Proton pump inhibitor prescriptions and breast cancer recurrence:

A Danish nationwide prospective cohort study

Research year Report

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PREFACE

This 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 sincere appreciation to my supervisors and collaborators. During my research year they have kindly guided me and opened my eyes to the broad field of epidemiology. They have shared their extensive knowledge and patiently taught me everything in the process from writing a protocol to correct even the smallest detail in the final paper.

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ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical classification system
BCS	Breast conserving surgery
CI	Confidence Interval
CPR	Civil Registration Number
DBCG	Danish Breast Cancer Cooperative Gruop
DNPreR	Danish National Prescription Registry
DNRP	Danish National Registry of Patients
ER	Estrogen receptor
ET	Endocrine therapy
HER-2	Human epidermal growth factor receptor-2
HR	Hazard ratio
HRT	Hormone replacement therapy
ICD	International Classification of Diseases
PPI	Proton pump inhibitor
UICC	Union for International Cancer control
V-ATPase	Vacuolar ATP-ase

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ABSTRACT

Background: Proton Pump Inhibitors (PPI) are indicated for various acid-peptic disorders. PPIs also inhibit the V-ATPase pump, sometimes overexpressed in breast cancer cells and implicated in chemotherapy resistance. We therefore investigated the association of PPI prescriptions during chemotherapy, overall through follow-up, and any time before diagnosis, with the risk of breast cancer recurrence.

Methods: Our cohort included all Danish women diagnosed with non-metastatic breast cancer registered in the Danish Breast Cancer Group (DBCG) between 1996 and 2008. We ascertained information on PPIs, and potentially confounding drugs from the National Prescription Registry. Follow-up began on the date of diagnosis in the overall analysis, or at 6 months after diagnosis (see below), and continued until the first of breast cancer recurrence, death or emigration, ten years, or 1st of January 2013. We considered PPI use during the first 6 months after diagnosis (≥1 prescription from diagnosis until 6 months after diagnosis) thereby approximating PPI use during chemotherapy; overall PPI use (≥1 prescription) as a time-varying exposure lagged by one year; and former PPI use (≥1 prescription any time before diagnosis). We used Cox regression models to calculate crude and adjusted hazard ratios (HRs) and associated 95% confidence intervals (95%CI) of recurrence adjusting for potential confounders.

Results: We included 34,189 patients with a total of 233,129 person years. Overall, 7,740 women had ≥1 PPI prescription after diagnosis. Overall, 5,320 patients developed recurrent disease. Median follow-up was (7.1) years. PPI use during the first 6 months after diagnosis was associated with a decreased rate of recurrence among patients who received chemotherapy ($HR_{adjusted}$=0.71, 95%CI=0.54;0.92), but not among patients who did not undergo chemotherapy ($HR_{adjusted}$=1.00, 95%CI=0.84;1.18). Overall, PPI use was not associated with recurrence ($HR_{adjusted}$=1.05 95%CI=0.92-1.20). Former PPI use was associated with a slightly lower recurrence rate ($HR_{adjusted}$=0.90, 95%CI=0.77-1.04).

Conclusion:

The decreased risk of breast cancer recurrence associated with PPI prescription use in the first 6 months after diagnosis among women who received chemotherapy suggests that PPI use may enhance the antitumor effect of chemotherapy. PPI prescription use overall did not associate with risk of breast cancer recurrence. Further, we observed that former use might correlate with decreased risk of breast cancer.

DANSK RESUME

Baggrund: Syrepumpehæmmere (PPI) er indiceret ved forskellige mavesyrerelaterede sygdomme, fx gastroøsofagal refluxsygdom. Laboratorieforsøg har vist at de også hæmmer væksten af brystkræft celler og funktionen vakuolær-ATPase (V-ATPase), som er opreguleret i cancerceller og muligvis medvirkende til resistens mod kemoterapi.

Formål: At undersøge associationen mellem brug af PPI med risikoen for brystkræft recidiv under kemoterapi og gennem hele opfølgningsperioden.

Metode: Vi inkluderede alle danske kvinder med diagnose på ikke-metastatisk brystkræft registreret i Dansk Brystkræft Gruppe database (DBCG) mellem 1996-2008. Vi hentede information om recepter på PPI og potentielt konfoundende medicin fra det nationale lægemiddelregister. Opfølgningen begyndte på dagen for diagnose i "overall" analysen, eller 6 måneder efter diagnose (se nedenfor) og fortsatte i 10 år eller til det første af brystkræft recidiv, emigration, død eller 1. januar 2013. Vi undersøgte PPI brug under de første 6 måneder efter diagnose (≥ 1 recept fra diagnose til 6 måneder efter) for at afdække forbruget under kemoterapi; og "overall" PPI brug (≥1 recept) som tids-varierende eksponering forskudt med et år; og tidligere PPI brugere (≥1 recept før diagnose). Vi anvendte Cox regressions analyser til at udregne hazard ratioer (HR) og tilhørende 95 % konfidensintervaller for recidiv, justeret for potentielle konfoundere.

Resultater: Vi inkluderede 34,189 patienter (233,129 personår). Ud af kohorten indløste 7740 patienter ≥1 recept på PPI efter diagnose og i alt 5,320 patienter fik brystkræft recidiv. PPI forbrug i de første 6 måneder efter diagnose var associeret med nedsat risiko for recidiv blandt patienter der var i kemoterapi ($HR_{justeret}$=0.71; 95%CI=0.54, 0.92), men ikke blandt patienter uden kemoterapi behandling ($HR_{justeret}$=0.71; 95%CI=0.54, 0.92). Overall PPI forbrug var ikke associeret med recidiv ($HR_{justeret}$=1.05; 95%CI=0.92, 1.20). Anvendelse af PPI før diagnose var associeret med et lille fald i recidiv risiko ($HR_{justeret}$=0.90, 95%CI=0.77-1.04).

Konklusion: Vi fandt en nedsat risiko for brystkræft recidiv associeret med PPI forbrug de første 6 måneder efter diagnose blandt kvinder der modtog kemoterapi, men ikke blandt kvinder uden kemoterapi behandling. Dette antyder at PPI muligvis forbedrer effekten af kemoterapi.

Overall forbrug af PPI var ikke associeret med recidivrisikoen, mens tidligere forbrug muligvis er associeret med nedsat risiko

MANUSCRIPT

INTRODUCTION

Breast cancer is the most common cancer in women. In Denmark, nearly 5000 women are diagnosed with breast cancer every year and the lifetime risk for a Danish woman is 11-13%[1]. Survival in breast cancer patients has improved substantially over the past thirty years[2], but patients with similar characteristics at diagnosis vary considerably in the clinical course of their disease. Some survive without any signs of cancer, while others develop recurrent disease resistant to further treatment.

A hallmark of malignant tumors is extracellular acidity.[3] This acidic environment helps cancer cells to invade and metastasize, and evolve into a more aggressive potentially drug resistant phenotype.[3,4] The pH-gradient in cancer cells is controlled by proton pumps, including the vacuolar-type H+ ATPase (V-ATPase). V-ATPase is upregulated in cancer cells where it is implicated in drug resistance.[4,5] In breast cancer cells, the density of V-ATPase at the cell membrane is positively correlated with their invasiveness.[6–8] Thus, disrupting the pH-gradient by targeting V-ATPases may sensitize cancer cells to cytotoxic treatment.

Proton pump inhibitors (PPIs) are indicated for a wide range of acid-peptic disorders like gastroesophageal reflux disease and peptic ulcers. PPI use is widespread and increasing.[9] PPIs are H+-ATPase inhibitors that prevent the acidification of the parietal cells in the stomach. PPIs also inhibit V-ATPase.[3,4,10,11] Laboratory studies in breast cancer cell lines suggest that PPI's can enhance tissue penetration and cytotoxicity of chemotherapy.[4,11] The PPI lansoprazole can inhibit tumorigenesis and induce apoptosis in mouse mammary tumors.[3] Likewise, esomeprazole suppresses the growth of triple negative breast cancer cell lines, *i.e.*, hormone receptor negative, human epidermal growth factor 2 (HER-2) negative cells, by increasing their *intra*cellular acidification.[12] A randomized clinical trial of 94 metastatic breast cancer patients, showed better survival among those who used PPIs along with chemotherapy compared with chemotherapy alone.[3]

Taken together, these studies suggest that PPIs may have a role in improving breast cancer prognosis via disruption of the tumor microenvironment acidity, thereby enhancing the effectiveness of cancer-directed treatment. However, to our knowledge, no observational studies or clinical trials have investigated the association of PPI use with breast cancer prognosis in *non-metastatic* breast cancer patients. This is an important oversight given the high incidence of breast cancer, and the increasing use of PPIs in the population.[6] We therefore evaluated the association of PPI prescription use with the risk of breast cancer recurrence in a large cohort of non-metastatic breast cancer patients.

METHODS

This study was approved by the Danish Breast Cancer Group, the Danish Medicines Agency, and the Danish Data Protection Agency (Aarhus University journal number 2016-051-000001, record number 552). This study is based on routinely collected registry data, therefore ethical approval was not necessary.

Study Population and Data Collection

The source population included Danish women aged at least 18 years who were diagnosed with non-metastatic breast cancer, resident in Denmark between 1996 and 2008, with potential follow-up to 1st of January, 2013. In Denmark, all inhabitants receive a unique ten-digit Civil Personal Registration number (CPR) at birth or upon immigration, which encodes gender and date of birth, and facilitates individual-level linkage across multiple population-based and medical registries[13,14]. This nationwide cohort study incorporated data linkage from the Danish Breast Cancer Group (DBCG), the Danish National Prescription Registry (DNPreR), and the Danish National Registry of Patients (DNRP).

