Evaluation of mammography screening programs: Treatment-related outcomes and importance of selected confounders

Cumulative dissertation

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Table of Contents

Abbreviations

ATC	Anatomisch-Therapeutisch-Chemisch / Anatomical Therapeutic Chemical
BCS	Breast conserving surgery
BMI	Body mass index
CCS	Cervical cancer screening
DALYs	Disability adjusted life years
DCIS	Ductal carcinoma in situ
DDD	Defined Daily Dose
EBM	Einheitlicher Bewertungsmaßstab / Uniform Rating Scale
ER	Estrogen receptor
GePaRD	German Pharmacoepidemiological Research Database
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
ICD(-10-GM)	International Statistical Classification of Diseases and Related Health Problems (,10th Revision, German Modification)
MHT	Menopausal hormone therapy
MSP	Mammography screening program
OPS	Operationen- und Prozedurenschlüssel / Code of Operations and Procedures
PAP	Papanicolaou
PR	Progesterone receptor
RCT	Randomized controlled trial
QoL	Quality of life
WHI	Women’s Health Initiative

Figures

Tables

This cumulative dissertation is based on the following peer-reviewed publications:

Self-selection for mammography screening according to use of hormone replacement therapy: A systematic literature review	Published in: Cancer epidemiology DOI: 10.1016/j.canep.2020.101812
Prescribing of menopausal hormone therapy in Germany: Current status and changes between 2004 and 2016	Published in: Pharmacoepidemiology and Drug Safety DOI: 10.1002/pds.5186
Initial and ten-year treatment patterns among 11,000 breast cancer patients undergoing breast surgery—an analysis of German claims data	Published in: BMC Cancer DOI: 10.1186/s12885-022-09240-w

Abstract

Evidence from randomized controlled trials (RCTs) of mammography screening indicates a reduction in breast cancer mortality of about 20%, but real-world evidence for some organized screening programs is still being evaluated, as is the case in Germany. In most cases, this has to be done with observational data comparing participants and non-participants. Addressing self-selection is therefore of utmost importance in these studies. Correction factors based on data from outdated RCTs became a simple way to deal with this issue, but often face stark compatibility issues regarding the underlying study populations as well the inability to take into account time-varying confounding. Beyond mortality reduction, less intense treatment of breast cancer detected through screening compared to clinically detected breast cancer may be another potential benefit of mammography screening, but there is currently a lack of comprehensive data on this topic. The present dissertation uses menopausal hormone therapy (MHT), an important breast cancer risk factor, as an example to illustrate the particular challenges in the evaluation of mammography screening programs with observational data. Further, it aims to highlight the importance of assessing treatment (-related) outcomes of mammography screening. Three studies were conducted. The systematic review showed a near unanimous association of MHT use with participation in mammography screening. The study on MHT use in Germany showed that from 2004 to 2016, MHT use changed substantially for most types and routes of administration. Finally, the third study showed considerable differences in initial and long-term breast cancer treatment by mode of detection (screen-detected vs. not screen-detected).

This dissertation highlights that great care should be taken in examining and discussing how self-selection can be adequately dealt with in any given study. Further, it may be beneficial to make use of data available outside of screening programs in order to better monitor the benefits and harms, especially with regard to the advances in breast cancer treatment in the future.

Zusammenfassung

Die Evidenz randomisierter kontrollierter Studien zeigt eine Reduktion der Brustkrebsmortalität von etwa 20% durch Mammographie-Screening, aber die Wirksamkeit einiger organisierter Screening-Programme wird derzeit noch evaluiert, wie zum Beispiel in Deutschland. Meistens geschieht dies mit Beobachtungsdaten, die Teilnehmerinnen und nicht-Teilnehmerinnen vergleichen. Der Umgang mit Selbstselektion ist daher von größtmöglicher Bedeutung in solchen Studien. Korrekturfaktoren, die auf Daten der veralteten kontrollierten Studien basieren, wurden hierfür zu einer einfachen Lösung. Häufige Probleme sind aber eine mangelnde Kompatibilität der zugrundeliegenden Studienpopulationen sowie das Unvermögen, zeitveränderliche Verzerrungen zu berücksichtigen. Neben der Mortalitätsreduktion ist die schonendere Therapie von im Screening entdecktem Brustkrebs ein weiterer möglicher Vorteil von Mammographie-Screening, aber hierzu fehlen derzeit umfangreichen Daten. Die vorliegende Dissertation soll am Beispiel des Brustkrebsrisikofaktors „Menopausale Hormontherapie“ (MHT) bestimmte Herausforderungen in der Evaluation von Mammographie-Screening-Programmen mit Beobachtungsdaten verdeutlichen. Überdies soll die Bedeutung der Brustkrebstherapie im Kontext von Mammographie-Screening herausgestellt werden. Dafür wurden drei Studien durchgeführt. Die systematische Übersichtsarbeit zeigte eine nahezu einstimmige Assoziation von MHT-Gebrauch mit Teilnahme am Mammographie-Screening. Die Studie zum Gebrauch von MHT in Deutschland zeigte einen deutlichen Rückgang des Gebrauchs zwischen 2004 und 2016. Und schließlich zeigte die dritte Studie substantielle Unterschiede in der Initial- und Langzeittherapie zwischen Brustkrebs, der im Screening entdeckt wurde, und Brustkrebs der außerhalb des Screenings entdeckt wurde. Die vorliegende Dissertation verdeutlicht dass der Umgang mit Selbstselektion in einer Studie mit großer Sorgfalt geprüft und diskutiert werden sollte. Darüber hinaus könnte es vorteilhaft sein verfügbare Daten außerhalb eines Screening-Programmes für ein „monitoring“ der Nutzen und Risiken zu verwenden, besonders in Hinblick auf die zukünftigen Fortschritte in der Brustkrebstherapie.

1. Introduction

Early detection of breast cancer can achieve detection at an earlier stage and early treatment and thus potentially prevent death from the disease. The efficacy of mammography screening for the early detection of breast cancer was evaluated in randomized controlled trials starting in the 1960s. Organized mammography screening programs have since been implemented in many countries, including most of Europe. Nevertheless, mammography screening remains controversial to this day. Some of the screening programs are still being evaluated, as is the case in Germany.

The present dissertation focuses on particular challenges in the evaluation of mammography screening programs with observational data. Further, it aims to highlight the importance of assessing treatment (-related) outcomes of mammography screening alongside the effect on breast cancer mortality.

The following sections of the introduction give an overview of the core topics of the present dissertation, namely breast cancer, mammography screening and the evaluation of mammography screening programs, and breast cancer treatment. The specific research questions addressed in the present dissertation as well as the corresponding publications and the methods used are then briefly introduced. The main body of the dissertation discusses the relevance of the corresponding research question in more detail and places the corresponding publication in its specific scientific context. Lastly, the insights gained from each study, as well as from the present work in general, are summarized, and conclusions as well as an outlook on future research are presented.

1.1. Epidemiology of breast cancer

Globally, breast cancer is the most common female cancer as well as the leading cause of cancer death among women [1]. Of all cases of cancer worldwide, breast cancer accounts for the second most frequent cancer in terms of new cases and number of deaths [1]. Overall, breast cancer incidence has increased during the past decades, while this increase has slowed or showed signs of plateauing mainly in some high-income countries [2]. In Germany, 69,900 women were diagnosed with breast cancer in 2018, corresponding to an age-standardized incidence ratio of 112.6 per 100,000 women [3]. As a result of advances in treatment, the absolute five-year survival for women is now at 79% (relative five-year survival: 88%) [3]. An estimated 1 of 8 women in Germany will be diagnosed with breast cancer during her lifetime [3].

Most breast cancers are adenocarcinomas that originate in the epithelial tissue of the terminal duct lobular units of the breast and invade the surrounding tissue [4]. Since the majority of breast cancers do not show sufficient characteristics on a histopathological level to be classified as a special type, the majority of breast cancers are classified as “invasive carcinoma of no special type” [4, 5]. Nonetheless, invasive breast cancer can be classified into several fairly heterogeneous subtypes. The most important classifications are staging, grading, histologic type, immunophenotype, and intrinsic subtype [6].

Staging gives information on the size and extensiveness of the tumor as well as lymph node involvement and presence of distant metastases [6]. This is called TNM (tumor, node, metastasis) staging [7]. Stage is an important predictor of survival independent of other tumor characteristics [8, 9].

Grading gives information on the histologic differentiation and growth pattern of the tumor tissue [6, 10]. As a complement to staging, grading is a good reflection of tumor aggressiveness [7]. While it is therefore an important factor for prognosis [10], it is not sufficient on its own when it comes to predicting prognosis and response to treatment [7].

The *histologic type* is a fairly broad category based on criteria such as cell type of origin [6]. As mentioned before, most breast cancers are classified as “invasive carcinoma of no special type”; however, tumors of the same histologic type can show very different biological behavior [6].

The *immunophenotype* (“receptor status”) describes the expression of certain proteins in tissue. For breast cancer, three main immunophenotypes have been recognized: hormone receptor positive (HR+), HER2 positive (human epidermal growth factor receptor 2, HER2+), and triple negative (HR- HER2-) [6]. Hormone receptors, specifically estrogen and progesterone receptors (usually shortened to “hormone receptor”, HR), are receptors that stimulate the growth of normal and neoplastic breast tissue epithelium [6]. These receptors are sufficiently expressed in the majority of breast cancers (about 70–75%) [6, 11, 12]. HR+ tumors are usually lower grade and less aggressive [6]. Amplification of the HER2 gene leads to an overexpression of the corresponding HER2 receptors in breast and tumor tissue, which is the case in around 15% of breast cancers [6, 12]. HER2+ tumors tend to be more aggressive and have a poorer prognosis [6, 13]. The third immunophenotype is termed triple negative. Triple negative breast cancers are defined by what they are not, i.e., they lack sufficient expression of hormone and HER2 receptors [14].

Finally, *intrinsic subtypes* have been determined through gene expression profiling [6]. These intrinsic subtypes (“gene expression profiles”) incorporate the aforementioned immunophenotypes in their classification, but are also characterized by markers related to cell proliferation, such as the protein Ki-67 [6]. The main intrinsic subtypes for breast cancer are Luminal A, Luminal B, basal-like and HER2 enriched [4, 6].

Besides invasive breast cancer, ductal carcinoma in situ (DCIS) plays an important role particularly in the discussion surrounding mammography screening. DCIS is a non-invasive proliferation of neoplastic luminal cells in the ducts of the breast [15]. Following the rise of mammography screening, DCIS is now almost exclusively detected

through mammography screening [15, 16]. Studies on DCIS that was previously misdiagnosed as benign indicate that up to half of DCIS may progress to invasive cancer over 10 or more years [17]. While all DCIS can progress, high-grade lesions progress more quickly than lower grade lesions [18].

