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**BREAST CANCER – BRAIN METASTASES AND
TREATMENT ASPECTS**

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Breast cancer – brain metastases and treatment aspects

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To all women with breast cancer

ABSTRACT

Background: In Sweden breast cancer is the most common malignant cancer disease among women, with 8000 new individual cases each year. The prognosis is generally very good, but nevertheless many patients still die of breast cancer every year. The general aim of this thesis is to gain increased knowledge of brain metastases due to breast cancer, including incidence, predictors and treatment aspects and better knowledge of the potential benefit of low-dose aspirin among women with breast cancer in different stages.

Patients, methods and results: In study I and II we aimed to assess if the incidence of brain metastases have increased in Sweden over time. In study I, all Swedish patients with breast cancer during 1998-2006 were identified from the Swedish National Cancer Register. These individuals were matched to the National Patient Register to get information on admissions to hospital due to distant metastases. In the cohort of 50 528 identified breast cancer patients, 696 (1.4%) had admissions to hospital due to brain metastases. Patients were at 44% increased risk of being admitted to hospital with brain metastases if diagnosed with a primary breast cancer in 2004-2006 compared with 1998-2000. In study II we used the BcBaSe cohort (based on three quality-of-care registers in the Stockholm-Gotland, Uppsala-Örebro and the North region). Here, we identified all women with a first breast cancer 2002-2012 (N=30 996) and used ICD-codes for distant metastases from both non-primary outpatient care and hospital admissions. Overall, 789 (2.5 %) patients were registered with brain metastases at diagnosis or during follow-up. According to preliminary results, patients diagnosed with breast cancer in 2009-2012 were at a 37% increased risk of developing brain metastases compared with the period 2002-2004.

In study III we aimed to evaluate survival and level of care following whole brain radiotherapy due to brain metastases among breast cancer patients in Stockholm. We identified 241 patients treated at the Karolinska University hospital radiotherapy units 1999 to 2012. We gathered data on outcome and prognostic factors including level of care before and after the radiotherapy treatment through reviews of the patients' medical files. Median survival following whole brain radiotherapy was 2.9 months and 57 (24%) of the patients could never be discharged from hospital-care. Patients with poor performance status (WHO 3-4) had a median survival of 0.9 months and women with triple-negative primary tumors a median survival of 2.0 months. Poor performance status and being admitted to hospital before radiotherapy were associated with increased risk of not coming home.

In study IV we aimed to evaluate if low-dose aspirin use may have a role in the treatment of breast cancer, accounting for clinical characteristics. In this study we used the BcBaSe linkage to identify a cohort of 21 414 women diagnosed with a primary stage I-III breast cancer and 621 women diagnosed in stage IV 2006 to 2012. We analysed information from Swedish health-care registers on dispensings of low-dose aspirin, comorbidity and dates and causes of death. We found no clear association between low-dose aspirin use and breast-cancer specific death overall, nor with risk of recurrence in a subgroup analysis. A possible benefit was however noted in women with smaller breast cancer tumors, stage I, which warrants further study.

Discussion: The incidence of brain metastases in breast cancer appears to have increased in Sweden in recent years perhaps due to improved disease control outside of the brain. When a decision is made of treating brain metastases in breast cancer with whole brain radiotherapy, we should take into account the patient's need of hospital care before treatment, performance status and choice of level of care in the late palliative stage of disease and the end-of-life period, since the median survival is short and many patients can never be discharged from the hospital after whole brain radiotherapy. Low-dose aspirin use in breast cancer does not seem to have any clear role in improving outcomes for breast cancer patients.

LIST OF SCIENTIFIC PAPERS

I. Incidence and time trends of brain metastases admissions among breast cancer patients in Sweden

Frisk G, Svensson T, Bäcklund LM, Lidbrink E, Blomqvist P, Smedby KE.
British Journal of Cancer. 2012 May 22;106(11):1850-3

II. Update on incidence of brain metastases by tumor characteristics in breast cancer 2002-2012 in Sweden

Frisk G, Ekberg S, Lidbrink E, Pettersson A, Bäcklund LM, Sund M, Fredriksson I, Lambe M, Smedby KE.
Manuscript

III. Survival and level of care among breast cancer patients with brain metastases treated with whole brain radiotherapy

Frisk G, Tinge B, Ekberg S, Eloranta S, Bäcklund LM, Lidbrink E, Smedby KE.
Breast Cancer Res Treat. 2017 Dec;166(3):887-896

IV. No association between low-dose aspirin use and breast cancer outcomes overall - a Swedish population-based study

Frisk G, Ekberg S, Lidbrink E, Eloranta S, Sund M, Fredriksson I, Lambe M, Smedby KE.
Breast Cancer Research. 2018 Dec; 20:142

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LIST OF ABBREVIATIONS

| | |
|------|---|
| AJCC | American Joint Committee for Cancer |
| ASA | Acetyl-Salicylic Acid |
| CI | Confidence Interval |
| COX | Cyclooxygenase |
| ER | Estrogen Receptor |
| ECOG | Eastern Cooperative Oncology Group |
| GPA | Graded Prognostic Assessment |
| HER2 | Human Epidermal growth factor Receptor 2 |
| HR | Hazard Ratio |
| ICD | International Classification of Disease |
| LISA | Longitudinal Integration database for health insurance and labor market Studies |
| NCR | National Cancer Register |
| NPR | National Patient Register |
| OR | Odds Ratio |
| RPA | Recursive Partitioning Analysis |
| PR | Progesterone Receptor |
| RTOG | Radiation Therapy Oncology Group |
| WBRT | Whole Brain Radiotherapy |
| WHO | World Health Organization |

1 BACKGROUND

1.1 EPIDEMIOLOGY

Breast cancer is the most common malignant disease in women, accounting for about 25% of all cancers worldwide and about 30% of all female cancers in Sweden. There are around 8000 patients, who get the diagnosis breast cancer, in Sweden each year. The median age at breast cancer diagnosis in 2016 was 65 years [1, 2]. The breast cancer incidence has increased by 1.4 % each year in Sweden during the last 20 years, and the increase is most evident in women between the ages of 50-69 years. A moderate increase is however seen in all other age groups. Previously, the incidence peak was amongst the oldest women, more recently the 60-69 year age group has the highest incidence [3]. The 10-year relative survival has gone from almost 50% to over 80%, similarly, 5-year relative survival has increased from 60% to about 90% from 1970 until 2016 [3]. Survival is dependent on the stage of breast cancer at primary diagnosis. The 5-year relative survival for women with a stage 0-I tumor is close to 100%, for stage II about 80%, for stage III approximately 60% and for stage IV only 20% [4]. Breast cancer mortality varies between countries. Sweden has had a relatively low mortality for several decades [5] despite a good survival approximately 1500 patients die each year due to breast cancer in Sweden and metastatic breast cancer is the over-all most common cause of death in Swedish females up to the age of 65.

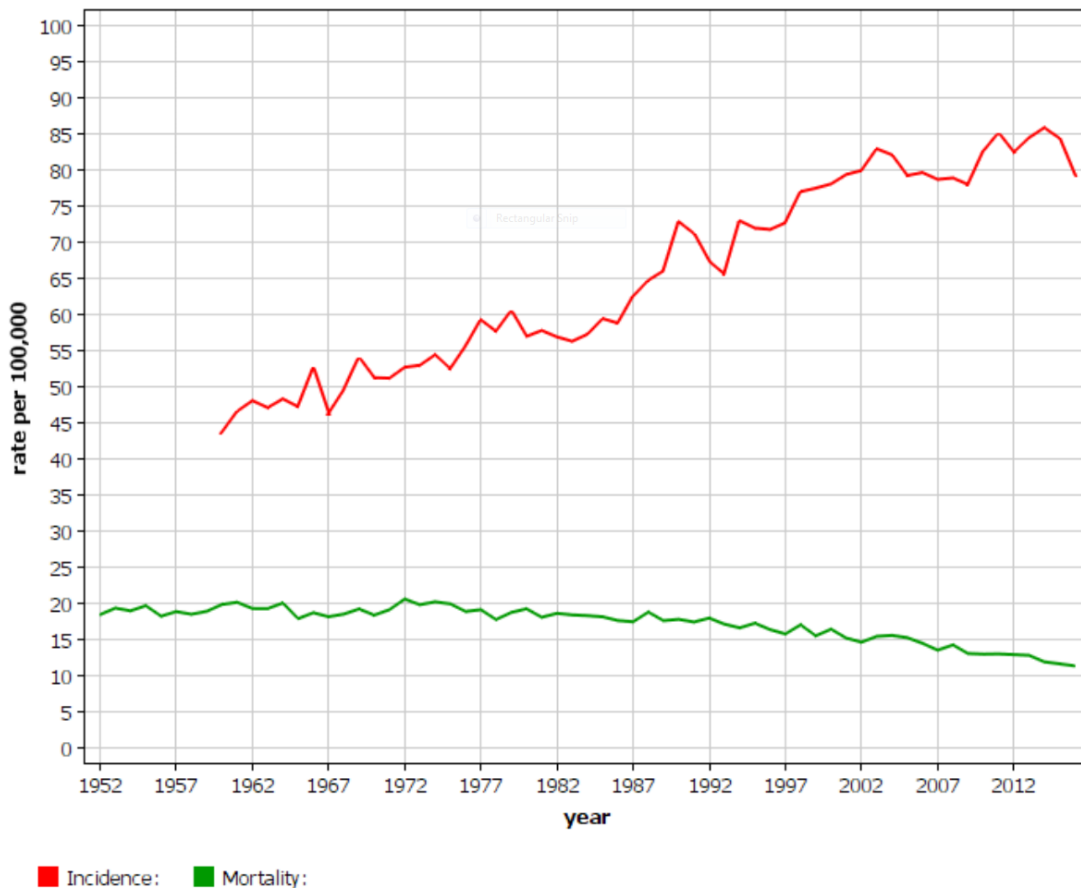


Figure 1. Incidence (red) of and mortality (green) due to breast cancer over time in women age 0-85+ in Sweden, (NORDCAN, Association of the Nordic Cancer Registries)

Although the treatment for breast cancer with metastases have improved the prognosis [6], this disease is still considered an incurable [7]. Symptoms of metastases in breast cancer can be presence of new lumps in the breast or axilla, pain from the bone, abdomen or chest, dyspnea or headache [8]. Common metastatic sites are bone, liver, lung, skin and brain.

Brain metastases are the most common type of tumors in the brain [9] and breast cancer is, after lung cancer, the second most common cause of brain metastases [10]. Brain metastases due to breast cancer may have increased in more recent years [10, 11]. This may be due to several factors, including technical advances in neuroimaging and modifications of systemic treatment schedules leading to an increased survival [9, 12].

1.2 BREAST CANCER TUMOR CHARACTERISTICS

Breast cancer is a heterogeneous type of cancer, with different histological and molecular clinical characteristics. The different characteristics lead to different clinical behavior and response to oncological treatment. In clinical practice, the categorization of breast cancer is the basis for decisions about oncological treatments, clinical trials and planning for follow-up schedules. The last decades there have been great progress in the molecular classification of the breast cancer disease.

1.2.1 Histological type

Breast cancer has historically only been sub-classified into subgroups based on histology [13, 14]. The main histological subtypes are the ductal and lobular types, constituting cancer, accounting for about 75% and 15%, respectively [15, 16], referring to the origin of the tumor (see Figure 2). Ductal breast cancer is also called “no special type” according to the latest WHO-classification from 2012 [17]. There are also other more uncommon histological types including the tubular, medullary and mucinous (colloid) types and sarcoma in the breast. The histological breast cancer types are not crucial for decisions about treatment, although the lobular breast cancer type can easily be underestimated in size clinically and radiologically before surgery.

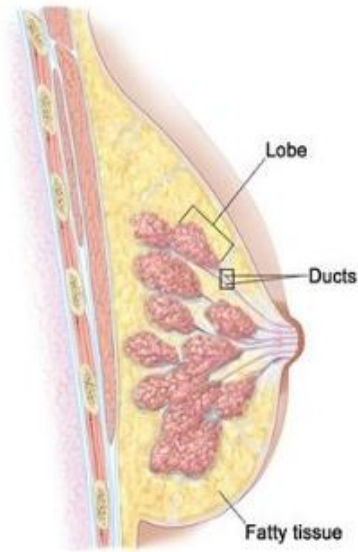


Figure 2. Breast cancer tissue. Ductal and Lobular histological types are most common. Reprinted with permission from the publisher [18].

1.2.2 Stage

The TNM staging classification system was introduced in 1959, developed by the American Joint Committee for Cancer (AJCC). TNM is the acronym for primary tumor (T), regional lymph nodes (N), distant metastases (M) and used for staging the majority of the solid tumors [19]. In breast cancer, tumor size (T) is a measure of the largest tumor in the breast, the presence and size of lymph node metastases (N) and the presence or not of distant metastases (M). The TNM-status in breast cancer is also a prognostic marker [20].