We included all Danish women diagnosed with non-metastatic breast cancer registered in the DBCG between 1996 and 2008. The DBCG was established in 1977 and has since registered almost all Danish women diagnosed with invasive breast cancer. It contains comprehensive data on diagnosis, treatment and follow-up[15,16]. Completeness has improved over time to over 95% in 2014.[17] All patients are followed for recurrent disease twice a year for the first 5 years after diagnosis, and annually 5-10 years post-diagnosis.[18] Follow-up examinations include a clinical evaluation and, if indicated a chest x-ray, computed tomographic scan, bone scan, or other investigation to detect recurrent disease[19]. From the DBCG, we also retrieved information on age and menopausal status at diagnosis, date and type of primary surgery (mastectomy or breast conserving surgery), WHO histological tumor type and grade, tumor size, lymph node status, tumor estrogen receptor (ER) status, adjuvant chemotherapy, endocrine therapy (ET), radiation therapy, date and site of breast cancer recurrence and date of death. Breast cancer recurrence was defined as any local, regional, distant recurrence, or contralateral breast cancer according to DBCG.

We ascertained information on prescriptions for medication from the DNPreR. The DNPreR is maintained by Statistics Denmark and has recorded information on prescription drugs sold in Denmark since 1995. For each prescription, the information recorded includes the Anatomical Therapeutic Chemical (ATC) code, date of prescription redemption, the strength and number of pills dispensed.[20,21] Via Statistics Denmark, prescription data was linked to the other registry data by CPR-number. We used the DNPreR to retrieve information on prescriptions for PPIs (ATC code: A02BC). We also ascertained information on potentially confounding co-medications including prescriptions for hormone replacement therapy (HRT) and simvastatin[22–25].

From the DNRP, we retrieved data on comorbid diseases present at the time of breast cancer diagnosis or registered up to ten years before breast cancer diagnosis. The DNRP has recorded information on all somatic hospital admissions since its establishment in 1977. It includes information on all outpatient and emergency room contacts since 1995.[26] Data includes the CPR number, admission - and discharge dates, and up to 20 discharge diagnoses coded according to the International Classification of Disease 10th Edition (ICD-10).

We excluded patients if they had missing information on stage according to Union for International Cancer Control (UICC), if they did not undergo surgery or if their status date was before date of diagnosis (Figure 1).

Analytic Variables

Age at diagnosis was categorized into decades in descriptive statistics and as a continuous variable in analyses. Menopausal status was defined as pre- or postmenopausal at the time of diagnosis. Histological grade was defined as low, medium, or high. Stage was classified using the (UICC) TNM classification as I-III.[27] Surgery was defined as mastectomy alone, mastectomy with radiation or breast conserving therapy with radiation. We summarized ER-status and ET as a joint variable (ER-/ET-, ER+/ET-, ER-/ET$^-$, ER-/ET-). Information on adjuvant chemotherapy treatment as intention to treat was categorized dichotomously. Information on comorbid diseases was summarized and defined according to the Charlson Comorbidity Index Score and categorized as 0, 1, 2 or $\geq$3.[28]

We modeled PPI exposure as any use within the first 6 months after diagnosis defined as a baseline dichotomous variable. This period corresponds to the period in which patients indicated for chemotherapy are most likely to receive their treatment. Patients were considered users if they filled at least 1 or more prescriptions from the date of diagnosis to 6 months after diagnosis (under the assumption that chemotherapy is completed at 6 months after diagnosis)[29]. For these analyses, PPI was a "baseline exposure" where follow-up began at 6 months after diagnosis (Figure 2).

We also modeled PPI exposure overall as a post-diagnostic time-varying exposure defined as at least 1 PPI prescription within the follow-up period, updated daily and lagged by 1 year[25,30] (Figure 2). We estimated the duration of each prescription as pack size multiplied by the number of packages prescribed, assuming a daily dose of 1 pill/day. For continuous use we accepted a lag of 30 days from the end of a prescription to the beginning of the next. Follow up of each patient began at the day of primary breast cancer surgery and continued until the first of breast cancer recurrence, death or emigration, accrual of ten years, or 1st of January 2013.

Further, we modeled exposure according to former PPI use at baseline categorized dichotomously and defined as 1 or more prescriptions before the date of diagnosis. For these models, follow-up began at date of diagnosis (Figure 2).

Given its documented association with breast cancer recurrence, simvastatin was modelled as time-varying exposure using a similar approach as for overall time-varying PPI exposure.[24,25] HRT was categorized dichotomously as a baseline covariate.[22,23]

Statistical analysis

We presented descriptive characteristics of the cohort in terms of frequency and proportion of patients, according to PPI exposure within the first year after diagnosis. We calculated crude and adjusted hazard ratios (HRs) and associated 95 % confidence intervals (95%CI) of breast cancer recurrence using Cox regression models, adjusting for age, menopausal status, Charlson comorbidity index score, UICC stage, histological grade, ER/ET-status, type of surgery, chemotherapy, HRT and simvastatin use. We stratified models by chemotherapy given PPIs possible effect of enhancing the chemotherapy uptake. Further, to evaluate effect modification we stratified by ER/ET-status, and HRT.

We performed several sensitivity analyses. First, for exposure in the first 6 months after diagnosis we changed the exposure window to the first 1 year (and accordingly, changed the start of follow-up to 1 year after diagnosis). Second, we divided the PPIs into separate groups according to ATC codes, looking at the most frequently prescribed drugs. This analysis was performed for exposure in the first 6 months after diagnosis. Third, in the overall PPI exposure model, we altered the lag period to 6 months and 2 years. Finally, we altered the definition to ≥2 prescriptions in all the 3 exposure definitions.
All statistical analyses were calculated using STATA version 14.2.

RESULTS

We included 34,189 Danish women diagnosed with non-metastatic breast cancer between 1996 and 2008. We observed 5,320 recurrences during 233,129 person years at risk (median follow-up = 7.1 Years). During the first 6 months after diagnosis 3.1% had a prescription on PPI and overall, 22.6% were ever users of PPIs during the entire follow-up period. Table 1 outlines the characteristics of patients according to PPI exposure within the first 6 months after diagnosis. Compared to non-users, PPI users were slightly older and more likely to be postmenopausal at the time of their breast cancer diagnosis. PPI users also had a higher Charlson comorbidity score at baseline. PPI users were more likely to undergo mastectomy as primary treatment than non-users. Compared with non-users, PPI users were less likely to be treated with adjuvant chemotherapy,

but more likely to have prescriptions for HRT and statins. The median duration of overall post-diagnostic PPI use was 0.50 years (Table 2).

Table 2 outlines the estimated associations between PPI exposure and risk of breast cancer recurrence. During entire follow-up we observed 199 recurrences among patients receiving PPIs within the first 6 months after diagnosis. There was a slight reduction in recurrence risk associated with exposure to PPIs during the first 6 months after diagnosis ($HR_{adjusted}$=0.89, 95%CI=0.78-1.04) (Table 2). After stratifying by the receipt of chemotherapy, PPI use during the first 6 months after diagnosis was associated with a decreased rate of recurrence among patients who received chemotherapy ($HR_{adjusted}$=0.71, 95%CI=0.54;0.93), but not among patients who did not undergo chemotherapy ($HR_{adjusted}$=1.00, 95%CI=0.84;1.18). Likewise, stratification by ER/ET status on PPI use during the first 6 months after diagnosis revealed evidence of a slightly decreased risk of recurrence among women with ER^{-}/ET^{-} status ($HR_{adjusted=}$ 0.75, 95%CI=0.65-1.00) (Table 3).
When we changed the exposure window to 1 year after diagnosis, we found no association in either adjusted or stratified analyses (Additional table 4).

Overall time-varying PPI use did not show any association with the risk of breast cancer recurrence ($HR_{adjusted}$=1.05 95%CI=0.92-1.20). Stratification by chemotherapy, HRT and ER/ET status did not reveal any evidence of effect modification in this exposure model (Table 3). Likewise, sensitivity analyses changing the lag period[25,30] from 1 year to 6 months or 2 years made no additional differences to the effect estimates (Additional table 5).

Findings for former use of PPIs associated with a slight reduction in the rate of breast cancer recurrence ($HR_{adjusted}$=0.90, 95%CI=0.77-1.04). There was little evidence of effect modification when models were stratified by clinical factors. (Tables 2 & 3).

The three most frequently prescribed PPIs in the cohort were Omeprazol, Lanzoprazol and Esomeprazol. Use of esomeprazole within the first 6 months after diagnosis was associated with a decreased risk of recurrence ($HR_{adjusted}$=0.63, 95%CI=0.44-0.89) (Additional table 6). This association was particularly apparent among users of Esomeprazole who underwent chemotherapy ($HR_{adjusted}$=0.52, 95%CI=0.29-0.95) but less so among those who did not receive chemotherapy ($HR_{adjusted}$=0.70, 95%CI=0.46-1.08), although estimates were imprecise. Pantoprazole and Omeprazole taken in the first 6 months after diagnosis also showed a tendency to associate with decreased risk of breast cancer recurrence ($HR_{adjusted}$=0.62, 95%CI=0.34-1.13) and ($HR_{adjusted}$=0.67, 95%CI=0.41-1.10) respectively.

Sensitivity analysis with ≥2 or more prescriptions in the overall analyses resulted in imprecise estimates and showed little evidence of an association of post-diagnostic overall PPI use with breast cancer recurrence. **(**Additional table 7a-b).

DISCUSSION

In this nationwide study of Danish breast cancer patients, we found that PPI use during the first six months after diagnosis is associated with decreased rate of breast cancer recurrence among women treated with chemotherapy, but not among women not treated with chemotherapy, which agrees with our hypothesis on potential chemo-sensitization. The decreased rate of recurrence among women undergoing chemotherapy was particularly evident among women prescribed esomeprazole although estimates were imprecise. Second, we found that PPI during the entire follow-up period does not alter the rate of recurrence. Third, we observed that women who used PPIs before breast cancer diagnosis had a tendency towards a decreased risk of recurrence.

