# Breast cancer and comorbidity: Risk and prognosis

PhD dissertation

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**This dissertation is based on the following papers, which are referred to in the text by their Roman numerals.**

**Paper I**

Hospital recorded morbidity and breast cancer incidence: a nationwide population-based case-control study.

Ording AG, Garne JP, Nyström PM, Cronin-Fenton D, Tarp M, Sørensen HT, Lash TL.

PLoS One. 2012;7(10).

**Paper II**

Comorbid diseases interact with breast cancer to affect mortality in the first year after diagnosis – a Danish nationwide matched cohort study.

Ording AG, Garne JP, Nyström PM, Frøslev T, Sørensen HT, Lash TL.

PLoS One. 2013;9;8(10).

**Paper III**

New disease and long-term mortality after breast cancer diagnosis: A 14 year follow-up of five year breast cancer survivors.

Ording AG, Garne JP, Nyström PM, Cronin-Fenton D, Frøslev T, Silliman RA, Sørensen HT, Boffetta P, Lash TL.

Submitted.

**Paper IV**

Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs.

Ording AG, Sørensen HT.

Clin Epidemiol. 2013 Jul 1;5:199-203.

**List of abbreviations**

| | |
|---|---|
| BC | Breast cancer |
| ER | Estrogen receptor |
| HRT | Hormone replacement therapy |
| CCI | Charlson Comorbidity Index |
| RR | Relative risk |
| IC | Interaction contrast |
| CI | Confidence interval |
| OR | Odds ratio |
| HR | Hazard ratio |
| ICD | International Classification of Disease |
| CPR | Central Personal Registration |
| CRS | Civil Registration System |
| DCR | Danish Cancer Registry |
| DNRP | Danish National Registry of Patients |
| DPR | Danish Pathology Registry |
| EB | Empirical-Bayes |
| MR | Mortality rate |
| MRR | Mortality rate ratio |
| PY | Person years |

## Content

# 1 Structure

This dissertation is about multimorbidity and female breast cancer. It builds on three research studies and a commentary. The studies are presented in detail whereas the commentary is incorporated into the text throughout the dissertation, mainly in the background and discussion.

The dissertation consists of eleven chapters. The background focused on brief description of breast cancer risk, development, and prognosis, followed by brief clarifications of the terminological confusion regarding the concepts of multimorbidity and interaction, and ends with an approach to the literature review and a description of the existing literature.

The next chapters present the studies in detail, including the aims, methods, and results. The discussion covers the main conclusions of the studies, followed by a discussion of the results in relation to the existing literature, and a thorough discussion of the methodology.

The last chapters describe the future perspectives followed by English and Danish summaries, references and appendixes.

## 2 Background

Breast cancer (BC) is the most common cancer among women in the developed world,[1] and incidence rates are increasing in traditionally low-risk, developing countries.[2] In 2008, 1.4 million incident cases of BC were estimated to occur globally.[1] The BC burden is projected to double by 2030.[2,3] Concurrently, mortality after BC has been stable or decreasing in many developed countries during the last decades.[4] Many BC patients are burdened with other medical conditions at diagnosis.[5-9]

The proportion of the global population aged 60 years or older is expected to increase from 10% in 2000 to 21% in 2050.[10] The prevalence of multimorbidity, i.e., the co-existence of at least two medical conditions, is higher than 80% among adults older than 85 years, and 48% of the total global disease burden is attributable to chronic conditions.[10,11] The result is considerable global health care costs, reduced quality of life, disability, and premature deaths. A tremendous challenge for global health care, therefore, is managing patients with multimorbidity.

The aim of this dissertation was to examine whether multimorbidity is associated with BC risk and prognosis and further, to examine the terminological confusion regarding the multimorbidity concept.

Before going into detail with the studies, an introduction to BC risk, development and prognosis is warranted.

### 2.1 Breast cancer risk

Established BC risk factors include sex and age, family history, and genetic predisposition.[12,13] Many reproductive patterns, such as nulliparity, age at first birth, early menarche, late menopause, postmenopausal obesity, and alcohol consumption are among established BC risk factors,[12,14] possibly mediated through elevated endogenous sex hormone levels.

Table 1 presents established risk factors for BC and the magnitude of increased relative risk adapted from "Breast Cancer Facts & Figures 2013-2014. Atlanta: American Cancer Society, Inc. 2013."[15]

**Table 1. Established risk factors for breast cancer and the magnitude of increased relative risk.**[15]

| Relative risk | Factor |
|---|---|
| >4.0 | • Age (65+ vs. <65 years, although risk increases across all ages until age 80)<br>• Biopsy-confirmed atypical hyperplasia<br>• Certain inherited genetic mutations for breast cancer (BRCA1 and/or BRCA2)<br>• Lobular carcinoma in situ<br>• Mammographically dense breasts<br>• Personal history of early onset (<40 years) breast cancer<br>• Two or more first-degree relatives with breast cancer diagnosed at an early age |
| 2.1–4.0 | • Personal history of breast cancer (40+ years)<br>• High endogenous estrogen or testosterone levels (postmenopausal)<br>• High-dose radiation to chest<br>• One first-degree relative with breast cancer |
| 1.1–2.0 | • Alcohol consumption<br>• Ashkenazi (Eastern Europe) Jewish heritage<br>• Diethylstilbestrol (DES) exposure<br>• Early menarche (<12 years)<br>• Height (tall)<br>• High socioeconomic status<br>• Late age at first full-term pregnancy (>30 years)<br>• Late menopause (>55 years)<br>• Never breastfed a child<br>• No full-term pregnancies<br>• Obesity (postmenopausal)/adult weight gain<br>• Personal history of endometrium, ovary or colon cancer<br>• Recent and long-term use of postmenopausal hormone therapy containing estrogen and progestin<br>• Recent oral contraceptive use |

### 2.2 Breast cancer development

A detailed description of BC development is beyond the scope of this dissertation. However, it is important to emphasize that BC is not a single disease, but rather is a heterogeneous group of tumors presenting with varying characteristics and associated treatment options and prognosis.[16] In developed countries, approximately 75% of all breast tumors are estrogen-receptor (ER) positive,[17] and estrogen is the main regulator of cell proliferation in normal breast tissue through the ER. The ER positive tumors are largely suggested to be linked to cumulative estrogen exposure and associated sex hormonal-related risk factors,[18] and often respond to anti-hormonal therapy, for example, tamoxifen, which blocks the ER.[19]

Multimorbidity may affect BC development. Obesity, for example, is a shared risk factor for diabetes and BC. In addition, diabetic patients have hyperinsulinemia, which has been associated with BC incidence, and may impact cancer morphology and proliferation.[20] Several

pharmacological agents have been associated with impaired cancer development, for example aspirin, other non-steroidal anti-inflammatory drugs, metformin, and bisphosphonates.[21-24] On the other hand, use of postmenopausal hormone replacement therapy (HRT) with combined estrogen and progestin increases BC risk, in particular when therapy is initiated close to menopause.[25] Many conditions and their pharmacological treatment may therefore impact BC development.

### 2.3 Breast cancer prognosis

The incidence of BC has increased in Denmark, but has been rather constant since the beginning of the 21st century, with about 4,000 new cases annually.[26] Concurrently, the five-year survival among BC patients from Denmark increased from 65% in 1977–1981 to 81% among patients diagnosed 2002–2006.[27] Similar trends have been observed in many other Westernized countries,[4] thus leading to an increasing number of BC survivors.

Prognostic factors associated with survival and recurrence includes BC stage, in particular axillary lymph node involvement, but also tumor grade, histological type, and hormonal receptor status.[28] Age is inversely associated with BC survival, most likely because younger women tend to present with aggressive tumors at diagnosis.[29] Some prognostic factors relate to socioeconomic status, e.g., by determining stage at diagnosis and adherence to treatment.[30,31] The role of ethnicity as a prognostic factor has been extensively studied in the United States, and African-American women tend to have poorer survival than Caucasian women, but it remains unknown whether the disparity relates to socioeconomic status or to underlying differences in tumor biology.[32] The presence of coexisting chronic disease at BC diagnosis is strongly associated with prognosis,[33] which will be described in detail below.

In a global perspective, many prognostic determinants may relate to the resources of health care systems, e.g., access to screening, diagnosis, and treatment facilities.[34] But also factors related to diagnostic work up, such as the accuracy and utility of diagnostic tests, efficacy and toxicity of treatments, clinical performance, and patient characteristics, such as age and compliance, are associated with prognosis.[35]

### 2.4 Multimorbidity – defining the burden of disease

Coexisting diseases at BC diagnosis are highly correlated with prognosis.[5,9] This burden of disease in a patient can be defined in several ways.[36] The term “multimorbidity” is often used to describe

the coexistence of at least two medical conditions without referring to a well-defined index disease under study. Multimorbidity is often measured by the burden of comorbidity at the time of diagnosis of an index disease, sometimes including predefined medical conditions or unlimited numbers and types of medical conditions, chronic conditions, or both acute and chronic conditions, physical diseases alone or physical and psychiatric conditions.[36-41]

In this dissertation, the term "multimorbidity" is operationally separated and defined as:

- *Index disease* – The well-defined disease under study (BC in this dissertation)
- *Multimorbidity* – Any existence of two or more chronic or long-term conditions
- *Comorbidity* – Medical conditions that exist at the time of diagnosis of the "index disease"
- *Complications* – Adverse events occurring after diagnosis of the index disease
- *New disease* – New medical conditions diagnosed during long-term follow-up, disregarding a potential etiologic relationship with the index disease

**2.5 The Charlson Comorbidity Index**

Many comorbidity indices have been developed to measure the comorbidity burden in populations under study,[37,39-41] and to account for case-mix (i.e., the mix of patient types treated at a hospital or department). The Charlson Comorbidity Index (CCI) is the main focus of this dissertation, and other indices will not be described.

The CCI is often used in etiologic studies when controlling for comorbidity as a confounder, or in studies as a single, combined exposure comprising several diseases. The index was originally designed for data collected from medical records,[39] but has been adapted to studies that build on data from administrative databases.[37,42]

The CCI was developed in the United States in 1987 in a cohort of 559 medical patients by extracting information about demographic- and comorbid diseases from medical records prior to hospital admission.[39] An index of diseases was created by classifying frequent comorbid diseases according to severity, and serious diseases according to presence. A relative risk (RR) of death was calculated for each disease and RRs of less than 1.2 were not included in the index. The remaining list consisted of 19 disease categories. If the relative risk was between 1.2 and 1.5, diseases were assigned a weight of 1; relative risks between ≥1.5 and <2.5 were assigned a weight of 2; relative risks between ≥2.5 and <3.5 were assigned a weight of 3; and relative risks of 6 and more were

assigned a weight of 6. There were no RRs between 3.5 and <6. The index for each patient was calculated by summarizing the weights for the 19 disease categories. The index was then validated in a cohort of 685 BC patients, and comorbidity-related 10-year mortality increased with increasing comorbidity score.[39]

The weights of the CCI have recently been updated to reflect medical advances, and frequent use of administrative databases as a source of data on comorbidities.[43] The updating of the index was conducted with a population of hospitalized patients in Canada in 2004. Conditions included in the CCI were extracted up to one year prior to the index admission. Cox regression models were built to re-evaluate the relationship between the comorbid diseases and in-hospital mortality. The updated weights were validated with discharge data from six countries on national or regional data.

Table 2 demonstrates the index weights of the original and the updated CCI. [39,43]

**Table 2. Charlson Comorbidity Index diseases and weights**

| Charlson comorbidity index disease category | Charlson weight[39] | Updated weight[43] |
|---|---|---|
| Myocardial infarction | 1 | 0 |
| Congestive heart failure | 1 | 2 |
| Peripheral vascular disease | 1 | 0 |
| Cerebrovascular disease | 1 | 0 |
| Dementia | 1 | 2 |
| Chronic pulmonary disease | 1 | 1 |
| Connective tissue disease | 1 | 1 |
| Ulcer disease | 1 | 0 |
| Mild liver disease | 1 | 2 |
| Diabetes type 1 and 2 | 1 | 0 |
| Hemiplegia | 2 | 2 |
| Moderate to severe renal disease | 2 | 1 |
| Diabetes with end organ damage, type 1 and 2 | 2 | 1 |
| Any tumor | 2 | 2 |
| Leukemia | 2 | 2 |
| Lymphoma | 2 | 2 |
| Moderate to severe liver disease | 3 | 4 |
| Metastatic solid tumor | 6 | 6 |
| AIDS | 6 | 4 |

In the literature, the burden of comorbidity based on the CCI among BC patients varies, due to varying BC populations, data source of comorbidity, and data collection methods. Not all studies explicitly report on the time period of data collection in relation to the diagnosis of BC[6,8,9,44-46] and whether both in- and outpatient hospital diagnoses are used,[45,47] and sometimes cancer diseases are excluded from the index,[44] or other diseases are added.[8]

A cohort study from the US published in 2010 showed that 23% of patients between 85–89 years and 11% of patients between 67–69 years at BC diagnosis had a high level of comorbidity.[45] Similarly, a cohort study from 2005 based on Dutch BC patients showed that 9% of patients younger than 50 years of age had at least one comorbid condition compared with 56% of patients 80 years or older.[8] Comorbidity, therefore is highly prevalent among older BC patients.

**2.6 Interaction**

The concepts "statistical interaction", "effect-measure modification", and "biological interaction" are often used interchangeably in the literature.[48] Frequently used terms include "heterogeneity of effects", "synergism", or "interdependence". To clarify the terminology, it has been suggested to use the term "descriptive interaction" to define effect-measure modification and the term "causal interaction" to define biological interaction.[49]

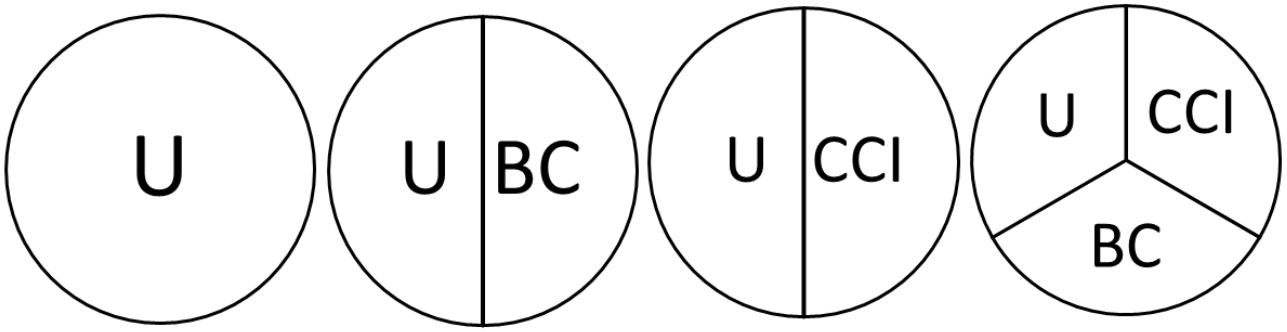
In statistics, "interaction" refers to the departure of the observed data from an underlying model, and is dependent on the underlying model scale, e.g., whether an additive scale in the case of linear regression or a multiplicative scale in the case of logistic or Cox regression.[50] For example, when the observed data deviate from an assumed additive model, an interaction term can be included in the model to explain the interaction. The analogue in epidemiology, "effect-measure modification" refers to the same situation, i.e., an observed effect varies by the level of another risk factor for the outcome. Effect-measure modification may be present on one scale, but not on the other.[50]

"Biological interaction", on the other hand, is present when the causal or preventive action of one or more factors is causally dependent on the presence of another factor in order for it to assert an effect.[50] Evidence of biological interaction is implied by a departure from additivity. Therefore, some suggest abandoning the term "biological interaction" as both statistical and biological interaction is examined using a statistical model,[51] while others advocate using the term "sufficient cause interaction" when the interaction only has an effect in the presence of both factors.[52] Despite these controversies, departure from additivity may have public health implications, because many clinical decisions are based on additivity of effect.

In this dissertation, we studied whether BC and comorbidity interact biologically to increase the risk of death. This biological interaction can be demonstrated using the sufficient cause model

illustrated in Figure 1, adapted and modified from Rothman KJ, Measuring Interaction, Epidemiology: An introduction, Oxford, 2002, p. 173.[50] In this model, there are four causal mechanisms leading to the outcome. First, there is a "background" sufficient cause of death that does not involve either BC or comorbidity; a mechanism constituted by BC alone with other component causes; a mechanism constituted by comorbidity alone with other component causes, and last, a mechanism that is dependent on the presence of both BC and comorbidity. The biological interaction between BC and comorbidity can be calculated with the interaction contrast (IC), as a measure of the outcome in patients with both risk factors, i.e., BC and comorbidity, which cannot be explained by the individual effects of BC alone or comorbidity alone.[53]

**Figure 1. The sufficient cause model illustrating mechanisms of biological interaction involving breast cancer (BC), comorbidity (CCI), and unknown component causes (U).**



### 2.7 Literature search strategy

The search strategy aimed at identifying English language literature regarding BC risk and prognosis on the following relationships:

- Preceding morbidity, associated risk factors and BC risk (Study I)
- Interaction between BC and comorbid conditions on subsequent risk of death (Study II)
- New morbidity acquired after BC diagnosis and subsequent risk of death (Study III)

The electronic database PubMed was searched for studies published up to and including December 2013.

The following terms were searched in combinations:
"Breast Neoplasms"[Mesh], “breast cancer”(free text), "Incidence"[Mesh], "Comorbidity"[Mesh],” multimorbidity”(free text), "Chronic Disease"[Mesh], “Disease”[Mesh], “conditions”(free text), “incident diseases”(free text), “Charlson Comorbidity Index”(free text), "Risk Factors"[Mesh], “Aged”[Mesh], "Age Distribution"[Mesh], “Survivors”[Mesh], “Survival”[Mesh], “Mortality”[Mesh], “general population”(free text).

Other sources of literature were found on web pages of official health authorities and health care organizations and in the reference lists of retrieved literature.

There was an overwhelming amount of literature on several associations between conditions included in the CCI, their medical treatment, shared risk factors, genetics, etc., and risk of BC, as well as comorbidity and BC prognosis. The main literature, therefore, was limited to the CCI diseases as well as recent meta-analyses and reviews.

### 2.8 Existing literature on preceding morbidity breast cancer risk

Whether chronic diseases and the total burden of morbidity are associated with BC occurrence may provide knowledge for understanding the etiology of BC and could enable identification of women at high risk for BC.

No study has examined the association between the multimorbidity burden measured by the CCI score and BC occurrence.

Five case-control studies showed increased risks of BC associated with several conditions, such as obesity, cholelithiasis, benign breast disease and previous breast biopsies, fertility problems and null pregnancies, recurrent amenorrhea, thyroid disorders, hypertension, ovarian diseases, and diabetes.[54-58] Whether diabetes mellitus and its pharmacological treatment affects subsequent risk of BC has been the topic of extensive discussion.[59,60]

A large meta-analysis including 40 research papers has shown elevated risk of BC in diabetic women overall compared with women without diabetes (summary RR = 1.27; 95% confidence interval (CI): 1.16, 1.39), which was lower in studies that adjusted for body mass index (summary RR = 1.16; 95%CI: 1.08, 1.24). Associations with BC were stronger among postmenopausal women (summary RR = 1.15; 95%CI: 1.07, 1.24) than among premenopausal women (summary HR = 0.86; 95%CI: 0.66, 1.12), and among women with type II diabetes (summary RR = 1.16; 95%CI: 1.04, 1.29) than among women with type I diabetes (summary RR = 1.0; 95%CI: 0.74, 1.35).[61] On the other hand, the diabetic treatment, metformin, may decrease BC risk compared with other anti-diabetic medications. A meta-analysis based on seven studies reported a summary odds ratio (OR) of 0.83 (95%CI; 0.71, 0.97), associating metformin use with BC risk in women with diabetes.[62]

Though evidence is sparse or still inconclusive, other studies suggest a number of BC mediators, for example, inflammation,[63] altered immune function,[64] viral infections,[65] and other gynecological cancers.[66] In addition, many chronic diseases are associated with pharmacological treatment,[67] which may impact BC development. Regular aspirin intake may decrease BC risk in patients with rheumatoid arthritis,[21] whereas other treatments for rheumatoid arthritis have been linked to the development of various solid cancers; yet, evidence for an association with BC is not convincing.[68]

In addition, many associations may relate to shared risk factors for some diseases and BC rather than the actual pharmacological treatment.

### 2.8.1 Limitations of the existing literature

Previous reports have identified diseases associated with BC through complex mechanisms; yet no publication has exhaustively investigated a comprehensive set of chronic diseases and their associations with BC risk, but such endeavor could identify novel associations for BC risk.

## 2.9 Existing literature on comorbidity and prognosis

The link between BC and chronic diseases on subsequent risk of death is important for understanding the clinical course of BC and for identification of patients in need of specialist care and follow-up.

Numerous studies have investigated the impact of comorbid conditions included in the CCI and BC prognosis. Much of the literature has recently been summarized in a large literature review and a Ph.D-dissertation.[33,69] Many publications focus on BC prognosis with respect to recurrence, survival, all-cause and disease-specific mortality, or completion of BC therapy. Cohort studies have shown increased mortality among BC patients with comorbidity compared with those without comorbidity. For example, in a Danish cohort study of 62,591 BC patients with early stage cancer, the five-year overall survival of patients diagnosed 2000–2004 was 44% among patients with a CCI score of ≥3, compared with 82% among patients without comorbidity, corresponding to an adjusted hazard ratio (HR) for all-cause mortality of 2.21 (95%CI: 2.08, 2.35).[9] Similar results are reported in other settings. In a study from the United States including 64,034 BC patients older than 65 years of age diagnosed 1992–2000,[5] the overall five-year survival decreased from 77% for patients without comorbidity to 32% among patients with a CCI score of ≥3, translating into an adjusted HR of 3.19 (95%CI: 3.06, 3.32). In addition, all individual conditions included in the CCI were associated with overall mortality.[5]

Many investigators have explicitly focused on diabetes and mortality in BC patients. Not all studies reported an association, but in a recent meta-analysis of studies published through June 2009, the summary HR for all-cause mortality in diabetic patients compared with non-diabetic patients was 1.49 (95%CI: 1.35, 1.65).[70] The association may relate to shared underlying risk or prognostic

factors, for example if diabetes masks the symptoms of BC, increases treatment toxicity, or precludes some BC treatments.[70]

Other studies focused on cause of death among BC patients. Two large, population-based cohort studies from the United States and Australia, compared cause-specific death rates in BC patients to those in the general population. The mortality due to causes other than BC was similar among BC patients and women from the general population.[71,72] On the other hand, a Swedish study demonstrated increased mortality associated with diseases of the heart (HR = 1.29; 95%CI: 1.22, 1.37), pulmonary circulation (pulmonary embolism and other diseases of pulmonary vessels, HR = 1.51; 95%CI: 1.36, 1.68), and gastric diseases (HR = 1.68; 95%CI: 1.62, 1.74) as an underlying cause or in combinations of multiple causes of death.[73]

To our knowledge, only one study has focused explicitly on statistical interaction between BC and the CCI score on mortality after BC,[74] measured with Rothman's synergy index.[75] This study provided evidence of statistical interaction between BC and the CCI score at the time of BC diagnosis. The authors observed a 17% excess mortality rate in BC patients with comorbidity,[74] given an expectation of additive effects, which suggests the presence of biological interaction.

### 2.9.1 Limitations of the existing literature

Many studies have examined the impact of overall comorbidity on BC mortality and survival,[33,69] and fewer studies have focused on the individual 19 CCI diseases included in the index, but none of them have compared the mortality of BC patients with the general population,[5,8,76] and just one study explicitly focused on statistical interaction between BC and comorbid conditions in hospitalized patients.[74] No publication has to our knowledge examined mortality in BC patients with different levels of comorbidity and compared it with that of women from the general population with the same comorbid conditions.

## 2.10 Existing literature on long-term mortality in BC patients with new disease

Long-term prognosis after BC may be affected by both comorbidity and new morbidity diagnosed during survivorship.

Medical conditions may be detected shortly after BC diagnosis through extensive diagnostic work-up or as complications to cancer treatment.[77] Previous research suggests that BC patients acquire

many medical conditions during the first years following their BC diagnosis.[78,79]

BC treatments have been associated with the occurrence of other medical conditions. Infections and bleeding are common complications to surgery and to chemotherapy, and cardiac toxicities are linked to anticancer agents, e.g., chemotherapy, targeted therapy, and radiotherapy.[80-82] Chemotherapies are also associated with other serious complications, such as venous thromboembolism, renal insufficiency, and new primary cancers.[83-85] BC patients may have at least a doubled risk of a second primary BC, and a 25% increase in risk for second primary cancers other than of the breast, compared to the general population.[86] The high risk of a new primary cancer may in part relate to the treatment of BC,[85] but may also be associated with other factors, for example age and menopausal status.[87,88] Among five-year BC survivors, the risk of new primary cancers was slightly increased (HR = 1.17; 95%CI: 0.94, 1.47) in a study of older BC patients compared with an age and site matched cohort from the general population.[89]

Incidence of other conditions may also be different among BC survivors than among women from the general population. One study showed that BC survivors have a modest increase in incidence of diabetes 10 years after their BC diagnosis compared with women from the general population (HR = 1.21; 95%CI: 1.09, 1.35),[90] possibly mediated by shared risk factors for BC and diabetes. In contrast, the risk of stroke was reduced in a cohort of 10-year Dutch BC survivors compared with women from the general population (HR = 0.8; 95%CI: 0.6, 0.9). Proposed explanations for this finding were late menopause associated with increased BC risk, but decreased risk of vascular diseases. But also changes toward a healthier lifestyle after BC diagnosis, and early detection and treatment of other risk factors for vascular diseases among BC survivors compared to the general population.[91]

Many prognostic factors for long-term survival after BC are similar to those of short-term survival, for example, stage,[92] but less is known about the impact of medical conditions diagnosed after BC. In one publication, the authors calculated the CCI score with both prevalent and incident diseases. A 40% increase in mortality risk was reported for each increase in the CCI during 85 months of follow-up in 689 women from the United States with early stage BC diagnosed between 1996 and 1999 (HR = 1.4; 95%CI: 1.2, 1.6).[79]

### 2.10.1 Limitations of the existing literature

Studies have described patterns of incident medical conditions in BC patients, but none has reported the mortality risk for long-term five-years survivors with new CCI diseases diagnosed during survivorship and compared it with women free of BC from the general population.

## 3 Specific aims

We conducted three studies with the following aims and hypotheses:

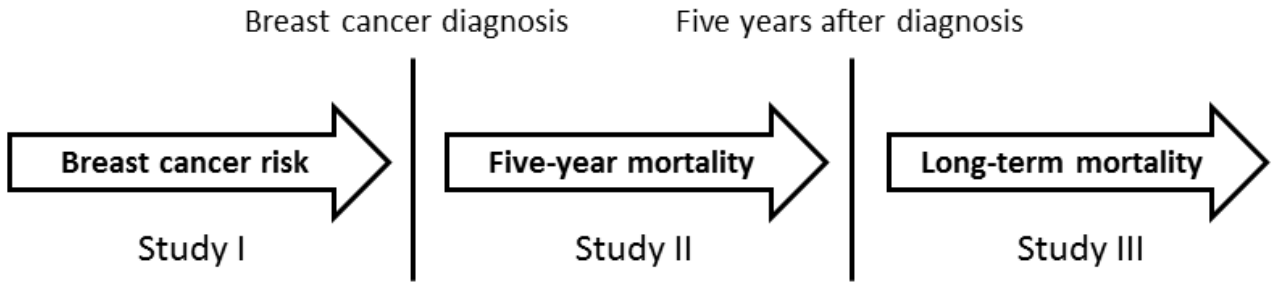
**Study I:** The aim was to study the association between the CCI score, individual CCI diseases (i.e., the 19 disease categories included in the CCI) and a subsequent diagnosis of BC. As a hypothesis-screening analysis, we categorized all International Classification of Disease (ICD) codes into 202 categories and examined their association with BC occurrence, using a statistical method to reduce emphasis on overestimated and unstable estimates. We hypothesized that increasing CCI score was associated with increasing risk of BC.

**Study II:** The aim was to study the biological interaction between BC and comorbidity measured with the CCI and the CCI diseases on the excess or deficit overall mortality rate five years after BC diagnosis. We hypothesized that the interaction may be different in the first year after BC diagnosis than in subsequent years.

**Study III:** The aim was to study whether individual CCI diseases diagnosed after the date of five-year survivorship after BC diagnosis affect mortality rates differently than in a comparison cohort of women from the general population. We hypothesized that five-year BC survivors diagnosed with new disease had a different risk of mortality than women without a history of BC.

The timing of studies I to III in relation to the BC diagnosis is illustrated in Figure 2.

**Figure 2. Timing of studies I to III in relation to the time of breast cancer diagnosis.**



# 4 Methods

## 4.1 Setting

The studies were nested within the entire female Danish population of approximately 2.8 million women.[93] There is virtually only one health care system caring for BC patients and chronic diseases in Denmark. Access to health care is free of charge for the entire population of legal residents through tax funding. All Danes are assigned a unique civil personal registration (CPR) number upon birth or immigration since 1968.[94] Information about the Danish population is routinely collected by the government and recorded in several administrative and medical databases. The databases can be unambiguously inked with the CPR-number to track and retrieve information on many aspects of daily life, including characteristics of health and vital status for the individual.

## 4.2 Data sources

Data for the studies were collected from population-based administrative and medical registries. The data were linked using the CPR-number.

### 4.2.1 The Civil Registration System

The Civil Registration System (CRS) tracks each legal resident through the CPR number and records contacts with official authorities. The CRS contains information about date of birth, residence, marital and vital status for all Danish residents since 1968. The information is updated on a daily basis.[95]

### 4.2.2 The Danish Cancer Registry

The Danish Cancer Registry (DCR) has recorded national cancer incidence since 1943. Reporting of all cancers was made mandatory from 1987.[96,97] The diagnosis, tumor and patient characteristics are recorded.

One study examined the completeness of BC diagnosed between 1983 and 1989 from the county of Aarhus and recorded in the DCR compared to medical records. The study included 1,749 BC patients, and the sensitivity of the BC diagnosis in the DCR was 100%.[98]

### 4.2.3 The National Registry of Patients

The Danish National Registry of Patients (DNRP) contains all non-psychiatric hospitalizations since 1977 and outpatient contacts since 1995. In 2003, data from private hospitals were added as well.

The DNRP records the CPR number and the date of each hospital visit, duration of hospital stay, site of stay, procedures, and discharge diagnoses entered by the physician.[99,100]

### 4.2.4 The Danish Pathology Registry

The Danish Pathology Registry (DPR) contains information on all diagnostic procedures conducted by all pathology departments in Denmark since 1997. Data on patient and pathology specimen characteristics are recorded in the registry.[101]

## 4.3 Study designs

Study I was designed as a case-control study due to the 202 exposure categories of the hypothesis-screening analysis (see below), while studies II and III were designed as matched cohort studies.

## 4.4 Study populations

For all three studies, we identified women aged 45 to 85 years at diagnosis of first incident BC between 1 January 1994 and 31 December 2008 registered in the DCR.

In study I we used the CRS to risk-set sample 10 female control women free of BC from the source population, matched to each case by year of birth and calendar year of BC diagnosis. The index date was defined as the date of BC for the cases and the corresponding matched controls.

In study II we used the CRS to select up to five women from the general population, matched to each BC patient on age and history of the specific comorbidities defined below to serve as a comparison cohort. The women in the comparison cohort had to be free of BC on the date of BC diagnosis for the corresponding case. The index date was defined as the BC diagnosis date for BC patients and also for the women matched to them in the comparison cohort.

