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Risk of infections and mortality in Danish patients with cancer diagnosed with bone metastases: a population-based cohort study

Thomas Johannesson Hjelholt ,[1,2] Thomas Bøjer Rasmussen,[1] Anouchka Seesaghur ,[3] Rohini K Hernandez,[4] Andrea Marongiu,[3] Niels Obel,[5] Henrik Toft Sørensen,[1,2] A B Pedersen[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Thomas Johannesson Hjelholt; tjh@clin.au.dk

ABSTRACT

Objectives Risk of infections in patients with solid cancers and bone metastases (BM) and the subsequent impact on prognosis is unclear. We examined the risk of infections among patients with cancer diagnosed with BM and the subsequent impact of infections on mortality.

Design Population-based cohort study.

Setting Danish medical databases holding information on all hospital contacts in Denmark.

Participants Adult patients with solid cancers and BM between 1 January 1994 and 30 November 2013.

Outcome measures In the risk analyses, the outcome was time to hospitalisation for common severe infections, pneumonia, sepsis and urinary tract infections. In the mortality analysis, we used Cox regression to compute HRs of death, modelling infection as time-varying exposure, stratifying for primary cancer type and adjusting for age, sex and comorbidities.

Results Among 23 336 patients with cancer and BM, cumulative incidences of common severe infections were 4.6%, 14.0% and 20.0% during 1 month, 1 year and 10 years follow-up. The highest incidence was observed for pneumonia, followed by urinary tract infections and sepsis. Infection was a strong predictor of 1 month mortality (adjusted HR: 2.1 (95% CI 1.8 to 2.3)) and HRs increased after 1 and 10 years: 2.4 (95% CI 2.3 to 2.6) and 2.4 (95% CI 2.4 to 2.6). Sepsis and pneumonia were the strongest predictors of death. Results were consistent across cancer types.

Conclusion Patients with cancer and BM were at high risk of infections, which was associated with a more than twofold increased risk of death for up to 10 years of follow-up. The findings underscore the importance of preventing infections in patients with cancer and BM.

Strengths and limitations of this study

- This study provides fundamental insight into the risk of infection and subsequent mortality of patients with solid tumour bone metastases.
- This is a prospective population-based cohort study with complete follow up based on Danish nationwide health registries and free access to hospital services regardless of socioeconomic status and geographical location.
- The validity of infection diagnoses is high and although the completeness of bone metastases diagnosis is low, the positive predictive value of registered bone metastases is good.
- We lacked information on cancer-specific treatment.
- Despite adjustment for patient comorbidity, residual confounding might be introduced because the Charlson Comorbidity Index does not contain information on disease severity.

INTRODUCTION

Patients with cancer are at increased risk of severe infections,[1–3] which contribute to increased morbidity (ie, pain, general health deterioration, increased need for hospitalisation and reduced quality of life) and mortality.[2 3] The increased risk of infection stems from general immune suppression from disease processes, reduced innate immunity, obstruction of normal anatomical channels and the disruption of anatomic barriers.[1] Moreover, infection risk is affected by iatrogenic factors, such as surgery, venous access, nosocomial infections and antineoplastic treatments, including chemotherapy and radiation.[1 4]

The risk of infections among patients with cancer varies greatly, due to heterogeneity in disease severity, complications and treatment side effects. While the risk of infection among patients with haematologic malignancies has been well described,[5] the risk of infection in patients with solid organ malignancies has been studied less frequently.[3 6 7] It remains poorly understood whether the risk of mortality in patients with cancer following an infection might be aggravated by bone involvement; that is, bone metastasis (BM). BM is reported to be one of the most

debilitating and costly complications among patients with cancer[8–12] and is associated with poor prognosis and impaired quality of life.[13–15]

We constructed a nationwide population-based cohort of patients with cancer and BM to examine the risk of infections requiring hospitalisation and the subsequent impact of infection on mortality.

MATERIALS AND METHODS

Study design and setting

We conducted this nationwide population-based cohort study based on data from Danish medical databases, which encompass the entire Danish population (5 602 628 inhabitants on 1 January 2013). The Danish National Health Service provides tax-supported healthcare for the entire population, guaranteeing universal access to all hospitals and primary medical care.[16]

Patient and public involvement

Patients and public were not involved in the development or the design of this study.