Table 1. The TNM Classification and staging of breast cancer [19]

| Stage | T | N | M |
|-------|-----|-----|----|
| 0 | Tis | N0 | M0 |
| IA | T1 | N0 | M0 |
| IB | T0 | N1* | M0 |
| | T1 | N1* | M0 |
| IIA | T0 | N1 | M0 |
| | T1 | N1 | M0 |
| | T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| IIIA | T0 | N2 | M0 |
| | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |

| | | | |
|------|-------|-------|----|
| IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| | T4 | N2 | M0 |
| IIIC | Any T | N3 | M0 |
| IV | Any T | Any N | M1 |

* There are cancer cells (0.2 mm-2 mm) in the lymph nodes

1.2.3 Grade

Grade is based on morphological characteristics of the breast cancer cells, including scores on tubular formation, nuclear polymorphism and mitotic count I-III [21]. To obtain the tumor grade, the scores for each category are summed up, giving scores from 3-9 points.

Grade I (3-5 points): These breast cancer cells are well differentiated and look very much like normal breast cells and they grow in well-organized patterns. Not that many cells are in cell division to make new breast cancer cells.

Grade II (6-7 points): These breast cancer cells are moderately differentiated and do not look like normal breast cells and are growing and dividing faster than normal breast cells.

Grade III (8-9 points): These breast cancer cells are poorly differentiated and look different from normal breast cells. They grow in irregular patterns, with many cells in cell division to make new breast cancer cells.[21]

1.2.4 Hormonal receptors

The estrogen receptor (ER) is an intracellular receptor expressed in several tissues, including in breast, endometrium, ovarian stroma and hypothalamus [22]. ER positivity in the breast cancer cells is a strong predictor of response to oncological endocrine therapy [23, 24]. Guidelines in Sweden recommend the cut-off to be less than 10% of the breast cancer cells to be stained positive for the hormone receptors to be classified as negative [5, 25, 26]. The progesterone receptor (PR) is also an intracellular receptor and its expression is induced by estrogen signaling via ER [27]. PR is therefore lower in breast cancer cells in postmenopausal women as the estrogen levels decreases [28]. In Sweden, about 85% of the breast cancer patients have cancer tumors that express hormone receptors ER and/or PR.

1.2.5 Human epidermal growth factor receptor 2 (HER2)

The Human epidermal growth factor receptor 2 (HER2), is a transmembrane receptor and member of the Epidermal Growth Factor Receptor Tyrosine Kinase group. It is coded by the erythroblastic oncogene B (ERBB2), which is located on the long arm of chromosome 17 [29]. This gene is coding for a network of proteins in signaling pathways controlling cellular proliferation, apoptosis and capacity to metastasize [30]. Amplification of this gene produce high HER2 protein levels, which are seen in 12-20 % of primary breast tumors [31]. HER2 positive breast cancer is associated with worse prognosis [32], but also with the possibility to administer treatments targeting the receptor [29, 33]. HER2 is routinely analysed on the primary

breast cancer tumors, either by HER2 protein quantity measurement or by determining gene amplification [34]. Treatment with anti-HER-2 antibodies, was introduced in year 2000 in Sweden and gradually introduced in oncological clinical practice.

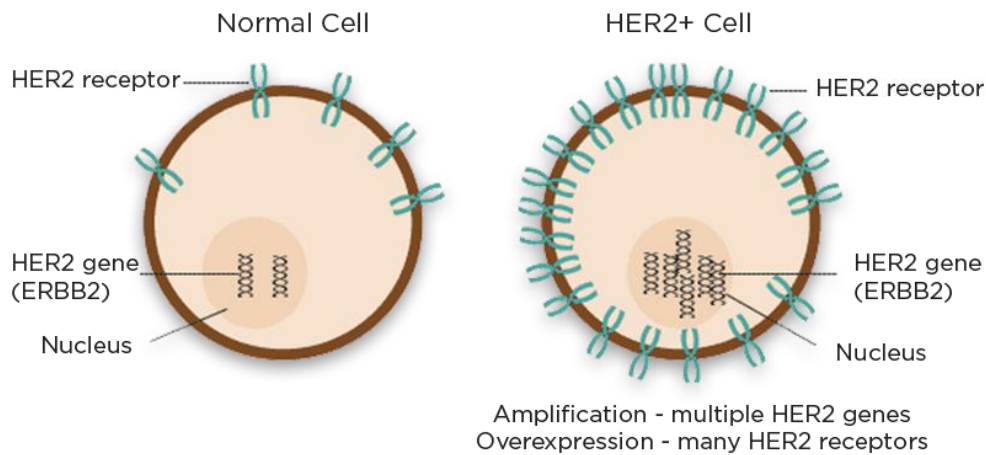


Figure 3. A HER2 amplified breast cancer cell and a normal cell. Reprinted with permission from the publisher [35].

1.2.6 Proliferation

Proliferation is a prognostic marker in most cancer types [36]. Proliferation is often measured in clinical practice by the biomarker Ki-67, which is a protein expressed during all the active dividing phases of the cell cycle, but not in the resting phase (G0) [37, 38]. Ki-67 acts as a surfactant and prevents the chromosome to collapse during cell division [39]. Tumor proliferation rate is assessed by the number of nuclei positively stained for Ki-67-antibodies divided by the total number of analysed breast cancer cells, presented in percentage [40]. This percentage level of Ki-67 is used in clinical practice as a prognostic marker and to separate breast cancer subtype Luminal A from Luminal B [41].

1.2.7 Molecular subtypes

The molecular subtypes in breast cancer were first described in 2000 by Perou and Sorlie et al. [42]. They found four subtypes with distinct gene expression patterns using frozen tumor material: Luminal, HER2-enriched, Basal-like and normal-breast-like. Later studies led to the Luminal subtype being divided into Luminal A and Luminal B [43]. The St Gallen International Breast Cancer Conference suggested in 2011 the following definition of subtypes of breast cancer: Luminal A (ER + and/or PR+, Ki-67 low and HER2-), Luminal B (ER + and/or PR+, Ki67 high and/or HER2+), HER2-positive (ER-, PR- and HER2+) and triple negative (ER-, PR-, and HER2-) [44]

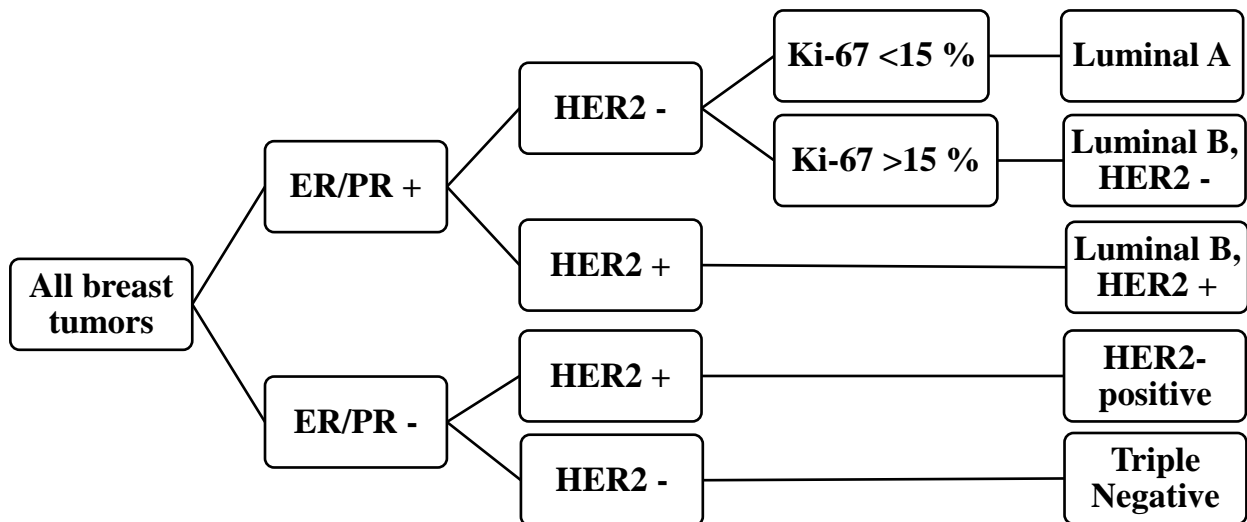


Figure 4. Molecular subtypes of breast cancer

1.3 BREAST CANCER TREATMENT

Based on the analysis of the breast cancer subtype and stage, patients are treated with surgery and individualized therapy (radiotherapy, chemotherapy, antibodies and/or endocrine therapy). The oncological treatments added to surgery are called adjuvant therapies.

1.3.1 Neoadjuvant chemotherapy

The majority of adjuvant breast cancer therapy is given post-operatively. When it instead is given pre-operatively, it is defined as neoadjuvant therapy. Neoadjuvant chemotherapy is offered to breast cancer patients with locally advanced tumors, i.e., T3-T4 or fixed lymph nodes [45], and to breast cancer patients who may benefit from breast tumor shrinkage before surgery. Neoadjuvant treatment in breast cancer has become more common in the last years [46]. There are regional differences in Sweden in the use of neoadjuvant chemotherapy, but the proportion is generally increasing. In 2016, 8,6 % of all breast cancer patients in Sweden received neoadjuvant chemotherapy before surgery [1].

1.3.2 Surgery

Surgery is one of the treatments in breast cancer and still considered as the most important one. Several randomized trials have compared breast preservation surgery with mastectomy [47, 48]. Breast preservation surgery (partial mastectomy followed by postoperative radiation therapy) is a safe medical alternative to mastectomy for unifocal breast tumors regardless of adjuvant treatment [47-49]. The upper size limit of the tumor for breast-preserving surgery has not been established, but studies have included few patients with tumors larger than 4 cm [48]. In 2016, 80% of all breast cancer patients were treated with breast-preserving surgery in Sweden [1]. The proportion of mastectomies has gradually decreased due to reduced tumor size at diagnosis, possibly due to mammographic screening. Mastectomy is a good alternative to breast-preserving surgery and postoperative radiotherapy, if there are any contraindications to radiotherapy after surgery, in multifocal tumors, after local recurrence after previous partial

mastectomy followed by postoperative radiotherapy, in inflammatory tumors or other T4 tumors after neoadjuvant treatment.

Surgery of the axillary lymph nodes are performed if there are known axillary metastases or macro metastasis in the sentinel node at the time of surgery. The sentinel node is the first lymph node reached from the breast and it has been shown that it is safe to not surgically remove the lymph nodes from the axilla, if the sentinel node is free from breast cancer. It is routine surgical practice to leave the lymph nodes if the sentinel node biopsy contains a minimal number of breast cancer tumor cells (isolated tumor cells or micrometastases < 2 mm). There is however a debate about whether it is safe to leave the axillary lymph nodes if there are macrometastases in the sentinel node. The rationale for not undergoing extensive axillary surgery is to avoid post-operative morbidity such as lymph edema, nerve sensations or pain in the arm. There are two ongoing studies in Sweden, SenoMic and SENOMAC, which are investigating the best way to handle micro- and macrometastases in sentinel nodes. SenoMic is a Swedish national cohort study, which investigates survival and axillary lymph node recurrences in breast cancer patients with sentinel node micrometastasis, who not have undergone axillary surgery [50]. SENOMAC is a randomized trial, including several centers in Sweden and other European countries. The hypothesis in this study is that axillary surgery can be avoided in breast cancer patients with 1 or 2 sentinel nodes with macrometastases without making the breast cancer specific survival worse [51, 52].

1.3.3 Chemotherapy

Adjuvant treatment with chemotherapy after primary surgery is used to treat micro metastasis and has been associated with an improved 5-year survival in breast cancer [53]. Results from 40 randomized trials with over 13,000 women further show that combination therapy is more effective than treatment with a single cytotoxic drug and that chemotherapy with 8-24 months duration was not beneficial compared to 4-6 months of treatment [53]. In 2016, 77% of the breast cancer patients with stage I-III received adjuvant chemotherapy after surgery in Sweden[1].

1.3.4 Radiotherapy

Postoperative radiotherapy reduces the risk of local breast cancer recurrence and increases breast cancer-specific survival, after breast-preserving surgery and after mastectomy [54]. In 2016 in Sweden 93% of the patients who had breast-preserving surgery received adjuvant treatment with radiation therapy, 90% among patients > 65 years of age [1].

1.3.5 Anti-HER2 treatment

As specified above, HER2 is an onco-protein overexpressed in 12-20% of primary breast cancer tumors, often referred to as HER2-positive tumors. The presence of overexpression of HER2 is associated with a worse prognosis [31, 32]. The most commonly used anti-HER2 therapy is trastuzumab, a monoclonal antibody binding to the extracellular part of HER2. Patients with a HER2-positive breast cancer should be offered with adjuvant anti-HER2 therapy. In Sweden

2016, 14% of the diagnosed breast cancer patients had HER2-positive tumors, of which 95% were treated with adjuvant Trastuzumab for one year [1].