1.1.1. Risk factors for breast cancer

The main (known) risk factors for breast cancer are not easily modifiable as they are related to endogenous hormone (primarily estrogen) exposure during a woman's life: early menarche and late menopause, nulliparity, older age at first birth, and fewer children [19]. Exogenous hormone exposure through oral contraceptives and particularly menopausal hormone therapy (MHT) also play an important role, as well as alcohol use and body mass index (BMI) [19]. For BMI, risk is strongly dependent on menopausal status (premenopausal vs. postmenopausal breast cancer) [19]. Apart from changes in the prevalence of known risk factors, screening efforts in the last decades also contributed to changing incidence rates in most countries [1, 3].

The fact that hormone receptors are sufficiently expressed in the majority of breast cancers highlights the significance of hormonal influences on the development of breast cancer. Indeed, many studies show that reproductive factors are associated with specific molecular subtypes of breast cancer. A review by Anderson et al. from 2014 summarized evidence from 35 studies published between 2006 and 2014 regarding the association between reproductive risk factors and molecular subtypes of breast cancer [20]. In this review, associations with the HR+ subtype were most consistently reported [20]. Nulliparity, older age at first pregnancy, and younger age at menarche were the most frequently reported associations with an increased risk of HR+ breast cancer [20]. Regarding other hormonal risk factors, some studies included in the review by Anderson et al. reported an increased risk of HR+ breast cancer with current use of menopausal hormone therapy, although there were fewer studies available compared to re-

productive risk factors [20]. Other studies not included in this review have shown positive associations of HR+ breast cancer with use of menopausal hormone therapy, particularly combined estrogen-progesterone MHT [21-23].

1.2. Early detection through mammography screening

Mammography screening aims to detect breast cancer in an asymptomatic population in a phase where the disease is not yet clinically manifest, in order to prevent death from the disease. As a strategy, early detection is technically distinguished from early diagnosis, which aims at identifying the disease early in symptomatic individuals and is more commonly a focus in countries where implementation of full-scale screening efforts may not be feasible [24, 25].

Eleven randomized controlled trials (RCTs), the first starting in New York in the early 1960s, evaluated the efficacy of mammography screening in reducing breast cancer mortality. A meta-analysis of these trials reported a mortality reduction of about 20% due to screening [26]. Estimates vary, but in absolute numbers, this translates to up to three per 1000 women who get screened annually for a decade [27] or invited biennially for 20 years [28] who will not die of breast cancer as a result of screening. Organized mammography screening programs have been implemented in Europe and many other countries [2]. An organized screening program is characterized by “centralized screening invitations to a well-defined target population, systemic call and recall for screening, delivery of test results, investigations, treatment and follow-up care, [and] centralized quality assurance […]” [2]. Opportunistic screening lacks this level of organization and population coverage and mainly provides screening at request [2]. With few exceptions regarding age range, a typical organized mammography screening program invites women to participate every two years from the ages 50–69 years [2].

As advances in breast cancer treatment have led to improved survival, it is debated whether the harms of screening (still) outweigh the benefits [28]. Predominant concerns

regarding harms of screening are overdiagnosis and overtreatment [16, 28, 29]—including harms and death from treatment [30]—as well as the psychological burden resulting from false-positive diagnoses [31-33]. There may further be short-term impairments related to the procedure of screening (such as pain or anxiety) [34, 35]. Radiation exposure from the mammography procedure itself is also of concern, although estimates (ranging from 2 to 11 deaths per 100,000 women due to radiation induced cancer) are only available from modeling studies so far [36].

The German mammography screening program (MSP) was implemented starting in 2005 and reached nationwide coverage in 2009 [37]. Women aged 50–69 years are invited by mail to participate every two years. In 2018, the participation rate was 50% [38], which is similar to previous years [39, 40]. The participation rate falls short by ~20 percentage points of the official goal of >70% set in the European guidelines for quality assurance in breast cancer screening and diagnosis [41]. Of all tumors detected in the 2018 round of screening, 19% were in-situ-carcinomas (23% among first examinations) [38]. The recommended age range for mammography screening in Europe was recently extended to every two or three years in women aged 45–49 and every three years in women aged 70–74 [42]. The effect of the German MSP on breast cancer mortality among women aged 50–69 years is currently being evaluated.

1.3. Evaluation of mammography screening programs with observational data

Organized mammography screening has been established throughout Europe [2]. Due to the nationwide scope of the programs, there are no uninvited women, so comparing participants in mammography screening with non-participants is commonly the only option for evaluating these programs. In some countries, the possibility of comparing invited and not invited women (e.g., by using historical cohorts or regional data) exists, although this mostly seems to be the case in Nordic countries [43].

This results in the issue of comparing women who (self-) select to participate in screening with those who choose not to participate. The “healthy screenee bias” is the most well-known instance relating to fundamental differences between participants and non-participants in screening [44]. Participants by definition have not yet been diagnosed with the disease or (at least in theory) with symptoms of the disease targeted by the screening program, while non-participants can already be diagnosed with the targeted disease or symptoms thereof [44]. Regarding self-selection specifically, there could be various mechanisms, such as higher participation in health-conscious women with a lower risk of breast cancer, higher participation in women with risk factors they are aware of, and so on. Differences in all-cause mortality between screening participants and non-participants have already been noted, e.g., in one of the first RCTs on mammography screening [45] as well as in observational studies [46]. Participants have been shown to differ substantially from non-participants regarding non-breast cancer, with lower incidence and mortality reported for some cancers among screening participants compared to non-participants [47, 48]. Differences between screening participants and non-participants regarding comorbidity or socio-demographic factors have been reported as well [49-53]. Therefore, balancing these two groups with regard to potential confounding factors is a main challenge when using observational data to evaluate screening programs [54]. As the RCTs on mammography screening are now a few decades old, observational studies have become the main contributor to the evidence [55]. Modern observational studies have the benefit of being conducted in a setting where breast cancer treatment is more advanced than it was when the RCTs were conducted, with modern mammography techniques (digital vs. screen-film) and standardized procedures such as the number and types of views [41].

In existing observational studies, the effect of self-selection is most commonly “corrected for” by using a correction factor as proposed by Duffy et al. [56] and others [57]. The most commonly used correction factor by Duffy et al. in its original version requires an estimate of breast cancer mortality among non-attenders vs. women not invited to

screening based on published data from the RCTs [56]. Combined data of breast cancer mortality among non-attenders and uninvited women from five RCTs conducted in the 1970s and 1980s resulted in a correction factor of 1.36 (i.e., based on the data from these five trials, the breast cancer mortality among non-attenders was higher by a factor of 1.36 compared to uninvited women) [56]. The authors themselves however acknowledge that this estimate has to be “applicable to the programme in question”, and that otherwise, adjustment for potentially important confounders is necessary [56]. The actual application of this correction factor varies, with some studies using data from the RCTs [58-61], and some using other published data [62] or a study’s own data if available [63, 64]. Instead of an estimate of breast cancer mortality among non-attenders vs. uninvited women, Maroni et al. for example used attendance at cervical screening (i.e., the risk of breast cancer death among attenders and non-attenders at cervical screening) among study members to correct for self-selection in their case-control study [65]. The assumption here was that a protective effect of cervical screening attendance on breast cancer mortality can only be the result of selection effects [65].

A systematic review published in 2020 summarized the available evidence (up until 2018) from RCTs and observational studies (cohort and case-control studies) conducted in European countries regarding the impact of organized mammography screening on breast cancer mortality [66]. Included were 38 cohort studies, 17 case-control studies, and 7 RCTs [66]. Of the observational studies comparing participants and non-participants only (as opposed to invited vs. not invited women), 10 did not correct in some form for self-selection [66].

Another systematic review summarized the evidence (up until 2011) from incidence-based mortality studies, case-control studies, and trend studies conducted in European countries [55]. All case-control studies included in this review used either the correction factor established by Duffy et al. or a version of their own. An update of this systematic review included incidence-based mortality studies published up until 2019 from Euro-

pean and non-European countries and also included studies comparing participants and non-participants only [62]. The results from these studies were corrected by the authors themselves for self-selection using the method by Duffy et al. [56] with an estimate of breast cancer mortality in non-attenders vs. not invited women from data published on organized screening and (incidence-based) breast cancer mortality in 13 regions in Sweden [62, 67]. In some of these regions, screening was conducted starting at age 40 instead of age 50 [67]. The age ranges for screening in the studies included in the review were somewhere between the ages 40 to 79 [62]. The five RCTs used for the correction factor by Duffy et al. also vary with regard to the age range of women investigated—for example, the Stockholm trial investigated women aged 39–65 years, the Göteborg trial women aged 39–59 years, and the Swedish Two County trial women aged 38–75 years [26, 56].

In a case-control study based on the UK Age Trial, two different methods were explored for adjustment for self-selection [68]. Contrary to the more common observation of higher risk of breast cancer death among non-attenders compared to uninvited women, the risk of breast cancer death (used for the method as proposed by Duffy et al. [56]) was lower among non-attenders compared to women not invited to screening in this study (not statistically significant) [68]. In a study from the Netherlands using this correction method, the risk of breast cancer death was similarly lower among unscreened compared to uninvited women [64].

These examples illustrate that not every observational study reporting on mammography screening in relation to breast cancer mortality addresses the issue of self-selection in some form. Further, the examples illustrate that correction factors are highly variable and dependent on the source of the data used for the correction, e.g., the estimate for mortality among non-attenders vs. uninvited women in the popular method by Duffy et al. [56]. Caution is therefore needed when using estimates that may not be relevant to the study population or screening program under study. Further, the prevalence of potential confounders has undergone partially drastic changes or is generally

time-varying. Therefore, relying on static data that is old (e.g., data from the old RCTs) or based on different populations than those under study may not be sufficient to address the issue of self-selection. Regardless of the limitations of such a correction factor, they are widely used in studies on the effect of mammography screening on breast cancer mortality. The issue of time-varying confounding applies to all types of observational studies comparing participants and non-participants in that they all have to address self-selection and produce comparable groups. Time-varying confounding is further an important factor in studies evaluating screening programs where the effect of screening is mainly realized through repeat participation, such as in mammography screening. If researchers are interested in investigating the effect of different screening strategies, i.e., some form of per-protocol analysis, time-varying confounding becomes an especially crucial issue to consider adequately.

One example of a potential confounder where the prevalence changed strongly over time is the use of menopausal hormone therapy (MHT).

