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Hospitalisation at the end of life among cancer and non-cancer patients: A nationwide study

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Abstract

Objectives: End-of-life hospitalisations may not be associated with improved quality of life. Studies indicate differences in end-of-life care for cancer and non-cancer patients, however, data on hospital utilisation are sparse. This study aimed to compare end-of-life hospitalisation and place of death among patients dying from cancer, heart failure or chronic obstructive pulmonary disease.

Methods: Using nationwide Danish medical registries, we conducted a nationwide follow-up study including all decedents dying from cancer, heart failure or chronic obstructive pulmonary disease in Denmark in 2006-2015. We obtained data on all in-hospital admissions within six months and 30 days before death as well as place of death. Comparisons were made according to cause of death while adjusting for age, gender, comorbidity, partner status and residential region.

Results: Among 197,472 decedents, the median total bed days in hospital within six months before death was 19 days for cancer patients and 13 days for patients with heart failure and chronic obstructive pulmonary disease. Within 30 days before death, this was 9 days for cancer patients and 7 days for patients with heart failure and chronic obstructive pulmonary disease. Compared with cancer patients, the adjusted relative bed day use was 0.70 (95% CI, 0.68; 0.72) for heart failure patients and 0.74 (95% CI, 0.72; 0.75) for patients with chronic obstructive pulmonary disease within both six months and 30 days before death.

Patients had almost the same risk of dying in hospital independently of death cause (48.0%-57.2%).

Conclusions: Patients with cancer, heart failure and chronic obstructive pulmonary disease all spent considerable part of their end of life in hospital. Hospital use was highest among cancer patients, however absolute differences were small.

Key words: Terminal care, Palliative care, Death, Hospital, Chronic disease, Neoplasms
Strengths and limitations of this study

- The main strengths include the nationwide population-based design in the setting of a uniformly organised healthcare system where accurate linkage between national medical registries is possible.

- The study was based on prospectively collected data from registries, which are considered to have a high validity.

- Analyses were based on the underlying cause of death of well-defined chronic diseases in order to avoid introducing misclassification, since it remains difficult to determine and differentiate between underlying and immediate cause of death.

- Register-based data give some limitations to the study as these cannot provide detailed information on patients’ disease status, palliative needs and preferences in order to differentiate whether non-cancer and cancer patients are hospitalised for comparable reasons.
INTRODUCTION

Most patients with chronic diseases prefer to remain home as much as possible towards the end of life, and a high level of hospital care in the last months of life may, therefore, not be associated with improved quality of life. Nevertheless, terminally ill patients may spend considerable time in hospitals and often die there.

Prior research indicate that end-of-life care to patients with non-cancer diagnoses may be sub-optimal compared with that of patients with cancer diagnoses, and that healthcare professionals are often better educated to identify the terminal phase and manage end-of-life care among cancer patients. Difficulties in predicting illness trajectories for non-cancer patients approaching the end of life are likely to explain some of the difference in access to palliative care services between cancer and non-cancer patients. Thus, even though incurably ill non-cancer patients experience similar physical and psychosocial needs as cancer patients, they may receive fewer palliative care services and thereby more often experience hospitalisations in the end of life. Hence, more insight into healthcare utilisation among terminally ill patients is warranted in order to address potential inequalities in care according to different diagnosis.

We therefore compared hospitalisation patterns within the last six months and 30 days before death as well as place of death for all Danes who died of cancer with those who died of heart failure or chronic obstructive pulmonary disease (COPD). We also examined the trends according to calendar years of death in order to identify any temporal changes.

METHODS

Study design and setting

We conducted a nationwide follow-up study among all adult decedents in Denmark who died from cancer, heart failure or COPD from 1 January 2006 to 31 December 2015. The study was based on individual-level linkage of national medical registries using the 10-digit unique personal civil registration number assigned to all Danish residents.
The healthcare system in Denmark is tax-supported and provided to all residents, who thereby have equal access to healthcare, including access to public hospitals, hospices, general practitioners and specialists in palliative care.

**Ethics and patient and public involvement**

In accordance with Danish law, non-interventional studies in Denmark do not require approval from ethics committees. The current study was approved by the Danish Data Protection Agency on 4 July 2014 (Central Denmark Region record number: 1-16-02-407-14).

There was no direct patient or public involvement in the analyses.

**Decedents**

We used the Danish Register of Causes of Death to identify all decedents at the age of 18 years or older, who had been residents in Denmark for at least six months before death and registered with cancer, heart failure or COPD as the underlying cause of death. The Danish Register of Causes of Death is a nationwide registry with data collection since 1970 with a completeness of approximately 97%[^34]. Data are obtained from death certificates filled for every decedent and include civil registration number, date of death, manner of death and cause of death, both immediate and underlying, reported as a chain of one to four conditions that led to death. Causes of death are coded according to the Danish version of International Classification of Diseases[^35].

**Hospital admissions**

We identified all hospital admissions within six months before death on all included patients using the Danish National Patient Registry. The Danish National Patient Registry was established in 1977, and since then it has been mandatory for all Danish hospitals to register information on hospital admissions, including dates of all admissions and discharges, patients’ discharge diagnoses, surgical procedures and patients’ residence[^36].
Using the Danish National Patient Registry, we retrieved the following data on the study population: 1) the total number of bed days, 2) the total number bed days initiated by acute and elective admissions, respectively, 3) the total number of admissions and the corresponding number of days per admission, 4) the number and proportion of patients hospitalised on date of death.

In addition, we retrieved data on age at death, gender, comorbidity (calculated according to Charlson Comorbidity Index, excluding cause of death \cite{37,38}) and residential region using the Danish National Patient Registry, and data regarding partner status using The Danish Civil Registration System for all patients \cite{33}.

**Statistical methods**

Median total bed days within six months and 30 days before death and the corresponding percentages of time spent in hospital were estimated for the three patient populations. In the same way, we estimated the median total bed days within six months and 30 days before death after acute and elective hospital admissions, respectively.

For each patient population, we computed the median number of hospital admissions and median days per hospital admission within six months and 30 days before death. We also computed the proportion of patients dying in hospital.

All analyses were made for the entire study period and stratified by year of death.

In addition, we stratified the analyses according to major cancer types (i.e. lung-, breast-, prostate-, colon-, pancreatic-, haematological cancer and malignant melanoma) \cite{34}.

Finally, we estimated the relative total bed days, relative bed days after acute admission and elective admission, respectively, relative number of hospital admissions, relative length per admission, and the relative risk of dying during hospital admission for patients who died of heart failure or COPD compared with patients who died of cancer. The relative estimates were adjusted for age, gender, comorbidity, partner status and residential region using linear
regression analysis transformed by natural logarithm. Similarly, the adjusted relative risk of
dying during hospital admission were estimated using multivariable binomial regression.
The statistical analyses were performed using STATA 14.2 (StataCorp. 2015. *Stata Statistical
Software: Release 14*. College Station, TX: StataCorp LP) on a secure remote server of
Statistics Denmark.

**RESULTS**

We identified 197,472 patients who died of cancer (n=151,786), heart failure (n=13,913) or
COPD (n=31,773) in 2006-2015. Among these decedents, 91.1% were admitted to hospital at
least once within the last six months of life (513,660 admissions) (Table 1).

**Table 1** Characteristics of patients who died of cancer, heart failure or COPD in Denmark between 2006 and 2015

| Patient characteristics | Died of cancer (n = 151,786) | Died of heart failure (n = 13,913) | Died of COPD (n = 31,773) | Total (n = 197,472) |
|-------------------------|-----------------------------|-----------------------------------|------------------------|---------------------|
| Age, years              |                             |                                   |                        |                     |
| Median (Q1; Q3)         | 73.8 (65.2; 81.8)            | 85.5 (78.0; 91.0)                 | 79.9 (73.0; 85.3)      | 75.8 (66.8; 83.4)   |
| Gender, n (%)           |                             |                                   |                        |                     |
| Female                  | 73,006 (48.1)               | 7,054 (50.7)                     | 17,119 (53.9)          | 97,179 (49.2)       |
| Male                    | 78,780 (51.9)               | 6,859 (49.3)                     | 14,654 (46.1)          | 100,293 (50.8)      |
| Partner status, n (%)   |                             |                                   |                        |                     |
| Living alone            | 72,864 (48.0)               | 9,940 (71.4)                     | 21,246 (66.9)          | 104,050 (52.7)      |
| Living with a partner   | 78,922 (52.0)               | 3,973 (28.6)                     | 10,527 (33.1)          | 93,422 (47.3)       |
### Geographical region of residence, n (%)

| Region                      | North Denmark Region | Central Denmark Region | Region of Southern Denmark | Capital Region | Zealand Region  |
|-----------------------------|----------------------|------------------------|---------------------------|----------------|----------------|
|                             | 16,654 (11.0)        | 32,449 (21.4)          | 33,957 (22.3)             | 43,224 (28.5) | 25,502 (16.8) |
|                             | 1,521 (10.9)         | 2,768 (19.9)           | 3,251 (23.4)              | 4,188 (30.1)  | 2,185 (15.7)  |
|                             | 3,740 (11.8)         | 6,711 (21.1)           | 7,224 (22.7)              | 9,039 (28.5)  | 5,059 (16.0)  |
|                             | 21,915 (11.1)        | 41,928 (21.2)          | 44,432 (22.5)             | 56,451 (28.6) | 32,746 (16.6) |

Admitted to hospital within six months before death, n (%)

| Region                      | 142,077 (93.6) | 10,935 (78.6) | 26,848 (84.5) | 179,860 (91.1) |
|-----------------------------|----------------|---------------|---------------|---------------|
| North Denmark Region        |                |               |               |               |
| Central Denmark Region      |                |               |               |               |
| Region of Southern Denmark  |                |               |               |               |
| Capital Region              |                |               |               |               |
| Zealand Region              |                |               |               |               |

Admitted to hospital within 30 days before death, n (%)

| Region                      | 137,646 (90.7) | 8,146 (58.5) | 21,135 (66.5) | 173,335 (87.8) |
|-----------------------------|----------------|--------------|---------------|---------------|
| North Denmark Region        |                |              |               |               |
| Central Denmark Region      |                |              |               |               |
| Region of Southern Denmark  |                |              |               |               |
| Capital Region              |                |              |               |               |
| Zealand Region              |                |              |               |               |

Comorbidity

| Region | Comorbidity n (%) |
|--------|-------------------|
|        | No                | Yes            |
| North Denmark Region | 47,260 (31.2)   | 104,329 (68.8) |
| Central Denmark Region | 3,902 (28.6)   | 9,747 (71.4)   |
| Region of Southern Denmark | 11,307 (35.9)  | 20,195 (64.1)  |
| Capital Region              | 62,469 (31.8)  | 134,271 (68.3) |

*Calculated according to Charlson Comorbidity Index for patients admitted to hospital within five years before death, excluding underlying cause of death.

### Bed day use

Among patients admitted to hospital within six months before death, the median total bed days in hospital within this period was 19 days for cancer patients, and 13 days for heart failure and COPD patients (Table 2).

The median total bed days among patients who were hospitalised within the last 30 days before death was 9 days for cancer patients and 7 days for heart failure and COPD patients (Table 2).