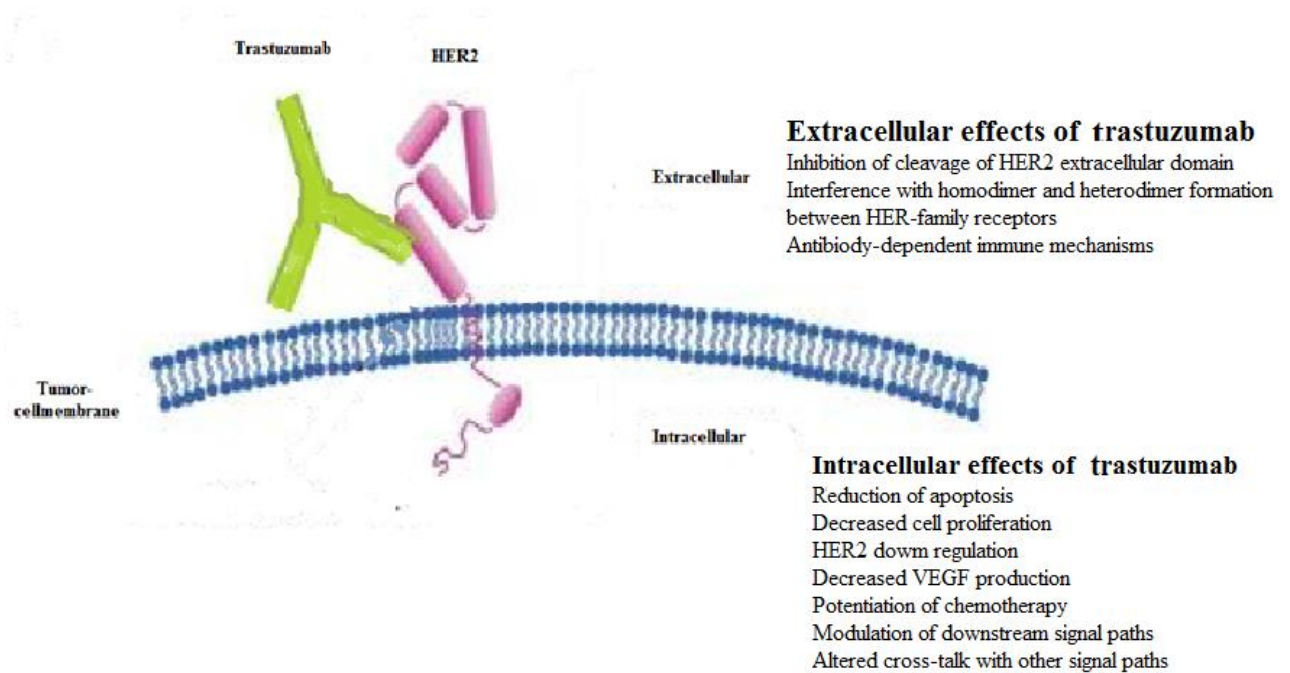


Figure 5. Extracellular and intracellular mechanisms of anti-HER2 treatment, trastuzumab

1.3.6 Endocrine therapy

Of all diagnosed breast cancer tumors, about 85% express estrogen receptors (ER) [1]. Through these receptors, the female sex hormone estrogen can bind to the tumor cell nuclei and stimulate cell division which leads to tumor growth. The options for endocrine therapy today is tamoxifen, mainly offered to premenopausal patients, or aromatase inhibitors mainly offered to postmenopausal patients. If aromatase inhibitors is to be used in the premenopausal setting, it needs to be combined with gonadotropin-releasing-hormone (GnRH) analogues for ovarian function suppression. When breast cancer patients with ER + tumors are treated with adjuvant tamoxifen for 5 years it is estimated to result in an approximately 13% absolute risk reduction in breast cancer recurrence and 9% absolute reduction in breast cancer mortality at fifteen year follow-up. Prolonged treatment with tamoxifen for a total of 10 years may provide a further 3% decrease in recurrence and just over 2% improved breast cancer survival. Adjuvant treatment with aromatase inhibitors as monotherapy for 5 years gives a reduced risk of recurrence by almost 4% compared to tamoxifen, and decreases breast cancer mortality after 10 years by 2.1% and overall mortality by 2.7% [55-60]. In Sweden about 89% of all who were diagnosed with an ER positive tumor received adjuvant endocrine therapy in 2016 [1].

1.3.7 Aspirin (acetyl-salicylic acid, ASA)

Even though we have a generally good prognosis overall in breast cancer, many patients still die every year due to metastatic breast cancer and therefore we still need new and cost-effective treatments. There are several recent studies indicating that low dose aspirin use and potentially also other non-steroidal anti-inflammatory drugs (NSAIDs) can improve the prognosis in cancer [61-63], mainly colorectal cancer, but perhaps also breast cancer [64, 65]. The mechanisms behind this are not clearly known, but possible biological mechanisms include anti-inflammatory effects, hormonal changes and inhibition of platelets [66]. Aspirin irreversibly inhibits cyclooxygenase, COX 1 and COX-2, which both are needed and involved in the synthesis of prostaglandins. Prostaglandins are found in higher levels in breast cancer tissues than in normal breast tissues. Prostaglandins seem to inhibit apoptosis and stimulate angiogenesis in breast cancer cells and may also stimulate aromatase activity, which increases circulation estrogen levels [67]. It has been reported that postmenopausal women using aspirin have lower estrogen levels in blood compared to non-users [68]. Aspirin may also have the ability to inhibit platelet-induced adhesion of tumor cells, circulation in the blood, which could have implications for the ability spread metastases [69-71].

Commonly used low-dose aspirin doses are 75 mg or 160 mg. The low-dose tablets of aspirin are only available by prescription from doctors and represent 90% of all aspirin sold in Sweden (including over the counter) [72].

Several studies have reported an association of low-dose aspirin use with lower risk of breast cancer-specific death among breast cancer patients, which has however been limited to current and not past use of low-dose aspirin [64, 73-75]. In a Swedish nested-case-control study, low-dose aspirin was only associated with a reduced risk of breast cancer deaths near death or end of follow-up with a decreased risk of breast cancer death HR 0.69 (95% CI 0.56, 0.86) [76]. Medication patterns may change in the end of life period, why the results in this study might be explained by reverse causation.

Because of the mixed results from previous studies of low-dose aspirin use in breast cancer and yet no results from randomized trials, information from observational studies remain important for the understanding of role for aspirin for breast cancer patients and among which subgroups that would benefit the most. There are two ongoing randomized trials (in US and UK), evaluating low-dose aspirin use and breast cancer disease free survival [77]. The results from these studies will still not be available in many years (preliminarily in 2026). In Sweden low-dose aspirin use is common for cardio-vascular disease prevention.

1.4 METASTATIC DISEASE

Despite a high cure rate and a long overall survival for breast cancer patients, 1400-1500 patients die of metastatic breast cancer per year in Sweden [78]. The clinical situation with distant metastases, referred to as stage IV or generalized breast cancer has historically been considered as non-curable. The mortality in breast cancer has decreased in the last decades from 30 cases per 100 000 in 1980 to 20 cases per 100 000 in 2017 [79]. Mammographic screening and new adjuvant oncological treatments are believed to explain the decrease in mortality.

Mammographic screening has been shown to reduce breast cancer mortality in the screened age groups of women 40-74 years old. The reduction of mortality has been 20-25% in the population [80] and even higher among the screening participants [81]. However, the screening program for breast cancer has been questioned and there is a concern that the screening leads to over diagnosis and treatment. A recent published Swedish study suggest that over diagnosis in the mammographic screening program for women 50-69 in Stockholm was a minor phenomenon [82]. More effective adjuvant breast cancer treatment can also explain the reduction in mortality in breast cancer.

Median overall survival in palliative breast cancer disease is approximately two years but can range from a few months to many years [76]. Prognosis for breast cancer patients with distant metastases seem to be better over time. In a Swedish study from 2011, they reported a trend of better survival over time for breast cancer patients with distant metastases 60 years or younger, but not for older patients [83].

Prognostic factors for breast cancer, stage IV are:

- **Age:** older age at the time of recurrence of distant metastases is associated with poorer prognosis and a shorter survival, probably in part due to comorbidity [76, 84].
- **Performance status:** a better performance status is associated with a better prognosis (chapter 1.5).
- **Recurrence free interval:** patients who have their first recurrence of distant metastases within two years since primary diagnosis have poorer prognosis after relaps in terms of overall survival compared with patients with a first recurrence after more than two years [76, 85-87].
- **Metastasis site:** lymph node or chest-wall metastases are associated with a better prognosis than distant metastases and bone metastases are associated with a better prognosis compared to other distant sites [83, 88-90]
- **ER and HER2-status:** breast cancer tumors that express hormone receptors have been associated with a better prognosis and survival also in stage IV disease [91]. HER2-positive tumors had a negative association with survival before trastuzumab was introduced. Triple negative breast cancer is the sub-type with worst prognosis [92-94].
- **Adjuvant treatment:** use of adjuvant systemic treatment may be associated with poorer survival after relapse, probably due to the selection of more aggressive cellular clones with higher resistance to treatment [83].

Bone, lung, liver and brain metastases are the most common distant metastases in breast cancer [95, 96]. The prevalence of both distant metastases and local recurrence (chest wall or lymph nodes) are more common in triple negative tumors followed by HER2-type [97, 98].

Brain metastases are associated with a particularly poor prognosis [84, 95] and have been reported to develop in about 5-10% in patients with breast cancer during follow-up up to 14 years [10, 12, 86, 87]. It has been suggested in a few studies that the incidence of brain metastases in breast cancer has increased [84]. If so, this may be due to improved survival after primary breast cancer and/or that available adjuvant and palliative treatments are less efficient

in treating micrometastatic disease in the central nervous system compared with in other organs. Studies indicate that the risk of brain metastases is more pronounced in breast cancer patients with a young age at primary diagnosis, and if the primary breast cancer tumor is triple negative (ER-negative, PR-negative and HER2-negative) or of HER2-type (ER-negative, PR-negative and HER2-positive) [99-101].

Stage IV breast cancer is treated with a palliative intent and with the aims of prolonged survival and to get symptom control of the disease. Treatment can be advanced and including surgery, radiotherapy, chemotherapy, endocrine therapy, anti-HER2 therapy or other targeted drugs depending on the tumor biology.

1.5 PERFORMANCE STATUS

In medicine, especially in oncology, performance status is a way of quantifying the patients' activities of daily life and general well-being. Performance status is also used in clinical practice to determine if a patient should be given the planned chemotherapy treatment or not and if dose adjustment is required. It can also be used to determine the general condition and well-being in palliative care.

There are several scoring systems to measure performance status; Karnofsky Performance score and ECOG/WHO/Zubrod score are two common ones used in clinical practice.

The Karnofsky Performance Score is a scale running from 100 to 0, where 100 is perfect health and 0 death. This scale is named after Dr. David A. Karnofsky, who described this scoring system in 1948 with the primary purpose to help the doctors to evaluate if the patient has the ability to survive cancer chemotherapy [102].

Table 2: Karnofsky Performance score

| | |
|-----|--|
| 100 | Normal; no complaints; no evidence of disease |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 80 | Normal activity with effort; some signs or symptoms of disease |
| 70 | Cares for self; unable to carry on normal activity or to do active work |
| 60 | Requires occasional assistance, but is able to care for most of their personal needs |
| 50 | Requires considerable assistance and frequent medical care |
| 40 | Disabled; requires special care and assistance |
| 30 | Severely disabled; hospital admission is indicated although death not imminent |
| 20 | Very sick; hospital admission necessary; active supportive treatment necessary |
| 10 | Moribund; fatal processes progressing rapidly |
| 0 | Dead |

The Eastern Cooperative Oncology Group (ECOG) score [103] also called the WHO or Zubrod score, runs from 0 to 5, where 0 is perfect health and 5 is death. It is simpler to use and therefore has an advantage over the Karnofsky Performance status scale.

Table 3: ECOG/WHO/Zubrod score

| | |
|---|---|
| 0 | Asymptomatic, fully active, able to carry on all predisease activities without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |

| | |
|---|---|
| 3 | Capable of only limited self-care, confined to bed or chair 50% or more of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

A translation exist between the Zubrod/ECOG/WHO and the Karnofsky systems that is clinically useful and has been validated in a large sample of lung cancer patients [104].

- Zubrod 0–1 equals Karnofsky 80–100
- Zubrod 2 equals Karnofsky 60–70
- Zubrod 3–4 equals Karnofsky 10–50

1.6 BRAIN METASTASES TREATMENT

Patients with breast cancer and brain metastases have a poor prognosis, however with a large variability in survival. Median overall survival from diagnosis of brain metastases in breast cancer vary from a few months up to several years [99]. Tumor subtype, performance status, age and other distant metastases have been showed as important prognostic predictors [105, 106]. The most frequent symptoms the patients with brain metastases in breast cancer have are headache, gait disturbance, nausea and vomiting [107].