Data sources

We retrieved data from four sources:

1. The Civil Registration System (CRS): a unique civil registration (CPR) number, recorded in the CRS, has been assigned to every Danish citizen and resident since 1968. This identifier allows linkage among multiple databases[17] and provides information on vital status and migration, ensuring complete follow-up.
2. The Danish National Registry of Patients (DNRP): the DNRP contains records of all inpatient admissions to Danish hospitals since 1977 and all outpatient clinic discharges and emergency room visits since 1995.[18] Patient visits to general practitioners are not registered in the DNRP. Each DNRP record is linked to the patient's CPR number and includes information on treatments and surgical procedures performed, as well as one primary and up to nineteen secondary discharge diagnoses. The discharge diagnoses are coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8; from 1977 to 1993) and *Tenth Revision* (ICD-10; starting in 1993).
3. The Danish Cancer Registry (DCR): the DCR has collected information on all incident diagnoses of cancer in Denmark since 1943. Diagnoses in the DCR were coded according to a Danish version of the *International Classification of Diseases, Seventh Revision* (ICD-7) from 1943 to 1977. Subsequently, cancers have been recoded or coded according to ICD-10.[19] The DCR's completeness and validity are estimated to be 95%–98%.[20 21]

Study cohort

See figure 1 for a study population flow chart including the inclusion criteria. The study included all individuals aged 18 and older who (1) were registered in the DCR with one or more cancer diagnoses (excluding basal cell carcinoma and haematological malignancies) between 1 January 1978 and 30 November 2013, (2) were registered in the CRS with a CPR number and (3) were living in Denmark and registered in the DNRP with a BM diagnosis during 1 January 1994 to 30 November 2013 and with a cancer diagnosis prior to or within 6 months after the BM diagnosis. This allowed inclusion of patients presenting with BM prior to a cancer diagnosis. The study population excluded patients with a BM diagnosis but no recorded cancer diagnosis (n<90 during the period 1978–2013). The study inclusion date was the BM diagnosis date.

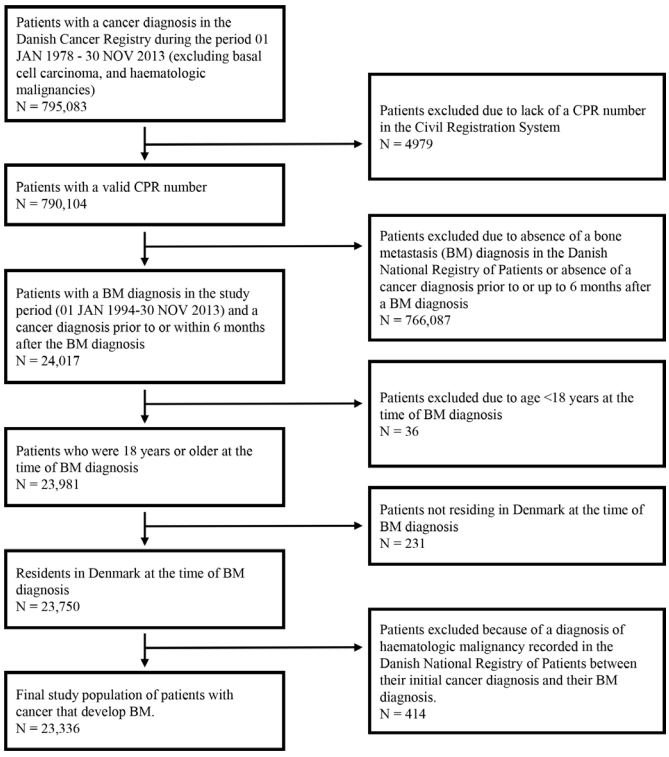

Figure 1 Flow chart showing the selection of the study population. N is the number of patients. CPR number, civil registration number.

Infections

Infections were identified by means of ICD-10 codes in the DNRP for primary and secondary discharge diagnoses among hospitalised patients. We identified the first date after study inclusion on which a patient was hospitalised with (1) any common severe infections, (2) pneumonia, (3) sepsis and (4) urinary tract infections. The common severe infections group included the three other groups and furthermore infections in the skin and connective tissue, circulatory system, central nervous system, bone and joints, and also infections with mycobacteria and mycoses. See online supplemental table 1 for an extensive list of ICD-10 codes.

Mortality

Date of death due to any cause was obtained from the CRS.