The median total bed days within six months before death decreased from 2006 to 2015 for cancer and COPD patients, whereas it remained unchanged within 30 days before death for all patient populations (Table 3).
Table 2 Hospitalisation use according to underlying disease: Total bed days in hospital, proportion of bed days, number of hospital admissions, length per admission, and proportion of patients dying in hospital

| Hospital admissions | Died of cancer | Died of heart failure | Died of COPD | Total |
|---------------------|----------------|-----------------------|--------------|-------|
|                     | Q1; Q3         | Q1; Q3                | Q1; Q3       | Q1; Q3|
| Total bed use, days | 19 (9; 34)     | 13 (5; 25)            | 13 (6; 26)   | 18 (8; 32) |
| Six months before   |                |                       |              |       |
| death               |                |                       |              |       |
| 30 days before      | 9 (4; 15)      | 7 (3; 12)             | 7 (3; 12)    | 8 (4; 15) |
| death               |                |                       |              |       |
| Proportion of bed   | 10.4           | 7.1                   | 7.1          | 9.9   |
| days, %             |                |                       |              |       |
| Six months before   |                |                       |              |       |
| death               |                |                       |              |       |
| 30 days before      | 30.0           | 23.3                  | 23.3         | 26.7  |
| death               |                |                       |              |       |
| Number of hospital  |                |                       |              |       |
| admissions, n       | 2 (1; 4)       | 2 (1; 3)              | 2 (1; 3)     | 2 (1; 4) |
| admission, days     |                |                       |              |       |
| admission, days     | 4 (1; 10)      | 6 (2; 11)             | 5 (2; 10)    | 4 (1; 10) |
| Proportion of       | 55.9           | 48.0                  | 57.2         | 55.6  |
| patients dying in   |                |                       |              |       |
| hospital, %         |                |                       |              |       |

\(^a\) For patients admitted to hospital within six months and 30 days before death, respectively

\(^b\) For all patients included in the study
| Hospital admissions | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
|---------------------|------|------|------|------|------|------|------|------|------|------|
| Total bed day use, days<sup>a</sup> |      |      |      |      |      |      |      |      |      |      |
| Died of cancer      |      |      |      |      |      |      |      |      |      |      |
| Six months before death | 21 (10; 36) | 21 (10; 37) | 21 (10; 36) | 19 (9; 34) | 19 (9; 33) | 19 (9; 33) | 18 (9; 32) | 18 (9; 32) | 18 (9; 31) | 17 (8; 31) |
| 30 days before death  | 9 (4; 15) | 9 (4; 15) | 9 (4; 16) | 9 (4; 15) | 9 (4; 15) | 9 (4; 15) | 9 (4; 15) | 9 (4; 15) | 9 (4; 15) | 9 (4; 15) |
| Died of heart failure |      |      |      |      |      |      |      |      |      |      |
| Six months before death | 13 (5; 28) | 12 (4; 25) | 14 (5; 27) | 13 (5; 26) | 12 (5; 24) | 12 (5; 24) | 12 (4; 24) | 13 (5; 26) | 12 (5; 24) | 12 (6; 25) |
| 30 days before death  | 7 (2; 13) | 6 (2; 12) | 6 (2; 13) | 7 (3; 13) | 7 (2; 13) | 7 (3; 12) | 6 (2; 11) | 7 (3; 12) | 7 (3; 12) | 7 (3; 12) |
| Died of COPD         |      |      |      |      |      |      |      |      |      |      |
| Six months before death | 14 (6; 29) | 14 (6; 28) | 14 (5; 27) | 13 (6; 26) | 13 (5; 26) | 13 (6; 25) | 13 (6; 25) | 12 (5; 24) | 12 (5; 24) | 12 (5; 24) |
| 30 days before death  | 7 (3; 12) | 7 (3; 13) | 6 (3; 12) | 7 (3; 13) | 7 (3; 12) | 6 (3; 12) | 7 (3; 13) | 7 (3; 12) | 6 (3; 12) | 7 (3; 12) |
| Proportion of bed days, %<sup>a</sup> |      |      |      |      |      |      |      |      |      |      |
| Died of cancer      |      |      |      |      |      |      |      |      |      |      |
| Six months before death | 11.5 | 11.5 | 11.5 | 10.4 | 10.4 | 10.4 | 9.9  | 9.9  | 9.9  | 9.3  |
| 30 days before death  | 3.0  | 3.0  | 3.0  | 3.0  | 3.0  | 3.0  | 3.0  | 3.0  | 3.0  | 3.0  |
| Died of heart failure |      |      |      |      |      |      |      |      |      |      |
| Six months before death | 7.1  | 6.6  | 7.7  | 7.1  | 6.6  | 6.6  | 6.6  | 7.1  | 6.6  | 6.6  |
| 30 days before death  | 2.3  | 2.0  | 2.0  | 2.3  | 2.3  | 2.3  | 2.0  | 2.3  | 2.3  | 2.3  |
Died of COPD

|                          | 6 months before death | 30 days before death |
|--------------------------|-----------------------|----------------------|
|                          | 7.7                   | 2.3                  |
|                          | 7.7                   | 2.0                  |
|                          | 7.1                   | 2.3                  |
|                          | 7.1                   | 2.0                  |
|                          | 7.1                   | 2.3                  |
|                          | 7.1                   | 2.0                  |
|                          | 6.6                   | 2.3                  |
|                          | 6.6                   | 2.3                  |

Number of hospital admissions, n (Q1; Q3)

Died of cancer

|                          | 6 months before death | 30 days before death |
|--------------------------|-----------------------|----------------------|
|                          | 2 (1; 4)              | 1 (1; 2)             |
|                          | 2 (1; 4)              | 1 (1; 2)             |
|                          | 2 (1; 4)              | 1 (1; 2)             |
|                          | 2 (1; 4)              | 1 (1; 2)             |
|                          | 3 (1; 4)              | 1 (1; 2)             |
|                          | 3 (1; 4)              | 1 (1; 2)             |
|                          | 2 (1; 4)              | 1 (1; 2)             |
|                          | 2 (1; 4)              | 1 (1; 2)             |

Died of heart failure

|                          | 6 months before death | 30 days before death |
|--------------------------|-----------------------|----------------------|
|                          | 1 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 2)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |

Died of COPD

|                          | 6 months before death | 30 days before death |
|--------------------------|-----------------------|----------------------|
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |
|                          | 2 (1; 3)              | 1 (1; 1)             |

Length of stay per hospital admission, days (Q1; Q3)

Died of cancer

|                          | 6 months before death | 30 days before death |
|--------------------------|-----------------------|----------------------|
|                          | 4 (1; 11)             | 5 (2; 12)            |
|                          | 4 (1; 11)             | 5 (2; 12)            |
|                          | 4 (1; 11)             | 5 (2; 12)            |
|                          | 4 (1; 10)             | 5 (2; 11)            |
|                          | 4 (1; 10)             | 5 (2; 11)            |
|                          | 4 (1; 10)             | 5 (2; 11)            |
|                          | 4 (1; 10)             | 5 (2; 11)            |
|                          | 4 (1; 9)              | 5 (2; 11)            |
The adjusted relative bed days within six months before death was 0.70 (95% CI, 0.68; 0.72) for heart failure patients and 0.74 (95% CI, 0.72; 0.75) for COPD patients when compared with cancer patients (Table 4). The adjusted relative bed days were the same when restricting the analyses to the last 30 days before death (Table 4).

Table 4 Adjusted relative use of hospital for patients who died of heart failure or COPD when compared with patients with cancer

| Hospital admissions | Died of cancer | Died of heart failure | Died of COPD |
|---------------------|---------------|----------------------|--------------|
|                     |               | 0.70 (0.68; 0.72)    | 0.74 (0.72; 0.75) |
| Relative total bed day use (95% CI)a |
| Six months before death | 1.0 (reference) |                |              |
| 30 days before death  | 1.0           | 0.70 (0.68; 0.73)   | 0.74 (0.72; 0.75) |
| Relative number of hospital admissions (95% CI)b |
| Six months before death | 1.0           | 0.85 (0.84; 0.86)   | 0.88 (0.87; 0.88) |
| 30 days before death  | 1.0           | 0.95 (0.95; 0.96)   | 0.96 (0.96; 0.97) |
| Relative length of stay per hospital admission (95% CI)a |
| Six months before death | 1.0           | 1.10 (1.08; 1.13)   | 1.16 (1.15; 1.18) |
| 30 days before death  | 1.0           | 0.81 (0.78; 0.83)   | 0.85 (0.83; 0.87) |
| Prevalence proportion ratio of in-hospital death (95% CI)b |
|                     | 1.0           | 1.03 (1.00; 1.05)   | 0.94 (0.93; 0.96) |

a For patients admitted to hospital within six months and 30 days before death, respectively. Adjusted for age, gender, comorbidity, partner status and residential region.

b For all patients included in the study. Adjusted for age, gender, comorbidity, partner status and residential region.
Within six months before death, acute admissions accounted for 76.9% of all hospital admissions of cancer patients, whereas this was 92.9% for heart failure patients and 95.2% for COPD patients. Correspondingly within 30 days before death, this was 84.7% for cancer patients, 96.0% for heart failure patients and 97.5% for COPD patients.

Among patients acutely admitted to hospital within six months before death, the median total bed days within this period was 16 days for cancer patients, 12 days for heart failure patients and 13 days for COPD patients. Within the last 30 days before death, the median total bed days initiated by acute admission was 8 days for cancer patients, 6 days for heart failure patients and 7 days for COPD patients.

Correspondingly, the median total bed days initiated by elective admission within six months before death was 5 days for cancer patients, 4 days for heart failure patients and 3 days for COPD patients, and within 30 days before death, this was 6 days for cancer patients, 2 days for heart failure patients and 4 days for COPD patients.

The adjusted relative bed days initiated by acute and elective admission, respectively, showed less difference between the three patient populations as for the total number of days in hospital, both within six months and 30 days before death.

**Number of hospital admissions and length per admission**

Patients who died from cancer, heart failure or COPD and were admitted to hospital within six months before death, all had a median of two hospital admissions (Table 2). Among patients admitted to hospital within the last 30 days leading up to death, all patient populations had a median of one hospital admission (Table 2). The number of admissions did not vary when stratified by calendar years of death (Table 3).

We observed variation in number of admissions within six months before death in the adjusted estimates, comparing heart failure patients (0.85 (95% CI, 0.84; 0.86)) and COPD patients (0.88
(95% CI, 0.87; 0.88)) with cancer patients (Table 4). Less variation in number of admissions was identified when restricting analyses to patients admitted to hospital within 30 days before death (heart failure patients: 0.95 (95% CI, 0.95; 0.96), COPD patients: 0.96 (95% CI, 0.96; 0.97)) (Table 4).

Patients’ median length of stay per hospital admission within the last six months of life was 4 days for cancer patients, 6 days for heart failure patients and 5 days for COPD patients (Table 2). Median length of stay within the last 30 days of life was 5 days for all patient populations. Limited differences between cancer and non-cancer patients were observed when adjusting for the covariates. For hospital admissions within six months before death, the adjusted relative median length per hospital admission was 1.10 (95% CI, 1.08; 1.13) for heart failure patients and 1.16 (95% CI, 1.15; 1.18) for COPD patients when compared with cancer patients (Table 4). Correspondingly, for hospital admissions within 30 days before death, the adjusted relative median length per hospital admission was 0.81 (95% CI, 0.78; 0.83) for heart failure patients and 0.85 (95% CI, 0.83; 0.87) for COPD patients when compared with cancer patients (Table 4).

**Place of death**

The proportion of patients dying in hospital was 55.9% of cancer patients, 48.0% of heart failure patients and 57.2% of COPD patients (Table 2).

The adjusted relative risk of dying in hospital was 1.03 (95% CI, 1.01; 1.06) for heart failure patients and 0.94 (95% CI, 0.93; 0.96) for COPD patients when compared with cancer patients (Table 4).

**DISCUSSION**

We found that hospitalisation near the end of life was common irrespective of the underlying disease, although the total number of bed days in hospital within six months before death has
been reduced for all patients in 2006-2015. Compared with patients dying of cancer, non-cancer patients had shorter total bed days but comparable length per hospital admission and number of hospital admissions within both the last six months and 30 days before death. Still, there were no major differences in the risk of dying in hospital for cancer versus non-cancer patients.

The main strengths of our study include the nationwide population-based design in the setting of a uniformly organised healthcare system where accurate linkage between national medical registries is possible. The study was based on prospectively collected data from registries, which are considered to have a high validity. However, the limitations should also be taken into account. The method that we used to examine hospitalisations for patients at the end of life using a sample of decedents only, has been criticised, as it artificially removes the uncertainty of prognostication in patients at the end of life. Yet, it is a clinical challenge to determine when patients enter the terminal phase of life, wherefore a traditional follow-up study would be difficult. Our analyses were based on the underlying cause of death of well-defined chronic diseases in order to avoid introducing misclassification, since it remains difficult to determine and differentiate between underlying and immediate cause of death. Validation of the Danish Register of Causes of Death is sparse and only performed for some diseases, leaving some uncertainty about classification of the causes of death, however, selection bias is unlikely. In the Danish National Patient Registry only few admissions and discharges are not registered, which indicates low risk of information bias concerning patients’ end-of-life hospitalisations.