In study III, we excluded all women who survived less than five years following the BC diagnosis date in order to study long-term mortality. Furthermore, to include at least one year of follow-up for each BC patient, we excluded all BC patients diagnosed in 2008. We accessed the CRS, which contains data on vital status and demographic information using the CPR, in order to select five women from the general population matched to each member of the BC survivor cohort on age and date of five-year BC survivorship.[94] The index date was defined as five years following the BC diagnosis date for each woman in the BC cohort and the corresponding date for the matched women in the comparison cohort. Women in the comparison cohort could not have a BC diagnosis

during the five years before the index date. If a woman in the comparison cohort developed BC after the index date, she was eligible for inclusion in the BC survivor cohort.

**4.5 Main exposures**

The exposure in study I was preceding morbidity defined with the CCI score and disease categories. Based on the DNRP, we identified all history of comorbidity 10 years preceding the index date. As a hypothesis-screening analysis, based on the 8$^{th}$ and 10$^{th}$ revision of the ICD World Health Organization morbidity tables,[102,103] we grouped all ICD-codes into 202 morbidity categories similar to categories previously used by our group.[104] We excluded from the analyses ICD-codes reflecting external causes of morbidity (such as accidents) recorded during routine hospital outpatient visits and diagnoses only affecting men.

In study II, the exposure was BC and comorbidity. We therefore included all available comorbidity history back to 1977. The CCI score was considered as well as the individual CCI diseases.

In study III, diagnosis of new diseases acquired after five-year survivorship of BC was the main exposure of interest. We therefore defined new CCI diseases as the first discharge diagnosis of any CCI disease included in the CCI after the index date (i.e., the incidence period) for the BC survivor and comparison cohorts, regardless of a potential etiologic relationship with BC. All diagnoses prevalent before the index date were not included in the incident follow-up period, but were considered as comorbidities (in the prevalence period). New diseases were furthermore dichotomized into “any disease” (i.e. any CCI disease diagnosed during follow-up) and “no disease”.

For all studies, we excluded from the CCI diagnoses of BC and non-malignant melanoma skin cancer. The ICD-codes are presented in Appendix 1.

Comorbidity is not necessarily etiologically different from BC (i.e., the index disease under study). For example, alcohol consumption is associated with both BC and liver disease. Therefore, we pragmatically defined the index date as the date that separated comorbidities from complications and new disease, regardless of potential etiological relations between the diseases. CCI diseases

were defined as present based on any recorded in- or outpatient diagnosis. For studies II and III, we included all available history of comorbidity from the DNRP,[100] but in study I, we only included preceding morbidity history from three to 10 years prior to the index date to allow for a plausible latency period of the medical condition to be associated with BC. However, including all diagnoses recorded in the DNRP preceding the index date, with or without a three-year latency period, did not change the results notably.

### 4.6 Outcomes

In study I, the outcome was a diagnosis of BC recorded in the DCR.

The outcomes of studies II and III were time to all-cause death. Because members of the comparison cohort had no history of BC, we did not ascertain cause-specific mortality.

### 4.7 Follow-up

In study II we followed the cohorts from the index date (date of BC diagnosis) until death, emigration, five years of follow-up, or 31 December 2011, whichever came first.

In study III we followed the cohorts from the index date (date of five-year survivorship of the BC cohort) until death, emigration, or 31 December 2012, whichever came first.

### 4.8 Statistical methods

We calculated frequencies of BC patients, controls, and women in the comparison cohort by age at the index date, index year, CCI score, and each of the 19 diseases included in the CCI. Contingency tables were constructed for each of the morbidity categories included in study I. In study III, we also described the BC and comparison cohort according to frequency of new CCI diseases acquired during follow-up.

#### 4.8.1 Kaplan-Meier method (studies II and III)

We used the Kaplan-Meier method to compute the curves and the cumulative mortality estimates in the BC and comparison cohorts during follow-up.

#### 4.8.2 Logistic regression (study I)

Conditional logistic regression models were used to estimate ORs and 95%CIs associating BC occurrence with original and updated CCI scores, individual CCI diseases, and each morbidity category within the risk-set matched strata. For the BC cases, we used logistic regression models

to calculate the OR for distant stage vs. local/regional stage BC at diagnosis, excluding patients with missing stage. CCI score in five categories and age as a continuous variable were included in the models as explanatory variables.

### 4.8.3 Empirical-Bayes shrinkage (study I)

The ICD includes codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases.[105] The morbidity categories in the hypothesis-screening analysis, therefore, were not independent. Due to this large number of estimates arising from the same population, a potential problem with overestimated and unstable estimates were introduced. The empirical-Bayes (EB) method shrinks the estimates toward the overall mean, taking into account the standard error of the original estimates. Estimates far from the null and imprecisely measured estimates shrink the most, thereby de-emphasizing the estimates with poor precision but strong magnitude. To further stabilize the EB adjusted estimates, we excluded morbidity categories with fewer than five exposed cases.[106] The assumption behind the EB shrinkage was satisfied.

### 4.8.4 Mortality rates and standardization (study II)

Within categories of baseline variables, we calculated crude mortality rates (MRs) by dividing the number of deaths by the total follow-up time for the BC and matched cohort and computed associated 95%CIs. We examined two periods of mortality: From the index date to one year of follow-up, and from more than one to five years of follow-up. The matching was dissolved when stratifying the follow-up period, because the age distribution differed by comorbidity strata in one-year survivors. We therefore used direct standardization of the mortality rates using age weights from the BC cohort on the index date as the standard.

### 4.8.5 Cox regression (studies II and III)

We used proportional Cox regression models to compute hazard ratios as a measure of the mortality rate ratios (MRRs) and 95%CIs for mortality in study II, comparing women within each stratum of the CCI score and individual diseases with women from the comparison cohort with the same comorbidity. For the individual diseases, we adjusted for presence of other CCI diseases. For the >1–5 year MRRs, we also adjusted the estimates for age group at diagnosis and year of index

date in three categories (1994–1999, 2000–2004, and 2005–2008).
The proportionality assumption as assessed with log-log plots was appropriate.

In study III, women were diagnosed with new diseases at varying rates during follow-up, therefore, we used time-dependent disease exposures in Cox regression to compare women with new disease to women who remained disease-free. The models adjusted for age group and CCI score at index date. As a sensitivity analysis, we excluded all women with a new diagnosis of metastatic solid tumor during follow-up (i.e., in the incidence period).

### 4.8.6 Interaction contrasts (study II)

We calculated the interaction contrast (IC) as a measure of the biological interaction between BC and comorbidity to estimate the mortality rates in patients with BC and comorbidity that cannot be explained by the individual effects of the diseases.[53]
The IC is calculated as the difference between the rate differences (MR in the BC cohort minus the MR in the comparison cohort) in the strata with and without comorbidity, using the comparison cohort members without comorbidity as the reference category.[53] An example of the calculation of the IC in BC patients with a CCI score of ≥3 is shown below:

$$IC = (MR_{BC\ \&\ CCI\geq 3} - MR_{BC\ \&\ CCI0}) - (MR_{Comparison\ \&\ CCI\geq 3} - MR_{Comparison\ \&\ CCI0})$$

### 4.8.7 Stratified analysis

All three studies included stratified analyses to evaluate whether the association between the exposure and outcome varied in subgroups, i.e., presence of effect-measure modification. We used the DCR to collect information on BC stage. The ER status was ascertained with the DPR. In all three studies, we stratified on BC stage, and computed stage-specific HR estimated with Cox regression.

All analyses were conducted with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA), and Stata 11 (StataCorp, College Station, TX, USA).
The studies were approved by the Danish Data Protection Agency (record number: 2006-41-6387 and 2011-41-6174).

# 5 Results

## 5.1 Study I: Breast cancer risk

### 5.1.1 Characteristics and breast cancer risk

The study included 46,324 BC cases and 463,240 population controls. The majority of BC patients were between 51 and 70 years of age at diagnosis, while the frequency of patients increased slightly each year; 5.7% of the BC cases were diagnosed in 1994 in contrast to 8.4% in 2008.

For both the original and updated CCI, increasing CCI score was associated with slightly increased risk of BC. Among the individual CCI diseases, moderate to severe liver disease (OR = 1.86; 95%CI: 1.32, 2.62), metastatic solid tumors (OR = 1.49; 95% CI: 1.17, 1.89), and moderate to severe renal disease (OR = 1.25; 95%CI: 1.06, 1.48) were associated with estimates of strongest magnitude for the risk of BC. Inversely associated estimates were observed for AIDS (OR = 0.50; 95%CI: 0.07, 3.73), leukemia (OR = 0.82; 95%CI: 0.53, 1.27), connective tissue disease (OR = 0.87; 95%CI: 0.80, 0.94), dementia (OR = 0.88; 95%CI: 0.71, 1.09), myocardial infarction (OR = 0.89; 95%CI: 0.81, 0.99), and ulcer disease (OR = 0.91: 95%CI: 0.83, 0.99). Results based on the original and updated CCI are shown in Table 3.

**Table 3. Original and updated Charlson Comorbidity Index (CCI) scores associated with breast cancer occurrence among cases and controls.**

| | Cases, Number (%) | Controls, Number (%) | Odds ratio (95%CI) |
|---|---|---|---|
| **Age group, years** | | | |
| 45-50 | 4,815 (10) | 48,494 (10) | |
| 51-60 | 13,273 (29) | 132,469 (29) | |
| 61-70 | 13,924 (30) | 139,025 (30) | |
| 71-80 | 10,020 (22) | 100,269 (22) | |
| 81-85 | 4,292(9.3) | 42,983 (9.3) | |
| **Original CCI score** | | | |
| 0 | 40,276 (87) | 403,983 (87) | Ref |
| 1 | 3,574 (7.9) | 36,999 (8.0) | 0.97 (0.94, 1.01) |
| 2 –3 | 2,228 (4.8) | 20,278 (4.4) | 1.10 (1.06, 1.16) |
| ≥4 | 246 (0.5) | 1,980 (0.4) | 1.25 (1.09, 1.43) |
| Any | 6,048 (13) | 59,257 (13) | 1.03 (1.00, 1.06) |
| **Updated CCI score** | | | |
| 0 | 42,423 (92) | 426,147(92) | Ref |
| 1 | 1,834 (4.0) | 19,071 (4.1) | 0.97 (0.92, 1.02) |
| 2–3 | 1,868 (4.0) | 16,597 (3.6) | 1.13 (1.08, 1.19) |
| ≥4 | 199 (0.4) | 1,425 (0.3) | 1.41 (1.21, 1.63) |
| Any | 3,901 (8.4) | 37,093 (8.0) | 1.06 (1.02, 1.10) |
| **Individual disease in the CCI** | | | |
| AIDS | 1 (0.0) | 20 (0.0) | 0.50 (0.07, 3.73) |
| Leukemia | 22 (0) | 267 (0.1) | 0.82 (0.53, 1.27) |
| Connective tissue disease | 641 (0.1) | 7,383 (1.5) | 0.87 (0.80, 0.94) |
| Dementia | 91 (0.02) | 1,039 (0.2) | 0.88 (0.71, 1.09) |
| Myocardial infarction | 432 (0.1) | 4,827 (1.0) | 0.89 (0.81, 0.99) |
| Ulcer disease | 525 (0.1) | 5,795 (1.1) | 0.91 (0.83, 0.99) |
| Peripheral vascular disease | 524 (0.1) | 5,207 (1.0) | 1.01 (0.92, 1.10) |
| Cerebrovascular disease | 1,098 (0.2) | 10,579 (2.1) | 1.04 (0.98, 1.10) |
| Chronic pulmonary disease | 1,260 (0.3) | 12,085 (2.4) | 1.04 (0.98, 1.11) |
| Diabetes with end organ damage | 270 (0.05) | 2,607 (0.5) | 1.04 (0.91, 1.18) |
| Lymphoma | 78 (0.02) | 727 (0.1) | 1.07 (0.85, 1.36) |
| Diabetes type I and II | 818 (0.2) | 7,468 (1.5) | 1.10 (1.02, 1.18) |
| Mild liver disease | 164 (0.03) | 1,481 (0.3) | 1.11 (0.94, 1.30) |
| Hemiplegia | 29 (0.01) | 254 (0.05) | 1.14 (0.78, 1.68) |
| Any tumor | 1,135 (0.2) | 9,712 (1.9) | 1.17 (1.10, 1.25) |
| Congestive heart failure | 485 (0.1) | 4,076 (0.8) | 1.19 (1.09, 1.31) |
| Moderate to severe renal disease | 159 (0.03) | 1,272 (0.3) | 1.25 (1.06, 1.48) |
| Metastatic solid tumor | 75 (0.01) | 5,050 (0.1) | 1.49 (1.17, 1.89) |
| Moderate to severe liver disease | 39 (0.01) | 210 (0.04) | 1.86 (1.32, 2.62) |

### 5.1.2 Stratified analyses

The proportion of distant stage BC increased with increasing CCI score and with the presence of some individual CCI diseases. However, with logistic regression models adjusted for age, there was no association between comorbidity and BC stage.

### 5.1.3 Hypothesis-screening analysis

In the hypothesis-screening analysis, ICD-codes in the three years preceding the index date represented 54.4% of all recorded codes in the 10 years preceding BC. After morbidity categories with fewer than five exposed cases and those affecting only men were excluded, 155 morbidity categories remained for analysis. Overall, ORs were skewed toward an increased risk of BC for these 155 morbidity categories, with few ORs below the null. We obtained a pooled OR estimate of 1.07 (95% CI: 1.06, 1.08) associating any morbidity in the three to ten years preceding the index date with BC risk. Several of the morbidity categories were initially positively associated with BC, such as previous cancer diseases. In contrast, iron deficiency anemia (OR = 0.61; 95% CI: 0.45, 0.81), other anemias (OR = 0.78; 95% CI: 0.66, 0.94), osteoporosis with and without fracture (OR = 0.87; 95% CI: 0.78, 0.96), rheumatoid arthritis and other inflammatory polyarthropathies (OR = 0.88; 95% CI: 0.80, 0.98), gastric and duodenal ulcer (OR = 0.89; 95% CI: 0.81, 0.98), and acute myocardial infarction (OR = 0.89; 95% CI: 0.81, 0.99) were among the morbidity categories inversely associated with subsequent BC. The data for the morbidity categories are presented in Appendix 2.

## 5.2 Study II: Comorbidity

### 5.2.1 Characteristics

Characteristics of the BC and matched cohorts are presented in Table 4. The study included 47,904 BC patients and 237,938 women in the comparison cohort. The median age at BC diagnosis was 63.2 years (interquartile range: 55.2 to 73.3 years). Frequent CCI diseases were cerebrovascular disease (3.7%), chronic pulmonary disease (4.3%), and “any tumor” (3.9%), while hemiplegia (0.1%), leukemia (0.1%), moderate to severe liver disease (0.1%), and AIDS (<0.1%) were among the more rare comorbid diseases.

**Table 4. Characteristics of the breast cancer cohort and the matched comparison cohort.**

| | Breast cancer cohort Number (%) | Comparison cohort Number (%) |
|---|---|---|
| **Age group in years** | | |
| ≤50 | 5,085 (11) | 25,560 (11) |
| 51–60 | 13,853 (29) | 68,975 (29) |
| 61–70 | 14,357 (30) | 71,193 (30) |
| 71–80 | 10,262 (21) | 50,710 (21) |
| 81–85 | 4,347 (9.1) | 21,500 (9.0) |
| **Charlson Comorbidity Index score** | | |
| 0 | 38,427 (80.2) | 192,135 (81) |
| 1 | 5,303 (11) | 26,515 (11.1) |
| 2–3 | 3,753 (7.8) | 17,821 (7.4) |
| ≥4 | 421 (0.8) | 1,467 (0.6) |
| **Individual disease in the CCI** | | |
| Myocardial infarction | 680 (1.4) | 3124 (1.3) |
| Congestive heart failure | 840 (1.8) | 3,724 (1.8) |
| Peripheral vascular disease | 836 (1.8) | 3,845 (1.6) |
| Cerebrovascular disease | 1,792 (3.7) | 8,479 (3.6) |
| Dementia | 231 (0.5) | 1,028 (0.4) |
| Chronic pulmonary disease | 2,054 (4.3) | 9,804 (4.1) |
| Connective tissue disease | 934 (2.0) | 4,393 (1.9) |
| Ulcer disease | 819 (1.7) | 3,808 (2.0) |
| Mild liver disease | 232 (0.5) | 1,016 (0.4) |
| Diabetes I and II | 1,229 (2.6) | 5,668 (2.0) |
| Hemiplegia | 42 (0.1) | 165 (0.1) |
| Moderate to severe renal disease | 209 (0.4) | 859 (0.4) |
| Diabetes with end organ damage | 472 (1.0) | 2,066 (0.9) |
| Any tumor (other than breast cancer) | 1,856 (3.9) | 8,967 (3.8) |
| Leukemia | 43 (0.1) | 192 (0.01) |
| Lymphoma | 101 (0.2) | 424 (0.2) |
| Moderate to severe liver disease | 39 (0.1) | 139 (0.1) |
| Metastatic solid tumor | 188 (0.4) | 864 (0.4) |
| AIDS | 1 (0) | 5 (0) |
| **Stage** | | |
| Local | 22,338 (47) | N/A |
| Regional | 18,976 (40) | N/A |
| Distant | 3,139 (6.6) | N/A |
| Unknown | 3,451 (7.2) | N/A |

### 5.2.2 Comorbidity and mortality

During the first year, the cumulative mortality was 6.4% among the BC cohort and 1.9% among women in the comparison cohort. During years 1–5 of follow-up, the cumulative mortality of the one-year survivors was 21% and 8.9%, respectively.

Table 5 shows the mortality rates, ICs, and MRRs for 0–1 and >1–5 year mortality in the BC and comparison cohorts. For all CCI scores, the BC patients had higher mortality rates than the matched cohort. The survival disparities were more marked in the first year of follow-up than in years one to five.

In the first year of follow-up, the biological interaction between BC and comorbidity accounted for 17 deaths per 1000 person-years (PY) (95% CI: 7.8, 27) for a CCI score of 1, 12 deaths per 1000 PY (95% CI: -1.8, 25) for CCI scores of 2–3, and 29 deaths per 1000 PY (95% CI: -33, 91) for a CCI score ≥4. These represented 17%, 9%, and 10% of total mortality rates, respectively, among the BC patients with comorbid diseases.

Although history of chronic pulmonary disease and “any tumor” were relatively common in the BC cohort, the 0–1 year ICs were only 8.6/1000 PY (95% CI: -8.1, 25) for chronic pulmonary disease and -13/1000 PY (95%CI: -31, 5.3) for “any tumor.” When we repeated all analyses for the CCI scores without assigning weights to these two disease types, the 0–1 year overall estimates of the ICs rose from 17 to 21/1000 PY (95% CI: 11, 32) for a CCI score of 1, from 12 to 31/1000 PY (95% CI: 11, 52) for a CCI score of 2–3, and from 29 to 67/1000 PY (95% CI: -19, 152) for a CCI score of ≥4. The ICs for the >1–5 year survivor cohort increased only slightly.

**Table 5. Mortality rates, mortality rate ratios (MRRs) and interaction contrasts overall and by Charlson Comorbidity Index (CCI) scores for the breast cancer (BC) cohort and the comparison cohort.**

| | CCI score | No. of deaths | Person years | Mortality rate per 1000 person years | Interaction contrast | MRRs |
|---|---|---|---|---|---|---|
| **0–1 year of follow–up** | | | | | | |
| Comparison | All | 4,422 | 235658 | 18.8 (18.2, 19.3) | | Ref |
| BC | All | 3,060 | 46102 | 66 (64, 69) | N/A | 3.6 (3.4, 3.8) |
| Comparison | 0 | 1,714 | 191,247 | 9.0 (8.5, 9.4) | | Ref |
| BC | 0 | 1,974 | 37,264 | 53 (51, 55) | Ref | 6.1 (5.7, 6.6) |
| Comparison | 1 | 1,010 | 26,021 | 39 (37, 41) | | Ref |
| BC | 1 | 500 | 4,999 | 100 (92, 109) | 17 (7.8, 27) | 2.7 (2.4, 3.0) |
| Comparison | 2-3 | 1,407 | 17,092 | 82 (78, 87) | | Ref |
| BC | 2-3 | 480 | 3,483 | 138 (126, 151) | 12 (-1.8, 25) | 1.6 (1.5, 1.8) |
| Comparison | ≥4 | 291 | 1,299 | 224 (200, 251) | | Ref |
| BC | ≥4 | 106 | 357 | 297 (246, 360) | 29 (-33, 91) | 1.5 (1.2, 1.9) |
| **>1–5 years of follow–up** | | | | | | |
| Comparison | All | 18,767 | 813,550 | 24.7 (23.9,25.4) | | |
| BC | All | 8,646 | 145,205 | 63 (60, 66) | N/A | 2.7 (2.6, 2.8) |
| Comparison | 0 | 10,411 | 676,070 | 18 (17, 19) | | Ref |
| BC | 0 | 6,244 | 120,248 | 57 (54, 60) | Ref | 3.6 (3.4, 3.7) |
| Comparison | 1 | 4,217 | 83,134 | 41 (38, 44) | | Ref |
| BC | 1 | 1,244 | 14,604 | 75 (66, 85) | -4.4 (-9.1, 0.4) | 1.7 (1.6, 1.9) |
| Comparison | 2-3 | 3,736 | 51,098 | 58 (53, 62) | | Ref |
| BC | 2-3 | 1,034 | 9,532 | 94 (79, 108) | -2.5 (-9.6, 4.1) | 1.5 (1.4, 1.6) |
| Comparison | ≥4 | 403 | 3,249 | 111 (86, 136) | | Ref |
| BC | ≥4 | 124 | 822 | 142 (80, 203) | -7.7 (-39, 23) | 1.2 (0.9, 1.4) |

Numbers in parentheses are 95% confidence intervals.

### 5.2.3 Individual Charlson Comorbidity Index diseases and mortality

The ICs between BC and the specific CCI diseases were larger during the first year of follow-up than during years one to five of follow-up. The disease with the largest IC in the first year of follow-up was dementia (IC=148/1000 PY; 95% CI: 58, 239), representing 40% of the total MR. When we stratified the analyses by BC stage, the interaction between BC and dementia was driven by interaction in the stratum of distant-stage cancers (IC =1150/1000PY; 95% CI: 162, 2137). The ICs for dementia in the strata of local-stage (IC=44/1000 PY; 95% CI:–68, 155) and regional-stage (IC=–31/1000 PY; 95% CI: –145, 82) cancers were much smaller. The stage distribution among BC patients with dementia was skewed toward a later stage at diagnosis compared with BC patients without dementia. In the first year after BC diagnosis, the mortality rate of BC patients with dementia exceeded that of BC patients without dementia in local-, regional-, and distant-stage strata, yielding a stage-adjusted MRR of 5.0 (95% CI: 3.6, 6.8).

In the first year after diagnosis, there was also interaction between BC and other comorbid diseases, including metastatic solid tumors (IC=66/1000 PY, 17% of the total MR), mild liver disease (IC=56/1000 PY, 37% of the total MR), moderate to severe renal disease (IC=43/1000 PY, 31% of the total MR), and diabetes with end-organ damage (IC=42/1000 PY, 27% of the total MR).

In the period one to five years after the index date, there was some interaction between BC and leukemia (IC=61/1000PY, 39% of the total mortality rate), moderate to severe liver disease (IC=49/1000PY, 25% of the total mortality rate), mild liver disease (IC= 19/1000PY, 16% of the total mortality rate), and diabetes with end-organ damage (IC= 14/1000PY, 12% of the total mortality rate). Data for the individual CCI diseases are presented in Figures 3 and 4.

### 5.2.4 Stratified analyses

When the ICs were stratified on BC stage, the interaction observed for the CCI score was primarily driven by distant and unknown stage cancer when analyzed within the matched strata. In the 1–5 year survivor cohort, the ICs were near null.

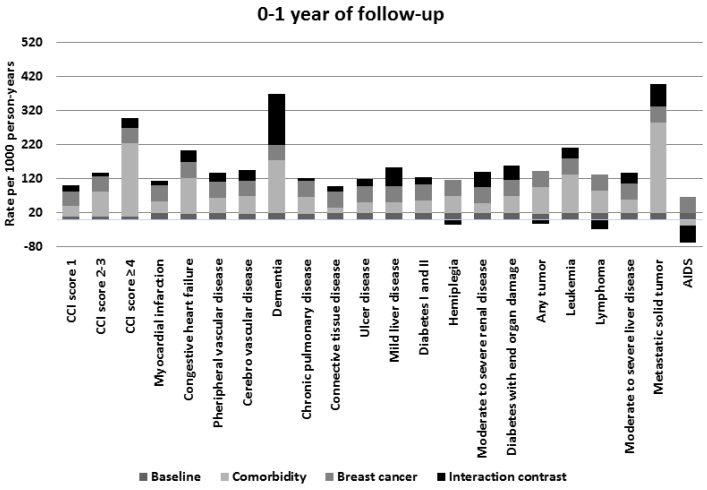



**Figure 3. Mortality rates per 1000 person-years for 0–1 year of follow-up by Charlson Comorbidity Index (CCI) scores and individual diseases in the comorbidity index.** The total mortality rate contribution is represented by the baseline rate, comorbidity, BC, and interaction.

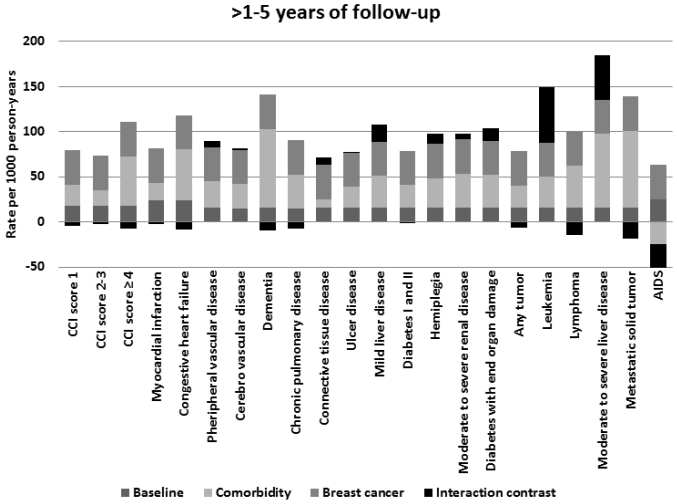



**Figure 4. Mortality rates per 1000 person-years for ≥1–5 years of follow-up by Charlson Comorbidity Index (CCI) scores and individual diseases in the comorbidity index.** The total mortality rate contribution is represented by the baseline rate, comorbidity, BC, and interaction.

### 5.3 Study III: Long-term prognosis

#### 5.3.1 Characteristics

As shown in Table 6, the study included 32,403 five-year BC survivors who were followed up for a median of 4.6 years. The 162,015 women in the comparison cohort were followed for a median of 5.3 years.

**Table 6. Characteristics of the five-year breast cancer survivor cohort diagnosed from 1994–2007 and the matched comparison cohort.**

| | Breast cancer survivor cohort Number (%) | Comparison cohort Number (%) |
|---|---|---|
| **Age group at index date, years** | | |
| 50–59 | 9,214 (28) | 42,925 (28) |
| 60–69 | 10,765 (33) | 54,013 (33) |
| 70–79 | 7,929 (24) | 39,723 (25) |
| 80–90 | 4,495 (14) | 22,354 (14) |
| **Breast cancer stage** | | |
| Localized | 17,417 (54) | N/A |
| Regional | 12,620 (39) | N/A |
| Distant | 570 (1.8) | N/A |
| Unknown | 1,796 (5.5) | N/A |
| **Estrogen receptor status** | | |
| Negative | 3,979 (12) | N/A |
| Positive | 19,703 (61) | N/A |
| Unknown | 8,721 (27) | N/A |

As shown in Table 7, 52% of the BC survivor cohort and 60% of the comparison cohort had no coexistent disease as defined by the CCI, as of the index date. In the BC cohort, 14% of women had a CCI score ≥4. Prevalent CCI diseases were any tumor (8.5%), metastatic solid tumors (9.5%), chronic pulmonary disease (7.3%), cerebrovascular disease (6.4%), and diabetes I and II (4.8%). In the comparison cohort, 4.5% had a CCI score ≥4. Prevalent diseases were chronic pulmonary diseases (6.6%), cerebrovascular disease (6.5%), any tumor (6.3%), and diabetes I and II (4.2%). The frequency of new CCI diseases diagnosed after the index date was somewhat higher in the BC survivor cohort (30%) than in the comparison cohort (26%). The proportion of patients reaching a CCI score of ≥4 was 9.4% in the BC survivor cohort and 4.0% in the comparison cohort. In calculating these scores, all CCI diseases diagnosed before the index date were excluded. When analyses were stratified by type of new CCI disease, frequencies were equivalently distributed, for most diseases, except for metastatic solid tumor (7.7% vs. 2.1%) (Table 7).

**Table 7. Characteristics of prevalent and incident diseases in the five-year breast cancer survivor cohort diagnosed from 1994–2007 and the matched comparison cohort.**

| | Prevalence period | | Incidence period | |
|---|---|---|---|---|
| | Breast cancer survivor cohort Number (%) | Comparison cohort Number (%) | Breast cancer survivor cohort Number (%) | Comparison cohort Number (%) |
| **CCI score at index date** | | | | |
| 0 | 16,738 (52) | 97,691 (60) | 22,556 (70) | 119,507 (74) |
| 1 | 6,016 (19) | 31,501 (19) | 3,525 (11) | 19,335 (12) |
| 2–3 | 5,157 (16) | 24,957 (15) | 3,262 (10) | 16,674 (10) |
| ≥4 | 4,492 (14) | 7,866 (4.5) | 3,060 (9.4) | 6,499 (4.0) |
| **CCI score excluding women with metastatic solid tumors** | | | | |
| 0 | 16,738 (57) | 97,691 (61) | 22,556 (75) | 119,507 (75) |
| 1 | 31,501 (20) | 31,501 (20) | 3,525 (12) | 19,335 (12) |
| 2–3 | 5,157 (18) | 24,957 (16) | 3,262 (11) | 16,674 (11) |
| ≥4 | 1,425 (4.9) | 6,758 (4.2) | 573 (1.9) | 3,054 (1.9) |
| **Individual diseases in the CCI** | | | | |
| Myocardial infarction | 758 (2.3) | 4,508 (2.3) | 591 (1.8) | 3,535 (2.2) |
| Congestive heart failure | 970 (3.0) | 4,314 (2.7) | 1,111 (3.4) | 5,521 (3.4) |
| Peripheral vascular disease | 1,003 (3.1) | 5,102 (3.2) | 706 (2.2) | 4,297 (2.7) |
| Cerebrovascular disease | 2,083 (6.4) | 10,494 (6.5) | 1,743 (5.4) | 9,300 (5.7) |
| Dementia | 385 (1.2) | 1,985 (1.2) | 818 (2.5) | 4,525 (2.3) |
| Chronic pulmonary disease | 2,363 (7.3) | 10,651 (6.6) | 1,444 (4.5) | 7,317 (4.5) |
| Connective tissue disease | 1,109 (3.4) | 5,999 (3.7) | 520 (1.6) | 2,704 (1.7) |
| Ulcer disease | 1,113 (3.4) | 5,642 (3.5) | 646 (2.0) | 3,102 (1.9) |
| Mild liver disease | 298 (0.9) | 1,323 (0.9) | 155 (0.5) | 725 (0.5) |
| Diabetes I and II | 1,544 (4.8) | 6,734 (4.2) | 934 (2.9) | 4,611 (2.3) |
| Hemiplegia | 72 (0.2) | 241 (0.2) | 59 (0.2) | 184 (0.1) |
| Moderate to severe renal disease | 336 (1.0) | 1,657 (1.0) | 512 (1.6) | 2,648 (1.6) |
| Diabetes with end organ damage | 619 (1.9) | 2,896 (1.8) | 449 (1.4) | 2,341 (1.4) |
| Any tumor* | 2,758 (8.5) | 10,138 (6.3) | 2,277 (7.0) | 9,663 (6.0) |
| Leukemia | 72 (0.2) | 298 (0.2) | 61 (0.2) | 384 (0.2) |
| Lymphoma | 205 (0.6) | 707 (0.4) | 125 (0.4) | 674 (0.4) |
| Moderate to severe liver disease | 73 (0.2) | 244 (0.2) | 106 (0.3) | 398 (0.3) |
| Metastatic solid tumor | 3,067 (9.5) | 1,108 (0.7) | 2,487 (7.7) | 3,445 (2.1) |
| AIDS | 5 (0.2) | 17 (0.0) | 1 (0.0) | 1 (0.0) |

The index date was defined as the date of five-year survivorship after breast cancer and the corresponding date for the matched members of the comparison cohort. The prevalence period covers diseases recorded up to the index date, and the incidence period covers diseases recorded during follow-up, that were not recorded in the prevalence period.