1.4. The case of menopausal hormone therapy

Menopause onset is defined as the cessation of menstrual periods for at least 12 months and occurs at around age 50 [69]. Common symptoms include hot flashes, night sweats, vaginal dryness, sleep disturbances, and mood changes [69]. Menopausal hormone therapy (MHT) is used to alleviate these symptoms. In the early years of MHT, estrogen was given unopposed (i.e., without progesterone), until it was discovered that estrogen increases the risk of endometrial cancer in women with a uterus [70]. The addition of progesterone counteracted this risk, and MHT was again prescribed liberally, with a peak in popularity in the 1960s and 1970s [70]. The publication of the Women's Health Initiative (WHI) trial results led to a substantial decrease in prescribing of MHT in many countries [71], including Germany [72]. After observational studies had reported a protective effect of MHT on coronary heart disease [73, 74], the

WHI trial was primarily designed to investigate the effect of MHT on this outcome, but was stopped early because increases in cardiovascular events as well as breast cancer in the MHT group were reported [75].

Many studies investigating the risk of MHT on breast cancer followed, and there is now more clarity on the effect of MHT on breast cancer risk, including the effect of hormonal type (estrogen, estrogen-progesterone combined, tibolone, progesterone-only), duration of use, and timing of treatment initiation [74, 76]. The (revised) Global Consensus Statement on Menopausal Hormone Therapy published in 2016 as well as guidelines state that the benefits of MHT outweigh the risks if MHT is initiated before the age of 60 or within ten years after menopause onset [77-80]. The adverse effects are mainly seen for (oral) combined estrogen-progesterone MHT, and risk generally increases with duration of use [76]. Regarding breast cancer, synthesis of available epidemiological evidence indicates a relative risk of 1.6 for 1–4 years, of 2 for 5–9 years, and of 2.3 for 10–14 years of current use of combined MHT [76]. In absolute terms, about 8 in 100 women (vs. 6 in 100 women without any MHT use) starting continuously combined MHT at age 50 for 5 years would develop breast cancer based on this evidence (20-year risk from age 50 to 69) [76].

While there is clear evidence for the relationship between MHT and breast cancer risk, this is less so for breast cancer mortality. In the 20-year follow-up of the WHI study, there was no statistically significant difference in breast cancer mortality for combined MHT [81]. For estrogen-only (conjugated equine estrogen specifically), there was a statistically significant decrease in breast cancer mortality (30 vs. 46 deaths in the placebo arm) [81]. In response to the recently published meta-analysis on MHT and breast cancer risk by the Collaborative Group on Hormonal Factors in Breast Cancer [76], an increase in the 20-year breast cancer mortality was reported for current combined use of MHT in the Million Women study [82]. It should be noted that both studies (i.e., the WHI and Million Women Study) have received criticism for various aspects of their de-

sign [83, 84], and differences in the results of observational studies and RCTs regarding the risks of MHT (notably cardiovascular risks) have occurred before [74].

Studies from various countries reported that MHT use was more common among participants in mammography screening [85-88]. Given the effects of MHT on breast cancer risk, an imbalance of MHT use among participants and non-participants in mammography screening has the potential to confound the evaluation of the effect of mammography screening on breast cancer mortality.

1.5. Treatment-related outcomes of mammography screening

The main goal of mammography screening is the reduction of breast cancer mortality, but the Guideline Development Group of the World Health Organization (WHO) also considers, among others, a reduction in mastectomies an import outcome of mammography screening programs [24]. Generally, less intense treatment (e.g., an increase in breast conserving surgery and a decrease in mastectomies) of breast cancers diagnosed through screening compared to breast cancer diagnosed outside of screening may be considered a potential benefit of mammography screening. Also conceivable is the potential of treatment with less harsh (e.g., less toxic) chemotherapy among screen-detected compared to clinically detected patients due to more favorable tumor characteristics, such as smaller size and lower grading [89]. Further, treatment-related outcomes of mammography screening programs may also have an impact on breast cancer patients' (health-related) quality of life. While the WHO considers health related quality of life (HRQoL) a critical outcome of mammography screening programs and a research priority [24], they concluded that "reliable quantitative data were not identified for DALYs [disability adjusted life years], health-related quality of life or overtreatment." [24]. Breast cancer treatment involves a range of potential long-term physical, psychosocial, and emotional consequences that can affect many areas of a patient's life [90]. Generally, as (breast) cancer therapy advances, de-escalation of treatment is more

and more a topic of discussion [91-93]. Thus, assessing the differences in breast cancer treatment by mode of detection (screen-detected vs. not screen-detected) is important in order to gain insight into how a screening program can potentially be beneficial beyond a reduction in breast cancer mortality.

Regarding treatment of invasive breast cancer, the goal is full resection. The options for removal are breast conserving surgery with subsequent radiotherapy, or mastectomy [94]. For systemic treatment (neoadjuvant/adjuvant), the immunophenotype of the tumor has been established as the main predictor for successful treatment [6]. Endocrine treatment is the standard for HR+ breast cancer (mainly Tamoxifen and aromatase inhibitors, depending on menopausal status) [11]. This is a long-term treatment with an intended duration of at least five years following other treatment if applicable (chemotherapy, radiotherapy) [94]. For HER2+ breast cancer, anti-HER2-treatment is standard (mainly targeted therapy with monoclonal antibodies such as Trastuzumab or the protein kinase inhibitor Lapatinib) [95]. This treatment is typically combined with chemotherapy (taxanes/anthracyclines) [94]. Because of their definition of exclusion, triple negative breast cancers are a fairly heterogeneous group for which chemotherapy is still the standard treatment [14]. While some triple negative breast cancers are highly sensitive to chemotherapy, the prognosis for this subtype overall tends to still be unfavorable [13, 14].

Regarding DCIS, because it is currently impossible to tell at diagnosis if DCIS will progress to invasive cancer or not, complete excision of the lesion is the standard treatment [94]. Radiotherapy is however not an obligatory component as it is with breast conserving surgery in invasive breast cancer [94]. Efforts have been made to explore how to potentially differentiate between indolent and aggressive DCIS [96].

2. Objective and research questions

While RCTs have shown the efficacy of mammography screening in reducing breast cancer mortality, the real-world effectiveness of some programs, as for example in Germany, has yet to be shown. By necessity, these evaluations have to be done with observational data comparing participants with non-participants in most cases. Addressing potentially confounding influences resulting from “self-selection” of individuals for screening becomes therefore crucial. Regarding outcomes of mammography screening, less intense treatment among breast cancer cases detected through screening (e.g., fewer mastectomies) can be another potential benefit of these programs. This may also involve the potential for improved quality of life for these women.

The objective of the present dissertation is twofold: a) to illustrate the particular challenges related to confounding influences in the context of the evaluation of mammography screening programs with observational data, using menopausal hormone therapy as an example, and b) to highlight the importance of treatment (-related) outcomes of mammography screening. In terms of concrete research questions, these objectives were addressed as follows:

1. What is the current evidence regarding a higher participation in mammography screening among users of menopausal hormone therapy as compared to non-users? (**Paper I**)
2. What is the current prevalence of menopausal hormone therapy in Germany, and how did the prevalence change over time? (**Paper II**)
3. What is the potential of claims data for providing information on initial and long-term treatment of breast cancer? Are there differences in treatment between screen-detected and not screen-detected breast cancer? (**Paper III**)

Figure 1 gives a brief overview of where the above mentioned objectives and their corresponding research questions can be placed in the context of evaluating screening programs with observational data.

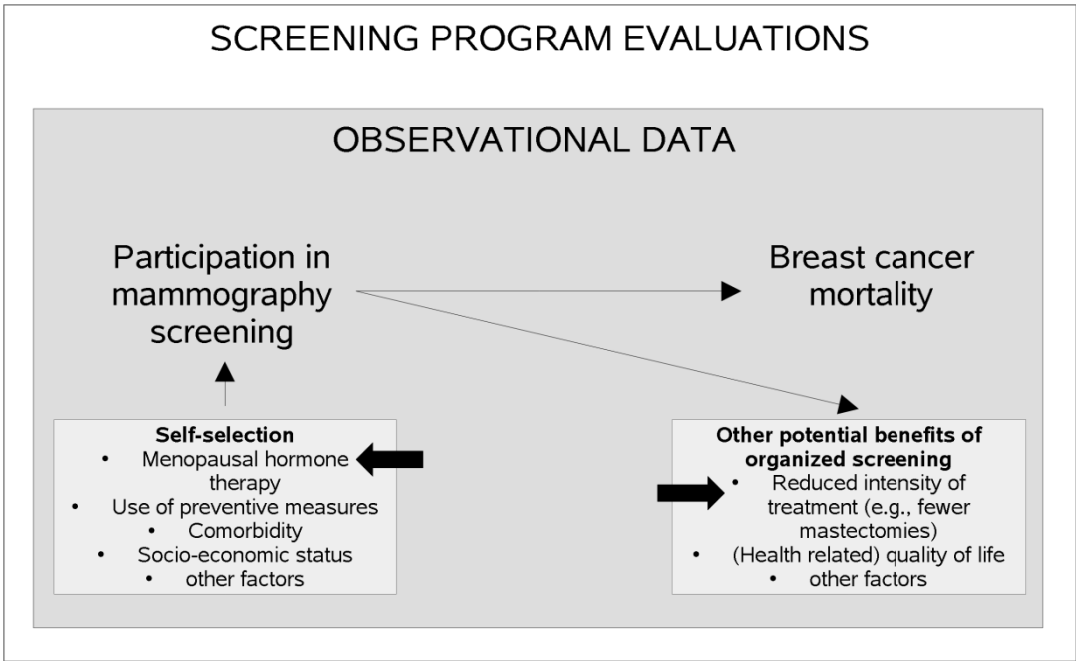

Figure 1 Overview of the focus of the present dissertation in the context of the evaluation of mammography screening programs with observational data

3. Material and methods

The first research question ("What is the current evidence regarding a higher participation in mammography screening among users of menopausal hormone therapy as compared to non-users?") was addressed by conducting a systematic literature review of relevant studies:

Paper I: "Self-selection for mammography screening according to use of hormone replacement therapy: A systematic literature review".

The goal of the systematic literature review was to clarify how consistently an increased use of MHT among participants in mammography screening (or increased participation among MHT users) was reported in the scientific literature. For this review, three databases (MEDLINE, EMBASE, CINAHL) were searched and information extracted on study characteristics, type of mammography screening (organized, opportunistic), and the outcome of interest (association between MHT use and screening participation) from eligible studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used when conducting the review. **Paper I** was published in *Cancer Epidemiology* (DOI: 10.1016/j.canep.2020.101812).

The second research question ("What is the current prevalence of menopausal hormone therapy in Germany, and how did the prevalence change over time?") was addressed by conducting cross-sectional and longitudinal birth cohort analyses over thirteen years of observation:

Paper II: "Prescribing of menopausal hormone therapy in Germany: Current status and changes between 2004 and 2016".