The main strengths of our study include the large nationwide study population, complete follow-up, and high-quality registry data. The data validity of the Danish registries, including the DBCG clinical database, is exceptionally high. Validation studies of the DBCG registry have found a positive predictive value of breast cancer recurrence of over 99%.[31] The DBCG records comprehensive data on breast cancer diagnosis and treatment and routine follow-up for recurrence, minimizing loss to follow-up[15–17,32]. The use of the Danish registry network minimized selection bias. The prospective design using data collected for administrative purposes, rather than relying on self-reported PPI use, ensured that the assessment of exposure to PPIs occurred before the outcome, thereby eliminating recall bias. Due to the comprehensive registries we had the possibility of adjusting for use of simvastatin and HRT along with several other potential confounding variables.

Nonetheless, our study has some limitations. The DNPreR lacks information on the clinical indication for drug use and in-hospital or over-the-counter drug use.[21,33] However, over-the-counter use of PPIs in Denmark is estimated at approximately 2%.[9] Thus our exposure may be misclassified. However, this potential misclassification of PPI exposure is likely non-differential and thus unlikely to be an explanation for our observed association. Lack of information on compliance may also lead to misclassification. Yet in Denmark patients pay for part of their redeemed medication, which makes the estimates likely to reflect actual use. Although we controlled for potential confounding in our adjusted models, we lacked information on lifestyle factors including body mass index (BMI), alcohol, smoking-status and socioeconomic status. These factors are all associated with poorer prognosis among cancer patients in general.[34–37] Previous research suggests that obesity associates with poorer breast cancer prognosis.[38–40] Ewertz et al. found that high BMI was associated exclusively with distant breast cancer recurrence.[41] We therefore ascertained information on obesity diagnoses from the DNRP, but there were very few patients in our cohort with a clinical diagnosis of obesity. We also ascertained information on diagnoses of alcohol related diseases, but again observed very few cases. Nonetheless, as BMI and alcohol are positively associated with both breast cancer recurrence and use of PPI, confounding by BMI or alcohol is unlikely to explain an association.[42,43]

On the contrary it would drive the association towards the null. To the best of our knowledge, smoking status and socioeconomic status have not been associated with PPI use, thus are unlikely to confound our findings.

Our observed association between PPIs taken during chemotherapy and risk of cancer recurrence is consistent with several laboratory studies[4,10–12] and with and the afore-mentioned clinical trial of metastatic patients.[3]

Goh et. al investigated the drug esomeprazole in breast cancer cell lines.[12] Goh et al. concluded an increased sensitivity to chemotherapy when treated simultaneously with esomeprazole, which is consistent with our findings and the aforementioned trial. Thus other laboratory-based studies have evaluated different PPIs and found the same effect.[4,11] These findings add weight to our chemo-sensitization theory and our results, though it also questions if all PPIs have effect.

The mentioned clinical trial[3] observed longer survival and median time to progression, between patients co-treated with PPI's and those receiving chemotherapy alone. The trial included patients with advanced breast cancer and adds weight to our finding that PPI's may enhance the effectiveness of chemotherapy.

Another finding from our study is an association between ER-/ET- status and PPI use and breast cancer recurrence. None of the afore-mentioned studies investigated this. To the best of our knowledge there is no direct drug interaction between endocrine therapy and PPI and no studies of this association have been conducted. This association might be due to unknown factors or may open to new research questions.

Our study has potential clinical implications. It might be possible to enhance the effect of chemotherapy when PPIs are taken during treatment with adjuvant chemotherapy. Adding PPIs to the treatment would be an easy and cost-effective way of potentially improving breast cancer prognosis. Nonetheless, we cannot be completely certain about the underlying mechanism of the association, because PPIs are prescribed for certain side effects of chemotherapy. We cannot rule out the possibility that patients treated for side effects might have greater tendency towards completing their chemotherapy, and PPI use therefore reflects therapy completeness rather than PPIs enhancing the effectiveness of chemotherapy.

In conclusion, we observed a decreased risk of breast cancer recurrence associated with PPI prescription use in the first 6 months after diagnosis among women who received chemotherapy, suggesting that PPI use may enhance the antitumor effect of chemotherapy. This finding is important given the increasing use of PPIs and its very few and mild side effects, and given the increasing need of improving breast cancer treatment. In this study we focused on breast cancer only, but existing experimental studies have found similar results in other cancer types also.[44–46] Therefore, future research on PPIs might focus not only on breast cancer, but other cancer types as well.

SUPPLEMENTERY

The following section of this report contains additional information on breast cancer and PPIs, as well as general methodological and statistical considerations and discussion of strengths and limitations. Finally, this section accounts for a clinical perspective of this study.

BACKGROUND

Breast cancer

Breast cancer is the most common type of cancer among women. In Denmark nearly 5000 is diagnosed with breast cancer every year and the lifetime risk for a Danish woman is 11-13 %.[1] The number of newly diagnosed has increased within the past 60 years, but in general the survival after diagnosis has improved during the past 20 years. The 5-year survival is estimated to 86%. Twenty years after diagnosis the mortality equals the background population.[47,48] However, a third of the diagnosed women get recurrent disease within 10 years.

The disease is usually discovered by the patient observing a mass, or through the screening program. The mean age at development of breast cancer is 65 years and about 50 % will be aged 50-70 years when they are diagnosed.[1] The screening program helps discovering cancers and was introduced in 2008. It consists of a mammography and is offered to all women between 50 and 69 years every second year. The final diagnosis is based on a triple test which consists of palpation, radiology (mammography, ultra and MRI) and biopsy.

Breast cancer consists of different types of cancer. Eighty percent of the cancers originate in the milk ducts, the so called ductal cancers, whereas only 15 % arise from the mammary glands, called lobular cancer. An important risk factor is considered to be exposure to hormones.[1] Thus, early menarche and late menopause increase the risk. Late age at first birth and exogenous hormones will also increase the risk. Another important risk factor is genetics. The BRCA-1 and 2 genes are associated with higher risk of breast cancer and ovarian cancer. Women who inherit a mutated allele of BRCA-1 from either/both parents have a lifetime risk of 60-80 % and the risk with a mutated BRCA-2 is slightly lower. Further, it has been shown that alcohol influences the risk, and also physical inactivity and obesity will increase the risk.[1]

The treatment in Denmark is primarily surgery. Ninety-five percent of the patients will get either lumpectomy (the tumor and its surrounding tissue is cut out), or mastectomy with complete removal of the breast. Fewer than 10 % of patients who receive surgery will be inoperable by the time of diagnosis. They will start out having neoadjuvant chemotherapy[48]. After surgery patients will receive adjuvant therapy depending on their status. Patients with high risk status: age < 60, tumor size > 10mm, malignity grade II-III,

metastases to axillary lymph nodes, ER-negative, HER-positive or TOP2A abnormality will be offered adjuvant medical treatment (chemotherapy and/or endocrine treatment). Radiation is offered to patients with tumor size > 5mm, metastases to axillary lymph nodes, non-radical surgery or lumpectomy.[48] The axillary lymph node status will be examined by sentinel-node technique.

The most important prognostic factor is stage, which encompasses tumor size and number of positive lymph nodes at time of the diagnosis. Other factors include age, ER-status, HER-2 status and cell differentiation.[48]

Proton pump inhibitors

PPIs are a cornerstone in the treatment of peptic disorders and gastric ulcers. It is a prodrug that depends on acidity to transform to the active drug and functions mainly by binding and inhibiting the H/K-ATPase in parietal cells.[49,50] In the stomach the H/K-ATPase actively pumps out H+-ions in return for K+-ions. This leads to an increase of acid secretion in the stomach. The PPI's also inhibit other proton pumps including the Vacuolar ATP-ase.[3,4,10,11] V-ATPase transports protons from the cytoplasm to the lumen of intracellular organels and from the cytoplasm to the extracellular space when it's placed in the outer membrane of the cell. This changes the environment of the cell and the cell's surroundings. The PPI's have very few and mild side effects limited to flatus, loose stool and abdominal pain and they are widely used.[49] The number of users has increased fourfold from 2002 to 2014 and reaches 7,4 % of the Danish population.[9] The use increases with increasing age. Denmark has five marketed drugs; Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole and Esomeprazole.

METHODOLOGICAL CONSIDERATIONS

Design

To address our research question, we conducted a prospective cohort study. In a cohort study a group of people sharing a common characteristic are followed over time to evaluate incidence of a specific outcome. Within the cohort people differ with respect to exposure and other factors.[51,52] In this case the common characteristic is breast cancer diagnosis, and the outcome of interest is recurrence. People differ with respect to PPI use and other co-variates.

In a prospective cohort study the exposure information is obtained before the outcome happens. It is carried out from the present time into the future. In contrast, a retrospective cohort study is carried out in present time and look back into the past with outcome happening before obtaining information about exposure. Advantages of a retrospective design are the typically cheaper price and often they are very easy to conduct. However, a main challenge with a retrospective study design is recall bias, which is eliminated in a

prospective study. Further, a prospective study design can adjust for several possible confounding factors also without recall bias. [51,52]

To minimize the problem of confounding and bias in general the choice could be a Randomized Clinical Trial (RCT). This type of study is ranked highest in validity of evidence and power.[53] In a RCT a group of people are randomly allocated into subgroups that either receive a treatment of interest (exposed) or a standard treatment as control (unexposed). In this way patients are even distributed regarding to known and unknown confounders between the intervention groups. After allocating into groups, patients will be followed over a certain amount of time, or until the outcome of interest occur.[51,52] It would be possible to apply the study design to our research question; with one group having PPI's in addition to standard treatment and another group only having the standard treatment. However, this type of study would be expensive and very time consuming, as patients needed to be followed over a great amount of time before any possible recurrence or other outcome might occur.

