 (1.05; 1.97)**	58	**1.67 (1.25; 2.23)**	19	1.49 (0.91; 2.44)
Tumor characteristics							
Size in mm							
<10	1867	71	REF (1.00)	69	REF (1.00)	37	REF (1.00)
10-20	3320	145	0.95 (0.70; 1.27)	149	0.94 (0.70; 1.26)	70	1.06 (0.70; 1.62)
>20	2348	104	0.83 (0.60; 1.16)	121	0.96 (0.69; 1.33)	35	0.79 (0.47; 1.33)
Histological grade†							
Low	899	26	REF (1.00)	26	REF (1.00)	22	REF (1.00)
Moderate	2390	111	1.52 (0.98; 2.34)	120	**1.65 (1.07; 2.54)**	44	0.77 (0.45; 1.29)
High	1476	91	1.53 (0.95; 2.47)	98	**1.73 (1.08; 2.77)**	36	0.77 (0.42; 1.42)
Lymph nodes							
Negative	4702	177	REF (1.00)	183	REF (1.00)	87	REF (1.00)
Positive	2750	149	**1.30 (1.00; 1.70)**	162	1.22 (0.95; 1.59)	54	1.20 (0.79; 1.80)
ER status							
Positive	5952	236	REF (1.00)	276	REF (1.00)	111	REF (1.00)
Negative	1271	73	1.33 (0.82; 2.15)	62	0.95 (0.58; 1.57)	28	0.76 (0.37; 1.58)
Treatment characteristics							
Endocrine therapy							
No	1346	75	REF (1.00)	64	REF (1.00)	33	REF (1.00)
Yes	6303	252	1.04 (0.65; 1.68)	283	1.22 (0.75; 2.00)	112	0.62 (0.31; 1.23)
Chemotherapy †							
No	4912	158	REF (1.00)	159	REF (1.00)	80	REF (1.00)
Yes	2720	167	1.16 (0.86; 1.55)	186	**1.36 (1.02; 1.81)**	64	0.82 (0.51; 1.29)
Radiotherapy							
No	1810	72	REF (1.00)	81	REF (1.00)	31	REF (1.00)
Yes	5839	254	1.11 (0.80; 1.53)	267	1.02 (0.75; 1.38)	114	0.91 (0.55; 1.50)
Surgery							
Partial mastectomy	4627	181	REF (1.00)	188	REF (1.00)	92	REF (1.00)
Total mastectomy	3048	147	1.18 (0.89; 1.57)	160	1.13 (0.86; 1.49)	53	0.83 (0.53; 1.31)

† Hazard ratios are adjusted for all variables listed in the table. The proportional hazards assumption was met for all variables, except for comorbidities, histological grade and chemotherapy. Abbreviations: Total No.=the total number of patients; No.=the number of observed cases.

We analyzed the risk profiles of mental disorders in the Libro-1 cohort and found the risk factors for depression and anxiety to be similar. Breast cancer patients at a younger age at diagnosis and with comorbid diseases were at increased risk of depression and anxiety. Considering the tumor characteristics, we observed an increased risk of depression in patients with lymph node-positive disease and increased risk of anxiety in patients with high histological grade tumors (Table 6.2). The risk of anxiety was also increased in breast cancer patients treated with chemotherapy. However, in general, stress-related disorders were not associated with these tumor and treatment factors, except for an increased risk with younger age at diagnosis.

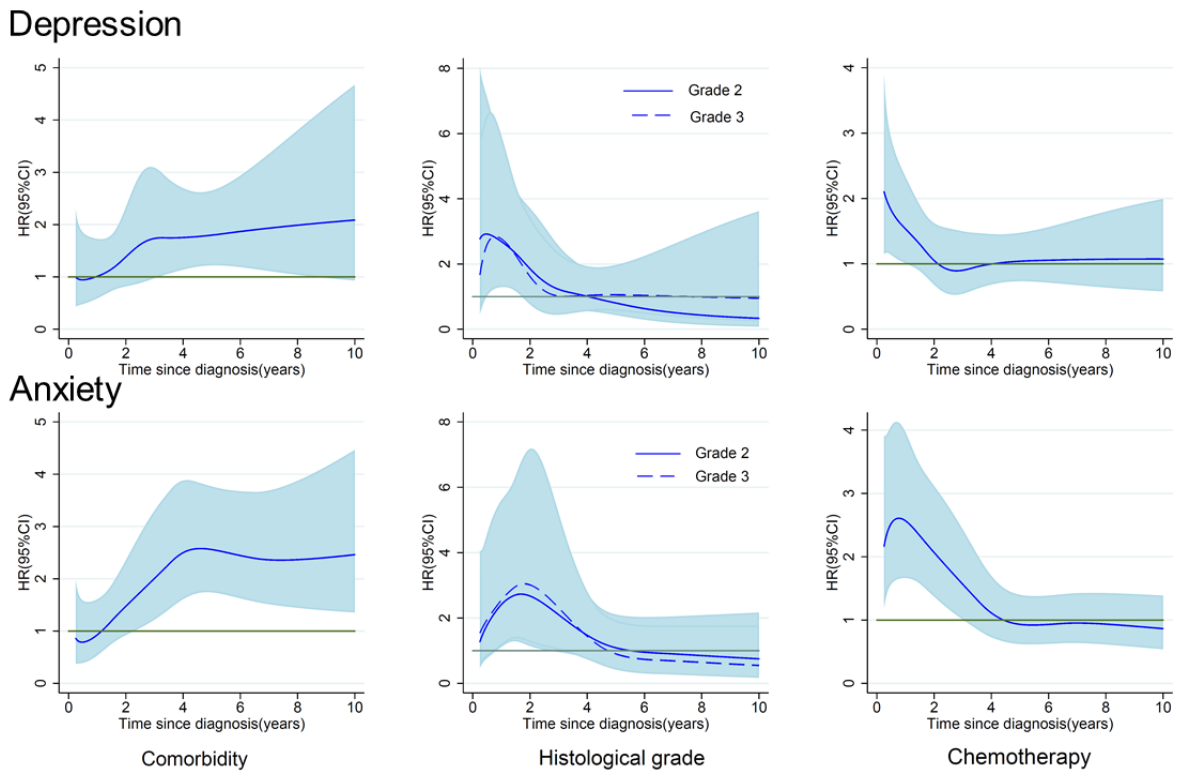

Figure 6.3 *Time-dependent effect of comorbidity, histological grade and chemotherapy on depression and anxiety in the regional breast cancer cohort.*

When testing the proportional hazard assumption for the risk factors, the effect of comorbidity, histological grade and chemotherapy was not constant over time. Comorbidity was associated with an increased risk of depression and anxiety 3 years after cancer diagnosis, while the effect of histological grade and chemotherapy was restricted within the first two years after cancer diagnosis (Figure 6.3).

6.3 PREDICTORS OF PSORIASIS IN BREAST CANCER PATIENTS

In the nationwide cohort of breast cancer patients, 599 patients were diagnosed with psoriasis, corresponding to an incidence rate of 1.9/1000 person-years and a 5-year cumulative incidence of 1%. In the matched general population, the incidence rate of psoriasis was 1.7/1000 person-years, with a 5-year cumulative incidence of 0.8%. Among the patients, the most common

psoriasis subtype was psoriasis vulgaris (n=298), followed by palmoplantar pustulosis and arthropathic psoriasis.

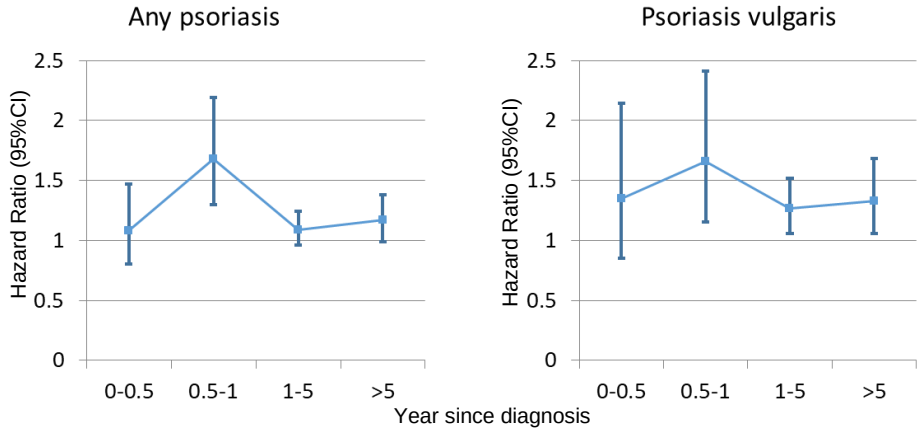

Figure 6.4 *Risk of any psoriasis and psoriasis vulgaris in the nationwide breast cancer cohort compared with matched individuals.*

Compared with the matched individuals, breast cancer patients had a 17% increased risk of psoriasis (HR=1.17, 95% CI=1.07; 1.28), and this risk increase was mainly caused by psoriasis vulgaris, with an HR of 1.33 (95% CI=1.17; 1.52). The risk of psoriasis was highest during the second half year after cancer diagnosis, and psoriasis vulgaris has a long-term increased risk for up to 12 years.

Table 6.3 *Hazard ratios of psoriasis according to treatment, genetic and lifestyle factors in the regional breast cancer cohort.*

	Total No.	No. of Cases	HR (95% CI)
Treatment factors			
Endocrine therapy			
No	1,533	27	1.00 (REF)
Yes	7,100	121	0.80 (0.52; 1.24)
Chemotherapy			
No	5,544	102	1.00 (REF)
Yes	3,070	46	0.70 (0.47; 1.04)
Radiotherapy			
No	2,061	23	1.00 (REF)
Yes	6,574	125	**2.44 (1.44; 4.12)**
Surgery			
Lumpectomy	5,203	94	1.00 (REF)
Mastectomy	3,459	55	**1.54 (1.03; 2.31)**
Genetic and lifestyle factors §			
Polygenic risk score (PRS)			
Tertile 1	1,440	13	1.00 (REF)
Tertile 2	1,442	36	**2.83 (1.50; 5.34)**
Tertile 3	1,483	40	**2.98 (1.59; 5.58)**
BMI			
<25 kg/m2	2,331	40	1.00 (REF)
25-30 kg/m2	1,434	28	1.15 (0.71; 1.87)
>30 kg/m2	536	19	**2.10 (1.20; 3.68)**
Regular smoker (cigarette smoking >1 year)			
No	1,773	26	1.00 (REF)
Yes	2,546	62	**1.59 (1.00; 2.52)**
Alcohol consumption			
No	104	2	1.00 (REF)
Yes	2,861	58	1.12 (0.27; 4.70)

§Analyses were based on a subset of the cohort with information on genetic and lifestyle factors. Abbreviations: CI=Confidence interval. Total No.=Number of breast cancer patients. No. of Cases=Number of psoriasis cases. HR=Hazard ratio.