Patients with minor small brain metastases may be treated with neuro-surgery, sometimes followed by radiotherapy, or with stereotactic radiosurgery [108]. Patients with multiple brain metastases or leptomeningeal carcinomatosis are commonly treated with whole brain radiotherapy (WBRT) and the goal for these patients is primarily improvement of symptoms and neurological deficits [109]. Studies that investigate chemotherapy regimens (for example cisplatin, capecitabine and temozolomide) in patients with brain metastases have reported response rates between 4% and 38 % [110]. The blood-brain-barrier is a selective diffusion barrier at the endothelium surrounding the brain. This endothelium is missing both fenestrations and tight junctions. It is like a barrier, from the blood to the brain, which regulates the exchange between blood and brain to prevent potentially toxic substances to enter the brain. [111]. The blood-brain-barrier stops most cytotoxic drugs from crossing over to the brain, but the role of systemic therapy is being re-evaluated given the availability of new monoclonal antibodies, antibody-drug conjugates, and new small molecules. Lapatinib is a small tyrosine kinase inhibitor, which can cross the blood-brain-barrier, showing activity against both the HER2 and EGFR receptors, and thus can be used for brain metastases in breast cancer [112]. In a trial (LANDSCAPE) including HER2-positive breast cancer patients with brain metastases they

reported a response of 0.66 (95% CI 0.50, 0.80) for a combination of lapatinib and capecitabine, all responders were partial [113].

Radiation Therapy Oncology Group’s recursive partitioning analysis (RPA) graded prognostic assessment (GPA) and diagnosis specific GPA are scores that are used to help predict the prognosis for breast cancer patients with brain metastases. These prognostic scales have been developed for prediction of prognosis in patients with brain metastases due to any cancer [114] and can be a useful tool when choosing different treatment options for patients or to identify patients with poorer prognosis to avoid overtreatment in a late palliative stage of brain metastases in breast cancer.

Table 4. Diagnosis-specific GPA score for breast cancer

| GPA | Significant prognostic factors | GPA scoring criteria | | | | |
|---------------|--------------------------------|----------------------|------|-----------------|-----------------|-----------------|
| | | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| Breast cancer | Karnofsky Performance score | < 60 | 60 | 70-80 | 90-100 | triple positive |
| | ER/PR/HER2 | triple negative | | ER/PR+ HER2- | ER/PR- HER2+ | |
| | Age | ≥ 70 | < 70 | | | |

1.6.1 Whole brain radiotherapy (WBRT)

Whole brain radiation therapy (WBRT) has been the most common treatment for brain metastases since 1950s [115-118]. Before WBRT, the standard treatment was steroids and the median survival was 1-2 months [119, 120]. The addition of WBRT extended the survival is about 3-6 months on average [117, 119-121]. Nowadays, the use of WBRT has decreased due to availability of other treatments, such as surgery for minor brain metastases, stereotactic radiosurgery and new oncological treatments. There are also concerns about late toxicity of WBRT in long-term survivors. However, WBRT is still the treatment of choice for patients with poor prognosis and massive numbers of brain metastases, poor performance status and progressive cancer disease. The goal of treatment with WBRT is symptom control. The most commonly used dose for WBRT in Sweden is 20 Gy, in 5 fractions (4 Gy per fraction).

If WBRT is initiated in late stages of brain metastases in breast cancer, it may however also affect the care in late palliative stages and the end-of-life period and the patient’s choices of care in this period. Among cancer patients in the Western world, deaths in hospital are common, although many patients prefer home as the place of death [122-124].

1.7 PALLIATIVE TREATMENT AND CARE

When curing the cancer disease no longer is possible, a clear and conscious approach is required in health care to help the patient as well as the family and other close persons. Palliative care is specialized medical care for patients with incurable life-threatening diseases. Palliative care has a focus on symptom relief, i.e., alleviating symptoms like pain, nausea or other symptoms of the disease or of the treatment. It also offers psychological, social and existential support for the patient, the family and close persons. The goal of palliative care is to improve the quality of life for these involved individuals. Palliative care is given by a specially-trained team of physicians, nurses, counselors and physiotherapists. This team also work together with the patient's other doctors in the hospital to provide extra support in this situation. Teamwork between different occupational groups in the palliative team and the hospital is needed for a high-quality palliative care. Palliative care is provided to patients in all ages and with serious diseases in all stages, and it can be given together with oncological or other treatments [125]. Palliative care can be offered at home, in nursing homes, in hospitals or at a specialized palliative care unit (hospice). When treating patients with a late stage cancer disease such as brain metastases, discussions with the patients, their families and close persons of their wishes and requests of the care in the late palliative stage and end-of-life setting should be considered aiming to avoid overtreatment and for the best quality of life for each patient.

2 AIMS OF THE THESIS

In this thesis, we aimed to study the incidence and predictors of brain metastases in breast cancer as well as treatment aspects in primary breast cancer and for patients with brain metastases.

More specifically, the aims were to:

Study I and II: Study time trends and if the incidence of brain metastases due to breast cancer has increased in Sweden in recent years

Study III: Study the benefits of whole brain radiotherapy for brain metastases in terms of level of care and survival

Study IV: Study if low-dose aspirin use improves the prognosis in patients with breast cancer in terms of survival

3 MATERIAL AND METHODS

The four studies included in this thesis are based on Swedish population-based registers, quality-of-care registers and radiotherapy files in ARIA and other medical records at Karolinska University hospital.

3.1 DATA SOURCES

3.1.1 The Swedish National Cancer Register (NCR)

The Swedish National Cancer Register is kept by the National Board of Health and Welfare. The register includes malignant diseases of Swedish residents since 1958. Reporting to this register is mandatory by law for all new malignant tumors by physicians in Sweden. This system guarantees completeness and reliability. The NCR is estimated to be >95% complete [126]. For each patient, the register keeps record of the personal identification number, sex, age, date of diagnosis and diagnostic methods, the hospital providing the diagnosis and type of malignancy stored as International Classification of Disease (ICD) codes [127].

3.1.2 The National Breast Cancer Quality Register

The National Breast Cancer Quality Register is based on information from six different regional breast cancer quality-of-care registers in Sweden. This national register was started in 2008. The regional Stockholm-Gotland register was started in 1976, The Uppsala-Örebro regional register in 1992 and the register of the North region in 1980. The National register is updated continuously by matching with the Total Population Register, The Swedish National Cancer Register and the Swedish Causes of Death Register. The National Breast Cancer Quality Register contains collected data on breast cancer patients, tumor characteristics, surgical treatment and intended oncological treatments. When evaluating the register, the variables including parameters during diagnosis and primary surgical treatment have a high coverage and concordance in the register (>95%), however intended oncological treatment have lower concordance (66%-95%) [128]. Regarding oncological treatment during follow up, including palliative treatments, these variables have less coverage, 67% in 2014 [129]. Since 2008, this register has been organized on a web-based platform, INCA. In 2016, the coverage was 98% for diagnosis and primary treatment, but there is a concern that the coverage is lower in the oldest women. The oldest women may not be examined and diagnosed, why they may be outside the registers.

3.1.3 The Swedish Cause of Death Register

The Swedish Cause of Death Register is kept by the National Board of Health and Welfare. This register was initiated in 1751, and digitalized in 1952 [130]. The date and conditions related to the death are reported to the register on a death certificate issued by the physician that verifies the death. The completeness of the register is >99%. The register has information on the date and place of residence, underlying cause of death and contributing causes of death of all Swedish residents who die in Sweden or abroad. Individuals are identified by their personal identification number and the cause of death is coded using ICD codes [130].

3.1.4 The Swedish National Patient Register

The Swedish National Patient Register (NPR) is kept by the National Board of Health and Welfare. All inpatient care in the country has been recorded in the register since 1987 and the hospital outpatient care (not primary health care) since 2001. The information in the register contains hospital admission and discharge dates, outpatient visit dates and diagnoses made by the physician. The diagnoses are coded according to the International Classification of Diseases 9th revision (ICD-9) since 1987 and the 10th revision (ICD 10) since 1997. The NPR has a coverage of 99% of all somatic and psychiatric hospital discharges [131].

3.1.5 Longitudinal Integration database for health insurance and labor market studies (LISA)

The Longitudinal Integration database for health insurance and labor market studies (LISA) is kept by The Statistics Sweden and Social Insurance Agency since 1990. It holds data from the labor market, social and educational sectors for individuals (≥ 16 years old) in Sweden. Data is collected from several national registers of high quality and coverage. For each individual, detailed socioeconomic data is available, including employment and level of education [132].

3.1.6 The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register is held by the National Board of Health and Welfare. This register records all the dispensed prescribed drugs of the Swedish population prospectively beginning July 1st 2005. The register contains information on the date of dispensing, name of drug, dose and number of tablets prescribed and the Anatomical Therapeutic Chemical (ATC) code. The ATC classification system consists of 14 main anatomical groups and further subgroups under each main group [133].

3.1.7 ARIA

The ARIA® oncology information system is a software for planning and handling the radiotherapy at the radiotherapy department at Karolinska University hospital in Stockholm. In ARIA there is information on cancer diagnosis, start date for radiotherapy, dose and fraction of radiotherapy given.

3.1.8 BcBaSe

BcBaSe is a database linkage of three quality-of-care registers of breast cancer in Sweden based on information from the Stockholm-Gotland, Uppsala-Örebro and the North regions [134]. The BcBaSe has been linked with other health care registers including the Patient register, the LISA-register, the National Cause of Death Register and the Swedish Prescription register.

3.2 STUDY DESIGN AND STATISTICS

3.2.1 Cohort study design

A cohort study design was used in all four studies.

Participants that fulfill the inclusion criteria and are free from the outcome are selected to the study cohort. The exposures as well as possible confounders of interest are measured for each study participant. The study participants are followed over time until they have reached the outcome of interest, or are censored (due to e.g., death, emigration or end of follow up). Data for cohorts can be obtained from national registers. The advantage of using national registers are that they are population-based and aim to include all Swedish citizens (no selection). Linkage between several national registers may provide a wide range of data. The registers usually span over a long time period, good for longitudinal studies.

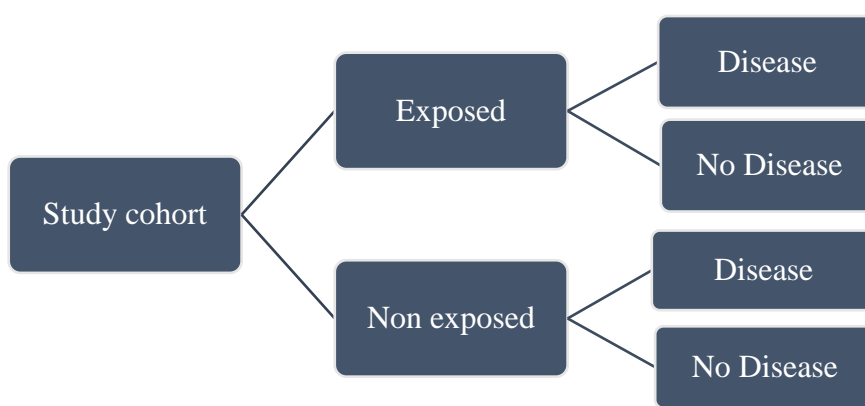


Figure 6. A cohort study outline

3.2.2 Study I

3.2.2.1 Study population:

We used a cohort study design to investigate the incidence of brain metastases over calendar time. To get this cohort we first identified 58 795 individuals with breast cancer in the Swedish National Cancer Register (NCR). The time period was from 1 January 1998 to 31 December 2006. Patients with other cancer diagnosis, except for non-melanoma skin cancer, before this time were excluded. We ended up with a final cohort of 50 528 patients in the study. The cohort was further linked to the National Patient Register, NPR, to obtain information on all admissions to hospital due to distant metastases during the follow-up. The cohort was also linked to the National Cause of Death Register to get information on dates of deaths.

3.2.2.2 Statistics:

Proportions of brain metastases and/or other distant metastases were compared and showed per time periods 1998–2000, 2001–2003 and 2004–2006. The first admission with metastases (brain metastases or other metastases outside of the brain) was denoted. We assessed

cumulative incidence of brain metastases admissions during follow-up by calendar period of breast cancer diagnosis. The incidence was plotted graphically with the Kaplan–Meier curve considering incidence during up to 3 years of follow-up. To compute hazard ratios (HR) and 95% confidence intervals (CI) we used a multivariate Cox proportional hazards model adjusted for year of birth, as a measure of the relative risk of admissions for brain metastases or other distant metastases comparing 3-year periods.

