FACULTY OF HEALTH SCIENCE, AARHUS UNIVERSITY

Reoperation due to surgical bleeding in breast cancer patients and breast cancer recurrence: A Danish population-based cohort study

Research year report

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PREFACE

The present report is based on a study conducted during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark.

First of all, I would like to express my profound gratitude to my supervisors and collaborators. During my research year, they have generously shared of their extensive knowledge and patiently taught me everything from developing the concept and writing the protocol to collecting data, conducting analyses and interpreting results.

I am deeply thankful to my main-supervisor, Deirdre Cronin-Fenton, who has been an outstanding supervisor. Dee have been very enthusiastic about my project and despite at times a very packed schedule, she has always been able to have time for me, commenting on my manuscript and given me constructive feedback. I have appreciated our weekly meetings, where you have provided excellent academic support and lots of laughs. I hope we will get to work together more in the future.

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ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical classification system
BCS	Breast-conserving surgery
CCI	Charlson Comorbidity Index
CI	Confidence interval
CRS	Civil Registration System
DBCG	Danish Breast Cancer Group Registry (formerly, Danish Breast Cancer Cooperative Group registry)
DNPR	Danish National Patient Registry
ER	Estrogen receptor
ET	Endocrine therapy
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRT	Hormone replacement therapy
ICD	International Classification of Diseases
IRs	Incidence rates
IQR	Interquartile range
PY	Person-years
RFS	Recurrence-free survival
UICC	Union for International Cancer control

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ABSTRACT

Background: Breast cancer patients who develop postsurgical bleeding requiring reoperation may be at increased risk of breast cancer recurrence, since bleeding activates platelets that can bind to tumor cells, potentially promoting metastatic growth. We investigated the association between postsurgical bleeding requiring reoperation and the rate of breast cancer recurrence.

Methods: Using the Danish Breast Cancer Group (DBCG) registry and the Danish National Patient Registry (DNPR), we identified women with incident stage I-III breast cancer, who underwent breast-conserving surgery or mastectomy during 1996-2008. We retrieved information on reoperation due to bleeding within 14 days of primary surgery from the DNPR. Follow-up began 14 days after primary surgery and continued to the first of recurrence, death, emigration, ten years, or 01/01/2013. We computed incidence rates (IRs) of recurrence per 1000 person-years (PY), and 5- and 10-year incidence accounting for death as a competing risk. Cox regression models were used to quantify the association between reoperation and recurrence, adjusting for potential confounders (age, menopausal status, stage, grade, surgery type, estrogen receptor status, cancer treatment, comorbidity, and co-medications). We stratified our analyses by age, receipt of chemotherapy, stage, and type of primary surgery. Furthermore, we computed crude and adjusted hazard ratio according to site of recurrence.

Results: Among the included 30,711 patients (205,926 PY of follow-up), 767 patients had at least one reoperation within 14 days of primary surgery and 4,769 patients developed breast cancer recurrence. The incidence rate of recurrence was 24/1000 PY for reoperated patients and 23/1000 PY for non-reoperated patients. The corresponding adjusted overall hazard ratio was 1.07 (95% CI, 0.89-1.28). The estimates did not vary by site of breast cancer recurrence. There was no evidence of effect modification in models stratified by stage, age, receipt of chemotherapy or type of primary surgery.

Conclusion: In this large prospective cohort study, we found no evidence of an association between reoperation due to bleeding and breast cancer recurrence.

DANSK RESUMÉ

Baggrund: Brystkræft patienter, som udvikler en postoperative blødning, der kræver en reoperation kan have en øget risiko for brystkræft recidiv. Dette kan skyldes, at blødning aktiverer blodpladerne som kan binde kræftcellerne og potentielt fremme metastatisk vækst. Vi undersøgte associationen mellem reoperation grundet postoperativ blødning og risikoen for brystkræft recidiv.

Metode: Ved hjælp af Dansk Brystkræft Gruppe database (DBCG) og Landspatientregisteret (DNPR) identificerede vi alle kvinder med en operabel stadie I-III brystkræftdiagnose som havde fået udført en brystbevarende operation eller en mastektomi mellem 1996 og 2008. Fra DNPR indhentede vi også information omkring reoperation grundet postoperativ blødning indenfor 14 dage efter den primære operation. Vi fulgte hver patient fra 14 dage efter den primære operation og opfølgningen fortsatte i 10 år eller indtil brystkræft recidiv, død, emigrering eller d. 1 januar 2013. Vi udregnede incidence rater (IRs) per 1000 personår (PY) for recidiv samt 5 og 10 års incidencen. Ved hjælp af cox regression udregnede vi en ujusteret samt en justeret hazard ratio (HRs) for associationen mellem reoperation grundet postoperativ blødning og brystkræft recidiv. I alle analyser tog vi hensyn til død som competing risk. Vi justerede for potentielle konfoundere (alder, menopausal status, stadie, grad, operationstype, østrogen receptor status, behandling, komorbiditet og potentielle konfounder medikamenter). Vi stratificerede vores analyser efter alder, modtagelse af kemoterapi, stadie og typen af primæroperation. Derudover udregnede vi en ujusteret og justeret hazard ratio i forhold til recidiv placeringen.

Resultater: Vi inkluderede 30.711 patienter med 205.926 personårs opfølgning. 767 patienter gennemgik mindst en reoperation indenfor 14 dage efter deres primære operation og 4.769 udviklede brystkræft recidiv under opfølgningen. Incidensraten for recidiv var henholdsvis 24/1000 PY for patienter med en reoperation og 23/1000 PY for patienter uden en reoperation. Den justerede hazard ratio var 1,07 (95% CI, 0,89-1,28). Estimaterne ændrede sig ikke i forhold til recidiv placering og der var ingen tegn på effekt modifikation ved stratificering.

Konklusion: Vi fandt ingen sammenhæng mellem reoperation grundet postoperativ blødning og brystkræft recidiv.

MANUSCRIPT

INTRODUCTION

Breast cancer is the second most common cancer in the world and the most frequent cancer among women, with an estimated 1.67 million new cases diagnosed in 2012 (25% of all cancers). With 522,000 annual breast cancer-related deaths estimated worldwide, it is the most frequent cause of cancer-related death in women in developing countries, and second only to lung cancer in more developed regions.[1]

Surgery, either breast-conserving surgery (BCS) or mastectomy is the primary treatment for breast cancer. Despite its therapeutic intent, surgery causes physiological stress, which, along with anesthesia,[2] may result in transient immunosuppression during the perioperative period.[3] During surgery, physical excision of a tumor may mobilize cancer cells and circulating tumor cells have been detected in breast cancer patients after surgery.[4,5] Accordingly, the excision process and transient immunosuppression during the perioperative period may aid cancer cells to avoid immune detection.[3]

Postsurgical bleeding requiring reoperation occurs in about 4% of women who undergo surgery for breast cancer.[6] Depending on patient age and primary surgery type (mastectomy versus BCS),[7] use of certain prescription drugs (such as selective serotonin reuptake inhibitors or glucocorticoids) increases the risk of postsurgical bleeding requiring reoperation.[7,8] However there is no evidence of an effect of SSRI and glucocorticoid use on breast cancer recurrence.[8,9] Bleeding activates platelets, which can bind tumor cells, promoting immune evasion, angiogenesis, tumor cell survival, and metastatic growth.[10] Cancer is associated with a hypercoagulable state,[11,12] with heightened platelet activation and a poor prognosis.[13] Thus, breast cancer patients who develop postsurgical bleeding requiring reoperation may be at increased risk of breast cancer recurrence.

We therefore conducted a clinical population-based cohort study to investigate the association between bleeding occurring within 14 days of primary breast cancer surgery and the rate of breast cancer recurrence among Danish breast cancer patients.