In breast cancer patients, radiotherapy was associated with an increased risk of psoriasis after adjusting for other treatment factors (HR=2.44, 95% CI=1.44; 4.12). In addition to radiotherapy, patients who underwent mastectomy also had an increased risk of psoriasis compared with patients with lumpectomy (HR=1.54, 95% CI=1.03; 2.31). Apart from these treatment factors, a significant risk increase for psoriasis was also observed in patients with a high genetic predisposition to psoriasis (HR=2.94, 95% CI=1.57; 5.49), with regular cigarette smoking (HR=1.59, 95% CI=1.00; 2.52), and with a BMI larger than 30 kg/m^2 at diagnosis (HR=2.10, 95% CI=1.20; 3.68).

6.4 DISEASE TRAJECTORIES AND MORTALITY IN BREAST CANCER PATIENTS

Among all the diseases in breast cancer patients, we selected 225 diseases with more than 100 cases after breast cancer diagnosis, and 45 of them had a significantly increased risk after breast cancer diagnosis, with number of cases>300, HR>1.5 and p<0.0002 compared with the matched controls. Diseases with the highest HRs included lymphedema, radiodermatitis and neutropenia, corresponding to the side effects of treatment (Figure 6.5). We also identified several side effects of treatment not yet reported, such as the risk of larynx disease (HR=1.86, 95% CI=1.67; 2.07) and several gynecological disorders.

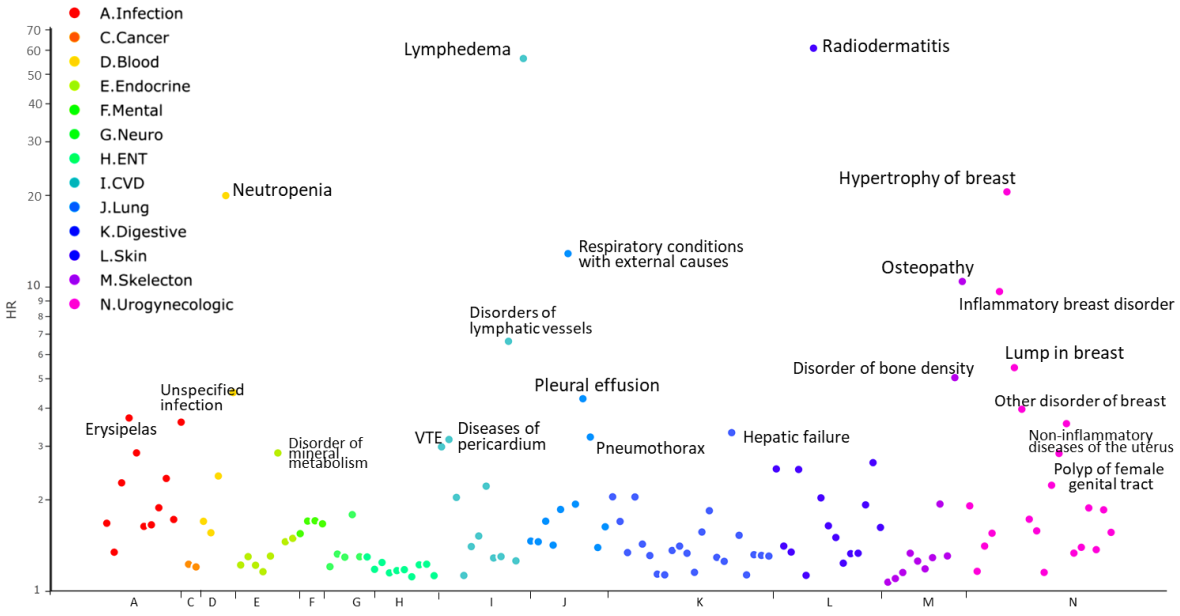

Figure 6.5 *Significant HRs of diseases among breast cancer patients, compared with matched individuals*
All risk increases are statistically significant after consideration of the multiple testing issue (p<0.0002). The Y axis is in the log scale. The X axis is the disease categories according to ICD codes A-N. Details of the case numbers, hazard ratios and confidence intervals are listed in Supplementary Table 1 of Study IV.

Compared with the matched controls, breast cancer patients had a 6% increased mortality due to other diseases. This increased mortality was mainly contributed by other solid cancers (HR=1.16, 95% CI=1.08; 1.24). However, all other causes of mortality were not significant after Bonferroni correction.

We combined the significant diseases in the aforementioned analyses into pairs and tested their directionality and strength. Finally, 15 disease pairs passed the tests, with an increased risk of D2 after D1 diagnosis ($p<0.0013$). Many of the disease trajectories were related to the side effects of chemotherapy and hormone therapy, such as neutropenia, anxiety, osteoporosis and menopausal disorders (Figure 6.6A). These disease pairs were grouped into trajectories for breast cancer mortality and other cancer mortality, supported by more than 20 patients in the cohort. Breast cancer mortality was associated with the previous diagnosis of neutropenia, dorsalgia, and anxiety (Figure 6.6B), while menopausal disorder was a diagnostic indicator for other cancers (Figure 6.6C).

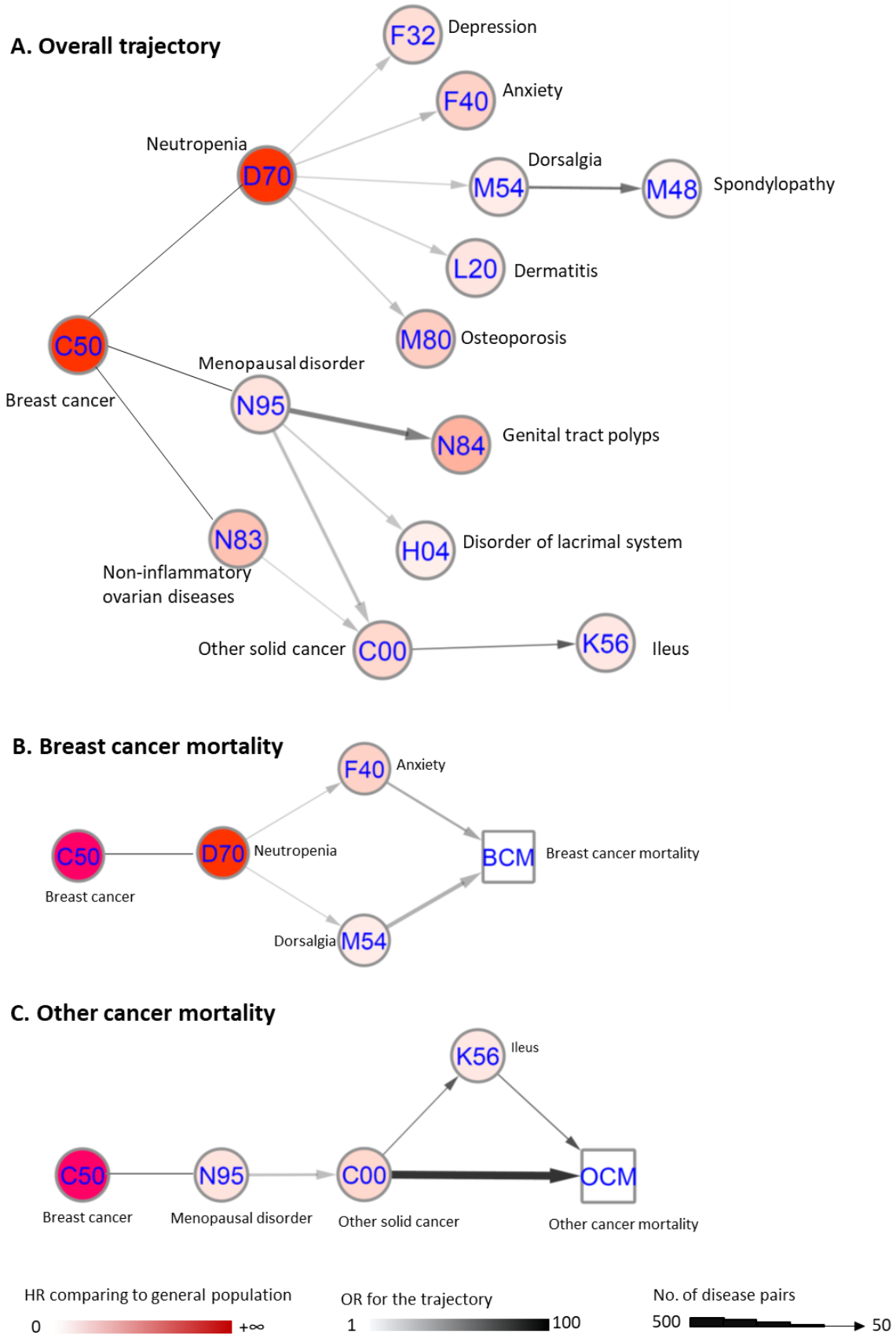

Figure 6.6 *Trajectories of other diseases in breast cancer patients*
The width of the arrows corresponds with the number of disease pairs among breast cancer patients. The color of the arrows indicates the OR of the sequential association between the two diseases. The color of the nodes represents the HR of this disease among the breast cancer patients, compared to the matched individuals. The codes in the nodes are the combined ICD-10 codes for the diseases.

7 DISCUSSION

7.1 METHODOLOGICAL CONSIDERATIONS

One of the main objectives of an epidemiological study is to discover the effect of exposure on outcome occurrence. This approach to measure causal effect usually starts from a valid and precise estimation of the statistical association between the exposure and outcome. One major goal in achieving this valid association is to avoid systemic error or bias. In addition, chance finding and external validity (generalizability) should also be considered.

7.1.1 Strengths of the studies

In this thesis, we used the Swedish population and health registers to investigate the associations between different diseases and breast cancer, which is the real world evidence of disease associations and reflects the clinical practice in Sweden. These registers have a nationwide coverage with complete follow-ups and eliminate the related biases for cohort studies. The long history of the registers also provide the possibility to study long-term associations between diseases and breast cancer.

Register-based studies are sometimes criticized for less information on covariates. However, in our studies, abundant clinical characteristics on tumor and treatment were retrieved through linkage to the breast cancer quality register in Study II and III. Lifestyle and genetic information is also available in the questionnaires and blood samples in Study III. In addition, in Study I, we used the questionnaire-based data and mammograms from KARMA cohort to confirm our findings in the registers.

Another strength of our studies is the statistical methods we used. In study II, we used the flexible parametric models to capture the time dependent effect of the exposures. In study IV the PheWAS and matched cohort design made it possible to investigate a broad spectrum of diseases among breast cancer patients. Furthermore, the disease trajectory analysis allowed us to reveal the sequential pattern of disease occurrences and identify key diagnostic indicators for poor survival.

7.1.2 Selection bias

Selection bias is a systemic error that distorts a valid estimation of the association, in which the association in the analyzed population is different from the source population. Selection bias is usually introduced during the participant enrollment procedure and follow-up. In the register-based studies, completeness of the enrollment and follow-up is less of a problem. However, we still need to consider the impact of right censoring in the cohorts.