The goal of this study was to describe the current (2016) prevalence of menopausal hormone therapy in Germany as well as the changes in prevalence from 2004 to 2016, including details on the type of hormone and the route of administration. Cross-sectional analyses stratified by age and calendar year were conducted to describe the

changes in prevalence of MHT use. Additionally, longitudinal analyses were conducted in order to determine if the number of women receiving a new prescription of MHT as well as the dose of the prescription (total sum of defined daily doses per woman, DDDs) changed between time periods in women of the same age.

Paper II was published in *Pharmacoepidemiology and Drug Safety* (DOI: 10.1002/pds.5186).

Finally, the third research question ("What is the potential of claims data for providing information on initial and long-term treatment of breast cancer? Are there differences in treatment between screen-detected and not screen-detected breast cancer?") was addressed by conducting a retrospective cohort study among incident breast cancer patients over ten years of observation:

Paper III: "Initial and ten-year treatment patterns among 11,000 breast cancer patients undergoing breast surgery—an analysis of German claims data".

In this study, descriptive analyses were conducted of patient characteristics and breast cancer treatment (surgery, systemic therapy, radiotherapy) received by breast cancer patients diagnosed in the year 2008. This was done for both the initial treatment phase (about the first year after diagnosis) as well as the phase after initial treatment (up to ten years after first breast surgery), stratified by age and stage at diagnosis as well as mode of detection (screen-detected, interval detected, unscreened).

Paper III was published in *BMC Cancer* (DOI: 10.1186/s12885-022-09240-w).

Papers II and **III** used the German Pharmacoepidemiological Research Database (GePaRD). GePaRD is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on drug dispensations as well as outpatient (i.e., from general practitioners and specialists) and inpatient ser-

vices and diagnoses. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented.

The following table gives a brief overview of the four main sources of information regarding diagnoses, treatment and health services available in GePaRD.

Table 1 Main sources of information regarding diagnoses, treatment and health services available in GePaRD

Domain	Description
ICD	➢ International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification (ICD-10-GM) ➢ For in- and outpatient diagnoses
EBM	➢ Uniform Rating Scale (“Einheitlicher Bewertungsmaßstab”) ➢ For services provided in the outpatient setting
OPS	➢ Code of operations and procedures (“Operationen- und Prozedurenschlüssel”) ➢ For diagnostic procedures, diagnostic imaging, surgeries, medications, non-surgical therapeutic procedures, and additional procedures in the inpatient setting
ATC	➢ Anatomical Therapeutic Chemical classification system ➢ For medications prescribed/dispensed in the outpatient setting ➢ Not directly available in GePaRD but information on prescribed/dispensed medication is linked with an external reference data base at BIPS

For diagnoses in the outpatient setting, coding of diagnostic certainty (e.g., confirmed, status post, suspected) is obligatory. These diagnoses are available on a quarterly basis. In the inpatient setting, there is no diagnostic certainty, but several different diagnosis types (such as admission and discharge diagnoses). As opposed to outpatient diagnoses, inpatient diagnoses are recorded in GePaRD with their exact date. For the definition of cases and events of illness, it is usually not sufficient to consider a single diagnosis code in the outpatient setting, as these can often constitute a “working hy-

pothesis" alongside diagnostic procedures [97]. Instead, the presence of multiple codes of specific types (e.g., confirmed outpatient diagnoses or main discharge diagnoses in the inpatient setting), ideally in different time periods (e.g., consecutive quarters for outpatient diagnoses) should be considered in order to define a case or event [97]. Outpatient diagnoses can also be combined with a coded treatment for the condition of interest to avoid misclassification.

Paper II (prescribing of MHT) was based on outpatient prescription data**.** Prescriptions were identified by their respective ATC code and classified according to the route of administration (oral, vaginal, transdermal, other) as well as the type of hormone (estrogen, estrogen-gestagen combined, tibolone, gestagens, other).

Paper III made use of the whole spectrum of information available in GePaRD, i.e., in- and outpatient diagnoses, in- and outpatient services and procedures, as well as outpatient prescription data. The first in- or outpatient breast cancer diagnosis in 2008 after a lookback period of four years without any coded diagnoses for breast cancer (inpatient, confirmed or status post outpatient) was defined as incident. The diagnosis then had to be confirmed at least once within four months. Similarly to an algorithm previously developed in a GePaRD-based study on colorectal cancer [98], the information available in GePaRD on diagnoses of lymph node or distant metastases was used to classify patients as having "no affected lymph nodes or distant metastases at diagnosis", "affected lymph nodes only at diagnosis", and "distant metastases at diagnosis". Treatment was assessed using in- and outpatient claims for surgery, systemic therapy (cytostatic drugs, hormone therapy, monoclonal antibodies), and radiotherapy. Treatment was assessed in different time frames starting from incident diagnosis and first breast surgery in order to differentiate initial (about the first year after diagnosis) from long-term treatment (years 2–10 following diagnosis). Further, a definition of mode of detection (screen-detected, interval-detected, not screen-detected) was developed for this paper, taking into account the regular screening interval of two years. In GePaRD, EBM codes for all services and procedures related to organized mammogra-

phy screening (screening mammography, follow-up diagnostics, and the multidisciplinary case conference held in case of suspicious findings) are available. The two years prior to the incident breast cancer diagnosis as well as the three quarters surrounding the diagnosis (i.e., the quarter of, before, and directly after) were searched for a coded screening mammography and a multidisciplinary case conference (**Figure 2**). The breast cancer was then classified as screen-detected if a screening mammography and a case conference were coded in the two years prior to the diagnosis, and at least one of these codes was present at least once in the quarters surrounding the diagnosis. A diagnosis was classified as interval-detected if a screening mammography was present in the two years prior to the diagnosis, but the above criteria for screen-detected were not fulfilled. Unscreened patients were classified as unscreened, but eligible if they were 50–69 years old at diagnosis, and as unscreened and ineligible if they were younger or older at diagnosis.

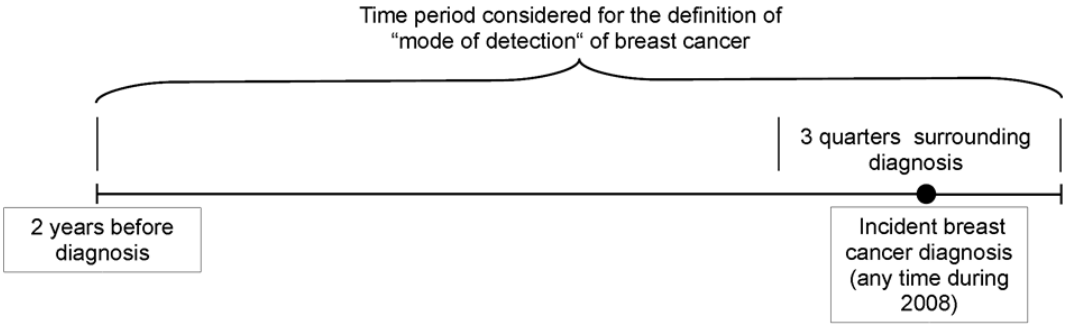

Figure 2 Visualization of the definition of mode of detection of breast cancer

To first gain a better understanding of the evidence available on differences in breast cancer treatment between screen-detected and not screen-detected patients, a search of the literature was conducted. For this, Title/Abstract searches of MEDLINE were conducted on 19.05.2021 using combinations of relevant key words: breast cancer, treatment, therapy, mammograph*, screen*, as well as the MeSH (Medical Subject Heading) terms mammography, screening, and early detection of cancer. The range of

publication dates was restricted to 1985 and later (up to the date of the search) to limit the number of results to somewhat recent studies. Multiple searches were conducted because not every study was assigned relevant MeSH terms.

Studies were identified as relevant if they were published in English or German and reported information on the treatment of breast cancer patients (proportion of patients with the respective treatment) stratified by mode of detection. The primary contrast of interest regarding mode of detection was the comparison of screen-detected patients vs. not screen-detected patients (i.e., interval-detected, unscreened, or both). The study population also had to comprise a somewhat relevant age range (i.e., screening-eligible groups). Results regarding study population, country of origin, and treatment differences were summarized descriptively. The results of the study on initial- and long-term breast cancer treatment conducted in the context of the present dissertation (**Paper III**) were then compared to the studies identified in the literature.

4. Evaluation of mammography screening programs with observational data: Importance of selected confounders

4.1. Who uses menopausal hormone therapy? (Paper I)

In order to answer the first research question ("What is the current evidence regarding a higher participation in mammography screening among users of menopausal hormone therapy as compared to non-users?"), the available evidence in the scientific literature on the association between MHT use and participation in mammography screening was summarized by conducting a systematic review was conducted as described in section 3 [99] (**Paper I**). Among 32 included studies from nine different countries, the review showed a near unanimous association of MHT use with participation in mammography screening. In studies reporting an odds ratio, about 70% reported an association of ≥2, meaning there was a 100% or higher increase in the odds of participation in mammography screening among MHT users compared to non-users (or of MHT use among participants compared to non-participants, depending on the study). In studies reporting prevalences (use of MHT among screening participants vs. non-participants or participation among MHT users vs. non-users), 65% reported differences of ≥10 percentage points. The association was present both in the time periods before and after publication of the WHI trial results (i.e., before and after 2002), as well as both in organized and opportunistic screening settings. Since only two studies stratified their results by hormonal type of MHT, no clear conclusion could be drawn whether the association between MHT use and screening participation differed in this regard. No study from Germany contributed evidence on this association, and there was a general lack of recent data (the most recent data were from 2012-2014).

Awareness of breast cancer risk may influence a woman's decision to participate in mammography screening. A survey conducted among ~3,000 women (2,107 in 2004 and 866 in 2016) visiting an outpatient gynecological practice in Germany found that in 2004, 36% of surveyed women and 57% in 2016 were aware of MHT as a risk factor

for breast cancer [100]. A woman's physician may also play an important role in this relationship [101, 102], especially after WHI, when the risks of MHT were widely publicized and discussed. For example, German MHT guidelines state that women should be made aware of screening tests for early detection of cancer [80].

It has also been suggested that associations with MHT use—especially in observational studies—have the potential to be confounded by "healthy user bias", which commonly denotes a higher propensity among healthy individuals to initiate and maintain treatment (be that through health seeking behavior or selective prescribing) [103-105]. Several large cohort studies have reported on reproductive, lifestyle, and health-related characteristics by MHT use that may provide further insight into some aspects of health and health-seeking behavior among MHT users and non-users besides differences in participation in mammography screening.

In a study among ~75,000 US women aged 50–78 years (enrolled between 1993 and 2001) participating in the "Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial", the proportion of current smokers was lowest among current MHT users (8% vs. 11–12% among former and never users) [106]. Regarding education, the percentage of women with college or postgraduate education was highest among current MHT users compared to never or former users (59% vs. 46%–51%). There was little difference in the proportion of individuals with a history of diabetes or coronary artery disease between current and former/never users (diabetes: 5% vs. 7–9%, coronary artery disease: 4% vs. 5–6%). Oral contraceptive use was more common among current MHT users (62% vs. 43% and 53% among never and former users, respectively).