*Any tumor other than breast cancer

### 5.3.2 New diseases and mortality

Figure 5 presents mortality curves for the BC survivor cohort and the comparison cohort. The cumulative mortality during 14 years of follow-up was 51% among women in the BC survivor cohort and 39% among women in the comparison cohort. The MRR adjusted for age and CCI score at index was 1.47 (95%CI: 1.44, 1.51). The MRRs for mortality associated with any new disease were similar in the BC survivor cohort (MRR = 7.1; 95%CI: 6.7, 7.4) and the comparison cohort (MRR = 7.5; 95%CI: 7.3, 7.7). When the analyses were stratified by each CCI disease, MRRs were similar or higher in the comparison cohort for most diseases (Table 8).

In a sensitivity analysis, we excluded all women with metastatic solid tumors diagnosed during follow-up. CCI scores for new diseases were then similar in the two cohorts: 75% of all women had a CCI score of 0 during follow-up. The MRRs for any new disease diagnosed during follow-up, compared with absence of any incident CCI disease decreased to 4.6 (95%CI: 4.4, 4.8) in the BC survivor cohort and 6.2 (95%CI: 6.0, 6.4) in the comparison cohort.

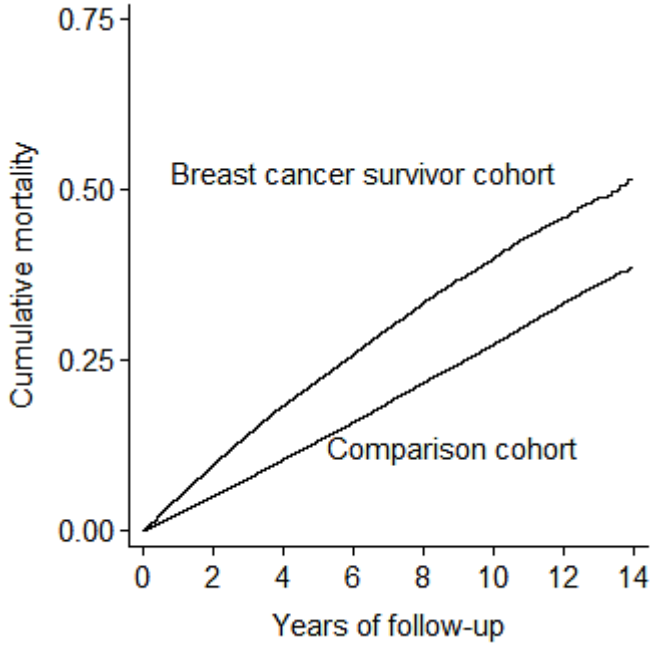



**Figure 5. Mortality curves for the five-year breast cancer survivor cohort and the comparison cohort of women from the general population followed from the index date (five-years of survivorship after breast cancer diagnosis).**

**Table 8. Crude mortality rates per 1000 person-years (PYs), with 95% confidence intervals, and mortality rate ratios in the five-year breast cancer survivor and the comparison cohorts during 14 years of follow-up, comparing patients with disease to patients without that disease.**

| | | Breast cancer survivor cohort | | | Comparison cohort | | |
|---|---|---|---|---|---|---|---|
| | Presence of disease | Number of deaths | Rate/1000PYs | Mortality rate ratio | Number of deaths | Rate/1000 PYs | Mortality rate ratio |
| Any disease | No | 3,712 | 26.3 (25.5, 27.1) | Ref | 11,055 | 13.9 (13.7, 14.2) | Ref |
| | Yes | 4,878 | 176 (171, 182) | 7.1 (6.7, 7.4) | 17,531 | 133 (131, 135) | 7.5 (7.3, 7.7) |
| Myocardial infarction | No | 8,287 | 49.5 (48.5, 50.6) | Ref | 26,840 | 29.3 (29.0, 29.7) | Ref |
| | Yes | 303 | 192 (171, 215) | 2.8 (2.5, 3.1) | 1,746 | 177 (168, 185) | 3.3 (3.1, 3.4) |
| Congestive heart failure | No | 7,909 | 47.6 (46.5, 48.6) | Ref | 25,377 | 27.8 (27.5, 28.2) | Ref |
| | Yes | 681 | 255 (237, 275) | 3.4 (3.1, 3.7) | 3,209 | 232 (224, 240) | 3.5 (3.4, 3.7) |
| Peripheral vascular disease | No | 8,283 | 49.7 (48.6, 50.7) | Ref | 26,901 | 29.5 (29.1, 29.8) | Ref |
| | Yes | 307 | 144 (129, 162) | 2.3 (2.0, 2.6) | 1,685 | 126 (120, 132) | 2.5 (2.4, 2.7) |
| Cerebrovascular disease | No | 7,835 | 47.8 (46.8, 48.9) | Ref | 24,708 | 27.5 (27.2, 27.9) | Ref |
| | Yes | 755 | 152 (141, 163) | 2.3 (2.2, 2.5) | 3,878 | 142 (138, 146) | 3.0 (2.9, 3.1) |
| Dementia | No | 8,101 | 48.5 (47.5, 49.6) | Ref | 25,943 | 28.3 (28.0, 28.7) | Ref |
| | Yes | 489 | 261 (237, 285) | 2.9 (2.7, 3.2) | 2,643 | 253 (243, 262) | 3.3 (3.2, 3.4) |
| Chronic pulmonary disease | No | 7,984 | 48.5 (47.5, 49.6) | Ref | 25,809 | 28.6 (28.3, 29.0) | Ref |
| | Yes | 606 | 140 (129, 151) | 2.5 (2.3, 2.7) | 2,777 | 120 (115, 124) | 3.2 (3.1, 3.4) |
| Connective tissue disease | No | 8,453 | 50.6 (49.5, 51.7) | Ref | 27,909 | 30.5 (30.1, 30.9) | Ref |
| | Yes | 137 | 73.0 (61.7, 86.3) | 1.2 (1.0, 1.5) | 677 | 64.1 (59.4, 69.1) | 1.5 (1.4, 1.7) |
| Ulcer disease | No | 8,241 | 49.3 (48.2, 50.4) | Ref | 27,136 | 29.6 (29.3, 30.0) | Ref |
| | Yes | 349 | 203 (182, 225) | 2.8 (2.6, 3.1) | 1,450 | 156 (148, 164) | 2.9 (2.8, 3.1) |
| Mild liver disease | No | 8,517 | 50.6 (49.5, 51.6) | Ref | 28,311 | 30.7 (30.3, 31.0) | Ref |
| | Yes | 73 | 176 (140, 221) | 4.0 (3.2, 5.0) | 275 | 128 (114, 144) | 5.4 (4.8, 6.1) |
| Diabetes I and II | No | 8,201 | 49.4 (48.3, 50.4) | Ref | 27,139 | 29.8 (29.5, 30.2) | Ref |
| | Yes | 389 | 141 (128, 156) | 2.3 (2.1, 2.6) | 1,447 | 92.8 (88.2, 97.8) | 2.2 (2.0, 2.3) |
| Hemiplegia | No | 8,558 | 50.7 (49.7, 51.8) | Ref | 28,487 | 30.8 (30.4, 31.2) | Ref |
| | Yes | 32 | 201 (142, 285) | 3.7 (2.6, 5.2) | 99 | 207 (170, 252) | 5.0 (4.1, 6.1) |
| Moderate to severe renal disease | No | 8,291 | 49.4 (48.3, 50.5) | Ref | 27,179 | 29.5 (29.2, 29.9) | Ref |
| | Yes | 299 | 302 (270, 338) | 4.0 (3.6, 4.5) | 1,407 | 281 (267, 296) | 4.7 (4.5, 5.0) |
| Diabetes with end organ damage | No | 8,372 | 50.0 (48.9, 51.1) | Ref | 27,665 | 30.1 (29.8, 30.5) | Ref |
| | Yes | 218 | 155 (136, 177) | 1.9 (1.6, 2.1) | 921 | 120 (113, 128) | 2.1 (2.0, 2.3) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Any tumor | No | 7,385 | 45.1 (44.0, 46.1) | Ref | 23,616 | 26.1 (25.7, 26.4) | Ref |
| | Yes | 1205 | 241 (228, 255) | 5.3 (5.0, 5.7) | 4,970 | 237 (230, 243) | 7.7 (7.5, 7.9) |
| Leukemia | No | 8,551 | 50.7 (49.6, 51.8) | Ref | 28,375 | 30.7 (30.3, 31.0) | Ref |
| | Yes | 39 | 297 (217, 406) | 4.9 (3.6, 6.8) | 211 | 245 (214, 280) | 5.6 (4.9, 6.4) |
| Lymphoma | No | 8,528 | 50.6 (49.5, 51.7) | Ref | 28,297 | 30.6 (30.3, 31.0) | Ref |
| | Yes | 62 | 179 (140, 230) | 3.6 (2.8, 4.6) | 289 | 167 (149, 188) | 4.2 (3.7, 4.7) |
| Moderate to severe liver disease | No | 8,510 | 50.4 (49.4, 51.5) | Ref | 28,332 | 30.6 (30.3, 31.0) | Ref |
| | Yes | 80 | 605 (486, 754) | 14 (11, 17) | 254 | 371 (328, 420) | 13 (11, 14) |
| Metastatic solid tumor | No | 6,789 | 41.3 (40.3, 42.3) | Ref | 25,968 | 28.2 (27.8, 28.5) | Ref |
| | Yes | 1,801 | 397 (379, 416) | 12 (11, 13) | 2,618 | 637 (613, 662) | 22 (21, 22) |
| AIDS | No | 8,590 | 50.9 (49.8, 51.9) | Ref | 28,585 | 30.9 (30.5, 31.2) | Ref |
| | Yes | 0 | | | 1 | 297 (41.8, 2106) | |

Notes: Parantheses are 95% confidence intervals.

Mortality rate ratios are adjusted for age group and CCI score as of the index date, defined as the date of five-year survivorship after breast cancer and the corresponding date for the matched members of the comparison cohort.

### 5.3.3 Stratified analyses

Patients with localized or regional breast cancer stage at diagnosis had higher MRRs associating any incident disease with no incident disease than patients with distant or unknown stage breast cancer.

# 6. Discussion

This chapter covers the main conclusions followed by a discussion of the results in relation to the literature, and a thorough discussion of the methodology.

## 6.1 Main conclusions

### 6.1.1 Study I (breast cancer risk)

The study does not support any substantial new association between morbidity measured with the original and an updated CCI and BC risk. Some previous identified associations were confirmed.

### 6.1.2 Study II (comorbidity)

The study demonstrates the presence of biological interaction between comorbidities and overall mortality in BC patients—particularly within one year after BC diagnosis, and mainly in patients with distant and unknown stage BC.

### 6.1.3 Study III (long-term prognosis)

Except for metastatic solid tumors, five-year BC survivors and women from the general population had similar incidence of new CCI diseases diagnosed during 14 years of follow-up, but BC survivors had a higher mortality rate. New CCI diseases were associated with similar or slightly lower mortality rate among five-year BC survivors than among women from the general population.

### 6.2 In light of the existing literature

The following three subsections discuss the studies in light of the existing literature.

#### 6.2.1 Study I (breast cancer risk)

The slight association between increasing CCI score and BC is likely related to shared risk factors or close medical follow-up of patients burdened with coexisting disease. Though studies have shown an increased risk of, for example, a second primary cancer arising in association with the treatment of the first primary BC,[107] different treatment types are associated with varying complications and levels of medical follow-up.[108] However, many cancers and other CCI diseases are associated with lifestyle factors that are also linked to BC, such as smoking and alcohol consumption.[109,110]

The five case-control studies, which specifically studied several medical conditions associated with BC risk[54-58] included rather small study populations and, with one exception,[57] were hospital-based,[54-56,58] and two of the studies included overlapping populations.[54,56] Most results were null, but many of them were imprecisely measured. The association with diabetes was examined in most of the studies,[54,56-58] with many ORs just above the null, ranging from 1.0 (95%CI: 0.8, 1.3) for all women included in a study,[54] to 2.2 (95%CI: 1.5, 3.3) for postmenopausal women.[56] We observed an OR of 1.10 (95%CI: 1.02, 1.18) for diabetes I and II and an OR of 1.04 (95%CI: 0.91, 1.18) for diabetes with end organ damage, which were slightly lower than observed for diabetes in a recent meta-analysis (summary HR = 1.23; 95%CI; 1.12, 1.34).[20] Diabetes can be induced by obesity or physical inactivity, which are also associated with cancer. Diabetes may mediate a carcinogenic effect through activation of the insulin pathway or the insulin-like growth factor pathway, which may induce malignant transformation, or by altered regulation of endogenous sex hormones.[111]

Many associations obtained in the hypothesis-screening analysis were not surprising. Some associations may relate to established risk factors, such as cumulative estrogen exposure, genetics, or lifestyle. Other conditions may relate to pharmacological agents.[24]
Osteoporosis, heart disease, gastric ulcer, and rheumatoid arthritis were inversely associated with BC before EB adjustment. Acetylsalicylic acid (aspirin) is used to treat rheumatoid arthritis, osteoporosis and heart disease. Gastric ulcer, bleeding and thus anemia are well known

complications to regular aspirin intake. A recent review and meta-analysis concluded that aspirin reduces the risk of BC,[21] so these associations may reflect a protective effect of aspirin treatment or other non-steroidal anti-inflammatory drugs associated with the preceding morbidities.[21,22] Also, treatment with bisphosphonates for osteoporosis may have a chemopreventive effect.[23,24]
Recent studies suggest that excess endogenous iron storage raises the risk of BC.[112] Though highly speculative, the negative association observed with anemia could be mediated by changes in iron homeostasis. Estrogen deficiency has been linked to BC, rheumatoid arthritis and to postmenopausal osteoporosis.[113,114] On the other hand, HRT can be used to inhibit this bone detrimental effect, but is associated with the incidence of BC.[25,115] Other medications, such as statins and glucocorticoids have been studied in relation to cancer, but the current evidence suggests no association with BC.[116,117]
Many of the observed associations may therefore arise from complex mechanisms.

### 6.2.2 Study II (comorbidity)

As described earlier, numerous studies have shown that BC patients with comorbidity have a poorer prognosis than those without comorbidity.[33,69] One study demonstrated the presence of statistical interaction on the additive scale between comorbidity and BC in a hospital-based study of BC patients and comparison cohort women.[74] Our study extends the previous investigations by computing the excess mortality caused by biological interaction between comorbidity and BC and by comparing the mortality experience in BC patients with that of the general population.

Biological interaction between BC and comorbidity was mainly observed during the first year after BC diagnosis, possibly due to inferior treatment of BC in patients with comorbidity compared with otherwise healthy BC patients. Previous studies have shown that BC patients with severe comorbidity receive altered or delayed courses of treatment or discontinue cancer therapy.[7,118,119]

In the time period one to five years after BC diagnosis, we observed no substantial interaction between BC and comorbidity, likely due to the quality of care of comorbid conditions being the same in the period after completion of primary BC treatment as among women without BC. Indeed, a recent cross-sectional study conducted in the United States indicated that the quality of care for comorbid conditions among three-year BC survivors was equal to that provided to a BC-free cohort.[120] The differential treatment of comorbidity in the BC and comparison cohorts is also

unlikely in Denmark.

Although often imprecisely measured, the ICs were negative in some analyses and often in the local and regional stage categories. This pattern suggests that prevalent and well-managed comorbidities brought BC patients to medical attention and diagnosis sooner, resulting in a shift within early BC stages to more treatable BC. A previous investigation has shown that patients with, for example, psychiatric diseases and diabetes, are at increased risk of a diagnosis with distant BC, whereas women with, for example, cardiovascular diseases are at decreased risk of being diagnosed with distant BC compared with otherwise healthy BC patients.[121] Other investigations also suggest that severe comorbid conditions are associated with late diagnosis of BC.[122] We have clearly demonstrated strong interaction in the first year after their BC diagnosis for BC patients with a CCI score ≥4 and for patients with dementia.

### 6.2.3 Study III (long-term prognosis)

Previous investigations have concluded that BC survivors often have similar prevalent burden of comorbid disease as women from the general population,[77,78,89,123] although the incidence of diseases may be greater shortly after BC diagnosis, and then diminish during follow-up.[78] We note that, except for metastatic solid tumors, the frequency of new CCI diseases diagnosed during follow-up was also comparable among BC survivors and members of the comparison cohort in our study. This similarity suggests that close medical follow-up and treatment toxicities likely have little impact on the pattern of new diseases diagnosed in our cohort of five-year BC survivors. As previously mentioned, the quality of care for comorbid conditions among three-year BC survivors in the United States was equal to that provided to a BC-free cohort,[120] supporting the notion that BC patients receive the same treatment as women from the general population. New metastatic solid tumors explained the greater frequency of BC survivors reaching a CCI score ≥4 during follow-up.

Not surprisingly, mortality among BC survivors was higher during follow-up than among women in the comparison cohort. BC continues to be associated with increased mortality risk beyond five years after diagnosis. [124,125] In our study, however, stratifying our results by breast cancer stage showed that patients with localized or regional stage had higher MRRs than patients with distant or unknown spread breast cancer. It may be that once a BC patient has survived to five years,

prognostic factors at her BC diagnosis, such as stage, are no longer the most important factors in determining her long-term survivorship.[124,125] Studies have shown that BC recurrence primarily occurs during the first few years after BC diagnosis among women with ER-negative tumors, but after the first five years is more comparable to that of women with ER positive tumors.[126,127]

Our study extends the previous research by studying mortality after diagnosis of new CCI disease in BC patients and compares it to that of the general population. A new diagnosis of CCI diseases in the incident period was associated with similar or slightly lower increased risk of mortality in the BC survivor cohort than in the comparison cohort. Thus, acquiring new diseases after five-year BC survival may be less hazardous to such survivors than to comparable women from the general population. We speculate that this may be because diseases were diagnosed and treated earlier in the BC survivor cohort than in the general population, owing to closer medical follow-up or increased health awareness among BC survivors.

### 6.3 Methodological considerations

The goal of our studies was to estimate precise and valid measures of the associations between the exposures and outcome, that could be generalized to similar female populations in other settings. A discussion of potential problems with precision and validity will follow below.

#### 6.3.1 Precision

All three studies included a large sample size and a large number of outcomes, resulting in rather narrow CIs for many results. However, our results were affected by random variation, in particular the stratified analyses, because of reduced sample size. Furthermore, our studies were built on 19 estimations of the associations between the individual CCI diseases and the respective outcomes. One method of overcoming the problem with overestimated or imprecise associations is the Bayesian shrinkage approach, which reduces the variance of the estimates toward the overall mean.[106] A potential important limitation of using such an approach, however, is overlooking potential important findings.[128] Therefore, we only applied the EB shrinkage method to data from the hypothesis-screening analysis.

#### 6.3.2 Selection bias

As described previously, we used nationwide and population-based study designs, and the capture of BC in the DCR is virtually complete.[98] The control women in study I and the comparison cohorts in studies II and III were sampled from the general population, thereby minimizing potential selection bias.

We had nearly complete follow-up of all BC patients and the comparison cohorts in studies II and III. Emigration out of the country among the study participants is rare and probably independent of the exposures and outcomes and thus the impact on loss-to-follow-up is likely negligible.

In studies II and III we matched comparison cohorts from the general population to the BC patients. The women in the comparison cohort were sampled from the CRS, which eliminates potential collider bias, arising from associations between the exposure or outcome and selection.[129]

#### 6.3.3 Information bias

The date of birth and death in the CRS are recorded with negligible error.[94] The positive predictive value of CCI diseases in the DNRP has been shown to be high,[130] but the sensitivity is likely low

because only hospital-diagnosed cases are recorded, and outpatient data were only included in 1995.[100] We could therefore have misclassified women with CCI diseases in the groups without CCI diseases.

There are other sources of misclassification that warrant consideration.

Detection bias refers to the situation when one study group is followed more closely than the other.[131] In our studies, this bias could be introduced if women with BC or other morbidity were more likely to consult a doctor than women without these diseases, resulting in diagnostic work-up and detection of a given condition at an early stage. This would result in BC or the other disease being recorded in the registries at an earlier, and presumably less severe stage, than among women free of BC or other morbidity.[131] It is likely that either patients with BC or multimorbidity have a different threshold for seeking medical attention than women without these disease, which could impact our results: – in study I, by increasing the rate of BC diagnosis in patients with multimorbidity; in study III, by recording of new diseases at lower stages than among women in the comparison cohort free of BC.

Another source of misclassification arises from the definition of comorbidity, complications and new disease. It might be difficult to distinguish complications from comorbidities, which can have a serious impact on prognostic studies.[129] A very broad definition of comorbidity must be used with caution to avoid misclassifying complications as comorbidities. In study II, complications were intermediate steps in the pathway from comorbidity and BC to death. Therefore complications must be considered separately from comorbidities to avoid overestimation of the total comorbidity burden. At the same time, a more restrictive definition of comorbidities could misclassify comorbidities as complications and therefore result in underestimation of the comorbidity burden, potentially leading to residual confounding by comorbidity in study III. Correct classification of medical conditions as comorbidities or complications is thus necessary to avoid inaccurate estimation of the comorbidity burden.
In cancer research, many diseases and conditions may not clearly meet the criteria of either comorbidities or complications, further highlighting the complexity. We therefore used the index dates to separate comorbidities from complications and new disease.

### 6.3.4 Confounding

In study I, we were unable to control for confounding by unmeasured factors potentially associated with preceding morbidity and BC, for example medication, socio-economic or lifestyle factors, such as alcohol and smoking, and menopausal status. Given the matching criteria, which included birth year, lack of information on menopausal status is unlikely to have had a major impact on our findings. To estimate the effect of reproductive history, data about age-at-first live birth is available in the CRS from 1968 and parity from the Danish Medical Birth Registry (DMBR) from 1973.[132] Multiple imputation methods for missing imputation methods could be applied to reconstruct reproductive history for older women; yet, unaccounted factors could be associated with reproductive history among older women compared with younger women. We therefore did not impute the missing reproductive history data in the study. However, it is unlikely that residual confounding completely explains our findings.

In studies II and III, we matched comparison women to the BC patients to balance the distribution of age in the cohorts and thereby reduce confounding by potential associations with the exposure and outcome. In study II, we further matched on comorbidity to allow for calculation of the IC for the individual CCI diseases. Due to the time-varying analysis of study III, an association between new CCI diseases and age may be introduced with person-time. Therefore, we adjusted for age categories in the Cox models.
However, we lacked information on other potential confounders, such as menopausal status, socio-economic factors, and lifestyle factors. Matching and adjustment, respectively, for comorbidity in studies II and III accounted for at least some of the effect of these factors.

Confounding could be introduced by failure to account for other diseases not included in the CCI that may impact the risk of BC or mortality, e.g., psychiatric diseases, would result in an underestimation of the burden of existing morbidity at the index dates. This would potentially bias towards the null (ORs, MRs and MRRs) if patients with other diseases were classified in the groups without diseases.

### 6.3.5 Limitations of the Charlson Comorbidity Index

Confounding in these studies arise mainly from misclassification of conditions included in the CCI. The CCI has several limitations, potentially resulting in bias and confounding. First, it incorporates

available information about comorbid conditions into an aggregate index, which precludes estimation of effects of individual comorbid diseases.

Second, it does not include all medical conditions and psychiatric diseases that can confer substantial morbidity even in patients with diagnosis of index diseases. Third, duration is not accounted for, and severity is only considered to a very limited extent. As an example, consider the effect of diabetes, which increases risk of death with duration, whereas the effect of cancer diseases often decreases with survival beyond five years. In the CCI, only diabetes and liver disease are divided into only two severity groups, both disease types can be more finely parsed, and other CCI diseases have important severity grades, for example chronic obstructive pulmonary disease. Fourth, the CCI diseases can be measured using several methods,[133] with varying weaknesses and no gold standard.

Furthermore, in the current dissertation, the nosocomial threshold needs to be reached in order for a diagnosis to be recorded in the DNRP, and a proportion of all diagnostic codes are incorrectly recorded. In addition, the duration from the first symptom until the condition is recorded will vary for different diseases and patients. Thus, there will be residual confounding in a study in which comorbidity is a confounding factor.

## 7. Future perspectives

Multimorbidity is increasingly becoming a worldwide problem associated with considerable health care costs, reduced quality of life, disability, and premature deaths. Novel approaches to treatment and research in multimorbidity are therefore warranted.[134,135]

This dissertation suggests that BC interacts biologically with comorbidity by increasing the mortality rate beyond that expected by the individual effects of the diseases acting alone, and by demonstrating that long-term BC survivors diagnosed with new diseases have similar or slightly lower mortality rates than women from the general population. Several questions, however, remain unanswered:

- What are the mechanisms behind the observed biological interaction?
- What are the clinical pathways associating multimorbidity with reduced BC prognosis?
- What is the impact of polypharmacy on prognosis in BC patients with multimorbidity?
- Are there important disease clusters that affect prognosis in BC patients?
- Are BC patients treated differently for comorbidities than women from the general population?
- Do clinical treatment guidelines apply to BC patients with multimorbidity?
- Should women with high level of comorbidity be offered extended screening for BC, or will they die from comorbidity rather than BC?

In order to answer these questions, there is an urgent need for improved methods for assessing comorbidity, complications, and polypharmacy, as well as data on the clinical course and treatment during long-term follow-up. The CCI has now existed for more than 30 years, likely as a consequence of its simplicity and feasibility. Despite efforts to update the index to modern health care, there is still no gold standard for the practical application, thus sensitive methods that can be standardized and used in many different research settings are warranted.

The Danish nationwide medical and administrative registries contain comprehensive information about health care and cover the entire population, which offers a unique opportunity for studying multimorbidity.

Future research could therefore elucidate the complex mechanisms involved in multimorbidity and the prognostic impact, and could add to knowledge about personalized prevention and

treatment options in BC as well as other diseases, but innovative approaches to measurement of comorbidity are needed in order to derive valid and comparable results.

## 8. Summary

Breast cancer (BC) is the most common cancer among women in the Western world, and many BC patients suffer from other chronic diseases.

The aim of this dissertation was to provide knowledge about the relationship between medical conditions and subsequent risk of BC and prognosis. In study I, we investigated whether previously diagnosed medical conditions were associated with subsequent risk of BC. In study II, we examined the interaction between comorbidity and BC on risk of subsequent death. In study III, we examined the long-term mortality after diagnosis of new diseases.

The studies included a case-control study and two matched cohorts nested within the entire female Danish population. The studies were based on the Civil Personal Registration Number (CPR) for data linkage in national registries. Comorbidity was measured with the Charlson Comorbidity Index (CCI), and the statistical analyses were conducted with logistic regression, Cox regression, and calculations of interaction contrasts.

In study I (1994–2008), we included 46,324 BC patients and ten times as many control women, and found that increasing CCI score was associated with slightly increased risk of BC. Among individual CCI disease, moderate to severe renal and liver disease, any tumor, and metastatic solid tumors were associated with increased BC risk, while, leukemia, connective tissue disease, dementia, and myocardial infarction were associated with reduced BC risk.

In study II (1994–2008), we included 47,904 BC patients and five times as many women in a matched comparison cohort. In the first year, we found that the interaction between comorbidity and BC could explain between 8% and 17% of the total mortality rate depending on the level of comorbidity. In particular dementia and BC strongly interacted: 40 % of the total mortality rate among BC patients with dementia could be explained by interaction. There was only modest negative interaction during years 1–5.

In study III (1994–2007), we included 32,403 five-year BC survivors and five times as many women in a matched comparison cohort. The risk of dying during 14 years of follow-up was 47% higher among BC patients than among comparison women. Compared with women not diagnosed with

new disease during follow-up, a diagnosis of any new disease was associated with similar or slightly lower risk of death among BC patients than among women in the comparison cohort.

The studies were observational and therefore subjected to bias and confounding. In particular, misclassification related to information about the diseases and residual confounding may explain our results. Our data were collected from existing records, and the use of the CCI as a measure of comorbidity is critical because of the lack of a reference standard for data collection and the inability to assess the effect of disease duration and severity.

## 9. Dansk resume

Brystkræft er den hyppigste kræftform blandt kvinder i den vestlige verden, og mange kvinder med brystkræft lider af andre kroniske sygdomme.
Formålet med denne afhandling var at bidrage med viden om kroniske sygdomme og efterfølgende risiko for brystkræft samt prognose. I studie I undersøgte vi, om tidligere diagnosticerede medicinske tilstande var forbundet med øget risiko for brystkræft. I studie II undersøgte vi biologisk interaktion mellem komorbiditet og brystkræft for overlevelseschancerne. I studie III undersøgte vi langtidsoverlevelsen i forbindelse med diagnosticering af nye sygdomme. Afhandlingen omfattede en case-kontrol undersøgelse og to matchede kohortestudier, indlejret i hele den kvindelige danske befolkning. Undersøgelserne byggede på CPR-nummeret til samkøring af data i landsdækkende registre. Komorbiditet blev målt med Charlson Comorbiditets Indexet (CCI), og de statistiske analyser blev udført ved hjælp af logistisk regression, Cox regression, og ved beregning af interaktions kontraster.

I studie I (1994–2008) inkluderede vi 46.324 brystkræftpatienter og ti gange så mange kontrol-kvinder og fandt, at stigende CCI score var forbundet med let øget risiko for brystkræft. Blandt CCI sygdomme var især svær nyre- og leversygdom, øvrig tumor samt metastatisk solide tumorer associeret med risiko for brystkræft, mens leukemi, bindevævssygdomme, demens og myocardieinfarkt var associeret med nedsat risiko for brystkræft.

I studie II (1994–2008) inkluderede vi 47.904 brystkræftpatienter og fem gange så mange sammenligningskvinder i en matchet kohorte. I det første år fandt vi, at interaktion mellem komorbiditet og brystkræft kunne forklare mellem 8% og 17% af den totale mortalitet, afhængig af sværhedsgraden af komorbiditeten. Især demens og brystkræft viste kraftig interaktion: 40% af den totale mortalitetsrate blandt brystkræftpatienter med demens kunne forklares af interaktion herimellem. Der var kun beskeden negativ interaktion for 1–5 års mortaliteten.