Register-based data give some limitations to the study as these cannot provide detailed information on patients’ disease status, palliative needs and preferences in order to differentiate whether non-cancer and cancer patients are hospitalised for comparable reasons. There may also be residual confounding and confounding from unmeasured factors, since information on
lifestyle factors, socioeconomic status, severity of illness etc. was not available in the current study.

Previous studies examining end-of-life care for deceased cancer patients have shown that hospitalisations near the end of life are very frequent across countries and healthcare systems. However, existing data directly comparing end-of-life care patterns for cancer and non-cancer patients are sparse, and the studies are small. In line with our study, a study from the Netherlands examining the final hospitalisation within three months before death of 317 patients, also found equal numbers of hospital admissions for cancer and non-cancer patients. Furthermore, they found that 22% of cancer patients and 49% of non-cancer patients died in hospital, whereas we found no major differences in proportions of in-hospital deaths between cancer and non-cancer patients. However, the results may not be fully comparable, since we examined all hospitalisations within six months in a larger patient population.

A US study comparing end-of-life care patterns within six months before death among COPD and lung cancer patients (n=1949) also found that COPD patients and lung cancer patients had a similar risk of dying in hospital. However, unlike our study, they found, that COPD patients had fewer hospital admissions compared with lung cancer patients, and that the total hospital bed days was similar for COPD and lung cancer patients. Since the sample population in the US study was smaller than in the current study and predominantly included elderly white men, this may explain some of the variation between the findings in the two studies. Studies have suggested that variation in end-of-life care among patients with different underlying disease is caused by the perceived unpredictable illness trajectories of non-malignant chronic illnesses. Since early recognition of impending death is known to be crucial for optimal care for terminally ill patients, end-of-life care is challenging among non-cancer patients, whose illness trajectories tend to be less predictable compared with that of cancer.
patients. Therefore, we expected the current study to reveal that non-cancer patients spent more time in hospital compared with cancer patients, but this was not the case. One reason may be that improved cancer treatments are likely to have implications for the disease course, wherefore this may begin to resemble that of non-cancer patients.

Studies report that patients with non-cancer conditions have equivalent or even greater symptom burden, compared to those with cancer. The slightly lower use of hospital among non-cancer patients found in the current study could therefore indicate that the symptom relief of non-cancer patients to a larger extent as for cancer patients were met in another setting (e.g. by general practitioners). In fact, previous findings indicate that patients who receive home-based palliative care or palliative care from their general practitioner spend less time in hospital at the end of life. However, it may also indicate that the palliative needs of symptom relief among non-cancer patients are not acknowledged as such. In a recent study, we found, that patients dying from non-cancer conditions were twice as likely to be admitted to intensive care units at the end of life. This may indicate that non-cancer patients are treated aggressively and maybe unnecessarily towards the end of life, although the current study showed that their overall bed-day use was somewhat lower compared with cancer patients. Still, non-cancer patients were more likely than cancer patients to be acutely admitted to hospital, and when looking only at acute and elective admissions, respectively, the bed day use of cancer and non-cancer patients was almost the same. This may suggest that non-cancer and cancer patients are not admitted to hospital for completely comparable reasons. Yet, further efforts are needed in order to disentangle the mechanisms leading to admissions for different patient populations and to explore whether these could have been avoided.

Our findings of decreased in hospital bed day use within the 2006-2015 period could be explained by increasing numbers of outpatient treatments in the Danish healthcare system in general, replacing some hospital admissions. Nevertheless, some of the decrease may also be explained by increased levels of out-of-hospital palliative care in Denmark during the period,
where the specialised palliative care approach has advanced substantially over the past decade
along with an increased focus on palliative care in the rest of the healthcare system.

The current study does not allow us to determine whether the observed high levels of end-of-life
hospitalisation are appropriate for cancer patients and non-cancer patients, nor whether it
reflects unmet palliative needs, lack of communication about end-of-life preferences, or
difficulties recognising patients having terminal prognosis. Nevertheless, the high levels of
hospitalisation use and death at hospital warrants consideration of whether palliative needs are
appropriately accommodated. Furthermore, the findings question the common belief that
inequality in palliative care exists among terminally ill patients with different underlying
diagnosis. Still, more extensive information on end-of-life care patterns will be required in order
to clarify these important issues.

CONCLUSIONS

Patients with cancer, heart failure and COPD all spent a substantial part of their time at the end
of life being hospitalised, and several patients died during hospital admission. The use of
hospitalisations was highest among cancer patients, although the absolute differences were
small, and for all patient populations it decreased in 2006-2015. Still, more insights in end-of-
life care patterns are required in order to clarify the balance between patient needs and the care
delivered by the healthcare system.
Footnotes

Contributors: All listed authors collaborated in designing the study. HN extracted the data, and AHSV carried out statistical analyses with input from HN and TL. AHHSV wrote the first draft of the manuscript, and all authors contributed to the writing and critical review of the manuscript and approved the final version. All authors meet the authorship criteria.

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Data sharing statement: Data are available as presented in the paper. According to Danish legislation, our approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties.

Patient consent for publication: None required.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

| Section/Topic                  | Item # | Recommendation                                                                 | Reported on page # |
|-------------------------------|--------|-------------------------------------------------------------------------------|--------------------|
| Title and abstract            | 1      | (a) Indicate the study’s design with a commonly used term in the title or the abstract | 2                  |
|                               |        | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 2                  |
| Introduction                  |        |                                                                               |                    |
| Background/rationale          | 2      | Explain the scientific background and rationale for the investigation being reported | 4                  |
| Objectives                    | 3      | State specific objectives, including any prespecified hypotheses                | 4                  |
| Methods                       |        |                                                                               |                    |
| Study design                  | 4      | Present key elements of study design early in the paper                        | 4, 5               |
| Setting                       | 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4, 5               |
| Participants                  | 6      | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5                  |
|                               |        | (b) For matched studies, give matching criteria and number of exposed and unexposed | -                  |
| Variables                     | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5, 6               |
| Data sources/measurement      | 8      | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 5, 6               |
| Bias                          | 9      | Describe any efforts to address potential sources of bias                       | 5, 6               |
| Study size                    | 10     | Explain how the study size was arrived at                                       | 5                  |
| Quantitative variables        | 11     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6, 7               |
| Statistical methods           | 12     | (a) Describe all statistical methods, including those used to control for confounding | 6, 7               |
|                               |        | (b) Describe any methods used to examine subgroups and interactions            | 6, 7               |
|                               |        | (c) Explain how missing data were addressed                                     | 6, 7               |
|                               |        | (d) If applicable, explain how loss to follow-up was addressed                   | -                  |
|                               |        | (e) Describe any sensitivity analyses                                           | -                  |
| Results                       |        |                                                                               |                    |
| Item | Code | Description | Reference(s) |
|------|------|-------------|--------------|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7 |
|  |  | (b) Give reasons for non-participation at each stage | - |
|  |  | (c) Consider use of a flow diagram | - |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 7, 8 |
|  |  | (b) Indicate number of participants with missing data for each variable of interest | 7 |
|  |  | (c) Summarise follow-up time (eg, average and total amount) | 7 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8-14 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8-14 |
|  |  | (b) Report category boundaries when continuous variables were categorized | 8-14 |
|  |  | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 8-14 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | - |
| Discussion | 18 | Summarise key results with reference to study objectives | 15 |
| Limitations | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15, 16 |
| Interpretation | 21 | Discuss the generalisability (external validity) of the study results | 15 |
| Generalisability | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 20 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
Hospitalisation at the end of life among cancer and non-cancer patients in Denmark: A nationwide study

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Hospitalisation at the end of life among cancer and non-cancer patients in Denmark: A nationwide study

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Abstract

Objectives: End-of-life hospitalisations may not be associated with improved quality of life. Studies indicate differences in end-of-life care for cancer and non-cancer patients, however, data on hospital utilisation are sparse. This study aimed to compare end-of-life hospitalisation and place of death among patients dying from cancer, heart failure or chronic obstructive pulmonary disease.

Methods: Using nationwide Danish medical registries, we conducted a nationwide follow-up study including all decedents dying from cancer, heart failure or chronic obstructive pulmonary disease in Denmark in 2006-2015. We obtained data on all in-hospital admissions within six months and 30 days before death as well as place of death. Comparisons were made according to cause of death while adjusting for age, sex, comorbidity, partner status and residential region.

Results: Among 154,235 decedents, the median total bed days in hospital within six months before death was 19 days for cancer patients, 10 days for patients with heart failure and 11 days for patients with chronic obstructive pulmonary disease. Within 30 days before death, this was 9 days for cancer patients and 6 days for patients with heart failure and chronic obstructive pulmonary disease. Compared with cancer patients, the adjusted relative bed day use was 0.65 (95% CI, 0.63; 0.68) for heart failure patients and 0.68 (95% CI, 0.66; 0.69) for patients with chronic obstructive pulmonary disease within six months before death. Correspondingly, this was 0.65 (95% CI, 0.63; 0.68) and 0.70 (95% CI, 0.68; 0.71) within 30 days before death. Patients had almost the same risk of dying in hospital independently of death cause (46.2%-56.0%).

Conclusions: Patients with cancer, heart failure and chronic obstructive pulmonary disease all spent considerable part of their end of life in hospital. Hospital use was highest among cancer patients, however absolute differences were small.

Key words: Terminal care, Palliative care, Death, Hospital, Chronic disease, Neoplasms
Strengths and limitations of this study

- The main strengths include the nationwide population-based design in the setting of a uniformly organised healthcare system where accurate linkage between national medical registries is possible.

- The study was based on prospectively collected data from registries, which are considered to have a high validity.

- Analyses were based on the underlying cause of death of well-defined chronic diseases in order to avoid introducing misclassification, since it remains difficult to determine and differentiate between underlying and immediate cause of death.

- Register-based data give some limitations to the study as these cannot provide detailed information on patients’ disease status, palliative needs and preferences in order to differentiate whether non-cancer and cancer patients are hospitalised for comparable reasons.
INTRODUCTION

Most patients with chronic diseases prefer to remain home as much as possible towards the end of life, and a high level of hospital care in the last months of life may, therefore, not be associated with improved quality of life. Nevertheless, terminally ill patients may spend considerable time in hospitals and often die there. Prior research indicates that end-of-life care to patients with non-cancer diagnoses may be suboptimal compared with that of patients with cancer diagnoses, and that healthcare professionals are often better educated to identify the terminal phase and manage end-of-life care among cancer patients. Difficulties in predicting illness trajectories for non-cancer patients approaching the end of life are likely to explain some of the difference in access to palliative care services between cancer and non-cancer patients. Thus, even though incurably ill non-cancer patients experience similar physical and psychosocial needs as cancer patients, they may receive fewer palliative care services and thereby more often experience hospitalisations in the end of life. However, there is a paucity of large scale population-based studies comparing healthcare utilisation among terminally ill non-cancer and cancer patients and it is consequently difficult for healthcare professionals, administrators and health policy makers to address potential inequalities. More insight is warranted on care needs among end-of-life patients across different disease conditions in order to understand current illness trajectories and to ensure that healthcare systems are responsive and appropriately organised to meet palliative care needs. We therefore compared hospitalisation patterns within the last six months and 30 days before death as well as place of death for all Danes who died of cancer with those who died of heart failure or chronic obstructive pulmonary disease (COPD). We also examined the trends according to calendar years of death in order to identify any temporal changes.

METHODS

Study design and setting
We conducted a nationwide follow-up study among all adult decedents in Denmark who died from cancer, heart failure or COPD from 1 January 2006 to 31 December 2015. The study was based on individual-level linkage of national medical registries using the 10-digit unique personal civil registration number assigned to all Danish residents.[32,33]

The healthcare system in Denmark is tax-supported and provided to all residents, who thereby have equal access to healthcare, including access to public hospitals, hospices, general practitioners and specialists in palliative care.

