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Infection-related hospitalizations in breast cancer patients: risk and impact on prognosis

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SUMMARY

Objectives: Infections are a common cause of hospitalization in breast cancer patients. We studied the risk, clinical characteristics and outcomes of infection-related hospitalizations in this patient population.

Methods: A Swedish registry-based study including 8,338 breast cancer patients diagnosed between 2001 and 2008, followed prospectively for infection-related hospitalizations until 2010. Standardized incidence ratios (SIRs) were calculated using background rates from the general female population. Associations with clinical characteristics and mortality were analyzed using flexible parametric survival models.

Results: In total, 720 patients experienced an infection-related hospitalization during a median follow-up of 4.9 years. Infection rates were highest within the first year of diagnosis (SIR = 5.61, 95% CI; 4.98-6.32), and site-specific risks were most pronounced for sepsis (SIR = 3.14, 95% CI; 2.66-3.71) and skin infections (SIR = 2.80, 95% CI; 2.24-3.50). Older age at diagnosis, comorbidities, markers of tumor aggressiveness, chemotherapy and axillary node dissection were independent predictors of infectious disease risk. Infection-related hospitalizations were also independently associated with overall and breast cancer-specific death.

Conclusions: A significant number of breast cancer patients are hospitalized with an infection following diagnosis, which in turn predicts poor prognosis. The risk profile of infection-related hospitalizations is multifactorial, including patient, tumor and treatment-related factors.

Key words: breast cancer, infection-related hospitalizations, risk factors, prognosis, epidemiology

INTRODUCTION

Breast cancer is the most common malignancy diagnosed in women worldwide and the number of prevalent cases is increasing due to the overall rise in breast cancer incidence and improved survival rate [1]. As a result of the increased life expectancy, morbidity after a breast cancer diagnosis has become more important from a clinical and public health perspective [2]. Infections are a common complication in breast cancer patients and result from immunosuppression due to treatment or the malignancy itself [3, 4]. Most infections are transient in nature, but their consequences may last longer. Severe infections, for instance, have been associated with prolonged hospitalization and treatment delay [5, 6], and are a major cause of future morbidity and mortality [3, 7].

Despite the considerable impact on patient outcome and health care use, limited data are available on the incidence of serious infections in breast cancer patients. Previous studies have primarily focused on infection-related hospitalizations during periods of chemotherapy-induced neutropenia [8, 9] and data beyond the initial treatment period are scarce. Moreover, breast cancer and its treatment may predispose to infections at certain organ sites, but no studies to date have reported risk estimates for site-specific infections. Also, little is known about the tumor and treatment dependent risk profile and the impact of infection-related hospitalizations on mortality.

In the present study we aimed to assess the risk and prognostic implications of serious infections in breast cancer patients. Using registry-based data, we studied the incidence of infection-related hospitalizations in breast cancer patients as compared to the general female population, overall and by time since diagnosis. We also examined associations with patient, tumor and treatment characteristics as well as the impact of infection-related hospitalizations on overall and breast cancer-specific survival.

PATIENTS AND METHODS

Study population

The Stockholm Breast Cancer Register (SBCR) is a population-based clinical register recording all breast cancer diagnoses occurring in the Swedish counties of Stockholm and Gotland since 1976. The register has more than 95% completeness for women aged less than 75 years at diagnosis and contains detailed information on tumor characteristics and primary breast cancer treatment, as well as routine follow-up information on locoregional recurrence and distant metastasis [10, 11]. For the present study, we identified all women diagnosed with primary invasive breast cancer at age 25-75 years between 2001 and 2008 (N = 8658). We excluded breast cancer patients with distant metastasis at diagnosis (N = 320), leaving a total of 8338 individuals for the analysis. All patients were linked by the unique personal identity number to the Swedish Inpatient Register, the Swedish Cancer Register, the Swedish Cause of Death Register and the Swedish Emigration Register and follow-up was complete until December 31, 2010. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. Background rates from the general female population were available through merges with the National Population Register. Since this is a registry-based study, no participant was contacted, and all data were anonymized prior to analysis.