3.2.3 Study II

3.2.3.1 Study population:

We used the BcBaSe linkage to study a cohort of 30 996 women diagnosed with a first breast cancer during the period 2002-2012, in Stockholm-Gotland, Uppsala Örebro and the North region in Sweden. Women with other cancer diagnoses before breast cancer were excluded, as well as patients who emigrated before breast cancer diagnosis. In the BcBaSe there is a linkage with the National Patient Register, the LISA Register and the Cause-of-death Register, used in this study to obtain information on records of health care visits for distant metastases during follow-up, highest level of education and dates of death. By combining these data, we were able to compare incidence of brain metastases in breast cancer over calendar time. We also assessed predictors of brain metastases in breast cancer patients.

3.2.3.2 Statistics:

The number of women with breast cancer registered with brain metastases and clinical and demographical characteristics were presented and compared per time periods 2002-2004, 2005-2008 and 2009-2012. We used univariable and multivariable Cox proportional hazards models to compute HRs and 95% CIs as a measure of the relative risks. Proportional hazards assumption was tested using Schoenfeld residuals test and fulfilled. HRs were estimated by clinical and demographical characteristics and over calendar time in the three-year periods. All women were followed from the date of breast cancer to the date of brain metastases or other distant metastases, emigration, death, or December 31st 2013, whichever came first. The cumulative incidence of brain metastases in the three calendar time periods of diagnosis of breast cancer was also estimated to demonstrate the absolute risk of brain metastases and presented in a graph using cumulative incidence functions (treating death as a competing event).

3.2.4 Study III

3.2.4.1 Study population:

We used a cohort study design and identified 281 patients with brain metastases due to breast cancer treated with WBRT. We used ARIA-software at the Radiotherapy department at the Karolinska University hospital to identify the patients. These patients were treated with WBRT during the years 1999-2012. Individuals with other cancer diagnoses, or who were treated with radiotherapy following surgery from brain metastases or with bone metastases in the scalp were excluded. Thus, we ended up with a final cohort of 241 patients. The brain

metastases were located in the cerebrum, cerebellum or the leptomeninges. Through reviews of the included patients' medical records in the Take Care-system, we collected data on clinical and biological factors from the breast cancer tumor, administered medical oncological treatments and details about the radiotherapy to the brain. We further noted the performance status the week before (as WHO score) the start date of initiation of WBRT, and the family situation. The level of care for the patient (hospital or home) the week before and after WBRT was also noted. The outcome was overall survival and if the breast cancer patient was able to come home after the treatment or not.

3.2.4.2 Statistics:

We calculated the median survival in months, with interquartile range, from start of the WBRT. Using Cox proportional hazards models with HR and 95% CI, we compared time to death by clinical and breast cancer tumor characteristics. Proportional hazards assumption was tested using Schoenfeld residuals test and fulfilled. In a multivariate analysis, we adjusted for age at time of WBRT and also for calendar period of WBRT. In a second multivariate model, we adjusted for performance status as well. An unconditional logistic regression model was used to identify protective factors for coming home again using Odds Ratios, OR and 95% CI. This model was also adjusted for age at WBRT and calendar period of WBRT, and a second model also for performance status.

3.2.5 Study IV

3.2.5.1 Study population:

We used a cohort study design to evaluate the association between the exposure, dispensed low-dose aspirin, and the primary outcome, risk for breast cancer-specific death. The BcBaSe-cohort was used to identify all women with a first breast cancer during the period 1st of April 2005 - 31st December 2012. This cohort was further linked to several other Swedish registers including the Prescribed Drug Register, the NPR, the Cause of Death Register and the LISA Register including information on highest achieved educational level (≤ 9 years, 10-12 years, >12 years). Educational level was used as a proxy for socioeconomic status. Aspirin dispensings were used as a proxy for aspirin use.

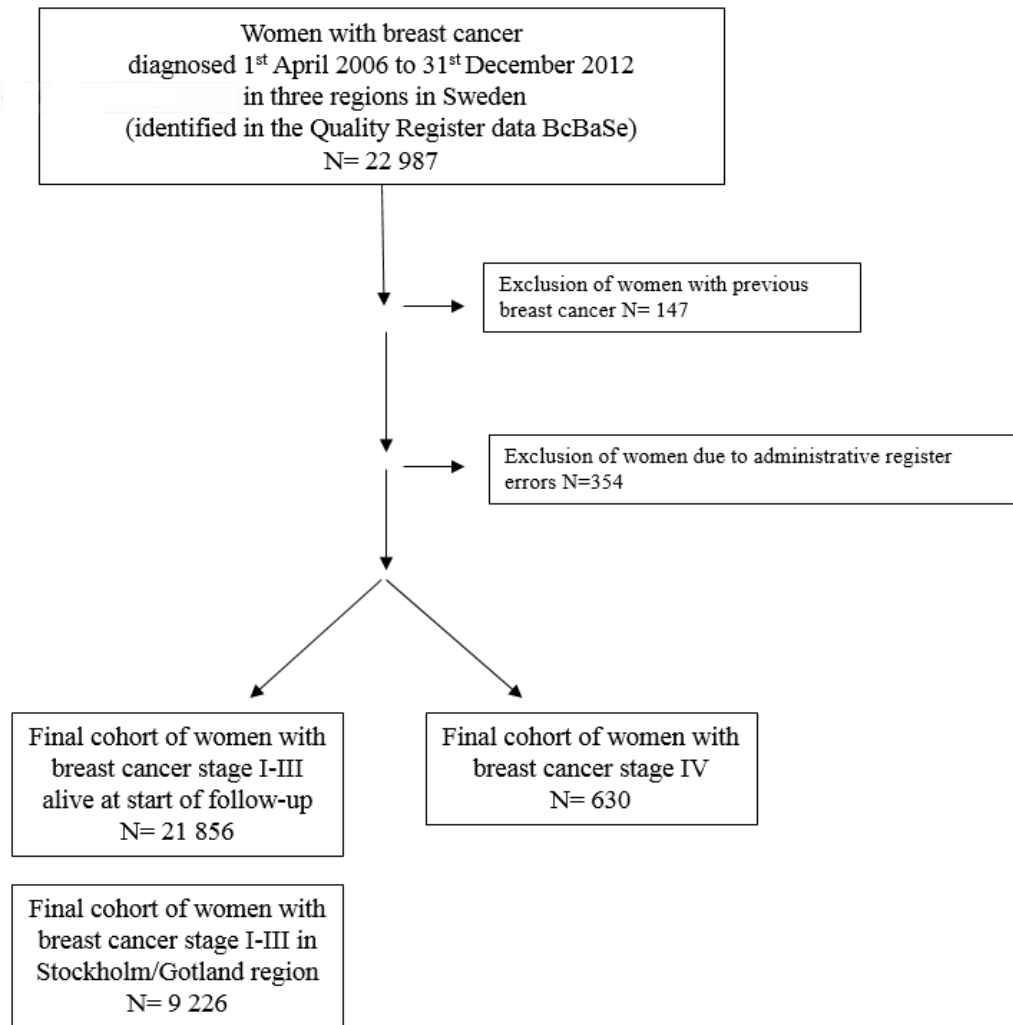


Figure 7. Flow-chart over the included breast cancer patients in study IV

3.2.5.2 Statistics:

We estimated the association between dispensed low-dose aspirin use before and after breast cancer diagnosis and the risk for breast cancer-specific deaths in three Swedish regions, and time to first recurrence or metastasis in the Stockholm-Gotland region. We used a Cox proportional hazards model with HR with 95% CI as a measure of association. Low-dose aspirin use before breast cancer diagnosis was assessed during the period 9-3 months before diagnosis, low-dose aspirin use (yes/no), if there was ≥ 1 dispensing of low-dose aspirin or not. Low-dose aspirin use was also assessed during 3-9 months after breast cancer diagnosis, (yes/no), if there were ≥ 1 dispensing or not. To estimate cumulative use, low-dose aspirin use was assessed during the entire follow-up from 3 months after diagnosis and onward as a time-varying exposure. During this classification a 180-day lag period was used in order to take into count changes in dispensing patterns immediately prior to death, since this period may entail changes in drug use due to end of life situation [135-137].

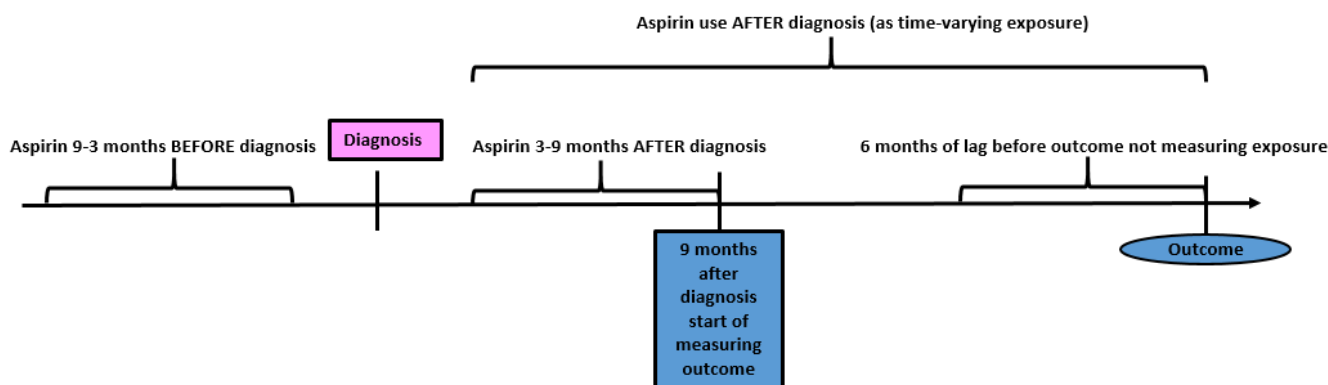


Figure 8. Flow-chart providing an overview of measurements of exposure and outcome after breast cancer diagnosis using a 180-day lag period.

We used one model with no adjustments, a second model adjusted for calendar-year of breast cancer diagnosis, age at breast cancer diagnosis, stage of breast cancer tumor, level of education and comorbidity diagnoses before breast cancer, and a third model adjusted for the same variables as in the second model plus metformin, statin and NSAID use as well as oncological treatments for breast cancer. In analyses of low-dose aspirin use after breast cancer diagnosis, the model was additionally adjusted for low-dose aspirin use before breast cancer diagnosis. We further studied low-dose aspirin use before and after diagnosis in subgroups of women by clinical and biological breast cancer characteristics, as well as for oncological treatment and risk of breast-cancer specific death.

All the analyses in study I and III were performed the SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002-2012 SAS Institute Inc was used for all analyses. The analyses in study II and IV was made in the Stata 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP)

4 RESULTS

4.1 STUDY I

In this Swedish cohort of 50 528 patients with breast cancer disease, median follow-up was 3.5 years and 696 (1.4%) were admitted to hospital with brain metastases during this time period. Among these 696 patients, 336 (0.7%) patients were admitted to hospital with brain metastases as their first and only distant metastasis and the other 360 (0.7%) patients were admitted to hospital with brain metastases along with other distant metastases. Brain metastases at time for breast cancer diagnosis and during follow-up were included. Admissions with other distant metastases, outside the brain, were found in 3 470 (6.9%) patients. The median time between breast cancer diagnosis and the first admission to hospital with brain metastases was 2.3 years for all the brain metastases patients, 1.8 years for the individuals with a first metastasis to the brain and 2.9 years for the individuals with brain metastases together with other metastases.

Incidence rates of brain metastases were lowest among patients diagnosed in 1999 and increased among patients diagnosed during the later time periods under study. When compared with the time period 1998–2000, patients diagnosed with a breast cancer during the time period 2004–2006 were at a 44% increased risk (HR 1.44, 95% CI 1.13, 1.85) of being admitted to hospital due to brain metastases.

The risk was more pronounced for breast cancer patients having brain metastases together with other distant metastases (HR 1.80, 95% CI 1.23, 2.63) than for the individuals with a first metastasis to the brain (HR 1.21, 95% CI 0.87, 1.68) in 2004–2006, compared with 1998–2000. The relative risk for admissions to hospital with other distant metastases were not significantly increased in 2001–2003, 1.02 (95% CI 0.95, 1.11), and borderline increased in 2004–2006, 1.11 (95% CI 1.00, 1.24), compared with 1998–2000. When estimating the risk of brain metastases by time of follow-up, the increased incidence was primarily observed the last 1.5 years of follow-up after breast cancer diagnosis 2004–2006 (HR 2.07, 95% CI 1.45, 2.94) than during the first 1.5 years (HR 1.08, 95% CI 1.76, 1.54), compared with 1998–2000.