I studie III (1994–2007) inkluderede vi 32.403 femårs-overlevende brystkræftpatienter og fem gange så mange kvinder i en matchet sammenligningskohorte. Risikoen for at dø i løbet af 14 års opfølgning var 47% højere blandt brystkræftpatienter end blandt kvinder i sammenligningskohorten, mens dødeligheden efter diagnosticering af en ny kronisk sygdom var sammenlignelig mellem kohorterne. Undersøgelserne var observationelle og derfor udsat for bias

og confounding. Navnlig misklssifikation relateret til information om sygdomme og residual confounding kan forklare vores resultater. Vores data var indsamlet fra eksisterende registre, og brugen af CCI som et mål for komorbiditet er kritisk på grund af manglen på en referencestandard for dataindsamling, samt manglende evne til at vurdere effekten afsygdomsvarighed og – sværhedsgrad.

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# 11. Appendixes

## 11.1 Appendix 1. ICD codes

## ICD codes included in studies I–III

| Condition | ICD code |
|---|---|
| Breast cancer | ICD-8: 174<br>ICD-10: C50 |
| **Charlson comorbidity index condition** | |
| Myocardial infarction | ICD-8: 410<br>ICD-10: I21, I22, I23 |
| Congestive heart failure | ICD-8: 427.09, 27.10, 427.11, 427.19, 428.99, 782.49<br>ICD-10: I50, I11.0, I13.0, I13.2 |
| Peripheral vascular disease | ICD-8: 440, 441, 442, 443, 444, 445<br>ICD-10: I70, I71, I72, I73, I74, I77 |
| Cerebrovascular disease | ICD-8: 430-438<br>ICD-10: I60-I69, G45, G46 |
| Dementia | ICD-8: 290.09-290.19, 293.09<br>ICD-10: F00-F03, F05.1, G30 |
| Chronic pulmonary disease | ICD-8: 490-493, 515-518<br>ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3 |
| Connective tissue disease | ICD-8: 712, 716, 734, 446, 135.99<br>ICD-10: M05, M06, M08, M09,M30,M31, M32, M33, M34, M35, M36, D86 |
| Ulcer disease | ICD-8: 530.91, 530.98, 531-534<br>ICD-10: K22.1, K25-K28 |
| Mild liver disease | ICD-8: 530.91, 530.98, 531-534<br>ICD-10: K22.1, K25-K28 |
| Diabetes type1 | ICD8: 249.00,249.06, 249.07, 249.09<br>ICD-10: E10.0, E10.1, E10.9 |
| Diabetes type2 | ICD-8: 250.00, 250.06, 250.07, 250.09<br>ICD-10: E11.0, E11.1, E11.9 |
| Hemiplegia | ICD-8: 344<br>ICD-10: G81, G82 |
| Moderate to severe renal disease | ICD-8: 403, 404, 580-583,584,590.09, 593.19, 753.10-753.19, 792<br>ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61 |
| Diabetes with end organ damage | |
| Type1 | ICD-8: 249.01-249.05, 249.08<br>ICD-10: E10.2-E10.8 |
| Type2 | ICD-8: 250.01-250.05, 250.08<br>ICD-10: E11.2-E11.8 |
| Any tumor (excluding breast cancer and non-malignant skin cancer) | ICD-8: 140-194<br>ICD-10: C00-C75 |
| Leukemia | ICD-8: 204-207<br>ICD-10: C91-C95 |
| Lymphoma | ICD-8: 200-203,275.59<br>ICD-10: C81-C85, C88, C90, C96 |
| Moderate to severe liver disease | ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09<br>ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85 |
| Metastatic solid tumor | ICD-8: 195-198, 199<br>ICD-10: C76-C80 |
| AIDS | ICD-8: 079.83<br>ICD-10: B21-B24 |

## Morbidity categories included in the hypothesis-screening analysis (Study I)

| | |
|---|---|
| Cholera | ICD-8: 0.0–0.9<br>ICD-10: A00.0–A00.9 |
| Typhoid and paratyphoid fevers | ICD-8: 1.0–1.9<br>ICD-10: A01.0–A01.9 |
| Other intestinal infectious diseases | ICD-8: 5.0–5.9, 7.0-7.9<br>ICD-10: A02.0–A02.9, A04.0–A05.9, A07.0–A08.9 |
| Shigellosis/Bacillary dysentery | ICD-8: 4.0–4.9<br>ICD-10: A03.0–A03.9 |
| Amoebiasis | ICD-8: 6.0–6.9<br>ICD-10: A06.0–A06.9 |
| Diarrhea and gastro-enteritis of presumed infectious origin | ICD-8: 8.0–9.9<br>ICD-10: A09.0–A09.9 |
| Respiratory tuberculosis | ICD-8: 10.0–12.3<br>ICD-10: A15.0–A16.9 |
| Other tuberculosis | ICD-8: 13.0–19.9<br>ICD-10: A17.0–A19.9,B90.0–B90.9 |
| Plague | ICD-8: 20.0–20.9<br>ICD-10: A20.0–A20.9 |
| Other bacterial diseases | ICD-8:21.0–22.9, 24.0–27.9, 31.0–31.9, 34.0–34.1, 35.0–35.9, 30.0–39.9<br>ICD-10: A21.0–A22.9,A24.0–A28.9, A31.0–A32.9, A38.0–A38.9, A42.0–A49.9, B96.0–B96.9 |
| Brucellosis | ICD-8: 23.0–23.9<br>ICD-10: A23.0–A23.9 |
| Leprosy | ICD-8:30.0–30.9<br>ICD-10: A30.0–A30.9, B92.0–B92.9 |
| Tetanus | ICD-8: 37.0–37.9<br>ICD-10: A33.0–A33.9, A34.0–A35.9 |
| Diphtheria | ICD-8: 32.0–32.9<br>ICD-10: A36.0–A36.9 |
| Whooping cough | ICD-8: 33.0–33.9<br>ICD-10: A37.0–A37.9 |
| Meningococcal infection | ICD-8: 36.0–36.9<br>ICD-10: A39.0–A39.9 |
| Septicemia | ICD-8: 38.0–38.9<br>ICD-10: A40.0–A41.9 |
| Early syphilis | ICD-8: 91.0–91.9<br>ICD-10: A51.0–A51.9 |
| Other syphilis | ICD-8: 90.0–90.9, 92.0–97.9<br>ICD-10: A50.0–A50.9, A52.0–A53.9 |
| Gonococcal infection | ICD-8: 98.0–98.9<br>ICD-10: A54.0–A54.9 |
| Other infectious and parasitic diseases | ICD-8: 130.0–136.9, 89.0–89.9<br>ICD-8: 99.0–117.9<br>ICD-10: A55.0–A67.9, A69.0–A70.9, A74.0–A74.9, A77.0–A79.9, B35.0–B49.9, B58.0–B64.9, B85.0–B89.9, B94.0–B94.9, B99.0–B99.9 |
| Relapsing fevers | ICD-8: 88.0–88.9<br>ICD-10: A68.0–A68.9 |
| Other viral diseases | ICD-8: 45.0–46.9, 50.0–54.9, 57.0–57.9, 61.0–61.9, 66.0–66.9, 68.0–68.9, 73.0–79.9<br>ICD-10: A71.0–A71.9, A81.0–A81.9, A87.0–A89.9, B00.0–B04.9, B07.0–B09.9, B20.0–B25.9, B27.0–B34.9, B97.0–B97.9 |
| Typhus and other rickettsioses | ICD-8: 80.0–83.9<br>ICD-10: A75.0–A75.9 |
| Acute poliomyelitis | ICD-8: 40.0–44.9<br>ICD-10: A80.0–A80.9, B91.0–B91.9 |
| Rabies | ICD-8: 71.0–71.9<br>ICD-10: A82.0–A82.9 |
| Viral encephalitis | ICD-8: 62.0–65.9<br>ICD-10: A83.0–A86.9 |
| Other arthropod-borne viral fevers and viral hemorrhagic fevers | ICD-8: 67.0–67.9<br>ICD-10: A90.0–A94.9, A96.0–A99.9 |

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| Yellow fever | ICD-8: 60.0–60.9<br>ICD-10: A95.0–A95.9 |
| Measles | ICD-8: 55.0–55.9<br>ICD-10: B05.0–B05.9 |
| Rubella | ICD-8: 56.0–56.9<br>ICD-10: B06.0–B06.9 |
| Hepatitis | ICD-8: 70.0–70.9<br>ICD-10: B15.0–B15.9, B16.0–B16.9, B17.0–B19.9 |
| Mumps | ICD-8: 72.0–72.9<br>ICD-10: B26.0–B26.9 |
| Malaria | ICD-8: 84.0–84.9<br>ICD-10: B50.0–B54.9 |
| Leishmaniasis | ICD-8: 85.0–85.9<br>ICD-10: B55.0–B55.9 |
| Trypanosomiasis | ICD-8: 86.0–87.9<br>ICD-10: B56.0–B57.9 |
| Schistosomiasis | ICD-8: 120.0–120.9<br>ICD-10: B65.0–B65.9 |
| Other helminthiase | ICD-8: 121.0–121.9, 123.0–125.9, 127.0–129.9<br>ICD-10: B66.0–B66.9, B68.0–B75.9, B77.0–B83.9 |
| Echinococcosis/hydatidosis | ICD-8: 122.0–122.9<br>ICD-10: B67.0–B67.9 |
| Hookworm diseases/Ankylostomiasis | ICD-8: 126–126.9<br>ICD-10: B76.0–B76.9 |
| Malignant neoplasm of lip, oral cavity and pharynx | ICD-8: 140.0–149.9<br>ICD-10: C00.0–C14.9 |
| Malignant neoplasm of other digestive organs and peritoneum | ICD-8: 150.0–150.9, 155.0–159.9<br>ICD-10: C15.0–C15.9, C17.0–C17.9, C22.0–C26.9 |
| Malignant neoplasm of stomach | ICD-8: 151.0–151.9<br>ICD-10: C16.0–C16.9 |
| Malignant neoplasm of colon | ICD-8: 152.0–153.9<br>ICD-10: C18.0–C18.9 |
| Malignant neoplasm of rectosigmoid junction, rectum, anus, and anal canal | ICD-8: 154.0–154.9<br>ICD-10: C19.0–C21.9 |
| Other malignant neoplasms of respiratory and intrathoracic organs | ICD-10: C30.0–C31.9<br>ICD-10: C37.0–C39.9 |
| Malignant neoplasm of other and unspecified respiratory organs | ICD-8: 160.0–160.9<br>ICD-8: 163.0–163.9 |
| Malignant neoplasm of larynx | ICD-8: 161.0–161.9<br>ICD-10:C32.0–C32.9 |
| Malignant neoplasm of trachea, bronchus and lung | ICD-8: 162.0–162.9<br>ICD-10: C33.0–C34.9 |
| Malignant neoplasm of bone and articular cartilage | ICD-8: 170.0–170.9<br>ICD-10: C40.0–C41.9 |
| Malignant neoplasm of skin | ICD-8: 172.0–173.9<br>ICD-10: C43.0–C43.9, C44.0–C44.9 |
| Malignant neoplasm of other specified sites | ICD-8: 171.0–171.9, 190.0–190.9, 192.0–195.9<br>ICD-10: C45.0–C49.9, C69.0–C70.9, C72.0–C72.9 |
| Other malignant neoplasms of female genital organs | ICD-8: 181.0–181.9, 183.0–183.1, 183.0–184.9<br>ICD-10: C51.0–C52.9, C56.0–C58.9 |
| Malignant neoplasm of *cervix uteri* | ICD-8: 180.0–180.9<br>ICD-10: C53.0–C53.9 |
| Malignant neoplasm of other and unspecified parts of uterus | ICD-8: 182.0–182.9<br>ICD-10: C54.0–C55.9 |
| Other malignant neoplasms of male genital organs | ICD-8: 186.0–186.9<br>ICD-10: C60.0–C60.9, C62.0–C63.9 |
| Malignant neoplasm of prostate | ICD-8: 185.0–185.9<br>ICD-10: C61.0–C61.9 |
| Other malignant neoplasms of urinary tract | ICD-10: C64.0–C66.9, C68.0–C68.9 |
| Malignant neoplasm of other genitourinary organs | ICD-8: 187.0–187.9, 189.0–189.9 |
| Malignant neoplasm of bladder | ICD-8: 188.0–188.9<br>ICD-10: C67.0–C67.9 |
| Malignant neoplasm of brain | ICD-8: 191.0–191.9<br>ICD-10: C71.0–C71.9 |
| Malignant neoplasm of other, ill-defined, secondary, unspecified, and multiple sites | ICD-8: 197.0–199.9<br>ICD-10: C73.0–C80, C97.0–C97.9 |
| Hodgkin's disease | ICD-8: 201.0–201.9<br>ICD-10: C81.0–C81.9 |
| Other malignant neoplasms of lymphoid, hematopoietic, and | ICD-8:196.0–196.9, 200.0–200.9, 202.0– |

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|---|---|
| related tissue | 203.9, 208.0–209.9<br>ICD-10: C82.0–C85.9, C88.0–C90.9, C96.0–C96.9 |
| Leukemia | ICD-8: 204.0–207.9<br>ICD-10: C91.0–C95.9 |
| Other *in situ* and benign neoplasms and neoplasms of uncertain and unknown behavior | ICD-8: 210.0–215.9, 217.0–217.9, 219.0–219.9, 221.0–222.9, 224.0–224.9, 226.0–228.9, 230.0–239.9<br>ICD-10: D00.0–D05.9, D07.0–D21.9, D24.0–D24.9, D26.0–D26.9, D28.0–D29.9, D31.0–D32.9, D34.0–D48.9 |
| Carcinoma *in situ* of *cervix uteri* | ICD-8: 234.0–234.0<br>ICD-10: D06.0–D06.9 |
| Benign neoplasm of skin | ICD-8: 216.0–216.9<br>ICD-10: D22.0–D23.9 |
| Leiomyoma of uterus | ICD-8: 218.0–218.9<br>ICD-10: D25.0–D25.9 |
| Benign neoplasm of ovary | ICD-8: 220.0–220.9<br>ICD-10: D27.0–D27.9 |
| Benign neoplasm of kidney and other urinary organs | ICD-8: 223.0–223.9<br>ICD-10: D30.0–D30.9 |
| Benign neoplasm of brain and other parts of central nervous system | ICD-8: 225.0–225.9<br>ICD-10: D33.0–D33.9 |
| Iron deficiency anemia | ICD-8: 280.0–280.9<br>ICD-10: D50.0–D50.9 |
| Other anemias | ICD-8: 281.0–285.9<br>ICD-10: D51.0–D64.9 |
| Hemorrhagic conditions and other diseases of blood and blood-forming organs | ICD-8:286.0–289.9<br>ICD-10: D65.0–D77.9 |
| Other endocrine, nutritional. and metabolic disorders | ICD-8: 251.0–258.9, 270.0–279.9<br>ICD-10: D80.0–D89.9, E15.0–E35.9, E58.0–E63.9, E65.0–E65.9, E66.0–E66.9, E67.0–E85.9, E87.0–E90.9 |
| Other disorders of thyroid | ICD-8: 240.0–241.9, 243.0–246.9<br>ICD-10: E03.0–E04.9, E06.0–E07.9 |
| Iodine-deficiency-related thyroid disorders | ICD-8: 242.0–242.9<br>ICD-10: E00.0–E02.9, E05.0–E05.9 |
| Diabetes mellitus | ICD-8: 249.0–250.9<br>ICD-10: E10.0–E14.9 |
| A-vitaminosis and other nutritional deficiency | ICD-8: 260.0–269.9<br>ICD-10: E40.0–E47.9, E50.0–E50.9, E51.0-E56.9, E64.0–E64.9 |
| Dementia | ICD-8: 290.0–290.0, 290.0–290.9<br>ICD-10: F00.0–F03.9, G31.0–G31.0 |
| Other mental and behavioral disorders | ICD-8: 292.0–294.9, 297.0–299.9, 305.0–309.9<br>ICD-10: F04.0–F09.9, F50.0–F69.9, F80.0–F99.9 |
| Alcohol-, drug-abuse-related disease | ICD-8: 291.0–291.9, 303.0–304.9<br>ICD-10: F10.0–F19.9 |
| Schizophrenia, schizotypal, and delusional disorders | ICD-8: 295.0–295.9<br>ICD-10: F20.0–F29.9 |
| Mood (affective) disorders | ICD-8: 296.0–296.1, 296.0–296.9<br>ICD-10: F30.0–F31.9, F34.0–F39.9 |
| Depression | ICD-8: 296.0–296.0, 296.0–296.2<br>ICD-10: F32.0–F33.9 |
| Neurotic, stress-related, and somatoform disorders | ICD-8: 300.0–302.9<br>ICD-10: F40.0–F48.9 |
| Mental retardation | ICD-8: 310.0–315.9<br>ICD-10: F70.0–F79.9 |
| Inflammatory diseases of the central nervous system | ICD-8: 320.0–320.9, 321.0–324.9<br>ICD-10: G00.0–G09.9 |
| Other diseases of the nervous system | ICD-8: 330.0–333.9, 343.0–344.9, 347.0–358.9,<br>ICD-10: G10.0–G13.9, G21.0–G26.9, G31.1–G32.9, G36.0–G37.9, G44.0–G44.9, G46.0–G47.9,G50.0–G73.9, G80.0–G83.9, G90.0–G99.9 |
| Parkinson’s disease | ICD-8: 342.0–342.9<br>ICD-10: G20.0–G20.9 |

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|---|---|
| Alzheimer's disease | ICD-8: 290.0–290.1<br>ICD-10: G30.0–G30.9 |
| Multiple sclerosis and other demyelinating diseases | ICD-8: 340.0–341.9<br>ICD-10: G35.0–G35.9 |
| Epilepsy | ICD-8: 345.0–345.9<br>ICD-10: G40.0–G41.9 |
| Migraine | ICD-8: 346.0–346.9<br>ICD-10: G43.0–G43.9 |
| Transient cerebral ischemic attacks and related syndromes | ICD-8: 435.0–435.9<br>ICD-10: G45.0–G45.9 |
| Other inflammatory diseases of eye | ICD-8: 360.0–369.9<br>ICD-10: H00.0–H01.9, H10.0–H13.9, H15.0–H19.9 |
| Other diseases of the eye and adnexa | ICD-8: 370.0–372.9, 377.0–379.9<br>ICD-10: H02.0–H06.9, H20.0–H22.9, H30.0–H32.9, H34.0–H36.9, H43.0–H48.9, H51.0–H59.9 |
| Cataract and other disorders of lens | ICD-8: 374.0–374.9<br>ICD-10: H25.0–H28.9 |
| Retinal detachments and breaks | ICD-8: 376.0–376.9<br>ICD-10: H33.0–H33.9 |
| Glaucoma | ICD-8: 375.0–375.9<br>ICD-10: H40.0–H42.9 |
| Strabismus | ICD-8: 373.0–373.9<br>ICD-10: H49.0–H50.9 |
| Other diseases of the ear and mastoid process | ICD-8: 380.0–380.9, 381.0–381.9, 382.0–383.9, 384.0–389.9<br>ICD-10: H60.0–H62.9, H65.0–H75.9, H80.0–H83.9, H90.0–H95.9 |
| Acute rheumatic fever | ICD-8: 390.0–392.9<br>ICD-10: I00.0–I02.9 |
| Chronic rheumatic heart disease | ICD-8: 393.0–392.2<br>ICD-10: I05.0–I09.9 |
| Essential (primary) hypertension | ICD-8: 400.0–404.9<br>ICD-10: I10.0–I15.9 |
| Angina pectoris | ICD-8: 413.0–413.9<br>ICD-10: I20.0–I20.9 |
| Acute myocardial infarction | ICD-8: 410.0–410.9<br>ICD-10: I21.0–I22.9 |
| Other ischemic heart diseases | ICD-8: 411.0–412.9<br>ICD-10: I23.0–I25.9 |
| Other ischemic heart disease | ICD-8: 414.0–414.9 |
| Pulmonary embolism | ICD-8: 450.0–450.9<br>ICD-10: I26.0–I26.9 |
| Other heart diseases | ICD-8: 420.0–426.9, 428.0–429.9<br>ICD-10: I27.0–I43.9, I51.0–I52.9 |
| Conduction disorders and cardiac arrhythmias | ICD-8: 427.0–427.9<br>ICD-10: I44.0–I49.9 |
| Congestive heart failure | ICD-8: 427.0–427.0<br>ICD-10: I50.0–I50.9 |
| Intracranial hemorrhage | ICD-8: 431.0–431.9<br>ICD-10: I60.0–I62.9 |
| Cerebral infarction | ICD-8: 432.0–434.9<br>ICD-10: I63.0–I63.9 |
| Other cerebrovascular diseases | ICD-8: 430.0–430.9, 436.0–436.9, 437.0–438.9<br>ICD-10: I64.0–I64.9, I65.0–I69.9 |
| Atherosclerosis | ICD-8: 440.0–440.9<br>ICD-10: I70.0–I70.9 |
| Other diseases of arteries, arterioles and capillaries | ICD-8: 441.0–442.9, 444.0–448.9<br>ICD-10: I71.0–I72.9, I74.0–I74.9, I77.0–I79.9 |
| Other peripheral vascular diseases | ICD-8: 443.0–443.9<br>ICD-10: I73.0–I73.9 |
| Phlebitis, thrombophlebitis, venous embolism and thrombosis | ICD-8: 451.0–453.9<br>ICD-10: I80.0–I82.9 |
| Varicose veins of lower extremities | ICD-8: 454.0–454.9<br>ICD-10: I83.0–I83.9 |
| Hemorrhoids | ICD-8: 455.0–455.9<br>ICD-10: I84.0–I84.9 |
| Other diseases of the circulatory system | ICD-8: 456.0–458.9<br>ICD-10: I85.0–I99.9 |
| Other acute upper respiratory infections | ICD-8: 460–461.9, 464.0–465.9<br>ICD-10: J00.0–J01.9, J04.0–J04.9, J05.0–J06.9 |

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| Acute pharyngitis and acute tonsillitis | ICD-8:34.0–34.0, 462.0–463.9<br>ICD-10: J02.0–J03.9 |
| Influenza | ICD-8: 470.0–474.9<br>ICD-10: J10.0–J11.9 |
| Pneumonia | ICD-8: 480.0–480.9, 481.0–481.9, 482.0–483.9, 484.0–486.9<br>ICD-10: J12.0–J18.9 |
| Acute bronchitis and acute bronchiolitis | ICD-8: 466.0–466.9<br>ICD-10: J20.0–J21.9 |
| Other diseases of the respiratory system | ICD-8: 510.0–514.9, 517.0–517.9, 519.0–519.9<br>ICD-10: J22.0–J22.9, J66.0–J99.9 |
| Other diseases of upper respiratory tract | ICD-8: 501.0–502.9, 504.0–504.9, 505.0–508.9<br>ICD-10: J30.0–J31.9, J33.0–J34.9, J36.0–J39.9 |
| Chronic sinusitis | ICD-8: 503.0–503.9<br>ICD-10: J32.0–J32.9 |
| Chronic disease of tonsils and adenoids | ICD-8: 500.0–500.9<br>ICD-10: J35.0–J35.9 |
| Bronchitis, emphysema and other chronic pulmonary diseases | ICD-8: 490.0–493.9<br>ICD-10: J40.0–J44.9, J45.0–J46.9 |
| Bronchiectasis | ICD-8: 518.0–518.9<br>ICD-10: J47.0–J47.9 |
| Pneumoconioses and related diseases | ICD-8: 515.0–516.9<br>ICD-10: J60.0–J65.9 |
| Other diseases of the teeth, oral cavity, salivary glands and jaws | ICD-8: 520.0–529.9<br>ICD-10: K00.0–K14.9 |
| Other diseases of esophagus, stomach and duodenum | ICD-8: 530.0–530.9, 536.0–537.9<br>ICD-10: K20.0–K23.9, K28.0–K28.9, K30.0–K31.9 |
| Gastric and duodenal ulcer | ICD-8: 531.0–534.9<br>ICD-10: K25.0–K27.9 |
| Gastritis and duodenitis | ICD-8: 535.0–535.9<br>ICD-10: K29.0–K29.9 |
| Diseases of appendix | ICD-8: 540.0–543.9<br>ICD-10: K35.0–K38.9 |
| Hernia | ICD-8: 550.0–553.9<br>ICD-10: K40.0–K46.9 |
| Crohn's disease and ulcerative colitis | ICD-8: 563.0–563.9<br>ICD-10: K50.0–K51.9 |
| Other diseases of the digestive system | ICD-8: 561.0–562.9, 564.0–569.9<br>ICD-10: K52.0–K55.9, K57.0–K67.9, K82.0–K83.9, K87.0–K93.9 |
| Paralytic ileus and intestinal obstruction without hernia | ICD-8: 560.0–560.9<br>ICD-10: K56.0–K56.9 |
| Other diseases of liver and gallbladder | ICD-8: 570.0–573.9, 576.0–576.9<br>ICD-10: K70.0–K77.9 |
| Cholelithiasis and cholecystitis | ICD-8: 574.0–575.9<br>ICD-10: K80.0–K81.9 |
| Acute pancreatitis and other diseases of the pancreas | ICD-8:577.0–577.9<br>ICD-10: K85.0–K86.9 |
| Infections of the skin and subcutaneous tissue | ICD-8: 680.0–686.9<br>ICD-10: L00.0–L08.9 |
| Other diseases of the skin and subcutaneous tissue | ICD-8:690.0–698.9, 700.0–709.9<br>ICD-10: L10.0–L99.9 |
| Other disorders of joints | ICD-8: 724.0–724.9, 726.0–727.9, 729.0–729.9, 737.0–737.9<br>ICD-10: M00.0–M03.9, M22.0–M25.9 |
| Rheumatoid arthritis and other inflammatory polyarthropathies | ICD-8: 712.0–712.9, 716.0–716.9<br>ICD-10: M05.0–M14.9 |
| Osteoarthritis and allied conditions | ICD-8: 710.0–711.9, 713.0–715.9<br>ICD-10: M15.0–M19.9, M47.0–M47.9, M48.3–M48.3 |
| Acquired deformities of limbs | ICD-8: 736.0–736.9<br>ICD-10: M20.0–M21.9 |
| Other diseases of the musculoskeletal system and connective tissue | ICD-8: 730.0–730.9, 733.0–734.9, 738.0–738.9<br>ICD-10: M30.0–M36.9, M87.0–M90.9, M94.0– |

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| | M99.9 |
| Other dorsopathies | ICD-8: 735.0–735.9<br>ICD-10: M40.0–M41.9, M43.0–M43.5, M43.7-M46.9, M48.0–M48.2, M48.4–M49.9, M53.0–M53.9 |
| Osteochondrosis | ICD-8: 722.0–722.9<br>ICD-10: M42.0–M42.9, M91.0–M93.9 |
| Rheumatism | ICD-8: 717.0–718.9<br>ICD-10: M43.6–M43.6, M79.0–M79.1 |
| Cervical and other intervertebral disc disorders | ICD-8: 725.0–725.9, 728.0–728.9<br>ICD-10: M50.0–M51.9, M54.0–M54.9 |
| Myositis | ICD-8: 732.0–732.9<br>ICD-10: M60.0–M60.9 |
| Soft tissue disorders | ICD-8: 731.0–731.9<br>ICD-10: M61.0–M78.9, M79.2–M79.5, M79.7–M79.9 |
| Osteoporosis with and without fracture | ICD-8: 723.0–723.0<br>ICD-10: M80.0–M81.9 |
| Other diseases of bone | ICD-8: 721.0–721.9, 723.0–723.9<br>ICD-10: M82.0–M85.9 |
| Osteomyelitis and periostitis | ICD-8: 720.0–720.9<br>ICD-10: M86.0–M86.9 |
| Nephritis and nephrosis | ICD-8: 580.0–584.9<br>ICD-10: N00.0–N08.9 |
| Infections of kidney | ICD-8: 590.0–590.9<br>ICD-10: N10.0–N16.9 |
| Other diseases of the urinary system | ICD-8: 591.0–591.9, 593.0–593.9, 596.0–599.9<br>ICD-10: N17.0–N19.9, N25.0–N29.9, N31.0–N39.9 |
| Urolithiasis/Calculus of urinary system | ICD-8: 592.0–592.9, 594.0–594.9<br>ICD-10: N20.0–N23.9 |
| Cystitis | ICD-8: 595.0–595.9<br>ICD-10: N30.0–N30.9 |
| Hyperplasia of prostate | ICD-8: 600.0–600.9<br>ICD-10: N40.0–N40.9 |
| Other diseases of male genital organs | ICD-8: 601.0–602.9, 604.0–604.9, 606.0–607.9<br>ICD-10: N41.0–N42.9, N44.0–N46.9, N48.0–N51.9 |
| Hydrocele and spermatocele | ICD-8: 603.0–603.9<br>ICD-10: N43.0–N43.9 |
| Redundant prepuce, phimosis and paraphimosis | ICD-8: 605.0–605.9<br>ICD-10: N47.0–N47.9 |
| Disorders of breast | ICD-8: 610.0–611.9<br>ICD-10: N60.0–N64.9 |
| Salpingitis and oophoritis | ICD-8: 612.0–614.9<br>ICD-10: N70.0–N70.9 |
| Other inflammatory diseases of female pelvic organs | ICD-8: 622.0–622.9<br>ICD-10:N71.0–N71.9, N73.0–N77.9 |
| Inflammatory disease of cervix uteri | ICD-8: 620.0–620.9<br>ICD-10: N72.0–N72.9 |
| Endometriosis | ICD-8: 625.0–625.3<br>ICD-10: N80.0–N80.9 |
| Female genital prolapse | ICD-8: 623.0–623.9<br>ICD-10: N81.0–N81.9 |
| Other disorders of genitourinary tract | ICD-8:621.0–621.9, 624.0–625.9, 627.0–627.9, 629.0–629.9<br>ICD-10: N82.0–N82.9, N84.0–N90.9, N93.0–N96.9, N98.0–N99.9 |
| Other diseases of ovary, fallopian tube and parametrium | ICD-8: 615.0–616.9<br>ICD-10: N83.0–N83.9 |
| Disorders of menstruation | ICD-8: 626.0–626.9<br>ICD-10: N91.0–N92.9 |
| Female infertility | ICD-8: 628.0–628.9<br>ICD-10: N97.0–N97.9 |