Infectious diseases

Infectious diseases were identified through the Swedish Inpatient Register which has nationwide coverage since 1987 and includes all inpatient hospitalizations in Sweden [12]. Diagnoses were coded according to the relevant International Classification of Diseases (ICD) codes and subdivided into site-specific groups of infections as described elsewhere [13] (**Supplementary Table S1**). For the present analysis, we only counted infectious diseases listed as principal diagnosis of hospitalization.

Clinical characteristics

We extracted the following patient, tumor and treatment characteristics from the Stockholm Breast Cancer Register: date of diagnosis, tumor size, histological grade, estrogen/progesterone receptor (ER/PR) status, axillary lymph node involvement, chemo/endocrine therapy, surgery and axillary lymph node dissection. Information on comorbid disease prior to diagnosis was obtained from the Swedish Inpatient Register and summarized into the Charlson Comorbidity Index (CCI) score, a widely used method for classifying chronic comorbid conditions [14].

Follow-up data

Information on emigrations was collected from the Swedish Emigration Register and date and cause of death until 31 December 2010 was extracted from the Swedish Cause of Death Register. The latter register covers all residents in Sweden with essentially no missing data, and has been shown to correctly classify 98% of all breast cancer deaths [15]. Follow-up information on distant metastasis, locoregional recurrence, and second primary breast cancers was obtained through the Stockholm Breast Cancer Register and the Swedish Cancer Register.

Statistical analyses

We first assessed the rate of infection-related hospitalizations, overall and by infection site. Numbers of person-years at risk were calculated from the date of breast cancer diagnosis until the date of infectious disease hospitalization, death, emigration, or December 31, 2010 whichever came first. To evaluate the impact of the primary tumor/treatment, person-time was ended at recurrent disease defined as locoregional recurrence, distant metastasis or a second primary breast cancer. Rates of infection-related hospitalizations were modeled using flexible parametric survival models (FPM) [16] with time since diagnosis as underlying time scale. We also compared rates of infectious disease hospitalization with those observed in the general population, by calculating age and calendar period standardized incidence ratios (SIRs) using background rates from the entire female population resident in the Stockholm-Gotland area between 2001 and 2010 (N = 454,704) [17]. For this analysis, we only

included breast cancer patients without a history of infectious disease hospitalization prior to diagnosis (N = 7550).

Next, we studied the risk of infection-related hospitalization by patient, tumor and treatment characteristics using FPM which is similar to the Cox proportional hazards model. The main advantage of FPM is that non-proportional hazards can easily be fitted, allowing the effect of exposure variables to vary over time. In all models, time since diagnosis was the underlying time scale and a spline with six knots (five degrees of freedom) was used for the baseline hazard. Proportional hazards assumptions were verified using likelihood ratio tests and in case of non-proportionality time-dependent effects were modelled by adding interaction terms with time using a second spline with four knots (three degrees of freedom). We conducted three analyses to assess the impact of clinical characteristics: 1). models adjusting for age and calendar year of diagnosis; 2). grouped models including respectively all patient, tumor and treatment characteristics with additional adjustment for age and calendar year of diagnosis and 3). a multivariable adjusted model including all variables. Treatment variables were entered as time-fixed variables at diagnosis in all models, as binary time-dependent modelling from treatment initiation yielded identical results, due to the short time span between diagnosis and therapy start.

Finally, we studied the impact of infectious disease hospitalization on overall and cause-specific mortality using FPM. Infections were entered as binary time-dependent variable, changing from unexposed at breast cancer diagnosis to exposed at the date of infection hospitalization. For this analysis, we only considered infection-related hospitalizations occurring prior to disease recurrence, as defined above. To examine the impact of infection site, we also modelled the effect for each site separately. All models were adjusted for patient, tumor and treatment characteristics to assess the independent prognostic effect of infection-related hospitalizations. Statistical analyses were carried out using SAS version 9.2 and STATA version 12.0.

RESULTS

Descriptive characteristics of the breast cancer cohort are summarized in **Table 1**. Mean age at diagnosis was 57.4 years and the median length of follow-up was 4.9 years. In total, 720 patients experienced an infection-related hospitalization following diagnosis. When comparing rates of site-specific infections, respiratory infections and sepsis were most frequently reported. The largest group of other infections was unspecified and not classifiable according to organ site **(Supplementary Table S2)**.