When studying other diseases in breast cancer patients, right censoring is usually used when the patients are dead. However, since breast cancer patients are more likely to die from diseases than the controls, this type of censoring is informative when the occurrence of the disease is related to censoring (patients cannot develop other diseases after death). Informative censoring will result in a shorter follow-up for the breast cancer patients compared with the controls.

However, currently, the survival of breast cancer patients is quite good, and thus, this informative censoring for mortality would not greatly influence our results. One method to address informative censoring is the competing risk model, which allows the follow-up time to be continued after a competing event (such as death). In study III, we performed a sensitivity analysis using a competing risk model to calculate the cumulative incidence rate. The estimates were quite similar to those obtained from the Kaplan-Meier method, confirming that selection bias due to informative censoring of death is negligible.

In the questionnaire-based data analysis in this thesis, we need to consider another type of selection bias: survival bias. When we select a subset of the population for study, such as the KARMA cohort, we actually selected women who were still alive in 2011. The women who died before 2011 were excluded from the cohort, making the KARMA cohort a "healthier" population. Since those excluded women likely died from breast cancer, this type of survival bias could attenuate the effect of risk factors on breast cancer risk (as the women at highest risk were already dead). In Study I, we therefore speculated that survival bias in the KARMA cohort would only attenuate the protective effect of preeclampsia and not influence our conclusion. In addition to survival bias, the KARMA cohort is actually a collection of health-oriented women with a higher level of education and family history, which is supported by a higher incidence of breast cancer in the KARMA cohort than in the nationwide cohort.

7.1.3 Information bias

Information bias occurs when the measurement or classification of the exposure, outcome or covariate is inaccurate. In disease outcome analysis, the main information bias is misclassification of the disease outcomes. If the misclassification is non-differential between the cases and controls or exposed and un-exposed groups, it will usually attenuate the effect and result in a null association. However, if the misclassification is differential between groups, it could either overestimate or underestimate the effect.

In this thesis, we defined other diseases associated with breast cancer by ICD codes, which might bias the results if misclassification has occurred. Generally, the validity of ICD codes used for disease identification in the Swedish Inpatient Register is approximately 85-95% [180], while for specific diseases, the validity for preeclampsia, depression and psoriasis is estimated to be 93%, 88% and 81%, respectively [196-199]. Therefore, it is possible that we misclassified these diagnoses. For the majority of the outcomes, we believe this misclassification in the Patient Register is non-differential between breast cancer patients and the healthy population. However, for psoriasis, the possibility of misclassifying it as radiodermatitis could be higher in breast cancer patients because radiodermatitis is a known side effect of radiotherapy, and the two conditions share several common symptoms in mild cases (such as erythema on the skin) [200]. Nevertheless, the severe symptoms of psoriasis are quite different from those of radiodermatitis and do not disappear after a couple of weeks. As the Patient Register mainly contains severe cases of psoriasis, this potential misclassification would not have influenced our results.

Another major type of misclassification comes from the medical surveillance of breast cancer patients. Because of the increased medical surveillance, as well as the cautiousness from both the patients and clinicians, breast cancer patients may receive a diagnosis that in healthy women would continue to be undiagnosed. Hence, misclassifying the cases into non-cases would be more frequent in the healthy population and consequently reduce the incidence of disease. Some observed increased risk of diseases shortly after breast cancer diagnosis could be overestimated because of this medical surveillance bias. However, those diseases with a considerably high HR or long-term increased risk should not be purely explained by surveillance bias.

For questionnaire-based data, misclassification may also occur when the participants have recall bias. When breast cancer patients recall their previous exposure to risk factors, they try their best to recall the memory. However, healthy women might not clearly remember the exposure, and thus, the exposure is underreported in these women. In the case of the KARMA cohort in Study I, preeclampsia history was defined by questionnaires, and breast cancer patients are likely to clearly remember their previous diagnosis of preeclampsia. As a result, we might underestimate the risk of breast cancer in nonpreeclamptic women. Considering the protective effect of preeclampsia on breast cancer risk, this recall bias could only have attenuated the association.

7.1.4 Confounding

Confounding refers to an association between exposure and outcome caused or influenced by a third factor. The confounders should be the risk factors (or ancestor) for both the exposure and disease outcome, which are not in the pathway from exposure to outcomes. Confounding is an important issue in observational studies when we want to examine the causal effect of exposure. Luckily, there are several approaches to exclude the effect of confounders at both the study design and statistical analysis stages.

At the stage of study design, confounders can be controlled by matching, randomization and restricting the enrollment criteria. A typical example of matching is the matched cohort design used in studies III and IV. In both of the studies, we matched non-cancer individuals to breast cancer patients according to age, county of residence and social-economic status. This was performed to ensure the distributions of these confounders were the same among the breast cancer patients and the controls, thus excluding the potential confounding effect. Another benefit of a matched cohort design is that we can use the controls to study many other diseases in breast cancer patients, as well as increase the computational efficiency.

At the stage of statistical analysis, we can use standardization, multivariable regression models and stratification to address confounders. In Study II, we used a SIR to control for the confounding effect of age, calendar period and residence place when we studied the risk of mental disorders in breast cancer patients. In Studies I-III, we always used a multivariable model to deal with the effect of potential confounders. For example, in Study I, after adjusting for various lifestyle and reproductive risk factors, we still observed a significant association

between preeclampsia and breast cancer, suggesting that these potential confounders could not explain the observed association. We then hypothesized that inherited factors may contribute to this association. When studying the effect of treatment on mental disorders in Study II, tumor characteristics were always considered as confounders, since the selection of treatment depends on tumor characteristics, while the severity of tumor status may also influence the risk of these mental disorders.

7.1.5 Chance finding and multiple testing

In hypothesis testing, we usually use the p-value to measure the significance of the association. The p-value is the probability that the null hypothesis of no association between the exposure and outcome is true. The lower the p-value, the less the probability that we obtain the same conclusion according to the null hypothesis of no association. The threshold of the p-value is often set at 0.05, allowing a 5% probability of agreement with the null hypothesis, and thus rejecting this hypothesis. However, in practice, it is still possible to have a subset of the population that incorrectly rejects the true null hypothesis by chance. We acknowledged this possibility of chance finding when testing the association between preeclampsia and the PRS for breast cancer in Study I since the sample size was limited and the association was weak. However, in the nationwide cohort, we found the association between genetic predisposition to breast cancer and preeclampsia, and there was a trend of greater risk reduction with a higher PRS. Both of these results argued against a chance finding for this association.

The 5% cut-off for a p-value is also problematic when a large amount of non-hypothesis testing has been conducted, simply because the possibility to observe a rare event increases. For example, if we perform non-hypothesis testing 100 times, we might find 5 false positive significant results just by chance. One method to correct this false positivity is Bonferroni correction, which sets the threshold by dividing 0.05 with the number of tested times. In the PheWAS analysis in Study IV, we set the threshold for p-value significance by using Bonferroni correction and solved the multiple testing problem.

7.1.6 Generalizability

In addition to bias, generalizability (also known as the external validity) is also important to evaluate the validity of a study. Generalizability evaluates the extent that the conclusion generated from one specific study would be true for the entire population or in other situations. Some studies may have quite a good design and restrict enrollment criteria, but the conclusion can be used only in that specific population (e.g., some clinical trials). In the population-based studies in this thesis, studies from Danish and Norwegian populations also reported a similar reduced risk of breast cancer in preeclampsia patients [106, 112], as well as a similar level of mental disorder risk in breast cancer patients [138, 201], supporting the generalizability of these results within Nordic countries.

However, studies in Asian populations did not find the inverse association between preeclampsia and breast cancer [202, 203]. Genetic heterogeneity could be an explanation for this difference since we have found that inherited factors contribute to this inverse association.

Therefore, caution should be taken in generalizing the findings in this thesis to the Asian and African population.

7.2 INTERPRETATION OF THE RESULTS

7.2.1 Association between preeclampsia and breast cancer

In our study, we found an inverse association between preeclampsia and a history of breast cancer in a sister, as well as an association between preeclampsia and the PRS for breast cancer, suggesting that inherited factors contribute to the inverse association between preeclampsia and breast cancer. Both preeclampsia and breast cancer have a heritability of approximately 30% [6, 204], and some of the genes related to preeclampsia risk overlap with breast cancer susceptibility genes. However, only FLT1 has been validated in a recent GWAS for preeclampsia using fetal samples [124]. This is also the reason that we used the PRS for breast cancer to predict the risk of preeclampsia in pregnant women and not vice versa.

In addition to the association between preeclampsia and breast cancer, we also found an inverse association between mammographic density, a proxy for breast cancer, and a history of preeclampsia in a woman or in her sisters. Therefore, we believe that the inverse association between breast cancer and preeclampsia was partly mediated through mammographic density. After investigating the genes related to breast cancer risk, higher mammographic density, and preeclampsia, we found the risk genes IGF1 to be shared by these three traits. Indeed, a lower level of IGF-1 was observed in preeclampsia patients [119], while a higher level of IGF-1 has been found in breast cancer patients and women with high mammographic density [120, 121]. Further genetic studies for preeclampsia are needed to reveal the exact genetic pathways shared by preeclampsia and breast cancer. Understanding the mechanism for this inverse association might help to improve the risk prediction for both diseases.

7.2.2 Time-dependent risk of mental disorders in breast cancer patients

Our study showed a long-term increased risk of mental disorders in invasive breast cancer patients, whereas only a short-term increased risk of stress-related disorders was observed with in-situ breast cancer patients. This could be explained by the direct psychological reaction of patients to the diagnosis of cancer. In-situ cancer is usually considered a less life-threatening disease, and patients are treated with surgery and radiotherapy, without suffering from the severe side effects of chemotherapy and endocrine therapy. Therefore, in-situ cancer patients generally have a less severe psychosocial reaction.

We found and confirmed several risk factors for depression and anxiety in breast cancer patients, such as younger age at diagnosis, comorbid disease, high tumor grade and chemotherapy. Breast cancer patients diagnosed at a younger age might be influenced by the change in work ability, sexual life, motherhood and fertility [130, 205-208], which are less of a concern in older patients. In addition, breast cancer patients with other comorbid diseases have an additional risk for mortality [101, 209]. These patients might worry more about their future survival and consequently develop mental disorders.

The effect of tumor grade and chemotherapy on depression and anxiety risk was limited to within two years after cancer diagnosis. Patients diagnosed with a high-grade tumor might consider it a more severe disease, and experience a stronger psychological reaction. Chemotherapy is associated with several side effects, such as alopecia, nausea and vomiting [142, 143], which may further increase the risk of depression and anxiety. Therefore, the effect of tumor grade and chemotherapy is expected to diminish once the diagnosis is set and the treatment is completed.