Further, the Danish registries in general are relatively easy to access and have very high-quality data on a large number of patients.[18,20,26] Information from the different databases is easy to link via the CPR-system, which makes it very suitable for observational studies. For these reasons, and taking into account the disadvantages of a RCT, we concluded that a prospective cohort study design would address our research question very well.

Statistical methods

Exposure and immortal time bias

We defined exposure in 3 different ways, to evaluate the effect of PPI on breast cancer recurrence. Overall use of drug during follow-up was modeled as time-varying exposure. This model takes into account that each individual exposure is not a one-time dichotomous event. Rather it is a dynamic and varying event where people can be exposed to a drug at one point during follow-up and unexposed later again. This moving in between exposed and unexposed can happen several times. The model also considers that patients having a prescription lasting 30 days do not contribute with the same amount of exposure as people having a prescription lasting 90 days. Further, the model avoids immortal time-bias which is a period during follow-up where a patient cannot die. The problem of immortal time bias would arise if we modelled the exposure as a one-time dichotomous event from the time they entered the cohort. Consequently, the period from entering the study and their first prescription will be event-free, and "immortal". Said in another way, the patient needs survive the period to be able to receive a prescription, thereby contributing with "immortal" time.

We also modelled the exposure as any PPI prescription during the first 6 months after diagnosis, corresponding to the period of potentially having chemotherapy treatment. To avoid any immortal time bias in this setup we relocated start of follow-up until 6 months after diagnosis.
To evaluate the effect, we also defined the exposure as any PPI prescription before diagnosis. Exposure was modelled as a baseline dichotomous variable and follow-up began on the day of diagnosis.
The reason for modelling the exposure as both before, during and after chemotherapy treatment and stratifying by chemotherapy was to address the question whether PPIs have possible anti-cancer properties itself, or if it might modify the chemotherapy treatment.

Survival analysis

The aim of a survival analysis is to evaluate data that measure follow-up time from a defined starting point to the occurrence of a given event, in this example from breast cancer diagnosis to event of recurrence. There are several ways to analyze time-to-event data, but Cox proportional hazards regression is the most common used. Compared to e.g. a logistic regression that compares proportions of events, the Cox-model incorporate time. The model assumes that the ratio of the instantaneous hazards of the different exposure groups remains constant over time, called the proportional hazard assumption. The model also assume that censoring is independent. People are censored when an event makes them unable to be followed any longer (e.g. death or emigration). By censoring on the day of another event than recurrence, we prevent follow-up from patients that are no longer able to experience recurrence. Independent censoring refers to the fact that censored patients are no more likely or less likely to experience recurrence than the patients remaining in the cohort.

ADDITIONAL STRENGTHS AND LIMITATIONS

When performing and interpreting epidemiological research you need to consider the validity of the study. External validity is the degree to which the observations hold true in other settings. Said in another way, it is the study's transmissibility to the general population. Due to the setting of this study using information from DBCG which has data on all surgical breast cancer patients in Denmark, the external validity is very good. The question to rise about external validity in this setting is whether the observation holds true to other countries as well. The best we can do to improve generalizability is to ensure the internal validity. Internal validity is the extent to which the result of a study is causal. It is determined by the degree of errors in the study. The errors can be either random or systematic.

Random error is the normal variation on an estimate due to variability in data by chance. They will be reduced to zero if a study become infinitely large. Opposite to random errors, systemic errors will remain constant even in an infinitely large study.

Systematic error is an error in the setting and design of the study, in the collection, analysis, interpretation or review of data that leads to results or conclusions that systematically are wrong. Another word for systemic error is bias and it is typically divided into selection bias, information bias and confounding.

Selection bias

Selection bias is an error that arises from the procedures used to select the study cohort and factors that influence the participation in the study. It appears when the association between exposure and outcome differs for those who participates in the study, and those who do not participate in the study (Rothman). A very well-known example of this is self-selected health surveys. In these types of studies, it is more likely that people concerning about their health is participating, and that these people in general are healthier than people choosing not to participate. This will skew the results and introduce selection bias.

This study was performed using population-based registries. These registries cover the entire population and all hospital contacts, and as mentioned before, the registries have very high quality and completeness. This setting minimizes the risk of selection bias.

Information bias

Information bias occurs when information on study-participants is not correct. It is typically referred to as misclassification and divided into differential and non-differential misclassification. Differential misclassification occurs when an outcome is misclassified differentially according to a patient's exposure or the exposure is misclassified differentially according to a patient's outcome. An example of this is recall bias. This occurs especially in case-control studies, where patients are interviewed to obtain exposure information after the outcome have occurred, and thereby patients may answer differently about exposure according to their outcome status. In this study recall bias would be introduced if we relied on self-reported use of PPI prescriptions rather than registries. Differential misclassification can drive an estimate in both directions; exaggerate and underestimate. In contrary non-differential misclassification arises when exposure or outcome is misclassified, but the misclassification is not depending on a patient's status of the other variable. This type of misclassification tends to produce estimates of the effect that are "diluted". In other words non-differential misclassification will bias an effect, if there is one, toward the null.(rothmann).

Confounding

Confounding is a distortion in the estimated measure of association which arises when the exposure of interest is mixed up with another factor that is associated with the outcome. A very simplified explanation is to say that it's the confusion of effects. For confounding to occur the confounder must fulfill three criteria's; the confounder must be associated with the outcome, it must be associated with the exposure and it must not be an effect of the exposure, a so-called intermediate step.

In observational studies confounding is a big concern because exposure is not randomly distributed. However, there is several ways of controlling for confounders. In the design setting it can be handled by either restriction or matching, and in the statistical analyses by adjustment, stratification or standardization. In this study we incorporated many covariates and performed both adjusted regressions and stratified analyses.

Effect measure modification

As mentioned we stratified our analyses by clinical factors to evaluate effect measure modification. This expression is used to describe situations in which the magnitude of the effect of the exposure of interest differs according to the level of a third variable. When we stratified by chemotherapy in this study, we found proof of effect measure modification, saying that the magnitude of effect changed regarding to if patients had chemotherapy or not.

Precision

When calculating and giving the point estimates we used the confidence interval. It is a range of values just above and under the point estimate. A narrow confidence interval gives a high precision, whereas a wide interval indicates a lower precision of the estimate. A study with a large number of participants the interval gets narrower, than a study with few participants. Despite our study size, some of the estimates were rather imprecise, but in some of the groups we had few PPI users and few recurrences, which lowered the imprecision.

CLINICAL PERSPECTIVES AND FUTURE STUDIES

This study adds important knowledge on the use of PPIs and breast cancer prognosis. It revealed several findings, some of which have potential practice changing implications. First, we found that PPI use during the first six months after diagnosis associates with a decreased risk of breast cancer recurrence among women treated with chemotherapy. This finding supports our hypothesis and indicate that we might be able to improve breast cancer prognosis and survival with readily available and affordable medication with a well-known safety profile.

Secondly, we observed that PPI use during the entire follow-up period does not alter the risk of recurrence. This is a relevant finding because it indicates that the use of PPIs does not increase the risk of breast cancer recurrence, thus probably can be prescribed without worsening the prognosis.

Thirdly, we found that women who used PPIs before breast cancer diagnosis had a tendency towards a decreased risk of recurrence. These findings were imprecise but any impact these drugs have on breast cancer recurrence is particularly important in view of the increasing use and access of PPIs in Denmark.

Our results have important implications for both practical clinic and future research. It is easy to apply to the clinic by offering PPIs to women treated with chemotherapy, but further relevant studies about the association is needed. It could be interesting to set up a Randomized Clinical Trial with PPIs in addition to chemotherapy and to investigate the importance of duration and dose of PPI. Further, our findings may be relevant to other cancer types, and would be easy to implicate in treatment, therefore it would be of high relevance to explore this further.

In conclusion our findings suggest that PPIs may improve the treatment of chemotherapy, thereby improving the prognosis and survival of breast cancer patients and may open to new treatment regimens.

REFERENCES

1. Brystkræft, Lægehåndbogen, sundhed.dk. https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/brystsygdomme/tilstande-og-sygdomme/kvinder/brystkraeft/. Accessed February 11, 2018.

2. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. *Lancet (London, England)*. 2000;355(9217):1822. doi:10.1016/S0140-6736(00)02277-7.

3. Wang B-Y, Zhang J, Wang J-L, et al. Intermittent high dose proton pump inhibitor enhances the antitumor effects of chemotherapy in metastatic breast cancer. *J Exp Clin Cancer Res*. 2015;34(1):85. doi:10.1186/s13046-015-0194-x.

4. Yu M, Lee C, Wang M, Tannock IF. Influence of the proton pump inhibitor lansoprazole on distribution and activity of doxorubicin in solid tumors. *Cancer Sci*. 2015;106(10):1438-1447. doi:10.1111/cas.12756.

5. Murakami T, Shibuya I, Ise T, et al. Elevated expression of vacuolar proton pump genes and cellular pH in cisplatin resistance. *Int J Cancer*. 2001;93(6):869-874. doi:10.1002/ijc.1418.

6. McGuire C, Cotter K, Stransky L, Forgac M. Regulation of V-ATPase assembly and function of V-ATPases in tumor cell invasiveness. *Biochim Biophys Acta - Bioenerg*. 2016;1857(8):1213-1218. doi:10.1016/j.bbabio.2016.02.010.

7. Hinton A, Sennoune SR, Bond S, et al. Function of a subunit isoforms of the V-ATPase in pH homeostasis and in vitro invasion of MDA-MB231 human breast cancer cells. *J Biol Chem*. 2009;284(24):16400-16408. doi:10.1074/jbc.M901201200.