MATERIALS AND METHODS

Setting

We conducted a nationwide cohort study using Danish population-based registries.[14] Denmark´s National Health Service provides tax-supported health care to Danish citizens and permanent residents, including unfettered access to hospital care and partial reimbursement for prescribed medications.[15] At birth or upon immigration, each person is assigned a unique civil personal registration number (CPR number) that allows unambiguous individual-level linkage among all Danish administrative and population-based registries, including medical registries.[16]

Source Population and Data Collection

We used the Danish Breast Cancer Group Registry (DBCG)[17,18] and the Danish National Patient Registry (DNPR) to identify all women with an incident diagnosis of operable stage I-III breast cancer who underwent BCS or mastectomy (codes KHAB and KHAC in the Danish Classification of Surgical Procedures and Therapy) between 1996 and 2008. To ensure correct retrieval of the exposure—reoperation due to postsurgical bleeding within 14 days following primary breast cancer-directed surgery—we considered patients eligible for inclusion in the study if there was no more than 1 day (+/- 1 day) difference between the primary surgery date recorded in the DNPR and the DBCG.

The DBCG was established in 1977. It has since registered almost all women with invasive breast cancer in Denmark.[19] Data on tumor and patient characteristics are prospectively collected by clinicians in surgery, oncology, and pathology departments. Completeness of registration is approximately 95%. [19] Patients registered in the DBCG undergo regular follow-up exams aimed at detecting recurrent disease. From DBCG we obtained information on age and menopausal status at diagnosis, type of surgery, WHO histological tumor type and grade, lymph node status, estrogen receptor (ER) status, receipt of adjuvant chemotherapy, endocrine therapy (ET) and/or radiation therapy, and date and site of recurrence.

The DNPR has collected data on all non-psychiatric hospital admissions since 1977 and on all outpatient and emergency contacts since 1995. Data in the DNPR include the CPR number,[20] one

primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases* (ICD), as well as data on diagnostic and surgical procedures.[20]

We used the DNPR to retrieve information on the exposure reoperation due to postsurgical bleeding (codes KHWD00 and KHWE00), within 14 days following primary breast cancer-directed surgery. We also retrieved information from the DNPR on potentially confounding comorbid diseases registered up to ten years before the breast cancer diagnosis. We summarized these using the Charlson Comorbidity Index (CCI),[21] modified to exclude breast cancer diagnoses. We examined specific comorbid diseases prevalent on the date of breast cancer surgery, which could potentially confound or modify the association between postsurgical bleeding and breast cancer recurrence.[22-25] These included diabetes, liver disease, chronic pulmonary disease, peripheral and cerebral vascular disease, any other cancer, myocardial infarction, and congestive heart failure (Appendix).

We retrieved information on death and emigration from the Civil Registration System (CRS). The CRS, established in 1968, contains information on the vital status of all Danish citizens. It is updated daily.[15]

The National Prescription Registry maintained by Statistics Denmark has automatically recorded detailed information on all prescriptions redeemed at Danish community pharmacies since 1995.[26] The registry contains detailed information on dispensed prescriptions, including full Anatomical Therapeutic Chemical (ATC) codes and date and quantity dispensed. [26] We retrieved data on drugs that could potentially confound the association between bleeding and recurrence, including simvastatin and aspirin, which have been shown to modify breast cancer prognosis,[27,28] and hormone replacement therapy.

Analytic variables

Age at diagnosis was categorized into decades. Histologic grade was defined as low, moderate, or high based on World Health Organization histological tumor type. Stage was defined as I, II, or III according to the International Union Against Cancer (UICC) classification. Estrogen receptor status (ER) and adjuvant endocrine therapy (ET) were summarized as following: ER+/ET+, ER-/ET-, ER+/ET-, and ER-/ET+. Surgery type was defined as mastectomy or breast-conserving surgery. Treatment with adjuvant chemotherapy was categorized dichotomously. Menopausal status was defined as premenopausal or postmenopausal, classified according to the DBCG.

Simvastatin and aspirin use were modelled as time-varying covariates. We used longitudinal prescription data to define time-updated exposure to these drugs. For each prescription, we calculated prescription duration time as pack size (*i.e.*, number of pills per pack) x number of packages redeemed, thereby assuming that a single pill was taken per day. In defining continuous use, we allowed a gap of 30 days from the end of one prescription (prescription start date + prescription duration) until the start of a new prescription. If a new prescription was redeemed within this window, then exposure was assumed to continue; if not, the patient was considered to have stopped the drug at the end of the 30-day grace period. The patient could later re-start if there were further prescriptions. Finally, we lagged the resulting time-updated current exposure variable by 1 year to allow the effect of the drug to accrue, since any effects on cancer are likely to be delayed. Hormone replacement therapy (HRT) was recorded as a baseline covariate among women with at least one year of prescription history.

Breast cancer recurrence was defined according to the DBCG, as any local, regional or distant recurrence or cancer of the contralateral breast up to ten years after the primary diagnosis.[17]

Follow-up began 14 days after primary breast cancer surgery (registered in the DNPR) and continued until breast cancer recurrence, death, emigration, ten years of follow-up, or 1 January 2013 (end of the study period), whichever came first. Patients who died or emigrated without a breast cancer recurrence were censored on their date of death or emigration.

Statistical analyses

We estimated the frequency and proportion of breast cancer patients with and without reoperation due to postsurgical bleeding, by patient, tumor, and treatment characteristics. We calculated incidence rates (IRs) (overall, 0-5 years and >5 years) of recurrence per 1000 persons-years (PY) and estimated the 5- and 10- year cumulative incidence of recurrence according to the receipt of reoperation due to postsurgical bleeding.

We used Cox regression models with time since start of follow-up as the underlying timescale to compute crude and adjusted recurrence hazard ratios (HRs) and associated 95% confidence intervals (95% CIs) for reoperation due to postsurgical bleeding. The adjusted model included the following potential confounders: age group at diagnosis, menopausal status, receipt of chemotherapy, UICC stage, grade, primary surgery type, estrogen receptor/endocrine therapy status,

comorbidity, baseline HRT, and post-diagnostic simvastatin/aspirin use (coded as time-varying covariates lagged by 1 year). Competing risk of death was taken into account in all models.[29]

We stratified our analyses by age, receipt of chemotherapy, UICC stage, and type of primary surgery. We computed the crude HR and adjusted HR according to site of recurrence.

We conducted the following sensitivity analyses: (1) altering the 14-day window for reoperation and start of follow-up to 7 and then 21 days after primary surgery; (2) altering the inclusion criteria (+/- 1day difference in surgery date between DNPR and DBCG) to +/-14 and then +/- 31 days; (3) altering the study population to include only patients with stage I and II disease at diagnosis; and (4) excluding patients with previous cancers.
Analyses were performed using STATA version 13.

RESULTS

We identified 33,162 incident breast cancer patients who underwent BCS or mastectomy between 1996 and 2008. The cohort consisted of 30,711 women after excluding women with more than 1 day difference in the date of surgery between the DNPR and the DBCG, and women with an event before start of follow-up.

Median age was 59 years (IQR: 50-66 years). Median follow-up was 7.0 years (IQR: 4.5-9.7). A total of 767 patients had at least one reoperation within 14 days of their primary surgery (2.5%) (Table 1). Compared to women without a reoperation, a slightly higher proportion of patients who underwent reoperation were postmenopausal (75% vs 72%), had evidence of comorbid disease (CCI score of at least 1 (23% vs 20%)), had a history of cerebrovascular disease (5.2% vs 3.4%), and had moderate-grade tumours (13% vs 11%). Patients who underwent reoperation were more likely to have received mastectomy than BCS as primary surgery (67% vs 56%) and less likely to receive chemotherapy (29% vs. 34%) A higher proportion of patients who did not undergo reoperation had stage III cancer (18% vs 14%). Overall 21% of the breast cancer cohort had been prescribed aspirin and 21% of the cohort had been prescribed simvastatin during follow-up, and 42% had been prescribed HRT at start of follow-up. Compared with patients without a reoperation, patients who underwent reoperation were more likely to be concurrent aspirin users.