7.2.3 Predictors of psoriasis in breast cancer patients

The psychological reaction to the cancer diagnosis can not only increase the risk of mental disorders in breast cancer patients but can also increase the risk of certain somatic symptoms, such as psoriasis. Severe stressful life events have been shown to increase the risk of psoriasis [152], and in our study, we found a slightly increased risk of psoriasis among breast cancer patients. The increased risk of psoriasis was mainly present during the first year after cancer diagnosis, confirming its association with the diagnosis event or treatment decision.

Another plausible explanation for the risk of psoriasis was the dermatological side effects of breast cancer treatment. Skin trauma is one of the major triggers for psoriasis onset [150]. We found a significantly increased risk of psoriasis in breast cancer patients treated with radiotherapy, suggesting ionized radiation as a cause of skin trauma to trigger psoriasis. We also identified that patients treated with mastectomy had an increased risk of psoriasis. Since patients that underwent a mastectomy usually have delayed wound healing [210] and an abnormal wound healing process is involved in the pathogenesis of psoriasis [151], we believe prolonged wound healing could partly explain this increased risk of psoriasis.

7.2.4 Disease trajectories and mortality in breast cancer patients

Many of the diseases with an increased risk after breast cancer diagnosis were associated with treatment side effects. For example, diseases with the highest HRs in the breast cancer patients included lymphedema, radiodermatitis and neutropenia, which are known side effects of surgery, radiotherapy and chemotherapy [75, 83, 211]. In addition, we also identified several diseases that had not been previously reported in breast cancer patients, such as larynx diseases and several gynecological disorders. Since larynx diseases are associated with exogenous hormones (e.g., oral contraceptives) [212], this increased risk of larynx diseases might be the side effect of hormonal therapy.

Among all the other diseases with an increased risk after breast cancer diagnosis, other cancers were the only cause of mortality with an increased mortality rate compared with the matched controls. In the further trajectory analysis for diseases leading to other cancer mortality, we found the increased incidence of menopausal disorders to be associated with the risk of other cancers. Menopausal disorder is a common side effect of hormonal therapy. One important symptom of menopausal disorder, uterine bleeding, is a known predictor of endometrial cancer [213]. Since tamoxifen increases the risk of endometrial cancer [50], a genital tract examination should be recommended during the follow-ups for patients treated with tamoxifen.

In the disease trajectories leading to breast cancer mortality, we found the diagnosis of neutropenia, dorsalgia and anxiety to be associated with breast cancer mortality. Since neutropenia is a side effect of chemotherapy and chemotherapy is usually given to patients with advanced tumors, it is reasonable that neutropenia is associated with breast cancer mortality. Dorsalgia has long been considered a sign of bone metastasis [214], while the risk of anxiety is increased after chemotherapy and associated with advanced tumor characteristics [215]. Indeed, all these three diseases are signs of aggressive tumor characteristics in breast cancer and consequently associated with a worse prognosis. Our findings further suggest that clinicians (especially general practitioners) and patients should pay special attention to dorsalgia symptoms, considering its association with bone metastasis.

8 CONCLUSION

In this thesis, we provided a broad picture of diseases associated with breast cancer. We selected preeclampsia before breast cancer diagnosis to test the inverse association between these two hormone-related diseases and to examine inherited factors contributing to this association. We also studied the risk of mental disorders and psoriasis after breast cancer diagnosis, with a focus on the treatment characteristics predicting risk of these diseases. Finally, in the attempt to describe a wide spectrum of diseases after breast cancer diagnosis, we detected some sequential associations between the incidence and mortality of different diseases. After the aforementioned studies, a few conclusions might be noted:

- Women with a disease history of preeclampsia have a lower risk of breast cancer and a lower mammographic density. This inverse association between preeclampsia and breast cancer can be partly explained by the shared genetic variants and suggests history of preeclampsia to be involved in the assessment for breast cancer risk.

- Invasive breast cancer diagnosis is a stressful life event and consequently influences both mental and somatic health, such as the increased risk of depression, anxiety, and psoriasis. In-situ cancer diagnosis is a less severe life event and only increases risk of stress-related disorders in a short-term.

- Younger age at cancer diagnosis, tumor grade, chemotherapy and comorbidity are independent risk factors for depression and anxiety in breast cancer patients, with tumor grade and chemotherapy conferring to short term risk increase, while comorbidity for long term risk increase.

- Many of the diseases with an increased risk after breast cancer diangosis are associated with treatments for breast cancer. For example, the risk of depression and anxiety is increased after chemotherapy, and radiotherapy and mastectomy may influence patients' risk of psoriasis. A multidisciplinary post cancer care is therefore needed to deal with these side effects of treatments.

- Despite the increased risk of many non-communicable diseases, other solid cancer is the only disease with a more lethal feature when diagnosed in breast cancer patients as compared to the general population, and its risk could be predicted by the occurrence of menopausal disorders. We therefore recommend closer surveillance for other solid cancer in breast cancer patients.

9 FUTURE PERSPECTIVES

As majority of the breast cancer cases are hormone related, many studies have already tested several diseases to be predictors of breast cancer incidence, such as benign breast disorders and preeclampsia. Although our study and some other studies have confirmed the inverse association between breast cancer and preeclampsia, and genetic variants may contribute to this inverse association, the exact genetic variants shared by both diseases are still unknown. Therefore, large scale GWAS for preeclampsia is needed to reveal the genetic background of preeclampsia and to combine with the GWAS results from breast cancer studies to identify the pleiotropic genes.

In addition, current studies usually hypothesized hormone-related diseases and autoimmune diseases to be associated with breast cancer risk. However, some other diseases might also predict breast cancer risk. For this reason, a hypothesis generating study is needed to screen across all the diseases before breast cancer diagnosis to identify new indicators. Considering the heterogeneity among different molecular subtypes of breast cancer, the associations between diseases and breast cancer risk might be different according to subtypes, which needs further tests.

Previously, several interventions were reported to be effective in controlling short-term depression and anxiety among cancer patients [216]. Considering that the highest risk of mental disorders occurs in the first year after breast cancer diagnosis, as well as the limited effect of tumor characteristics and chemotherapy within two years, these interventions are strongly recommended for younger patients with advanced tumor characteristics scheduled for chemotherapy. Future clinical trials could be initiated to evaluate these psychosocial and pharmacologic interventions in this targeted group of breast cancer patients.

We found genetic predisposition to psoriasis can predict the risk of psoriasis in breast cancer patients. Together with evidence on the genetic prediction of other diseases in breast cancer patients [217], we believe that the PRS could be used to predict side effects of treatment with an inheritable feature. In order to validate the role of PRS in treatment side effects prediction, we should first of all find out those side effects (or diseases) strongly influenced by family history, and with known GWAS results. A further attempt could be to develop a package of SNPs (in combination with other biomarkers) as a toolkit to predict all the severe side effects of breast cancer treatments and provide clinical awareness for treatment decision.

We have identified several communicable and non-communicable diseases with an increased risk after breast cancer diagnosis. Since many of the diseases are related to cancer treatment and treatment patterns may vary in different health care settings, replication of our results in US and Asian populations is needed before initiating interventions for these diseases. In addition, validation of the disease trajectories after breast cancer diagnosis should be performed outside the Nordic countries.

The improvement of cancer treatments has already turned breast cancer from a fatal disease to a chronic disease, which is frequently comorbid with other disorders. Therefore, long term survival of the breast cancer patients might also be influenced by comorbidities. Nevertheless, the current prognostic prediction models mainly focus on five or ten years survival and depend on only tumor characteristics [218]. Development and validation of a new comorbidity index focusing on long-term survival in breast cancer patients are needed to subdivide the patients and provide personalized follow-ups and interventions accordingly.

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11 REFERENCES

1. Global Burden of Disease Cancer Collaboration: **Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: A systematic analysis for the global burden of disease study**. *JAMA Oncology* 2018.
2. Gómez-Raposo C, Zambrana Tévar F, Sereno Moyano M, López Gómez M, Casado E: **Male breast cancer**. *Cancer treatment reviews* 2010, **36**(6):451-457.
3. **GBD Compare Data Visualization** [http://vizhub.healthdata.org/gbd-compare]
4. Cancerfonden S: **Cancer i siffror 2018**. In. Stockholm: Socialstyrelsen & Cancerfonden; 2018.
5. **NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.3 (08.07.2016)** [http://www.ancr.nu]
6. Möller S, Mucci LA, Harris JR, Scheike T, Holst K, Halekoh U, Adami H-O, Czene K, Christensen K, Holm NV *et al*: **The Heritability of Breast Cancer among Women in the Nordic Twin Study of Cancer**. *Cancer Epidemiology Biomarkers and Prevention* 2016, **25**(1):145-150.
7. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA: **Family history and the risk of breast cancer: a systematic review and meta-analysis**. *Int J Cancer* 1997, **71**(5):800-809.
8. Collaborative Group on Hormonal Factors in Breast Cancer: **Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease**. *The Lancet* 2001, **358**(9291):1389-1399.
9. Stratton MR, Rahman N: **The emerging landscape of breast cancer susceptibility**. *Nature genetics* 2008, **40**(1):17-22.
10. Michailidou K, Lindstrom S, Dennis J, Beesley J, Hui S, Kar S, Lemacon A, Soucy P, Glubb D, Rostamianfar A *et al*: **Association analysis identifies 65 new breast cancer risk loci**. *Nature* 2017, **551**(7678):92-94.
11. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT *et al*: **Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations**. *Nature genetics* 2018, **50**(9):1219-1224.
12. Darabi H, Czene K, Zhao W, Liu J, Hall P, Humphreys K: **Breast cancer risk prediction and individualised screening based on common genetic variation and breast density measurement**. *Breast cancer research : BCR* 2012, **14**(1):R25.
13. Allred DC, Brown P, Medina D: **The origins of estrogen receptor alpha-positive and estrogen receptor alpha-negative human breast cancer**. *Breast Cancer Research* 2004, **6**(6):240-245.
14. Fuhrman BJ, Schairer C, Gail MH, Boyd-Morin J, Xu X, Sue LY, Buys SS, Isaacs C, Keefer LK, Veenstra TD *et al*: **Estrogen metabolism and risk of breast cancer in postmenopausal women**. *J Natl Cancer Inst* 2012, **104**(4):326-339.
15. Missmer SA, Eliassen AH, Barbieri RL, Hankinson SE: **Endogenous estrogen, androgen, and progesterone concentrations and breast cancer risk among postmenopausal women**. *J Natl Cancer Inst* 2004, **96**(24):1856-1865.
16. Endogenous H, Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarte A, Berrino F, Krogh V *et al*: **Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies**. *Lancet Oncol* 2013, **14**(10):1009-1019.