Decedents

We used the Danish Register of Causes of Death to identify all decedents at the age of 18 years or older, who had been residents in Denmark for at least six months before death and registered with cancer (International Classification of Diseases, Tenth Revision (ICD-10) codes: DC00-14, DC15-26, DC30-39, DC40-41, DC43-44, DC50, DC51-58, DC60-63, DC64-68, DC69-72, DC73-75, DC76-80, DC81-96), heart failure (ICD-10 codes: I11.9, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9) or COPD (ICD-10 codes: J41-44, J47) as the underlying cause of death.

Independence between the three patient populations was ensured by excluding patients, who died of one of the three conditions while also having a history of one or both of the other conditions according to information from the Danish National Patient Registry (please see below for information on this registry). Hence, a patient with cancer as the underlying cause of death was excluded if he/she had one or more previous hospital contacts for COPD and/or heart failure.

The Danish Register of Causes of Death is a nationwide registry with data collection since 1970 with a completeness of approximately 97%.[34] Data are obtained from death certificates filled for every decedent and include civil registration number, date of death, manner of death and cause of death, both immediate and underlying, reported as a chain of one to four conditions that led to death. Causes of death are coded according to the Danish version of ICD.[35]
Hospital admissions

We identified all hospital admissions within six months before death on all included patients using the Danish National Patient Registry. The Danish National Patient Registry was established in 1977, and since then it has been mandatory for all Danish hospitals to register information on hospital admissions, including dates of all admissions and discharges, patients’ discharge diagnoses, surgical procedures and patients’ residence.

Using the Danish National Patient Registry, we retrieved the following data on the study population: 1) the total number of bed days, 2) the total number bed days initiated by acute and elective admissions, respectively, 3) the total number of admissions and the corresponding number of days per admission, 4) the number and proportion of patients hospitalised on date of death.

In addition, we retrieved data on age at death, sex, comorbidity (assessed using the Charlson Comorbidity Index) and residential region using the Danish National Patient Registry, and data regarding partner status using The Danish Civil Registration System for all patients. We computed the Charlson Comorbidity Index based on the entire hospitalisation history of each patient in the 10 years leading up to death, including both admissions with overnight stay and outpatient visits. The weights of 19 selected conditions were summed to a comorbidity score excluding the cause of death.

Statistical methods

Median total bed days within six months and 30 days before death and the corresponding percentages of time spent in hospital were estimated for the three patient populations. In the same way, we estimated the median total bed days within six months and 30 days before death after acute and elective hospital admissions, respectively.
For each patient population, we computed the median number of hospital admissions and median days per hospital admission within six months and 30 days before death. We also computed the proportion of patients dying in hospital.

Finally, we estimated the relative total bed days, relative bed days after acute admission and elective admission, respectively, relative number of hospital admissions, relative length per admission, and the relative risk of dying during hospital admission for patients who died of heart failure or COPD compared with patients who died of cancer. The relative estimates were adjusted for age, sex, comorbidity, partner status and residential region using linear regression analysis transformed by natural logarithm. Similarly, the adjusted relative risk of dying during hospital admission were estimated using multivariable binomial regression.

The statistical analyses were performed using STATA 14.2 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP) on a secure remote server of Statistics Denmark.

**Patient and Public Involvement**

In accordance with Danish law, non-interventional studies in Denmark do not require approval from ethics committees. The current study was approved by the Danish Data Protection Agency on 4 July 2014 (Central Denmark Region record number: 1-16-02-407-14).

There was no direct patient or public involvement in the analyses.

**RESULTS**

We identified 154,235 patients who died of cancer (n=123,212), heart failure (n=9,758) or COPD (n=21,265) in 2006-2015. Among these decedents, 90.7% were admitted to hospital at least once within the last six months of life (398,983 admissions) (Table 1).
| Patient characteristics | Died of cancer | Died of heart failure | Died of COPD | Total |
|-------------------------|----------------|----------------------|-------------|-------|
|                         | (n = 123,212)  | (n = 9,758)          | (n = 21,265) | (n = 154,235) |
| Age, years              |                |                      |             |       |
| Median (Q1; Q3)         | 73.0 (64.3; 81.4) | 86.7 (79.0; 91.8)   | 79.7 (72.5; 85.3) | 75.0 (65.7; 83.1) |
| Sex, n (%)              |                |                      |             |       |
| Female                  | 59,645 (48.4)  | 5,225 (53.6)         | 11,921 (56.1) | 76,791 (49.8) |
| Male                    | 63,567 (51.6)  | 4,533 (46.5)         | 9,344 (43.9)  | 77,444 (50.2) |
| Partner status, n (%)   |                |                      |             |       |
| Living alone            | 57,671 (46.8)  | 7,250 (74.3)         | 14,598 (68.7) | 79,519 (51.6) |
| Living with a partner   | 65,541 (53.2)  | 2,503 (25.7)         | 6,667 (31.4)  | 74,716 (48.4) |
| Geographical region of  |                |                      |             |       |
| residence, n (%)        |                |                      |             |       |
| North Denmark Region    | 13,776 (11.2)  | 1,121 (11.5)         | 2,671 (12.6)  | 17,568 (11.4) |
| Central Denmark Region  | 26,623 (21.6)  | 1,936 (19.8)         | 4,624 (21.7)  | 33,183 (21.5) |
| Region of Southern Denmark | 27,690 (22.5) | 2,281 (23.4)         | 4,829 (22.7)  | 34,800 (22.6) |
| Capital Region          | 34,490 (28.0)  | 2,885 (29.6)         | 5,783 (27.2)  | 43,158 (28.0) |
| Zealand Region          | 20,633 (16.8)  | 1,535 (15.7)         | 3,358 (15.8)  | 25,526 (16.6) |
| Admitted to hospital within six months before death, n (%) | 115,093 (93.4) | 7,359 (75.4) | 17,387 (81.8) | 139,839 (90.7) |
| Admitted to hospital within 30 days before death, n (%) | 82,079 (66.6) | 5,447 (55.8) | 13,624 (64.1) | 101,150 (65.6) |
Comorbidity, points

| Points | Total | Cancer | Heart failure | COPD | Total |
|--------|-------|--------|---------------|------|-------|
| 0      | 47,260 (38.4) | 3,902 (40.0) | 11,307 (53.2) | 62,469 (40.5) |
| 1      | 16,704 (13.6) | 2,491 (25.5) | 5,466 (26.6) | 24,651 (16.1) |
| 2-3    | 15,290 (12.4) | 2,401 (24.6) | 3,384 (15.9) | 21,075 (13.7) |
| 4+     | 43,958 (35.7) | 964 (9.9) | 914 (4.3) | 45,836 (29.7) |

*Calculated according to Charlson Comorbidity Index, excluding underlying cause of death.

**Bed day use**

Among the decedents included in the study, the median total bed days in hospital within six months before death was 19 days for cancer patients, 10 days for heart failure patients and 11 days for COPD patients (Table 2).

The median total bed days within the last 30 days before death was 9 days for cancer patients and 6 days for heart failure and COPD patients (Table 2).

The median total bed days within six months before death decreased from 2006 to 2015 for cancer patients, whereas it remained unchanged for heart failure and COPD patients (Figure 1).

The number of total bed days within 30 days as well as the number of hospitals admissions and length of stay per admission within 6 months and 30 days before death remained stable for all patient populations during the study period (Data not shown).

**Table 2** Hospitalisation use according to underlying disease: Total bed days in hospital, proportion of bed days, number of hospital admissions, length per admission, and proportion of patients dying in hospital

| Hospital admissions | Died of cancer | Died of heart failure | Died of COPD | Total |
|---------------------|----------------|----------------------|--------------|-------|
| Total bed day use, days, median (Q1; Q3) | | | | |
| Six months before death | 19 (9; 34) | 10 (4; 23) | 11 (5; 23) | 17 (8; 32) |
| 30 days before death | 9 (4; 15) | 6 (2; 11) | 6 (2; 12) | 8 (3; 15) |
|                                | Six months before death | 30 days before death |
|--------------------------------|-------------------------|----------------------|
| Proportion of bed days, %      | 10.4                    | 5.5                  |
|                                | 6.0                     | 9.3                  |
| Number of hospital admissions, | n (Q1; Q3)              |                      |
|                                |                         |                      |
| Six months before death        | 2 (1; 4)                | 1 (1; 2)             |
|                                | 2 (1; 3)                | 2 (1; 4)             |
| 30 days before death           | 1 (1; 2)                | 1 (1; 1)             |
|                                | 1 (1; 1)                | 1 (1; 2)             |
| Length of stay per hospital    |                         |                      |
| admission, days, median (Q1; Q3) |                        |                      |
| Six months before death        | 4 (1; 10)               | 6 (2; 11)            |
|                                | 5 (2; 10)               | 4 (1; 10)            |
| 30 days before death           | 5 (2; 11)               | 5 (2; 10)            |
|                                | 5 (2; 10)               | 5 (2; 11)            |
| Proportion of patients dying in |                         |                      |
| hospital, %                    | 56.0                    | 46.2                 |
|                                | 55.5                    | 55.3                 |
Figure 1. Total bed day use within 6 months before death according to cause of death and calendar year.
The adjusted relative bed days within six months before death was 0.65 (95% CI, 0.63; 0.67) for heart failure patients and 0.68 (95% CI, 0.66; 0.69) for COPD patients when compared with cancer patients (Table 3). The adjusted relative bed days were relatively unchanged when restricting the analyses to the last 30 days before death (Table 3).

Table 3 Adjusted relative use of hospital for patients who died of heart failure or COPD when compared with patients with cancer.

| Hospital admissions | Died of cancer | Died of heart failure* | Died of COPD* |
|---------------------|----------------|-----------------------|--------------|
| Relative total bed day use (95% CI) | | | |
| Six months before death | 1.0 (reference) | 0.65 (0.63; 0.67) | 0.68 (0.66; 0.69) |
| 30 days before death | 1.0 | 0.65 (0.63; 0.68) | 0.70 (0.68; 0.71) |
| Relative number of hospital admissions (95% CI) | | | |
| Six months before death | 1.0 | 0.84 (0.83; 0.85) | 0.85 (0.84; 0.86) |
| 30 days before death | 1.0 | 0.95 (0.94; 0.96) | 0.95 (0.95; 0.96) |
| Relative length of stay per hospital admission (95% CI) | | | |
| Six months before death | 1.0 | 1.07 (1.04; 1.10) | 1.15 (1.13; 1.17) |
| 30 days before death | 1.0 | 0.75 (0.72; 0.78) | 0.82 (0.80; 0.84) |
| Prevalence proportion ratio of in-hospital death (95% CI) | | | |
| 1.0 | 1.03 (1.00; 1.06) | 0.95 (0.93; 0.97) |

*Adjusted for age, sex, comorbidity, partner status and residential region
Within six months before death, acute admissions accounted for 76.0% of all hospital admissions of cancer patients, whereas this was 93.5% for heart failure patients and 96.0% for COPD patients. Correspondingly within 30 days before death, this was 84.3% for cancer patients, 96.3% for heart failure patients and 97.9% for COPD patients.

Among patients acutely admitted to hospital within six months before death, the median total bed days within this period was 16 days for cancer patients, 11 days for heart failure patients and 12 days for COPD patients. Within the last 30 days before death, the median total bed days initiated by acute admission was 8 days for cancer patients and 6 days for both heart failure and COPD patients.

Correspondingly, the median total bed days initiated by elective admission within six months before death was 5 days for cancer patients, 4 days for heart failure patients and 3 days for COPD patients, and within 30 days before death, this was 6 days for cancer patients and 4 days for both heart failure and COPD patients.

The adjusted relative bed days initiated by acute and elective admission, respectively, showed less difference between the three patient populations as for the total number of days in hospital, both within six months and 30 days before death.

**Number of hospital admissions and length per admission**

Patients who died from cancer or COPD had a median of two hospital admissions within six months before death, whereas patients who died of heart failure had a median of one hospital admission within six months before death (Table 2). Within the last 30 days leading up to death, all patient populations had a median of one hospital admission (Table 2). The number of admissions did not vary when stratified by calendar years of death (Data not shown).