In a study among ~29,000 Danish women aged 50–64 years (in 1993–1997), there was a higher proportion of women within the normal BMI range among current MHT users (55% vs. 43% among former and 49% among never users) [107]. There was not much difference in the proportion of women with the highest duration of education (≥10 years) compared to non-users: among current MHT users, this was 20%, vs. 16%

among previous and 19% among never users. Ever use of oral contraceptives was highest among current users compared to the other two groups (62% vs. 56–57% among previous and never users).

A study among ~680,000 Norwegian women aged 45–79 in 2004 (followed until 2008) used prescription data to assess MHT use [108]. In this study, the proportion of women with university education and above was higher among MHT users (23% vs. 18% in non-users). Use of antihypertensives (prescription during follow-up) or thyroid therapy was higher among MHT users (for antihypertensives, 43% vs. 40% in non-users, for thyroid therapy, 14% vs. 11% in non-users).

Among ~800 Swiss postmenopausal women aged 50 to 80 years (enrollment 2009–2012), there was not much difference in education by MHT use (university educated: 19% among current users, 16% among past und never users) [109]. Current smoking was lower among current and past MHT users (15–17% vs. 20% in never users). The highest proportion of normal BMI was reported in current MHT users (56% vs. 47–48%), and the proportion of women with a sedentary physical activity status was lowest in current MHT users (61% vs. 65–68%).

In ~57,000 French postmenopausal women (followed from 1992 until 2002), ever contraceptive use was higher among ever MHT users compared to never users (65% vs. 48%) [110]. There was no difference in current smoking between ever and never users of MHT (9–10% for both groups).

There does seem to be some evidence that MHT users differ from non-users. Differences in use of other medication are difficult to judge health-wise, seeing as a greater propensity for health-seeking behavior may reflect a higher percentage of medication use or therapy for other conditions and not necessarily a higher percentage of women who have those conditions. There was some indication toward higher use of other treatments among MHT users in these studies, although the extent of the difference was fairly small (e.g., three percentage points difference in use of antihypertensive and

thyroid medication use among MHT users vs. non-users in a large Norwegian study [108]). Differences in use of oral contraceptives were larger and ranged from 5–19 percentage points in current/ever MHT users vs. never users [106, 107, 110], which may be reflective of health-seeking behavior. MHT users did seem to be more educated as well as more commonly in the normal BMI range as reported in several studies [106-109]. Regarding socioeconomic position, a study among ~4,000 British women aged 60–79 years further reported that indicators of adverse life-course socioeconomic position were associated with lower odds of MHT use [111]. Data regarding smoking behavior seem to be inconclusive. It should be noted that these studies tended to compare baseline characteristics, which may be partially or fully before 2002 when the WHI results were published, resulting in a sharp decline in MHT use.

Two other studies provided evidence regarding MHT use and participation in other screening measures. In a nationally representative prospective cohort study from Australia, MHT users also had statistically significant higher odds of having had a PAP test in the previous three years (OR 1.46, adjusted for socio-demographic variables) [112]. A German study assessed the effectiveness of providing women with an invitation to cervical cancer screening (CCS; at the time a PAP test without test for HPV) or an invitation plus a brochure, vs. a control group receiving neither, on the three-year participation in CCS (before 2020, cervical cancer screening was opportunistic in Germany) [113]. They also analyzed the whole study population (intervention arms plus control group, n=4,379) and reported that women currently using MHT had statistically significant higher odds for participation in CCS compared to non-users (OR 2.75 unadjusted, OR 3.88 adjusted for socio-demographic variables, current smoking status, and current use of oral contraceptives) [113]. Interestingly, the odds of participation within three years decreased and became statistically non-significant among MHT users when women were excluded who had already participated in CCS annually before study start (OR 1.36 unadjusted, OR 1.73 adjusted) [113]. This may further support the idea that the association between MHT

use and participation in screening is mainly reflective of health-seeking behavior in general—rather than increased participation in specifically breast cancer screening among MHT users—as the exclusion of very active screeners attennuated the association in this study.

An imbalance of MHT use between participants and non-participants in mammography screening has the potential to lead to the imbalance of another important factor that is connected to MHT use: breast density.

4.2. Breast density

Breast density refers to the tissue composition of the breast [4]. While adipose tissue appears translucent on a mammogram, fibroglandular tissue appears white (as a lesion would) [4]. A high percentage (relative to the total breast area) of fibroglandular tissue thus constitutes a dense breast [4]. In Germany, the two highest categories of density (heterogeneously dense and extremely dense, out of four categories) occur at about 48% and 7% [114], respectively. In the USA, they occur at about 36–46% and 8–9%, respectively [115, 116].

In the context of mammography screening, two main issues are connected to breast density. First, higher breast density is an independent risk factor for breast cancer [117]. The biological mechanisms of this relationship are not quite clear yet [118]. Second, dense breast tissue can mask lesions on a mammogram. Analyzing about 25,000 screening examinations among German women, Weigel et al. reported that the sensitivity of screening mammography (screen-detected cancers divided by the sum of screen-detected plus interval cancers over a period of 24 months) decreased substantially with increasing percent density, which may create a shift toward interval cancers among women with dense breasts as a result [114]. Interval cancers are breast cancers detected between two rounds of screening.

In a study using data from three nested case-control studies among 1,112 case-control pairs, the odds of (invasive) interval-detected breast cancer were almost 18 times higher for the interval of <12 months after the negative screen and almost 6 times higher for the interval of ≥12 months after the negative screen in women with dense breasts (75% or more dense tissue) compared to women with very low breast density [117]. The authors of this study hypothesized that the highly increased odds of interval cancers by a factor of 17.8 for the shorter interval of <12 months after the negative screen in particular indicated that the masking of tumors due to high breast density was likely responsible for this observation (as opposed to “true” interval cancers that grew during this interval) [117]. In their analysis of about 1,000 Swedish patients with invasive breast cancer aged 40–71 years at diagnosis, Holm et al. reported that the characteristics of interval cancers differed by breast density: interval cancers among patients with lower density had higher odds of increased tumor size, lymph node involvement, and of higher grading compared to interval cancers among patients with higher breast density [119]. The authors of this study hypothesized that the interval cancers among the patients with low breast density were enriched with “true” interval cancers while those among the patients with high density were partly cancers missed at screening, hence the more favorable characteristics, comparatively, in the latter group [119].

While breast density generally decreases with age [116], (current) use of MHT is associated with an increase in breast density [120]. This effect appears to be stronger for combined MHT compared to estrogen-only MHT [120]. In the Million Women Study, both sensitivity and specificity of screening mammography were lower among current users of MHT in 122,000 women aged 50–64 years compared to past and never users (adjusted for age and body mass index [BMI]) [121]. It has been suggested that specificity may also be affected because not only may lesions be missed due to dense breast tissue, the dense tissue may also falsely lead to suspicious findings due to a similar appearance to lesions on the mammogram [122]. In the full cohort of 4,000 Swedish breast cancer patients (1,247 with an interval cancer) in the previously men-

tioned study by Holm et al., current use of MHT was still associated with higher odds of an interval cancer compared to a screen-detected cancer when adjusted for age, BMI, and percent density (OR 1.8, 95% confidence interval 1.4–2.4), indicating that the increase in odds of interval cancer among current MHT users may not solely due to increased breast density [119].

Differences in breast density among participants and non-participants in mammography screening due to imbalanced distribution of MHT use can therefore have multiple potentially confounding effects on the relationship between participation and breast cancer mortality, beyond a differential distribution of breast cancer risk due to MHT itself.

4.3. Time-varying nature of use (Paper II)

Studies from many different countries reported a decline in MHT use after 2002 [71], the year the WHI trial results were published, but there was no recent data on MHT use available for Germany. The latest data from 2000–2005 indicated a decline in the number of prescriptions by about half for oral combined MHT and by about a third for oral estrogen MHT [123].

In order to answer the second research question ("What is the current prevalence of menopausal hormone therapy in Germany, and how did the prevalence change over time?"), a study was conducted on the prescribing of MHT in Germany as described in section 3 (**Paper II**). The goal of this study was to gain a detailed understanding of how prescribing of MHT changed over time and how many women were still using the different types of MHT in Germany. Conceivably, MHT use may have declined primarily in the time period directly following WHI, but then increased again after the discussion surrounding its risks had subsided. Additionally, published data on MHT use in general often lacks details of use—namely, hormonal type and route of administration. Given that the risk profile of MHT is strongly dependent on hormonal type and route of administration [76], insight into the details of use is important.

The study showed that from 2004 to 2016, MHT use had declined substantially for most types and routes of administration. For systemic MHT (i.e., excluding vaginal MHT), the largest decline in prescribing was observed for women aged 55 and 60, where prevalence declined by 153 and 160 per 1000 women between 2004 and 2016, respectively (relative decline: 61% and 67%, respectively). For combined estrogen-gestagen prescriptions (fixed or individual combination), the decline was about 60% or higher in women aged 45–75 (maximum 67% at age 60).

In 2016, about 13% of women aged 45–75 were using MHT. The prescription prevalence among 55-year-old women in 2016 was 7% for vaginal estrogen (no change compared to 2004) and 4% for combined MHT (down from 15% in 2004). Use of local estrogen (vaginal MHT) remained mostly at the same level for all ages from 2004–2016.

In a longitudinal analysis on new prescribing of MHT, the proportion of women who received a new prescription in the next five years declined between the two time periods 2005–2009 and 2012–2016, both for systemic MHT overall as well as for combined MHT specifically. For example, among 50-year-old women who did not have a prescription of MHT in the previous year, 11% received a new prescription of combined MHT between 2005 and 2009 (i.e., between age 50 and 54). This proportion was 7% in the time period of 2012 to 2016. For systemic MHT overall, this decline was from 21% to 16%. There was also a decrease in the median number of defined daily doses (DDDs) prescribed during the next five years between these two time periods. For example, 50-year-old women who did not have a prescription of MHT in the previous year were prescribed 259 median DDDs of combined MHT between 2005 and 2009, which declined to 210 median DDDs between 2012 and 2016.

While this limitation is not commonly mentioned, in at least one case-control study on the effect of mammography screening on breast cancer mortality that used the correc-

tion method by Duffy et al. [56], the authors acknowledged that such a correction factor would, contrary to how it was used in the study, in actuality be time-varying [58].

5. Evaluation of mammography screening programs with observational data: Treatment-related outcomes

5.1. Overview of the literature

Fourteen relevant studies were identified [89, 124-136]. Of these, four studies compared screen-detected vs. interval detected patients [126, 128, 134, 136] and ten studies compared screen-detected vs. not screen-detected patients [89, 124, 125, 127, 129-133, 135].