17. Collaborative Group on Hormonal Factors in Breast Cancer: **Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies**. *Lancet Oncol* 2012, **13**(11):1141-1151.
18. Collaborative Group on Hormonal Factors in Breast Cancer: **Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease**. *The Lancet* 2002, **360**(9328):187-195.
19. Cnattingius S, Torrang A, Ekbom A, Granath F, Petersson G, Lambe M: **Pregnancy characteristics and maternal risk of breast cancer**. *JAMA : the journal of the American Medical Association* 2005, **294**(19):2474-2480.
20. Hajiebrahimi M, Cnattingius S, Lambe M, Bahmanyar S: **Pregnancy history and risk of premenopausal breast cancer-a nested case-control study**. *Int J Epidemiol* 2016, **45**(3):816-824.
21. Hickey M, Elliott J, Davison SL: **Hormone replacement therapy**. *Bmj* 2012, **344**.
22. Collaborative Group on Hormonal Factors in Breast Cancer: **Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer**. *The Lancet* 1997, **350**(9084):1047-1059.
23. Jernström H, Bendahl P-O, Lidfeldt J, Nerbrand C, Agardh C-D, Samsioe G: **A prospective study of different types of hormone replacement therapy use and the risk of subsequent breast cancer: the women's health in the Lund area (WHILA) study (Sweden)**. *Cancer Cause Control* 2003, **14**(7):673-680.
24. Collaborative Group on Hormonal Factors in Breast Cancer: **Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies**. *The Lancet* 1996, **347**(9017):1713-1727.
25. Johns PC, Yaffe MJ: **X-ray characterisation of normal and neoplastic breast tissues**. *Physics in Medicine & Biology* 1987, **32**(6):675.
26. Eriksson M, Li J, Leifland K, Czene K, Hall P: **A comprehensive tool for measuring mammographic density changes over time**. *Breast Cancer Res Treat* 2018, **169**(2):371-379.
27. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, Jong RA, Hislop G, Chiarelli A, Minkin S *et al*: **Mammographic Density and the Risk and Detection of Breast Cancer**. *New England Journal of Medicine* 2007, **356**(3):227-236.
28. Eriksson M, Czene K, Pawitan Y, Leifland K, Darabi H, Hall P: **A clinical model for identifying the short-term risk of breast cancer**. *Breast cancer research : BCR* 2017, **19**(1):29.
29. Gabrielson M, Eriksson M, Hammarstrom M, Borgquist S, Leifland K, Czene K, Hall P: **Cohort profile: The Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA)**. *Int J Epidemiol* 2017.
30. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ: **Active Smoking and Breast Cancer Risk: Original Cohort Data and Meta-Analysis**. *J Natl Cancer Inst* 2013, **105**(8):515-525.
31. Jung S, Wang M, Anderson K, Baglietto L, Bergkvist L, Bernstein L, van den Brandt PA, Brinton L, Buring JE, Eliassen AH *et al*: **Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies**. *Int J Epidemiol* 2016, **45**(3):916-928.

32. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC: **Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk**. *JAMA : the journal of the American Medical Association* 2011, **306**(17):1884-1890.
33. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, Ochs-Balcom HM, Thomson CA, Caan BJ, Tinker LF *et al*: **Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials**. *JAMA Oncol* 2015, **1**(5):611-621.
34. The Premenopausal Breast Cancer Collaborative Group: **Association of body mass index and age with subsequent breast cancer risk in premenopausal women**. *JAMA Oncology* 2018:e181771.
35. Pizot C, Boniol M, Mullie P, Koechlin A, Boniol M, Boyle P, Autier P: **Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies**. *Eur J Cancer* 2016, **52**:138-154.
36. Regional Cancer Centrum: **Breast cancer: Description of standardized care process**. 2015.
37. He W, Sofie Lindström L, Hall P, Czene K: **Cause-specific mortality in women with breast cancer in situ**. *International Journal of Cancer* 2017, **140**(11):2414-2421.
38. Wadsten C, Heyman H, Holmqvist M, Ahlgren J, Lambe M, Sund M, Warnberg F: **A validation of DCIS registration in a population-based breast cancer quality register and a study of treatment and prognosis for DCIS during 20 years**. *Acta Oncol* 2016, **55**(11):1338-1343.
39. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MMA: **Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173 797 patients**. *Bmj* 2015, **351**.
40. Foulkes WD, Reis-Filho JS, Narod SA: **Tumor size and survival in breast cancer[mdash]a reappraisal**. *Nature reviews Clinical oncology* 2010, **7**(6):348-353.
41. Jatoi I, Hilsenbeck SG, Clark GM, Osborne CK: **Significance of Axillary Lymph Node Metastasis in Primary Breast Cancer**. *Journal of Clinical Oncology* 1999, **17**(8):2334-2334.
42. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, Costa A, de Cicco C, Geraghty JG, Luini A *et al*: **Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes**. *Lancet* 1997, **349**(9069):1864-1867.
43. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E: **Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**. *Annals of Oncology* 2012, **23**(suppl_7):vii11-vii19.
44. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, Weaver DL, Winchester DJ, Hortobagyi GN: **Breast Cancer—Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual**. *CA: A Cancer Journal for Clinicians* 2017:n/a-n/a.
45. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A: **Breast cancer statistics, 2015: Convergence of incidence rates between black and white women**. *CA: A Cancer Journal for Clinicians* 2016, **66**(1):31-42.
46. Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T, Eusebi V, Fox SB, Ichihara S, Jacquemier J, Lakhani SR *et al*: **Breast cancer prognostic classification in the molecular era: the role of histological grade**. *Breast cancer research : BCR* 2010, **12**(4):207-207.
47. Deroo BJ, Korach KS: **Estrogen receptors and human disease**. *The Journal of Clinical Investigation* 2006, **116**(3):561-570.

48. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M *et al*: **American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer**. *J Clin Oncol* 2010, **28**(16):2784-2795.
49. Yi M, Huo L, Koenig KB, Mittendorf EA, Meric-Bernstam F, Kuerer HM, Bedrosian I, Buzdar AU, Symmans WF, Crow JR *et al*: **Which threshold for ER positivity? a retrospective study based on 9639 patients**. *Ann Oncol* 2014, **25**(5):1004-1011.
50. Early Breast Cancer Trialists' Collaborative Group: **Tamoxifen for early breast cancer: an overview of the randomised trials**. *Lancet* 1998, **351**(9114):1451-1467.
51. Dowsett M, Allred C, Knox J, Quinn E, Salter J, Wale C, Cuzick J, Houghton J, Williams N, Mallon E *et al*: **Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial**. *J Clin Oncol* 2008, **26**(7):1059-1065.
52. Dunnwald LK, Rossing MA, Li CI: **Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients**. *Breast Cancer Research* 2007, **9**(1):R6.
53. Early Breast Cancer Trialists' Collaborative Group: **Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials**. *The Lancet* 2011, **378**(9793):771-784.
54. Yan M, Schwaederle M, Arguello D, Millis SZ, Gatalica Z, Kurzrock R: **HER2 expression status in diverse cancers: review of results from 37,992 patients**. *Cancer and Metastasis Reviews* 2015, **34**(1):157-164.
55. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN: **The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine**. *The oncologist* 2009, **14**(4):320-368.
56. Wolff AC, Hammond MEH, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JMS, Bilous M, Fitzgibbons P *et al*: **Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update**. *Journal of Clinical Oncology* 2013, **31**(31):3997-4013.
57. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, Watson M, Davies S, Bernard PS, Parker JS *et al*: **Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer**. *J Natl Cancer Inst* 2009, **101**(10):736-750.
58. Petrelli F, Viale G, Cabiddu M, Barni S: **Prognostic value of different cut-off levels of Ki-67 in breast cancer: a systematic review and meta-analysis of 64,196 patients**. *Breast Cancer Res Treat* 2015, **153**(3):477-491.
59. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA: **Ki67 in breast cancer: prognostic and predictive potential**. *Lancet Oncol* 2010, **11**(2):174-183.
60. Guiu S, Michiels S, Andre F, Cortes J, Denkert C, Di Leo A, Hennessy BT, Sorlie T, Sotiriou C, Turner N *et al*: **Molecular subclasses of breast cancer: how do we define them? The IMPAKT 2012 Working Group Statement**. *Ann Oncol* 2012, **23**(12):2997-3006.
61. Blows FM, Driver KE, Schmidt MK, Broeks A, van Leeuwen FE, Wesseling J, Cheang MC, Gelmon K, Nielsen TO, Blomqvist C *et al*: **Subtyping of Breast Cancer by Immunohistochemistry to Investigate a Relationship between**

Subtype and Short and Long Term Survival: A Collaborative Analysis of Data for 10,159 Cases from 12 Studies. *PLoS medicine* 2010, **7**(5):e1000279.
62. Moore W: **Extreme measures: the history of breast cancer surgery**. *Bmj* 2012, **344**.
63. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N: **Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer**. *The New England journal of medicine* 2002, **347**(16):1233-1241.
64. Yeo B, Turner NC, Jones A: **An update on the medical management of breast cancer**. *BMJ : British Medical Journal* 2014, **348**.
65. Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H: **Prevalence of and factors associated with persistent pain following breast cancer surgery**. *JAMA : the journal of the American Medical Association* 2009, **302**(18):1985-1992.
66. Hoffmann J: **Analysis of surgical and diagnostic quality at a specialist breast unit**. *The Breast* 2006, **15**(4):490-497.
67. Hack TF, Cohen L, Katz J, Robson LS, Goss P: **Physical and psychological morbidity after axillary lymph node dissection for breast cancer**. *J Clin Oncol* 1999, **17**(1):143-149.
68. Brand JS, Colzani E, Johansson ALV, Giesecke J, Clements M, Bergh J, Hall P, Czene K: **Infection-related hospitalizations in breast cancer patients: Risk and impact on prognosis**. *Journal of Infection* 2016.
69. Togawa K, Ma H, Sullivan-Halley J, Neuhouser ML, Imayama I, Baumgartner KB, Smith AW, Alfano CM, McTiernan A, Ballard-Barbash R *et al*: **Risk factors for self-reported arm lymphedema among female breast cancer survivors: a prospective cohort study**. *Breast Cancer Research* 2014, **16**(4):414.
70. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, Yiangou C, Horgan K, Bundred N, Monypenny I *et al*: **Randomized Multicenter Trial of Sentinel Node Biopsy Versus Standard Axillary Treatment in Operable Breast Cancer: The ALMANAC Trial**. *JNCI: Journal of the National Cancer Institute* 2006, **98**(9):599-609.
71. Giuliano AE, Hunt KK, Ballman KV, et al.: **Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial**. *JAMA : the journal of the American Medical Association* 2011, **305**(6):569-575.
72. Wickberg A, Holmberg L, Adami HO, Magnuson A, Villman K, Liljegren G: **Sector resection with or without postoperative radiotherapy for stage I breast cancer: 20-year results of a randomized trial**. *J Clin Oncol* 2014, **32**(8):791-797.
73. Early Breast Cancer Trialists' Collaborative Group: **Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials**. *Lancet* 2011, **378**(9804):1707-1716.
74. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T *et al*: **Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials**. *Lancet* 2014, **383**(9935):2127-2135.
75. Yoshikawa N, Inomata T, Shimbo T, Takahashi M, Uesugi Y, Juri H, Narumi Y: **Appropriate evaluation of and risk factors for radiation dermatitis in breast cancer patients receiving hypofractionated whole-breast irradiation after breast-conserving surgery**. *Breast cancer* 2014, **21**(2):170-176.