8. Sennoune SR, Bakunts K, Martínez GM, et al. Vacuolar H^+-ATPase in human breast cancer cells with distinct metastatic potential: distribution and functional activity. *Am J Physiol Physiol*. 2004;286(6):C1443-C1452. doi:10.1152/ajpcell.00407.2003.

9. Pottegard A, Broe A, Hallas J, de Muckadell OBS, Lassen AT, Lodrup AB. Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. *Therap Adv Gastroenterol*. 2016:1-8. doi:10.1177/1756283X16650156.

10. Zhang S, Wang Y, Li SJ. Lansoprazole induces apoptosis of breast cancer cells through inhibition of intracellular proton extrusion. *Biochem Biophys Res Commun*. 2014;448(4):424-429. doi:10.1016/j.bbrc.2014.04.127.

11. Patel KJ, Lee C, Tan Q, Tannock IF. Use of the Proton Pump Inhibitor Pantoprazole to Modify the Distribution and Activity of Doxorubicin: A Potential Strategy to Improve the Therapy of Solid Tumors. *Clin Cancer Res*. 2013;19(24):6766-6776. doi:10.1158/1078-0432.CCR-13-0128.

12. Goh W, Sleptsova-Freidrich I, Petrovic N. Use of proton pump inhibitors as adjunct treatment for triple-negative breast cancers. An introductory study. *J Pharm Pharm Sci*. 2014;17(3):439-446. http://www.ncbi.nlm.nih.gov/pubmed/25224353. Accessed February 6, 2017.

13. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3.

14. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7_suppl):22-25. doi:10.1177/1403494810387965.

15. Møller S, Jensen M-B, Ejlertsen B, et al. The clinical database and the treatment guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience and future promise. *Acta Oncol (Madr)*. 2008;47(4):506-524. doi:10.1080/02841860802059259.

16. Blichert-Toft M, Christiansen P, Mouridsen HT. Danish Breast Cancer Cooperative Group – DBCG: History, organization, and status of scientific achievements at 30-year anniversary. *Acta Oncol (Madr)*. 2008;47(4):497-505. doi:10.1080/02841860802068615.

17. Christiansen P, Ejlertsen B, Jensen M-B, Mouridsen H. Danish Breast Cancer Cooperative Group. *Clin Epidemiol*. 2016;8:445-449. doi:10.2147/CLEP.S99457.

18. Møller S, Jensen M-B, Ejlertsen B, et al. The clinical database and the treatment guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience and future promise. *Acta Oncol*. 2008;47(4):506-524. doi:10.1080/02841860802059259.

19. Christiansen P, Al-Suliman N, Bjerre K, Møller S. Recurrence pattern and prognosis in low-risk breast cancer patients--data from the DBCG 89-A programme. *Acta Oncol*. 2008;47(February):691-703. doi:10.1080/02841860802056594.

20. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Heal*. 2011;39(7 Suppl):38-41. doi:10.1177/1403494810394717.

21. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2016:dyw213. doi:10.1093/ije/dyw213.

22. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet*. 1997;350(9084):1047-1059. doi:10.1016/S0140-6736(97)08233-0.

23. Kuhle CL, Kapoor E, Sood R, Thielen JM, Jatoi A, Faubion SS. Menopausal hormone therapy in cancer survivors: A narrative review of the literature. *Maturitas*. 2016;92:86-96. doi:10.1016/J.MATURITAS.2016.07.018.

24. Ahern TP, Lash TL, Damkier P, Christiansen PM, Cronin-Fenton DP. Statins and breast cancer prognosis: evidence and opportunities. *Lancet Oncol*. 2014;15(10):e461-8. doi:10.1016/S1470-2045(14)70119-6.

25. Ahern TP, Pedersen L, Tarp M, et al. Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. *J Natl Cancer Inst*. 2011;103(19):1461-1468. doi:10.1093/jnci/djr291.

26. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*.

2011;39(7_suppl):30-33. doi:10.1177/1403494811401482.

27. Uehiro N, Horii R, Iwase T, et al. Validation study of the UICC TNM classification of malignant tumors, seventh edition, in breast cancer. *Breast Cancer*. 2014;21(6):748-753. doi:10.1007/s12282-013-0453-7.

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8.

29. Medicinsk behandling efter operationen - Kræftens Bekæmpelse. https://www.cancer.dk/brystkraeft-mammacancer/behandling-brystkraeft/medicinsk-efterbehandling/. Accessed January 9, 2018.

30. Pottegård A, Hallas J. New use of prescription drugs prior to a cancer diagnosis. *Pharmacoepidemiol Drug Saf*. 2016;6(5):188-191. doi:10.1002/pds.4145.

31. Cronin-Fenton DP, Kjærsgaard A, Ahern TP, et al. Validity of Danish Breast Cancer Group (DBCG) registry data used in the predictors of breast cancer recurrence (*ProBeCaRe*) premenopausal breast cancer cohort study. *Acta Oncol (Madr)*. 2017;56(9):1155-1160. doi:10.1080/0284186X.2017.1327720.

32. Kvalitetsindikatorrapport for Brystkraeft 2016. https://www.sundhed.dk/content/cms/79/4679_årsrapport2016_diskret_fig_bilag.pdf. Accessed January 9, 2018.

33. Rasmussen L, Valentin J, Gesser KM, Hallas J, Pottegård A. Validity of the Prescriber Information in the Danish National Prescription Registry. *Basic Clin Pharmacol Toxicol*. 2016;119(4):376-380. doi:10.1111/bcpt.12610.

34. Simapivapan P, Boltong A, Hodge A. To what extent is alcohol consumption associated with breast cancer recurrence and second primary breast cancer?: A systematic review. *Cancer Treat Rev*. 2016;50:155-167. doi:10.1016/J.CTRV.2016.09.010.

35. Padron-Monedero A, Tannenbaum SL, Koru-Sengul T, et al. Smoking and survival in female breast cancer patients. *Breast Cancer Res Treat*. 2015;150(2):395-403. doi:10.1007/s10549-015-3317-3.

36. Bjerkaas E, Parajuli R, Engeland A, Maskarinec G, Weiderpass E, Gram IT. The association between lifetime smoking exposure and breast cancer mortality--results from a Norwegian cohort. *Cancer Med*. 2014;3(5):1448-1457. doi:10.1002/cam4.304.

37. Agarwal S, Ying J, Boucher KM, Agarwal JP. The association between socioeconomic factors and breast cancer-specific survival varies by race. *PLoS One*. 2017;12(12):e0187018. doi:10.1371/journal.pone.0187018.

38. Jiralerspong S, Goodwin PJ. Obesity and Breast Cancer Prognosis: Evidence, Challenges, and Opportunities. *J Clin Oncol*. 2016;34(35):4203-4216. doi:10.1200/JCO.2016.68.4480.

39. Neuhouser ML, Aragaki AK, Prentice RL, et al. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk. *JAMA Oncol*. 2015;1(5):611. doi:10.1001/jamaoncol.2015.1546.

40. Crispo A, Grimaldi M, D'Aiuto M, et al. BMI and breast cancer prognosis benefit: Mammography screening reveals differences between normal weight and overweight women. *The Breast*. 2015;24(1):86-89. doi:10.1016/J.BREAST.2014.11.005.

41. Ewertz M, Jensen M-B, Gunnarsdóttir KÁ, et al. Effect of obesity on prognosis after early-stage breast cancer. *J Clin Oncol*. 2011;29(1):25-31. doi:10.1200/JCO.2010.29.7614.

42. Richter JE. Gastroesophageal Reflux Disease and Obesity: Not as Simple as We May Think. *Dig Dis Sci*. 2012;57(7):1748-1750. doi:10.1007/s10620-012-2251-z.

43. Chen S, Wang J, Li Y. Is alcohol consumption associated with gastroesophageal reflux disease? *J Zhejiang Univ Sci B*. 2010;11(6):423-428. doi:10.1631/jzus.B1000013.

44. Spugnini E, Fais S. Proton pump inhibition and cancer therapeutics: A specific tumor targeting or it is a phenomenon secondary to a systemic buffering? *Semin Cancer Biol*. 2017;43:111-118. doi:10.1016/J.SEMCANCER.2017.01.003.

45. Lee Y-Y, Jeon H-K, Hong JE, et al. Proton pump inhibitors enhance the effects of cytotoxic agents in chemoresistant epithelial ovarian carcinoma. *Oncotarget*. 2015;6(33):35040-35050. doi:10.18632/oncotarget.5319.

46. Song T, Jeon H-K, Hong JE, et al. Proton Pump Inhibition Enhances the Cytotoxicity of Paclitaxel in Cervical Cancer. *Cancer Res Treat*. 2016:1-12. doi:10.4143/crt.2016.034.

47. Brystkræft - mammacancer | Kræftens Bekæmpelse. https://www.cancer.dk/brystkraeft-mammacancer/. Accessed February 19, 2018.

48. Specht L, Herrstedt J, Storm HH, Rørth M. *Klinisk Onkologi*. 1st ed. Copenahgen: Munksgaard; 2015.

49. Lauritsen K, Madsen JR. Midler mod fordøjelseskanalens sygdomme. In: *Basal Og Klinisk Farmakologi*. 4th ed. Copenhagen: FADL's forlag; 2010.

50. pro.medicin.dk – information om medicin. https://pro.medicin.dk/. Accessed February 19, 2018.

51. FLetcher RH, Fletcher, Suzanne W, Fletcher GS. *Clinical Epidemiology the Essentials*. 5th ed. Lippincott Willians & Wilkins, Wolter Kluwer business; 2014.