Regarding country of origin, seven studies were from Europe [126, 127, 129, 131-133, 136], four from the USA [89, 124, 130, 135], two from Australia [125, 134], and one from Canada [128]. The size of the study population ranged from 718 patients (a study from the USA [124]) to 23,310 patients (a study from Italy [127]). In all but four studies [127, 128, 132, 133] the study population comprised <2000 breast cancer cases. Only three studies used data from 2009 or later [131, 134, 136]. Of the fourteen studies, seven included DCIS as well [125-128, 130, 131, 133]. In one study, the study population was restricted to patients aged 40-49 years at diagnosis [130] and two studies analyzed early-stage invasive breast cancer only [134, 135]. All fourteen studies used medical records or (cancer) registry data to identify breast cancer patients and the mode of detection.

Regarding treatment differences, all studies reported information on initial treatment, while no study reported on treatment beyond initial treatment. Eleven studies reported on differences regarding breast surgery by mode of detection [89, 124, 125, 127, 128, 130-132, 134-136]. Of these, all studies reported higher proportions of screen-detected patients receiving BCS compared to not screen-detected [89, 124, 125, 127, 130-132, 135] or interval detected [128, 134, 136] patients. One study from Italy additionally reported that the proportion of patients with re-excision after BCS was lower among patients detected in the organized screening program compared to patients detected outside the program (5% vs. 13%, respectively) [131]. Two studies further reported lower

proportions of axillary lymph node surgery among screen-detected patients compared to patients detected outside the organized screening program [131] and interval-detected patients [134].

Nine studies reported on adjuvant treatment (chemotherapy, hormone therapy, or radiotherapy) [89, 126, 128-130, 133-136]. Of the four studies reporting information on hormone therapy, three reported lower proportions of patients with hormone therapy among screen-detected patients compared to not screen-detected patients [89, 126, 133] and one reported higher proportions of patients who were recommended hormone therapy among early-stage screen-detected patients compared to interval-detected patients [134].

Of the seven studies reporting on chemotherapy, five reported lower proportions of patients with chemotherapy among screen-detected patients compared to not screen-detected [89, 133] or interval detected [126, 128, 136] patients. One study reported lower proportions of patients who were recommended chemotherapy among early-stage screen-detected patients compared to interval-detected patients [134]. One German study reported that fewer screen-detected patients had an indication for chemotherapy compared to interval-detected patients [136].

Information on neoadjuvant treatment was reported by one study from Germany [136]. Here, fewer screen-detected patients received neoadjuvant treatment compared to interval-detected patients [136].

Information on radiotherapy was reported by five studies [124, 126, 130, 134, 135]. One study focused on older patients and reported that screen-detected patients were more often referred to a radiation oncologist compared to not screen-detected patients [124]. A study from Finland reported that radiotherapy was less common among screen-detected patients compared to interval detected patients (65% vs. 70%, respectively) [126]. Two studies reported on radiotherapy in combination with surgery [130, 135] and one on recommendation for post-surgery radiotherapy [134]. In one study

from the USA among patients aged 40–49 years, the proportion of patients with surgery and radiotherapy was higher among screen-detected patients compared to clinically detected patients (38% vs. 12%, respectively) [130]. This was also found for radiotherapy after BCS with lymph node biopsy in a study from the USA for early-stage invasive breast cancer [135]. In a study among early-stage breast cancer patients from Australia, the proportion of patients having been recommended post-surgery radiotherapy (BCS or mastectomy) was lower among screen-detected patients compared to interval-detected and unscreened patients [134]. Lastly, one study reported that surgery and chemotherapy as well as surgery, radiotherapy, and chemotherapy were less common among screen-detected patients compared to clinically detected patients (31% vs. 59%, respectively, and 13% vs. 22%, respectively) [130].

5.2. Discussion of treatment (-related) outcomes (Paper III)

In order to answer the third research question ("What is the potential of claims data for providing information on initial and long-term treatment of breast cancer? Are there differences in treatment between screen-detected and not screen-detected breast cancer?"), a retrospective cohort study among incident breast cancer patients was conducted as described in section 3. Together with the studies identified in the literature review, it provides comprehensive insight into the available evidence on differences in breast cancer treatment by mode of detection.

Regarding breast surgery, the available data seem to be unanimous—all studies reporting on surgery found that BCS was more common among screen-detected patients. This is also what was found in **Paper III** [137]. For the most part, this also seems to be the case for chemotherapy, which was less common among screen-detected patients in most studies, including in **Paper III**.

The results regarding hormone therapy were inconsistent. Given that many studies in the literature report that HR+ breast cancer was more common among screen-detected

patients [136, 138, 139], it seems plausible that the proportion of patients receiving hormone therapy should be higher in this group as well. This is what was found in **Paper III** [137], and another recent study in this review reported that screen-detected patients were more commonly recommended hormone therapy (early-stage patients only) [134]. Even though two of the three studies reporting lower proportions of patients with hormone therapy in the screen-detected group did also find a higher proportion of HT+ patients among the screen-detected (one reported no information on receptor status), this did not result in a higher proportion of patients with hormone therapy among the screen-detected [89, 126]. Given that many studies used older data (e.g., the three studies that reported lower proportions of patients with hormone therapy in the screen-detected group used data from 1985–2004), less widely use adjuvant systemic therapy at the time as well as differences in or outdated guidelines may be responsible for some of the discrepancies between studies. The most recent data come from Italy (2010–2016) [131] and Australia (2007–2013) [134]. Both countries have an organized screening program and the studies investigated 50-69-year-old women, thus making these two studies more comparable to the current German setting with regard to screening (although one of these studies analyzed early-stage patients only [134] and the other included DCIS cases [131]).

Few studies reported information on radiotherapy [124, 126, 130, 134, 135]. Radiotherapy can be expected to be more common among screen-detected patients due to the higher proportions of BCS performed in this group, which is what was found in **Paper III** [137]. Only three studies had information on actual receipt of radiotherapy [126, 130, 135], and two of these included DCIS cases [126, 130]. The study not including DCIS cases focused on surgically treated early-stage breast cancer patients aged 40 years and older and reported higher proportions of patients with radiotherapy among screen-detected vs. clinically detected cases [135].

Of the two studies reporting on radiotherapy in relation to surgery in early-stage invasive breast cancer, one reported that radiotherapy was less commonly recommended

in screen-detected compared to interval-detected patients after mastectomy or BCS [134], and the other reported that radiotherapy was more common among early-stage screen-detected patients after BCS compared to clinically detected patients [135]. In **Paper III**, there was little difference in initiation of radiotherapy within ten months after breast surgery by mode of detection—this proportion was higher by only three percentage points among screen-detected compared to interval-detected patients and by five percentage points compared to unscreened patients (83% vs. 80% and 78%, respectively) [137]. Stratified further by type of breast surgery, there was no difference in initiation of radiotherapy for patients who had received BCS, but initiation of radiotherapy within ten months after breast surgery differed for patients with mastectomy (**Table 2**).

Table 2 Initiation of radiotherapy within ten months after surgery by type of breast surgery among screening-eligible breast cancer patients

	Mode of detection			
	Screening participants			
	All	**Screen-detected[1]**	**Interval-detected**	**Unscreened (eligible)**
	6065 (100%)	2049 (33.8%)	476 (7.8%)	3540 (58.4%)
Breast conserving surgery[2]	4608 (76.0%)	1756 (85.7%)	348 (73.1%)	2504 (70.7%)
Of these, radiotherapy	4172 (90.5%)	1613 (91.9%)	318 (91.4%)	2241 (89.5%)
Mastectomy	1457 (24.0%)	293 (14.3%)	128 (26.9%)	1036 (29.3%)
Of these, radiotherapy	694 (47.6%)	95 (32.4%)	63 (49.2%)	536 (51.7%)

[1] Breast cancer was classified as "screen-detected" if a screening mammography and multidisciplinary case conference were coded in relevant time periods before and surrounding the diagnosis. It was classified as "interval-detected" if the woman had a screening mammography in the regular interval (two years) before diagnosis, but the criteria for "screen-detected" were not fulfilled. Patients without a screening mammography in the regular interval and aged 50–69 years at diagnosis were classified as unscreened, but eligible. The remaining patients were classified as "unscreened and ineligible" (not included in this table).

[2] Within one year after diagnosis. Mastectomy includes those with both types of surgery.

Of the patients whose breast cancer was screen-detected, 32% received radiotherapy within ten months after mastectomy, while this proportion was 49% among interval-detected and 52% among unscreened patients. It seems plausible that for BCS, there should be little difference, as the guidelines are clear on radiotherapy being an obligate component of BCS for invasive breast cancer [94]. For patients receiving a mastecto-

my, the criteria for when radiotherapy is appropriate are highly variable. Radiation of the chest wall after mastectomy, of the lymph nodes in locally advanced disease, as well as radiotherapy for metastases or palliative radiotherapy are all relevant options to consider [94]. Further, some patients received both BCS and radical surgery, so it is possible that some patients initially received BCS and radiotherapy which then had to be followed up by radical surgery after all. Differences in receipt of radiotherapy by surgery type between the three groups may be explained by the overall more favorable tumor characteristics (e.g., lower grade and smaller tumor size [136, 140]) and prognosis among screen-detected patients compared to those not detected through screening.

No study explicitly reported on receipt of monoclonal antibodies (e.g., Trastuzumab, Pertuzumab) or other targeted therapies (e.g., Lapatinib), which are an important component of treatment of HER2+ breast cancer. Given that not many studies using recent data are available, this is however not surprising. In some studies, these treatments may have also been grouped under “chemotherapy” without explicit mention. In **Paper III** [137], use of monoclonal antibodies was less common among screen-detected patients, which may indicate a lower proportion of HER2+ patients in this group.

Since there is a larger proportion of early stage tumors detected through screening compared to in the clinical setting (interval and unscreened groups), differences in treatment by mode of detection may be explained by this larger proportion of early stage cancers among screen-detected patients. In **Paper III**, differences in initial treatment by mode of detection remained when the population of screening-eligible patients was restricted to patients without affected lymph nodes or distant metastases at diagnosis (n=5,015) (**Table 3**).