Variables

We collected information on the following variables recorded at the time of study inclusion:

1. Patient age and gender (collected from the CRS).
2. Cancer diagnosis and location (obtained from the DCR): patients with several cancers registered between 1 January 1978 and the BM diagnosis date were allocated to the 'multiple cancers' group. Information on cancer-specific treatments and cancer histology was unavailable.
3. Comorbidities (obtained from the DNRP): based on ICD-8 and ICD-10 codes, we calculated a Charlson Comorbidity Index (CCI) score[22] adapted for administrative data[23 24] for every patient at the time of BM diagnosis. Cancer diagnoses included in the CCI's 19 disease categories were excluded from the calculation of CCI scores. Three levels of comorbidity were defined: a CCI score of 0 (low), for patients with no previous record of the diseases included in the Index; a CCI score of 1–2 (medium); and a CCI score of 3 or more (high).[23] Additional information on osteoporosis and other metastases was obtained from the DNRP.

All codes used in this study are listed in online supplemental table 1.

Statistical analyses

Patient characteristics were described at the time of study inclusion (date of BM).

Risk of infection analysis

In the risk analyses, follow-up time was calculated from study inclusion until first diagnosis date of the infections under consideration, the end of the study period (30 November 2013), the date of emigration, or the date of death, whichever occurred first. We computed the cumulative incidences of infections, starting follow-up at study inclusion and treating death as a competing risk.[25] Cumulative incidences were calculated for the time periods 0–1 month, 0–1 year and 0–10 years after study inclusion, overall and by the three most common primary cancer types (breast, lung and prostate cancer). We estimated 95% CIs using a log normal-approximation (27).

Mortality analyses

In the mortality analyses, the main exposure was infection and the outcome was time to death. Mortality was estimated in two dynamic risk periods: the risk period until potential development of infection (if it occurred) and the risk period after infection. The date of diagnosis of an infection was treated as a time-varying exposure. Follow-up started on the study inclusion date, when a patient started contributing time-at-risk to the 'risk period until development of infection'. If an infection occurred, the patient would start contributing time-at-risk to the 'risk period after development of infection'. If an infection did not occur, the patient would only contribute time-at-risk to the first risk period. Patients were followed until the end of the study period (30 November 2013), the date of emigration or the date of death, whichever occurred first.

We used Cox regression analyses to compute HRs for death with 95% CIs. We computed HRs for death comparing the risk period until development of infection to the risk period after infection, overall and by the three most common primary cancer types (breast, lung and prostate cancer). The analysis was adjusted for age, gender and CCI score. Cancer stage and chemotherapy treatment was not adjusted for. The HRs generated from mortality analyses were interpreted as the overall impact of specific infections on all-cause mortality. The content of this paper follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[26] and the REporting of studies Conducted using Observational Routinely-collected Data guidelines.[27] Analyses were performed using SAS V.9.4 (SAS Institute) and R V.3.6.1 (R Foundation for Statistical Computing).

RESULTS

Study cohort

The study cohort included 23 336 patients. The three most common primary cancers were prostate cancer (30.5%), breast cancer (22.8%) and lung cancer (17.3%). Overall, 57.3% of patients were men and 67.9% were aged ≥60 years at the time of BM diagnosis (table 1). The median time (IQR) from the primary cancer diagnosis to the BM diagnosis was 1.5 years (IQR 0.2–4.7 years). At the time of the BM diagnosis, 36.1% of patients presented with comorbidity (CCI score ≥1) and 41% (n=9633) of the overall population had metastases other than BM. To further describe the study population, details on types of comorbidities are provided in online supplemental table 2.

Common severe infections

The cumulative incidences of common severe infections were 4.6% within 30 days after BM, 14.0% within 1 year and 20.0% within 10 years (figure 2). Within 30 days of study inclusion, the cumulative incidence was highest among patients with primary lung cancer. Within 1 and 10 years of study inclusion, the highest cumulative incidence of common severe infections was observed in patients with primary prostate cancer (table 2).

Infection was a predictor of death, with an adjusted HR for death of 2.1 (95% CI 1.8 to 2.3) during the first month of follow-up. Adjusted HRs for death increased slightly during longer follow-up periods (table 3). Infection was a stronger predictor for death in patients with BM and primary prostate cancer than in patients with primary breast or lung cancer (table 3).