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| Ectopic pregnancy | ICD-8: 631.0–631.9<br>ICD-10: O00.0–O00.9 |
| Pregnancies with abortive outcome | ICD-8: 640.0–645.9<br>ICD-10: O01.0–O08.9 |
| Other complications of pregnancy or delivery | ICD-8: 630.0–639.9, 651.0–666.9, 670.0–678.9<br>ICD-10: O10.0–O16.9, O20.0–O48.9, O60.0–O75.9, O81.0–O99.9 |
| Delivery without mention of complication | ICD-8: 650.0–650.9<br>ICD-10: O80.0–O80.9 |
| Conditions originating in the perinatal period | ICD-8: 760.0–773.9, 776.0–779.9<br>ICD-10: P00.0–P54.9, P56.0–P96.9 |
| Hemolytic disease of fetus and newborn | ICD-8: 774.0–775.9<br>ICD-10: P55.0–P55.9 |
| Spina bifida and congenital hydrocephalus | ICD-8: 741.0–742.9<br>ICD-10: Q05.0–Q05.9 |
| Congenital malformations of the circulatory system | ICD-8: 746.0–747.9<br>ICD-10: Q20.0–Q28.9 |
| Cleft lip and cleft palate | ICD-8: 749.0–749.9<br>ICD-10: Q35.0–Q37.9 |
| Other congenital malformations of the digestive system | ICD-8: 750.0–750.0, 750.0–750.9, 751.0–751.9<br>ICD-10: Q38.0–Q40.9, Q42.0–Q45.9 |
| Absence, atresia and stenosis of small intestine | ICD-8: 750.0–750.1<br>ICD-10: Q41.0–Q41.9 |
| Other malformations of the genitourinary system | ICD-8: 752.2–753.9<br>ICD-10: Q50.0–Q52.9, Q54.0–Q64.9 |
| Undescended testicle | ICD-8: 752.0–752.1<br>ICD-10: Q53.0–Q53.9 |
| Congenital deformities of hip | ICD-8: 755.0–755.6<br>ICD-10: Q65.0–Q65.9 |
| Congenital deformities of feet | ICD-8: 754.0–754.9<br>ICD-10: Q66.0–Q66.9 |
| Other and unspecified congenital anomalies | ICD-8: 740.0–740.9, 743.0–745.9, 748.0–748.9, 757.0–759.9<br>ICD-10: Q00–Q04.9, Q06.0–Q07.9, Q10–Q18.9, Q30.0–Q34.9, Q80.0–Q99.9 |
| Other congenital malformations and deformations of the musculoskeletal system | ICD-8: 755.0–755.9, 755.0–756.9, 756.0–756.9<br>ICD-10: Q67.0–Q79.9 |
| Abdominal and pelvic pain | ICD-8: 785.0–785.5<br>ICD-10: R10.0–R10.9 |
| Senility | ICD-8: 794.0–794.9<br>ICD-10: R54.0–R54.9 |

## 11.2 Appendix 2. Hypothesis-screening analysis results (study I)

# Morbidity categories and breast cancer risk.

| Preceding morbidity | # exposed cases | Original OR estimates | Empirical-Bayes adjusted estimates |
|---|---|---|---|
| Iron deficiency anemia | 32 | 0.61 (0.45, 0.81) | 0.91 (0.73, 1.15) |
| Chronic disease of tonsils and adenoids | 59 | 0.74 (0.52, 1.06) | 0.99 (0.78, 1.25) |
| Dementia | 5 | 0.77 (0.59, 1.00) | 0.96 (0.77, 1.20) |
| Malignant neoplasm of bone and articular cartilage | 50 | 0.77 (0.31, 1.91) | 1.05 (0.82, 1.33) |
| Other tuberculosis | 10 | 0.78 (0.41, 1.48) | 1.04 (0.81, 1.32) |
| Other anemias | 133 | 0.78 (0.66, 0.94) | 0.91 (0.74, 1.13) |
| Alzheimer's disease | 18 | 0.79 (0.49, 1.28) | 1.02 (0.81, 1.30) |
| Other diseases of the bone | 104 | 0.83 (0.68, 1.01) | 0.95 (0.77, 1.19) |
| Other malignant neoplasms of urinary tract | 16 | 0.85 (0.51, 1.41) | 1.03 (0.81, 1.31) |
| Septicemia | 53 | 0.85 (0.64, 1.12) | 0.99 (0.79, 1.25) |
| Influenza | 39 | 0.85 (0.61, 1.18) | 1.01 (0.80, 1.27) |
| Hepatitis | 19 | 0.86 (0.54, 1.37) | 1.03 (0.81, 1.31) |
| Migraine | 114 | 0.86 (0.71, 1.04) | 0.96 (0.78, 1.19) |
| Osteoporosis with and without fracture | 369 | 0.87 (0.78, 0.96) | 0.92 (0.75, 1.11) |
| Rheumatoid arthritis and other inflammatory polyarthropathies | 438 | 0.88 (0.80, 0.98) | 0.92 (0.76, 1.12) |
| Gastric and duodenal ulcer | 467 | 0.89 (0.81, 0.98) | 0.93 (0.77, 1.12) |
| Acute myocaridal infarction | 429 | 0.89 (0.81, 0.99) | 0.93 (0.76, 1.13) |
| Benign neoplasm of brain and other parts of central nervous system | 45 | 0.90 (0.67, 1.23) | 1.02 (0.81, 1.28) |
| Epilepsy | 185 | 0.91 (0.78, 1.05) | 0.97 (0.79, 1.19) |
| Malignant neoplasm of larynx | 47 | 0.91 (0.49, 1.70) | 1.05 (0.82, 1.33) |
| Other acute upper respiratory infections | 59 | 0.91 (0.70, 1.19) | 1.01 (0.81, 1.27) |
| Gastritis and duodenitis | 353 | 0.92 (0.82, 1.02) | 0.95 (0.79, 1.16) |
| A-vitaminosis and other nutritional deficiency | 21 | 0.93 (0.59, 1.45) | 1.04 (0.82, 1.32) |
| Other infectious and parasitic diseases | 112 | 0.94 (0.77, 1.14) | 1.00 (0.81, 1.24) |
| Chronic sinusitis | 61 | 0.94 (0.72, 1.22) | 1.02 (0.81, 1.28) |
| Leukemia | 28 | 0.94 (0.64, 1.38) | 1.04 (0.82, 1.31) |
| Congenital deformations of hip | 12 | 0.94 (0.52, 1.71) | 1.05 (0.83, 1.33) |
| Cataract and other disorders of lens | 164 | 0.95 (0.89, 1.01) | 0.96 (0.80, 1.15) |
| Glaucoma | 1210 | 0.95 (0.81, 1.12) | 1.00 (0.81, 1.23) |
| Other peripheral vascular disease | 82 | 0.96 (0.76, 1.20) | 1.02 (0.82, 1.27) |
| Malignant neoplasm of stomach | 11 | 0.96 (0.52, 1.78) | 1.05 (0.83, 1.33) |
| Inflammatory diseases of *cervix uteri* | 14 | 0.96 (0.55, 1.66) | 1.05 (0.83, 1.33) |
| Other diseases of oesophagus, stomach and duodenum | 710 | 0.96 (0.89, 1.04) | 0.97 (0.81, 1.17) |

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| Other congenital malformations and deformations of the musculoskeletal system | 45 | 0.96 (0.71, 1.31) | 1.03 (0.82, 1.30) |
| Other ischemic heart disease | 403 | 0.96 (0.87, 1.07) | 0.99 (0.81, 1.20) |
| Other endocrine, nutritional, and metabolic disorders | 492 | 0.97 (0.88, 1.06) | 0.99 (0.82, 1.19) |
| Female genital prolapse | 882 | 0.97 (0.90, 1.03) | 0.98 (0.81, 1.18) |
| Infections of the skin and subcutaneous tissue | 746 | 0.97 (0.88, 1.08) | 1.00 (0.82, 1.21) |
| Other disease of the nervous system | 861 | 0.98 (0.91, 1.05) | 0.99 (0.82, 1.19) |
| Benign neoplasm of kidney and other urinary organs | 81 | 0.98 (0.78, 1.23) | 1.03 (0.83, 1.28) |
| Other disorders of joints | 746 | 0.98 (0.91, 1.06) | 0.99 (0.83, 1.20) |
| Ectopic pregnancy | 24 | 0.99 (0.65, 1.50) | 1.05 (0.83, 1.32) |
| Congenital malformations of the circulatory system | 25 | 0.99 (0.66, 1.49) | 1.05 (0.83, 1.32) |
| Other and unspecified congenital anomalities | 78 | 0.99 (0.79, 1.25) | 1.03 (0.83, 1.29) |
| Atherosclerosis | 347 | 0.99 (0.89, 1.11) | 1.01 (0.83, 1.23) |
| Salpingitis and oophoritis | 75 | 0.99 (0.78, 1.26) | 1.03 (0.83, 1.29) |
| Other mental and behavioral disorders | 65 | 0.99 (0.77, 1.28) | 1.04 (0.83, 1.30) |
| Acquired deformities of limbs | 447 | 1.00 (0.90, 1.10) | 1.01 (0.83, 1.22) |
| Paralytic ileus and intestinal obstruction without hernia | 152 | 1.00 (0.85, 1.18) | 1.03 (0.83, 1.27) |
| Hernia | 647 | 1.00 (0.92, 1.08) | 1.01 (0.84, 1.22) |
| Hemorrhoids | 356 | 1.00 (0.90, 1.12) | 1.02 (0.84, 1.24) |
| Transient cerebral ischemic attacks and related syndromes | 301 | 1.01 (0.89, 1.13) | 1.02 (0.84, 1.25) |
| Pneumonia | 636 | 1.01 (0.93, 1.09) | 1.02 (0.84, 1.23) |
| Crohn's disease and ulcerative colitis | 183 | 1.01 (0.87, 1.18) | 1.03 (0.84, 1.27) |
| Malignant neoplasm of *cervix uteri* | 70 | 1.01 (0.79, 1.30) | 1.04 (0.84, 1.30) |
| Malignant neoplasm of other digestive organs and peritoneum | 13 | 1.02 (0.57, 1.80) | 1.05 (0.83, 1.34) |
| Pregnancies with abortive outcome | 383 | 1.02 (0.91, 1.13) | 1.03 (0.85, 1.25) |
| Urolithiasis/calculus of urinary system | 228 | 1.02 (0.89, 1.17) | 1.03 (0.84, 1.26) |
| Bronchitis, emphysema and other chronic obstructive pulmonary diseases | 937 | 1.02 (0.95, 1.09) | 1.02 (0.85, 1.23) |
| Other inflammatory diseases of eye | 334 | 1.02 (0.91, 1.14) | 1.03 (0.85, 1.26) |
| Other heart disease | 220 | 1.02 (0.89, 1.17) | 1.04 (0.85, 1.27) |
| Other diseases of arteries, arterioles, and capillaries | 195 | 1.02 (0.88, 1.18) | 1.04 (0.84, 1.27) |
| Varicose veins of lower extremities | 888 | 1.03 (0.96, 1.10) | 1.03 (0.86, 1.24) |
| Soft tissue disorders | 1765 | 1.03 (0.98, 1.08) | 1.03 (0.86, 1.23) |
| Other diseases of the teeth, oral cavity, salivary glands, and jaws | 368 | 1.03 (0.92, 1.14) | 1.04 (0.85, 1.26) |
| Hemorrhagic conditions and other diseases of blood and blood-forming organs | 76 | 1.03 (0.81, 1.30) | 1.05 (0.84, 1.31) |
| Essential (primary) hypertension | 734 | 1.03 (0.95,1.11) | 1.03 (0.86, 1.24) |
| Angina pectoris | 892 | 1.03 (0.96, 1.10) | 1.03 (0.86, 1.24) |
| Retinal detachments and breaks | 119 | 1.03 (0.85, 1.24) | 1.05 (0.84, 1.29) |

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| Other diseases of the ear and mastoid process | 1942 | 1.03 (0.99, 1.09) | 1.04 (0.87, 1.24) |
| Other diseases of the musculoskeletal system and connective tissue | 472 | 1.04 (0.94, 1.14) | 1.04 (0.86, 1.26) |
| Cerebral infarction | 267 | 1.04 (0.91, 1.18) | 1.04 (0.85, 1.27) |
| Multiple sclerosis and other demyelinating diseases | 102 | 1.04 (0.85, 1.28) | 1.05 (0.85, 1.31) |
| Abdominal and pelvic pain | 1031 | 1.04 (0.98, 1.11) | 1.04 (0.87, 1.25) |
| Other diseases of the respiratory system | 221 | 1.05 (0.91, 1.20) | 1.05 (0.86, 1.29) |
| Acute bronchitis and acute bronchiolitis | 120 | 1.05 (0.87, 1.26) | 1.05 (0.85, 1.30) |
| Acute pancreatitis and other diseases of the pancreas | 146 | 1.05 (0.88, 1.24) | 1.05 (0.85, 1.30) |
| Acute pharyngitis and acute tonsilitis | 44 | 1.05 (0.77, 1.43) | 1.06 (0.84, 1.33) |
| Parkinson's disease | 53 | 1.05 (0.79, 1.39) | 1.06 (0.84, 1.32) |
| Other diseases of upper respiratory tract | 365 | 1.05 (0.94, 1.17) | 1.05 (0.87, 1.28) |
| Other diseases of the urinary system | 549 | 1.05 (0.96, 1.15) | 1.05 (0.87, 1.27) |
| Osteoarthritis and allied conditions | 2217 | 1.05 (1.00, 1.10) | 1.05 (0.88, 1.26) |
| Other diseases of the eye and adnexa | 766 | 1.05 (0.98, 1.13) | 1.05 (0.87, 1.27) |
| Diabetes mellitus | 663 | 1.05 (0.97, 1.14) | 1.05 (0.87, 1.27) |
| Cystitis | 359 | 1.05 (0.95, 1.18) | 1.06 (0.87, 1.28) |
| Other diseases of the skin and subcutaneous tissue | 828 | 1.06 (0.98, 1.13) | 1.06 (0.88, 1.27) |
| Other cerebrovascular disease | 592 | 1.06 (0.97, 1.16) | 1.06 (0.88, 1.28) |
| Cervical and other intervertebral disc disorders | 1550 | 1.06 (1.01, 1.12) | 1.06 (0.89, 1.27) |
| Other inflammatory diseases of female pelvic organs | 204 | 1.06 (0.92, 1.23) | 1.06 (0.87, 1.30) |
| Cholelithiasis and cholecystitis | 892 | 1.07 (1.00, 1.14) | 1.07 (0.89, 1.28) |
| Malignant neoplasm of rectosigmoideum junction, rectum, anus, and anal canal | 84 | 1.07 (0.85, 1.34) | 1.06 (0.85, 1.32) |
| Other disorders of genitourinary tract | 1155 | 1.08 (1.01, 1.14) | 1.07 (0.90, 1.29) |
| Malignant neoplasm of bladder | 41 | 1.08 (0.78, 1.49) | 1.06 (0.84, 1.34) |
| Other bacterial disease | 169 | 1.08 (0.92, 1.27) | 1.07 (0.87, 1.32) |
| Infections of kidney | 157 | 1.08 (0.92, 1.28) | 1.07 (0.87, 1.32) |
| Other diseases of the digestive system | 1520 | 1.08 (1.03, 1.14) | 1.08 (0.90, 1.29) |
| Other viral diseases | 167 | 1.09 (0.93, 1.28) | 1.07 (0.87, 1.32) |
| Other disorders of ovary, fallopian tube and parametrium | 259 | 1.09 (0.96, 1.24) | 1.08 (0.88, 1.34) |
| Carcinoma *in situ* of *cervix uteri* | 199 | 1.09 (0.94, 1.26) | 1.08 (0.88, 1.32) |
| Other dorsopathies | 352 | 1.09 (0.98, 1.22) | 1.08 (0.89, 1.32) |
| Other malignant neoplasms of lymphoid, hematopoietic, and related tissue | 81 | 1.10 (0.87, 1.38) | 1.07 (0.86, 1.33) |
| Benign neoplasm of the skin | 167 | 1.11 (0.94, 1.30) | 1.08 (0.88, 1.33) |
| Malignant neoplasm of trachea, bronchus, and lung | 47 | 1.11 (0.82, 1.50) | 1.07 (0.85, 1.34) |
| Endometriosis | 121 | 1.11 (0.92, 1.34) | 1.08 (0.87, 1.34) |
| Alcohol-, drug-abuse-related disease | 280 | 1.11 (0.98, 1.26) | 1.10 (0.90, 1.34) |
| Congenital deformations of feet | 23 | 1.12 (0.73, 1.72) | 1.07 (0.84, 1.35) |
| Diseases of appendix | 252 | 1.12 (0.98, 1.28) | 1.10 (0.90, 1.34) |

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| Iodine-deficiency-related thyroid disorders | 490 | 1.12 (1.02, 1.23) | 1.11 (0.92, 1.34) |
| Neurotic, stress-related, and somatoform disorders | 130 | 1.13 (0.94, 1.35) | 1.09 (0.88, 1.35) |
| Malignant neoplasm of other genitourinary organs | 13 | 1.13 (0.64, 2.01) | 1.06 (0.84, 1.35) |
| Disorders of menstruation | 2007 | 1.13 (1.08, 1.19) | 1.13 (0.94, 1.35) |
| Acute rheumatic fever | 5 | 1.14 (0.45, 2.87) | 1.06 (0.83, 1.35) |
| Respiratory tuberculosis | 15 | 1.15 (0.67, 1.95) | 1.07 (0.84, 1.35) |
| Phlebitis, thrombophlebitis, venous embolism and thrombosis | 184 | 1.15 (1.01, 1.30) | 1.12 (0.92, 1.36) |
| Other diseases of the circulatory system | 106 | 1.15 (0.94, 1.41) | 1.10 (0.88, 1.36) |
| Other disorders of thyroid | 646 | 1.16 (1.06, 1.25) | 1.14 (0.94, 1.37) |
| Osteochrondrosis | 35 | 1.16 (0.81, 1.64) | 1.08 (0.85, 1.36) |
| Depression | 88 | 1.16 (0.93, 1.44) | 1.09 (0.88, 1.36) |
| Chronic rheumatic heart disease | 44 | 1.16 (0.85, 1.59) | 1.08 (0.86, 1.36) |
| Other diseases of liver and gallbladder | 193 | 1.17 (1.01, 1.36) | 1.12 (0.91, 1.38) |
| Rheumatism | 342 | 1.17 (1.05, 1.31) | 1.14 (0.93, 1.38) |
| Inflammatory disease of the central nervous system | 27 | 1.17 (0.79, 1.75) | 1.08 (0.85, 1.36) |
| Strabismus | 81 | 1.18 (0.94, 1.49) | 1.10 (0.88, 1.37) |
| Other complications of pregnancy or delivery | 280 | 1.18 (1.04, 1.34) | 1.14 (0.93, 1.39) |
| Malignant neoplasm of skin | 290 | 1.18 (1.05, 1.34) | 1.14 (0.93, 1.39) |
| Malignant neoplasm of other specified sites | 34 | 1.19 (0.83, 1.70) | 1.08 (0.86, 1.36) |
| Benign neoplasm of ovary | 345 | 1.20 (1.07, 1.34) | 1.15 (0.95, 1.40) |
| Leiomyoma of uterus | 931 | 1.21 (1.13, 1.29) | 1.18 (0.99, 1.42) |
| Diarrhea and gastro-enteritis of presumed infectious origin | 269 | 1.21 (1.06, 1.37) | 1.15 (0.94, 1.41) |
| Other malignant neoplasms of respiratory and intrathoracic organs | 8 | 1.21 (0.58, 2.52) | 1.07 (0.84, 1.36) |
| Pulmonary embolism | 94 | 1.22 (0.98, 1.51) | 1.12 (0.90, 1.39) |
| Malignant neoplasm of other unspecified parts of uterus | 190 | 1.22 (1.05, 1.42) | 1.15 (0.93, 1.41) |
| Bronchiestasis | 21 | 1.22 (0.78, 1.92) | 1.08 (0.85, 1.36) |
| Other malignant neoplasm of female genital organs | 121 | 1.22 (1.01, 1.48) | 1.13 (0.91, 1.40) |
| Conditions originating in the perinatal period | 6 | 1.22 (0.52, 2.86) | 1.06 (0.84, 1.36) |
| Conduction disorders and cardiac arrhythmias | 998 | 1.23 (1.15, 1.31) | 1.20 (1.00, 1.44) |
| Intracranial hemorrhage | 114 | 1.23 (1.01, 1.50) | 1.13 (0.91, 1.40) |
| Congestive heart failure | 469 | 1.24 (1.12, 1.36) | 1.19 (0.98, 1.44) |
| Delivery without mention of complication | 217 | 1.24 (1.07, 1.43) | 1.16 (0.95, 1.42) |
| Other intestinal infectious disease | 79 | 1.26 (1.00, 1.60) | 1.13 (0.90, 1.41) |
| Malignant neoplasm of colon | 171 | 1.27 (1.08, 1.48) | 1.17 (0.95, 1.44) |
| Mood affective disorders | 36 | 1.31 (0.93, 1.85) | 1.10 (0.88, 1.39 |
| Other *in situ* and benign neoplasms and neoplasms of uncertain and unknown behaviour | 2179 | 1.32 (1.26, 1.38) | 1.30 (1.09, 1.55) |
| Female infertility | 48 | 1.32 (0.98, 1.79) | 1.12 (0.89, 1.40) |

| | | | |
|---|---|---|---|
| Malignant neoplasm of other, ill-defined, secondary, unspecified and multiple sites | 69 | 1.33 (1.03, 1.70) | 1.14 (0.91, 1.42) |
| Osteomyelitis and periostitis | 27 | 1.37 (0.92, 2.05) | 1.10 (0.87, 1.39) |
| Nephritis and nephrosis | 44 | 1.38 (1.01, 1.89) | 1.13 (0.89, 1.42) |
| Myositis | 15 | 1.39 (0.81, 2.38) | 1.09 (0.86, 1.38) |
| Hodgkin's disease | 11 | 1.39 (0.74, 2.62) | 1.08 (0.85, 1.37) |
| Schizophrenia, schizotypal, and delusional disorders | 31 | 1.51 (1.04, 2.21) | 1.13 (0.89, 1.42) |
| Malignant neoplasm of lip, oral cavity and pharynx | 46 | 1.51 (1.11, 2.07) | 1.15 (0.92, 1.45) |
| Other congenital malformations of the digestive system | 26 | 1.56 (1.03, 2.35) | 1.12 (0.89, 1.42) |
| Other malformations of the genitourinary system | 49 | 1.62 (1.20, 2.19) | 1.18 (0.94, 1.48) |
| Disorders of breast | 1052 | 1.62 (1.52, 1.73) | 1.54 (1.28, 1.84) |
| Acute poliomyelitis | 18 | 1.94 (1.17, 3.21) | 1.13 (0.89, 1.43) |
| *Pooled effect estimate* | | *1.07 (1.06, 1.08)* | *1.06 (1.04, 1.08)* |

Numbers in parentheses are 95% confidence intervals.

# Paper I

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PLOS ONE

# Hospital Recorded Morbidity and Breast Cancer Incidence: A Nationwide Population-Based Case-Control Study

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## Abstract

***Introduction:*** Chronic diseases and their complications may increase breast cancer risk through known or still unknown mechanisms, or by shared causes. The association between morbidities and breast cancer risk has not been studied in depth.

***Methods:*** Data on all Danish women aged 45 to 85 years, diagnosed with breast cancer between 1994 and 2008 and data on preceding morbidities were retrieved from nationwide medical registries. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression associating the Charlson comorbidity score (measured using both the original and an updated Charlson Comorbidity Index (CCI)) with incident breast cancer. Furthermore, we estimated associations between 202 morbidity categories and incident breast cancer, adjusting for multiple comparisons using empirical Bayes (EB) methods.

***Results:*** The study included 46,324 cases and 463,240 population controls. Increasing CCI score, up to a score of six, was associated with slightly increased breast cancer risk. Among the Charlson diseases, preceding moderate to severe renal disease (OR = 1.25, 95% CI: 1.06, 1.48), any tumor (OR = 1.17, 95% CI: 1.10, 1.25), moderate to severe liver disease (OR = 1.86, 95% CI: 1.32, 2.62), and metastatic solid tumors (OR = 1.49, 95% CI: 1.17, 1.89), were most strongly associated with subsequent breast cancer. Preceding myocardial infarction (OR = 0.89, 95% CI: 0.81, 0.99), connective tissue disease (OR = 0.87, 95% CI: 0.80, 0.94), and ulcer disease (OR = 0.91, 95% CI: 0.83, 0.99) were most strongly inversely associated with subsequent breast cancer. A history of breast disorders was associated with breast cancer after EB adjustment. Anemias were inversely associated with breast cancer, but the association was near null after EB adjustment.

***Conclusions:*** There was no substantial association between morbidity measured with the CCI and breast cancer risk.

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## Introduction

Breast cancer is one of the most frequent cancers affecting women worldwide, with an estimated 1.38 million new cases diagnosed in 2008 [1]. Major breast cancer risk factors are sex and age [2–4], family history including BRCA1 and 2 mutations, oral contraceptives and postmenopausal hormone use [4,5]. Other established risk factors are associated with endogenous sex hormones, such as reproductive history, lifestyle factors, physical inactivity, high postmenopausal body weight, and alcohol consumption [4,6]. Only a fraction of all breast cancer cases can be explained by these risk factors, however [7].

Previous reports have identified diseases associated with breast cancer; yet no publication has exhaustively investigated a comprehensive set of diseases and their associations with breast cancer occurrence. Some suggested breast cancer mediators are estrogen-related diseases [8–12], some endocrine disorders [13], immune function [2,3,14,15], inflammation [16], viral infections [17], and medication [18,19]. Other diseases could be linked to breast cancer through various biologic or other underlying mechanisms, and the Charlson Comorbidity Index (CCI), which includes 19 disease categories weighted by their adjusted risk of one-year mortality [20], could be useful in measuring any combined effect of morbidities on breast cancer incidence.

We evaluated the associations between preceding morbidities, their complications, and subsequent breast cancer incidence using both the original [20] and an updated [21] CCI, and individual diseases included in the CCI [20]. As a hypothesis-screening

analysis [22], we studied associations between an exhaustive set of preceding morbidities and subsequent breast cancer incidence. In a sub-analysis including only the breast cancer patients, we examined any association between morbidity and breast cancer stage at diagnosis.

## Methods

### Ethics Statement

The conduct of this study was approved by the Danish Data Protection Agency. In Denmark, no further permissions are needed to conduct registry-based studies such as our study. Informed consent from participants is therefore not needed.

### Source Population

We conducted this nested case-control study in a source population of all Danish women aged 45 to 85 years registered in the Danish Civil Registration System (CRS). Women with breast cancer diagnosed before 1 January 1994 were excluded. The CRS has collected information on date of birth, residence, and marital status for all Danish residents since 1968, when each was assigned a unique Civil Personal Registration (CPR) number encoding gender and date of birth. The CPR number is used in all Danish population and medical registries, and thus permits accurate individual-level linkage among registries [23].

The Danish Cancer Registry (DCR) has recorded national cancer incidence since 1943. It contains data on all cancers diagnosed through 2009 [24,25]. The DCR used International Classification of Diseases (ICD)-7 codes until 2003 and have been converted to ICD-10 codes. Registration of breast cancer in the DCR is almost 100% complete [26].

All inpatient discharge diagnoses from non-psychiatric hospitals have been recorded in the Danish National Registry of Patients (NRP) since 1977. Outpatient data from all hospital departments and clinics were added in 1995. The DNRP records the CPR number and the date of each hospital visit, together with primary and secondary discharge diagnoses [27]. Diagnoses were coded according to ICD-8 from 1977–1993 and ICD-10 thereafter.

### Identification of Cases and Controls

We defined cases as all female patients aged 45 to 85 years who were diagnosed with incident breast cancer (ICD-10: C50) between 1 January 1994 and 31 December 2008 and registered in the DCR. Risk-set sampling without replacement was used to select 10 female controls without prevalent breast cancer from the source population, matched to each case by year of birth and calendar year. We defined the index date as the date of breast cancer diagnosis for cases and the date of the index case's breast cancer diagnosis for controls.

### Data Collection

Date on breast cancer occurrence and stage at diagnosis were collected from the DCR. Data on all primary hospital diagnoses including the diseases in the CCI [20] up to 10 years before the index date were retrieved from the DNRP for each case and control. The CCI has been shown to be a valid prognostic marker of mortality in breast cancer patients [20]. It is based on selected disease categories that are weighted according to the adjusted one-year mortality risk [20]. It has recently been updated to reflect changes in survival due to medical advances and to administrative databases as a source of data [21]. Age was ascertained from the CRS. Because of the potential latency period preceding breast cancer diagnosis, we excluded all conditions registered for cases and controls in the three years preceding the index date.

### Analytic Variables

Age was categorized into five groups (45–50, 51–60, 61–70, 71–80, and 81–85 years). Morbidity was measured with the original [20] and an updated [21] CCI (scores of 0, 1, 2, 3, 4, 5, 6, 7, and $\geq$8) (Table S1). In the models associating CCI scores with breast cancer stage, CCI was categorized as 0, 1, 2, 3, and $\geq$4. Each individual disease in the CCI also was analyzed separately (presence/absence). Stage was categorized as local, regional, distant, and missing.

Based on the ICD-8 and ICD-10 World Health Organization morbidity tables [28,29], we grouped all ICD-codes into 202 morbidity categories (Table S2), similar to categories previously used by our group [30]. We excluded from the analyses diagnoses reflecting external causes of morbidity (such as accidents) recorded during routine hospital outpatient visits and diagnoses only affecting men.

### Statistical Methods

We calculated distributions and frequencies of cases and controls by age at inclusion, index year, CCI score, and each of the 19 diseases included in the CCI. Contingency tables were constructed for each of the 202 morbidity categories. Conditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) associating breast cancer incidence with original and updated CCI scores, individual diseases included in the CCI, and each morbidity category within the risk-set matched strata. For the breast cancer patients, we used logistic regression models to calculate the OR for distant stage vs. local/regional stage breast cancer at diagnosis. CCI score in five categories (0, 1, 2, 3, and $\geq$4) and age as a continuous variable were included in the models as independent variables. Breast cancer patients with missing stage were excluded from this analysis.

In the hypotheses-screening analysis, the associations between 202 morbidity categories and breast cancer incidence were estimated. Given the study sample, these associations were not independent, leading to a statistical problem with type I errors, since the risk of obtaining 95% confidence intervals that do not contain the true population parameter by chance increases with the number of comparisons. The hypothesis-screening part of the study was conducted to identify both weak and strong associations, and had no a priori expectations of which comparison may be true. Confidence intervals centered far from the null may reflect unstable estimates of the true association, particularly when the interval is wide. The empirical-Bayes (EB) method shrinks the parameters toward the null association, taking into account the standard deviation of the original estimates. Estimates far from the null and imprecisely measured shrink the most, thereby de-emphasizing the associations most likely to be false-positives. Therefore, an EB method was applied to bring the size of the estimates and variances towards the overall mean and reduce the potential for spurious associations. To further stabilize the EB adjusted estimates, we excluded morbidity categories with fewer than five exposed cases. The assumptions behind the EB estimations, such as normality of the estimates, were satisfied [31].

All analyses were performed with SAS version 9.2 and Stata IC version 11.1.

## Results

The study included 46,324 breast cancer cases and 463,240 population controls. Table 1 presents the distributions of cases and controls categorized by age group and index year. For both the original and updated CCI, increasing scores up to a score of six

were associated with slightly increased risk of breast cancer. Among the individual diseases included in the CCI and diagnosed three to ten years before the index date, moderate to severe renal disease (OR = 1.25, 95% CI: 1.06, 1.48), any tumor (OR = 1.17, 95% CI: 1.10, 1.25), moderate to severe liver disease (OR = 1.86, 95% CI: 1.32, 2.62), and metastatic solid tumors (OR = 1.49, 95% CI: 1.17, 1.89), were most strongly associated with subsequent breast cancer. Myocardial infarction (OR = 0.89, 95% CI: 0.81, 0.99), connective tissue disease (OR = 0.87, 95% CI: 0.80, 0.94), and ulcer disease (OR = 0.91, 95% CI: 0.83, 0.99) were most strongly inversely associated with subsequent breast cancer. Results based on the original and updated CCI are shown in Table 2, and results for the individual 19 diseases included in the CCI are shown in Table 3. The proportion of distant stage breast cancer increased with increasing CCI score and with the presence of some individual Charlson diseases. However, with logistic regression models adjusted for age, there was no association between comorbidity and breast cancer stage (Table 4).