We observed variation in number of admissions within six months before death in the adjusted estimates, comparing heart failure patients (0.84 (95% CI, 0.83; 0.85)) and COPD patients (0.85
(95% CI, 0.84; 0.86)) with cancer patients (Table 3). Less variation in number of admissions was
identified when restricting analyses to patients admitted to hospital within 30 days before death
(heart failure patients: 0.95 (95% CI, 0.94; 0.96), COPD patients: 0.95 (95% CI, 0.95; 0.96)).
Patients’ median length of stay per hospital admission within the last six months of life was 4
days for cancer patients, 6 days for heart failure patients and 5 days for COPD patients (Table 2).
Median length of stay within the last 30 days of life was 5 days for all patient populations.
Limited differences between cancer and non-cancer patients were observed when adjusting for
the covariates. For hospital admissions within six months before death, the adjusted relative
median length per hospital admission was 1.07 (95% CI, 1.04; 1.10) for heart failure patients and
1.15 (95% CI, 1.13; 1.17) for COPD patients when compared with cancer patients (Table 3).
Correspondingly, for hospital admissions within 30 days before death, the adjusted relative
median length per hospital admission was 0.75 (95% CI, 0.72; 0.78) for heart failure patients and
0.82 (95% CI, 0.80; 0.84) for COPD patients when compared with cancer patients (Table 3).

**Place of death**

The proportion of patients dying in hospital was 56.0% of cancer patients, 46.2% of heart failure
patients and 55.5% of COPD patients (Table 2).

The adjusted relative risk of dying in hospital was 1.03 (95% CI, 1.00; 1.06) for heart failure
patients and 0.95 (95% CI, 0.93; 0.97) for COPD patients when compared with cancer patients
(Table 3).

**DISCUSSION**

We found that hospitalisation near the end of life was common irrespective of the underlying
disease, although the total number of bed days in hospital within six months before death has
been reduced for all patients in 2006-2015. Compared with patients dying of cancer, non-cancer
patients had shorter total bed days but comparable length per hospital admission and number of hospital admissions within both the last six months and 30 days before death. Still, there were no major differences in the risk of dying in hospital for cancer versus non-cancer patients.

The main strengths of our study include the nationwide population-based design in the setting of a uniformly organised healthcare system where accurate linkage between national medical registries is possible. The study was based on data from registries, which are considered to have a high validity. However, the limitations should also be taken into account. The method that we used to examine hospitalisations for patients at the end of life using a sample of decedents only, has been criticised, as it artificially removes the uncertainty of prognostication in patients at the end of life. Yet, it is a clinical challenge to determine when patients enter the terminal phase of life, wherefore a traditional follow-up study would be difficult. Our analyses were based on the underlying cause of death of well-defined chronic diseases in order to avoid introducing misclassification, since it remains difficult to determine and differentiate between underlying and immediate cause of death. Validation of the Danish Register of Causes of Death is sparse and only performed for some diseases, leaving some uncertainty about classification of the causes of death, however, selection bias is unlikely. In the Danish National Patient Registry only few admissions and discharges are not registered, which indicates low risk of information bias concerning patients’ end-of-life hospitalisations. Register-based data give some limitations to the study as these cannot provide detailed information on patients’ disease status, palliative needs and preferences in order to differentiate whether non-cancer and cancer patients are hospitalised for comparable reasons. There may also be residual confounding and confounding from unmeasured factors, since information on lifestyle factors, socioeconomic status, severity of illness etc. was not available in the current study.
Previous studies examining end-of-life care for deceased cancer patients have shown that hospitalisations near the end of life are very frequent across countries and healthcare systems. However, existing data directly comparing end-of-life care patterns for cancer and non-cancer patients are sparse, and the studies are small with a few exceptions.

A US study comparing end-of-life care patterns within six months before death among COPD and lung cancer patients (n=1949) also found that COPD patients and lung cancer patients had a similar risk of dying in hospital. However, unlike our study, they found, that COPD patients had fewer hospital admissions compared with lung cancer patients, and that the total hospital bed days was similar for COPD and lung cancer patients. Since the sample population in the US study was smaller than in the current study and predominantly included elderly white men, this may explain some of the variation between the findings in the two studies.

Teno et al. examined changes in site of death, place of care, and healthcare transitions between 2000, 2005, and 2009 among a 20% sample of Medicare beneficiaries, aged 66 years and older. Improvements in care were observed over time for all patients, however, COPD patients were consistently more likely to die in acute care settings and received less hospice care compared with cancer patients. In contrast, no major difference in bed day use within 90 days before death was observed.

Wachterman et al. conducted a cross-sectional study in all 146 inpatient facilities within the Veteran Affairs health system. The study included 57,753 decedents, who all died in inpatients facilities. Patients with COPD and/or heart failure had a lower chance of receiving palliative care consultations and a higher risk of dying in the intensive care unit compared with patients with cancer. Moreover, the chance of receiving excellent quality of end-of-life care as reported by the decedents' families was also lower for patients with COPD and/or heart failure.
Finally, Lastrucci et al. recently reported a registry study from the Tuscany region in Italy where they compared indicators for quality of end-of-life care between patients with COPD or heart failure and cancer, respectively. For all indicators, patients dying from COPD or heart failure came out worse, including a higher risk of dying in an acute care hospital and being hospitalised or admitted to the emergency department and a lower chance of using hospice services in the last month of life compared with cancer patients.

Studies have suggested that variation in end-of-life care among patients with different underlying disease is caused by the perceived unpredictable illness trajectories of non-malignant chronic illnesses. Since early recognition of impending death is known to be crucial for optimal care for terminally ill patients, end-of-life care is challenging among non-cancer patients, whose illness trajectories tend to be less predictable compared with that of cancer patients. Therefore, we expected the current study to reveal that non-cancer patients spent more time in hospital compared with cancer patients, but this was not the case. One reason may be that improved cancer treatments are likely to have implications for the disease course, wherefore this may begin to resemble that of non-cancer patients.

Studies report that patients with non-cancer conditions have equivalent or even greater symptom burden, compared to those with cancer. The slightly lower use of hospital among non-cancer patients found in the current study could therefore indicate that the symptom relief of non-cancer patients to a larger extent as for cancer patients were met in another setting (e.g. by general practitioners). In fact, previous findings indicate that patients who receive home-based palliative care or palliative care from their general practitioner spend less time in hospital at the end of life. However, it may also indicate that the palliative needs of symptom relief among non-cancer patients are not acknowledged as such. In a recent study, we found, that patients dying from non-cancer conditions were twice as likely to be admitted to intensive care.
units at the end of life. This may indicate that non-cancer patients are treated aggressively and maybe unnecessarily towards the end of life, although the current study showed that their overall bed-day use was somewhat lower compared with cancer patients. Still, non-cancer patients were more likely than cancer patients to be acutely admitted to hospital, and when looking only at acute and elective admissions, respectively, the bed day use of cancer and non-cancer patients was almost the same. This may suggest that non-cancer and cancer patients are not admitted to hospital for completely comparable reasons. Yet, further efforts are needed in order to disentangle the mechanisms leading to admissions for different patient populations and to explore whether these could have been avoided.

Our findings of decreased in hospital bed day use within the 2006-2015 period could be explained by increasing numbers of outpatient treatments in the Danish healthcare system in general, replacing some hospital admissions. Nevertheless, some of the decrease may also be explained by increased levels of out-of-hospital palliative care in Denmark during the period, where the specialised palliative care approach has advanced substantially over the past decade along with an increased focus on palliative care in the rest of the healthcare system.

The current study does not allow us to determine whether the observed high levels of end-of-life hospitalisation are appropriate for cancer patients and non-cancer patients, nor whether it reflects unmet palliative needs, lack of communication about end-of-life preferences, or difficulties recognising patients having terminal prognosis. Nevertheless, the high levels of hospitalisation use and death at hospital warrants consideration of whether palliative needs are appropriately accommodated. Furthermore, the findings question the common belief that inequality in palliative care exists among terminally ill patients with different underlying diagnosis. Still, more extensive information on end-of-life care patterns will be required in order to clarify these important issues.
CONCLUSIONS

Patients with cancer, heart failure and COPD all spent a substantial part of their time at the end of life being hospitalised, and a high proportion of the patients continues to die in hospital settings. The use of hospitalisations was highest among cancer patients, although the absolute differences were small, and for all patient populations it decreased in 2006-2015. Still, more insights in end-of-life care patterns are required in order to clarify the balance between patient needs and the care delivered by the healthcare system.
Footnotes

Contributors: AHSV, MAN and SPJ initiated and designed the study. CFC, HN, TL and KGL performed further development. Acquisition of data was done by AHSV, HN and SPJ. AHSV performed the statistical analysis with assistance from HN and TL. AHSV drafted the manuscript which was critically reviewed by all authors. AHSV, MAN, CFC, HN, TL, KGL and SPJ all read and approved the final version of the manuscript.

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Data sharing statement: Data are available as presented in the paper. According to Danish legislation, our approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties.

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Figure 1. Total bed day use within 6 months before death according to cause of death and calendar year.

142x95mm (300 x 300 DPI)
**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

| Section/Topic            | Item # | Recommendation                                                                                       | Reported on page # |
|--------------------------|--------|------------------------------------------------------------------------------------------------------|--------------------|
| **Title and abstract**   | 1      | (a) Indicate the study’s design with a commonly used term in the title or the abstract                | 2                  |
|                          |        | (b) Provide in the abstract an informative and balanced summary of what was done and what was found   | 2                  |
| **Introduction**         | 2      | Explain the scientific background and rationale for the investigation being reported                  | 4                  |
| **Objectives**           | 3      | State specific objectives, including any prespecified hypotheses                                      | 4                  |
| **Methods**              | 4      | Present key elements of study design early in the paper                                              | 4, 5               |
| **Study design**         | 4      | Present key elements of study design early in the paper                                              | 4, 5               |
|                          | 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5                  |
| **Participants**         | 6      | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5                  |
|                          |        | (b) For matched studies, give matching criteria and number of exposed and unexposed                   |                    |
| **Variables**            | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5, 6               |
| **Data sources/ measurement** | 8*     | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 5, 6               |
| **Bias**                 | 9      | Describe any efforts to address potential sources of bias                                             | 5, 6               |
| **Study size**           | 10     | Explain how the study size was arrived at                                                             | 5                  |
| **Quantitative variables** | 11   | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6, 7               |
| **Statistical methods**  | 12     | (a) Describe all statistical methods, including those used to control for confounding               | 6, 7               |
|                          |        | (b) Describe any methods used to examine subgroups and interactions                                   | 6, 7               |
|                          |        | (c) Explain how missing data were addressed                                                           | 6, 7               |
|                          |        | (d) If applicable, explain how loss to follow-up was addressed                                       |                    |
|                          |        | (e) Describe any sensitivity analyses                                                                  |                    |
| Item | Description | Pages |
|------|-------------|-------|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7 |
| | | (b) Give reasons for non-participation at each stage | - |
| | | (c) Consider use of a flow diagram | - |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 7, 8 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 7 |
| | | (c) Summarise follow-up time (eg, average and total amount) | 7 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8-14 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8-14 |
| | | (b) Report category boundaries when continuous variables were categorized | 8-14 |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 8-14 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | - |
| Discussion | 18 | Summarise key results with reference to study objectives | 15 |
| Limitations | 19 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15, 16 |
| Interpretation | 20 | Discuss the generalisability (external validity) of the study results | 15 |
| Generalisability | 21 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 20 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
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Hospitalisation at the end of life among cancer and non-cancer patients in Denmark: A nationwide register based cohort study

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Abstract

Objectives: End-of-life hospitalisations may not be associated with improved quality of life. Studies indicate differences in end-of-life care for cancer and non-cancer patients, however, data on hospital utilisation are sparse. This study aimed to compare end-of-life hospitalisation and place of death among patients dying from cancer, heart failure or chronic obstructive pulmonary disease.

Design: A nationwide register based cohort study.

Setting: Data on all in-hospital admissions obtained from nationwide Danish medical registries.

Participants: All decedents dying from cancer, heart failure or chronic obstructive pulmonary disease in Denmark in 2006-2015.

Outcome measures: Data on all in-hospital admissions within six months and 30 days before death as well as place of death. Comparisons were made according to cause of death while adjusting for age, sex, comorbidity, partner status and residential region.