Supplementary Table S3 shows the SIRs by time since diagnosis. Overall, breast cancer patients showed increased rates of infection-related hospitalizations compared to the general female population (SIR = 2.04, 95% CI; 1.89-2.21). Relative risks varied by site, and were most pronounced for sepsis (SIR = 3.14, 95% CI; 2.66-3.71) and skin infections (SIR = 2.80, 95% CI; 2.24-3.50) and lowest for gastrointestinal infections (SIR = 1.14, 95% CI; 0.92-1.42). For most sites, the risk of infection was highest within the first year of diagnosis (SIR = 5.61, 95% CI; 4.98-6.32) with a steep decline thereafter, except for urinary tract infections for which no time-dependent risk pattern was observed **(Supplementary Table 3)**. Rates for sepsis and skin infections remained increased up to 5 years after diagnosis (SIR = 1.95, 95% CI; 1.37-2.78 and 2.37, 95% CI; 1.60-3.50 respectively), while the excess rate for all other infections was limited to the first year of diagnosis.

Figure 1 shows the absolute rates of infection-related hospitalizations by time since diagnosis and organ site. The highest infection rate after diagnosis was found for sepsis and respiratory infections, with a peak rate of respectively 15 and 22 events per 1000 person-years. Absolute rates were lower for skin and gastrointestinal infections, but again with a peak rate in the first year of diagnosis. Interestingly, a small second peak in skin infection rate was found 2 years after diagnosis. On the other hand, no increased rate was observed for urinary tract infections shortly after diagnosis.

Table 2 lists the HRs for infection-related hospitalizations by patient, tumor and treatment characteristics. Older age at diagnosis and comorbid conditions including a history of infectious disease hospitalization were associated with an increased risk of infections. All tumor characteristics showed a consistent pattern with the hazard of infection being higher for more aggressive tumors

(larger tumors, high-grade tumor and tumors with axillary lymph node involvement), although the overall HR was only significant for lymph node status after multivariable adjustment **(Table 2)**. Associations with patient and tumor characteristics were similar in analyses excluding chemotherapy-treated patients **(Supplementary Table S4)**.

The strongest treatment effect was observed for chemotherapy and axillary node dissection. An increased hazard was also found in patients undergoing axillary radiotherapy, but this association did not retain significance in multivariable analyses **(Table 2)**. More details on chemotherapy treatment were available for 1861 patients, and agent-specific analyses showed a tendency towards a higher risk of infection-related hospitalizations among patients receiving taxanes compared to other chemotherapy agents **(Table 3)**.

The proportional hazards assumption was met for all variables except for age, tumor size, histological grade, axillary lymph node status, chemotherapy and axillary node dissection **(Supplementary Table S5)**. The impact of age varied over time, with older age only having an impact on risk 2 years after diagnosis. While not being significant in overall analysis, large and high-grade tumors were independently associated with an increased risk of infection-related hospitalizations in the first 6 months after diagnosis. Time-dependent analyses further showed that the impact of chemotherapy and axillary lymph node status and dissection, were only short-term, i.e. not detectable 1 year after diagnosis.

We also assessed the impact of infection-related hospitalizations on mortality, after adjustment for patient, tumor and treatment characteristics As shown in **Table 4**, patients who were hospitalized with an infection were at increased risk of dying from any cause during follow-up (HR = 1.83, 95% CI = 1.51-2.22). The impact of infection-related hospitalizations was strongest for non-breast cancer mortality (HR = 2.85, 95% CI = 2.13-3.80), although risk of breast cancer-specific death was also slightly increased in patients experiencing an infection-related hospitalization (HR = 1.37, 95% CI = 1.05-1.79). Analyses by infection site showed that the adverse impact on breast cancer death was mainly driven by respiratory infections (HR = 1.92, 95% CI = 1.26-2.91), and that associations with other-cause mortality were strongest for sepsis (HR = 4.51, 95% CI = 2.87-7.09) and respiratory infections (HR = 3.61, 95% CI = 2.49-5.24).