Overall 4,769 developed breast cancer recurrence during follow-up. The IR of recurrence was 24.0 (95% CI, 20.2-28.6) and 23.1 (95% CI, 22.5-23.8) per 1000 PY for reoperated and non-reoperated patients respectively (Table 2). Both for patients with and without a reoperation, the IR of recurrence decreased during follow-up (Table 3). In the cohort of patients with a reoperation, the IR of recurrence decreased from 27.7 (95% CI, 22.6-33.9) per 1000 PY after 0-5 years follow-up to 17.5 (95% CI, 12.5-24.7) per 1000 PY after 5 years follow-up. In the cohort of patients without reoperation, the IR of recurrence decreased from 26.9 (95% CI, 26.1-27.8) per 1000 PY after 0-5 years follow-up to 15.9 (95% CI, 15.0-16.9) per 1000 PY after 5 years follow-up. The 5-year cumulative incidence of recurrence was 12.8% and 12.5% for patients with and without a reoperation respectively and the 10-year cumulative incidence of recurrence was 19.9% and 18.9% for reoperated and non-reoperated patients, respectively (Table 3).

Among 767 patients who underwent a reoperation, there were 126 recurrences in 5,241 PY of follow-up, while among 29,944 with no reoperation, there were 4,643 recurrences in 200,685 PY follow-up. After adjusting for potential confounders, we observed no association between postsurgical bleeding and breast cancer recurrence (adjusted hazard ratio, 1.07; 95% CI, 0.89 -1.28), regardless of time interval (7, 14, or 21 days after primary operation) (Table 2). The null association did not change in sensitivity analyses where the study population included only patients with stage I and II disease at diagnosis, where patients with previous cancers were excluded, or where we included patients with a difference in surgery date between DNPR and DBCG less than 14 days and less than 31 days (Supplemental Table 4). The estimates did not vary by site of breast cancer recurrence (Figure 1).

Finally, there was no evidence of effect modification in models stratified by stage, age, receipt of chemotherapy or type of primary surgery (Figure 2).

DISCUSSION

Our study showed no evidence of an association between reoperation due to postsurgical bleeding and breast cancer recurrence, regardless of time interval (7, 14, or 21 days after the primary operation). The estimates also did not vary in analyses stratified by clinical factors or by site of breast cancer recurrence. The stratified incidence rates (0-5 years, >5 years) of recurrence were

similar between patients with a reoperation and patients without a reoperation. Therefore it seems unlikely that reoperated patients would develop a recurrence earlier than non-reoperated patients.

Previous research in Danish patients reported an association between re-excision (repeat surgery due to insufficient surgical margins within 2 months of BCS) and increased risk of ipsilateral breast tumor recurrence.[30] However, this finding was largely due to residual disease.[30] We therefore hypothesized that patients who underwent reoperation due to postsurgical bleeding would be at increased risk of ipsilateral breast tumor recurrence. However, our findings did not vary by site of disease recurrence.

The null associations we observed are somewhat similar to those observed in patients with gastrointestinal cancers. A recently published paper suggested that blood transfusion rather than intraoperative blood loss correlated with decreased recurrence-free survival (RFS) in hepatocellular carcinoma patients after hepatectomy.[31] The association between blood transfusion and RFS remained after adjusting for potential confounding clinical and pathological variables, such as age, gender, tumor diameter, and frequency of liver cirrhosis among others. Research also suggests that blood loss during surgery, regardless of receipt of blood transfusion, is a risk factor for peritoneal recurrence after curative resection of gastric cancer.[32] This result is supported by another study which found that intraoperative blood loss associated with surgery of upper gastrointestinal tract tumors decreases the activity of natural killer cells, which is the body´s primary arsenal against cancer.[33]

The main strengths of this study include its large size and population-based nationwide design within a setting of universal tax-supported health care. The prospective data collection reduced the potential for selection bias and ensured virtually complete follow-up. Furthermore, we had comprehensive data on potential confounders, including prescription data. We were able to include prescribed aspirin and simvastatin as time-varying exposures, allowing for fluctuations in drug exposure during follow-up. It is also a strength of the study that the exposure—reoperation due to postsurgical bleeding—is a surgical code. Although the positive predictive value of the code for reoperation due to postsurgical bleeding has not been assessed in the DNPR, we expect it to be high, as hospitals in Denmark are reimbursed only after registration of surgical procedures. Nonetheless, it is possible that other operative procedures could be misclassified as reoperation due to postsurgical bleeding. These include reoperation due to postsurgical infection (surgical codes KHWB, KHWC) or reoperation due to other causes, which may include insufficient surgical

margins (surgical code KHWW). However, the latter misclassification is likely to bias our findings away from the null since residual disease is associated with recurrence.[30] Nonetheless, the impact of postsurgical infection on breast cancer recurrence remains unclear.

Earlier studies used blood transfusion as a proxy for perioperative bleeding.[34,35] However, in the case of breast cancer surgery, perioperative bleeding does not always result in blood transfusion. Furthermore, patients who receive blood transfusions are often sicker, with disseminated cancer, and more extensive comorbidity.

Our study has some limitations. We lacked information on the extent of postsurgical bleeding, in terms of blood loss. We also had no information on surgical complications that may have precipitated postsurgical bleeding. Another concern was the risk of selection bias due to exclusion of patients; however, the excluded patients were younger, had less advanced disease stage at diagnosis, and were less likely to receive mastectomy and endocrine therapy (Supplemental Table 5). Our sensitivity analyses also showed that the inclusion of these patients did not alter our findings (Supplemental Table 4).

Although we had information on prescribed aspirin, we were unable to account for aspirin bought over the counter. Aspirin has been shown to decrease the risk of breast cancer mortality by up to 50% in some,[27] but not all studies;[36,37] while simvastatin has been consistently associated with a decreased risk of breast cancer recurrence/mortality.[38] All aspirin formulations are available over the counter in Denmark. Aspirin is prescribed almost exclusively in low doses for cardiovascular prevention. Because over the counter aspirin is only available in small packs, supplies for regular usage are usually prescribed by physicians and reimbursable via the Danish National Health Insurance System. The proportions of total sales of low-dose aspirin dispensed by prescription and thus captured in prescription registries is high (92% in 2012),[39] thus residual confounding is minor. We also had no information on prescription compliance. However, in Denmark patients pay part of the cost of redeemed prescriptions, so our estimates are likely to reflect actual use. Nonetheless, adjustment for prescribed aspirin and simvastatin also did not alter our findings. Finally, despite our large study size, reoperation due to postsurgical bleeding is relatively rare in the population. Therefore, the precision of some of our estimates was low.

Our findings may have important clinical implications, providing reassurance to patients and physicians that there is no evidence that reoperation due to postsurgical bleeding increases the risk

of breast cancer recurrence. Thus, patients who undergo reoperation due to bleeding are unlikely to need more aggressive adjuvant therapy or more frequent and extensive follow-up exams to control recurrence, compared with patients who do not undergo reoperation. Breast cancer surgery involves a soft tissue surface and is often characterized by extensive dissection, which increases the risk of postsurgical bleeding. Our findings may therefore be relevant to other soft-tissue surgical procedures used as primary therapy.

In conclusion, findings from our large population-based study provide no evidence of an association between reoperation due to postsurgical bleeding and breast cancer recurrence.

SUPPLEMENTERY INFORMATION

The following section of the research year report contains background, general methodological considerations including strengths and limitations of the current study. Furthermore, results of additional analyses, that were not included in the final manuscript, are presented.