Results: Among 154,235 decedents, the median total bed days in hospital within six months before death was 19 days for cancer patients, 10 days for patients with heart failure and 11 days for patients with chronic obstructive pulmonary disease. Within 30 days before death, this was 9 days for cancer patients and 6 days for patients with heart failure and chronic obstructive pulmonary disease. Compared with cancer patients, the adjusted relative bed day use was 0.65 (95% CI, 0.63; 0.68) for heart failure patients and 0.68 (95% CI, 0.66; 0.69) for patients with chronic obstructive pulmonary disease within six months before death. Correspondingly, this was 0.65 (95% CI, 0.63; 0.68) and 0.70 (95% CI, 0.68; 0.71) within 30 days before death.

Patients had almost the same risk of dying in hospital independently of death cause (46.2%-56.0%).

Conclusions: Patients with cancer, heart failure and chronic obstructive pulmonary disease all spent considerable part of their end of life in hospital. Hospital use was highest among cancer patients, however absolute differences were small.
Key words: Terminal care, Palliative care, Death, Hospital, Chronic disease, Neoplasms
Strengths and limitations of this study

- The main strengths include the nationwide population-based design in the setting of a uniformly organised healthcare system where accurate linkage between national medical registries is possible.

- The study was based on prospectively collected data from registries, which are considered to have a high validity.

- Analyses were based on the underlying cause of death of well-defined chronic diseases in order to avoid introducing misclassification, since it remains difficult to determine and differentiate between underlying and immediate cause of death.

- Register-based data give some limitations to the study as these cannot provide detailed information on patients’ disease status, palliative needs and preferences in order to differentiate whether non-cancer and cancer patients are hospitalised for comparable reasons.
INTRODUCTION

Most patients with chronic diseases prefer to remain home as much as possible towards the end of life, and a high level of hospital care in the last months of life may, therefore, not be associated with improved quality of life. Nevertheless, terminally ill patients may spend considerable time in hospitals and often die there.

Prior research indicate that end-of-life care to patients with non-cancer diagnoses may be suboptimal compared with that of patients with cancer diagnoses, and that healthcare professionals are often better educated to identify the terminal phase and manage end-of-life care among cancer patients. Difficulties in predicting illness trajectories for non-cancer patients approaching the end of life are likely to explain some of the difference in access to palliative care services between cancer and non-cancer patients. Thus, even though incurably ill non-cancer patients experience similar physical and psychosocial needs as cancer patients, they may receive fewer palliative care services and thereby more often experience hospitalisations in the end of life. However, there is a paucity of large scale population-based studies comparing healthcare utilisation among terminally ill non-cancer and cancer patients and it is consequently difficult for healthcare professionals, administrators and health policy makers to address potential inequalities. More insight is warranted on care needs among end-of-life patients across different disease conditions in order to understand current illness trajectories and to ensure that healthcare systems are responsive and appropriately organised to meet palliative care needs.

We therefore compared hospitalisation patterns within the last six months and 30 days before death as well as place of death for all Danes who died of cancer with those who died of heart failure or chronic obstructive pulmonary disease (COPD). We also examined the trends according to calendar years of death in order to identify any temporal changes.

METHODS

Study design and setting
We conducted a nationwide follow-up study among all adult decedents in Denmark who died from cancer, heart failure or COPD from 1 January 2006 to 31 December 2015. The study was based on individual-level linkage of national medical registries using the 10-digit unique personal civil registration number assigned to all Danish residents.32,33

The healthcare system in Denmark is tax-supported and provided to all residents, who thereby have equal access to healthcare, including access to public hospitals, hospices, general practitioners and specialists in palliative care. Private hospitals play a minor role in Denmark and only for elective surgical and diagnostic procedures. Only public hospitals are involved in acute medical and palliative care.

In accordance with Danish law, non-interventional studies in Denmark do not require approval from ethics committees. The current study was approved by the Danish Data Protection Agency on 4 July 2014 (Central Denmark Region record number: 1-16-02-407-14).

Decedents

We used the Danish Register of Causes of Death to identify all decedents at the age of 18 years or older, who had been residents in Denmark for at least six months before death and registered with cancer (International Classification of Diseases, Tenth Revision (ICD-10) codes: DC00-14, DC15-26, DC30-39, DC40-41, DC43-44, DC50, DC51-58, DC60-63, DC64-68, DC69-72, DC73-75, DC76-80, DC81-96), heart failure (ICD-10 codes: I11.9, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9) or COPD (ICD-10 codes: J41-44, J47) as the underlying cause of death.

Independence between the three patient populations was ensured by excluding patients, who died of one of the three conditions while also having a history of one or both of the other conditions according to information from the Danish National Patient Registry (please see below for information on this registry). Hence, a patient with cancer as the underlying cause of death was excluded if he/she had one or more previous hospital contacts for COPD and/or heart failure.
The Danish Register of Causes of Death is a nationwide registry with data collection since 1970 with a completeness of approximately 97% \(^{34}\). Data are obtained from death certificates filled for every decedent and include civil registration number, date of death, manner of death and cause of death, both immediate and underlying, reported as a chain of one to four conditions that led to death. Causes of death are coded according to the Danish version of ICD \(^{35}\).

**Hospital admissions**

We identified all hospital admissions, including public and private hospitals, within six months before death on all included patients using the Danish National Patient Registry. The Danish National Patient Registry was established in 1977, and since then it has been mandatory for all Danish hospitals to register information on hospital admissions, including dates of all admissions and discharges, patients’ discharge diagnoses, surgical procedures and patients’ residence \(^{36}\).

Using the Danish National Patient Registry, we retrieved the following data on the study population: 1) the total number of bed days, 2) the total number bed days initiated by acute and elective admissions, respectively, 3) the total number of admissions and the corresponding number of days per admission, 4) the number and proportion of patients hospitalised on date of death.

In addition, we retrieved data on age at death, sex, comorbidity (assessed using the Charlson Comorbidity Index \(^{37,38}\)) and residential region using the Danish National Patient Registry, and data regarding partner status using The Danish Civil Registration System for all patients \(^{33}\). We computed the Charlson Comorbidity Index based on the entire hospitalisation history of each patient in the 10 years leading up to death, including both admissions with overnight stay and outpatient visits. The weights of 19 selected conditions were summed to a comorbidity score excluding the cause of death. \(^{37,38}\)

**Statistical methods**
Median total bed days within six months and 30 days before death and the corresponding percentages of time spent in hospital were estimated for the three patient populations. In the same way, we estimated the median total bed days within six months and 30 days before death after acute and elective hospital admissions, respectively.

For each patient population, we computed the median number of hospital admissions and median days per hospital admission within six months and 30 days before death. We also computed the proportion of patients dying in hospital.

Finally, we estimated the relative total bed days, relative bed days after acute admission and elective admission, respectively, relative number of hospital admissions, relative length per admission, and the relative risk of dying during hospital admission for patients who died of heart failure or COPD compared with patients who died of cancer. The relative estimates were adjusted for age, sex, comorbidity, partner status and residential region using linear regression analysis transformed by natural logarithm. Similarly, the adjusted relative risk of dying during hospital admission were estimated using multivariable binomial regression.

The statistical analyses were performed using STATA 14.2 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP) on a secure remote server of Statistics Denmark.

**Patient and Public Involvement**

There were no patients or members of the public involved in the design, or conduct, or analyses, or reporting of our research.

**RESULTS**

We identified 154,235 patients who died of cancer (n=123,212), heart failure (n=9,758) or COPD (n=21,265) in 2006-2015. Among these decedents, 90.7% were admitted to hospital at least once within the last six months of life (398,983 admissions) (Table 1).
Table 1 Characteristics of patients who died of cancer, heart failure or COPD in Denmark between 2006 and 2015

| Patient characteristics | Died of cancer (n = 123,212) | Died of heart failure (n = 9,758) | Died of COPD (n = 21,265) | Total (n = 154,235) |
|-------------------------|-------------------------------|-------------------------------|------------------------|-------------------|
| Age, years              |                               |                               |                        |                   |
| Median (Q1; Q3)         | 73.0 (64.3; 81.4)             | 86.7 (79.0; 91.8)             | 79.7 (72.5; 85.3)     | 75.0 (65.7; 83.1) |
| Sex, n (%)              |                               |                               |                        |                   |
| Female                  | 59,645 (48.4)                 | 5,225 (53.6)                  | 11,921 (56.1)         | 76,791 (49.8)     |
| Male                    | 63,567 (51.6)                 | 4,533 (46.5)                  | 9,344 (43.9)          | 77,444 (50.2)     |
| Partner status, n (%)   |                               |                               |                        |                   |
| Living alone            | 57,671 (46.8)                 | 7,250 (74.3)                  | 14,598 (68.7)         | 79,519 (51.6)     |
| Living with a partner   | 65,541 (53.2)                 | 2,503 (25.7)                  | 6,667 (31.4)          | 74,716 (48.4)     |
| Geographical region of  |                               |                               |                        |                   |
| residence, n (%)        |                               |                               |                        |                   |
| North Denmark Region    | 13,776 (11.2)                 | 1,121 (11.5)                  | 2,671 (12.6)          | 17,568 (11.4)     |
| Central Denmark Region  | 26,623 (21.6)                 | 1,936 (19.8)                  | 4,624 (21.7)          | 33,183 (21.5)     |
| Region of Southern Denmark | 27,690 (22.5)           | 2,281 (23.4)                  | 4,829 (22.7)          | 34,800 (22.6)     |
| Capital Region          | 34,490 (28.0)                 | 2,885 (29.6)                  | 5,783 (27.2)          | 43,158 (28.0)     |
| Zealand Region          | 20,633 (16.8)                 | 1,535 (15.7)                  | 3,358 (15.8)          | 25,526 (16.6)     |
| Admitted to hospital within six months before death, n (%) | 115,093 (93.4) | 7,359 (75.4) | 17,387 (81.8) | 139,839 (90.7) |
Admitted to hospital within 30 days before death, n (%)  
|               | 82,079 (66.6) | 5,447 (55.8) | 13,624 (64.1) | 101,150 (65.6) |

| Comorbidity, points\(^a\) |               |               |               |               |
|---------------------------|---------------|---------------|---------------|---------------|
| 0                         | 47,260 (38.4) | 3,902 (40.0)  | 11,307 (53.2) | 62,469 (40.5) |
| 1                         | 16,704 (13.6) | 2,491 (25.5)  | 5,660 (26.6)  | 24,855 (16.1) |
| 2-3                       | 15,290 (12.4) | 2,401 (24.6)  | 3,384 (15.9)  | 21,075 (13.7) |
| 4+                        | 43,958 (35.7) | 964 (9.9)     | 914 (4.3)     | 45,836 (29.7) |

\(^a\)Calculated according to Charlson Comorbidity Index, excluding underlying cause of death.

**Bed day use**

Among the decedents included in the study, the median total bed days in hospital within six months before death was 19 days for cancer patients, 10 days for heart failure patients and 11 days for COPD patients (Table 2).

The median total bed days within the last 30 days before death was 9 days for cancer patients and 6 days for heart failure and COPD patients (Table 2).

The median total bed days within six months before death decreased from 2006 to 2015 for cancer patients, whereas it remained unchanged for heart failure and COPD patients (Figure 1).