DISCUSSION

Hospitalization due to infection is a common cause of hospitalization in breast cancer patients, but estimates of the actual risk and prognostic implications of infection-related hospitalizations are scarce. This is the first study reporting risk estimates by time since diagnosis and infection site. In total, 720 patients experienced an infection-related hospitalization during a median follow-up of 4.9 years. Infection rates were highest within the first year of diagnosis, and site-specific risks were most pronounced for sepsis and skin infections compared to rates observed in the general population. Older age at diagnosis, comorbidities, markers of tumor aggressiveness, chemotherapy and axillary node dissection were all independently associated with the risk of infections in multivariable analyses. Our data further indicate that infection-related hospitalizations are an independent predictor of overall and breast cancer specific survival, associations that are mainly driven by respiratory infections and sepsis.

The infectious disease pattern with high relative risks of sepsis and skin infections is in accordance with complications that are commonly seen in breast cancer patients: neutropenia and lymphedema [18]. Chemotherapy-induced neutropenia is a major risk factor for sepsis [19] and lymphedema is one of the strongest risk factors for skin infections [20]. Previous studies have shown that the risk of lymphedema remains elevated several years after the breast cancer diagnosis [18, 21], which is in line with the long-term risk of skin infections found in the present study. The main driver of the long-term sepsis risk is not fully understood, but possible explanations include a suppressed immune system that is further weakened by other breast cancer comorbidities and the use of antibiotics for previous infectious events not requiring hospitalization. For all other infections, excess rates were limited to the first year of diagnosis, except for urinary tract infections for which no time-dependent risk pattern was observed.

The risk of infections after a cancer diagnosis is determined by treatment-related adverse effects, underlying immune deficiencies and associated comorbidities [3]. Since more than one predisposing factor may exist in a patient, their cumulative burden may better reflect the actual risk of infections. In

the present study, chemotherapy increased the risk of infection-related hospitalization within the first year of diagnosis, i.e. the period of active treatment. Chemotherapy can predispose to infections in various ways, namely by direct damage to anatomical barriers (i.e. ulceration of gastrointestinal tract) bone marrow suppression and neutropenia, but also indirectly through the use of central venous catheters (CVCs) [3]. When comparing different chemotherapy agents, a tendency was observed towards a higher risk of infection-related hospitalizations in patients receiving taxanes. This finding, while observational in nature, corresponds with clinical trial data showing a higher incidence of neutropenic events with taxane-based regimens compared to other chemotherapy agents [22]. We also found a short-term increased risk of infections in patient undergoing axillary node dissection, irrespective of the number of nodes dissected. Apart from treatment-specific factors, the tumor itself may also contribute to infectious disease susceptibility. Although breast cancers, in contrast to hematological cancers, are not inherently linked to an immune deficit, several lines of evidence support a role for immunosuppression in tumor initiation and progression.[23-26] Metastatic processes may also compromise the immune system through invasion and mechanical obstruction [3], and this could explain the observed increased risk of infections in node-positive patients, an association that has been reported previously [8]. Short-term associations with tumor-specific factors may, however, also reflect postsurgical complications, which are more common with extensive surgery of large tumors [3]. Besides treatment and tumor related factors, our study shows that a patient's health status, in terms of age and comorbid conditions, is another predisposing factor. Likewise, a previous infectious episode could lead to infection reactivation, especially in patients undergoing immunosuppressive therapy [3]. Thus, the underlying mechanisms of infection-related hospitalizations in breast cancer patients are complex and multifactorial.

We also observed an independent effect of infection-related hospitalizations on overall and breast cancer specific survival, associations that were mainly driven by respiratory infections and sepsis. There are several explanations for the worsened outcome with infection-related hospitalizations in

breast cancer patients. First of all, as a marker of immunosuppression, infections may provide additional information that is not captured by traditional prognosticators. Several studies have shown that immune parameters have added prognostic value in breast cancer patients in terms of future relapses and overall survival.[26, 29, 30] Second, infection-related hospitalizations may influence prognosis through a delay or discontinuation of breast cancer treatment. According to several reports, neutropenia and infections, especially those involving the respiratory system, are strong independent predictors of chemotherapy interruption [6, 31], which in turn impacts disease control. However, the observed association between respiratory infections and breast cancer death can also be interpreted as early symptom of lung metastases. Since the impact of infection-related hospitalizations on breast cancer death was observed for respiratory infections solely, this is also a plausible explanation for this specific outcome.