76. Cook C, Wongkittiroch K, Miller R: **Erythrodermic Psoriasis Post Radiation Treatment: A Case Presentation and Literature Review**. *Practical Dermatology* 2011, **October**:36-38.
77. Prochazka M, Hall P, Gagliardi G, Granath F, Nilsson BN, Shields PG, Tennis M, Czene K: **Ionizing Radiation and Tobacco Use Increases the Risk of a Subsequent Lung Carcinoma in Women With Breast Cancer: Case-Only Design**. *Journal of Clinical Oncology* 2005, **23**(30):7467-7474.
78. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B *et al*: **Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer**. *New England Journal of Medicine* 2013, **368**(11):987-998.
79. Del Turco MR, Ponti A, Bick U, Biganzoli L, Cserni G, Cutuli B, Decker T, Dietel M, Gentilini O, Kuehn T *et al*: **Quality indicators in breast cancer care**. *Eur J Cancer* 2010, **46**(13):2344-2356.
80. Ragnhammar P, Brorsson B, Nygren P, Glimelius B: **A prospective study of the use of chemotherapy in Sweden and assessment of the use in relation to scientific evidence**. *Acta Oncol* 2001, **40**(2-3):391-411.
81. National Board of Health and Welfare: **National guidelines for breast, prostate, colon and rectal cancer**. In., 2014-4-2 edn; 2014.
82. Albain K, Anderson S, Arriagada R, Barlow W, Bergh J, Bliss J, Buyse M, Cameron D, Carrasco E, Clarke M *et al*: **Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials**. *Lancet* 2012, **379**(9814):432-444.
83. Hassett MJ, O'Malley AJ, Pakes JR, Newhouse JP, Earle CC: **Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer**. *J Natl Cancer Inst* 2006, **98**(16):1108-1117.
84. Azim JHA, de Azambuja E, Colozza M, Bines J, Piccart MJ: **Long-term toxic effects of adjuvant chemotherapy in breast cancer**. *Annals of Oncology* 2011, **22**(9):1939-1947.
85. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Rowden D, Solky AJ *et al*: **Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update**. *Journal of Clinical Oncology* 2014, **32**(21):2255-2269.
86. Early Breast Cancer Trialists' Collaborative Group, Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, Boccardo F, Coates A, Coombes RC *et al*: **Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials**. *Lancet* 2015, **386**(10001):1341-1352.
87. Chlebowski RT, Schottinger JE, Shi J, Chung J, Haque R: **Aromatase inhibitors, tamoxifen, and endometrial cancer in breast cancer survivors**. *Cancer* 2015, **121**(13):2147-2155.
88. Garreau JR, DeLaMelena T, Walts D, Karamlou K, Johnson N: **Side effects of aromatase inhibitors versus tamoxifen: the patients' perspective**. *The American Journal of Surgery* 2006, **192**(4):496-498.
89. O'Sullivan CC, Bradbury I, Campbell C, Spielmann M, Perez EA, Joensuu H, Costantino JP, Delaloge S, Rastogi P, Zardavas D *et al*: **Efficacy of Adjuvant Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer and Tumors </= 2 cm: A Meta-Analysis of the Randomized Trastuzumab Trials**. *J Clin Oncol* 2015, **33**(24):2600-2608.

90. Advani PP, Ballman KV, Dockter TJ, Colon-Otero G, Perez EA: **Long-Term Cardiac Safety Analysis of NCCTG N9831 (Alliance) Adjuvant Trastuzumab Trial**. *J Clin Oncol* 2016, **34**(6):581-587.
91. Kalimutho M, Parsons K, Mittal D, Lopez JA, Srihari S, Khanna KK: **Targeted Therapies for Triple-Negative Breast Cancer: Combating a Stubborn Disease**. *Trends in pharmacological sciences* 2015, **36**(12):822-846.
92. Blakely T, Costilla R, Soeberg M: **Cancer excess mortality rates over 2006-2026 for ABC-CBA**: Department of Public Health, University of Otago, Wellington; 2012.
93. Louwman WJ, Klokman WJ, Coebergh JWW: **Excess mortality from breast cancer 20 years after diagnosis when life expectancy is normal**. *Br J Cancer* 2001, **84**(5):700-703.
94. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R, Jemal A: **Cancer treatment and survivorship statistics, 2016**. *CA: A Cancer Journal for Clinicians* 2016, **66**(4):271-289.
95. Halmin M, Bellocco R, Lagerlund M, Karlsson P, Tejler G, Lambe M: **Long-term inequalities in breast cancer survival--a ten year follow-up study of patients managed within a National Health Care System (Sweden)**. *Acta Oncol* 2008, **47**(2):216-224.
96. Riihimäki M, Thomsen H, Brandt A, Sundquist J, Hemminki K: **Death causes in breast cancer patients**. *Annals of Oncology* 2012, **23**(3):604-610.
97. Du XL, Fox EE, Lai D: **Competing Causes of Death for Women With Breast Cancer and Change Over Time From 1975 to 2003**. *American journal of clinical oncology* 2008, **31**(2):105-116.
98. Ording AG, Boffetta P, Garne JP, Nyström PMW, Cronin-Fenton D, Frøslev T, Silliman R, Sørensen HT, Lash TL: **Relative mortality rates from incident chronic diseases among breast cancer survivors – A 14 year follow-up of five-year survivors diagnosed in Denmark between 1994 and 2007**. *Eur J Cancer* 2015, **51**(6):767-775.
99. Li J, Humphreys K, Eriksson M, Dar H, Brandberg Y, Hall P, Czene K: **Worse quality of life in young and recently diagnosed breast cancer survivors compared with female survivors of other cancers: A cross-sectional study**. *Int J Cancer* 2016, **139**(11):2415-2425.
100. Fu AZ, Jhaveri M: **Healthcare cost attributable to recently-diagnosed breast cancer in a privately-insured population in the United States**. *Journal of medical economics* 2012, **15**(4):688-694.
101. Berglund A, Wigertz A, Adolfsson J, Ahlgren J, Fornander T, Warnberg F, Lambe M: **Impact of comorbidity on management and mortality in women diagnosed with breast cancer**. *Breast Cancer Res Treat* 2012, **135**(1):281-289.
102. Edwards BK, Noone AM, Mariotto AB, Simard EP, Boscoe FP, Henley SJ, Jemal A, Cho H, Anderson RN, Kohler BA *et al*: **Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer**. *Cancer* 2014, **120**(9):1290-1314.
103. Lambe M, Wigertz A, Garmo H, Walldius G, Jungner I, Hammar N: **Impaired glucose metabolism and diabetes and the risk of breast, endometrial, and ovarian cancer**. *Cancer causes & control : CCC* 2011, **22**(8):1163-1171.
104. Ording AG, Garne JP, Nystrom PM, Cronin-Fenton D, Tarp M, Sorensen HT, Lash TL: **Hospital recorded morbidity and breast cancer incidence: a nationwide population-based case-control study**. *PloS one* 2012, **7**(10):e47329.

105. Hemminki K, Liu X, Ji J, Forsti A, Sundquist J, Sundquist K: **Effect of autoimmune diseases on risk and survival in female cancers**. *Gynecologic oncology* 2012, **127**(1):180-185.
106. Pacheco NL, Andersen AM, Kamper-Jorgensen M: **Preeclampsia and breast cancer: The influence of birth characteristics**. *Breast* 2015, **24**(5):613-617.
107. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation**. *Journal of chronic diseases* 1987, **40**(5):373-383.
108. Pennington KA, Schlitt JM, Jackson DL, Schulz LC, Schust DJ: **Preeclampsia: multiple approaches for a multifactorial disease**. *Disease models & mechanisms* 2012, **5**(1):9-18.
109. Williams D, Craft N: **Pre-eclampsia**. *Bmj* 2012, **345**:e4437.
110. Mol BW, Roberts CT, Thangaratinam S, Magee LA, de Groot CJ, Hofmeyr GJ: **Pre-eclampsia**. *Lancet* 2016, **387**(10022):999-1011.
111. Kim JS, Kang EJ, Woo OH, Park KH, Woo SU, Yang DS, Kim AR, Lee JB, Kim YH, Kim JS *et al*: **The relationship between preeclampsia, pregnancy-induced hypertension and maternal risk of breast cancer: A meta-analysis**. *Acta Oncol* 2013, **52**(8):1643-1648.
112. Opdahl S, Romundstad PR, Alsaker MD, Vatten LJ: **Hypertensive diseases in pregnancy and breast cancer risk**. *Br J Cancer* 2012, **107**(1):176-182.
113. Audette M, Pillai K, Wrana J, Kingdom J: **Does Preeclampsia Reduce the Risk of Breast Cancer?** *Journal of Obstetrics and Gynaecology Canada* 2015, **37**(8):736-739.
114. Rosing U, Carlstrom K: **Serum levels of unconjugated and total oestrogens and dehydroepiandrosterone, progesterone and urinary oestriol excretion in pre-eclampsia**. *Gynecologic and obstetric investigation* 1984, **18**(4):199-205.
115. Lee IS, Chung DY, Cole LA, Copel JA, Isozaki T, Hsu CD: **Elevated serum nicked and urinary beta-core fragment hCG in preeclamptic pregnancies**. *Obstet Gynecol* 1997, **90**(6):889-892.
116. Russo IH, Koszalka M, Russo J: **Human Chorionic Gonadotropin and Rat Mammary Cancer Prevention**. *JNCI: Journal of the National Cancer Institute* 1990, **82**(15):1286-1289.
117. Russo J, Russo IH: **Hormonally induced differentiation: a novel approach to breast cancer prevention**. *Journal of cellular biochemistry Supplement* 1995, **22**:58-64.
118. Huynh H: **In vivo regulation of the insulin-like growth factor system of mitogens by human chorionic gonadotropin**. *International journal of oncology* 1998, **13**(3):571-575.
119. Ingec M, Gursoy HG, Yildiz L, Kumtepe Y, Kadanali S: **Serum levels of insulin, IGF-1, and IGFBP-1 in pre-eclampsia and eclampsia**. *Int J Gynaecol Obstet* 2004, **84**(3):214-219.
120. Byrne C, Colditz GA, Willett WC, Speizer FE, Pollak M, Hankinson SE: **Plasma insulin-like growth factor (IGF) I, IGF-binding protein 3, and mammographic density**. *Cancer Res* 2000, **60**(14):3744-3748.
121. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M: **Circulating concentrations of insulin-like growth factor-I and risk of breast cancer**. *Lancet* 1998, **351**(9113):1393-1396.
122. Gilbert JS, Ryan MJ, LaMarca BB, Sedeek M, Murphy SR, Granger JP: **Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction**. *American journal of physiology Heart and circulatory physiology* 2008, **294**(2):H541-550.