52. Rothman KJ. *Epidemiology An Introduction*. 2nd ed. Oxford University Press, Inc.; 2012.

53. Juul S. *Epidemiologi Og Evidens*. 2nd ed. Copenhagen: Munksgaard; 2012.

FIGURES AND TABLES

Figure 1. Flowchart:

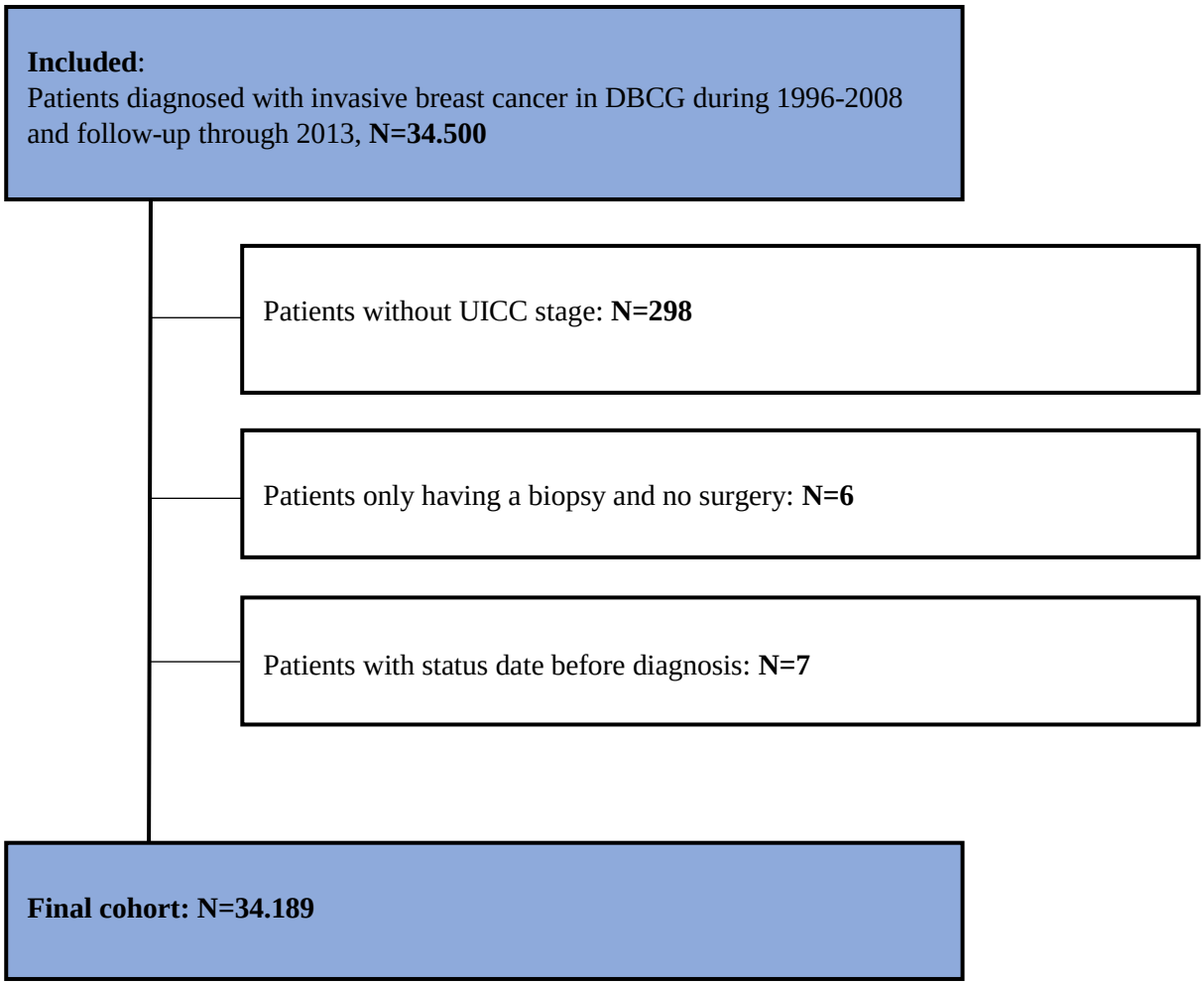
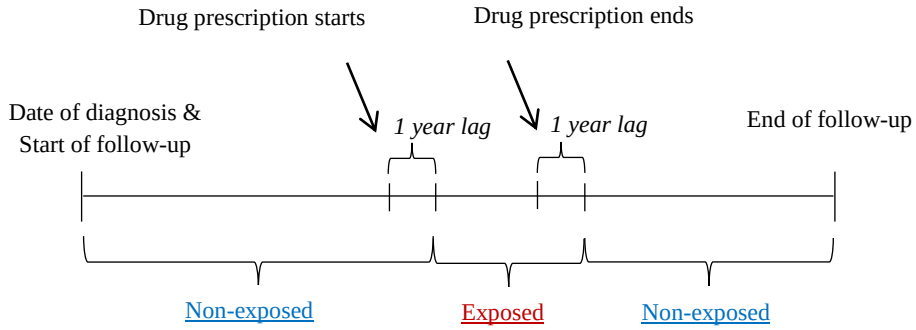


Figure 2. Exposure definitions:

Example of PPI use first 6 months after diagnosis:

Example of time-varying use:



Example of former PPI exposure:

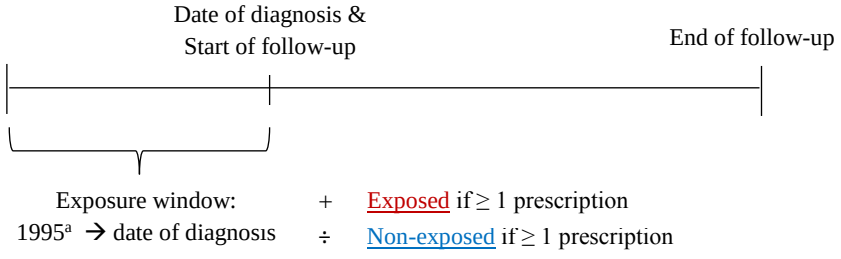


Table 1. Baseline Characteristics of patients diagnosed with breast cancer stage I, II and III in Denmark during 1996-2008 (n=34.189) according to PPI use within the first 6 months after cancer diagnosis.

Characteristics	No. of Patients (%)	
	PPI users[a]	Non users
All	*1,769 (5.2)*	*32,189 (94.8)*
Age at diagnosis		
<29	<5 (>1)	118 (<1)
30-39	47 (2.7)	1,532 (4.8)
40-49	251 (14.2)	5,685 (17.7)
50-59	509 (28.8)	9,805 (30.5)
60-69	581 (32.8)	9,798 (30.4)
70-79	312 (17.6)	4,395 (13.7)
>80	67 (3.8)	856 (2.7)
Menopausal status		
Premenopausal	395 (22.3)	9,184 (28.5)
Postmenopausal	1,373 (77.6)	22,991 (71.4)
Unknown	<5 (<1)	14 (<1)
Charlson Score		
0	1,141 (64.5)	26,105 (81.1)
1	334 (18.9)	3,412 (10.6)
2	162 (9.2)	1,710 (5.3)
3	132 (7.5)	962 (3)
UICC		
I	681 (38.5)	12,241 (38)
II	779 (44)	14,397 (44.7)
III	472 (17.5)	5,551 (17.2)
Histologic grade		
Low	1,444 (81.6)	26,261 (81.6)
Moderate	199 (11.2)	3,539 (11)
High	122 (6.9)	2,251 (7)
Missing	4 (<1)	138 (<1)
ER/ ET status		
ER-/ET-	372 (21)	6,198 (19.3)
ER+/ET-	386 (22.8)	8,103 (25.2)
ER+/ET+	961 (54.3)	16,770 (52.1)
Other/unknown	50 (2.9)	1,118 (3.5)
Type of Primary surgery		
Mastectomy	702 (39.7)	11,434 (35.5)
Mastectomy + RT	366 (20.7)	6,697 (20.8)
BCS+RT	701 (39.6)	14,058 (43.7)

Adjuvant Chemotherapy		
Yes	516 (29.2)	10,861 (33.7)
No	1,253 (70.8)	21,328 (66.3)
Prediagnostic exposure to HRT		
Yes	1,007 (56.9)	13,072 (40,6)
No	762 (43.1)	19,117 (59.4)
Simvastatin exposure during study		
Yes	492 (27.8)	6519 (20.3)
No	1,277 (72.2)	25,670 (79.7)

[a]PPI use defined as ≥1 prescription during the first year after diagnosis.
Abbreviations: -, negative, +, positive, BCS, breast conserving surgery, ER, estrogen receptor, ET, endocrine therapy, HRT, hormone-replacement therapy, RT, radiotherapy, UICC, Union for International Cancer Control.

Table 2. Breast cancer recurrences, hazard ratios (HRs) and associated 95% confidence intervals (CIs) for stages I, II and III breast cancer patients diagnosed in Denmark during 1996 -2008 according to different patterns of PPI use.

Exposure definition	Person-years at risk	N	Median exposure time	Number Recurrence	Crude model		Adjusted model[a]	
					HR	95% CI	HR	95% CI
PPI use within first 6 months after diagnosis[b]								
Non-use	184,204	32,189		4,566	1	Reference	1	Reference
PPI use	6,733	1,769		199	0.83	0.71–0.95	0.89	0.78-1.04
Overall PPI use[c]								
Non-use	221,289	26,449		4,646	1	Reference	1	Reference
PPI use	11,840	7,740		674	0.95	0.83–1.08	1.05	0.92–1.20
Former PPI use								
Non-use	172,811	30,578		4,244	1	Reference	1	Reference
PPI use	9,042	3,611		178	0.79	0.68-0.92	0.90	0.77-1.04

[a]Adjusted for: age (continuous), menopausal status, charlson score, UICC stage, histologig grade, ER/ET status, type of surgery, chemotherapy, HRT, simvastatin.
[b]Defined as ≥1 prescription of PPI within the first 6 months after diagnosis.
[c]Defined as time-varying PPI use from start of follow-up to end of follow-up. Lagged by 1 year.
[d]Defined as never/ever user. Ever users having ≥1 prescription of PPI anytime before diagnosis.