Strengths of our study are the population-based design and linkage to register-based data which minimizes loss-to follow-up. Other strengths are the large breast cancer cohort with long-term follow-up and detailed information on patient, tumor and treatment characteristics. By use of flexible parametric models, we were able to investigate time-dependent patterns in infectious disease hospitalization and its underlying risk factors. Our study also had limitations. Compared to the general population, breast cancer patients may experience a lower threshold for infectious disease hospitalization. Referral bias could have resulted in inflated SIRs close to diagnosis, but long-term risk estimates are less subject to this type of bias. Another limitation is the potential misclassification of the outcome. A recent evaluation of the Swedish Inpatient Register indicates high coverage and validity for most hospital diagnoses [12], but infectious diseases have not been extensively validated in this particular setting. However, previous studies show that inpatient diagnoses are suitable for monitoring overall and site-specific infections [34, 35]. We further tried to minimize the impact of potential misclassification by analyzing main diagnoses only. Also, we were unable to study risk factors per organ site, due to the limited number of incident events per site-specific infection. Finally, we could not investigate the impact of immunomodulatory therapies such as Traztuzumab for human

epidermal growth factor receptor 2 (HER2) positive cancers, as this therapy was not routinely prescribed during the study period.

From a clinical perspective, the adverse effect of treatment including chemotherapy needs to be balanced against the survival benefit, with recent trial data showing a ~30% reduction in 10-year mortality with even moderate chemotherapy regimens [36]. Moreover, short-term prevention of infection-related hospitalizations is challenging in an immunocomprised host, although several strategies have been proposed for infectious disease prevention in chemotherapy-treated patients including immunizations and simple hygiene measures [37, 38]. Apart from chemotherapy, we identified several patient, tumor and treatment-related risk factors, and this information may aid in the development of tailored, preventive strategies. Since more patients survive breast cancer today, the number of prevalent cases with infectious complications will increase. Given the impact of infection-related hospitalizations on morbidity, mortality, and health care associated costs, more efforts are needed to reduce the burden of this complication.

Collectively, our study shows that a significant number of breast cancer patients are hospitalized with an infection following diagnosis, which in turn predicts poor prognosis. The excess rate of infection-related hospitalization is highest within the first year of diagnosis, with site-specific risks being most pronounced for sepsis and skin infections. We further demonstrate that the risk profile for infection-related hospitalizations is multifactorial, with patient, tumor and treatment characteristics contributing to risk in a time-dependent manner. In light of the growing number of prevalent breast cancer cases, this complication deserves more clinical awareness and investigation.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: JSB, EC, PH, KC

Acquisition, analysis or interpretation of data: All authors

Statistical analyses: JSB, ALVJ, MC

Drafting of the manuscript: JSB, KC

Critical revision and approval of the manuscript: All authors

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FIGURE LEGENDS

Figure 1. Rates of infection-related hospitalizations by time since diagnosis and organ site.

Abbreviations: CI = confidence interval; py's = person-years. Estimated rates of infection-related hospitalization per site, as obtained from flexible parametric survival models with time since diagnosis as underlying time scale.

Table 1. Descriptive characteristics of the study population.

	Stockholm breast cancer cohort (*N* = 8,338)
Cohort period	2001/2008-2010
Age at diagnosis (years)	
Mean (SD)	57.4 (10.2)
Min – Max	25-75
Duration of follow-up (years)	
Median (IQR)	4.9 (4.1)
Total no. of person years at risk	42,576
Infection rate (per 1000 person years)	16.9
Age at infection diagnosis	
Mean (SD)	60.7 (11.5)
No. of infection diagnoses, N	
Any infection [a]	720
Respiratory infections	237
Sepsis	161
Skin infections	83
Gastrointestinal infections	104
Urinary tract infections	82
Other infections	145

Abbreviations: SD = standard deviation; IQR = interquartile range. The study population comprises all women diagnosed with primary invasive non-metastatic breast cancer at age 25-75 years in the Stockholm-Gotland region between 2001 and 2008. [a] Total no. of infection diagnoses is smaller than the sum of site-specific infections due to co-occurrence of infections within the same patient.