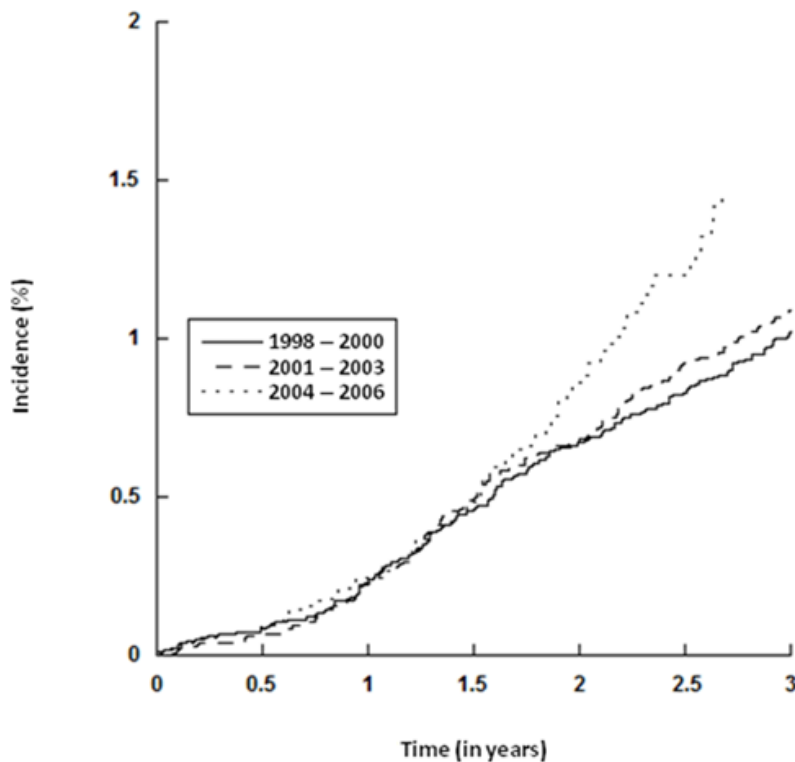


Figure 9. Breast cancer patients 1998-2006 in Sweden and the cumulative incidence of brain metastases

4.2 STUDY II

In the cohort of 30 996 patients, the median age at primary breast cancer diagnosis was 62 years (range 19-102 years). Demographically 13 050 (42.1%) of the patients were from Stockholm-Gotland, 12 861 (41.5%) from Uppsala-Örebro and 5 085 (16.4%) from the North region of Sweden. In the cohort 16 415 patients (54.1%) had a stage I tumor, 11 512 (38.0%) had a stage II tumor, 1 542 (5.1%) had a stage III tumor and 860 (2.8%) had a stage IV tumor at the time of breast cancer diagnosis. Regarding the primary breast cancer tumor characteristics, 24 260 (84.5%) were ER positive and 4 457 (15.5%) were ER negative, 2 658 (13.4%) were HER2 positive and 17 107 (86.6%) were reported as HER2 negative. There were 11 231 missing HER2. The most common clinical subtype was the luminal subtype (ER+, HER2-/HER2+), noted in 16 598 (85.9%) of the patients, whereas 974 (5.0%) had a non-luminal HER2 (ER-, HER2+) breast cancer and 1 974 (10.1%) of the women had an ER-HER2- breast cancer tumor. There were 11 450 missing subtype due to missing variables (mostly HER2). Stratified per time period there were 7 872 (25.4%) patients in the first time period 2002-2004, 10 954 (35.3%) 2005-2008 and 12 170 (39.3%) 2009-2012.

In the cohort, 789 (2.5 %) were registered with brain metastases at diagnosis and during follow-up. The median follow up was 5 years. The time to brain metastasis from primary breast cancer diagnosis was median 31 months (range 0-142 months). Number of brain

metastases per time period were 269 in period 2002-2004, 321 in 2005-2008 and 199 in the last period 2009-2012. Compared with the time period 2002-2004 the patients diagnosed with a primary breast cancer 2005-2008 had a risk estimate of 1.09 of having a brain metastasis (HR 1.09 95% CI 0.93, 1.30) and 2009-2012, patients were at 37% risk of having a brain metastases (HR 1.37 95% CI 1.12, 1.68) when adjusted for age and stage at time for primary breast cancer diagnosis

Table 5. Relative risks for brain metastases in breast cancer in Sweden 2002-2012

| Years | HR (95 % CI) | HR¹ (95 % CI) |
|----------------------|---------------------|---------------------------------|
| 2002-2004 | 1.0 | 1.0 |
| 2005-2008 | 1.09 (0.92, 1.29) | 1.09 (0.93, 1.30) |
| 2009-2012 | 1.19 (0.97, 1.44) | 1.37 (1.12, 1.68) |
| | | |
| HER2-positive | 1.0 | 1.0 |
| HER2-negative | 0.29 (0.24, 0.36) | 0.41 (0.33, 0.51) |
| | | |
| ER-positive | 1.0 | 1.0 |
| ER-negative | 4.93 (4.24, 5.72) | 3.73 (3.20, 4.34) |

¹Adjusted for **age and stage** at the time of breast cancer diagnosis

The median age at primary diagnosis was lower among patients with brain metastases than among other patients 56 years versus 62 years. Three-hundred and twenty-four patients (1.0%) were registered with brain metastases as their first distant metastasis and the remaining 465 (1.5 %) were registered with brain metastases in parallel with or following other distant metastases due to breast cancer. Among the patients with brain metastases 138 (34.2%) had a HER2 positive and 265 (65.8%) had a HER2-negative breast cancer tumor at primary diagnosis. Regarding ER, 372 (54.1%) were positive, 315 (45.9 %) were ER-negative.

During follow up 1 667 (5.4%) of the patients were registered with lung metastases, 1 642 (5.3%) with liver metastases and 2 297 (7.4%) with bone metastases.

4.3 STUDY III

In this cohort study, the breast cancer patients with brain metastases were treated with whole brain radiotherapy (WBRT). The median age at start of treatment was 58 years. The majority of the patients (n=212, 88%) were treated with 20 Gy in 5 fractions. Median survival after WBRT was 2.9 months (interquartile range 1.1-6.6 months). Survival was shorter if the patient was over 50 years old, had a poor performance status (>2 WHO score) or had a triple negative tumor.

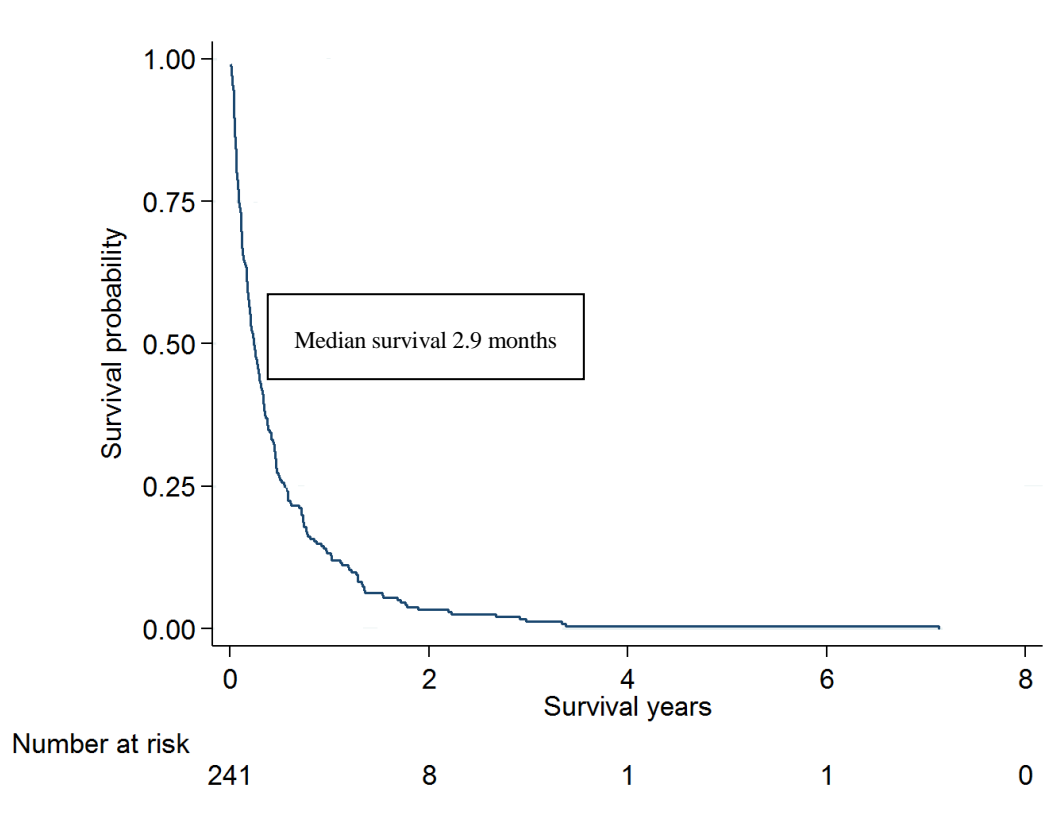


Figure 10. Survival after whole brain radiotherapy for brain metastases due to breast cancer

After WBRT, 57 (24%) patients could not be discharged from the hospital. Among the individuals that were in hospital before WBRT, 45 (47%) died in the hospital without coming home again and 12 (8%) patients could be discharged from the hospital to come home again.

Among patients with performance status score WHO 0-1 before WBRT, 124 (97%) returned to home after treatment and if the WHO score was 2, 46 (65%) patients returned to home, and if the WHO score was 3-4, 14 (34%) returned home. These associations could not be explained by age.

Table 6. Number and proportions of patients coming home again after WBRT at Karolinska University hospital 1999-2012

| | Ever at home after WBRT | | |
|----------------------------------|--------------------------------|-----------|--------------|
| Level of care before WBRT | Yes | No | Total |
| Home | 133 (92 %) | 12 (8%) | 145 (100%) |
| Hospital | 51 (53%) | 45 (47%) | 96 (100%) |
| Total | 184 (76%) | 57 (24%) | 241 (100%) |

4.4 STUDY IV

This cohort of breast cancer patients consisted of 21 414 patients diagnosed in stage I-III. The median follow-up time in the cohort was 3.8 years (range 0.75-7.75) and median age at primary breast cancer diagnosis was 63 years old.

Before breast cancer diagnosis (9-3 months before) 2 660 (12.4 %) patients were treated with low-dose aspirin and 2 813 (13.1%) after diagnosis (3-9 months after). Low-dose aspirin users were older at breast cancer diagnosis (median age 75 years), and more often diagnosed with breast cancer stage II-III than stage I tumors compared with non-users. When the entire follow-up period was considered, 4 091 of the women (19.1 %) used low-dose aspirin.

Regarding breast cancer characteristics at the time of breast cancer diagnosis, 12 546 (58.6%), were diagnosed with a stage I breast cancer, 7 879 (36.8 %) had stage II and 989 (4.6%) had a stage III breast cancer. The most common subtype of breast cancer was the luminal subtype (ER+, HER2-/HER2+), recorded in 15 529 women (72.5%), 857 women (4%) had non-luminal HER2 (ER-, HER2+) and 1 739 patients (8.1%) an ER-HER2- breast cancer tumor.

Among all patients, we found no associations between low-dose aspirin use 9 to 3 months before breast cancer diagnosis and risk of breast cancer death in the adjusted models (HR 0.93, 95% CI 0.77, 1.12). The aspirin dose (≤ 75 or >75 mg/day) did not change the null association. In breast cancer subgroups by clinical and biological characteristics, reduced risks of breast cancer death were however noticed in women with ER positive breast cancer tumors (HR 0.74, 95% CI 0.57, 0.97) and among the patients who were intended for adjuvant treatment with endocrine therapy (HR 0.75, 95% CI 0.59, 0.96).

Low-dose aspirin use during the period 3 to 9 months after breast cancer diagnosis did not affect risk of breast cancer specific deaths in the fully adjusted model, including adjustment for pre-diagnostic aspirin use (HR 1.00, 95% CI 0.74, 1.37).

Dose and duration of low-dose aspirin use after diagnosis were in general not associated with breast cancer-specific deaths. However, in one subgroup of women treated with low-dose aspirin >75 mg per day during the entire follow-up, we observed an increased risk of breast cancer-specific deaths (HR 1.62, 95% CI 1.09, 2.40).

In subgroups of breast cancer patients with different clinical and tumor characteristics (stage, ER-status, HER2-status, breast cancer subtype and intended oncological treatment), low-dose aspirin use after diagnosis was associated with a reduced risk of breast cancer specific death for women with a stage I breast cancer tumor at diagnosis (HR 0.53, 95% CI 0.29, 0.96).