Table 3 Characterization of included breast cancer patients who were eligible for screening and description of initial treatment phase by mode of detection in patients without affected lymph nodes or distant metastases at diagnosis

	Mode of detection							
	Screening participants							
	All		Screen-detected[1]		Interval-detected		Unscreened (eligible)	
	5015	(100%)	1807	(36.0%)	392	(7.8%)	2816	(56.2%)
Age at diagnosis								
Mean age at diagnosis (SD)	61.2	(6.0)	62.0	(5.9)	61.8	(6.1)	60.7	(6.0)
<50 years at diagnosis	0	(0%)	N/A	(0%)	N/A	(0%)	N/A	(0%)
50-69 years at diagnosis	4910	(97.9%)	1733	(95.9%)	361	(92.1%)	2816	(100%)
70-79 years at diagnosis	105	(2.1%)	74	(4.1%)	31	(7.9%)	N/A	(0%)
80+ years at diagnosis	0	(0%)	N/A	(0%)	N/A	(0%)	N/A	(0%)
Breast surgery[2]								
Within one year of diagnosis	5015	(100%)	1807	(100%)	392	(100%)	2816	(100%)
Breast conserving surgery	3986	(79.5%)	1568	(86.8%)	301	(76.8%)	2117	(75.2%)
Radical breast surgery	1029	(20.5%)	239	(13.2%)	91	(23.2%)	699	(24.8%)
Both types of surgery	468	(9.3%)	127	(7.0%)	44	(11.2%)	297	(10.5%)
Two or more surgeries	1323	(26.3%)	429	(23.7%)	113	(28.8%)	781	(27.7%)
Neoadjuvant systemic therapy								
Yes	367	(7.3%)	36	(2.0%)	34	(8.7%)	297	(10.5%)
Adjuvant systemic therapy[3]								
Within four months after breast surgery	4344	(86.6%)	1559	(86.3%)	336	(85.7%)	2449	(87.0%)
Cytostatic drugs	1999	(46.0%)	587	(37.7%)	165	(49.1%)	1247	(50.9%)
Monoclonal antibody	36	(0.8%)	4	(0.3%)	4	(1.2%)	28	(1.1%)
Hormone therapy	2559	(58.9%)	1031	(66.1%)	188	(56%)	1340	(54.7%)
Radiotherapy[3]								
Within ten months after breast surgery	4047	(80.7%)	1509	(83.5%)	312	(79.6%)	2226	(79.0%)
Before breast surgery	13	(0.3%)	3	(0.2%)	2	(0.5%)	8	(0.3%)

Abbreviations: SD = standard deviation; N/A = not applicable

[1] Breast cancer was classified as “screen-detected” if a screening mammography and multidisciplinary case conference were coded in relevant time periods before and surrounding the diagnosis. It was classified as “interval-detected” if the woman had a screening mammography in the regular interval (two years) before diagnosis, but the criteria for “screen-detected” were not fulfilled. Patients without a screening mammography in the regular interval and aged 50–69 years at diagnosis were classified as unscreened, but eligible. The remaining patients were classified as “unscreened and ineligible” (not included in this table).Some patients may be diagnosed, e.g., at age 70 and screened at age 69.

[2] Within one year after diagnosis. Mastectomy includes those with both types of surgery. “Two or more surgeries” refers to additional breast conserving surgery/mastectomy in the first year after the first surgery.

[3] Initiation of systemic therapy is assessed within four months after breast surgery and initiation of radiotherapy within ten months after breast surgery. Patients can receive multiple adjuvant systemic therapies.

This was also true for the long-term treatment patterns (years 2–10 after first breast surgery). Among screening-eligible patients without affected lymph nodes or distant metastases at diagnosis, screen-detected patients received radiotherapy, chemotherapy, and further surgery (at least one additional breast conserving surgery or mastectomy) less frequently in years 2–10 compared to interval-detected and unscreened patients. For example, 14.8% of screen-detected patients received cytostatic drugs in the years 2–10 vs. 23.5% among interval-detected patients. The proportion of patients who died in this time period overall was also lower in screen-detected patients (e.g., 8.9% vs. 14.8% among interval-detected) (data not shown).

Among patients with affected lymph nodes and no distant metastases at diagnosis (n=788, of these, 206 screen-detected and 72 interval-detected patients), the differences regarding surgery persisted (lower proportion of mastectomies and patients with both types of surgery among screen-detected patients compared to interval-detected and unscreened patients). The differences regarding systemic therapy were less pronounced: for example, 84% of screen-detected patients initiated cytostatic drugs within four months of breast surgery, compared to 90% of interval-detected patients (data not shown). However, group sizes were small particularly among interval-detected patients, and among patients with distant metastases, no meaningful comparison could be made due to small group sizes (n=262, of these, 36 screen-detected and 12 interval-detected patients).

It should be noted that the classification of stage used in **Paper III** was an approximation using the information available in GePaRD, while actual TNM staging also considers factors such as tumor size and number of affected lymph nodes. Within patients classified as “without affected lymph nodes or distant metastases at diagnosis”, there may be differences in tumor size, which there was no information on. Grading would be another tumor characteristic of interest. It seems likely that, within the same stage group, the tumors detected through screening still differ from tumors detected in the interval and in the unscreened group beyond the information that was possible to cap-

ture in GePaRD. Regarding the patients diagnosed with affected lymph nodes or distant metastases, since screening is targeting asymptomatic women, it is plausible that the differences in treatment by mode of detection attenuated with later stages (as far as group sizes still allowed for some interpretation).

Some studies also reported further indications for less intense treatment not reported in many other studies, such as lower proportions of re-excision after BCS and lower proportions of axillary lymph node dissections among screen-detected patients [131, 134]. While re-excision was not directly determined in **Paper III**, the proportion of patients who had at least one more surgery within one year after the first surgery was lowest among screen-detected patients compared to interval-detected and unscreened patients [137]. This may in part also include re-excisions.

The available studies on treatment differences by mode of detection varied with regard to the age range of the study population and screening modalities present in the country of origin. Especially in studies from the USA, where screening is mainly opportunistic, some studies focused on screening among 40-49-year-old women [130] or women 40 years and older [135]. Further, many studies included DCIS cases alongside invasive cases, which skewed results in favor of less intense treatment among screen-detected cases, given that DCIS is almost entirely detected through screening [15, 16] and thus much more common in this group [130, 131, 136]. Due to its ability to progress to invasive cancer [17, 18], the detection of DCIS commonly seems to be perceived as a favorable effect of screening rather than an issue of potential overdiagnosis and overtreatment [15, 16, 141], so it is not surprising that many studies did not exclude these cases. Some studies also restricted their study population to certain stages of breast cancer [124, 129, 134, 135], which impaired the comparison between studies.

Less intense treatment among screen-detected patients may also have an effect on the patients' quality of life. In the following section, the data available on quality of life by mode of detection will be briefly summarized.

5.3. Breast cancer treatment and quality of life

Arndt et al. examined the differences in (functional) quality of life between women receiving breast conserving surgery or mastectomy one, three, and five years after diagnosis of early stage breast cancer. While this study was based on older data (patients were diagnosed between October 1996 and February 1998), it suggests long-term differences in quality of life between these groups [142]. Not only does this highlight the lack of current data relating to the topic of quality of life with regard to treatment in the context of mammography screening, it also provides an indication that analyzing differences in treatment between screen-detected and non-screen-detected breast cancer cases is an important area of study.

One recent study from Germany assessed quality of life in 735 invasive breast cancer patients who were newly diagnosed between the ages of 50–69 in 2006–2012 by mode of detection (screen-detected, interval-detected, clinically detected) [143]. Quality of life (QoL) was assessed in 2015, on average 6 years after diagnosis. The dimensions were overall QoL, breast and body image, cognitive functioning, emotional functioning, physical functioning, role functioning, and social functioning (questions regarding sexual functioning and symptoms were not asked). Results were adjusted for time since diagnosis, age at survey, self-reported comorbidities, education, and current medical treatment. There were no substantial differences in QoL by mode of detection. Age at diagnosis (>60 vs. 50–59, adjusted) made a significant difference in cognitive and emotional functioning only for screen-detected patients (lower scores in younger age group).

6. Summary

The present dissertation aimed to highlight the importance of selected confounders and treatment-related outcomes in the evaluation of mammography screening programs with observational data. This was done by conducting three studies. The first two studies focused on menopausal hormone therapy as a concrete example of an important confounding influence in the relationship between participation in mammography screening and breast cancer mortality. The third study addressed the importance of analyzing and comparing treatment and treatment-related outcomes in breast cancer patients according to mode of detection, as differences in treatment may present another potential benefit of mammography screening besides a mortality reduction.

Using observational data to evaluate screening programs is challenging because individuals who decide to participate in screening differ from individuals who decide not to participate. While in a few studies, comparisons between invited and not-invited populations can be made, this is often not possible for many programs. In a trial of mammography screening, effective randomization would lead to an even distribution of potential influencing factors between groups of interest. In studies using observational data attempting to evaluate mammography screening, great care has to be taken when determining how to deal with confounding, particularly self-selection.

Correction factors became a simple way to address this challenge of self-selection in observational studies of mammography screening. They attempt to correct the results of a given study regarding participation in mammography screening and breast cancer mortality for the effect of self-selection by—in most cases—using an estimate of breast cancer mortality among non-attenders vs. women not invited to screening based on published data from applicable studies. The most popular correction factor combines data on breast cancer mortality among non-attenders and uninvited women from five RCTs conducted in the 1970s and 1980s [56]. Not all of these trials investigated, for example, the same age range or screening modalities as the study the correction factor

is being applied to. Apart from data from RCTs, data from other published studies with an approximately similar study population are being used as well for this correction factor by some studies. Apart from issues of compatibility with the underlying data, the self-selection effects from about two to three decades ago are being applied to current (or somewhat current) studies. This means that potential changes in the extent of the effects of self-selection are not being taken into account.

Self-selection of screening participants for mammography screening results in many potential confounding factors that can affect the relationship between screening participation and breast cancer mortality. Differential interaction with the health system or differences in health among screening participants as well as differences in the prevalence of breast cancer risk factors constitute factors of particular interest. The case of MHT exemplifies the importance and the complexity of confounding in the evaluation of mammography screening with observational data. MHT is the most effective medication for the relief of vasomotor symptoms during menopause, and it is also an important hormonal risk factor for breast cancer. In the systematic review (**Paper I**), the association between MHT use and participation in mammography screening was clarified. This study showed that MHT use was associated with participation in mammography screening in nearly all of the 32 studies included in the review. This association of MHT use with participation in mammography screening is likely reflective of health-seeking behavior on both sides: both MHT users and screening participants are more likely than non-users and non-participants to engage in health-seeking behavior, of which increased MHT use (among screening participants) and increased screening participation (among MHT users) is a reflection.

Apart from the differences in breast cancer risk directly due to MHT use, an imbalanced distribution of MHT use may also result in an imbalanced distribution of other factors related to MHT, such as breast density. This has the potential to further confound the effect of mammography screening on breast cancer mortality. High breast density is an independent breast cancer risk factor and can mask changes on a mammogram. There

is evidence that cancers that have been missed at screening due to high breast density are still similar in characteristics to screen-detected cancers and not necessarily “true” interval cancers. In this case, there may not be an enrichment of later stage tumors/tumors with worse characteristics among participants. The issue with potentially increased breast density among screening participants due to more frequent MHT use may therefore be the corresponding increase in breast cancer risk and less so a masking effect.