Table 2. Association of patient, tumor and treatment characteristics with risk of infection-related hospitalization in breast cancer patients.

		HR (95% CI) [a]		
	***N* total / cases**	**Model 1**	**Model 2**	**Model 3**
Patient characteristics				
Age at diagnosis [c]				
< 55 years	3063 / 238	REF (1.00)	REF (1.00)	REF (1.00)
55-64 years	3033 / 256	1.05 (0.88-1.26)	0.99 (0.83-1.18)	1.12 (0.93-1.34)
≥ 65 years	2242 / 226	1.33 (1.11-1.59)	1.15 (0.96-1.39)	1.34 (1.10-1.64)
Charlson comorbidity index score				
0	7385 / 564	REF (1.00)	REF (1.00)	REF (1.00)
1	514 / 83	2.20 (1.74-2.78)	2.03 (1.61-2.58)	1.97 (1.55-2.50)
≥ 2	439 / 73	2.43 (1.89-3.11)	2.27 (1.77-2.92)	2.17 (1.63-2.62)
Infectious disease history				
No	7550 / 607	REF (1.00)	REF (1.00)	REF (1.00)
Yes	788 / 113	1.86 (1.52-2.27)	1.62 (1.32-1.99)	1.62 (1.32-1.99)
Tumor characteristics				
Size in mm [c]				
<10	2086 / 134	REF (1.00)	REF (1.00)	REF (1.00)
10-20	3555 / 297	1.37 (1.11-1.68)	1.14 (0.96-1.37)	1.22 (0.98-1.52)
>20	2438 / 259	1.89 (1.53-2.33)	1.42 (1.18-1.70)	1.28 (1.00-1.62)
Histological grade (Elston) [c]				
Low	963 / 53	REF (1.00)	REF (1.00)	REF (1.00)
Moderate	2557 / 181	1.30 (0.96-1.77)	1.34 (1.08-1.66)	1.04 (0.76-1.41)
High	1539 / 145	1.92 (1.40-2.64)	1.51 (1.19-1.90)	1.17 (0.83-1.64)
ER status				
Positive	6353 / 515	REF (1.00)	REF (1.00)	REF (1.00)
Negative	1376 / 146	1.45 (1.20-1.74)	1.23 (0.97-1.56)	1.36 (0.97-1.89)
PR status				
Positive	5176 / 422	REF (1.00)	REF (1.00)	REF (1.00)
Negative	2419 / 229	1.28 (1.09-1.50)	1.06 (0.86-1.30)	1.07 (0.87-1.31)
No. positive lymph nodes [c]				
0	5033 / 345	REF (1.00)	REF (1.00)	REF (1.00)
1-4	2241 / 233	1.64 (1.38-1.93)	1.52 (1.28-1.80)	1.18 (0.96-1.46)
≥ 5	714 / 100	2.58 (2.07-3.23)	2.20 (1.72-2.75)	1.50 (1.10-2.05)
Treatment characteristics				
Endocrine therapy				
No	1472 / 139	REF (1.00)	REF (1.00)	REF (1.00)
Yes	6701 / 554	0.79 (0.66-0.95)	0.98 (0.81-1.19)	1.28 (0.92-1.49)
Chemotherapy [c]				
No	5113 / 363	REF (1.00)	REF (1.00)	REF (1.00)
Yes	3060 / 330	1.87 (1.60-2.19)	1.54 (1.29-1.84)	1.34 (1.10-1.65)
Radiotherapy				
No	1882 / 176	REF (1.00)	REF (1.00)	REF (1.00)
Yes, local	3960 / 259	0.72 (0.59-0.87)	0.80 (0.60-1.05)	0.78 (0.59-1.03)
Yes, (loco) regional	1423 / 175	1.56 (1.26-1.93)	1.28 (1.03-1.60)	1.08 (0.84-1.39)
Yes, site not specified	935 / 90	0.92 (0.71-1.20)	0.90 (0.66-1.22)	0.87 (0.64-1.19)
Surgery				
Partial mastectomy	5014 / 377	REF (1.00)	REF (1.00)	REF (1.00)
Total mastectomy	3205 / 325	1.44 (1.24-1.67)	0.98 (0.78-1.23)	0.90 (0.71-1.13)
No. of dissected lymph nodes [b, c]				
< 5	2741 / 154	REF (1.00)	REF (1.00)	REF (1.00)
5-10	2662 / 244	1.61 (1.30-1.98)	1.25 (0.99-1.56)	1.18 (0.93-1.49)
>10	3584 / 281	2.02 (1.65-2.47)	1.46 (1.17-1.82)	1.32 (1.04-1.69)