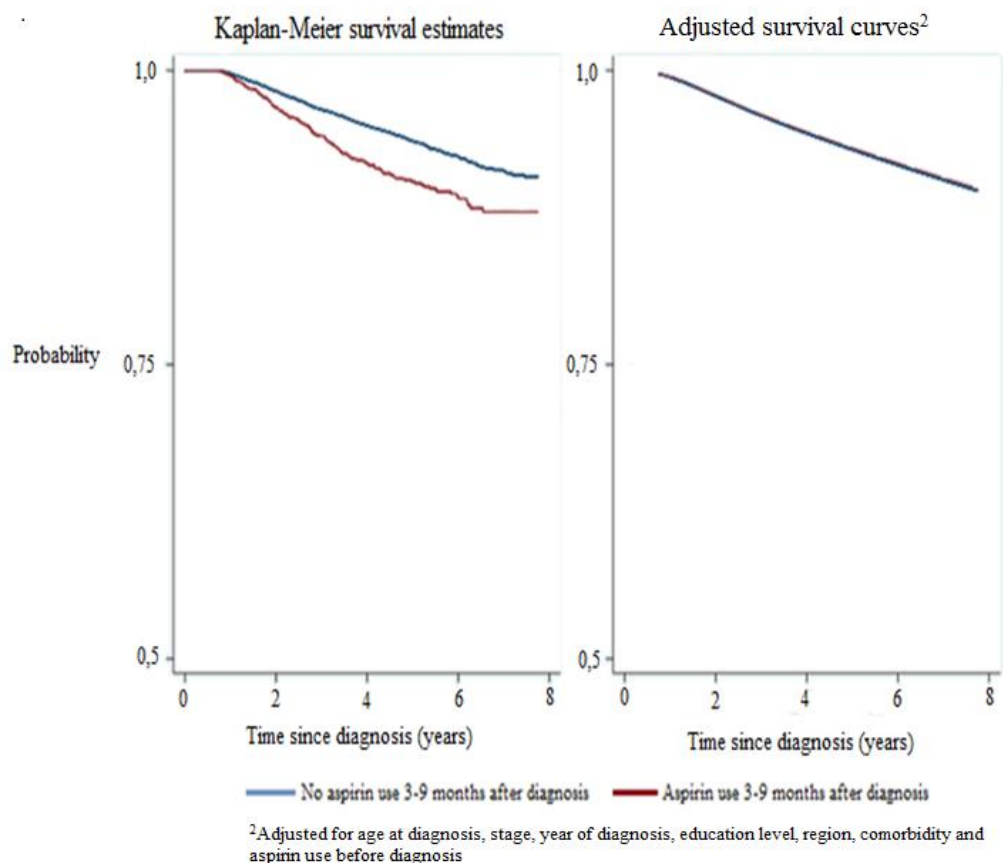


Figure 11. Survival of women with stage I-III breast cancer tumors by use of low-dose aspirin after diagnosis illustrated graphically in a Kaplan-Meier curve (to the left) and with adjusted survival curves (to the right)

In the sub cohort of women from Stockholm-Gotland, there were 9 226 women with stage I-III breast cancer, of whom 1 048 women (11.4%) used low-dose aspirin before their breast cancer diagnosis. During follow-up, 2 800 women, who were not using low-dose aspirin (34.2%) and 347 women who were using low-dose aspirin (33.1%) had a record of a first distant metastasis. Low-dose aspirin use was not associated with a reduced risk of recurrence/metastases in the adjusted model (HR 0.97, 95% CI 0.8, 1.10).

In another separate analysis of 621 women with stage IV disease at diagnosis, we studied low-dose aspirin use before breast cancer diagnosis and time to breast cancer death. There were no protective association for low-dose aspirin users (N=61) with stage IV disease when compared to non-users in the adjusted analyses (N= 334) (HR 0.91, 95% CI 0.67, 1.23).

5 DISCUSSION

In Sweden we have well developed national registration of diseases in registers and with often highly valid data. Due to this we have the opportunity to identify a certain population with a disease and study exposure and outcome within this cohort, using epidemiological strategies to understand associations. Patients with breast cancer are registered in several registries and therefore this disease is possible to study in large observational studies, such as cohort studies [138]. The National Breast Cancer Quality Register contains collected data on breast cancer patients, tumor characteristics, surgical treatment intended oncological treatment and have a high validity. In 2016, the coverage was 98% [134].

In Sweden breast cancer is the most common malignant disease among women and it is also the most diagnosed malignant disease in women worldwide, affecting 1.7 million individuals in 2012 [139, 140]. When the breast cancer reaches its most advanced stage, tumor cells have the ability to spread out to form new tumors in different organs in the body, such as liver, lungs, bone, skin or brain. Breast cancer with distant metastases are rarely curable [141].

Breast cancer is also the second most common cause (after lung cancer) of brain metastases [96, 142, 143]. Among patients diagnosed with breast cancer, about 5-10% will develop brain metastases [10, 12]. Studies indicate that the risk of brain metastases is higher among patients of young age at primary breast cancer diagnosis, and if the primary tumor is triple negative (ER-negative, PR-negative and HER2-negative) or of HER2-type (ER-negative, PR-negative and HER2-positive) [99, 100, 144].

It has been suggested in a few studies that the incidence of brain metastases in breast cancer has increased over time [84, 85, 87]. If so, this may be due to improved survival after primary breast cancer and/or that available adjuvant and palliative treatments are believed to be less efficient in treating micrometastatic disease in the central nervous system compared with in other organs. We also have refined imaging and maybe greater attention to neurological symptoms which could lead to an increase in diagnosed and registered brain metastases [145, 146].

Patients with minor brain metastases due to cancer may be treated with neuro-surgery, sometimes followed by radiotherapy or with stereotactic radiotherapy [5, 108, 147]. However, whole brain radiotherapy (WBRT) is still a common treatment for patients with poor performance status, poor prognosis, massive burden of brain metastases and uncontrolled systemic disease.

The goal of WBRT is symptom control and if there are neurological deficits, improvement of those [109]. In some subgroups of patients, there is a risk of overtreatment, particularly among poor prognosis patients [114]. When treating with WBRT previous studies indicate that 50-80% of the patients respond to treatment and experience improvement of neurological symptoms [120, 148-150] However, improvements of symptoms or

neurological deficits may occur several days or up to a few weeks after treatment with WBRT [151]. Also, the duration of symptom control after treatment with WBRT may be short. In one earlier study, the median duration of symptom control was 3.7 months [152].

As considerable number of patients still die from the breast cancer [153], and thus there are still needs for new cost-effective therapies. Several earlier studies have indicated that medication with low-dose aspirin at the time of breast cancer diagnosis may reduce risk of all-cause and breast cancer-specific mortality [64, 73-75], however the results are not consistent. It has also been reported that there are no associations between low-dose aspirin use after breast cancer diagnosis in relation to breast cancer-specific death [154, 155]. In Sweden, we have detailed information from the population-based breast cancer quality-of-care registers as well as the national drug prescription register. This gave us the good ability to study associations between low-dose aspirin use and outcomes in breast cancer patients and breast cancer subgroups.

5.1 METHODOLOGICAL CONSIDERATIONS

Internal validity is a term for how well a study is measuring what it is intended to. It has a high internal validity if the risk of systematic errors that have affected the results is low. Epidemiological research have identified three categories of systematic errors: selection bias, information bias and confounding

5.1.1 Selection bias

Selection bias is a systematic error that occurs when recruiting the study population or in the process of making the study participants stay in the study. Selection bias is also when the study participants not are distributed in a correct way, which is leading to two not comparable groups. In cohort studies selection bias means that the exposed and unexposed group are different in a way other than the exposure, which is studied. This difference also has an association with the outcome. [138]. Selection bias can occur in registers if certain groups are registered less often than others. The Swedish national breast cancer quality register is however continuously validated with upgrades from the National Cancer Register and the National Cause of Death Register and has therefore a low degree of selection.

5.1.2 Information bias

Information bias is a systematic error in the measuring or classification of the study participants. This is occurring when the information, which is gathered is different for different participants. For example biased follow up in a cohort study may occur when participants in a cohort study are excluded because of loss to follow up [138, 156].

5.1.3 Confounding

Confounders are variables associated with both the exposure and the outcome. Confounders can make the association stronger or weaker. So called positive confounding makes the

association stronger and a negative confounding makes the association weaker (“bias towards the null”). Age is often a confounding factor in epidemiological studies [138].

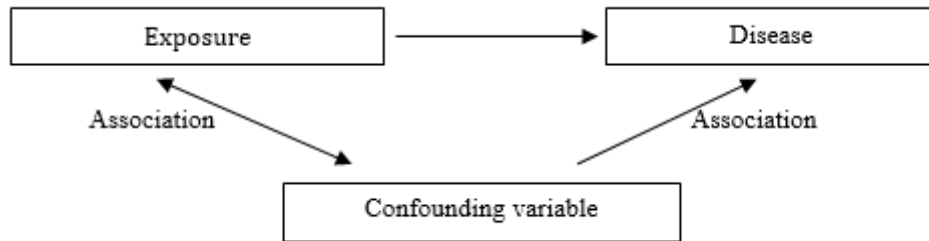


Figure 12. Confounding variable

5.1.4 Confounding by indication

Confounding by indication is an important factor to take into account in epidemiological research. This is a phenomenon occurring when the cause of a certain treatment (the indication for treatment) also is a prognostic factor for the outcome in the study [157]

5.1.5 Immortal time bias

Immortal time bias is also called “survivorship bias”. This type of bias can occur if an unexposed person-time is misclassified. Patients are not truly immortal during this time, but have to be alive at the start of exposure to get classified as exposed. The time between the follow up and the start of intervention gives “Immortal time bias” [158]

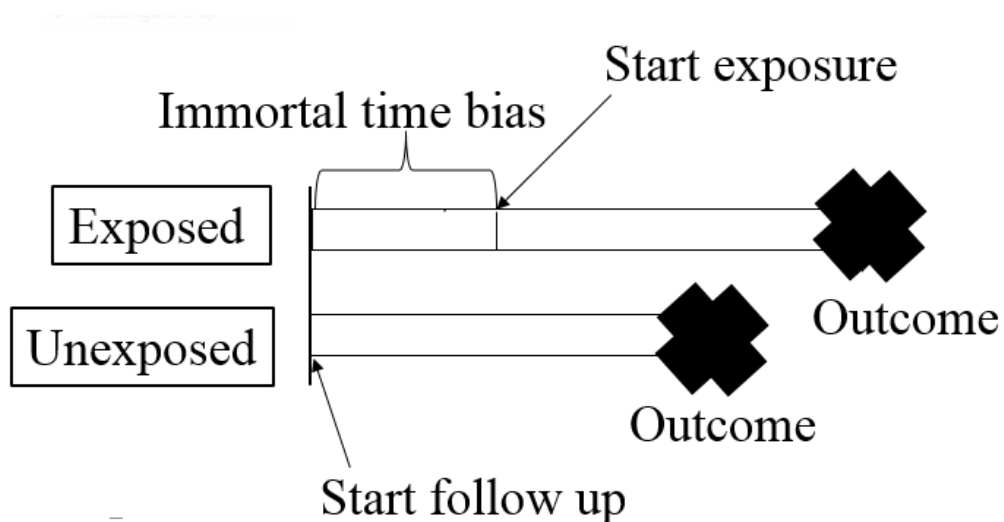


Figure 13. Immortal time bias

5.1.6 Reverse causality

Reverse causality occurs when the outcome in the study leads to changes in the exposure status (patients start or stop a certain medication/exposure due to symptoms of the disease, protopathic bias)

Approaches to handle and minimize this type of bias:

- Restrict the study participants to patients who are believed to be free from outcome at the time of exposure
- Not classify a patient as being “exposed” until a certain time period has passed after the start of exposure (“lagging” exposure)

5.1.7 Missing data

Missing data occur when a variable of interest has no data stored. This is common in observational studies and can have large effects on the conclusions that can be drawn from the study [159].

5.2 STUDY I

In study I, our main finding was that the risk of being admitted with brain metastases in breast cancer increased from 1998 to 2006 in Sweden. The increase was not explained by an increase in prevalence of breast cancer per se. Admissions to hospital for other distant metastases during the same time did not increase to the same extent. The increase was more pronounced in the group of breast cancer patients who were admitted for brain metastases at the same time or after other distant metastases, which could indicate better treatment and survival overall in breast cancer and that you live longer with palliative treatment for a stage IV disease. In this study the incidence of brain metastases in the cohort was 1.4 %, which is probably an underestimation of the true value, because of missing data or misclassification. We got our information about the brain metastases only from admissions to hospital in the NPR, which may have led to an underestimation of the occurrence of brain metastases.

Regarding selection and information bias, we included patients with all stages of breast cancer in this cohort. Most of the patients had no metastases at the time of diagnosis (M0 MX). Our results are unlikely to be due to an increase of breast cancer patients with stage IV, since there are data indicating that it is earlier stages that is increasing when mammographic screening for breast cancer was introduced [160].

More advanced radiological techniques such as CT and MR in later years, could be an explanation for our findings, however since brain metastases do not occur more frequently among cancer patients other than those with lung and breast cancer over time, better techniques unlikely explain all of the observed trend [87].

Changes in how we register diseases in the registers may influence the outcome. However, other distant metastases did not increase at the same rate as for brain metastases. Also, our results cannot be explained by an increased number of hospital beds since these have decreased over time in Sweden [161].