BACKGROUND

In Denmark about 4,600 women are diagnosed with breast cancer each year.[40] Breast cancer is the most common cancer among women.[41] The incidence has increased by approximately 1.3% per year in the last ten years,[42] due to changes in reproductive patterns, increasing uptake of mammography screening, menopausal hormone use, rising prevalence of obesity and population aging.[43] Breast cancer incidence peaks among women around age 60.[43] Approximately 25% of breast cancer cases occur in women <50 years and 20% of cases occur in women >75 years.[44] Life expectancy has improved during the past 70 years in developed countries.[45] The number of people aged 65 or older is expecting to increase.[46] Due to population aging, an increasing proportion of elderly women are likely to present with breast cancer and comorbidities,[47] and accordingly, the population of breast cancer survivors is likely to increase.[48]

Several non-modifiable risk factors for breast cancer have been identified including sex, age, family history and genetic predisposition, while risk factors like alcohol consumption, obesity, and exposure to drugs containing hormones are modifiable.[43]

Breast cancer is a heterogeneous malignancy. The two main categories (depending on site of origin) are ductal carcinomas with the origin in the epithelium of the milk ducts (85% of the cases in Denmark) and lobular carcinomas with origin in the epithelium in the lobules (10% in Denmark).[49] Breast tumors are also categorized according to tumor characteristics example tumor size, lymph node involvement, expression of human epidermal growth factor receptor 2 (HER2) and estrogen receptor status. Primary treatment is usually surgery, with either breast-conserving surgery (BCS) or mastectomy. Other treatment options include neo-adjuvant and adjuvant chemotherapy, radiation therapy, biological treatment, and anti-hormone treatment.[50]

Breast cancer prognosis is determined by multiple prognostic factors. These include tumor stage, tumor grade, histological type, age at diagnosis, hormone receptor status, treatment, extent of

comorbid diseases, and co-medications.[51] Breast cancer survival has improved over the past thirty years—facilitated by earlier detection and increasingly effective targeted therapy. In Denmark, the 5 year overall survival of women at any age diagnosed with breast cancer is 75% in 2007-2009.[48] Nonetheless, patients with similar characteristics at diagnosis vary considerably in the clinical course of their disease; some survive their cancer disease-free, while others experience adverse events such as bleeding, or disease recurrence.

Almost all breast cancer patients undergo surgery.[47] Postsurgical bleeding warranting reoperation occurs in about 4% of women operated for breast cancer. Such reoperation can delay hospital discharge, warrants general anaesthesia and therefore is associated with substantial costs to both the patient and the healthcare system.[6] As elaborated in the manuscript, breast cancer patients who develop a postsurgical bleed requiring reoperation, may have an increased risk of breast cancer recurrence.

METHODOLOGICAL CONSIDERATIONS

Study design

The present study was an observational study, which is a study where the researcher gathers data by simply observing events as they happen.[52]

We designed a nationwide population-based cohort study, using data from national population-based registries. A cohort is defined as a group of patients who are followed for a period of time and share a similar condition or other characteristics. Our cohort was defined by patients with breast cancer who underwent mastectomy or BCS between 1996 and 2008. The goal of a cohort study is to measure and, usually, to compare the incidence of disease in one or more study populations.[53] In the present study, the outcome was breast cancer recurrence, which was defined according to the DBCG, as any local, regional or distant recurrence or cancer of the contralateral breast up to ten years after the primary diagnosis.[17] Upon entry into the study, people are classified according to characteristics (possible risk factors) which might be related to the outcome. For each possible risk factor, members of the cohort are classified either exposed or unexposed.[52] In this study, the exposure was reoperation due to bleeding within 14 days after primary surgery registered in the DNPR. The purpose of following the cohort was to measure the occurrence of breast cancer

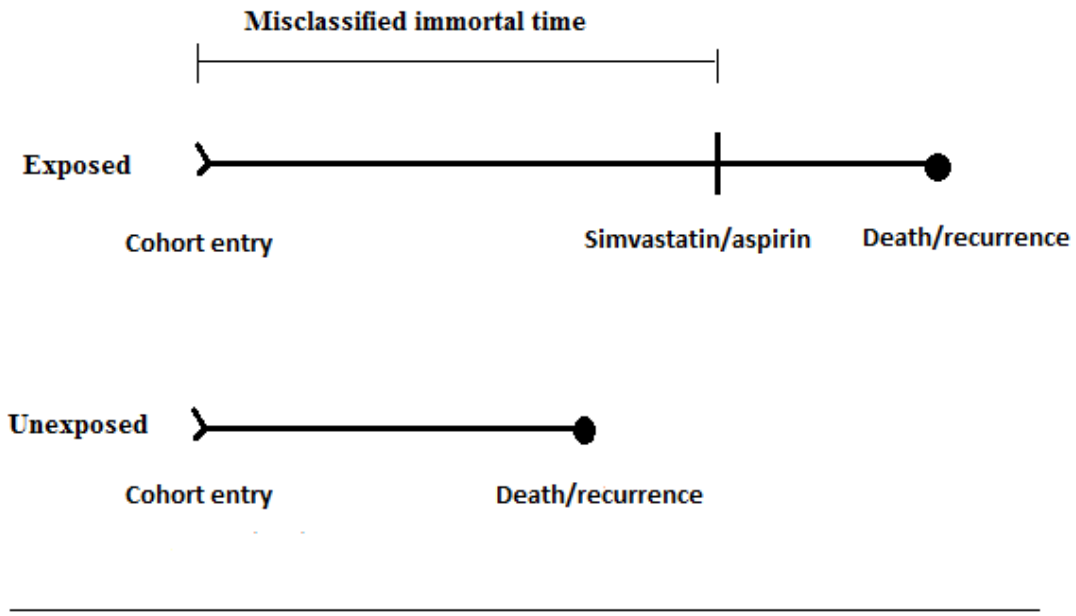
recurrence during the follow-up period, comparing the recurrence rates in the exposed group with the unexposed group. A criterion for being a cohort member is to be at risk. The cohort members had to be free of the outcome (recurrence) because if they had the disease they usually cannot develop it anew. To be at risk also implies that everyone in the population at risk must be alive at the start of follow-up. In this study, we had to be aware of competing risks. Competing risks occur when a patient is at risk of more than one mutually exclusive event, here death and recurrence, and the occurrence of this event will prevent any other events from ever happening.[53] Competing risk of death was taken into account in all statistical models.

Our aim was to investigate the association between postsurgical bleeding within 14 days of breast cancer primary surgery with the rate of breast cancer recurrence among Danish breast cancer patients. To our knowledge this association has never been investigated. For the purpose of our study, we found a cohort study most suitable.

Immortal time

Immortal time refers to a period of cohort follow-up, during which death cannot occur. This often arises in cohort studies of drug effects, where exposure to a drug is established from the prescriptions given during the follow-up. Consequently, the period between cohort entry and the first prescription for the drug under study will necessarily be event-free and thus 'immortal'. In other words, in order to be able to receive the prescription, the patient must have survived this "immortal" period. Immortal time bias can then arise, when the exposure during this immortal time period is either misclassified or simply excluded and not accounted for in the data analysis.[54] Supplemental Figure 1 illustrates misclassified immortal time. The drug exposure is defined after cohort entry: the time between cohort entry and the first drug exposure is immortal, and is misclassified as exposed, when in fact, it is unexposed.

Supplemental figure 1. Misclassified immortal time.

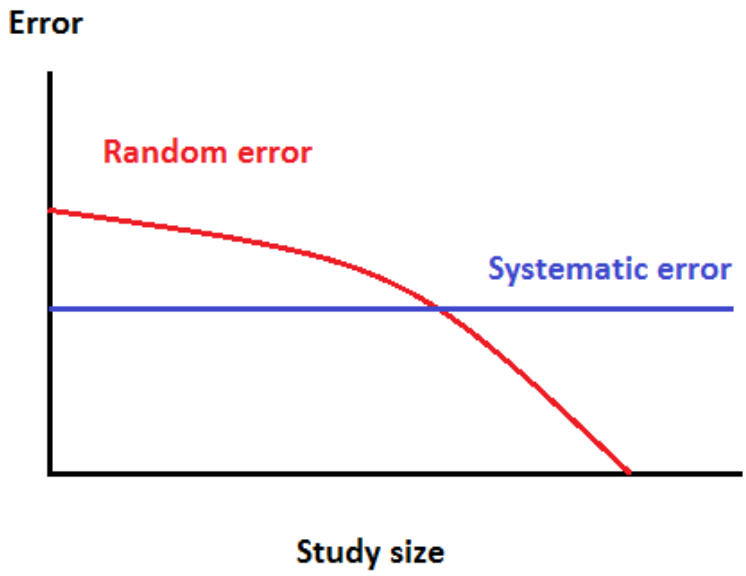


We adjusted for simvastatin and aspirin, which reportedly can modify breast cancer prognosis.[27,28] Simvastatin and aspirin were treated as time-varying covariates to avoid immortal time bias. If we did not consider this, the exposed time would be overestimated.