Pneumonia

The cumulative incidences of pneumonia were 2.2% within 30 days, 6.9% within 1 year and 10.5% within 10 years of study inclusion (figure 2). Cumulative incidences

Table 1 Characteristics of patients with bone metastasis (BM)

Characteristic	All patients N (%)
Number of patients	23336
Age at BM diagnosis	
<60 years	5361 (23.0)
60–69 years	6980 (29.9)
+70 years	10995 (47.1)
Age at primary cancer diagnosis	
<60 years	7483 (32.1)
60–69 years	7362 (31.5)
+70 years	8491 (36.4)
Gender	
Male	13378 (57.3)
Female	9958 (42.7)
Year of BM diagnosis	
1994–2000	4942 (21.2)
2001–2005	6984 (29.9)
2006–2010	6685 (28.6)
2011–2013	4725 (20.2)
Year of primary cancer diagnosis	
1978–2000	9395 (40.3)
2001–2005	6545 (28.0)
2006–2010	5308 (22.7)
2011–2013	2088 (8.9)
Primary cancer site	
Prostate	7113 (30.5)
Breast	5328 (22.8)
Lung	4044 (17.3)
Intestine, including the colon, rectosigmoid, and rectum	963 (4.1)
Urinary tract cancers including the kidneys	1493 (6.4)
Metastases and non-specified cancer in lymph nodes	328 (1.4)
Other	2233 (9.6)
Multiple cancers	1834 (7.9)
Charlson Comorbidity Index score (excluding cancer)	
0	14911 (63.9)
1–2	7010 (30.0)
+3	1415 (6.1)

of pneumonia by primary cancer type are presented in table 2.

Pneumonia also predicted death with an adjusted HR during the first month of follow-up of 2.8 (95% CI 2.4 to 3.2), and the HR remained at a similarly high level for up to 10 years of follow-up (table 3). The HRs for death were slightly higher in patients with BM and primary prostate cancer than in patients with primary breast or lung cancer (table 3).

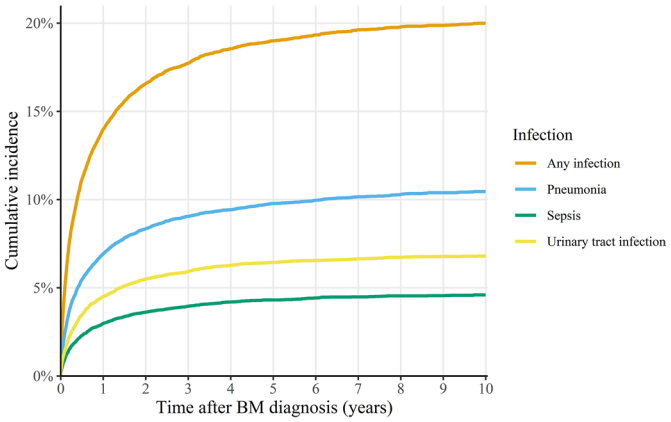

Figure 2 Cumulative incidences of common severe infections ten years after a bone metastasis diagnosis, with death as competing risk. BM, bone metastasis.

Sepsis

The cumulative incidences of sepsis were 0.9% within 30 days, 3.0% within 1 year and 4.6% within 10 years of study inclusion (figure 2). Within the first 30 days following study inclusion, the cumulative incidence of sepsis did not differ substantially between cancer types, but was slightly higher during 1 and 10 years of follow-up for patients with primary prostate cancer than for patients with primary breast or lung cancer (table 2).

Sepsis was likewise an even stronger predictor of death, with an adjusted HR of 3.5 (95% CI 2.8 to 4.3) during the first month of follow-up. The adjusted HR of death declined to 2.6 within 1 year of follow-up and stayed at this level during 10 years of follow-up (table 3). Sepsis was a slightly stronger predictor for death in patients with primary breast cancer within the first 30 days of follow-up. In contrast, patients with primary prostate cancer had higher HRs during 1 and 10 years of follow-up (table 3).

Urinary tract infection

Within the first 30 days of study inclusion, the cumulative incidence of urinary tract infections was 1.3%. This increased to 4.5% within 1 year (figure 2) and to 6.8% within 10 years.

Urinary tract infection was associated with an adjusted HR of death of 0.6 (95% CI 0.4 to 0.9) within the first month of follow-up. However, the adjusted HR of death rose to 1.6 (95% CI 1.5 to 1.7) within 1 year and to 1.7 (95% CI 1.6 to 1.8) within 10 years of follow-up (table 3). Stratified by cancer type, an association between urinary tract infection and mortality was not observed within the first 30 days of follow-up. However, during 1 year and 10 years of follow-up, urinary tract infection was associated with increased mortality among patients with all three primary cancer types (table 3).

DISCUSSION

This large cohort study examined the risk of common severe infections and associated mortality in patients diagnosed with cancer and BM. We found that the risk of

Table 2 Cumulative incidences with 95% CIs of common severe infections after a bone metastasis diagnosis, with death as a competing risk.