123. Beeghly-Fadiel A, Shu XO, Lu W, Long J, Cai Q, Xiang YB, Zheng Y, Zhao Z, Gu K, Gao YT *et al*: **Genetic variation in VEGF family genes and breast cancer risk: a report from the Shanghai Breast Cancer Genetics Study**. *Cancer Epidemiology Biomarkers and Prevention* 2011, **20**(1):33-41.
124. McGinnis R, Steinthorsdottir V, Williams NO, Thorleifsson G, Shooter S, Hjartardottir S, Bumpstead S, Stefansdottir L, Hildyard L, Sigurdsson JK *et al*: **Variants in the fetal genome near FLT1 are associated with risk of preeclampsia**. *Nature genetics* 2017, **49**(8):1255-1260.
125. Henningson M, Hietala M, Torngren T, Olsson H, Jernstrom H: **IGF1 htSNPs in relation to IGF-1 levels in young women from high-risk breast cancer families: implications for early-onset breast cancer**. *Familial cancer* 2011, **10**(2):173-185.
126. Koh WP, Yuan JM, Sun CL, van den Berg D, Seow A, Lee HP, Yu MC: **Angiotensin I-converting enzyme (ACE) gene polymorphism and breast cancer risk among Chinese women in Singapore**. *Cancer Res* 2003, **63**(3):573-578.
127. Mütze S, Rudnik-Schöneborn S, Zerres K, Rath W: **Genes and the preeclampsia syndrome**. In: *Journal of Perinatal Medicine.* vol. 36; 2008: 38.
128. Morgan L, McGinnis R, Steinthorsdottir V, Svyatova G, Zakhidova N, Lee WK, Iversen A-C, Magnus P, Walker J, Casas JP *et al*: **InterPregGen: genetic studies of pre-eclampsia in three continents**. *Norsk epidemiologi = Norwegian journal of epidemiology* 2014, **24**(1-2):141-146.
129. Mehnert A, Brahler E, Faller H, Harter M, Keller M, Schulz H, Wegscheider K, Weis J, Boehncke A, Hund B *et al*: **Four-week prevalence of mental disorders in patients with cancer across major tumor entities**. *J Clin Oncol* 2014, **32**(31):3540-3546.
130. Carlsen K, Jensen AJ, Rugulies R, Christensen J, Bidstrup PE, Johansen C, Huitfeldt Madsen IE, Dalton SO: **Self-reported work ability in long-term breast cancer survivors. A population-based questionnaire study in Denmark**. *Acta Oncol* 2013, **52**(2):423-429.
131. Demissie S, Silliman RA, Lash TL: **Adjuvant tamoxifen: Predictors of use, side effects, and discontinuation in older women**. *Journal of Clinical Oncology* 2001, **19**(2):322-328.
132. He W, Fang F, Varnum C, Eriksson M, Hall P, Czene K: **Predictors of Discontinuation of Adjuvant Hormone Therapy in Patients With Breast Cancer**. *J Clin Oncol* 2015.
133. Montazeri A: **Quality of Life in Breast Cancer Patients: An Overview of the Literature**. In: *Handbook of Disease Burdens and Quality of Life Measures.* edn. Edited by Preedy V, Watson R: Springer New York; 2010: 2829-2855.
134. Spiegel D: **Mind matters in cancer survival**. *JAMA : the journal of the American Medical Association* 2011, **305**(5):502-503.
135. Thornton LM, Andersen BL, Blakely WP: **The pain, depression, and fatigue symptom cluster in advanced breast cancer: covariation with the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system**. *Health Psychology* 2010, **29**(3):333-337.
136. O'Connor M, Christensen S, Jensen AB, Moller S, Zachariae R: **How traumatic is breast cancer? Post-traumatic stress symptoms (PTSS) and risk factors for severe PTSS at 3 and 15 months after surgery in a nationwide cohort of Danish women treated for primary breast cancer**. *Br J Cancer* 2011, **104**(3):419-426.
137. Vin-Raviv N, Hillyer GC, Hershman DL, Galea S, Leoce N, Bovbjerg DH, Kushi LH, Kroenke C, Lamerato L, Ambrosone CB *et al*: **Racial disparities in posttraumatic stress after diagnosis of localized breast cancer: the BQUAL study**. *J Natl Cancer Inst* 2013, **105**(8):563-572.

138. Suppli NP, Johansen C, Christensen J, Kessing LV, Kroman N, Dalton SO: **Increased risk for depression after breast cancer: a nationwide population-based cohort study of associated factors in denmark, 1998-2011**. *J Clin Oncol* 2014, **32**(34):3831-3839.
139. Mehnert A, Koch U: **Psychological comorbidity and health-related quality of life and its association with awareness, utilization, and need for psychosocial support in a cancer register-based sample of long-term breast cancer survivors**. *Journal of psychosomatic research* 2008, **64**(4):383-391.
140. Hung YP, Liu CJ, Tsai CF, Hung MH, Tzeng CH, Liu CY, Chen TJ: **Incidence and risk of mood disorders in patients with breast cancers in Taiwan: a nationwide population-based study**. *Psycho-oncology* 2013.
141. Lu D, Andersson TL, Fall K, et al.: **Clinical diagnosis of mental disorders immediately before and after cancer diagnosis: A nationwide matched cohort study in sweden**. *JAMA Oncology* 2016.
142. Choi EK, Kim IR, Chang O, Kang D, Nam SJ, Lee JE, Lee SK, Im YH, Park YH, Yang JH *et al*: **Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients**. *Psycho-oncology* 2014, **23**(10):1103-1110.
143. Farrell C, Brearley SG, Pilling M, Molassiotis A: **The impact of chemotherapy-related nausea on patients' nutritional status, psychological distress and quality of life**. *Supportive Care in Cancer* 2013, **21**(1):59-66.
144. Charalambous H, Bloomfield D: **Psoriasis and radiotherapy: exacerbation of psoriasis following radiotherapy for carcinoma of the breast (the Koebner phenomenon)**. *Clinical oncology* 2000, **12**(3):192-193.
145. Tomlinson MJ: **Psoriasis and radiotherapy**. *Clinical oncology* 2001, **13**(2):145.
146. Obradors M, Blanch C, Comellas M, Figueras M, Lizan L: **Health-related quality of life in patients with psoriasis: a systematic review of the European literature**. *Quality of Life Research* 2016, **25**(11):2739-2754.
147. Hrehorow E, Salomon J, Matusiak L, Reich A, Szepietowski JC: **Patients with psoriasis feel stigmatized**. *Acta dermato-venereologica* 2012, **92**(1):67-72.
148. Schmid-Ott G, Schallmayer S, Calliess IT: **Quality of life in patients with psoriasis and psoriasis arthritis with a special focus on stigmatization experience**. *Clin Dermatol* 2007, **25**(6):547-554.
149. Alolabi N, White CP, Cin AD: **The Koebner phenomenon and breast reconstruction: Psoriasis eruption along the surgical incision**. *The Canadian journal of plastic surgery* 2011, **19**(4):143-144.
150. Farber EM, Nall ML: **The natural history of psoriasis in 5,600 patients**. *Dermatologica* 1974, **148**(1):1-18.
151. Ortonne JP: **Aetiology and pathogenesis of psoriasis**. *The British journal of dermatology* 1996, **135 Suppl 49**:1-5.
152. Naldi L, Peli L, Parazzini F, Carrel CF, Psoriasis Study Group of the Italian Group for Epidemiological Research in D: **Family history of psoriasis, stressful life events, and recent infectious disease are risk factors for a first episode of acute guttate psoriasis: results of a case-control study**. *Journal of the American Academy of Dermatology* 2001, **44**(3):433-438.
153. Brenaut E, Horreau C, Pouplard C, Barnetche T, Paul C, Richard MA, Joly P, Le Maitre M, Aractingi S, Aubin F *et al*: **Alcohol consumption and psoriasis: a systematic literature review**. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2013, **27 Suppl 3**:30-35.
154. Armstrong AW, Harskamp CT, Dhillon JS, Armstrong EJ: **Psoriasis and smoking: a systematic review and meta-analysis**. *The British journal of dermatology* 2014, **170**(2):304-314.

155. Armstrong AW, Harskamp CT, Armstrong EJ: **The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies**. *Nutr Diabetes* 2012, **2**:e54.
156. Tsankov N, Kazandjieva J, Drenovska K: **Drugs in exacerbation and provocation of psoriasis**. *Clin Dermatol* 1998, **16**(3):333-351.
157. Telfer NR, Chalmers RJ, Whale K, Colman G: **The role of streptococcal infection in the initiation of guttate psoriasis**. *Archives of dermatology* 1992, **128**(1):39-42.
158. de Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F: **Management of febrile neutropenia: ESMO Clinical Practice Guidelines**. *Annals of Oncology* 2010, **21**(suppl_5):v252-v256.
159. Younis T, Rayson D, Thompson K: **Primary G-CSF prophylaxis for adjuvant TC or FEC-D chemotherapy outside of clinical trial settings: a systematic review and meta-analysis**. *Supportive Care in Cancer* 2012, **20**(10):2523-2530.
160. Truong J, Lee EK, Trudeau ME, Chan KKW: **Interpreting febrile neutropenia rates from randomized, controlled trials for consideration of primary prophylaxis in the real world: a systematic review and meta-analysis**. *Annals of Oncology* 2016, **27**(4):608-618.
161. Lyman GH, Abella E, Pettengell R: **Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review**. *Crit Rev Oncol Hematol* 2014, **90**(3):190-199.
162. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad, II, Rolston KV, Young JA, Wingard JR: **Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america**. *Clinical infectious diseases* 2011, **52**(4):e56-93.
163. Bhatt V, Saleem A: **Review: Drug-induced neutropenia--pathophysiology, clinical features, and management**. *Annals of clinical and laboratory science* 2004, **34**(2):131-137.
164. Ording AG, Horvath-Puho E, Garne JP, Nystrom PW, Vyberg M, Sorensen HT, Lash TL: **Impact of comorbidity on risk of venous thromboembolism in patients with breast cancer: a Danish population-based cohort study**. *Bmj Open* 2014, **4**(6).
165. Brand JS, Hedayati E, Bhoo-Pathy N, Bergh J, Hall P, Humphreys K, Ludvigsson JF, Czene K: **Time-dependent risk and predictors of venous thromboembolism in breast cancer patients: A population-based cohort study**. *Cancer* 2017, **123**(3):468-475.
166. Winter PC: **The pathogenesis of venous thromboembolism in cancer: emerging links with tumour biology**. *Hematological oncology* 2006, **24**(3):126-133.
167. Mandala M, Tondini C: **Adjuvant therapy in breast cancer and venous thromboembolism**. *Thrombosis research* 2012, **130 Suppl 1**:S66-70.
168. Doroshow JH: **Effect of anthracycline antibiotics on oxygen radical formation in rat heart**. *Cancer Res* 1983, **43**(2):460-472.
169. Nilsson G, Holmberg L, Garmo H, Duvernoy O, Sjogren I, Lagerqvist B, Blomqvist C: **Distribution of coronary artery stenosis after radiation for breast cancer**. *J Clin Oncol* 2012, **30**(4):380-386.
170. Gianni L, Salvatorelli E, Minotti G: **Anthracycline cardiotoxicity in breast cancer patients: synergism with trastuzumab and taxanes**. *Cardiovascular toxicology* 2007, **7**(2):67-71.
171. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE: **Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen**. *Lancet* 2000, **356**(9233):881-887.