STRENGTHS AND LIMITATIONS

Validity of epidemiological studies can be divided into internal validity and external validity. Internal validity implies validity of inference for the source population of study subjects and external validity or generalizability refers to the validity of the inferences as they pertain to people outside the source population.[53] The internal validity is determined by how well the design, data collection and analyses are carried out. To evaluate the internal validity, the risk of systematic error and random errors must be addressed. Random error occurs due to variability in the data that is present by chance. Random error can be reduced if the study is sufficiently large.[55] Our large study size with more than 30,000 patients reduced the random error. On the other hand, systematic error remains unaffected by study size (Supplemental Figure 2). Systematic error refers to selection bias, information bias and confounding. Selection bias and information bias occur due to systematic errors in the study design, which cannot be corrected for during statistical analysis. Confounding can be controlled by both study design and statistical analysis.[53]

Supplemental Figure 2. The relation of systematic error and random error to study size



Selection bias

Selection bias is a systematic error associated with selection of the study participants. It can occur if those who participate and those who do not participate differ in ways that can affect the study outcome, other than the factors under study. [55] An often used example is voluntary health surveys. The persons volunteering are often more health conscious than those who not volunteer and patients who are more health conscious may have a better diet etc. This will skew the results systematically and introduce selection bias.

The present study was based on a population-based design. The Danish population-based registries minimize the risk of selection bias as they cover the entire population and all hospital contacts. We used the DBCG registry and the DNPR to define our cohort. Completeness of registration in DBCG is approximately 95%.[19] Completeness is high for patients aged up to 70 years. Therefore, we cannot omit the possibility of selection bias among women aged over 70 years registered in the DBCG. Furthermore we had to exclude 2,425 patients with more than 1 day (+/- 1 day) difference between the primary surgery date recorded in the DNPR and the DBCG. The excluded patients were younger, had less advanced breast cancer stage at diagnosis and were less likely to receive mastectomy and endocrine therapy (Supplemental Table 5). Our sensitivity analyses showed that the inclusion of these patients did not alter our findings (Supplemental Table 4).

Information bias

Information bias can arise because the information collected about or from the study subjects is erroneous. Such information is often referred to as misclassification if the variable (exposure or outcome) is measured categorically and the error leads to a person being categorized incorrectly. Misclassification can be divided into differential and non-differential misclassification. Non-differential misclassification is where the misclassification in unrelated to other variables. A misclassification of a dichotomous exposure that is non-differential with respect to the disease tends to produce estimates closer to the null than the actual effect. Differential misclassification is where the misclassification differs according to other variables. If the exposure is misclassified differentially according to the person´s disease status or the disease is misclassified differentially according to the exposure status, the misclassification can exaggerate or underestimate an effect. An example of differential misclassification is recall bias. In this study differential misclassification was eliminated by use of prospectively collected mandatory registered data. Non-differential misclassification is difficult to avoid in epidemiological studies.[55]

Misclassification of exposure:

Information on reoperation due to postsurgical bleeding within 14 days of primary breast cancer-directed surgery was retrieved from the DNPR. The exposure was defined by a surgical code which expectedly has a high predictive value as hospitals in Denmark are reimbursed only after registration of surgical codes. If patients were misclassified, it would be a non-differential misclassification since the exposure was not misclassified differentially according the outcome.

Misclassification of outcome:

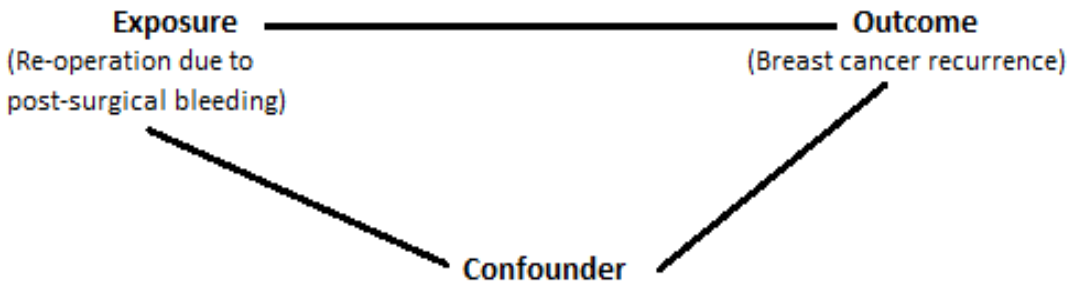
A major strength of the study was the high quality information about breast cancer recurrence in the DBCG. During the first year after diagnosis, women undergo physical examinations every 3 months to detect any evidence of recurrent disease and an exam every 6 months in years 2-5 following diagnosis. In year 6-10 after diagnosis some patients undergo an annual physical examination in the hospitals, other patients are followed by their general practitioner and others are followed based on individual needs. Women who are treated for breast cancer, is recommended to continue mammography screening every two years until the age of 80 years.[56] Overall, the positive predictive value for classification of breast cancer recurrence was found to be 99.4% using medical records as

a gold standard.[57] Therefore a misclassification is unlikely, but if there was misclassification it would be non-differential since the outcome was not associated with the exposure.

Confounding

Confounding can be thought of as mixing of effects, which implies that the effect of the exposure is mixed with the effect of another variable, leading to bias. A confounding variable is one that is associated with the disease, associated with the exposure, but not an effect of the exposure (not on the causal pathway). [55] In observational studies, confounding is important to discuss, because the exposure is not assigned randomly and confounding will arise from imbalances in risk factors for the outcome across the exposure categories. Confounding can be controlled in the study design through randomization, restriction and matching, and by statistical analysis through stratification, standardization or by adjustment in multivariable regression. [55]

Supplemental figure 2. Correlation of exposure, outcome and confounder general and examples of correlations in the current study



In the present study we incorporated a large number of potential confounding covariates. The correlation of exposure and the confounding covariates is shown in Table 1. We controlled for potential confounders by adjustment in multivariable regression models.

Effect measure modification

Effect measure modification is a term used to describe the situation where a measure of effect changes values of some other variable.[55] We found no evidence of effect modification in models stratified by stage, age, chemotherapy or primary surgery.

Precision

To indicate the precision of a point estimate we used the confidence interval, which is a range of values around the point estimate. A narrow interval indicates high precision, while a wide confidence interval indicates low precision. The present study included a large sample size retrieved from high quality and valid national population-based registries reducing the risk of random error. Despite our large sample size, the exposure, reoperation due to postsurgical bleeding, is a rare event and therefore the precision of some of our estimates was low.

ADDITIONAL ANALYSIS AND RESULTS

Time-varying exposure

Simvastatin and aspirin use were modelled as time-varying covariates. We used longitudinal prescription data to define time-updated exposure to these drugs. We allowed a gap of 30 days from the end of the prescription (prescription start date + prescription duration) until the start of a new prescription to define continuous use. Finally, we lagged the resulting time-updated current exposure variable by 1 year.

We did a sensitivity analysis using an alternative strategy of defining drug exposure. Current exposure was simply defined as having at least one prescription in the previous year (time-updated); a one-year lag was then applied as before. We also did two separate sensitivity analyses using the original strategy to define time-updated current exposure, but altering the final lag time to six months and then to two years.