The number of total bed days within 30 days as well as the number of hospitals admissions and length of stay per admission within 6 months and 30 days before death remained stable for all patient populations during the study period (Data not shown).
Table 2 Hospitalisation use according to underlying disease: Total bed days in hospital, proportion of bed days, number of hospital admissions, length per admission, and proportion of patients dying in hospital

| Hospital admissions | Died of cancer | Died of heart failure | Died of COPD | Total |
|---------------------|----------------|----------------------|--------------|-------|
|                     | (Q1; Q3)       |                      |              |       |
| Total bed day use, days, median |                  |                      |              |       |
| Six months before death | 19 (9; 34)     | 10 (4; 23)           | 11 (5; 23)   | 17 (8; 32) |
| 30 days before death | 9 (4; 15)      | 6 (2; 11)            | 6 (2; 12)    | 8 (3; 15) |
| Proportion of bed days, % |                  |                      |              |       |
| Six months before death | 10.4           | 5.5                  | 6.0          | 9.3   |
| 30 days before death | 30.0           | 20.0                 | 20.0         | 26.7  |
| Number of hospital admissions, n (Q1; Q3) |                  |                      |              |       |
| Six months before death | 2 (1; 4)        | 1 (1; 2)             | 2 (1; 3)     | 2 (1; 4) |
| 30 days before death | 1 (1; 2)        | 1 (1; 1)             | 1 (1; 1)     | 1 (1; 2) |
| Length of stay per hospital admission, days, median (Q1; Q3) |                  |                      |              |       |
| Six months before death | 4 (1; 10)       | 6 (2; 11)            | 5 (2; 10)    | 4 (1; 10) |
| 30 days before death | 5 (2; 11)       | 5 (2; 10)            | 5 (2; 10)    | 5 (2; 11) |
| Proportion of patients dying in hospital, % | 56.0 | 46.2 | 55.5 | 55.3 |
Figure 1. Total bed day use within 6 months before death according to cause of death and calendar year.
The adjusted relative bed days within six months before death was 0.65 (95% CI, 0.63; 0.67) for heart failure patients and 0.68 (95% CI, 0.66; 0.69) for COPD patients when compared with cancer patients (Table 3). Unadjusted results are available in Supplement table 1. The adjusted relative bed days were relatively unchanged when restricting the analyses to the last 30 days before death (Table 3).

**Table 3** Adjusted relative use of hospital for patients who died of heart failure or COPD when compared with patients with cancer.

| Hospital admissions | Died of cancer | Died of heart failure* | Died of COPD* |
|---------------------|----------------|------------------------|--------------|
| Relative total bed day use (95% CI) |                |                        |              |
| Six months before death | 1.0 (reference) | 0.65 (0.63; 0.67)       | 0.68 (0.66; 0.69) |
| 30 days before death    | 1.0            | 0.65 (0.63; 0.68)       | 0.70 (0.68; 0.71) |
| Relative number of hospital admissions (95% CI) | |                        |              |
| Six months before death | 1.0           | 0.84 (0.83; 0.85)       | 0.85 (0.84; 0.86) |
| 30 days before death    | 1.0            | 0.95 (0.94; 0.96)       | 0.95 (0.95; 0.96) |
| Relative length of stay per hospital admission (95% CI) | |                        |              |
| Six months before death | 1.0           | 1.07 (1.04; 1.10)       | 1.15 (1.13; 1.17) |
| 30 days before death    | 1.0            | 0.75 (0.72; 0.78)       | 0.82 (0.80; 0.84) |
| Prevalence proportion ratio of in-hospital death (95% CI) | 1.0           | 1.03 (1.00; 1.06)       | 0.95 (0.93; 0.97) |

*Adjusted for age, sex, comorbidity, partner status and residential region
Within six months before death, acute admissions accounted for 76.0% of all hospital admissions of cancer patients, whereas this was 93.5% for heart failure patients and 96.0% for COPD patients. Correspondingly within 30 days before death, this was 84.3% for cancer patients, 96.3% for heart failure patients and 97.9% for COPD patients.

Among patients acutely admitted to hospital within six months before death, the median total bed days within this period was 16 days for cancer patients, 11 days for heart failure patients and 12 days for COPD patients. Within the last 30 days before death, the median total bed days initiated by acute admission was 8 days for cancer patients and 6 days for both heart failure and COPD patients.

Correspondingly, the median total bed days initiated by elective admission within six months before death was 5 days for cancer patients, 4 days for heart failure patients and 3 days for COPD patients, and within 30 days before death, this was 6 days for cancer patients and 4 days for both heart failure and COPD patients.

The adjusted relative bed days initiated by acute and elective admission, respectively, showed less difference between the three patient populations as for the total number of days in hospital, both within six months and 30 days before death.

**Number of hospital admissions and length per admission**

Patients who died from cancer or COPD had a median of two hospital admissions within six months before death, whereas patients who died of heart failure had a median of one hospital admission within six months before death (Table 2). Within the last 30 days leading up to death, all patient populations had a median of one hospital admission (Table 2). The number of admissions did not vary systematically when stratified by calendar years of death (Supplement table 2).
We observed variation in number of admissions within six months before death in the adjusted estimates, comparing heart failure patients (0.84 (95% CI, 0.83; 0.85)) and COPD patients (0.85 (95% CI, 0.84; 0.86)) with cancer patients (Table 3). Less variation in number of admissions was identified when restricting analyses to patients admitted to hospital within 30 days before death (heart failure patients: 0.95 (95% CI, 0.94; 0.96), COPD patients: 0.95 (95% CI, 0.95; 0.96)).

Patients’ median length of stay per hospital admission within the last six months of life was 4 days for cancer patients, 6 days for heart failure patients and 5 days for COPD patients (Table 2). Median length of stay within the last 30 days of life was 5 days for all patient populations. Limited differences between cancer and non-cancer patients were observed when adjusting for the covariates. For hospital admissions within six months before death, the adjusted relative median length per hospital admission was 1.07 (95% CI, 1.04; 1.10) for heart failure patients and 1.15 (95% CI, 1.13; 1.17) for COPD patients when compared with cancer patients (Table 3).

Correspondingly, for hospital admissions within 30 days before death, the adjusted relative median length per hospital admission was 0.75 (95% CI, 0.72; 0.78) for heart failure patients and 0.82 (95% CI, 0.80; 0.84) for COPD patients when compared with cancer patients (Table 3).

**Place of death**

The proportion of patients dying in hospital was 56.0% of cancer patients, 46.2% of heart failure patients and 55.5% of COPD patients (Table 2).

The adjusted relative risk of dying in hospital was 1.03 (95% CI, 1.00; 1.06) for heart failure patients and 0.95 (95% CI, 0.93; 0.97) for COPD patients when compared with cancer patients (Table 3).

**DISCUSSION**
We found that hospitalisation near the end of life was common irrespective of the underlying

disease, although the total number of bed days in hospital within six months before death has

been reduced for all patients in 2006-2015. Compared with patients dying of cancer, non-cancer

patients had shorter total bed days but comparable length per hospital admission and number of

hospital admissions within both the last six months and 30 days before death. Still, there were

no major differences in the risk of dying in hospital for cancer versus non-cancer patients.

The main strengths of our study include the nationwide population-based design in the setting of

a uniformly organised healthcare system where accurate linkage between national medical

registries is possible. The study was based on data from registries, which are considered to have

a high validity 36.

However, the limitations should also be taken into account. The method that we used to

examine hospitalisations for patients at the end of life using a sample of decedents only, has

been criticised, as it artificially removes the uncertainty of prognostication in patients at the end

of life 39. Yet, it is a clinical challenge to determine when patients enter the terminal phase of

life, wherefore a traditional follow-up study would be difficult. Our analyses were based on the

underlying cause of death of well-defined chronic diseases in order to avoid introducing

misclassification, since it remains difficult to determine and differentiate between underlying

and immediate cause of death. Validation of the Danish Register of Causes of Death is sparse

and only performed for some diseases, leaving some uncertainty about classification of the

causes of death, however, selection bias is unlikely 40. In the Danish National Patient Registry

only few admissions and discharges are not registered, which indicates low risk of information

bias concerning patients’ end-of-life hospitalisations 36.

Register-based data give some limitations to the study as these cannot provide detailed

information on patients’ disease status, palliative needs and preferences in order to differentiate

whether non-cancer and cancer patients are hospitalised for comparable reasons. There may also
be residual confounding and confounding from unmeasured factors, since information on lifestyle factors, socioeconomic status, severity of illness etc. was not available in the current study.

Previous studies examining end-of-life care for deceased cancer patients have shown that hospitalisations near the end of life are very frequent across countries and healthcare systems\(^4\). However, existing data directly comparing end-of-life care patterns for cancer and non-cancer patients are sparse, and the studies are small with a few exceptions.

A US study comparing end-of-life care patterns within six months before death among COPD and lung cancer patients (n=1949) also found that COPD patients and lung cancer patients had a similar risk of dying in hospital\(^3\). However, unlike our study, they found, that COPD patients had fewer hospital admissions compared with lung cancer patients, and that the total hospital bed days was similar for COPD and lung cancer patients. Since the sample population in the US study was smaller than in the current study and predominantly included elderly white men, this may explain some of the variation between the findings in the two studies.

Teno et al. examined changes in site of death, place of care, and healthcare transitions between 2000, 2005, and 2009 among a 20% sample of Medicare beneficiaries, aged 66 years and older\(^4\). Improvements in care were observed over time for all patients, however, COPD patients were consistently more likely to die in acute care settings and received less hospice care compared with cancer patients. In contrast, no major difference in bed day use within 90 days before death was observed.

Wachterman et al. conducted a cross-sectional study in all 146 inpatient facilities within the Veteran Affairs health system\(^4\). The study included 57,753 decedents, who all died in inpatients facilities. Patients with COPD and/or heart failure had a lower chance of receiving palliative care consultations and a higher risk of dying in the intensive care unit compared with
patients with cancer. Moreover, the chance of receiving excellent quality of end-of-life care as reported by the decedents’ families was also lower for patients with COPD and/or heart failure. Finally, Lastrucci et al. recently reported a registry study from the Tuscany region in Italy where they compared indicators for quality of end-of-life care between patients with COPD or heart failure and cancer, respectively. For all indicators, patients dying from COPD or heart failure came out worse, including a higher risk of dying in an acute care hospital and being hospitalised or admitted to the emergency department and a lower chance of using hospice services in the last month of life compared with cancer patients.

Studies have suggested that variation in end-of-life care among patients with different underlying disease is caused by the perceived unpredictable illness trajectories of non-malignant chronic illnesses. Since early recognition of impending death is known to be crucial for optimal care for terminally ill patients, end-of-life care is challenging among non-cancer patients, whose illness trajectories tend to be less predictable compared with that of cancer patients. Therefore, we expected the current study to reveal that non-cancer patients spent more time in hospital compared with cancer patients, but this was not the case. One reason may be that improved cancer treatments are likely to have implications for the disease course, wherefore this may begin to resemble that of non-cancer patients.

Studies report that patients with non-cancer conditions have equivalent or even greater symptom burden, compared to those with cancer. The slightly lower use of hospital among non-cancer patients found in the current study could therefore indicate that the symptom relief of non-cancer patients to a larger extent as for cancer patients were met in another setting (e.g. by general practitioners). In fact, previous findings indicate that patients who receive home-based palliative care or palliative care from their general practitioner spend less time in hospital at the end of life. However, it may also indicate that the palliative needs of symptom relief...
among non-cancer patients are not acknowledged as such. In a recent study, we found, that patients dying from non-cancer conditions were twice as likely to be admitted to intensive care units at the end of life. This may indicate that non-cancer patients are treated aggressively and maybe unnecessarily towards the end of life, although the current study showed that their overall bed-day use was somewhat lower compared with cancer patients. Still, non-cancer patients were more likely than cancer patients to be acutely admitted to hospital, and when looking only at acute and elective admissions, respectively, the bed day use of cancer and non-cancer patients was almost the same. This may suggest that non-cancer and cancer patients are not admitted to hospital for completely comparable reasons. Yet, further efforts are needed in order to disentangle the mechanisms leading to admissions for different patient populations and to explore whether these could have been avoided.

Our findings of decreased in hospital bed day use within the 2006-2015 period could be explained by increasing numbers of outpatient treatments in the Danish healthcare system in general, replacing some hospital admissions. Nevertheless, some of the decrease may also be explained by increased levels of out-of-hospital palliative care in Denmark during the period, where the specialised palliative care approach has advanced substantially over the past decade along with an increased focus on palliative care in the rest of the healthcare system.