Table 3. Hazard ratios and 95% Confidence Intervals associating prescriptions for PPIs and breast cancer recurrence among women diagnosed with stage I, II and II breast cancer I Denmark during 1996-2008. Stratified by clinical factors.

	PPI use 6 months after diagnosis[a]		Time varying Exposure of PPI[b]		Former PPI use[c]	
Stratified clinical factor	**Crude HR (95 % CI)**	**Adjusted HR[d] (95 %CI)**	**Crude HR (95 % CI)**	**Adjusted HR[d] (95 % CI)**	**Crude HR (95% CI)**	**Adjusted HR[d] (95% CI)**
Chemotherapy						
No	0.89 (0.76-1.06)	1.00 (0.84-1.18)	0.96 (0.83-1.12)	1.08 (0.93-1.25)	0.81 (0.68-0.97)	0.92 (0.77-1.11)
Yes	0.70 (0.54-0.92)	0.71 (0.54-0.93)	0.90 (0.67-1.20)	0.92 (0.69-1.23)	0.79 (0.60-1.04)	0.84 (0.64-1.11)
HRT						
No	0.95 (0.78-1.16)	0.94 (0.77-1.15)	1.05 (0.86-1.26)	1.10 (0.91-1.33)	0.79 (0.64-0.97)	0.89 (0.72-1.10)
Yes	0.83 (0.69-1.01)	0.84 (0.70-1.02)	0.96 (0.80-1.16)	1.01 (0.84-1.22)	0.88 (0.71-1.09)	0.91 (0.73-1.12)
ER/ET Status						
ER-/ET-	0.72 (0.54-0.96)	0.75 (0.56-1.00)	0.98 (0.73-1.31)	1.05 (0.78-1.41)	0.76 (0.56-1.02)	0.82 (0.60-1.11)
ER+/ET-	0.82 (0.61-1.11)	1.05 (0.77-1.43)	0.92 (0.71-1.20)	1.18 (0.90-1.54)	0.71 (0.49-1.03)	0.90 (0.62-1.32)
ER+/ET+	0.91 (0.75-1.11)	0.96 (0.79-1.17)	0.97 (0.81-1.17)	1.01 (0.84-1.21)	0.88 (0.72-1.07)	0.93 (0.76-1.14)

[a]Defined as ≥1 prescription of PPI within the first 6 months after diagnosis.
[b]Defined as time-varying PPI use from start of follow-up to end of follow-up. Lagged by 1 year.
[c]Defined as never/ever user. Ever users having ≥1 prescription of PPI anytime before diagnosis.
[d]Adjusted for: age (continuous), menopausal status, charlson score, UICC stage, histologig grade, ER/ET status, type of surgery, chemotherapy, HRT, simvastatin.

SENSITIVITY ANALYSIS: PPI-USE DURING FIRST YEAR AFTER DIAGNOSIS:

Additional table 4: Hazard ratios and 95% Confidence Intervals associating prescriptions for PPIs and breast cancer Recurrence among women diagnosed with stage I, II and II breast cancer I Denmark during 1996-2008.

Stratified clinical factor	Crude HR (95 % CI)	Adjusted HR[a] (95 %CI)
PPI use within first year after diagnosis[b]		
Non-user	1 Reference	1 Reference
PPI user	0.89 (0.79-1.00)	0.94 (0.83-1.07)
Stratified by:		
Chemotherapy		
No	0.90 (0.77-1.04)	0.98 (0.84-1.14)
Yes	0.88 (0.71-1.10)	0.87 (0.69-1.08)
HRT		
No	1.05 (0.86-1.26)	1.10 (0.91-1.33)
Yes	0.96 (0.80-1.16)	1.01 (0.84-1.22)
ER/ET Status		
ER-/ET-	0.89 (0.71-1.15)	0.93 (0.73-1.18)
ER+/ET-	0.81 (0.62-1.05)	0.98 (0.75-1.27)
ER+/ET+	0.93 (0.77-1.11)	0.94 (0.79-1.13)

[a]Adjusted for: age (continuous), menopausal status, charlson score, UICC stage, histologig grade, ER/ET status, type of surgery, chemotherapy, HRT, simvastatin

[b]Defined as ≥1 prescription of PPI within the first year after diagnosis.

SENSITIVITY ANALYSIS: TIMEVARYING-EXPOSURE, CHANGED LAG PERIOD:

Additional table 5. Breast cancer recurrences, hazard ratios (HRs) and associated 95% confidence intervals (CIs) for stages I, II or III breast cancer patients diagnosed in Denmark during 1996 -2008 according to different patterns of PPI use.

Exposure definition	Crude model		Adjusted model[a]	
	HR	95% CI	HR	95% CI
Lagged 6 months[b]				
Non-use	1	Reference	1	Reference
PPI use	0.94	0.82–1.07	1.04	0.91–1.19
Lagged by 2 years[c]				
Non-use	1	Reference	1	Reference
PPI use	1.14	1.01–1.27	1.06	0.93–1.21

[a]Adjusted for: age (continuous), menopausal status, charlson score, UICC stage, histologig grade, ER/ET status, type of surgery, chemotherapy, HRT, simvastatin.
[b]Defined as time-varying PPI use from start of follow-up to end of follow-up. Lagged by 6 months.
[c]Defined as time-varying PPI use from start of follow-up to end of follow-up. Lagged by 2 years.

SENSITIVITY ANALYSIS: LOOKING AT DIFFERENT PPI'S SEPERATELY:

Additional table 6. Hazard ratios and 95% Confidence Intervals associating prescriptions for PPIs and breast cancer recurrence among women diagnosed with stage I, II and II breast cancer I Denmark during 1996-2008. Stratified by clinical factors.

	Omeprazol		Pantoprazol		Esomeprazol	
Cox model:	**Crude HR (95 % CI)**	**Adjusted HR[a] (95 %CI)**	**Crude HR (95 % CI)**	**Adjusted HR[a] (95 % CI**	**Crude HR (95% CI)**	**Adjusted HR[a] (95% CI)**
PPI first 6 months after diagnosis[b]						
No	1.00 Reference	1.00 Reference	1.00 Reference	1.00 Reference	1.00 Reference	1.00 Reference
Yes	0.98 (0.78-1.22)	1.00 (0.80-1.25)	0.79 (0.60-1.05)	0.89 (0.67-1.17)	0.57 (0.40-0.81)	0.63 (0.44-0.89)
Stratified by:						
Chemotherapy						
No	1.07 (0.84-1.37)	1.13 (0.88-1.45)	0.88 (0.65-1.22)	1.01 (0.74-1.39)	0.62 (0.41-0.96)	0.70 (0.46-1.08)
Yes	0.75 (0.46-1.22)	0.67 (0.41-1.10)	0.61 (0.34-1.11)	0.62 (0.34-1.13)	0.49 (0.27-0.88)	0.52 (0.29-0.95)

[a]Adjusted for: age (continuous), menopausal status, charlson score, UICC stage, histologig grade, ER/ET status, type of surgery, chemotherapy, HRT, simvastatin.
[b]Defined as >=1 prescription of PPI within the first 6 months after diagnosis.

SENSITIVITYANALYSES WITH PPI PRESCRIPTIONS DEFINED AS >1 PRESCRIPTION:

Additional table 7a. Breast cancer recurrences, hazard ratios (HRs) and associated 95% confidence intervals (CIs) for stages I, II and III breast cancer patients diagnosed in Denmark during 1996 -2008 according to different patterns of PPI use.

Exposure definition	Person-years at risk	N	Median exposure time in years	Number Recurrence	Crude model		Adjusted model[a]	
					HR	95% CI	HR	95% CI
PPI use within first 6 months after diagnosis[b]								
Non-use	188,430	32,916		4,633	1	Reference	1	Reference
PPI use	5,506	1,042		132	0.97	0.81–1.15	1.06	0.89–1.27
Overall PPI use[c]								
Non-use	223,952	29,249	0	4,912	1	Reference	1	Reference
PPI use	9,177	4,940	0.86	408	0.95	0.82–1.18	1.08	0.93–1.26
Former PPI use								
Non-use	177,020	31,826		4,329	1	Reference	1	Reference
PPI use	4,842	2,363		93	0.78	0.64-0.96	0.89	0.72-1.09

[a]Adjusted for: age (continuous), menopausal status, charlson score, UICC stage, histologig grade, ER/ET status, type of surgery, chemotherapy, HRT, simvastatin.
[b]Defined as >=1 prescription of PPI within the first 6 months after diagnosis.
[c]Defined as time-varying PPI use from start of follow-up to end of follow-up. Lagged by 1 year.
[d]Defined as never/ever user. Ever users having ≥1 prescription of PPI any time before diagnosis.

SENSITIVITYANALYSES WITH PPI PRESCRIPTIONS DEFINED AS >1 PRESCRIPTION:

Additional table 7b. Hazard ratios and 95% Confidence Intervals associating prescriptions for PPIs and breast cancer recurrence among women diagnosed with stage I, II and II breast cancer I Denmark during 1996-2008. Stratified by clinical factors.