Population	Follow-up	Outcome	Cumulative incidence with 95% CI (%)
All patients	1 month	Any infection	4.59 (4.32 to 4.86)
		Pneumonia	2.23 (2.04 to 2.42)
		Sepsis	0.88 (0.77 to 1.01)
		Urinary tract infection	1.31 (1.17 to 1.47)
	1 year	Any infection	13.98 (13.54 to 14.44)
		Pneumonia	6.93 (6.61 to 7.27)
		Sepsis	2.99 (2.77 to 3.21)
		Urinary tract infection	4.50 (4.24 to 4.78)
	10 years	Any infection	19.99 (19.46 to 20.53)
		Pneumonia	10.45 (10.04 to 10.87)
		Sepsis	4.60 (4.32 to 4.89)
		Urinary tract infection	6.80 (6.46 to 7.15)
Breast cancer	1 month	Any infection	3.65 (3.17 to 4.17)
		Pneumonia	1.41 (1.12 to 1.75)
		Sepsis	0.88 (0.66 to 1.16)
		Urinary tract infection	1.05 (0.80 to 1.36)
	1 year	Any infection	12.05 (11.18 to 12.94)
		Pneumonia	5.22 (4.64 to 5.84)
		Sepsis	2.75 (2.33 to 3.22)
		Urinary tract infection	3.50 (3.03 to 4.02)
	10 years	Any infection	20.75 (19.61 to 21.92)
		Pneumonia	9.68 (8.85 to 10.55)
		Sepsis	4.61 (4.04 to 5.23)
		Urinary tract infection	6.88 (6.18 to 7.63)
Lung cancer	1 month	Any infection	5.90 (5.20 to 6.65)
		Pneumonia	3.72 (3.16 to 4.33)
		Sepsis	0.99 (0.72 to 1.33)
		Urinary tract infection	0.87 (0.62 to 1.19)
	1 year	Any infection	14.98 (13.89 to 16.10)
		Pneumonia	9.75 (8.86 to 10.70)
		Sepsis	2.69 (2.22 to 3.23)
		Urinary tract infection	2.39 (1.95 to 2.90)
	10 years	Any infection	16.96 (15.80 to 18.16)
		Pneumonia	11.34 (10.36 to 12.38)
		Sepsis	2.92 (2.42 to 3.48)
		Urinary tract infection	2.75 (2.27 to 3.30)
Prostate cancer	1 month	Any infection	4.57 (4.10 to 5.07)
		Pneumonia	2.07 (1.76 to 2.42)
		Sepsis	0.82 (0.63 to 1.05)
		Urinary tract infection	1.69 (1.41 to 2.01)
	1 year	Any infection	15.97 (15.12 to 16.84)
		Pneumonia	7.22 (6.63 to 7.85)
		Sepsis	3.52 (3.11 to 3.97)
		Urinary tract infection	6.72 (6.15 to 7.32)
	10 years	Any infection	24.20 (23.17 to 25.25)
		Pneumonia	12.19 (11.41 to 13.01)
		Sepsis	6.04 (5.48 to 6.65)
		Urinary tract infection	10.08 (9.36 to 10.82)

infections was higher in the first month following the BM diagnosis than later during follow-up. The hospitalisation for infection, particularly sepsis and pneumonia, was associated with a more than twofold increased risk of dying during up to 10 years of follow-up.

Interpretation

Among patients with cancer, those with BM represent one of the most severely ill groups, with a high risk of infection. Williams *et al*[6] reported that the incidence of sepsis was 1.6 per 100 person years (PYs) among 606 176 patients with cancer (any type) in the USA. Similarly, Pelton *et al*[28] reported an incidence rate of pneumonia of 4.96 per 100 PYs among adult German patients over age 60 years with cancer (observed over 379 086 PYs). Although not directly comparable to the incidences in this study, the occurrence of infection was substantially higher among the patients with BM reported here. This discrepancy was most likely due to the advanced cancers experienced by our patients, which increased the likelihood that they harboured known risk factors for infection, such as immobilisation, general deterioration and malnutrition. Patients with cancer and BM may also more likely be exposed to iatrogenic risk factors for infection, such as surgery, venous access, nosocomial infections and chemotherapy.[1 4] Furthermore, because our study patients had disseminated cancer by definition, they might have harboured metastases at other sites, in addition to the BM. Finally, we found that one-third of our patients had a moderate or high level of non-malignant comorbidities, many of which are also known risk factors for infection.