Abbreviations: HR = hazard ratio; CI = confidence interval. [a] Hazard ratios as estimated from flexible parametric survival models with time since diagnosis as underlying time scale. Model 1: adjusted for age and calendar year of diagnosis; Model 2: grouped models including respectively all patient, tumor and treatment characteristics with additional adjustment for age and calendar year of diagnosis; Model 3: multivariable adjusted including all variables listed in the table and calendar year of diagnosis. Missingness on individual variables < 5%, except for histological grade (39.3%, N = 3279), which was included in the Stockholm-Gotland Breast Cancer Register from 2004 onwards and ER status (7.3%, N = 609) and PR status (8.9%, N = 743). [b] No. of dissected lymph nodes refers to the total number of lymph nodes dissected at sentinel node procedure and axillary surgery. [c] The proportional hazards assumption was not met for age at diagnosis, tumor size, histological grade, no. of positive lymph nodes, chemotherapy and no. of dissected lymph nodes.

Table 3. Chemotherapy and risk of infection-related hospitalizations in breast cancer patients, analysis by chemotherapy agent.

	N total/cases	HR (95% CI) [a] Model 1	Model 2	Model 3
Chemotherapy				
No	5113/363	REF (1.00)	REF (1.00)	REF (1.00)
Yes, anthracyclines	1543/170	1.94 (1.60-2.34)	1.59 (1.29-1.95)	1.39 (1.11-1.74)
Yes, taxanes	215/30	3.26 (2.22-4.79)	2.32 (1.55-3.47)	1.96 (1.29-2.98)
Yes, CMF	103/14	1.98 (1.15-3.39)	1.74 (1.01-3.00)	1.34 (0.77-2.34)
Yes, type unknown	1199/116	1.61 (1.30-2.00)	1.37 (1.09-1.74)	1.22 (0.95-1.58)

Abbreviations: HR = hazard ratio; CI = confidence interval; CMF = cyclophosphamide, methotrexate and fluorouracil based chemotherapy.
[a] Hazard ratios as estimated from flexible parametric survival models with time since diagnosis as underlying time scale. Model 1: adjusted for age and calendar year of diagnosis; Model 2: grouped models including respectively all patient, tumor and treatment characteristics with additional adjustment for age and calendar year of diagnosis; Model 3: multivariable adjusted including all variables listed in the table and calendar year of diagnosis.

Table 4. Infection-related hospitalizations and future risk of breast cancer death, distant metastasis and locoregional recurrence, overall and by infection site.

	HR (95% CI) [a]		
	Overall death (N = 926)	**Breast cancer death (N = 589)**	**Other causes of death (N = 337)**
Infection-related hospitalization			
Any infection	1,83 (1,51-2,22)	1,37 (1,05-1,79)	2,85 (2,13-3,80)
Respiratory infections	2.58 (1.96-3.40)	1.92 (1.26-2.91)	3.61 (2.49-5.24)
Sepsis	1.99 (1.45-2.73)	1.28 (0.82-2.00)	4.51 (2.87-7.09)
Skin infections	1.66 (0.91-3.03)	1.30 (0.58-2.93)	2.58 (1.05-6.35)
Gastrointestinal infections	1.29 (0.73-2.29)	1.00 (0.45-2.26)	1.51 (0.66-3.45)
Urinary tract infections	1.19 (0.69-2.06)	0.88 (0.33-2.39)	1.36 (0.68-2.73)
Other infection	1.88 (1.26-2.81)	1.46 (0.84-2.54)	2.77 (1.53-4.99)