In the study of MHT prescribing in Germany, substantial reductions in use of almost all types of MHT were found, including combined MHT, which is the type that bears the greatest breast cancer risk. Nonetheless, combined MHT is still the most commonly used type of MHT in Germany. The history of MHT use and its strongly time-varying nature demonstrates the importance of considering the time-varying nature of confounding factors in the evaluation of mammography screening in general, which a static correction factor can hardly account for. MHT use changed over time to a large degree, recommendations for its use have changed, it has a large potential user base among screening-eligible women with (post)menopausal women aged 45+, and is connected to another potentially confounding factor with breast density. Since there is little information on differences between participants and non-participants in the German MSP, it would be insightful to broaden the focus and determine these differences more in detail in the future. Screening participants may be also utilizing other preventive measures such as other screenings more often, or be generally healthier than non-participants.

Regarding the hormonal type of MHT, the main risks of MHT, and its influence on breast density, are mainly related to use of oral combined preparations [76]. While prescribing of combined MHT declined considerably between 2004 and 2016, combined MHT is still the most commonly used type of systemic MHT. Estrogen preparations may still present a (smaller) breast cancer risk, but even if that were not the case, a potential “healthy user” effect would likely apply to all forms of MHT use. Therefore, it

seems prudent to consider, if possible, use of all hormonal types and routes of administration as potential confounding influences.

The primary goal of mammography screening is a reduction in breast cancer mortality. The main reason for this is thought to be the detection of the disease at an earlier stage, although advances in treatment may also play a critical role. Ideally, detection at earlier stages would enable the possibility of less intense treatment. Since cancer treatment (surgery, chemotherapy, radiotherapy) can have a variety of adverse effects, both physical and psychological, less intense treatment can be thought of as a potential secondary benefit of breast cancer detected through mammography screening. The study on breast cancer treatment (**Paper III**) was the first study to provide long-term treatment information according to mode of detection (screen-detected, interval-detected, unscreened) in Germany. There were considerable differences both in initial treatment as well as treatment in the years following the initial treatment phase. A literature review was additionally conducted in order to provide context for the results of this study as well as insight into areas where there is still a lack of data regarding treatment by mode of detection. While the available studies differed with regard to screening setting (opportunistic, organized), age range of patients, and characteristics of the study population, the results overall did point to less intense treatment among screen-detected patients. Regarding surgery, the studies were unanimous—BCS was more common among screen-detected patients. Data on radiotherapy was often not available, and existing studies provided discrepant results in early-stage patients only. **Paper III** pointed towards differences by in the initiation of radiotherapy by mode of detection for patients receiving a mastectomy, but not for patients receiving BCS. Regarding systemic therapy, no data was available on treatment with monoclonal antibodies (e.g., Trastuzumab) in the literature. In **Paper III**, treatment with a monoclonal antibody in the years after first breast surgery was lowest among screen-detected patients. Chemotherapy was less common among screen-detected patients both in **Paper III** and most of the studies in the literature review. Results regarding hormone therapy

were inconsistent, despite studies reporting higher proportions of HR+ patients among screen-detected patients. In **Paper III**, there was a higher proportion of patients receiving hormone therapy among screen-detected compared to not screen-detected patients. Overall, there is a lack of data on long-term treatment—only **Paper III** so far provided data on treatment beyond the initial treatment phase. Further, treatment was often restricted to certain types (mainly surgery and chemotherapy) in other studies, while there was comparatively little insight into radiotherapy treatment. Many other studies included DCIS cases alongside invasive breast cancer cases, which likely skewed the results of these studies in favor of less intense treatment. In **Paper III**, differences in treatment by mode of detection persisted when the study population was restricted to screening-eligible patients diagnosed without affected lymph nodes or distant metastases. This may indicate that detection at an earlier stage through screening is still more beneficial than detection at an earlier stage outside of screening, although tumor characteristics such as size and grading likely played a role in this observation, which there was no information on in the study.

6.1. Conclusion and outlook

As not all data of importance are always available to all researchers, addressing confounding influences beyond simplified correction factors is not always possible in practice. Nonetheless, this work highlights that great care should be taken in examining how issues like self-selection can be adequately dealt with, to make sure to have an idea what information would in theory be needed for an unbiased estimate (as far as possible), and to address to which extent there may still be confounding present in a given study. As the history of mammography screening is fraught with controversy, it seems only fair to the target population to aim at providing them (and policy makers) with the best available evidence and an honest discussion of the results of a given study.

The study on breast cancer treatment conducted as part of the present dissertation indicated substantial differences in both the initial and long-term treatment of breast cancer in screen-detected patients compared to not screen-detected patients. Given the discussion around the benefits and harms of mammography screening, it is important to consider possible other benefits beyond the main aim of screening (i.e., the reduction in breast cancer mortality). Given that only limited data on cancer treatment—particularly on long-term treatment—are available from clinical cancer registries in Germany currently, other data sources such as claims data have shown great potential in addressing questions related to screening and cancer treatment.

Regarding possible improvements in quality of life among patients who had their breast cancer detected through screening, one recent study from Germany did not find substantial differences in various dimension of QoL by mode of detection [143]. However, there are overall still very few studies available, and no clear conclusions can be drawn yet whether the mode of detection has a substantial influence on the (health-related) quality of life of patients.

A next step would be to gain a better understanding of potential differences in the characteristics of mammography screening participants and non-participants using German claims data. Regarding MHT, there was no study from Germany that provided information on MHT use in screening participants and non-participants in the systematic review on MHT use and participation in mammography screening. There are also currently no comprehensive studies on differences between participants and non-participants in the German MSP. So far, studies from Germany have mainly focused on comparing sociodemographic characteristics [144-148], with little information available on other important differences, such as comorbidities [53]. Given that the German mammography screening program is currently being evaluated using observational data, insight into differences between participants and non-participants, especially with regard to potential confounders, would be highly beneficial. This comparison may further provide insight for organizers of the German mammography screening program

into which groups of their target population participate less in the program than others. This information may then be used to increase efforts to reach these specific populations.

Regarding breast cancer treatment, the study on initial and long-term breast cancer treatment primarily explored the potential of German claims data to describe breast cancer treatment. Future studies may explore the potential of claims data to identify treatment regimen (e.g., chemotherapy regimen, cumulative doses of systemic treatment, number of radiotherapy cycles). In this way, treatment intensity may be described in more detail. Further, it may be of interest to describe the treatment of DCIS in Germany, particularly in the context of overdiagnosis and overtreatment, given that ~20% of tumors detected through screening are DCIS. Regarding mode of detection, there may be further benefits for patients to have their breast cancer detected through screening as opposed to in a clinical setting when the disease is already symptomatic. A study analyzing differences such as rates of complications after surgery, ancillary treatments, or newly made diagnoses such as mood disorders (as far as available in claims data) by mode of detection may provide further insight as to potential benefits of mammography screening apart from a reduction in breast cancer mortality. Further, the study on breast cancer treatment focused on patients diagnosed in 2008 in order to achieve the longest follow-up possible, but it would be interesting to also analyze treatment differences in later years to see if treatment differences persist (or change) under more current circumstances. Lastly, given that treatment differences by mode of detection were also present among patients without affected lymph nodes or distant metastases at diagnosis, it would be of interest to explore synergies between claims data and data from cancer registries, as the latter have detailed information on tumor characteristics. This would allow for a highly insightful and more detailed comparison of treatment differences—including long-term treatment—by mode of detection with regard to stage at diagnosis.

In general, it may be beneficial to complement the monitoring of the German screening program using data available outside the program itself, especially with regard to the advances in breast cancer treatment in the future. Beyond mortality reduction, the discussion around screening programs centers around the harms-benefit ratio, and continuous monitoring would enable the evaluation of the most recent data while taking into account recent developments in treatment and recommendations with regard to screening schedule. This may also be possible for research questions related to other screening measures.

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Quantifizierung der Eigenanteile an den Publikationen

Quantifizierung der Eigenanteile der Kandidatin an den Publikationen gemäß §6, Abs. (2) Punkt 2 und 4 der Promotionsordnung Dr. rer. nat.

Paper I **Heinig M**, Schwarz S, Haug U. Self-selection for mammography screening according to use of hormone replacement therapy: A systematic literature review. Cancer Epidemiol. 2021;71:101812. DOI: 10.1016/j.canep.2020.101812

Paper II **Heinig M**, Braitmaier M, Haug U. Prescribing of menopausal hormone therapy in Germany: Current status and changes between 2004 and 2016. Pharmacoepidemiol Drug Saf. 2021;30(4):462-71. DOI: 10.1002/pds.5186

Paper III **Heinig M**, Heinze F, Schwarz S, Haug U. Initial and ten-year treatment patterns among 11,000 breast cancer patients undergoing breast surgery—an analysis of German claims data. BMC Cancer. 2022;22(1):130. DOI: 10.1186/s12885-022-09240-w

	Eigenanteil[1]		
Arbeitsschritt	Paper I	Paper II	Paper III
Theoretische Konzeption (inklusive Fragestellung)	überwiegend	überwiegend	überwiegend
Literaturrecherche	vollständig	vollständig	vollständig
Studienplanung	überwiegend	überwiegend	überwiegend
Datenerhebung[2]	überwiegend	N/A	
Datenauswertung	vollständig	vollständig	vollständig
Diskussion und Interpretation	überwiegend	überwiegend	überwiegend
Manuskripterstellung	vollständig	vollständig	vollständig
Revision	überwiegend	überwiegend	überwiegend

N/A = nicht anwendbar

[1] Gemäß den „Empfehlungen für eine formale Gestaltung der Dissertation“ (Stand: 11.12.2018) erfolgt die Quantifizierung der Eigenanteile in: vollständig (alle Arbeitsschritte im regelmäßigen Austausch mit Kollegen), überwiegend (die Mehrheit der Arbeitsschritte eigenständig), gleichwertig (zu gleichen Teilen von Doktorand und Koautor(en)).

[2] Bei Paper I bezieht sich „Datenerhebung“ auf die Prozedur der systematischen Literaturrecherche, Begutachtung und Auswahl der relevanten Artikel. Paper II und III basieren auf der Sekundärdaten-Datenbank GePaRD (German Pharmacoepidemiological Research Database).

Eigenständigkeitserklärung

Ich versichere, dass die vorliegende Arbeit

- ohne unerlaubte fremde Hilfe angefertigt wurde,
- keine anderen als die angegebenen Quellen und Hilfsmittel benutzt wurden und
- die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht worden sind.

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