In our analysis we found that use of simvastatin and hormone replacement therapy had a protective effect against recurrence with an adjusted hazard ratio of 0.79 (95% CI, 0.69-0.90) and 0.81 (CI, 95% 0.76-0.86) respectively. The observed association is similar to those in previously published papers.[28,58] In contrast, the use of aspirin had no association with breast cancer recurrence (adjusted hazard ratio, 1.02; 95% CI, 0.90 -1.14). Former papers suggest a decreased risk of breast cancer recurrence after aspirin use,[27] but a paper *in press* from our group found no evidence of such a protective association.[36]

However, adjustment for prescribed aspirin, simvastatin and HRT had no effect on our estimated associations. The above mentioned sensitivity analysis did not alter the estimates.

CLINICAL PERSPECTIVES AND FUTURE STUDIES

Our study showed that patients receiving a reoperation due to postsurgical bleeding may not have an increased risk of breast cancer recurrence. As such, compared with patients without a reoperation, those who undergo reoperation due to bleeding are unlikely to need more aggressive adjuvant therapy or more frequent follow-up exams to control recurrence.

We did not have information about the extent of the bleeding. Therefore it could be interesting to measure the blood loss during surgery and categorize in less, moderate and severe blood loss, to see if it would alter our findings.

Furthermore, we found that patients who underwent a reoperation due to postsurgical bleeding had a decreased risk of recurrence in the bones compared with those who did not undergo reoperation. The estimates were very imprecise. It could be interesting to explore the site of recurrent disease, particularly the bone recurrences. Studies with longer follow-up would be necessary to explore this issue.

Breast cancer surgery is a soft tissue surgery often characterized by extensive dissection, which increases the risk of postsurgical bleeding. Our findings may be relevant to other soft tissue surgical procedures of similar character and it would be highly relevant to explore this further.

To our knowledge, no previous studies have examined the effect of reoperation due to postsurgical bleeding in breast cancer patients and the risk of breast cancer recurrence. We have gained valuable knowledge that can help women with breast cancer and their physicians.

The Danish nationwide administrative and medical tax-supported and equal access to high quality health care, provide unique opportunity for answering some of the above research issues.

In conclusion, findings from our large population-based study provided no evidence of an association between reoperation due to postsurgical bleeding and breast cancer recurrence.

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TABLES

Table 1. Baseline characteristics of patients diagnosed with breast cancer in Denmark during 1996-2008 (n=30,711), according to reoperation due to postsurgical bleeding.

	Patients n(%)		**Recurrences n(%)**		**Total person-years**	
Variable	**Reoperation** **n**=767	**No reoperation** **n**=29,944	**Reoperation** **n**=126	**No reoperation** **n**=4,643	**Reoperation** **n**=5,241	**No reoperation** **n**=200,685
Age at diagnosis (years)						
≤29	0 (0)	98 (<1)	0 (0)	32 (<1)	0	578
30-39	30 (3.9)	1,357 (4.5)	<10	311 (6.7)	217	9,073
40-49	112 (15)	5,070 (17)	20 (16)	838 (18)	850	36,701
50-59	237 (31)	8,962 (30)	43 (34)	1,455 (31)	1,683	63,381
60-69	230 (30)	9,258 (31)	31 (25)	1,357 (29)	1,550	61,232
70-79	131 (17)	4,254 (14)	23 (18)	576 (12)	816	25,602
≥80	27 (3.5)	945 (3.2)	<5	74 (1.6)	124	4,118
Menopausal status at diagnosis						
Premenopausal	191 (25)	8,226 (28)	36 (29)	1,380 (30)	1,411	59,317
Postmenopausal	576 (75)	21,704 (72)	90 (71)	3,262 (70)	3,830	141,296
(Missing)	0 (0)	14 (<1)	0 (0)	<5	0	72
Charlson Comorbidity Index score						
0	589 (77)	23,913 (80)	110 (87)	3,879 (84)	4,152	165,150
1	107 (14)	3,357 (11)	12 (9.5)	446 (9.6)	701	20,666
2	47 (6.1)	1,683 (5.6)	<5	209 (4.5)	265	9,947
>=3	24 (3.1)	991 (3.3)	<5	109 (2.4)	123	4,922
Specific comorbidities						
Myocardial infarction	15 (2.0)	356 (1.2)	<5	42 (<1)	79	1,987
Congestive heart failure	18 (2.4)	385 (1.3)	<5	35 (<1)	74	1,937
Vascular disease	21 (2.7)	518 (1.7)	<5	68 (1.5)	127	2,818
Cerebrovascular disease	40 (5.2)	1,013 (3.4)	<5	114 (2.5)	274	5,597
Chronic pulmonary disease	39 (5.1)	1,459 (4.9)	7 (5.6)	174 (3.8)	211	8,467
Diabetes types I &II	20 (2.6)	811 (2.7)	<5	114 (2.5)	112	4,491
Diabetes w/organ damage	8 (1)	346(1.2)	<5	41 (<1)	41	1,824
Liver disease	10 (1.3)	250 (<1)	<5	33 (<1)	29	1,296
Any other cancer	24 (3.1)	1,286 (4.3)	<5	154 (3.3)	152	7,360
UICC stage						
I	284 (37)	10,852 (36)	36 (29)	1,157 (25)	2,095	78,669
II	367 (48)	13,465 (45)	52 (41)	1,844 (40)	2,539	92,554
III	107 (14)	5,406 (18)	38 (30)	1,620 (35)	550	28,262
(Missing)	9 (1.2)	221 (<1)	0 (0)	22 (<1)	57	1,200

Histologic grade						
Low	621 (81)	24,522 (82)	105 (83)	3,846 (83)	4,218	163,024
Moderate	100 (13)	3,301 (11)	11 (8.7)	548 (12)	714	22,769
High	44 (5.7)	2,992 (6.7)	<10	222 (4.8)	297	13,972
(Missing)	<5	129 (<1)	<5	27 (<1)	11	920
ER/adjuvant ET status						
ER-/ET-	134 (17)	5,818 (19)	21 (17)	1,174 (25)	892	35,750
ER+/ET-	184 (24)	7,143 (24)	25 (20)	1,087 (23)	1,399	52,922
ER+/ET+	420 (55)	15,985 (53)	76 (60)	2,177 (47)	2,736	104,739
ER-/ ET+	5 (<1)	181 (<1)	<5	27 (<1)	39	1,330
Unknown	24 (3.1)	817 (2.7)	<5	178 (3.8)	174	5,944
Type of primary surgery						
Mastectomy	373 (49)	10,838 (36)	65 (52)	1,867 (40)	2,527	74,573
Mastectomy + RT	159 (21)	6,486 (22)	34 (27)	1,445 (31)	1,074	41,563
BCS + RT	235 (31)	12,620 (42)	27 (21)	1,331 (29)	1,639	84,550
Adjuvant chemotherapy received						
Yes	220 (29)	10,075 (34)	33 (26)	1,628 (35)	1,509	65,009
No	547 (71)	19,869 (66)	93 (74)	3,050 (65)	3,732	135,676
Prediagnosis exposure to HRT						
Yes	316 (41)	12,452 (42)	37 (29)	1,634 (35)	2,220	83,790
No	451 (59)	17,492 (58)	89 (71)	3,009 (65)	3,021	116,896
Drug exposures during study period						
Simvastatin	148 (19)	6,286 (21)	7 (5.5)	349 (7.5)	538	22,527
Aspirin (high and low doses)	190 (25)	6,233 (21)	15 (12)	556 (12)	532	17,613

Abbreviations: -, negative; +, positive; BCS, breast-conserving therapy; ER, estrogen receptor; ET, endocrine therapy; HRT, hormone-replacement therapy; RT, radiotherapy; UICC, Union for International Cancer control

Cell sizes less than 5 are reported in aggregate to reduce identifiability of individuals in the data.