Although preventing infections in patients with advanced cancers is of great importance, it has proven difficult, possibly due to several unmodifiable risk factors.[1] Antibiotic prophylaxis in patients with neutropenia has been shown to decrease infection rates but not mortality.[4] Still, a review indicated that such prophylactic treatment showed promise for improving overall survival.[29] Surprisingly, few patients with cancer have been vaccinated against *Streptococcus pneumoniae*, which is the etiologic agent in 6.5% of all bacteraemia diagnoses in this patient group.[30]

In our study, common severe infections, particularly pneumonia and sepsis, led to a higher rate of death among patients with cancer. This result was expected, due to the general mortality associated with these complications.[2] Additionally, infection is likely a marker for heightened immune dysfunction and disruption of anatomic barriers. Furthermore, infections can cause clinical challenges, such as the need to postpone chemotherapy and other treatments. In addition, it can be difficult to clear the infection or even recognise its presence in the midst of coping with cancer. Finally, patients with cancer might develop opportunistic infections with otherwise non-pathogenic bacteria or viruses, and they are at increased risk of multidrug-resistant bacterial infections.[1]

We found, unexpectedly, that urinary tract infections were associated with a reduced rate of death during

Table 3 Adjusted HRs with 95% CIs for death, comparing mortality in the risk period until development of infection versus the risk period after infection within 1 month, 1 year and 10 years after diagnosis of bone metastasis

Population	Follow-up period	Infection type	Risk period until development of infection	Risk period after infection	Adjusted HR
			Deaths (N)	Deaths (N)	95% CI
All patients	1 month	Any infection	5926	276	2.05 (1.82 to 2.30)
		Pneumonia	6029	173	2.76 (2.38 to 3.19)
		Sepsis	6128	74	3.45 (2.78 to 4.30)
		Urinary tract infection	6172	30	0.62 (0.43 to 0.89)
	1 year	Any infection	14371	2321	2.40 (2.29 to 2.51)
		Pneumonia	15460	1232	3.01 (2.84 to 3.19)
		Sepsis	16205	487	2.63 (2.40 to 2.87)
		Urinary tract infection	16001	691	1.60 (1.48 to 1.73)
	10 years	Any infection	17571	3925	2.43 (2.35 to 2.52)
		Pneumonia	19460	2036	2.85 (2.72 to 2.99)
		Sepsis	20631	865	2.55 (2.38 to 2.73)
		Urinary tract infection	20182	1314	1.73 (1.63 to 1.83)
Breast cancer	1 month	Any infection	998	32	2.07 (1.48 to 2.89)
		Pneumonia	1016	14	2.38 (1.45 to 3.91)
		Sepsis	1018	12	4.08 (2.44 to 6.81)
		Urinary tract infection	1027	NA	0.49 (0.16 to 1.53)
	1 year	Any infection	2586	332	2.20 (1.96 to 2.47)
		Pneumonia	2764	154	2.49 (2.12 to 2.93)
		Sepsis	2842	76	2.64 (2.11 to 3.31)
		Urinary tract infection	2833	85	1.43 (1.15 to 1.78)
	10 years	Any infection	3825	879	2.17 (2.01 to 2.34)
		Pneumonia	4299	405	2.20 (1.98 to 2.44)
		Sepsis	4511	193	2.36 (2.04 to 2.72)
		Urinary tract infection	4420	284	1.63 (1.44 to 1.84)
Lung cancer	1 month	Any infection	1513	98	2.08 (1.70 to 2.55)
		Pneumonia	1543	68	2.45 (1.93 to 3.11)
		Sepsis	1587	24	3.04 (2.05 to 4.51)
		Urinary tract infection	1603	8	1.00 (0.50 to 2.01)
	1 year	Any infection	3119	520	2.22 (2.02 to 2.44)
		Pneumonia	3298	341	2.45 (2.18 to 2.74)
		Sepsis	3547	92	2.42 (1.97 to 2.97)
		Urinary tract infection	3559	80	1.44 (1.15 to 1.80)
	10 years	Any infection	3289	612	2.28 (2.09 to 2.49)
		Pneumonia	3495	406	2.48 (2.24 to 2.76)
		Sepsis	3798	103	2.42 (1.99 to 2.94)
		Urinary tract infection	3802	99	1.44 (1.17 to 1.76)
Prostate cancer	1 month	Any infection	1326	67	2.31 (1.82 to 2.93)
		Pneumonia	1347	46	3.81 (2.88 to 5.04)
		Sepsis	1379	14	3.47 (2.12 to 5.69)
		Urinary tract infection	1384	9	0.66 (0.34 to 1.27)