172. Colzani E, Clements M, Johansson ALV, Liljegren A, He W, Brand J, Adolfsson J, Fornander T, Hall P, Czene K: **Risk of hospitalisation and death due to bone fractures after breast cancer: a registry-based cohort study**. *Br J Cancer* 2016, **115**(11):1400-1407.
173. Rizzoli R, Body JJ, DeCensi A, Reginster JY, Piscitelli P, Brandi ML: **Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESCEO position paper**. *Osteoporosis international* 2012, **23**(11):2567-2576.
174. **Historical statistics** [https://www.scb.se/sv_/Hitta-statistik/Historisk-statistik/]
175. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A: **The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research**. *European journal of epidemiology* 2009, **24**(11):659-667.
176. Bruhn A: **The next population and housing census in sweden is planned for 2005-it will be totally register-based**. In: *Symposium on Global Review of 2000 Round of Population and Housing Censuses: 2001; New York*; 2001.
177. Ekbom A: **The Swedish Multi-generation Register**. *Methods in molecular biology* 2011, **675**:215-220.
178. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, Feychting M, Ljung R: **The Swedish cause of death register**. *European journal of epidemiology* 2017, **32**(9):765-773.
179. Johansson LA, Bjorkenstam C, Westerling R: **Unexplained differences between hospital and mortality data indicated mistakes in death certification: an investigation of 1,094 deaths in Sweden during 1995**. *Journal of clinical epidemiology* 2009, **62**(11):1202-1209.
180. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO: **External review and validation of the Swedish national inpatient register**. *BMC public health* 2011, **11**:450.
181. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, Persson I, Sundstrom A, Westerholm B, Rosen M: **The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months**. *Pharmacoepidemiology and drug safety* 2007, **16**(7):726-735.
182. Cnattingius S, Ericson A, Gunnarskog J, Kallen B: **A quality study of a medical birth registry**. *Scand J Soc Med* 1990, **18**(2):143-148.
183. National Board of Health and Welfare: **The Swedish Medical Birth Register–a summary of content and quality**. In.: National Board of Health and Welfare Stockholm, Sweden; 2003.
184. Barlow L, Westergren K, Holmberg L, Talback M: **The completeness of the Swedish Cancer Register: a sample survey for year 1998**. *Acta Oncol* 2009, **48**(1):27-33.
185. Garne JP, Aspegren K, Moller T: **Validity of Breast-Cancer Registration from One Hospital into the Swedish National Cancer Registry 1971-1991**. *Acta Oncol* 1995, **34**(2):153-156.
186. Kemetli L, Erik Rutqvist L, Jonsson H, Nyström L, Lenner P, Törnberg S: **Temporal trends in the use of adjuvant systemic therapy in breast cancer – a population based study in Sweden 1976–2005**. *Acta Oncol* 2009, **48**(1):59-66.
187. Wennman-Larsen A, Nilsson MI, Saboonchi F, Olsson M, Alexanderson K, Fornander T, Sandelin K, Petersson L-M: **Can breast cancer register data on recommended adjuvant treatment be used as a proxy for actually given treatment?** *European Journal of Oncology Nursing* 2016, **22**:1-7.

188. Holm J: **Aggressive breast cancer: epidemiological studies addressing disease heterogeneity**: Inst för medicinsk epidemiologi och biostatistik/Dept of Medical Epidemiology and Biostatistics; 2018.
189. Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, Maranian MJ, Bolla MK, Wang Q, Shah M *et al*: **Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer**. *Nature genetics* 2015, **47**(4):373-380.
190. Holt J, Prentice R: **Survival analyses in twin studies and matched pair experiments**. *Biometrika* 1974, **61**(1):17-30.
191. Sjolander A, Greenland S: **Ignoring the matching variables in cohort studies - when is it valid and why?** *Stat Med* 2013, **32**(27):4696-4708.
192. Royston P, Parmar MKB: **Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects**. *Stat Med* 2002, **21**(15):2175-2197.
193. Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, Ding J, Li Y, Tejasvi T, Gudjonsson JE *et al*: **Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity**. *Nature genetics* 2012, **44**(12):1341-1348.
194. Denny JC, Ritchie MD, Basford MA, Pulley JM, Bastarache L, Brown-Gentry K, Wang D, Masys DR, Roden DM, Crawford DC: **PheWAS: demonstrating the feasibility of a phenome-wide scan to discover gene–disease associations**. *Bioinformatics* 2010, **26**(9):1205-1210.
195. Jensen AB, Moseley PL, Oprea TI, Ellesøe SG, Eriksson R, Schmock H, Jensen PB, Jensen LJ, Brunak S: **Temporal disease trajectories condensed from population-wide registry data covering 6.2 million patients**. *Nature Communication* 2014, **5**:4022.
196. Ros HS, Cnattingius S, Lipworth L: **Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study**. *Am J Epidemiol* 1998, **147**(11):1062-1070.
197. Lofvendahl S, Theander E, Svensson A, Carlsson KS, Englund M, Petersson IF: **Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden--a population-based register study**. *PloS one* 2014, **9**(5):e98024.
198. Fazel S, Wolf A, Chang Z, Larsson H, Goodwin GM, Lichtenstein P: **Depression and violence: a Swedish population study**. *Lancet Psychiatry* 2015, **2**(3):224-232.
199. Svensson E, Lash TL, Resick PA, Hansen JG, Gradus JL: **Validity of reaction to severe stress and adjustment disorder diagnoses in the Danish Psychiatric Central Research Registry**. *Clin Epidemiol* 2015, **7**:235-242.
200. Singh M, Alavi A, Wong R, Akita S: **Radiodermatitis: A Review of Our Current Understanding**. *American journal of clinical dermatology* 2016, **17**(3):277-292.
201. Hjerl K, Andersen EW, Keiding N, Mortensen PB, Jorgensen T: **Increased incidence of affective disorders, anxiety disorders, and non-natural mortality in women after breast cancer diagnosis: a nation-wide cohort study in Denmark**. *Acta psychiatrica Scandinavica* 2002, **105**(4):258-264.
202. Calderon-Margalit R, Friedlander Y, Yanetz R, Deutsch L, Perrin MC, Kleinhaus K, Tiram E, Harlap S, Paltiel O: **Preeclampsia and subsequent risk of cancer: update from the Jerusalem Perinatal Study**. *American journal of obstetrics and gynecology* 2009, **200**(1):63 e61-65.
203. Lin LT, Hu LY, Tang PL, Tsui KH, Cheng JT, Huang WC, Chang HT: **Do racial differences exist in the association between pregnancy-induced hypertension and breast cancer risk?** *Hypertens Pregnancy* 2017:1-7.

204. Nilsson E, Salonen Ros H, Cnattingius S, Lichtenstein P: **The importance of genetic and environmental effects for pre-eclampsia and gestational hypertension: a family study**. *BJOG : an international journal of obstetrics and gynaecology* 2004, **111**(3):200-206.
205. Plym A, Bower H, Fredriksson I, Holmberg L, Lambert PC, Lambe M: **Loss in working years after a breast cancer diagnosis**. *Br J Cancer* 2018, **118**(5):738-743.
206. Kedde H, van de Wiel HB, Weijmar Schultz WC, Wijsen C: **Sexual dysfunction in young women with breast cancer**. *Supportive care in cancer* 2013, **21**(1):271-280.
207. Ebenhan K, Leuteritz K, Barthel Y, Beutel ME, Papsdorf K, Weissflog G, Brahler E: **Children and Employment - Resource or Stressors after Breast Cancer?** *Geburtshilfe und Frauenheilkunde* 2013, **73**(8):792-799.
208. Ruddy KJ, Gelber SI, Tamimi RM, Ginsburg ES, Schapira L, Come SE, Borges VF, Meyer ME, Partridge AH: **Prospective study of fertility concerns and preservation strategies in young women with breast cancer**. *J Clin Oncol* 2014, **32**(11):1151-1156.
209. Cronin-Fenton DP, Norgaard M, Jacobsen J, Garne JP, Ewertz M, Lash TL, Sorensen HT: **Comorbidity and survival of Danish breast cancer patients from 1995 to 2005**. *Br J Cancer* 2007, **96**(9):1462-1468.
210. Vinton AL, Traverso LW, Jolly PC: **Wound complications after modified radical mastectomy compared with tylectomy with axillary lymph node dissection**. *Am J Surg* 1991, **161**(5):584-588.
211. Khan NF, Mant D, Carpenter L, Forman D, Rose PW: **Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study**. *Br J Cancer* 2011, **105 Suppl 1**:S29-37.
212. Amir O, Kishon-Rabin L: **Association between birth control pills and voice quality**. *The Laryngoscope* 2004, **114**(6):1021-1026.
213. Burbos N, Musonda P, Giarenis I, Shiner AM, Giamougiannis P, Morris EP, Nieto JJ: **Predicting the risk of endometrial cancer in postmenopausal women presenting with vaginal bleeding: the Norwich DEFAB risk assessment tool**. *Br J Cancer* 2010, **102**(8):1201-1206.
214. Palmer E, Henrikson B, McKusick K, Strauss HW, Hochberg F: **Pain as an indicator of bone metastasis**. *Acta radiologica (Stockholm, Sweden : 1987)* 1988, **29**(4):445-449.
215. Yang H, Brand JS, Fang F, Chiesa F, Johansson AL, Hall P, Czene K: **Time-dependent risk of depression, anxiety, and stress-related disorders in patients with invasive and in situ breast cancer**. *Int J Cancer* 2017, **140**(4):841-852.
216. Faller H, Schuler M, Richard M, Heckl U, Weis J, Kuffner R: **Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis**. *J Clin Oncol* 2013, **31**(6):782-793.
217. Brand JS, Hedayati E, Humphreys K, Ludvigsson JF, Johansson AL, Bergh J, Hall P, Czene K: **Chemotherapy, Genetic Susceptibility, and Risk of Venous Thromboembolism in Breast Cancer Patients**. *Clin Cancer Res* 2016, **22**(21):5249-5255.
218. Sestak I, Buus R, Cuzick J, Dubsky P, Kronenwett R, Denkert C, Ferree S, Sgroi D, Schnabel C, Baehner FL: **Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor–Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial**. *JAMA oncology* 2018, **4**(4):545-553.