Table 2. Breast cancer recurrences, incidence rates and hazard ratios of breast cancer recurrence, and associated 95% confidence intervals (95% CI) for stages I, II, or III breast cancer patients in Denmark during 1996-2008, by presence/absence of reoperation due to postsurgical bleeding.

Exposure definition	Number of recurrences (person-years)	Crude incidence rate (95% CI)[a]	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)[b]
10-year Recurrences				
Overall				
No reoperation	4,643 (200,685)	23.1 (22.5-23.8)	1.00	1.00
Reoperation	126 (5,241)	24.0 (20.2-28.6)	1.05 (0.88-1.25)	1.07 (0.89-1.28)
Reoperation within 7 days				
No reoperation	4,650 (201,520)	23.1 (22.4-23.7)	1.00	1.00
Reoperation	121 (4,995)	24.2 (20.3-28.9)	1.06 (0.88-1.27)	1.08 (0.91-1.30)
Reoperation within 21 days				
No reoperation	4,627 (199,943)	23.1 (22.5-23.8)	1.00	1.00
Reoperation	131 (5,395)	24.3 (20.5-28.8)	1.06 (0.89-1.26)	1.07 (0.90-1.27)

Abbreviations: CI, confidence interval; HR, hazard ratio
[a] Per 1000 person-years
[b] HRs were adjusted for age (as a categorical variable), menopausal status at diagnosis (premenopausal or post-menopausal), disease stage (I,II or III), histological grade (low, moderate, or high), surgery type, estrogen receptor (ER) status and endocrine therapy (ET) receipt (ER+/ET-, ER+ET+, ER-/ET-, ER-/ET+), receipt of chemotherapy (yes/no), simvastatin use and aspirin use (both as time-varying covariates lagged by 1 year), comorbidity, and receipt of prediagnostic hormone-replacement therapy (yes/no).

Table 3. Stratified five- and ten-year cumulative incidence and incidence rate of breast cancer recurrence for stages I, II, or III breast cancer patients in Denmark during 1996-2008, by presence/absence of reoperation due to postsurgical bleeding patients [a]

Patient characteristics	N (total)	Recurrences	5-year cumulative incidence (95% CI)	Recurrences	10-year cumulative incidence (95% CI)
No Reoperation	29,944	3,547	12.5 % (12.2 % - 12.9 %)	4,643	18.9 % (18.4 % - 19.5 %)
Reoperation	767	93	12.8 % (10.5 % -15.4 %)	126	19.9 % (16.8 % - 23.4 %)
Patient characteristics	**N (total)**	**Recurrences (PY)**	**0-5 year incidence rate[b] (95% CI)**	**Recurrences (PY)**	**>5 year incidence rate[b] (95% CI)**
No reoperation	29,944	3,547(131,718)	26.9 (26.1-27.8)	1,096(68,968)	15.9 (15.0-16.9)
Reoperation	767	93 (3,361)	27.7 (22.6-33.9)	33 (1,880)	17.5 (12.5-24.7)

[a]All estimates are unadjusted, but account for death as a competing risk.
[b] Per 1000 person-years

Supplemental Table 4. Breast cancer recurrences, hazard ratios, and associated 95% confidence intervals (95% CI) for stage I and II breast cancer patients only, for patients without any previous cancers, and for patients with more than 1 day between the primary surgery date registered in DNPR and the DBCG (in Denmark during 1996-2008), by reoperation due to postsurgical bleeding.

Exposure definition	Number of recurrences (person-years)	Crude incidence rate (95% CI)[a]	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)[b]
10-year Recurrences				
Stage I and II breast cancer patients only				
No reoperation	3,023 (172,423)	17.5 (16.9-18.2)	1.00	1.00
Reoperation	88 (4,691)	18.8 (15.2-23.1)	1.08 (0.87-1.33)	1.05 (0.85-1.30)
Patients without previous cancers				
No reoperation	4,489 (193,325)	23.2 (22.6-23.9)	1.00	1.00
Reoperation	125 (5,089)	24.6 (20.6-29.3)	1.07 (0.89-1.27)	1.09 (0.91-1.30)
Patients with ≤ 14 days difference in primary surgery date between DNPR and DBCG				
No reoperation	4,837 (208.732)	23.2 (22.5-23.8)	1.00	1.00
Reoperation	132 (5,509)	24.0 (20.2-28.4)	1.04 (0.88-1.24)	1.06 (0.90-1.27)
Patients with ≤ 31 days difference in primary surgery date between DNPR and DBCG				
No reoperation	4,904 (213,096)	23.0 (22.4-23.7)	1.00	1.00
Reoperation	133 (5,579)	23.8 (20.1-28.3)	1.04 (0.88-1.24)	1.07 (0.90-1.27)

Abbreviations: CI, confidence interval; HR, hazard ratio

[a] Per 1000person-years

[b] HRs were adjusted for age (as a categorical variable), menopausal status at diagnosis (premenopausal or post-menopausal), disease stage (I,II or III), histological grade (low, moderate, or high), surgery type, estrogen receptor (ER) status and endocrine therapy (ET) receipt (ER+/ET-, ER+ET+, ER-/ET-, ER-/ET+), receipt of chemotherapy (yes/no), simvastatin use and aspirin use (both as time-varying covariates lagged by 1 year), comorbidity, and receipt of prediagnostic hormone-replacement therapy (yes/no).

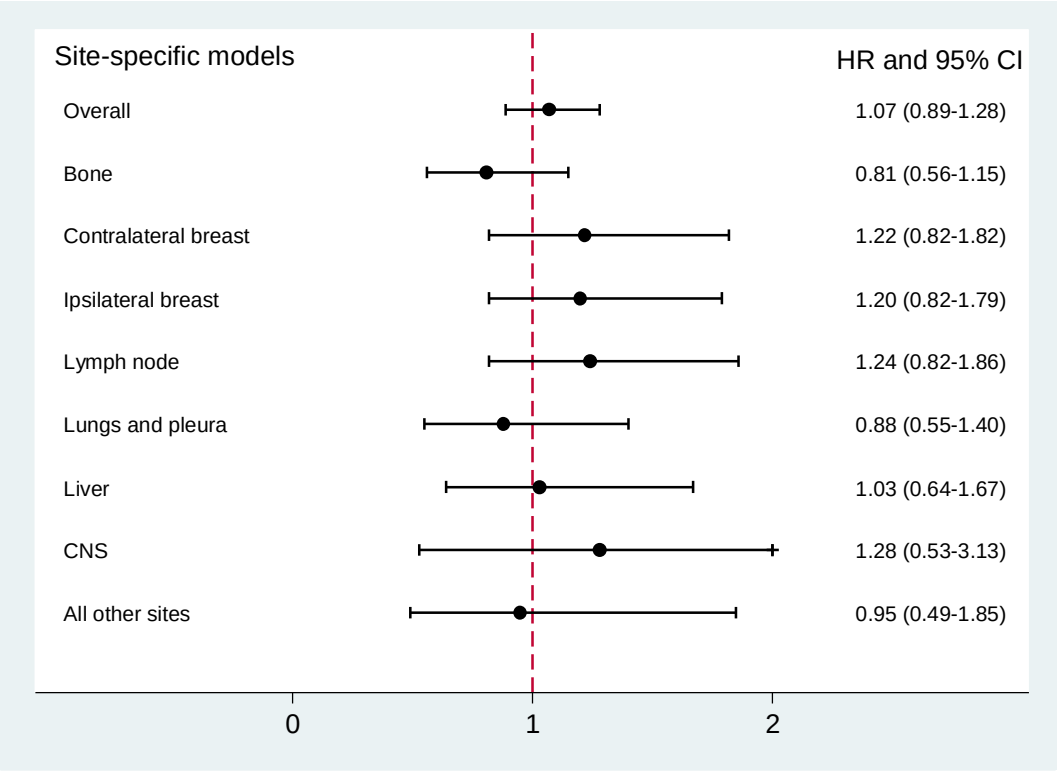
Supplemental Table 5. Baseline Characteristics of patients retained in the cohort versus patients excluded from the cohort.