Continued

Table 3 Continued

Population	Follow-up period	Infection type	Risk period until development of infection	Risk period after infection	Adjusted HR
			Deaths (N)	Deaths (N)	95% CI
	1 year	Any infection	3888	800	2.80 (2.59 to 3.03)
		Pneumonia	4300	388	3.54 (3.19 to 3.93)
		Sepsis	4511	177	3.24 (2.79 to 3.77)
		Urinary tract infection	4369	319	1.94 (1.73 to 2.18)
	10 years	Any infection	5108	1479	2.78 (2.62 to 2.95)
		Pneumonia	5854	733	3.30 (3.05 to 3.57)
		Sepsis	6234	353	3.01 (2.70 to 3.35)
		Urinary tract infection	5969	618	1.92 (1.77 to 2.10)

Infections were included in the model as a time-dependent exposure. HRs adjusted for age, gender and Charlson Comorbidity Index score.

the first 30 days after a diagnosis of BM. We believe this was due to under-registration of urinary tract infections during hospital contacts in the most diseased patients. Patients who die from cancer within 1 month of a BM diagnosis often suffer from several concurrent diseases and complications, among which a urinary tract infection is considered a minor problem that may not be reported to the national hospital databases. Hospitals also are not reimbursed for registering urinary tract infections, even when treatment is provided. In addition, cancer in many patients, particularly patients with prostate cancer, is detected initially due to urinary tract infections. Associated use of urinary catheters reduces the incentive to register this type of infection.

Strengths and limitations

This study was based on routinely collected healthcare data for patients who received care in a system that provides equal access to hospital services, regardless of socioeconomic status or geographical location.[16] Nearly all patients with cancer in Denmark are cared for in government-funded hospitals, because no private hospitals offer inpatient cancer care.

A previous validation study of the DNRP found that only 32%–44% of patients with BM were registered in the DNRP, but the 86%–100% of registered patients had 'true' BM diagnosis.[31] The study found that under-registration was related to a high comorbidity burden. Consequently, patients who were severely ill with many comorbid conditions were less likely to be included in our study population, leading to a potential underestimation of our absolute risk estimates. In contrast, the diagnoses used to define infections in patients with cancer showed high validity. A validation study of those data in the DNRP reported a positive predictive value of 98% for infections overall, 93% for pneumonia and 84% for sepsis.[32] However, the incidence of infections in patients who did not receive hospital treatment remains unknown.

The validity of DNRP data on recorded comorbidities among hospitalised patients is generally good.[33] However, the paucity of data on the severity of some diseases included in the CCI and the lack of data from general practitioners and psychiatric departments introduced the risk of residual and unmeasured confounding in the adjusted HRs. Furthermore, CCI scores are not as comprehensive as clinical data for measuring the degree of comorbidity[34] and also, the adjustment for CCI was based on the baseline score only. This could potentially increase residual confounding slightly. Another study limitation was lack of cancer-specific treatment information. Certain types of cancer therapies are more likely than other types to increase the risk of infections. Anticancer therapy has also changed over the study period; however, calendar year of diagnosis is not accounted for in the analyses. Also, cancer stage was not adjusted for in the analyses, but considering the study population only included patients with bone metastases, all had advanced cancers. Finally, when a patient was diagnosed with several different types of cancer, we were unable to link a given BM diagnosis to any specific primary cancer.[13 14]

CONCLUSION

In this national cohort study of 23 336 patients with BM arising from a solid cancer, we found a high risk of common severe infections requiring hospital admission. Infection is associated with a high mortality rate. Taking steps to minimise or prevent infection in patients with cancer has always been a part of standard oncological treatment. However, prevention of infection, which is crucial to reducing cancer mortality, is not always successful in high-risk patients, such as those with cancer and BM.

Author affiliations
[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Clinical Medicine, Aarhus University, Aarhus, Midtjylland, Denmark

[3]Centre for Observational Research, Amgen Ltd, Uxbridge, UK
[4]Center for Observational Research, Amgen, Inc, Thousand Oaks, California, USA
[5]Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

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Twitter Thomas Johannesson Hjelholt @ThomasJHjelholt

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ORCID iDs
Thomas Johannesson Hjelholt http://orcid.org/0000-0003-0112-5801
Anouchka Seesaghur http://orcid.org/0000-0003-2997-5867