## Hypothesis-screening Analysis

In the hypothesis-screening analysis, hospital diagnoses recorded in the three years preceding the index date, representing 54.4% of all diagnoses, were excluded. After morbidity categories with fewer than five exposed cases and those affecting only men were excluded, 155 morbidity categories remained for analysis. Overall, ORs were skewed towards an increased risk of breast cancer for these 155 morbidity categories, with few ORs below the null. We obtained a pooled OR estimate of 1.07 (95% CI: 1.06, 1.08) associating any morbidity in the three to ten years preceding the index date with breast cancer risk. Of the 155 morbidity categories, iron deficiency anemia (OR = 0.61, 95% CI: 0.45, 0.81), other anemias (OR = 0.78, 95% CI: 0.66, 0.94), osteoporosis with and without fracture (OR = 0.87, 95% CI: 0.78, 0.96), rheumatoid arthritis and other inflammatory polyarthropathies (OR = 0.88, 95% CI: 0.80, 0.98), gastric and duodenal ulcer (OR = 0.89, 95% CI: 0.81, 0.98), and acute myocardial infarction (OR = 0.89, 95% CI: 0.81, 0.99) were inversely associated with subsequent breast cancer. Several morbidity categories, such as previous cancer diseases, were initially positively associated with breast cancer. After EB adjustment, however, ORs for only two diseases indicated a statistically significant association: disorders of the breast (EB−OR = 1.54, 95% CI: 1.28, 1.84) and other *in situ* and benign neoplasms and neoplasms of uncertain and unknown behavior (EB−OR = 1.30, 95% CI: 1.09, 1.55). The 20 associations most strongly negatively and positively associated with breast cancer are presented in Table 5 and Table 6, respectively. A complete list of the associations of the 155 morbidity categories with breast cancer and the corresponding original and EB-adjusted estimates are presented in Table S3.

**Table 1.** Frequencies and proportions of breast cancer cases and controls by age group and index years of diagnosis.

| | Cases n = 46,324 | (%[a]) | Controls n = 463,240 | (%[a]) |
|---|---|---|---|---|
| **Age group** | | | | |
| 45–50 | 4,815 | (10) | 48,494 | (10) |
| 51–60 | 13,273 | (29) | 132,469 | (29) |
| 61–70 | 13,924 | (30) | 139,025 | (30) |
| 71–80 | 10,020 | (22) | 100,269 | (22) |
| 81–85 | 4,292 | (9.3) | 42,983 | (9.3) |
| **Index year** | | | | |
| 1994 | 2,659 | (5.7) | 26,590 | (5.7) |
| 1995 | 2,658 | (5.7) | 26,580 | (5.7) |
| 1996 | 2,787 | (6.0) | 27,870 | (6.0) |
| 1997 | 2,799 | (6.0) | 27,990 | (6.0) |
| 1998 | 2,880 | (6.2) | 28,800 | (6.2) |
| 1999 | 2,992 | (6.5) | 29,920 | (6.5) |
| 2000 | 3,036 | (6.6) | 30,360 | (6.6) |
| 2001 | 3,108 | (6.7) | 31,080 | (6.7) |
| 2002 | 3,300 | (7.1) | 33,000 | (7.1) |
| 2003 | 3,215 | (6.9) | 32,150 | (6.9) |
| 2004 | 3,174 | (6.9) | 31,740 | (6.9) |
| 2005 | 3,172 | (6.9) | 31,720 | (6.9) |
| 2006 | 3,322 | (7.2) | 33,220 | (7.2) |
| 2007 | 3,350 | (7.2) | 33,500 | (7.2) |
| 2008 | 3,872 | (8.4) | 38,720 | (8.4) |

[a]Because of rounding, percentages may not add to 100%.
[b]Controls were matched to cases on this variable.
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**Table 2.** Original and updated Charlson Comorbidity Index (CCI) scores associated with breast cancer incidence among cases and controls.

| Cases, n (%[a]) | Controls, n (%[a]) | OR (95% CI) |
|---|---|---|
| **Original CCI score** | | |
| 0 40,276 (87) | 403,983 (87) | Ref |
| 1 3,574 (7.9) | 36,999 (8.0) | 0.97 (0.94, 1.01) |
| 2 1,781 (3.8) | 16,650 (3.6) | 1.08 (1.02, 1.13) |
| 3 447 (1.0) | 3,628 (0.8) | 1.24 (1.12, 1.37) |
| 4 129 (0.3) | 1,076 (0.2) | 1.21 (1.00, 1.45) |
| 5 33 (0.1) | 260 (0.1) | 1.28 (0.89, 1.83) |
| 6 65 (0.1) | 452 (0.1) | 1.44 (1.11, 1.87) |
| 7 11 (0.02) | 117 (0.03) | 0.95 (0.51, 1.78) |
| ≥8 8 (0.02) | 75 (0.02) | 1.01 (0.52, 2.22) |
| **Updated CCI score** | | |
| 0 42,423 (92) | 426,147 (92) | Ref |
| 1 1,834 (4.0) | 19,071 (4.1) | 0.97 (0.92, 1.02) |
| 2 1,625 (3.5) | 14,450 (3.1) | 1.13 (1.07, 1.19) |
| 3 243 (0.5) | 2,147 (0.5) | 1.14 (1.00, 1.30) |
| 4 105 (0.2) | 736 (0.2) | 1.44 (1.17, 1.76) |
| 5 17 (0.04) | 131 (0.03) | 1.31 (0.79, 2.17) |
| 6 64 (0.1) | 452 (0.1) | 1.42 (1.10, 1.85) |
| 7 5 (0.01) | 49 (0.01) | 1.03 (0.41, 2.58) |
| ≥8 8 (0.02) | 57 (0.01) | 1.41 (0.67, 2.96) |

Abbreviations. OR: Odds ratio.
[a]Because of rounding percentages may not add to 100.
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## Discussion

In the present study, increasing CCI score calculated by either the original [20] or an updated [21] CCI score, and based on diagnoses three to ten years before the index date, were associated with subsequent risk of breast cancer. The distribution of odds ratios for 155 morbidity categories was skewed towards a causal

**Table 3.** Individual diseases included in the Charlson Comorbidity Index (CCI) three to ten years preceding the index date and their association with breast cancer incidence.

| Charlson disease | Exposed cases, n | OR (95% CI) |
|---|---|---|
| Myocardial infarction | 432 | 0.89 (0.81, 0.99) |
| Congestive heart failure | 485 | 1.19 (1.09, 1.31) |
| Peripheral vascular disease | 524 | 1.01 (0.92, 1.10) |
| Cerebrovascular disease | 1,098 | 1.04 (0.98, 1.10) |
| Dementia | 91 | 0.88 (0.71, 1.09) |
| Chronic pulmonary disease | 1,260 | 1.04 (0.98, 1.11) |
| Connective tissue disease | 641 | 0.87 (0.80, 0.94) |
| Ulcer disease | 525 | 0.91 (0.83, 0.99) |
| Mild liver disease | 164 | 1.11 (0.94, 1.30) |
| Diabetes type I and II | 818 | 1.10 (1.02, 1.18) |
| Hemiplegia | 29 | 1.14 (0.78, 1.68) |
| Moderate to severe renal disease | 159 | 1.25 (1.06, 1.48) |
| Diabetes with end organ damage | 270 | 1.04 (0.91, 1.18) |
| Any tumor | 1,135 | 1.17 (1.10, 1.25) |
| Leukemia | 22 | 0.82 (0.53, 1.27) |
| Lymphoma | 78 | 1.07 (0.85, 1.36) |
| Moderate to severe liver disease | 39 | 1.86 (1.32, 2.62) |
| Metastatic solid tumor | 75 | 1.49 (1.17, 1.89) |
| AIDS | 1 | 0.05 (0.07, 3.73) |

Abbreviations. OR: odds ratio.
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association. After EB adjustment was applied to the estimates obtained in the hypothesis-screening analysis, however, only "disorders of the breast" and "other *in situ* and benign neoplasms and neoplasms of uncertain and unknown origin" remained clearly associated with breast cancer.

## Strengths and Limitations

The relatively homogeneous Danish population and Denmark's tax-supported health care system provide an optimal setting for the conduct of population-based case-control studies. This nationwide study comprised all Danish women between 45 and 85 years of age diagnosed with breast cancer between 1994 and 2008 and their matched controls. Registration of breast cancer diagnoses in the DCR is nearly complete [26].

Study limitations include the completeness of diagnoses recorded in the NRP and several potential confounding factors. While the positive predictive values of the Charlson diseases in the NRP are high [32], many diseases and complications diagnosed in primary care are not recorded in the NRP. This under-registration could diminish potential effects of specific conditions.

Misclassification of diseases, such as those resulting from changes in clinical interpretations of ICD-codes [33], could also bias associations. In the hypothesis-screening analysis, some morbidity categories represented combinations of ICD-codes for medical conditions with different etiologies, possibly leading to bias. Another concern is that we excluded all diagnoses between the index date and the three preceding years, and this presumed latency period may not be appropriate for all diseases. However, including all diagnoses recorded in the NRP preceding the index

**Table 4.** Original and updated Charlson Comorbidity Index (CCI) score, individual Charlson diseases, age groups and their association with distant breast cancer stage.

| | Cases, N | OR (95% CI)[a] |
|---|---|---|
| Stage | | |
| Local | 21,576 (47) | |
| Regional | 18,306 (40) | |
| Distant | 3,058 (6.6) | |
| **Original CCI score[b]** | | |
| 0 | 37,539 (87) | ref |
| 1 | 3,201 (7.4) | 0.90 (0.79, 1.04) |
| 2 | 1,601 (3.7) | 0.85 (0.70, 1.03) |
| 3 | 380 (0.9) | 0.95 (0.66, 1.37) |
| ≥4 | 219 (0.5) | 0.97 (0.60, 1.58) |
| **Updated CCI score[b]** | | |
| 0 | 39,444 (92) | ref |
| 1 | 1,656 (3.9) | 0.93 (0.77, 1.22) |
| 2 | 1,454 (3.4) | 0.86 (0.70, 1.05) |
| 3 | 215 (0.5) | 1.20 (0.77, 1.87) |
| ≥4 | 171 (0.4) | 0.77 (0.41, 1.41) |
| **Charlson disease[b]** | | |
| Myocardial infarction | 373 (0.9) | 0.68 (0.44, 1.04) |
| Congestive heart failure | 410 (1.1) | 0.79 (0.55, 1.15) |
| Peripheral vascular disease | 466 (1.1) | 1.00 (0.72, 1.38) |
| Cerebrovascular disease | 942 (2.2) | 0.78 (0.60, 1.00) |
| Dementia | 69 (0.2) | 1.03 (0.47, 2.27) |
| Chronic pulmonary disease | 1,141 (2.7) | 0.88 (0.70, 1.11) |
| Connective tissue disease | 576 (1.3) | 1.03 (0.76, 1.39) |
| Ulcer disease | 468 (1.1) | 1.05 (0.76, 1.46) |
| Mild liver disease | 150 (0.4) | 0.84 (0.43, 1.65) |
| Diabetes type I and II | 733 (1.7) | 0.94 (0.72, 1.24) |
| Hemiplegia | 27 (0.06) | 2.03 (0.70, 5.94) |
| Moderate to severe renal disease | 141 (0.3) | 1.24 (0.70, 2.21) |
| Diabetes with end organ damage | 237 (0.6) | 1.00 (0.63, 1.59) |
| Any tumor | 1,031 (2.4) | 0.90 (0.71, 1.14) |
| Leukemia[c] | 21 (0.05) | 1.22 (0.28, 5.28) |
| Lymphoma[c] | 70 (0.2) | – |
| Moderate to severe liver disease | 36 (0.08) | – |
| Metastatic solid tumor | 66 (0.2) | 1.64 (0.78, 3.46) |
| AIDS[c] | 1 (0) | – |
| **Age group[d]** | | |
| 45–50 | 4,630 (11) | ref |
| 51–60 | 12,651 (29) | 1.18 (1.01, 1.39) |
| 61–70 | 13,211 (31) | 1.54 (1.32, 1.80) |
| 71–80 | 9,050 (21) | 2.26 (1.93, 2.64) |
| 81–85 | 3,398 (7.9) | 2.99 (2.51, 3.55) |

[a]Calculated as distant stage vs. local/regional stage breast cancer at diagnosis. Patients with unknown stage (n = 3,384) were excluded from the analysis.
[b]Adjusted for age as a continuous variable.
[c]Zero cases of distant stage breast cancer.
[d]Adjusted for original CCI score in five categories.
Abbreviations. OR: odds ratio.
doi:10.1371/journal.pone.0047329.t004

**Table 5.** The 20 preceding morbidity categories most strongly associated with decreased breast cancer incidence.

| Preceding morbidity category | Exposed cases, n | OR (95% CI) | EB-OR (95% CI) |
|---|---|---|---|
| Iron deficiency anemia | 32 | 0.61 (0.45, 0.81) | 0.91 (0.73, 1.15) |
| Chronic disease of tonsils and adenoids | 59 | 0.74 (0.52, 1.06) | 0.99 (0.78, 1.25) |
| Dementia | 5 | 0.77 (0.59, 1.00) | 0.96 (0.77, 1.20) |
| Malignant neoplasm of bone and articular cartilage | 50 | 0.77 (0.31, 1.91) | 1.05 (0.82, 1.33) |
| Other tuberculosis | 10 | 0.78 (0.41, 1.48) | 1.04 (0.81, 1.32) |
| Other anemias | 133 | 0.78 (0.66, 0.94) | 0.91 (0.74, 1.13) |
| Alzheimer's disease | 18 | 0.79 (0.49, 1.28) | 1.02 (0.81, 1.30) |
| Other diseases of the bone | 104 | 0.83 (0.68, 1.01) | 0.95 (0.77, 1.19) |
| Other malignant neoplasms of urinary tract | 16 | 0.85 (0.51, 1.41) | 1.03 (0.81, 1.31) |
| Septicemia | 53 | 0.85 (0.64, 1.12) | 0.99 (0.79, 1.25) |
| Influenza | 39 | 0.85 (0.61, 1.18) | 1.01 (0.80, 1.27) |
| Hepatitis | 19 | 0.86 (0.54, 1.37) | 1.03 (0.81, 1.31) |
| Migraine | 114 | 0.86 (0.71, 1.04) | 0.96 (0.78, 1.19) |
| Osteoporosis with and without fracture | 369 | 0.87 (0.78, 0.96) | 0.92 (0.75, 1.11) |
| Rheumatoid arthritis and other inflammatory polyarthropathies | 438 | 0.88 (0.80, 0.98) | 0.92 (0.76, 1.12) |
| Gastric and duodenal ulcer | 467 | 0.89 (0.81, 0.98) | 0.93 (0.77, 1.12) |
| Acute myocaridal infarction | 429 | 0.89 (0.81, 0.99) | 0.93 (0.76, 1.13) |
| Benign neoplasm of brain and other parts of central nervous system | 45 | 0.90 (0.67, 1.23) | 1.02 (0.81, 1.28) |
| Epilepsy | 185 | 0.91 (0.78, 1.05) | 0.97 (0.79, 1.19) |
| Malignant neoplasm of larynx | 47 | 0.91 (0.49, 1.70) | 1.05 (0.82, 1.33) |

Abbreviations. OR: odds ratio; EB-OR: Empirical-Bayes adjusted odds ratios.
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**Table 6.** The 20 preceding morbidity categories most strongly associated with increased breast cancer incidence.

| Preceding morbidity category | Exposed cases, n | OR (95% CI) | EB-OR (95% CI) |
|---|---|---|---|
| Conduction disorders and cardiac arrhythmias | 998 | 1.23 (1.15, 1.31) | 1.20 (1.00, 1.44) |
| Intracranial hemorrhage | 114 | 1.23 (1.01, 1.50) | 1.13 (0.91, 1.40) |
| Congestive heart failure | 469 | 1.24 (1.12, 1.36) | 1.19 (0.98, 1.44) |
| Delivery without mention of complication | 217 | 1.24 (1.07, 1.43) | 1.16 (0.95, 1.42) |
| Other intestinal infectious disease | 79 | 1.26 (1.00, 1.60) | 1.13 (0.90, 1.41) |
| Malignant neoplasm of colon | 171 | 1.27 (1.08, 1.48) | 1.17 (0.95, 1.44) |
| Mood affective disorders | 36 | 1.31 (0.93, 1.85) | 1.10 (0.88, 1.39) |
| Other *in situ* and benign neoplasms and neoplasms of uncertain and unknown behavior | 2179 | 1.32 (1.26, 1.38) | 1.30 (1.09, 1.55) |
| Female infertility | 48 | 1.32 (0.98, 1.79) | 1.12 (0.89, 1.40) |
| Malignant neoplasm of other, ill-defined, secondary, unspecified and multiple sites | 69 | 1.33 (1.03, 1.70) | 1.14 (0.91, 1.42) |
| Osteomyelitis and periostitis | 27 | 1.37 (0.92, 2.05) | 1.10 (0.87, 1.39) |
| Nephritis and nephrosis | 44 | 1.38 (1.01, 1.89) | 1.13 (0.89, 1.42) |
| Myostitis | 15 | 1.39 (0.81, 2.38) | 1.09 (0.86, 1.38) |
| Hodgkin's disease | 11 | 1.39 (0.74, 2.62) | 1.08 (0.85, 1.37) |
| Schizophrenia, schizotypal, and delusional disorders | 31 | 1.51 (1.04, 2.21) | 1.13 (0.89, 1.42) |
| Malignant neoplasm of lip, oral cavity and pharynx | 46 | 1.51 (1.11, 2.07) | 1.15 (0.92, 1.45) |
| Other congenital malformations of the digestive system | 26 | 1.56 (1.03, 2.35) | 1.12 (0.89, 1.42) |
| Other malformations of the genitourinary system | 49 | 1.62 (1.20, 2.19) | 1.18 (0.94, 1.48) |
| Disorders of breast[a] | 1052 | 1.62 (1.52, 1.73) | 1.54 (1.28, 1.84) |
| Acute poliomyelitis | 18 | 1.94 (1.17, 3.21) | 1.13 (0.89, 1.43) |

Abbreviations. OR: odds ratio; EB-OR: Empirical-Bayes adjusted odds ratios.
[a]Disorders of the breast include benign mammary dysplasia, inflammatory disorders of breast, hypertrophy of breast, unspecified lump in breast, and other disorders of breast.
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date, with or without a three year latency period, did not change the results notably (data not shown).

We were unable to control for confounding by differential treatment of diseases and complications, genetic markers, reproductive history, oral contraceptives, hormone replacement therapy, lifestyle, or region of residence, and many of those factor could themselves explain the increased or decreased risk of breast cancer associated with diseases. Given the matching criteria, which included birth year, lack of information on menopausal status is unlikely to have had a major impact on our findings. Results were stratified by age groups corresponding to typical categories of pre-menopausal, peri-menopausal, and post-menopausal women.

The association between increasing CCI score of up to six and breast cancer could be related to close medical surveillance of patients burdened with many medical conditions. However, it is also possible that physicians caring for patients with high numbers of diseases may tend to focus on these diseases and neglect to search for non-symptomatic conditions, such as breast cancer. Increasing CCI score and presence of individual Charlson diseases were associated with elevated proportions of distant stage breast cancer; however, with logistic regression models that adjusted for age, there was no association between the original or updated CCI score or individual Charlson diseases and distant stage breast cancer at diagnosis.

The updated CCI included only the 14 diseases from the original CCI, with "any tumor", "leukemia" and "lymphoma" combined with a weight of 2 [21]. In the current study, the latter diseases were each assigned a weight of 2, both with the original and the updated CCI versions. This approach did not noticeably affect our estimates (data not shown). When we excluded any cancer disease from the CCI, resulting in decreased overall CCI score, the risk of breast cancer associated with scores of up to six was reduced for the original index but not for the updated index (data not shown). It may be, therefore, that cancer diseases drive much of the observed association, for example through shared risk factors between breast cancer and other cancer diseases or as a side effect of treatment for the original cancer. Moreover, many cancers and many other Charlson diseases are associated with lifestyle factors, such as smoking and alcohol consumption [34]. Renal failure is a serious side effect of adjuvant chemotherapy [35], and diabetes can be induced by glucocorticoids or physical inactivity [36].

The associations found between many of the individual 155 morbidity categories and breast cancer is not surprising (Table 5 and 6 and Table S3). Some associations may relate to established risk factors, such as cumulative estrogen exposure, genetics, or lifestyle. For example, "disorders of breast" was strongly associated with breast cancer even after EB adjustment. However, this morbidity category consists of several diseases (see notes under Table 6), some of which are not established breast cancer risk factors. Osteoporosis, heart disease, gastric ulcer, and rheumatoid arthritis, were initially inversely associated with breast cancer. Acetylsalicylic acid (aspirin) is used to treat rheumatoid arthritis, osteoporosis and heart disease, and gastric ulcer and bleeding and thus anemia are well known complications to regular aspirin intake. A recent review and meta-analysis concluded that aspirin reduces the risk of breast cancer [19], so these associations may reflect a protective effect of aspirin associated with the preceding morbidities. Anemia was also associated with a decreased risk of breast cancer before EB adjustment, and recent studies suggest that excess endogenous iron storage raises the risk of breast cancer [37,38]. It is possible, therefore, that the negative association observed with anemia could be mediated by changes in iron homeostasis.

## Conclusions

In conclusion, our study does not provide support for any substantial association between morbidity measured with the original and an updated CCI and breast cancer risk. The hypothesis-screening analysis suggests novel associations that may merit further attention, such as potential protective effects of acetylsalicylic acid or iron deficiency.

## Supporting Information

**Table S1** Specification of Charlson diseases, ICD-8 and ICD-10 codes, and the original and updated Charlson morbidity index score weights.
(DOC)

**Table S2** List of 202 disease categories and associated ICD-8 and ICD-10 codes.
(DOC)

**Table S3** Morbidity categories preceding breast cancer diagnosis, number of exposed cases, corresponding odds ratios (ORs) and Empirical-Bayes-adjusted estimates accompanied by 95% CI for associations between morbidity categories and breast cancer incidence.
(DOC)

## Author Contributions

Conceived and designed the experiments: AGO TLL. Analyzed the data: AGO MT JPG PMWN DCF HTS TLL. Wrote the paper: AGO JPG PMWN DCF MT HTS TLL.

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# Paper II

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PLOS ONE

# Comorbid Diseases Interact with Breast Cancer to Affect Mortality in the First Year after Diagnosis—A Danish Nationwide Matched Cohort Study

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## Abstract

***Background:*** Survival of breast cancer patients with comorbidity, compared to those without comorbidity, has been well characterized. The interaction between comorbid diseases and breast cancer, however, has not been well-studied.

***Methods:*** From Danish nationwide medical registries, we identified all breast cancer patients between 45 and 85 years of age diagnosed from 1994 to 2008. Women without breast cancer were matched to the breast cancer patients on specific comorbid diseases included in the Charlson comorbidity Index (CCI). Interaction contrasts were calculated as a measure of synergistic effect on mortality between comorbidity and breast cancer.

***Results:*** The study included 47,904 breast cancer patients and 237,938 matched comparison women. In the first year, the strongest interaction between comorbidity and breast cancer was observed in breast cancer patients with a CCI score of ≥4, which accounted for 29 deaths per 1000 person-years. Among individual comorbidities, dementia interacted strongly with breast cancer and accounted for 148 deaths per 1000 person-years within one year of follow-up. There was little interaction between comorbidity and breast cancer during one to five years of follow-up.

***Conclusions:*** There was substantial interaction between comorbid diseases and breast cancer, affecting mortality. Successful treatment of the comorbid diseases or the breast cancer can delay mortality caused by this interaction in breast cancer patients.

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## Introduction

Breast cancer patients with comorbidities have poorer survival than breast cancer patients without comorbidity [1-5]. Few studies have compared mortality in breast cancer patients with coexisiting diseases to mortality in a comparable cohort of women free of breast cancer. One study provided evidence of statistical interaction between breast cancer and the Charlson Comorbidity Index (CCI [6]) score at the time of breast cancer diagnosis, but this study was hospital-based, only included 5,663 older patients, and did not study specific comorbidities [7]. Whether the survival difference is due to only the comorbidity or to an interaction between the comorbidity and breast cancer diagnosis is therefore not known. Such an interaction may have implications for disease treatment.

To resolve these limitations, we estimated the difference between the overall mortality rate and the expected mortality rate, given the baseline mortality rate, the effect of breast cancer on the mortality rate, and the effect of comorbidity on the mortality rate. We hypothesized *a priori* that the interaction may depend on the specific comorbid disease(s), and that the interaction may be different in the first year after breast cancer diagnosis than in subsequent years, since mortality in the first

year is more likely affected by delayed breast cancer diagnosis and by treatment and toxicities.

## Methods

This nationwide study included a cohort of Danish breast cancer patients aged 45 to 85 years who were diagnosed between 1994 and 2008, and a comparison cohort of women without breast cancer matched to the breast cancer patients on specific diseases included in the CCI [6]. The population of Denmark has access to a national health care system that is uniformly organized, tax supported, and provides free access to health care [8]. We used national medical and administrative databases in Denmark to identify the source population of women aged 45–85 years registered in the Civil Registration System (CRS). This registry contains information on civil and vital status for all Danish residents since 1968. Each resident is assigned a unique civil personal registration number (CPR) that permits accurate linkage between registries [9].

### Ascertainment of the breast cancer and comparison cohorts

The Danish Cancer Registry (DCR) contains nearly complete data on cancers diagnosed in Denmark [10,11]. Diagnoses were coded according to the *International Classification of Diseases*, revision 7 (ICD-7) until 2003, when recorded diagnoses were converted to ICD-10. From the DCR, we identified female breast cancer patients diagnosed between 1994 and 2008 (ICD-10 code: DC50). We used the CRS to select up to five comparison women from the general population, matched to each breast cancer patient on age and history of the specific comorbidities defined below. The women in the comparison cohort had to be free of breast cancer on the date of breast cancer diagnosis for the corresponding case. The index date was defined as the breast cancer diagnosis date for cases in the breast cancer cohort and also for the women matched to them in the comparison cohort.

**Comorbidity.** The Danish National Registry of Patients (NRP) has recorded all non-psychiatric discharge diagnoses from inpatient admissions since 1977 and from outpatient clinic visits since 1995 [12]. Diagnoses were coded according to ICD-8 1977–1993 and ICD-10 thereafter. The Charlson Comorbidity Index (CCI) provides a summary score based on the presence and severity of 19 individual diseases. It has been validated as a predictor of mortality in breast cancer patients [6]. We used the NRP to identify all recorded diagnoses of diseases, except for breast cancer, included in the CCI for women in the two study cohorts during the ten years before their index date.

**Mortality.** With linkage to the CRS, we followed the breast cancer and matched cohorts until death, emigration or 31 December 2011. Because members of the comparison cohort had no history of breast cancer, we did not ascertain breast-cancer specific or other cause-specific mortality.

**Statistical analysis.** We calculated the frequency of women in the breast cancer cohort and the matched comparison cohort within categories of age (≤50, 51–60, 61–70, 71–80, 81–85 years), year of index date, CCI score (0, 1, 2–3, ≥4), individual diseases included in the CCI index (presence/absence), and, for the breast cancer cohort, cancer stage (local, regional, distant, unknown).

Crude mortality rates with 95% confidence intervals (CIs) were calculated within categories of baseline variables for 0–1 and >1–5 years of follow-up. The matching was dissolved when stratifying the follow-up period, so age-standardized mortality rates were calculated using age weights from the breast cancer cohort on the index date as the standard.

We calculated the interaction contrast (IC), which measures the departure of the mortality rates from an additive model [13]. It is calculated as the difference between the rate differences (mortality rate in the breast cancer cohort minus the mortality rate in the comparison cohort) in the strata with and without comorbidity [13]. We used proportional hazards regression to compute crude hazard ratios as a measure of mortality rate ratios (MRRs), and for the effect of individual diseases, we adjusted for presence of other CCI diseases. For the >1–5 year MRRs, we also adjusted the estimates for age group at diagnosis and year of index date in three categories (1994–1999, 2000–2004, and 2005–2008).

Although chronic pulmonary disease and “any tumor” were prevalent comorbidities in the breast cancer cohort, these diseases did not interact with breast cancer to affect mortality rates. We therefore *a posteriori* repeated all interaction analyses excluding these diseases from the CCI.

The initial cohorts consisted of 48,292 breast cancer patients and 237,938 matched women from the general population. In the breast cancer cohort, 390 (0.81%) women were not matched with any woman in the comparison population. Of these unmatched breast cancer patients, 20% were between 81 and 85 years of age, compared to 9.1% of the matched breast cancer patients. A larger proportion of the unmatched breast cancer patients had a CCI score of ≥4 compared to the matched breast cancer patients (15% vs. 0.9%). Therefore, the combination of old age and multiple comorbidities precluded matching on both age and specific comorbid conditions, resulting in exclusion of these breast cancer patients from the analyses.

Analyses were conducted with SAS version 9.2 (SAS Institute Inc., Cary, NC). This study was approved by the Danish Data Protection Agency (2011-41-6174). No further permissions are needed to conduct studies with no intervention or participant contact in Denmark.

## Results

Characteristics of the breast cancer and matched cohorts are presented in Table 1. The median age at breast cancer diagnosis was 63.2 years (interquartile range: 55.2 to 73.3 years). The most frequent CCI diseases were cerebrovascular disease (3.7%), chronic pulmonary disease (4.3%), and “any tumor” (3.9%), while hemiplegia (0.1%), leukemia (0.1%), moderate to severe liver disease (0.1%), and AIDS (<0.1%) were among the more rare comorbid diseases. In the breast cancer cohort, 47% had local disease, 40% had regional disease, 6.6% had distant disease, and 7.2% had an unknown breast cancer stage at diagnosis.