5.3 STUDY II

In study II, we observed a 37% increased risk of having a brain metastases in the later time period 2009-2012 compared with 2002-2004. These findings are consistent with what we found in study I and corroborate what other studies have been reported earlier.

The incidence of brain metastases visits/admissions in our cohort in study II was 2.5 %, which still is a low estimate of incidence compared with previous studies [9, 12, 162, 163]. The exact incidence of brain metastases in breast cancer is not clear. Although most epidemiological studies use death certificates, hospital records, tumor registries or combination of these to obtain information on brain metastases, they probably often underestimate the true incidence [9]. As part of the present study, we performed a validation of the recording of brain metastases in the register through evaluation in the patients' medical files, which showed that the register recording had a high positive predictive value.

As expected and reported in other studies [142, 164, 165], we observed an increased incidence of ER-negative tumors among the patients with brain metastases, 315 (45.9%) patients, compared with 4 457 (15.5) in the cohort of breast cancer women and HER-2 positive breast cancer, we observed an increased incidence, 138 (34.2%) of the patients with brain metastases had a HER2-positive breast cancer compared with 2 658 (13.4%) in the cohort. Trastuzumab, the anti-HER-2 treatment, was introduced in year 2000 and was then gradually introduced in clinical practice in Sweden, why there are more missing data for the HER-2 variable in the earlier time periods. Although we had missing data for HER2, we had more HER2-positive tumors in the brain metastases cohort as expected.

5.4 STUDY III

In study III, our main results suggest some overtreatment of WBRT for patients in late palliative stages and encourages the use of existing scores such as the breast cancer specific GPA to help decide about the most optimal treatment and care together with the patient. One in four patients could not be discharged from hospital-care after treatment. The median survival was very short, less than 3 months from the start of the radiotherapy. We observed, as expected, a significant association between poor performance status, triple negative breast cancer tumors and short survival. Breast cancer patients with poor performance status, WHO score 3-4, had a short median survival of less than 1 month and two thirds of these patients were not able to be discharged from hospital and get home again. The risk for not being able to be discharged from hospital was associated with performance status, but also if the patient was admitted to hospital the week before radiotherapy treatment with WBRT and to some extent with family situation (living with a partner and having children at home or not).

As mentioned, a triple-negative primary breast cancer and poor performance status were associated with a poor prognosis following WBRT. When using GPA, breast cancer specific scores, when deciding about treatment for brain metastases high age > 70 years old, poor performance status, and Karnofsky score less than 60 and a triple negative primary breast cancer tumor predict short survival, as well as multiple brain metastases [106, 166]. When treating brain metastases in breast cancer with WBRT, level of care before treatment was

associated with survival when adjusted for age, but not when adjusting for performance status additionally. However, the odds ratio for not coming home after treatment with WBRT was still significantly higher after adjustment for both performance status and age.

Given the fact that the effect of WBRT is delayed, our results support that patients with need of hospital-care, who have with poor performance status and short expected survival may benefit more from best supportive care, including treatment with steroids and abstaining from WBRT rather than receiving it. Time spent on hospital for patients in late palliative stages of the disease for WBRT treatment would then be spared and side effects would be avoided..

The strengths in present study is the inclusion of all consecutively WBRT-treated breast cancer brain metastases patients in the Stockholm region, as well as the use of prospectively recorded exposure data and outcome data from medical files. There were not much missing data, except for HER2-status in the earlier time periods. A limitation in this study was the relatively small number of breast cancer patients in the cohort, leading to low precision in some analyses. In some cases, we also had to estimate data such as WHO performance status score based on the information in the medical files. This can lead to information bias in some cases. However, there were only one person working and collecting these data leading to low variation in evaluations.

5.5 STUDY IV

In study IV, we did not find any evidence for a benefit of low-dose aspirin use before or after breast cancer diagnosis or any reduced risk for breast cancer-specific deaths overall. There was no evidence of any dose-response relationship by duration or dose of low-dose aspirin use. However, in a subgroup of patients with a stage I breast cancer tumor at diagnosis, low-dose aspirin use after diagnosis was associated with a reduced risk of breast cancer specific deaths. We also noticed a possible reduced risk in women with ER+ tumors, who used low-dose aspirin before primary breast cancer diagnosis.

There are several challenges in pharmacoepidemiological studies, such as in this study, including to look out for and reduce the risk of confounding, selection bias, information bias and reverse causation [135]. Confounding in this study may occur when exposure (low-dose aspirin use) and the outcome share a common cause, like confounding by disease progression. When having cancer specific deaths as outcome, disease progression may act as a confounder. The progression of cancer increases the risk of death, but may also lead to changes in medication status. The patients with cancer progression may take less or stop use of low-dose aspirin. To deal with this we used a 6 month time-lag for changes in exposure status before measuring outcome, ie death in breast cancer. Confounding in this study can also occur through precancer exposures, if low-dose aspirin use before cancer diagnosis affects risk of recurrence/mortality and is associated with exposure after cancer diagnosis, treatment before cancer diagnosis can lead to the development of less aggressive cancer forms. The patients treated before also get exposed longer time with low-dose aspirin. To handle this issue we adjusted for aspirin use before breast cancer diagnosis. Immortal time bias is a kind of selection bias. Patients are not truly immortal during this time, but have to stay alive until the start of exposure. To avoid immortal time bias in this study, we started to

measure exposure at 3 months after diagnosis for all the patients and the outcome after 9 months after diagnosis. It means that the participants had to stay alive until 9 months after diagnosis to be included in the study analyses. A small number of patients died before 9 months and were not included in the analyses. Reverse causation can occur in this study when the studied outcome leads to changes in the exposure status (patients start or stop low-dose aspirin because of symptoms of the disease). To reduce this bias we restricted the study population to persons believed to be recurrence-free at the time of exposure, which we did for stage I-III patients in the cohort and did not classify a person as being “exposed” until 180 days of lag had passed after the start of exposure. Even though we adjusted for comorbidity, there might be residual confounding due to comorbidity in this study. To handle this we could have used a propensity score method to make the distribution of observed comorbidities at baseline more similar between the low-dose aspirin group and the untreated group.

The results in this study IV need further subgroup-specific analyses in larger cohorts to explore possible variation by clinical characteristics. Low-dose aspirin use did not reduce the risk of distant metastases among breast cancer patients with stage I-III disease and did not extend the time to breast-cancer specific deaths for breast cancer patients with stage IV disease. But there might be positive effects in smaller stage I breast cancer tumors treated with low-dose aspirin after breast cancer diagnosis and for low-dose aspirin use before breast cancer diagnosis and ER+ tumors.

Theoretically, there are possible biological mechanisms for a potential benefit of low-dose aspirin use for breast cancer patients. This effect might be due to anti-inflammation, platelet inhibition and hormonal alterations [66]. Aspirin is an inhibitor of cyclooxygenase (COX) 1 and COX-2 irreversibly. Cyclooxygenases are needed for the synthesis of prostaglandins. Prostaglandins are involved in proliferation and cellular migration and are found in high levels in breast cancer tumor tissues. Here they probably stimulate angiogenesis and inhibit apoptosis [67]. Prostaglandins can further stimulate aromatase activity, which increases estrogen levels [68]. Aspirin can also probably inhibit platelet-induced adhesion, preventing circulating tumor cells from initiating metastases [69, 70]. Therefore, there are several biological and theoretical mechanisms of why there might be an effect in ER+ tumors, as seen in this study for low-dose aspirin use before breast cancer diagnosis.

6 CONCLUSIONS

Some conclusions can be drawn from the studies in this thesis:

- The incidence of brain metastases in breast cancer may have increased in Sweden in the last years.
- As expected, patients with HER2-type or triple negative tumors at breast cancer diagnosis are at risk of developing brain metastases.
- Breast cancer patients with brain metastases with poor performance status and who are hospitalized before planned treatment with WBRT, have a bad prognosis and predicted short survival. When deciding about whole brain radiotherapy, these factors and very importantly the patient's choice of care in the late palliative period should be considered.
- There was no evidence for any protective effect of low-dose aspirin use before or after breast cancer diagnosis among breast cancer patients overall. However, in subgroups of patients with more favorable breast cancer tumor characteristics, such as stage I, low-dose aspirin use can potentially be associated with a better outcome.

7 FUTURE PERSPECTIVES

Based on the results and findings in the current projects, additional research questions are raised and include:

- We already know that the incidence of brain metastases in cancer overall, increases in Sweden. This increase is mostly due to an increase of brain metastases in breast cancer and lung cancer. After these studies, we know what patients that are at risk in breast cancer (HER2-type and triple negative primary breast cancer tumors) with metastatic disease. Further investigation would be interesting in lungcancer as well, what patients are at risk for the increased incidence in brain metastases in lungcancer?
- Study why brain metastases seem to increase in breast cancer
- It would be interesting to set up and evaluate a clinical surveillance program to study if early CT scans of the brain would add any benefit regarding survival in HER2-type or triple negative breast cancer patients with a high risk for brain metastases
- For doctors and nurses in the hospital treating patients in late stages of cancer, such as breast cancer patients with brain metastases, it would be of interest to investigate obstacles for necessary conversations about the “end-of-life” situations and to further explore how to increase the support to health care professionals in this regard.
- In subgroups of women with more favorable breast cancer tumor, such as stage I or ER+ disease, low-dose aspirin use may be associated with a better outcome. It would be interesting with further studies in these subgroups of patients. Are there any positive effects in these subgroups?

8 SVENSK SAMMANFATTNING

Dottertumörer till hjärnan är en relativt ovanlig komplikation till bröstcancer men den är förenad med stort lidande och mycket dålig prognos. Flera tidigare studier talar för att spridning till hjärnan har blivit vanligare vid bröstcancer på senare år. Vi har i denna avhandlings studie I och II påvisat att förekomsten av dottertumörer, metastaser till hjärnan verkar öka även i Sverige över tid. Det är framförallt i gruppen patienter som får spridning till hjärnan och redan har en spridd bröstcancer, där förekomsten verkar öka. Detta skulle kunna förklaras av att vi är idag bra på att behandla spridd bröstcancer, men cancerläkemedel har en dålig penetration till hjärnan, varför spridningen dyker upp här efter en tid. Vi har även i studie II påvisat att det är de patienter som har en trippelnegativ tumör (ER-, PR- samt HER2- samt HER2-typ (ER-, PR- samt HER2+) som har en ökad risk att utveckla hjärnmetastaser.

När det gäller hjärnmetastaser vid bröstcancer är strålbehandling av hela hjärnan en vanlig behandlingsmetod för de patienterna med mest avancerad spridning till hjärnan. Kliniskt finns dock frågan om behandlingen gör nytta för alla patienter som får den. Tidigare studier har visat att de patienter som erhåller strålbehandling av hela hjärnan har kort tid kvar i livet, och ibland kan det därför vara så att behandlingen till och med gör mer skada än nytta. I denna avhandlings studie III påvisades att patienternas allmäntillstånd eller behov av inläggande sjukhusvård veckan innan planerad strålbehandling var prediktiva faktorer för en sämre prognos och överlevnad. Av de patienter som var inlagda på sjukhus veckan innan avled 45 % på sjukhus utan att kunna skrivas ut efter behandlingen. Om däremot allmäntillståndet var gott och opåverkat veckan innan planerad strålbehandling kunde 97 % fortsätta leva hemma efter avslutad strålbehandling. Dessa associationer kunde inte förklaras av ålder. Även här sågs en sämre prognos hos de patienter som hade en trippel negativ bröstcancer vid diagnos.

I västvärlden har en successivt förbättrad adjuvant behandling av bröstcancer under senare år gradvis ökat överlevnaden. Trots detta är andelen av bröstcancer-relaterad död hög hos kvinnor som dör i tumorsjukdomar. Följdaktligen behövs fortfarande ytterligare nya och kostnadseffektiva läkemedel vid bröstcancer. Flera experimentella och epidemiologiska studier tyder på att aspirin (acetylsalicylsyra) och möjligen NSAID kan förbättra prognosen vid bröstcancer. Mekanismen bakom varför dessa preparat verkar vara verksamma är inte helt känd. En av förklaringarna verkar vara hämning av prostaglandiner, vilka stimulerar angiogenes, hämmar apoptos samt stimulerar aromatasaktivitet och därmed ökar östrogennivåerna. Aspirin anses också hämma trombocytinducerad adhesion av cirkulerande tumörceller vilket anses initiera metastasering. I studie IV kunde vi inte hitta någon skyddande effekt av aspirin vid behandling av bröstcancer stadium I-III, varken innan eller efter bröstcancer diagnosen. Möjligen sågs en skyddande effekt vid aspirinbehandling innan diagnos hos de patienter som hade en ER+ bröstcancer samt vid aspirinbehandling efter diagnos hos de patienter som hade en stadium I bröstcancer men dessa subgruppsresultat kan också ha uppkommit av slumpen.

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