Abbreviations: HR = hazard ratio; CI = confidence interval. [a] Hazard ratios are derived from flexible parametric survival models with infection-related hospitalization as time-varying exposure and time since diagnosis as underlying time scale. All hazard ratios are adjusted for patient (age at diagnosis, CCI, infectious disease history), tumor (size, grade, ER status, PR status, no. of positive lymph nodes) and treatment-related factors (endocrine therapy, chemotherapy, radiotherapy, surgery and no. of dissected lymph nodes) and calendar year of diagnosis.

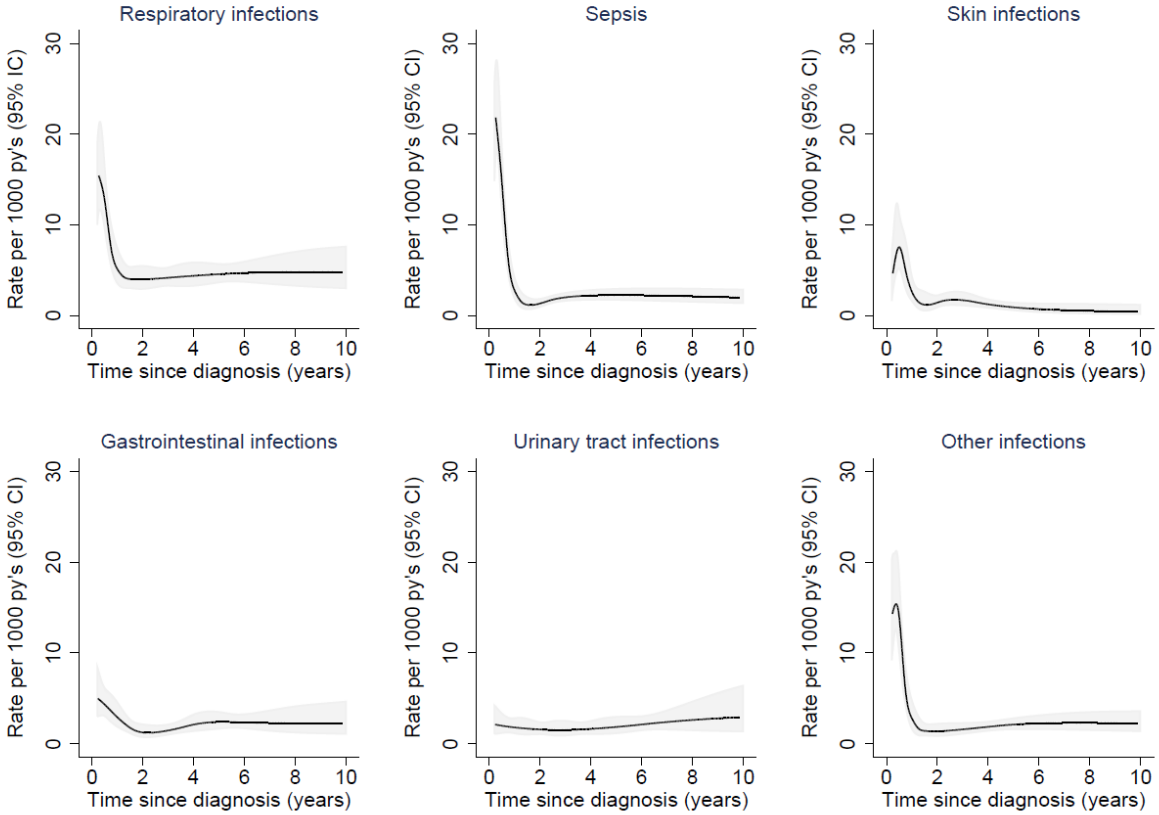
Respiratory infections
Sepsis
Skin infections
Gastrointestinal infections
Urinary tract infections
Other infections
Rate per 1000 py's (95% IC)
Rate per 1000 py's (95% CI)
0
10
20
30
0
2
4
6
8
10
Time since diagnosis (years)

Figure 1.