**Table 1.** Characteristics of the breast cancer cohort and the matched population cohort.

| | Breast cancer cohort (n=47,904), Number (%) | Matched population cohort (n=237,938), Number (%) |
|---|---|---|
| **Age group (years)** | | |
| ≤50 | 5,085 (11) | 25,560 (11) |
| 51-60 | 13,853 (29) | 68,975 (29) |
| 61-70 | 14,357 (30) | 71,193 (30) |
| 71-80 | 10,262 (21) | 50,710 (21) |
| 81-85 | 4,347 (9.1) | 21,500 (9.0) |
| **Index year** | | |
| 1994 | 2,726 (5.6) | 13,564 (5.7) |
| 1995 | 2,743 (5.7) | 13,636 (5.7) |
| 1996 | 2,890 (6.0) | 14,387 (6.1) |
| 1997 | 2,883 (6.0) | 14,356 (6.0) |
| 1998 | 2,958 (6.2) | 14,699 (6.2) |
| 1999 | 3,087 (6.4) | 15,325 (6.4) |
| 2000 | 3,137 (6.6) | 15,601 (6.6) |
| 2001 | 3,204 (6.7) | 15,930 (6.7) |
| 2002 | 3,407 (7.1) | 16,911 (7.1) |
| 2003 | 3,329 (7.0) | 16,504 (6.9) |
| 2004 | 3,283 (6.8) | 16,268 (6.8) |
| 2005 | 3,279 (6.8) | 16,247 (6.8) |
| 2006 | 3,463 (7.2) | 17,162 (7.2) |
| 2007 | 3,497 (7.2) | 17,367 (7.3) |
| 2008 | 4,018 (8.4) | 19,981 (8.4) |
| **Original CCI score** | | |
| 0 | 38,427 (80.2) | 192,135 (81) |
| 1 | 5303 (11) | 26,515 (11.1) |
| 2 | 2,925 (6.1) | 14,432 (6.1) |
| 3 | 828 (1.7) | 3,389 (1.4) |
| 4 | 205 (0.1) | 563 (0.2) |
| 5 | 25 (0.01) | 33 (0.01) |
| 6 | 167 (0.4) | 826 (0.4) |
| 7 | 23 (0.1) | 44 (0.02) |
| 8 | 1 (0) | 1 (0) |
| **Individual diseases in the CCI** | | |
| Myocardial infarction | 680 (1.4) | 3124 (1.3) |
| Congestive heart failure | 840 (1.8) | 3,724 (1.8) |
| Peripheral vascular disease | 836 (1.8) | 3,845 (1.6) |
| Cerebrovascular disease | 1,792 (3.7) | 8,479 (3.6) |
| Dementia | 231 (0.5) | 1,028 (0.4) |
| Chronic pulmonary disease | 2,054 (4.3) | 9,804 (4.1) |
| Connective tissue disease | 934 (2.0) | 4,393 (1.9) |
| Ulcer disease | 819 (1.7) | 3,808 (2.0) |
| Mild liver disease | 232 (0.5) | 1,016 (0.4) |
| Diabetes I and II | 1,229 (2.6) | 5,668 (2.0) |
| Hemiplegia | 42 (0.1) | 165 (0.1) |
| Moderate to severe renal disease | 209 (0.4) | 859 (0.4) |
| Diabetes with end organ damage | 472 (1.0) | 2,066 (0.9) |
| Any tumor (other than breast cancer) | 1,856 (3.9) | 8,967 (3.8) |
| Leukemia | 43 (0.1) | 192 (0.01) |
| Lymphoma | 101 (0.2) | 424 (0.2) |
| Moderate to severe liver disease | 39 (0.1) | 139 (0.1) |
| Metastatic solid tumor | 188 (0.4) | 864 (0.4) |
| AIDS | 1 (0) | 5 (0) |
| **Stage** | | |
| Local | 22,338 (47) | |

**Table 1 (continued).**

| | Breast cancer cohort (n=47,904), Number (%) | Matched population cohort (n=237,938), Number (%) |
|---|---|---|
| Regional | 18,976 (40) | |
| Distant | 3,139 (6.6) | |
| Unknown | 3,451 (7.2) | |

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**Table 2.** Mortality rates, adjusted hazard ratios (HRs), and interaction contrasts (ICs) by Charlson Comorbidity Index (CCI) scores for the breast cancer cohort and the matched comparison cohort for 1 year and >1–5 years of follow–up.

| | CCI score | No. of deaths | Person-years | Crude rate (95%CI)/ 1000 person-years[A] | IC (95% CI) /1000 person-years | Adj HR (95% CI)[B,C] |
|---|---|---|---|---|---|---|
| **0–1 year of follow–up** | | | | | | |
| Comparison | 0 | 1,714 | 191,247 | 9.0 (8.5, 9.4) | | Ref |
| Breast cancer | 0 | 1,974 | 37,264 | 53 (51, 55) | Ref | 6.1 (5.7, 6.6) |
| Comparison | 1 | 1,010 | 26,021 | 39 (37, 41) | | Ref |
| Breast cancer | 1 | 500 | 4,999 | 100 (92, 109) | 17 (7.8, 27) | 2.7 (2.4, 3.0) |
| Comparison | 2-3 | 1,407 | 17,092 | 82 (78, 87) | | Ref |
| Breast cancer | 2-3 | 480 | 3,483 | 138 (126, 151) | 12 (-1.8, 25) | 1.6 (1.5, 1.8) |
| Comparison | ≥4 | 291 | 1,299 | 224 (200, 251) | | Ref |
| Breast cancer | ≥4 | 106 | 357 | 297 (246, 360) | 29 (-33, 91) | 1.5 (1.2, 1.9) |
| **>1–5 years of follow–up** | | | | | | |
| Comparison | 0 | 10,411 | 676,070 | 18 (17, 19) | | Ref |
| Breast cancer | 0 | 6,244 | 120,248 | 57 (54, 60) | Ref | 3.6 (3.4, 3.7) |
| Comparison | 1 | 4,217 | 83,134 | 41 (38, 44) | | Ref |
| Breast cancer | 1 | 1,244 | 14,604 | 75 (66, 85) | -4.4 (-9.1, 0.4) | 1.7 (1.6, 1.9) |
| Comparison | 2-3 | 3,736 | 51,098 | 58 (53, 62) | | Ref |
| Breast cancer | 2-3 | 1,034 | 9,532 | 94 (79, 108) | -2.5 (-9.6, 4.1) | 1.5 (1.4, 1.6) |
| Comparison | ≥4 | 403 | 3,249 | 111 (86, 136) | | Ref |
| Breast cancer | ≥4 | 124 | 822 | 142 (80, 203) | -7.7 (-39, 23) | 1.2 (0.9, 1.4) |

[A] Crude rates for 0–1 year of follow–up. For >1–5 years of follow–up, the matching was dissolved and standardized rates were calculated.

[B] Matching dissolved.

[C] For >1–5 years of follow–up, HRs were adjusted for age group and index years.

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## Mortality

Table 2 shows the mortality rates, ICs, and MRRs for 0–1 and >1–5 year mortality in the breast cancer and comparison cohorts. For all CCI score categories, the breast cancer patients had higher mortality rates than the matched cohort. The survival disparities were more marked in the first year of follow-up than in years one to five.

In the first year of follow-up, the interaction between breast cancer and comorbidity accounted for 17 deaths per 1000 person-years (PY) (95% CI: 7.8, 27) for a CCI score of 1, 12 deaths per 1000 PY (95% CI: -1.8, 25) for CCI scores of 2–3, and 29 deaths per 1000 PY (95% CI: -33, 91) for a CCI score ≥4. These represented 17%, 9%, and 10% of total mortality rates, respectively, among the breast cancer patients with comorbid diseases. When the ICs were stratified on breast cancer stage, the interaction observed for the CCI score was primarily driven by distant and unknown stage cancer, as shown in Table 3. The comparison cohort members followed their matched breast cancer patient into the stage category in these stage-stratified analyses. In the 1–5 year survivor cohort, the ICs were near null.

Although history at index date of chronic pulmonary disease and “any tumor” were relatively common in the breast cancer cohort, the 0–1 year ICs were only 8.6/1000 PY (95% CI: -8.1, 25) for chronic pulmonary disease and -13/1000 PY (95% CI -31, 5.3) for “any tumor.” When we repeated all analyses for the CCI scores without assigning weights to these two disease types, the 0–1 year overall estimates of the ICs rose from 17 to 21/1000 PY (95% CI: 11, 32) for a CCI score of 1, from 12 to 31/1000 PY (95% CI: 11, 52) for a CCI score of 2–3, and from 29 to 67/1000 PY (95% CI: -19, 152) for a CCI score of ≥4. The ICs for the >1–5 year survivor cohort increased only slightly.

The interaction contrasts between breast cancer and the specific Charlson comorbid diseases were larger during the first year of follow-up than during years one to five of follow-up. The disease with the largest IC in the first year of follow-up was dementia (IC=148/1000PY (95% CI: 58, 239)). When we stratified analyses by breast cancer stage, the interaction between breast cancer and dementia was driven by interaction

**Table 3.** Interaction contrasts (ICs) and 95% confidence intervals by Charlson comorbidity (CCI) score for 1 year of follow–up.

| Stage | Interaction contrast/1000 | Interaction contrast/1000 | Interaction contrast/1000 |
|---|---|---|---|
| | CCI score 1 vs. 0 | CCI score 1 vs. 0 | CCI score ≥4 vs. 0 |
| **Local** | 7.8 (-16, 0.53) | -19 (-33, -4.9) | -101 (-168, -35) |
| **Regional** | 0.59 (-11, 12) | -12 (-30, 5.9) | -43 (-125, 39) |
| **Distant** | 228 (115, 341) | 150 (28, 272) | 370 (11, 729) |
| **Unknown** | 76 (22, 130) | 91 (25, 157) | 326 (30, 624) |

[A] Crude rates for 0–1 year of follow–up. For >1–5 years of follow–up, the matching was dissolved and standardized rates were calculated.

[B] Matching dissolved.

[C] For >1–5 years of follow–up, HRs were adjusted for age group and index years.

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in the stratum of distant-stage cancers (IC =1150/1000PY (95% CI: 162, 2137)). The ICs for dementia in the strata of local-stage (IC=44/1000PY (95% CI: –68, 155) and regional-stage (IC=-31/1000PY (95% CI: –145, 82) cancers were much smaller. The stage distribution among breast cancer patients with dementia was skewed toward later stage at diagnosis compared with breast cancer patients without dementia. In the first year after breast cancer diagnosis, the mortality rate of breast cancer patients with dementia exceeded that of breast cancer patients without dementia in local-, regional-, and distant-stage strata, yielding a stage-adjusted MRR of 5.0 (95% CI: 3.6, 6.8).

In the first year after diagnosis, there was also interaction between breast cancer and other comorbid diseases, including metastatic solid tumors (IC=66/1000PY, 17% of the total mortality rate), mild liver disease (IC=56/1000PY, 37% of the total mortality rate), moderate to severe renal disease (IC=43/1000PY, 31% of the total mortality rate), and diabetes with end-organ damage (IC=42/1000PY, 27% of the total mortality rate).

In the period one to five years after the index date, there was some interaction between breast cancer and leukemia (IC=61/1000PY, 39% of the total mortality rate), moderate to severe liver disease (IC=49/1000PY, 25% of the total mortality rate), mild liver disease (IC= 19/1000PY, 16% of the total mortality rate), and diabetes with end-organ damage (IC= 14/1000PY, 12% of the total mortality rate). Data for the individual Charlson diseases are presented in Figure 1 and Figure 2 and in Table S1 and Table S2.

## Discussion

In this large, population-based cohort study from Denmark, including more than 47,000 breast cancer patients and 200,000 matched women from the general population, we found that overall mortality in the first year after breast cancer diagnosis was influenced by interaction between breast cancer and comorbid diseases present at diagnosis. The interaction was most pronounced in the strata of distant and unknown breast cancer stage. Among individual diseases, dementia interacted most strongly with breast cancer, but metastatic solid tumors, mild liver disease, moderate to severe renal disease, and diabetes with end-organ damage also showed strong interactions. In the >1–5 year survivor cohort, there was no strong interaction with the CCI summary comorbidity score, although some interaction was observed with leukemia, moderate to severe liver disease, mild liver disease, and diabetes with end-organ damage.

A particular strength of this study is the inclusion of a comparison cohort free of breast cancer matched to the breast cancer cohort on specific comorbidities, which allows for the study of disease-specific clinical interactions between breast cancer and comorbidity. A concomitant limitation was our inability to study disease-specific causes of death, since members of the comparison cohort were unlikely to die of breast cancer. We included all women with breast cancer diagnoses from the entire country and achieved complete follow-up through the CRS. Registration of breast cancer in the DCR is nearly complete [14]. The validity of the CCI diseases recorded in the NRP has been shown to be consistently high [15]. However, outpatient data were not included before 1995, so under-registration could bias results. Such misclassification should bias the comparison of mortality in breast cancer patients with mortality in the comparison cohort toward the null, since the misclassification rate should not depend on the subsequent breast cancer diagnosis. The impact of misclassification on estimates of the interaction contrast is less predictable [16]. In addition, we lacked information on potential other confounders, such as lifestyle-related factors.

The interaction between breast cancer and comorbidity was mainly observed during the first year after breast cancer diagnosis, possibly due to lack of focus on care for comorbid diseases during cancer treatment. A recent study based on SEER data showed equal quality of care for comorbid conditions in breast cancer patients and non-cancer controls, but this was at three years after the cancer diagnosis [17]. In the time period one to five years after breast cancer diagnosis, we observed no substantial interaction between breast cancer and comorbid diseases, possibly due to equal quality of care of comorbid conditions in the period after completion of primary breast cancer treatment.

Interaction contrasts were negative in some analyses, although often imprecisely measured. Negative interaction contrasts were observed most often in the local and regional stage categories. This pattern suggests that prevalent and well-managed comorbidities brought breast cancer patients to

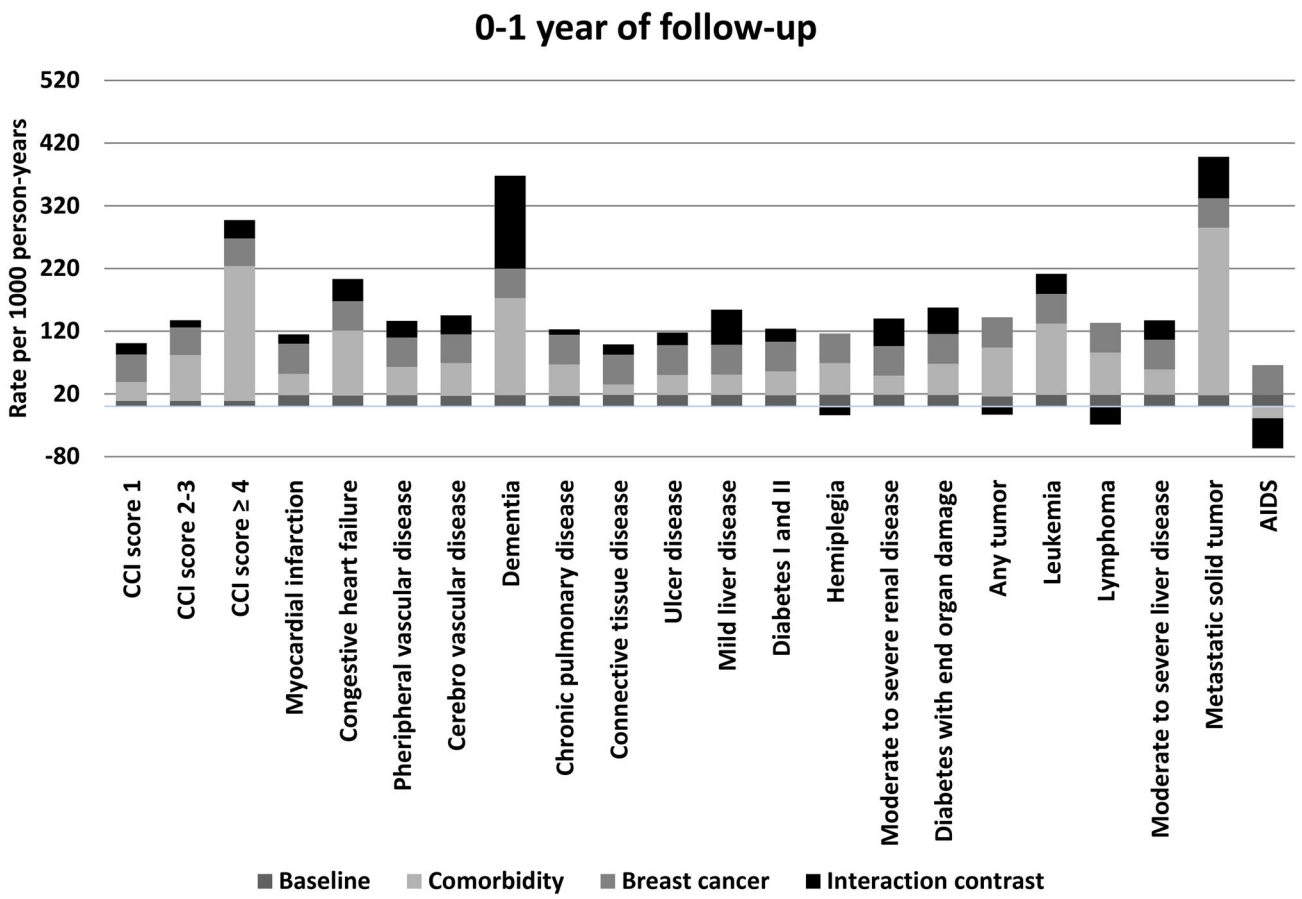


**Figure 1. Mortality rates per 1,000 person-years for 0–1 year of follow-up by Charlson Comorbidity Index (CCI) scores and individual diseases in this comorbidity index.** The total mortality rate contribution is represented by the baseline rate, comorbidity, breast cancer, and interaction.

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medical attention and diagnosis sooner, resulting in a stage-shift to earlier and more treatable breast cancers within the early-stage categories. In later stage categories, breast cancer patients with severe comorbidity may be diagnosed with breast cancer late and at an unfavorable cancer stage, as some comorbid conditions could mask evidence of this cancer [18]. We have clearly demonstrated this explanation for breast cancer patients with a CCI score ≥4 and for patients with dementia. Breast cancer patients with severe comorbidity may not receive cancer treatment in accordance with the treatment guidelines [19,20], because the comorbidity, its treatment, the cancer treatment, or its side-effects preclude the most aggressive treatments. Less aggressive treatment of cancer patients with dementia has been previously documented [21-23], which provides one explanation for the excess mortality rate for breast cancer patients with dementia in the first year after their breast cancer diagnosis.

To our knowledge, this study is the first to report specific interaction contrasts between breast cancer and the CCI score or individual diseases included in the CCI that affect the mortality rate. Studies that lacked a cohort free of breast cancer have shown that comorbidity and associated suboptimal breast cancer treatment increase the risk of death without recurrence in older women [2]. Other studies did not report increased mortality due to causes other than breast cancer in breast cancer cohorts compared to the general population [24,25]. However, a Swedish study reported increased mortality associated with diseases of the heart, pulmonary circulation (pulmonary embolism and other diseases of pulmonary vessels), and gastric diseases [26]. In addition to the interaction with dementia, we also observed interactions between breast cancer and renal diseases, liver diseases, diabetes, and other cancers. Compared to breast cancer patients without these comorbid diseases, patients with these comorbidities may not tolerate adjuvant chemotherapy and radiotherapy as well [27,28].

In summary, our study shows a clinical interaction between prevalent comorbidities and overall mortality in breast cancer patients—particularly within one year after breast cancer diagnosis and mainly in patients with distant and unknown stage breast cancer. There was substantial interaction between dementia and breast cancer, suggesting that these patients

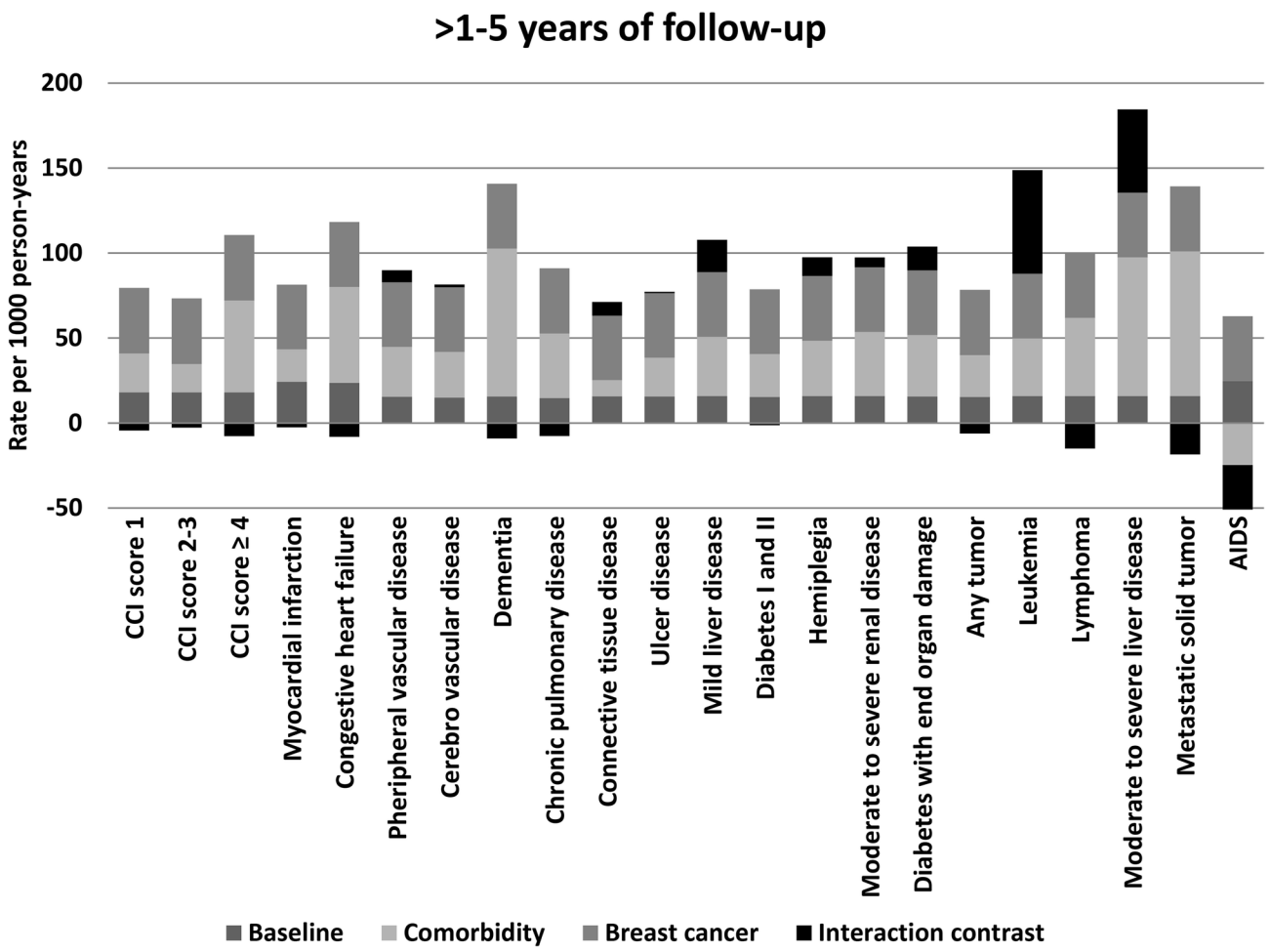


**Figure 2. Standardized mortality rates per 1,000 person-years for >1–5 years of follow-up by Charlson Comorbidity Index (CCI) scores and individual diseases in the CCI.** The total mortality rate contribution is represented by the baseline rate, comorbidity, breast cancer, and interaction.

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tend to have breast cancer diagnosed at later stages. Successful treatment of the comorbid diseases or the breast cancer can delay mortality caused by this interaction.

## Supporting Information

**Table S1. Crude mortality rates, adjusted HRs, and interaction contrasts (ICs) by individual diseases in the Charlson Comorbidity Index for the breast cancer cohort and the matched comparison cohort during 0-1 year of follow–up.**
(DOCX)

**Table S2. Standardized mortality rates, adjusted HRs, and interaction contrasts (ICs) by individual diseases in the Charlson Comorbidity Index for the breast cancer cohort and the matched comparison cohort during 1-5 years of follow–up.**
(DOCX)

## Author Contributions

Conceived and designed the experiments: AGO HTS TLL. Performed the experiments: AGO TF. Analyzed the data: AGO TF HTS TLL. Wrote the manuscript: AGO TF JPG PMWN HTS TLL.

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# Paper III

**New disease and long-term mortality in five-year breast cancer survivors**

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**Keywords**: Breast neoplasm, comorbidity, multimorbidity, complications, survival, mortality, epidemiology

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**Key words:** breast neoplasm, multimorbidity, comorbidity, mortality, survival, epidemiology.

**Abbreviations**

BC: Breast cancer

CCI: Charlson Comorbidity Index

DCR: Danish Cancer Registry

CRS: Civil Registration System

CPR: Civil Personal Registration Number

DNRP: Danish National Registry of Patients

ER: Estrogen receptor

**Abstract**

**Background:** Breast cancer (BC) survival continues to improve and, combined with an aging population, the proportion of BC survivors who develop additional medical conditions will increase. How diseases diagnosed after BC affect mortality in long-term survivors is currently not well described.

**Methods:** Using medical databases, we examined the association between the Charlson Comorbidity Index (CCI) diseases diagnosed during follow-up and all-cause mortality in a cohort of BC patients diagnosed 1994–2007 in Denmark, who had survived at least five years, and in a comparison cohort of women without a history of BC from the general population. Crude mortality rates were computed and Cox regression models were used to examine the mortality associated with new CCI diseases identified using inpatient and outpatient discharge diagnoses.

**Results:** Women in the BC survivor and comparison cohorts had a similar frequency of new CCI diseases during 14 years of follow-up. As expected, BC survivors had a higher mortality rate than women in the comparison cohort (hazard ratio (HR)= 1.47, 95% confidence interval (CI), 1.44, 1.51). However, comparing women with new disease to women who remained disease-free, mortality associated with new CCI diseases was similar in the comparison cohort (HR= 7.5, 95% CI, 7.3, 7.7) and in BC survivors (HR= 7.1, 95% CI, 6.7, 7.4).

**Conclusion:** New CCI diseases were associated with similar or slightly lower mortality among five-year BC survivors than among women from the general population. Preventing new diseases and managing existing comorbidity in older women is crucial for maximizing survival and quality of life.

## Introduction

More than 20% of breast cancer (BC) patients present with comorbid disease at diagnosis.[1-3] Survival after BC has improved in recent years and as the populations of many countries age, increased mortality from chronic disease is expected.[4] Comorbid conditions can complicate BC treatment choices and lead to substandard therapy. [5,6] A link between comorbid diseases in BC patients and poor survival has been established in several previous investigations. [1,2,5,6] For example, five-year survival was 82% in Danish BC patients without comorbidity diagnosed between 2000 and 2004 compared to 44% in BC patients with a Charlson Comorbidity Index (CCI) score ≥3.[3]

Less is known about the impact on mortality of medical conditions diagnosed after BC. Subclinical medical conditions often are detected through the extensive diagnostic work-up associated with BC diagnosis and treatment.[7] Previous research suggests that BC patients acquire a high disease burden at least during the three years following their BC diagnosis.[8,9] A 40% increase in risk of mortality during 85 months of follow-up has been reported for each CCI score increase acquired during follow-up.[9] However, the impact of new diseases on long-term mortality in BC patients has not been thoroughly studied.

We therefore examined the association of incident diseases with all-cause mortality over 14 years of follow-up in a cohort of five-year BC survivors and a comparison cohort of women with no history of BC.

## Methods

*Setting*

We used information from Danish nationwide health and administrative registries. In Denmark, access to health care is universal, tax supported and free of charge for the entire population, which includes about 2.8 million females.[10]

*Identification of breast cancer and comparison cohorts*

We accessed the Danish Cancer Registry (DCR) to identify women aged 45–85 years with a first incident diagnosis of BC between 1994 and 2007.[11] We excluded all women who survived less than five years following the BC diagnosis date, in order to study long-term mortality. We accessed the Civil Registration System (CRS), which maintains data on vital status and demographic information using the unique civil personal registration (CPR) number assigned to all Danish residents.[12] in order to select five women from the general population matched to each member of the BC survivor cohort on age and date of five-year BC survivorship.[12] The index date was defined as five years following the BC diagnosis date for each woman in the BC cohort and the corresponding date for the matched women in the comparison cohort. Women in the comparison women could not have a BC diagnosis during the five years before the index date. If a comparison woman developed BC after the index date, she was eligible for inclusion in the BC survivor cohort.

*Identification of comorbid diseases*

We collected information on comorbidities from the Danish National Registry of Patients (DNRP). These included all hospital inpatient and outpatient discharge diagnoses for diseases in

the CCI for members of the BC survivor and comparison cohorts prior to their index dates. The DNRP has recorded patient information for inpatient hospital stays since 1977 and outpatient visits since 1995.[13]

*Identification of new diseases*

We defined new CCI diseases as the first inpatient or outpatient discharge diagnosis of any disease included in the CCI after the index date for the BC survivor and comparison cohorts, thus excluding all diagnoses that were not incident (i.e. those diagnosed before the five-year survival index date).

*Covariates*

BC characteristics could potentially modify the associations under study. To take this into account, we collected information on BC stage from the DCR and information on estrogen receptor (ER) status from the Danish Pathology Registry, which contains information on all diagnostic procedures conducted by pathology departments in Denmark since 1997.[11,14]

*Follow-up*

We assessed new CCI diseases and mortality among women in the BC survivor and comparison cohorts during the follow-up period, *i.e.*, from the index date until death, emigration, or 1 January 2013 (end of follow up), whichever came first.[12,13] Because women in the comparison cohort were unlikely to die of BC, we did not conduct cause-specific analyses.

*Analytic variables*

Analytic variables included age at index date in four categories (50–59, 60–69, 70–79, and 80–90 years), comorbid diseases, and the CCI score at index date (0, 1, 2–3, ≥4). Exposure categories of new CCI diseases were "any CCI disease" and each CCI disease individually. For the BC survivor cohort, we categorized stage as localized, regional, distant, and unknown stage, and ER status as positive or negative.

*Statistical analysis*

We described the BC survivor and comparison cohorts in terms of characteristics and new diseases. We used the Kaplan-Meier method to compute crude mortality in each cohort. We then computed the number of deaths and person-time and used Cox regression models to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for mortality. We compared women with new disease to women without new disease, using time-dependent disease exposure. The models were adjusted for age group and baseline CCI scores. In a sensitivity analysis, we excluded all women with a new diagnosis of metastatic solid tumor during follow-up.

We stratified all Cox models on BC stage, ER status, and CCI scores at index date to explore potential modification of the associations under study by these factors.

Analyses were conducted using Stata 11 (StataCorp, College Station, Texas, USA). The study was approved by the Danish Data Protection Agency (record number: 2011-41-6174). No further permissions are needed to conduct studies with no intervention or participant contact in

Denmark.

## Results

*Descriptive characteristics*

This study included 32,403 five-year BC survivors who were followed for a median of 4.6 years. The 162,015 women in the comparison cohort were followed for a median of 5.3 years. As shown in Table 1, 52% of the BC survivor cohort and 60% of the comparison cohort had no coexistent disease as defined by the CCI, as of the index date. In the BC cohort, 14% of women had a CCI score ≥4.The most prevalent diseases were any tumor (8.5%), metastatic solid tumors (9.5%), chronic pulmonary disease (7.3%), cerebrovascular disease (6.4%), and diabetes I and II (4.8%). In the comparison cohort, 4.5% had a CCI score ≥4, and the most prevalent diseases were chronic pulmonary diseases (6.6%), cerebrovascular disease (6.5%), any tumor (6.3%), and diabetes (4.2%).

The frequency of new CCI diseases diagnosed after the index date was somewhat higher in the BC survivor cohort (30%) than in the comparison cohort (26%). The proportion of patients reaching a CCI score ≥4 during follow-up was 9.4% in the BC survivor cohort and 4.0% in the comparison cohort. In calculating these scores, all CCI diseases diagnosed before the index date was excluded. When analyses were stratified by type of new CCI disease, frequencies were slightly higher in the comparison cohort compared with the BC survivor cohort or equivalently distributed, for most diseases. An exception was metastatic solid tumor (7.7% in the BC survivor cohort and 2.1% in the comparison cohort) (Table 2).

*New diseases and mortality*

Figure 1 presents mortality curves for the BC survivor cohort and the comparison cohort. During 14 years of follow-up, 51% of women in the BC survivor cohort died compared to 39% in the comparison cohort. The crude mortality rates per 1000 person-years (PYs) were 50.9 (95%CI, 49.8, 51.9) for the BC survivor cohort and 30.9 (95%CI, 30.5, 31.2) for the comparison cohort, and the HR adjusted for age and CCI score at index was 1.47 (95%CI, 1.44, 1.51). The HRs for mortality associated with any new disease were almost similar in the BC survivor cohort (HR= 7.1, 95%CI, 6.7, 7.4) and the comparison cohort (HR= 7.5, 95%CI, 7.3, 7.7).
When the analyses were stratified by each CCI disease, HRs were similar or slightly higher in the comparison cohort than in the BC survivor cohort (Table 3).

In a sensitivity analysis, we excluded all women with metastatic solid tumors diagnosed during follow-up. CCI scores for new diseases were then similar in the two cohorts; 75% of all women had a CCI score of 0 during follow-up. The HRs for any new CCI disease diagnosed during follow-up were 6.2 (95%CI, 6.0, 6.4) in the comparison cohort and 4.6 (95%CI: 4.4, 4.8) in the BC survivor cohort.