	Final cohort		Excluded patients	
Characteristic	N	%	N	%
Age at diagnosis (years)				
≤29	98	<1	14	<1
30-39	1,387	4.5	143	5.8
40-49	5,182	17	592	24
50-59	9,199	30	807	33
60-69	9,488	31	637	26
70-79	4,385	14	229	9.4
≥80	972	3.2	29	1.2
Menopausal status at diagnosis				
Pre-menopausal	8,417	27	895	37
Post-menopausal	22,280	73	1,556	63
(Missing)	14	<1	0	0
Charlson Comorbidity Index score				
0	24,502	80	2,013	82
1	3,464	11	240	9.8
2	1,730	5.6	120	4.9
>=3	1,015	3.3	78	3.2
UICC stage				
I	11,136	36	1,245	51
II	13,832	45	913	37
III	5,513	18	266	11
(Missing)	230	<1	27	1
Histologic grade				
Low	25,143	82	1,910	78
Moderate	3,401	11	249	10
High	2,036	6.6	274	11
(Missing)	131	<1	18	<1
ER/adjuvant ET status				
ER-/ET-	5,952	19	489	20
ER+/ET-	7,327	24	881	36
ER+/ET+	16,405	53	957	39
ER-/ ET+	186	<1	11	<1
Unknown	841	2.7	113	4.6
Type of primary surgery				
Mastectomy	11,211	36	646	26
Mastectomy + RT	6,645	22	338	14
BCS + RT	12,855	42	1,467	60
Adjuvant chemotherapy received				
Yes	10,295	34	1,643	33
No	20,416	66	808	67

Abbreviations: -, negative; +, positive; BCS, breast-conserving therapy; ER, estrogen receptor; ET, endocrine therapy; HRT, hormone-replacement therapy; RT, radiotherapy; UICC, Union for International Cancer control

FIGURES

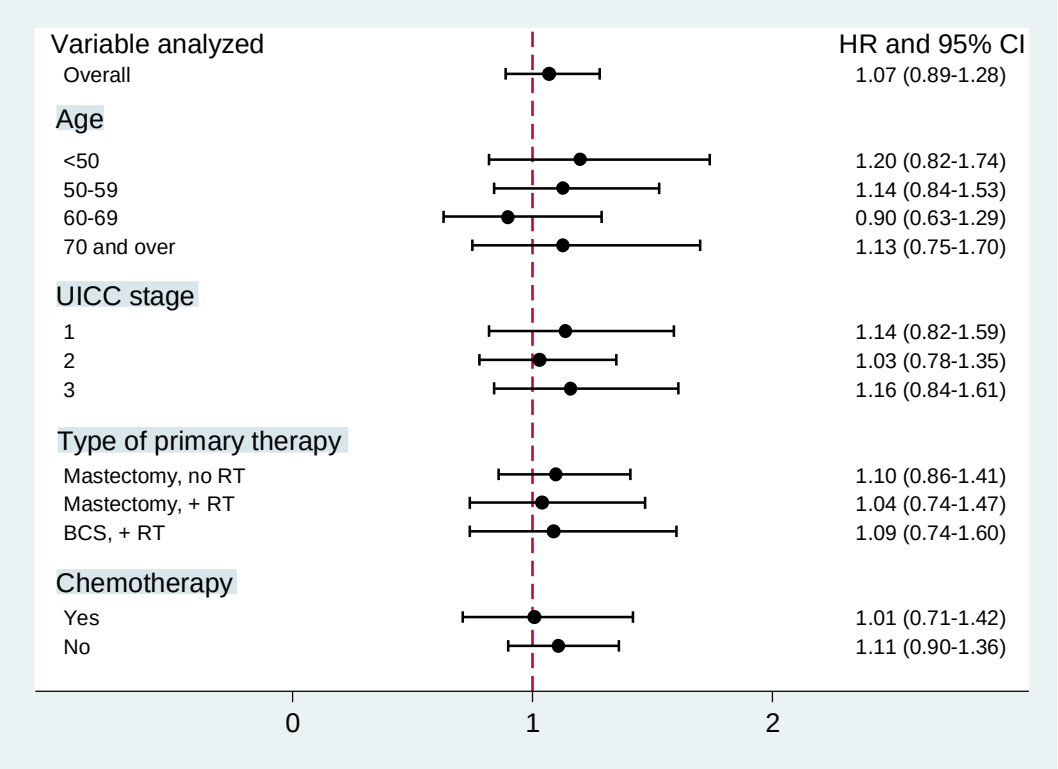
Figure 1. Forest plot showing associations between reoperation due to postsurgical bleeding and anatomical site of recurrence among women with stage I , II or III breast cancer in Denmark, 1996-2008.



Abbreviations: CI, confidence interval; HR, hazard ratio adjusted; +, HR > 2

[a] HRs were adjusted for age (as a categorical variable), menopausal status at diagnosis (premenopausal or post-menopausal), disease stage (I,II or III), histological grade (low, moderate, or high), surgery type, estrogen receptor (ER) status and endocrine therapy (ET) receipt (ER+/ET-, ER+ET+, ER-/ET-, ER-/ET+), receipt of chemotherapy (yes/no), simvastatin use and aspirin use (both as time-varying covariates lagged by 1 year), comorbidity, and receipt of prediagnostic hormone-replacement therapy (yes/no).

Figure 2. Forest plot showing associations between reoperation due to postsurgical bleeding and rate of breast cancer recurrence, stratified by age, UICC stage and type of primary therapy among women with stage I, II or III breast cancer in Denmark, 1996-2008.



Abbreviations: CI, confidence interval; HR, hazard ratio adjusted

[a] HRs were adjusted for age (as a categorical variable), menopausal status at diagnosis (premenopausal or post-menopausal), disease stage (I,II or III), histological grade (low, moderate, or high), surgery type, estrogen receptor (ER) status and endocrine therapy (ET) receipt (ER+/ET-, ER+ET+, ER-/ET-, ER-/ET+), receipt of chemotherapy (yes/no), simvastatin use and aspirin use (both as time-varying covariates lagged by 1 year), comorbidity, and receipt of prediagnostic hormone-replacement therapy (yes/no).

APPENDIX

Comorbidity

Charlson comorbidity category	ICD8	ICD10	Score	Comorbidity groups
Myocardial infarction	410	I21;I22;I23	1	Myocardial infarction
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1	Congestive heart failure
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1	Vascular disease
Cerebrovascular disease	430-438	I60-I69; G45; G46	1	Cerebrovascular disease
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1	-
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1	Chronic pulmonary disease
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1	-
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1	-
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1	Liver disease
Diabetes type1	249.00; 249.06; 249.07; 249.09	E10.0, E10.1; E10.9	1	Diabetes types I & II
Diabetes type2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9		
Hemiplegia	344	G81; G82	2	-
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2	-
Diabetes with end organ damage type1	249.01-249.05; 249.08	E10.2-E10.8	2	Diabetes w/organ damage
type2	250.01-250.05; 250.08	E11.2-E11.8		
Any tumor	140-194	C00-C75	2	Any other cancer
Leukemia	204-207	C91-C95	2	Any other cancer
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96	2	Any other cancer
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3	Liver disease
Metastatic solid tumor	195-198; 199	C76-C80	6	Any other cancer
AIDS	079.83	B21-B24	6	-

Confounder drugs

We retrieved prescription information on full Anatomical Therapeutic Chemical (ATC) codes, and the date and quantity dispensed for relevant drugs.

Potential confounder drugs	ATC codes
Simvastatin	C10AA01
Low-dose aspirin (75, 100 or 150 mg)	B01AC06
High-dose aspirin, combinations	N02BA51
Aspirin; 500 mg	N02BA01
Hormone Replacement Therapy	G03C, L02AA, G03F, G03H, and G03D