REFERENCES

1 Rolston KVI. Infections in cancer patients with solid tumors: a review. *Infect Dis Ther* 2017;6:69–83.
2 Bos MMEM, Smeets LS, Dumay I, *et al*. Bloodstream infections in patients with or without cancer in a large community hospital. *Infection* 2013;41:949–58.
3 Brand JS, Colzani E, Johansson ALV, *et al*. Infection-Related hospitalizations in breast cancer patients: risk and impact on prognosis. *J Infect* 2016;72:650–8.
4 Gudiol C, Aguado JM, Carratalà J. Bloodstream infections in patients with solid tumors. *Virulence* 2016;7:298–308.
5 Tumbarello M, Spanu T, Caira M, *et al*. Factors associated with mortality in bacteremic patients with hematologic malignancies. *Diagn Microbiol Infect Dis* 2009;64:320–6.
6 Williams MD, Braun LA, Cooper LM, *et al*. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care* 2004;8:R291.
7 Schelenz S, Nwaka D, Hunter PR. Longitudinal surveillance of bacteraemia in haematology and oncology patients at a UK cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. *J Antimicrob Chemother* 2013;68:1431–8.
8 Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer* 2000;88:2989–94.
9 Coleman RE. Skeletal complications of malignancy. *Cancer* 1997;80:1588–94.
10 Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006;12:6243s–9.
11 Viadana E, Bross ID, Pickren JW. An autopsy study of some routes of dissemination of cancer of the breast. *Br J Cancer* 1973;27:336–40.
12 Viadana E, Cotter R, Pickren JW, *et al*. An autopsy study of metastatic sites of breast cancer. *Cancer Res* 1973;33:179–81.
13 Cetin K, Christiansen CF, Jacobsen JB, *et al*. Bone metastasis, skeletal-related events, and mortality in lung cancer patients: a Danish population-based cohort study. *Lung Cancer* 2014;86:247–54.
14 Nørgaard M, Jensen Annette Østergaard, Jacobsen JB, *et al*. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). *J Urol* 2010;184:162–7.
15 Yong M, Jensen Annette Östergaard, Jacobsen JB, *et al*. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999-2007). *Breast Cancer Res Treat* 2011;129:495–503.
16 Schmidt M, Schmidt SAJ, Adelborg K, *et al*. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;11:563–91.
17 Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
18 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al*. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
19 The Danish cancer registry documentation, 2018. Available: https://www.esundhed.dk/Dokumentation/DocumentationExtended?id=23
20 Storm HH. Completeness of cancer registration in Denmark 1943-1966 and efficacy of record linkage procedures. *Int J Epidemiol* 1988;17:44–9.
21 Storm HH, Michelsen EV, Clemmensen IH, *et al*. The Danish Cancer Registry--history, content, quality and use. *Dan Med Bull* 1997;44:535–9.
22 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
23 de Groot V, Beckerman H, Lankhorst GJ, *et al*. How to measure comorbidity. A critical review of available methods. *J Clin Epidemiol* 2003;56:221–9.
24 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–9.
25 Kirkwood BR, Sterne AC. *Essential medical statistics*. 2nd eition, 2003.
26 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007;4:e296.
27 Benchimol EI, Smeeth L, Guttmann A, *et al*. The reporting of studies conducted using observational Routinely-collected health data (record) statement. *PLoS Med* 2015;12:e1001885.
28 Pelton SI, Shea KM, Farkouh RA, *et al*. Rates of pneumonia among children and adults with chronic medical conditions in Germany. *BMC Infect Dis* 2015;15:470.
29 Lyman GH, Yau L, Nakov R, *et al*. Overall survival and risk of second malignancies with cancer chemotherapy and G-CSF support. *Ann Oncol* 2018;29:1903–10.
30 Garcia-Vidal C, Ardanuy C, Gudiol C, *et al*. Clinical and microbiological epidemiology of Streptococcus pneumoniae bacteremia in cancer patients. *J Infect* 2012;65:521–7.
31 Jensen Annette Østergaard, Nørgaard M, Yong M, *et al*. Validity of the recorded International classification of diseases, 10th edition diagnoses codes of bone metastases and skeletal-related events in

breast and prostate cancer patients in the Danish national Registry of patients. *Clin Epidemiol* 2009;1:101–8.
32 Holland-Bill L, Xu H, Sørensen HT, *et al*. Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish national Registry of patients. *Ann Epidemiol* 2014;24:593–7.
33 Thygesen SK, Christiansen CF, Christensen S, *et al*. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish national Registry of patients. *BMC Med Res Methodol* 2011;11:83.
34 Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. *J Clin Epidemiol* 2004;57:131–41.