	Time varying Exposure of PPI		PPI use 6 months after diagnosis		Baseline PPI use	
Stratified clinical factor	**Crude HR (95 % CI)**	**Adjusted HR (95 %CI)**	**Crude HR (95 % CI)**	**Adjusted HR (95 % CI**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Chemotherapy						
No	0.96 (0.81-1.14)	1.10 (0.93-1.30)	1.02 (0.83-1.24)	1.15 (0.94-1.40)	0.83 (0.65-1.05)	0.95 (0.75-1.21)
Yes	0.91 (0.65-1.28)	0.95 (0.68-1.33)	0.88 (0.62-1.24)	0.87 (0.62-1.23)	0.71 (0.47-1.06)	0.76 (0.50-1.15)
HRT						
No	1.07 (0.86-1.33)	1.15 (0.92-1.43)	1.13 (0.88-1.45)	1.19 (0.92-1.52)	0.81 (0.60-1.08)	0.90 (0.68-1.22)
Yes	0.96 (0.78-1.18)	1.02 (0.83-1.26)	0.95 (0.74-1.21)	0.97 (0.76-1.23)	0.84 (0.63-1.12)	0.89 (0.67-1.20)
ER/ET Status						
ER-/ET-	1.01 (0.73-1.41)	1.11 (0.79-1.55)	0.87 (0.62-1.23)	0.92 (0.65-1.30)	0.86 (0.58-1.27)	0.94 (0.63-1.39)
ER+/ET-	0.88 (0.65-1.20)	1.16 (0.85-1.58)	0.99 (0.69-1.42)	1.29 (0.89-1.86)	0.58 (0.33-1.03)	0.77 (0.43-1.36)
ER+/ET+	0.99 (0.81-1.22)	1.05 (0.85-1.30)	1.04 (0.81-1.32)	1.10 (0.86-1.41)	0.82 (0.62-1.08)	0.88 (0.67-1.17)

[a]Adjusted for: age (continuous), menopausal status, charlson score, UICC stage, histologig grade, ER/ET status, type of surgery, chemotherapy, HRT, simvastatin.
[b]Defined as time-varying PPI use from start of follow-up to end of follow-up. Lagged by 1 year.
[c]Defined as >=1 prescription of PPI within the first 6 months after diagnosis.
[d]Defined as never/ever user. Ever users having ≥1 prescription of PPI anytime before diagnosis.

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. PhD thesis. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. PhD thesis. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. PhD thesis. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. PhD thesis. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. PhD thesis. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. PhD thesis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. PhD thesis. *2002*.

8. Bente Nørgård: Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling. PhD thesis. *2002*.

9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. PhD thesis. *2002*.

10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. PhD thesis. *2003*.

11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. PhD thesis. *2004*.

12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. PhD thesis. *2004*.

13. Kort-og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg og Århus amter 1985-2003. *2004*.

14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. PhD thesis. *2004*.

15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

17. Kort- og langtidsoverlevelse efter indlæggelse for nyre-, bugspytkirtel- og leverkræft i Nordjyllands, Viborg, Ringkøbing og Århus amter 1985-2004. *2005*.

18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.

19. Mette Nørgaard: Haematological malignancies: Risk and prognosis. PhD thesis. *2006*.

20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. PhD thesis. *2006*.

    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.

21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. PhD thesis. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. Research year report. *2007*.

28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. PhD thesis. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. PhD thesis. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. Research year report. *2007*.

31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.

32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. PhD thesis. *2007*.

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34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.

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37. Use of medical databases in clinical epidemiology. *2008*.

38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. PhD thesis. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.

41. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.

    Sandra Kruchov Thygesen. Atrial fibrillation in patients with ischemic stroke: A population-based study. Research year report. *2008*.

42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Not published*.

43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. PhD thesis. *2009*.

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63. Sigrún Alba Jóhannesdóttir: Mortality in cancer patients following a history of squamous cell skin cancer – A nationwide population-based cohort study. Research year report. *2011*.

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70. Alkoholisk leversygdom i Region Midtjylland og Region Nordjylland. 2007-2011. *2012*.

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76. Malene Kærslund Hansen: Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients: A cohort study. Research year report. *2013*.

77. Astrid Blicher Schelde: Impact of comorbidity on the prediction of first-time myocardial infarction, stroke, or death from single-photon emission computed tomography myocardial perfusion imaging: A Danish cohort study. Research year report. *2013*.

78. Risiko for kræft blandt patienter med kronisk obstruktiv lungesygdom (KOL) i Danmark. (Online publication only). *2013*.

79. Kirurgisk fjernelse af milten og risikoen for efterfølgende infektioner, blodpropper og død. Danmark 1996-2005. (Online publication only). *2013*.

    Jens Georg Hansen: Akut rhinosinuitis (ARS) – diagnostik og behandling af voksne i almen praksis. *2013*.

80. Henrik Gammelager: Prognosis after acute kidney injury among intensive care patients. PhD thesis. *2014*.

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    Mikkel S. Andersen: Danish Criteria-based Emergency Medical Dispatch – Ensuring 112 callers the right help in due time? PhD thesis. *2014*.

92. Jonathan Montomoli: Short-term prognosis after colorectal surgery: The impact of liver disease and serum albumin. PhD thesis. *2014*.

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98. Niwar Faisal Mohamad: Improving logistics for acute ischaemic stroke treatment: Reducing system delay before revascularisation therapy by reorganisation of the prehospital visitation and centralization of stroke care. Research year report. *2015*.

99. Malene Schou Nielsson: Elderly patients, bacteremia, and intensive care: Risk and prognosis. PhD thesis. *2015*.

100. Jens Tilma: Treatment Injuries in Danish Public Hospitals 2006-2012. Research year report. *2015*.

101. Thomas Lyngaa: Intensive care at the end-of-life in patients dying of cancer and non-cancer chronic diseases: A nationwide study. Research year report. *2015*.

102. Lone Winther Lietzen: Markers of immune competence and the clinical course of breast cancer. PhD thesis. *2015*.

103. Anne Høy Seemann Vestergaard: Geographical Variation in Use of Intensive Care in Denmark: A Nationwide Study. Research year report. *2015*.

104. Cathrine Wildenschild Nielsen: Fecundability among Danish pregnancy planners. Studies on birth weight, gestational age and history of miscarriage. PhD thesis. *2015*.

105. Kathrine Dyhr Lycke: Preadmission use of antidepressants and quality of care, intensive care admission and mortality of colorectal cancer surgery – a nationwide population-based cohort study. Research year report. *2015*.

106. Louise Bill: Hyponatremia in acute internal medicine patients: prevalence and prognosis. PhD thesis. *2015*.

107. Kirstine Kobberøe Søgaard: Risk and prognosis of venous thromboembolism in patients with liver disease. PhD thesis. *2015*.

108. Rikke Nørgaard Pedersen: Reoperation due to surgical bleeding in breast cancer patients and breast cancer recurrence: A Danish population-based cohort study. Research year report. *2015*.

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110. Anne Mette Falstie-Jensen: Hospital accreditation – what's in it for the patients? PhD thesis. *2016*.

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112. Alma Bečić Pedersen: Total hip replacement surgery - occurrence and prognosis. Doctoral dissertation. *2016*.

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115. Simon Ramsdal Sørensen: Anti-platelet and Anti-coagulant Prescriptions and Breast Cancer Recurrence: a Danish Nationwide Prospective Cohort Study. Research year report. *2016*.

116. Regional Differences in Treatment of Patients with Inflammatory Bowel Disease in Denmark

117. Clara Reece Medici: Impact of preadmission anti-inflammatory drug use on risk of depression and anxiety after intensive care requiring mechanical ventilation. Research year report. *2016*.

118. Johan Frederik Håkonsen Arendt. Clinical implications and biochemical understanding of high plasma vitamin B12 levels. PhD thesis. *2016*.

119. Manual for using the LABKA database for research projects. *2016*.

120. Søren Christiansen: Timing of renal replacement therapy and long-term risk of chronic kidney disease and death in intensive care patients with acute kidney injury. Research year report. *2017*.

121. Ellen Hollands Steffensen: Preadmission antidepressant use and bladder cancer: a population-based cohort study of stage at diagnosis, time to surgery, and surgical outcomes. Research year report. *2017*.

122. Sara Søndergaard Schwartz: Incidence and mortality of pulmonary hypertension in adults with congenital heart disease. Research year report. *2017*.

123. Jesper Smit: Community-acquired Staphylococcus aureus bacteremia: Studies of risk and prognosis with special attention to diabetes mellitus and chronic heart failure. PhD thesis. *2017*.

124. Carina Nørskov Bagge: Risk of Dementia in Adults with Congenital Heart Disease: A Nationwide Population-Based Cohort Study. Research year report. *2017*.

125. Pia Kjær Kristensen: Hip fracture in Denmark: Quality of in-hospital care and clinical outcomes. PhD thesis. *2017*.

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128. Jens Sundbøll: Depression, stroke, and dementia in patients with myocardial infarction — Studies of risk and prognosis. PhD thesis. *2017*.

129. Sigrún Alba Jóhannesdóttir Schmidt: Herpes zoster: Occurrence and risk factors. PhD thesis. *2017*.

130. Mette Glavind Bülow Pedersen: Ischemic Stroke in Adults with Congenital Heart Disease: a population-based cohort study. Research year report. *2017*.

131. Sidse Høyer: Male alcohol intake and couples' time to pregnancy - A prospective cohort study. Research year report. *2017*.

132. Cecilie Daugaard: Socioeconomic inequality in drug reimbursement during end-of-life care: A nationwide study. Research year report. *2018*.

133. Stine Bakkensen Bruun: Selective Serotonin Reuptake Inhibitor Use and Mortality, Postoperative Complications, and Quality of Care in Hip Fracture Patients - A population-based cohort study. Research year report. *2018*.

134. Maria Møller Pedersen: Prognostic role of neutrophil-lymphocyte ratio in localized and metastatic renal cell carcinoma: A population-based cohort study. Research year report. *2018*.