*Stratified analyses*

Stratified HR-estimates for any incident CCI disease are provided in Table 4. Patients with localized or regional breast cancer stage at diagnosis had higher HR for mortality associating any incident disease with no incident disease than patients with distant or unknown stage breast cancer.

**Discussion**

Five-year BC survivors and women from the general population had similar frequencies of new CCI diseases diagnosed during 14 years of follow-up, but BC survivors had higher mortality, most likely as a consequence of their cancer. New CCI diseases were associated with similar or slightly lower mortality among five-year BC survivors than among matched women from the general population.

Our study was based on a nationwide cohort of BC survivors in Denmark. The CRS provided complete information on vital status, eliminating bias from loss to follow-up.[12] Capture of BC diagnoses in the DCR is almost complete and the positive predictive value of diagnoses in the DNRP for CCI diseases consistently has been found to be high.[15,16] We included all available information on history of comorbidity to minimize the number of false positive incident CCI diagnoses.[17,18] However, a concern is that outpatient diagnoses were added to the DNRP only in 1995, so diseases diagnosed in the outpatient setting only prior to 1995 would not have been identified as prevalent comorbidities. Furthermore, we defined prevalent and incident diseases on the basis of just one recorded discharge diagnosis. This method potentially could lead to misclassification comorbidity at index as well as new diseases. Other limitations include lack of information on lifestyle-related factors and menopausal status. Except for "any tumor" and metastatic solid tumors, frequencies of new CCI diseases during follow up were similar for BC survivors and women in the comparison cohort. This similarity suggests that surveillance bias and treatment toxicities likely have little impact on the pattern of new diseases diagnosed in our

cohort of five-year BC survivors, but we were not able to estimate their impact on disease severity. Furthermore, a recent cross-sectional study conducted in the United States indicated that quality of care for comorbid conditions among three-year BC survivors was equal to that provided to a BC-free cohort.[19] Differential treatment of new diseases in the BC survivor and comparison cohorts is also unlikely in Denmark.

Previous investigations have concluded that five-year BC survivors have a similar frequency of prevalent and incident new diseases as women from the general population.[7,8,20,21] This is supported by a recent study suggesting that smoking, diabetes and hypertension are associated with incident cardiovascular conditions in five-year BC survivors rather than a diagnosis of BC as compared with women from the general population.[22] We note that, except for metastatic solid tumors, the frequency of new CCI diseases diagnosed during follow-up also was comparable among the BC survivors and comparison cohort. New metastatic solid tumors explained the greater frequency of BC survivors reaching a CCI score ≥4 during follow up.

Not surprisingly, mortality among BC survivors was higher during follow-up than among women in the comparison cohort. BC continues to be associated with increased mortality risk beyond five years after diagnosis.[23,24] Stratifying our results by breast cancer stage showed that patients with localized or regional stage had higher HR for mortality than patients with distant or unknown spread breast cancer. It may be that once a BC patient has survived to five years, prognostic factors at her BC diagnosis, such as stage, is no longer the most important factor in determining her long-term survivorship.[23,24]

New CCI diseases were associated with similar or lower increased risk of mortality in the BC survivor cohort than in the comparison cohort. Thus, acquiring new CCI diseases after five-year BC survival may be less hazardous to such survivors than to comparable women from the general population. We speculate that this may result from potentially earlier diagnosis and treatment of diseases in the BC survivor cohort than in the general population, associated with medical follow-up or increased health awareness among BC survivors.

In summary, five-year BC survivors and women from the general population had similar incidence of new CCI diseases diagnosed during 14 years of follow-up, but BC survivors had a higher mortality rate. New CCI diseases were associated with a similar or slightly lower mortality rate among five-year BC survivors than among women from the general population. It appears that BC survivors are more likely to have new CCI diseases diagnosed and treated, resulting in better outcomes than women from the general population.

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**Conflict of interest**

The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. PB was involved in research funded by manufacturers of blood glucose lowering medications, and consulted for manufacturers of blood glucose lowering medications. The authors declare no other conflict of interest.

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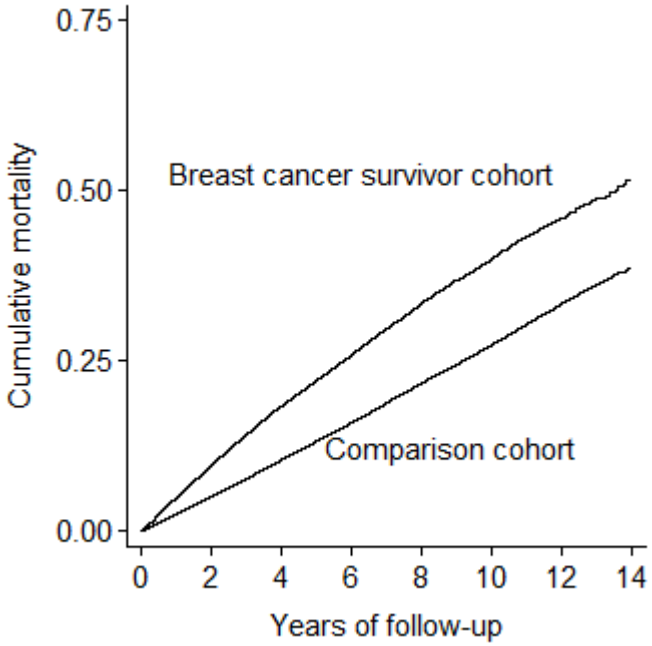


**Figure 1. Mortality curves for the five-year breast cancer survivor cohort and the general comparison cohort.**

**Table 1. Descriptive characteristics of the five-year breast cancer survivor cohort diagnosed during 1994–2007 and the matched comparison cohort.**

| | **Breast cancer survivor cohort** (N=32,403) Number (%) | **Comparison cohort** (n =162,015) Number (%) |
|---|---|---|
| **Age group at index date (years)** | | |
| 50–59 | 9,214 (28) | 42,925 (28) |
| 60–69 | 10,765 (33) | 54,013 (33) |
| 70–79 | 7,929 (24) | 39,723 (25) |
| 80–90 | 4,495 (14) | 22,354 (14) |
| **Breast cancer stage** | | |
| Localized | 17,417 (54) | N/A |
| Regional | 12,620 (39) | N/A |
| Distant | 570 (1.8) | N/A |
| Unknown | 1,796 (5.5) | N/A |
| **Estrogen receptor status** | | |
| Negative | 3,979 (12) | N/A |
| Positive | 19,703 (61) | N/A |
| Unknown | 8,721 (27) | N/A |
| **CCI score at index date** | | |
| 0 | 16,738 (52) | 97,691 (60) |
| 1 | 6,016 (19) | 31,501 (19) |
| 2–3 | 5,157 (16) | 24,957 (15) |
| ≥4 | 4,492 (14) | 7,866 (4.5) |
| **Prevalent comorbid disease at index date** | | |
| Myocardial infarction | 758 (2.3) | 4,508 (2.3) |
| Congestive heart failure | 970 (3.0) | 4,314 (2.7) |
| Peripheral vascular disease | 1,003 (3.1) | 5,102 (3.2) |
| Cerebrovascular disease | 2,083 (6.4) | 10,494 (6.5) |
| Dementia | 385 (1.2) | 1,985 (1.2) |
| Chronic pulmonary disease | 2,363 (7.3) | 10,651 (6.6) |
| Connective tissue disease | 1,109 (3.4) | 5,999 (3.7) |
| Ulcer disease | 1,113 (3.4) | 5,642 (3.5) |
| Mild liver disease | 298 (0.9) | 1,323 (0.9) |
| Diabetes I and II | 1,544 (4.8) | 6,734 (4.2) |
| Hemiplegia | 72 (0.2) | 241 (0.2) |
| Moderate to severe renal disease | 336 (1.0) | 1,657 (1.0) |
| Diabetes with end organ damage | 619 (1.9) | 2,896 (1.8) |
| Any tumor* | 2,758 (8.5) | 10,138 (6.3) |
| Leukemia | 72 (0.2) | 298 (0.2) |

| | | |
|---|---|---|
| Lymphoma | 205 (0.6) | 707 (0.4) |
| Moderate to severe liver disease | 73 (0.2) | 244 (0.2) |
| Metastatic solid tumor | 3,067 (9.5) | 1,108 (0.7) |
| AIDS | 5 (0.2) | 17 (0.0) |

Note: The index date was defined as the date of five-year survivorship after breast cancer and the corresponding date for the age-matched members of the comparison cohort.
*Any tumor other than breast cancer.

**Table 2. Incident CCI diseases diagnosed during 14 years of follow-up in the five-year breast cancer survivor cohort diagnosed during 1994–2007 and the comparison cohort.**

| | Breast cancer survivor cohort (N = 32,403) Number (%) | Comparison cohort (n = 162,015) Number (%) |
|---|---|---|
| **Incident CCI score** | | |
| 0 | 22,556 (70) | 119,507 (74) |
| 1 | 3,525 (11) | 19,335 (12) |
| 2–3 | 3,262 (10) | 16,674 (10) |
| ≥4 | 3,060 (9.4) | 6,499 (4.0) |
| **Incident CCI disease** | | |
| Any | 9,847 (30) | 42,508 (26) |
| Myocardial infarction | 591 (1.8) | 3,535 (2.2) |
| Congestive heart failure | 1,111 (3.4) | 5,521 (3.4) |
| Peripheral vascular disease | 706 (2.2) | 4,297 (2.7) |
| Cerebrovascular disease | 1,743 (5.4) | 9,300 (5.7) |
| Dementia | 818 (2.5) | 4,525 (2.3) |
| Chronic pulmonary disease | 1,444 (4.5) | 7,317 (4.5) |
| Connective tissue disease | 520 (1.6) | 2,704 (1.7) |
| Ulcer disease | 646 (2.0) | 3,102 (1.9) |
| Mild liver disease | 155 (0.5) | 725 (0.5) |
| Diabetes I and II | 934 (2.9) | 4,611 (2.3) |
| Hemiplegia | 59 (0.2) | 184 (0.1) |
| Moderate to severe renal disease | 512 (1.6) | 2,648 (1.6) |
| Diabetes with end organ damage | 449 (1.4) | 2,341 (1.4) |
| Any tumor | 2,277 (7.0) | 9,663 (6.0) |
| Leukemia | 61 (0.2) | 384 (0.2) |
| Lymphoma | 125 (0.4) | 674 (0.4) |
| Moderate to severe liver disease | 106 (0.3) | 398 (0.3) |
| Metastatic solid tumor | 2,487 (7.7) | 3,445 (2.1) |
| AIDS | 1 (0.0) | 1 (0.0) |

**Table 3. Crude mortality rates per 1000 person-years (PYs), with 95% confidence intervals, and hazard ratios (HRs) for mortality in the five-year breast cancer survivor and the comparison cohorts during 14 years of follow-up, comparing patients with disease to patients without that disease.**

| | | Breast cancer survivor cohort | | | Comparison cohort | | |
|---|---|---|---|---|---|---|---|
| | Presence of disease | Deaths, n | Rate/1000 PYs | HR | Deaths, n | Rate/1000 PYs | HR |
| Any disease | No | 3,712 | 26.3 (25.5, 27.1) | Ref | 11,055 | 13.9 (13.7, 14.2) | Ref |
| | Yes | 4,878 | 176 (171, 182) | 7.1 (6.7, 7.4) | 17,531 | 133 (131, 135) | 7.5 (7.3, 7.7) |
| Myocardial infarction | No | 8,287 | 49.5 (48.5, 50.6) | Ref | 26,840 | 29.3 (29.0, 29.7) | Ref |
| | Yes | 303 | 192 (171, 215) | 2.8 (2.5, 3.1) | 1,746 | 177 (168, 185) | 3.3 (3.1, 3.4) |
| Congestive heart failure | No | 7,909 | 47.6 (46.5, 48.6) | Ref | 25,377 | 27.8 (27.5, 28.2) | Ref |
| | Yes | 681 | 255 (237, 275) | 3.4 (3.1, 3.7) | 3,209 | 232 (224, 240) | 3.5 (3.4, 3.7) |
| Peripheral vascular disease | No | 8,283 | 49.7 (48.6, 50.7) | Ref | 26,901 | 29.5 (29.1, 29.8) | Ref |
| | Yes | 307 | 144 (129, 162) | 2.3 (2.0, 2.6) | 1,685 | 126 (120, 132) | 2.5 (2.4, 2.7) |
| Cerebrovascular disease | No | 7,835 | 47.8 (46.8, 48.9) | Ref | 24,708 | 27.5 (27.2, 27.9) | Ref |
| | Yes | 755 | 152 (141, 163) | 2.3 (2.2, 2.5) | 3,878 | 142 (138, 146) | 3.0 (2.9, 3.1) |
| Dementia | No | 8,101 | 48.5 (47.5, 49.6) | Ref | 25,943 | 28.3 (28.0, 28.7) | Ref |
| | Yes | 489 | 261 (237, 285) | 2.9 (2.7, 3.2) | 2,643 | 253 (243, 262) | 3.3 (3.2, 3.4) |
| Chronic pulmonary disease | No | 7,984 | 48.5 (47.5, 49.6) | Ref | 25,809 | 28.6 (28.3, 29.0) | Ref |
| | Yes | 606 | 140 (129, 151) | 2.5 (2.3, 2.7) | 2,777 | 120 (115, 124) | 3.2 (3.1, 3.4) |
| Connective tissue disease | No | 8,453 | 50.6 (49.5, 51.7) | Ref | 27,909 | 30.5 (30.1, 30.9) | Ref |
| | Yes | 137 | 73.0 (61.7, 86.3) | 1.2 (1.0, 1.5) | 677 | 64.1 (59.4, 69.1) | 1.5 (1.4, 1.7) |
| Ulcer disease | No | 8,241 | 49.3 (48.2, 50.4) | Ref | 27,136 | 29.6 (29.3, 30.0) | Ref |
| | Yes | 349 | 203 (182, 225) | 2.8 (2.6, 3.1) | 1,450 | 156 (148, 164) | 2.9 (2.8, 3.1) |
| Mild liver disease | No | 8,517 | 50.6 (49.5, 51.6) | Ref | 28,311 | 30.7 (30.3, 31.0) | Ref |
| | Yes | 73 | 176 (140, 221) | 4.0 (3.2, 5.0) | 275 | 128 (114, 144) | 5.4 (4.8, 6.1) |
| Diabetes I and II | No | 8,201 | 49.4 (48.3, 50.4) | Ref | 27,139 | 29.8 (29.5, 30.2) | Ref |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Yes | 389 | 141 (128, 156) | 2.3 (2.1, 2.6) | 1,447 | 92.8 (88.2, 97.8) | 2.2 (2.0, 2.3) |
| Hemiplegia | No | 8,558 | 50.7 (49.7, 51.8) | Ref | 28,487 | 30.8 (30.4, 31.2) | Ref |
| | Yes | 32 | 201 (142, 285) | 3.7 (2.6, 5.2) | 99 | 207 (170, 252) | 5.0 (4.1, 6.1) |
| Moderate to severe renal disease | No | 8,291 | 49.4 (48.3, 50.5) | Ref | 27,179 | 29.5 (29.2, 29.9) | Ref |
| | Yes | 299 | 302 (270, 338) | 4.0 (3.6, 4.5) | 1,407 | 281 (267, 296) | 4.7 (4.5, 5.0) |
| Diabetes with end organ damage | No | 8,372 | 50.0 (48.9, 51.1) | Ref | 27,665 | 30.1 (29.8, 30.5) | Ref |
| | Yes | 218 | 155 (136, 177) | 1.9 (1.6, 2.1) | 921 | 120 (113, 128) | 2.1 (2.0, 2.3) |
| Any tumor | No | 7,385 | 45.1 (44.0, 46.1) | Ref | 23,616 | 26.1 (25.7, 26.4) | Ref |
| | Yes | 1205 | 241 (228, 255) | 5.3 (5.0, 5.7) | 4,970 | 237 (230, 243) | 7.7 (7.5, 7.9) |
| Leukemia | No | 8,551 | 50.7 (49.6, 51.8) | Ref | 28,375 | 30.7 (30.3, 31.0) | Ref |
| | Yes | 39 | 297 (217, 406) | 4.9 (3.6, 6.8) | 211 | 245 (214, 280) | 5.6 (4.9, 6.4) |
| Lymphoma | No | 8,528 | 50.6 (49.5, 51.7) | Ref | 28,297 | 30.6 (30.3, 31.0) | Ref |
| | Yes | 62 | 179 (140, 230) | 3.6 (2.8, 4.6) | 289 | 167 (149, 188) | 4.2 (3.7, 4.7) |
| Moderate to severe liver disease | No | 8,510 | 50.4 (49.4, 51.5) | Ref | 28,332 | 30.6 (30.3, 31.0) | Ref |
| | Yes | 80 | 605 (486, 754) | 14 (11, 17) | 254 | 371 (328, 420) | 13 (11, 14) |
| Metastatic solid tumor | No | 6,789 | 41.3 (40.3, 42.3) | Ref | 25,968 | 28.2 (27.8, 28.5) | Ref |
| | Yes | 1,801 | 397 (379, 416) | 12 (11, 13) | 2,618 | 637 (613, 662) | 22 (21, 22) |
| AIDS | No | 8,590 | 50.9 (49.8, 51.9) | Ref | 28,585 | 30.9 (30.5, 31.2) | Ref |
| | Yes | 0 | | | 1 | 297 (41.8, 2106) | |

Notes: HRs are adjusted for age group and CCI score as of the index date, defined as the date of five-year survivorship after breast cancer and the corresponding date for the matched members of the comparison cohort.

**Table 4. Stratified HR estimates for women in the breast cancer survivor cohort associating any new CCI disease, compared with no incidence CCI disease, with mortality during 14 years of follow-up.**

| | Women, n (%) | Deaths, n (%) | Adjusted HR (95% CI) |
|---|---|---|---|
| Breast cancer stage[1] | | | |
| Localized | 5,302 (54) | 2,448 (50) | 7.5 (7.0, 8.1) |
| Regional | 3,720 (38) | 1,924 (39) | 7.2 (6.7, 7.7) |
| Distant | 145 (1.5) | 87 (1.8) | 4.7 (3.5, 6.4) |
| Unknown | 680 (6.9) | 419 (8.6) | 4.7 (4.0, 5.5) |
| Prevalent CCI score[2] | | | |
| 0 | 4,977 (51) | 2,243 (46) | 13 (12, 15) |
| 1 | 1,924 (20) | 897 (19) | 7.0 (6.3, 7.9) |
| 2–3 | 1,760 (18) | 1,005 (21) | 5.6 (5.0, 6.2) |
| ≥4 | 1,186 (12) | 733 (15) | 3.5 (3.2, 3.9) |

[1]HRs are adjusted for age group and prevalent CCI score as of the index date, defined as the date of five-year survivorship after breast cancer and the corresponding date for the matched members of the comparison cohort.
[2]HRs adjusted for age group as of the index date.

# Paper IV

Clinical Epidemiology

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COMMENTARY

# Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs

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**Abstract:** The proportion of older people in the world population is expected to increase rapidly during the upcoming decades. Consequently, the number of patients with multimorbidity will increase dramatically. In epidemiologic research, the concepts of multimorbidity, comorbidity, and complications have been confusing, and some of these concepts are used interchangeably. In this commentary, the authors propose a clear terminology for clinical concepts describing different aspects of multimorbidity and elucidate the relationship between these clinical concepts and their epidemiologic analogs. Depending on whether a study uses causal or predictive models, a proper distinction between concepts of multimorbidity is important. It can be very difficult to separate complications of the index disease under study from comorbidity. In this context, use of comorbidity indices as confounding scores should be done with caution. Other methodologic issues are type, duration, severity, and number of comorbidities included in the ascertainment methods, as well as sources included in the research. Studies that recognize these challenges have the potential to yield valid estimates of the comorbidity burden and results that can be compared with other studies.

**Keywords:** epidemiology, epidemiologic methods, comorbidity, complications, diagnosis-related groups, risk adjustment

## Multimorbidity

The major challenge facing modern health care systems is aging of the population in the context of significant pressure to contain costs. The proportion of people aged 60 years or more in the world population is expected to increase rapidly from 10% in 2000 to 21% in 2050.[1] Concurrently, the number of patients with multimorbidity, ie, coexistence of several chronic diseases, will increase dramatically. The prevalence of multimorbidity has been estimated at more than 80% among persons aged older than 85 years.[2] Up until now, clinical research has focused predominantly on single disease and episode, often with a focus on mortality as the main endpoint. Thus, one of the most important tasks in clinical medicine today is managing multimorbidity. This requires an evolution away from the single disease focus that has dominated medicine for centuries.[3] The aim of this commentary is to propose clear terminology for the clinical concepts describing different aspects of multimorbidity and to elucidate the relationship between these clinical concepts and their epidemiologic analogs.

## Confusion concerning terminology used in clinical epidemiology

The concept of multimorbidity varies widely in the literature.[4,5] It has been used to describe the number of morbidities, the number and severity of morbidities, and the

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number and severity of morbidities together with concurrent limitations in functional status or frailty. In addition, multimorbidity is often measured by the burden of comorbidity at time of diagnosis of an index disease.[4] The numerous definitions of multimorbidity include predefined medical conditions or unlimited numbers and types of medical conditions, chronic conditions, or both acute and chronic conditions, physical diseases alone, or physical and psychiatric conditions. Further, the various definitions include comorbidities diagnosed before or both before and concurrent with the index disease.[6–14]

Because of the existing confusion concerning terminology, we propose more stringent definition of five commonly used concepts. We suggest that the "index disease" describes the main condition under study, while "comorbidity" describes medical conditions that exist at the time of diagnosis of the index disease or later, but that are not a consequence of the index disease. In contrast, "multimorbidity" can be described as existence of two or more chronic diseases. "Complications" of an index disease are adverse events occurring after diagnosis of that disease. "Case-mix" refers most often to the mix of patient types treated at hospitals or departments, and the case-mix index is a measure of the complexity of illness used in health service research or in clinical medicine as, for example, a clinical prediction score.

In clinical epidemiology, these concepts are used in two main types of models with the purposes of control for confounding (causal models) or clinical prediction.

## Causal models

These concepts can be translated into epidemiologic analogs in causal models with a well-defined exposure and outcome.[15] In this context, the index disease defines the study population or the exposure under study. The term "comorbidity" can have three roles in epidemiologic studies, depending on the exposure and endpoint. First, in some circumstances, comorbidity can be a part of the exposure complex under study. An example is the impact of comorbidities on mortality in patients with diabetes. Second, comorbidity can interact with the exposure and modify the association between that exposure and an endpoint. Third, in many studies of a defined index disease, comorbidity qualifies as a potential confounding factor in the association between an exposure and an endpoint, given that the burden of comorbidity varies for different patient populations based on characteristics such as age and lifestyle.[16] It is important to emphasize that there are three criteria for a confounding factor: a confounder must be associated with the disease (either as a cause or as a proxy for a cause but not as an effect of the disease); a confounder must be associated with the exposure; and a confounder must not be an effect of the exposure.[15]

In contrast, "complications" of the index disease can arise after diagnosis of that disease and therefore qualify as an endpoint or an intermediate step in the pathway from exposure to a more distal endpoint in the clinical pathway. For example, multiple sclerosis and sarcoidosis can be comorbid conditions in diabetics, while retinopathy, cardiomyopathy, and nephropathy are well defined complications of diabetes.[17] Other comorbidities may modify the effect between the index disease and survival. Thus, cancer may modify the effect between diabetes and survival (Figure 1).

## Risk prediction models

While causal models are used in the research setting to evaluate the causal role of one or more exposures while simultaneously controlling for possible confounding factors,[15] risk or prognosis prediction models may be useful tools in several clinical settings taking multiple clinical variables into consideration. The American Society for Anesthesiology score, for example, is used in acute medicine to evaluate the physical status of a patient and the impact of the index disease, comorbidity, and complications on mortality.[18] The Acute Physiology and Chronic Health Evaluation scale is used in intensive care to evaluate the burden of morbidity from the index disease, comorbidity, and acute clinical status.[19,20]

In health service management, the Diagnosis-Related Group system is used as a way to classify hospital cases into one of 467 original groups (now 745). This system of classification was developed by Fetter and Thompson.[21] Their intention was to identify the "products" that a hospital provides. Diagnosis-Related Groups are assigned by a "grouper" program based on International Classification of Diseases (ICD) diagnoses, procedures, age, gender, discharge status, and the presence of complications or comorbidities.[22]

In practical clinical epidemiology, it might be difficult to distinguish complications from comorbidities. Such evaluation might most often require data information outside the actual study.[23] Evidence from particular experimental studies and theory, for example, must be considered.

# Complications versus comorbidity in epidemiologic research

Failure to separate complications from comorbidities can have a serious impact on clinical epidemiology research. A very broad definition of comorbidity must be used with caution to avoid misclassifying complications as

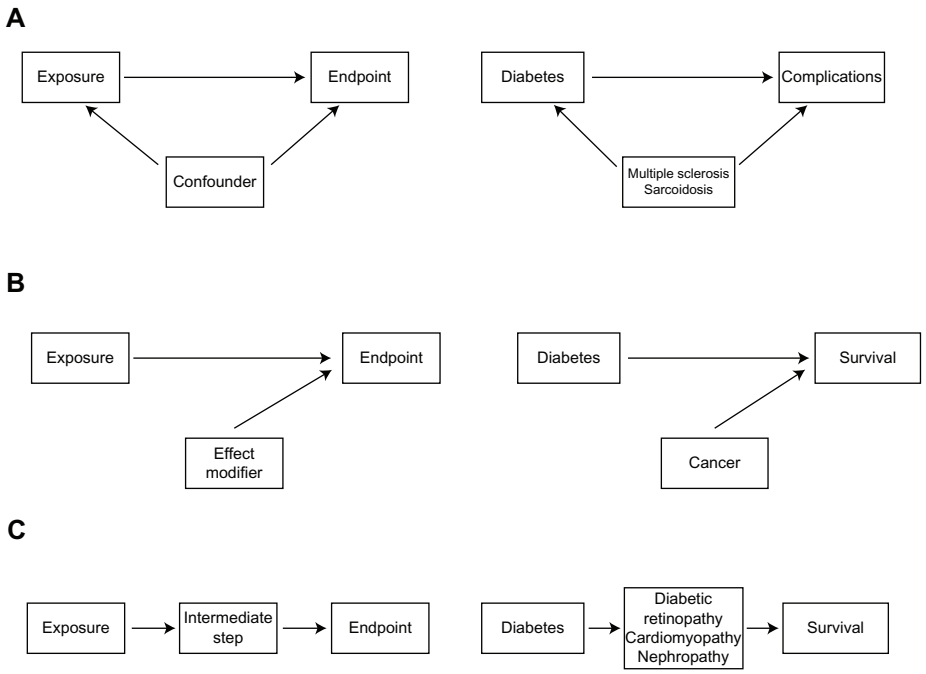


**Figure 1** Simple epidemiological models illustrating the association between the exposure variable and the outcome under study.
**Notes:** (**A**) Illustrates the confounding pathway from the exposure to the endpoint. (**B**) Illustrates effect modification of the association between the exposure and the endpoint, and (**C**) Illustrates an intermediate step from the exposure to the endpoint.

comorbidities. As shown in Figure 1, complications are endpoints or intermediate steps in the pathway from an exposure to an endpoint. Therefore, they must be considered separately from comorbidities. Otherwise, the total comorbidity burden would be overestimated and misclassification of information about comorbidity would be introduced. If complications are regarded as comorbidities and handled as confounders, some of the effect between the exposure and outcome is masked, resulting in distorted estimates of association.[24] At the same time, a more restrictive definition of comorbidities could misclassify comorbidities as complications, and therefore result in underestimation of the comorbidity burden, potentially leading to residual confounding if comorbidity is a confounder in the study.

Correct classification of medical conditions as comorbidities or complications is necessary to avoid inaccurate estimation of the comorbidity burden. As described above, in examining the association between diabetes and survival, diseases such as multiple sclerosis or sarcoidosis are not known to be related to diabetes. Therefore, these diseases should be clearly defined as comorbidities in patients with diabetes as an index disease. Other diseases and conditions may not clearly meet the criteria of either comorbidities or complications of diabetes. Hypertension may be a common complication of diabetes as a result of vascular changes, but may also arise independently. This illustrates the complexity of separating medical conditions into comorbidities and complications, but also stresses its importance. Directed acyclic graphs may help clarify the role of different variables in a study.[24]

## Comorbidity scores and indices

Comorbidity scores or indices combine information about several comorbidities into one score. The idea behind a confounder summarization, for example, is to define a single continuous variable that pulls together relevant information on the confounding properties of all variables.[25] Several indices have been developed to account for comorbidity as a confounding factor in research studies. Frequently used indices include the Charlson Comorbidity Index, the Cumulative Illness Rating Scale, the Index of Co-existing Disease, and the Kaplan–Feinstein Index.[7,9,12–14] These indices are based on information about severity or number and severity of comorbid conditions, defined by organ systems and severity of diverse aspects of each comorbid disease, or on the degree of pathologic changes of the comorbid condition defined by organ systems. These indices incorporate available information about comorbid conditions into an aggregate index, which precludes estimation of effects of individual comorbid diseases. In addition, the definition of a comorbid condition and its role in the index varies for different indices.

The Charlson Comorbidity Index is frequently used in clinical epidemiology studies to quantify the level of comorbidity. This index is based on 19 comorbid diseases weighted according to adjusted one-year cumulative mortality risk,[7] and has been validated as a prognostic marker of comorbidity for several index diseases.[26–32] However, the Charlson Comorbidity Index has several limitations. It does not include psychiatric diseases, which can confer substantial morbidity, even in patients with physical index diseases. The Charlson Comorbidity Index also evaluates disease severity only for a few diseases and to a very limited extent. Diabetes and cancer, for example, are categorized into only two severity groups, although the prognostic impact of disease severity can be more finely parsed. The prognostic impact of disease duration varies for different diseases. For instance, it increases with duration for diabetes, but may decrease for successfully treated ulcer disease and cancer.

## Limitations of confounding indices

The burden of comorbidity is measured by extracting data from medical records or medical databases, physical examination, personal interview, or questionnaires.[33] These methods have many weaknesses and there is no gold standard. First, the sensitivity and specificity of comorbid diagnoses, whether they come from medical files, databases, or patient report, are never complete. Therefore, there will be residual confounding in a study where comorbidity is a confounding factor. Due to variation in sensitivity and specificity for different comorbid diagnoses and potential failure to account for disease severity and duration, which may be highly correlated with an exposure and endpoint, comorbidity indices cannot accurately measure the comorbidity burden for each patient, thus leading to residual confounding. Any underestimation of the comorbidity burden, for example, by using restrictive definitions of comorbidity, may also introduce residual confounding into a research study. In view of these limitations, all confounding score indices must be used with caution.[14]

## Conclusion

Research on multimorbidity is urgently needed to understand the clinical course of disease in detail in order to improve clinical outcomes. Depending on whether a study uses causal or prediction models, a proper distinction between concepts of multimorbidity is important. It can be very difficult to separate complications of the index disease under study from comorbidity. In this context, use of comorbidity indices as confounding scores should be undertaken with caution. Other methodologic issues are type, duration, severity, and number of comorbidities included in the ascertainment methods, as well as sources included in the research. Studies that recognize these challenges have the potential to yield valid estimates of the comorbidity burden and results that can be compared with those from other studies.

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## Disclosure

The authors declare no conflicts of interest in this work.

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