The current study does not allow us to determine whether the observed high levels of end-of-life hospitalisation are appropriate for cancer patients and non-cancer patients, nor whether it reflects unmet palliative needs, lack of communication about end-of-life preferences, or difficulties recognising patients having terminal prognosis. Nevertheless, the high levels of hospitalisation use and death at hospital warrants consideration of whether palliative needs are appropriately accommodated. Furthermore, the findings question the common belief that inequality in palliative care exists among terminally ill patients with different underlying
CONCLUSIONS

Patients with cancer, heart failure and COPD all spent a substantial part of their time at the end of life being hospitalised, and a high proportion of the patients continues to die in hospital settings. The use of hospitalisations was highest among cancer patients, although the absolute differences were small, and for all patient populations it decreased in 2006-2015. Still, more insights in end-of-life care patterns are required in order to clarify the balance between patient needs and the care delivered by the healthcare system.
Footnotes

Contributors: AHSV, MAN and SPJ initiated and designed the study. CFC, HN, TL and KGL performed further development. Acquisition of data was done by AHSV, HN and SPJ. AHSV performed the statistical analysis with assistance from HN and TL. AHSV drafted the manuscript which was critically reviewed by all authors. AHSV, MAN, CFC, HN, TL, KGL and SPJ all read and approved the final version of the manuscript.

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Data sharing statement: Data are available as presented in the paper. According to Danish legislation, our approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties.

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Figure 1. Total bed day use within 6 months before death according to cause of death and calendar year.

142x95mm (300 x 300 DPI)
**Supplement table 1** Unadjusted relative use of hospital for patients who died of heart failure or COPD when compared with patients with cancer

| Hospital admissions | Died of cancer | Died of heart failure | Died of COPD |
|---------------------|----------------|----------------------|--------------|
| Relative total bed day use (95% CI) | | | |
| Six months before death | 1.00 (reference) | 0.37 (0.36; 0.39) | 0.50 (0.49; 0.51) |
| 30 days before death | 1.00 | 0.40 (0.38; 0.42) | 0.57 (0.55; 0.58) |
| Relative number of hospital admissions (95% CI) | | | |
| Six months before death | 1.00 | 0.50 (0.49; 0.51) | 0.63 (0.62; 0.64) |
| 30 days before death | 1.00 | 0.59 (0.58; 0.61) | 0.78 (0.76; 0.79) |
| Relative length of stay per hospital admission (95% CI) | | | |
| Six months before death | 1.00 | 1.31 (1.27; 1.35) | 1.34 (1.32; 1.37) |
| 30 days before death | 1.00 | 0.85 (0.82; 0.89) | 0.90 (0.87; 0.92) |
| Prevalence proportion ratio of in-hospital death (95% CI) | | | |
| 1.00 | 1.24 (1.21; 1.28) | 1.15 (1.13; 1.17) |
### Supplement table 2 Adjusted relative use of hospital for patients who died of heart failure or COPD when compared with patients with cancer, stratified by calendar year of death

| Hospital admissions | 2006   | 2007   | 2008   | 2009   | 2010   | 2011   | 2012   | 2013   | 2014   | 2015   |
|---------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| **Relative total bed day use (95% CI)** |        |        |        |        |        |        |        |        |        |        |
| **Six months before death** |        |        |        |        |        |        |        |        |        |        |
| Died of cancer      | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   |
| Died of heart failure | 0.60 (0.55; 0.65) | 0.56 (0.51; 0.61) | 0.63 (0.57; 0.69) | 0.67 (0.62; 0.74) | 0.66 (0.60; 0.72) | 0.69 (0.63; 0.76) | 0.58 (0.53; 0.64) | 0.69 (0.62; 0.76) | 0.71 (0.64; 0.78) | 0.73 (0.66; 0.81) |
| Died of COPD        | 0.65 (0.61; 0.69) | 0.52 (0.58; 0.66) | 0.63 (0.59; 0.67) | 0.69 (0.65; 0.73) | 0.69 (0.64; 0.73) | 0.70 (0.66; 0.74) | 0.71 (0.67; 0.75) | 0.72 (0.68; 0.77) | 0.72 (0.67; 0.77) |        |
| **30 days before death** |        |        |        |        |        |        |        |        |        |        |
| Died of cancer      | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   |
| Died of heart failure | 0.62 (0.55; 0.71) | 0.62 (0.55; 0.70) | 0.63 (0.56; 0.71) | 0.72 (0.64; 0.81) | 0.67 (0.59; 0.75) | 0.75 (0.67; 0.84) | 0.54 (0.47; 0.61) | 0.64 (0.57; 0.72) | 0.67 (0.59; 0.77) | 0.71 (0.63; 0.80) |
| Died of COPD        | 0.64 (0.59; 0.70) | 0.69 (0.64; 0.76) | 0.67 (0.61; 0.73) | 0.71 (0.66; 0.77) | 0.68 (0.63; 0.74) | 0.74 (0.68; 0.79) | 0.67 (0.62; 0.73) | 0.69 (0.64; 0.75) | 0.77 (0.65; 0.76) | 0.75 (0.70; 0.82) |
| **Relative number of hospital admissions (95% CI)** |        |        |        |        |        |        |        |        |        |        |
| **Six months before death** |        |        |        |        |        |        |        |        |        |        |
| Died of cancer      | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   |
| Died of heart failure | 0.81 (0.77; 0.85) | 0.83 (0.80; 0.87) | 0.83 (0.79; 0.87) | 0.83 (0.79; 0.87) | 0.82 (0.78; 0.86) | 0.85 (0.81; 0.90) | 0.88 (0.83; 0.92) | 0.86 (0.82; 0.90) | 0.85 (0.81; 0.90) |        |
| Died of COPD        | 0.83 (0.80; 0.86) | 0.81 (0.78; 0.83) | 0.81 (0.78; 0.84) | 0.85 (0.82; 0.87) | 0.86 (0.83; 0.89) | 0.84 (0.82; 0.87) | 0.87 (0.84; 0.90) | 0.86 (0.83; 0.89) | 0.86 (0.83; 0.89) | 0.89 (0.86; 0.92) |
| **30 days before death** |        |        |        |        |        |        |        |        |        |        |
| Died of cancer      | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   | 1.00   |
| Died of heart failure | 0.95 (0.93; 0.98) | 0.96 (0.93; 0.99) | 0.94 (0.91; 0.97) | 0.94 (0.91; 0.97) | 0.95 (0.92; 0.98) | 0.97 (0.94; 1.00) | 0.96 (0.93; 0.99) | 0.96 (0.92; 0.99) | 0.95 (0.92; 0.98) | 0.96 (0.93; 0.99) |
| Died of COPD        | 0.95 (0.93; 0.97) | 0.93 (0.91; 0.95) | 0.95 (0.93; 0.97) | 0.95 (0.93; 0.97) | 0.95 (0.93; 0.97) | 0.96 (0.94; 0.98) | 0.96 (0.94; 0.98) | 0.97 (0.95; 0.99) | 0.95 (0.93; 0.97) | 0.97 (0.95; 0.99) |
Relative length of stay per hospital admission (95% CI)

|                  | Died of cancer | Died of heart failure | Died of COPD |
|------------------|----------------|-----------------------|--------------|
| **Six months before death** |                |                       |              |
| Died of cancer   | 1.00           | 1.04 (0.95; 1.14)     | 1.19 (1.12; 1.27) |
| Died of heart failure | 0.98 (0.90; 1.07) | 0.98 (0.90; 1.07)     | 0.72 (0.64; 0.82) |
| Died of COPD     | 1.00           | 1.12 (1.03; 1.22)     | 1.19 (1.12; 1.27) |
|                  | 1.00           | 0.92 (0.87; 0.98)     | 0.87 (0.80; 0.95) |
| **30 days before death** |                |                       |              |
| Died of cancer   | 1.00           | 1.04 (0.95; 1.14)     | 1.03 (0.94; 1.13) |
| Died of heart failure | 0.98 (0.89; 1.07) | 0.98 (0.89; 1.07)     | 0.97 (0.91; 1.04) |
| Died of COPD     | 1.00           | 1.04 (0.95; 1.14)     | 0.97 (0.91; 1.03) |

Prevalence proportion ratio of in-hospital death (95% CI)

|                  | Died of cancer | Died of heart failure | Died of COPD |
|------------------|----------------|-----------------------|--------------|
| **Six months before death** |                |                       |              |
| Died of cancer   | 1.00           | 1.04 (0.95; 1.14)     | 1.19 (1.12; 1.27) |
| Died of heart failure | 0.98 (0.90; 1.07) | 0.98 (0.90; 1.07)     | 0.72 (0.64; 0.82) |
| Died of COPD     | 1.00           | 1.12 (1.03; 1.22)     | 1.19 (1.12; 1.27) |
|                  | 1.00           | 0.92 (0.87; 0.98)     | 0.87 (0.80; 0.95) |
| **30 days before death** |                |                       |              |
| Died of cancer   | 1.00           | 1.04 (0.95; 1.14)     | 1.03 (0.94; 1.13) |
| Died of heart failure | 0.98 (0.89; 1.07) | 0.98 (0.89; 1.07)     | 0.97 (0.91; 1.04) |
| Died of COPD     | 1.00           | 1.04 (0.95; 1.14)     | 0.97 (0.91; 1.03) |
## STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

| Section/Topic          | Item # | Recommendation                                                                                                                                                                                                 | Reported on page # |
|------------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **Title and abstract** | 1      | (a) Indicate the study’s design with a commonly used term in the title or the abstract                                                                                                                      | 2                 |
|                        |        | (b) Provide in the abstract an informative and balanced summary of what was done and what was found                                                                                                         | 2                 |
| **Introduction**       | 2      | Explain the scientific background and rationale for the investigation being reported                                                                                                                       | 4                 |
| **Objectives**         | 3      | State specific objectives, including any prespecified hypotheses                                                                                                                                             | 4                 |
| **Methods**            | 4      | Present key elements of study design early in the paper                                                                                                                                                     | 4, 5              |
| **Setting**            | 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection                                                                           | 4, 5              |
| **Participants**       | 6      | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up                                                                                 | 5                 |
|                        |        | (b) For matched studies, give matching criteria and number of exposed and unexposed                                                                                                                         | -                 |
| **Variables**          | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable                                                                       | 5, 6              |
| **Data sources/        | 8*     | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group                             | 5, 6              |
| measurement**          |        |                                                                                                                                                                                                             |                   |
| **Bias**               | 9      | Describe any efforts to address potential sources of bias                                                                                                                                                     | 5, 6              |
| **Study size**         | 10     | Explain how the study size was arrived at                                                                                                                                                                     | 5                 |
| **Quantitative         | 11     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why                                                                               | 6, 7              |
| variables**            |        |                                                                                                                                                                                                             |                   |
| **Statistical methods**| 12     | (a) Describe all statistical methods, including those used to control for confounding                                                                                                                       | 6, 7              |
|                        |        | (b) Describe any methods used to examine subgroups and interactions                                                                                                                                       | 6, 7              |
|                        |        | (c) Explain how missing data were addressed                                                                                                                                                                  | 6, 7              |
|                        |        | (d) If applicable, explain how loss to follow-up was addressed                                                                                                                                             | -                 |
|                        |        | (e) Describe any sensitivity analyses                                                                                                                                                                       | -                 |
| Section          | Item* | Description                                                                 | Page |
|------------------|-------|-----------------------------------------------------------------------------|------|
| Participants     | 13    | (a) Report numbers of individuals at each stage—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7    |
|                  |       | (b) Give reasons for non-participation at each stage                         | -    |
|                  |       | (c) Consider use of a flow diagram                                           | -    |
| Descriptive data | 14    | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 7, 8  |
|                  |       | (b) Indicate number of participants with missing data for each variable of interest | 7    |
|                  |       | (c) Summarise follow-up time (eg, average and total amount)                  | 7    |
| Outcome data     | 15    | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8-14 |
|                  |       | (b) Report category boundaries when continuous variables were categorized    | 8-14 |
|                  |       | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 8-14 |
| Main results     | 16    | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8-14 |
|                  |       | (b) Report category boundaries when continuous variables were categorized    | 8-14 |
| Other analyses   | 17    | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | -    |
| Discussion       |       |                                                                             |      |
| Key results      | 18    | Summarise key results with reference to study objectives                      | 15   |
| Limitations      |       |                                                                             |      |
| Interpretation   | 20    | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15, 16|
| Generalisability | 21    | Discuss the generalisability (external validity) of the study results         | 15   |
| Other information|       |                                                                             |      |
| Funding          | 22    | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 20   |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.