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Original research

Four decades of lung cancer: Trends in comorbidities and causes of death in a nationwide Danish cohort

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ABSTRACT

Background: Lung cancer remains the leading cause of cancer-related deaths globally, with gradual improvements in patient survival attributed to early detection through low-dose computed tomography screening and advances in oncological therapies. Despite these advancements, the management of comorbidities, particularly cardiovascular disease and chronic obstructive pulmonary disease, is critical due to their shared causal link with lung cancer - smoking. This study explores the prevalence of comorbidities among lung cancer patients in Denmark over four decades, using comprehensive national registry data.

Methods: By examining the Danish National Patient Register and Danish Cancer Registry, we identified all Danish lung cancer cases diagnosed from 1980 to 2018, analyzing comorbidities and causes of death. A comparison cohort matched by age, sex, municipality, and marital status was also established.

Findings: The findings reveal a significant increase in comorbidities among lung cancer patients over time, while this increase was less significant in the comparison cohort. Almost half of lung cancer patients had at least one comorbidity in the most recent period, 2008–2018. Cardiovascular disease, chronic obstructive pulmonary disease, diabetes, stroke, and peripheral atherosclerosis were the most prevalent comorbidities. Among patients diagnosed with lung cancer, it was the cause of death in 84 % of cases. The study also highlights a notable decrease in deaths from ischemic heart disease, with an increase in dementia-related deaths, suggesting an increasing burden of neurodegenerative diseases in aging populations.

Interpretation: This longitudinal analysis highlights that as the burden of comorbidities increases, comprehensive management strategies become increasingly crucial. These strategies could include less invasive diagnostic approaches, such as endobronchial evaluation, as well as treatment options like segmental resection and stereotactic body radiation. Addressing comorbidities alongside cancer treatment may improve patient outcomes and overall quality of life in aging populations.

1. Introduction

Lung cancer remains the leading cause of cancer-related death in both men and women [1]. The survival of lung cancer patients is slowly increasing [2], likely attributed to several factors. These include a more streamlined lung cancer investigation process [3], earlier diagnosis facilitated by low-dose computed tomography (CT) screening in several countries, including the US [4–7], and the widespread use of CT scans in society, leading to more incidentally found cancers detected at an early stage [8]. Additionally, more effective oncological therapies such as

check point inhibitors and targeted treatments have emerged [9], and also play a significant role in improving survival rates [10,11].

As survival has improved, managing comorbidities has become increasingly important in further enhancing survival rates among lung cancer patients. The major conditions are cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD), which share a causal link with lung cancer – smoking [12]. Consequently, lung cancer patients bear one of the highest burdens of comorbidity [13]. It has been shown that the comorbidities of lung cancer patients significantly contribute to mortality [14,15] – partly due to the fact, that because of

Abbreviations: CCI, Charlson's comorbidity index; COPD, Chronic obstructive pulmonary disease; CT, Computed tomography; CVD, Cardiovascular disease; DCDR, Danish Causes of Death Register; DNPR, Danish National Patient Register; ICD, International Classification of Diseases.

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comorbidities, some patients cannot undergo surgical or oncological curative treatment, even when the disease is localized [16]. It is also possible, that patients die from their comorbidities rather than from lung cancer itself. However, even though many lessons have been learned, the evolution of comorbidities among patients with lung cancer has vastly remained unknown through the past decades.

In high-income countries, the impact of CVD on mortality in the general population has significantly decreased in recent years [17]. This reduction is largely attributed to improved secondary prophylaxis and new treatment options for myocardial infarction, stroke, and congestive heart disease [18]. However, it remains unclear how this decline in CVD mortality has affected lung cancer patients - including the causes of death.

Although several studies have explored the relationship between comorbidities and lung cancer outcomes, there are still gaps in our understanding. Existing research often focus on specific comorbidities or patient populations, which may limit the generalizability of findings. In this study, we aim to address these knowledge gaps by investigating the prevalence of comorbidities among lung cancer patients in Denmark at a national level over a period of four decades. Additionally, we will analyze the causes of death during the same period to assess temporal changes and gain insight into the patterns of mortality in this population.

2. Methods

2.1. Data sources

The Danish National Health Service offers tax-funded universal healthcare [19]. Each Danish resident is assigned a unique ten-digit Civil Registration System number upon birth or immigration, allowing precise individual-level record linkage across national registries and life-long follow-up. Patients aged 18 years or older diagnosed with first-time lung cancer between January 1, 1980, and December 31, 2018, were identified in the Danish National Patient Register (DNPR). This administrative registry has provided complete nationwide coverage for all non-psychiatric diagnoses since 1978 [20]. Registration in the DNPR is mandatory and submitted by treating physicians, continually monitoring hospital and health service utilization and facilitates billing. The Danish Cancer Registry is providing its cancer records to the DNPR. It has demonstrated nearly complete coverage of cancer diagnoses in Denmark since 1943 [21].

Diagnoses, primary and secondary, are classified according to the International Classification of Diseases (ICD) [22]. Lung cancer cases were identified using ICD-8 codes 163 and 164 from 1980 to 1993, and ICD-10 codes c33-c34 from 1994 to 2022. The Civil Registration System number reveals both age and sex.

A comparison cohort at a 1:4 ratio was formed. Comparison subjects were randomly selected from the Danish population during the same inclusion period as the lung cancer patients and were matched based on age, sex, municipality, and marital status.

Comorbidity diagnoses were obtained from the DNPR and recorded if registered up to three years before the diagnosis of lung cancer, including both primary and secondary diagnoses for both inpatient and outpatient hospital contacts. This timeframe was chosen to ensure the comorbidities were relevant to patient outcomes. Comorbidity is reported both as diagnoses and Charlson's comorbidity index (CCI) [23]. Lung cancer is excluded from the CCI.

Causes of death were retrieved from the Danish Causes of Death Register (DCDR). Since 1943, the DCDR has recorded data on death certificates of all Danish citizens ensuring universal coverage.

Lung cancer patients and comparison subjects were divided into three time periods (1980–1993, 1994–2007, and 2008–2018) to evaluate temporal changes. The periods were segmented at 1993/1994 to account for the switch from ICD-8 to ICD-10 for coding consistency and at 2007/2008 to ensure three comparably sized groups.

2.2. Statistical analyses

Differences in distribution of age, comorbidities and causes of death were analyzed using logistic regression adjusted for sex, age, marital status and municipality. Each comorbidity is treated as a separate outcome in the logistic regression model. Statistical analyses were performed using SAS 9.4 TS Level 1M5 (SAS, Inc., Cary, NC, USA), and graphs were produced in Microsoft Excel, version 16.71.

2.3. Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

2.4. Ethical considerations

Data from the Danish National Patient Register is analyzed without access to personally identifiable information, ensuring the privacy and confidentiality of individuals included in the registry. The study is approved by the Danish Data Protection Agency.

3. Results

During the study period, 162,996 patients diagnosed with lung cancer were identified. The mean age was 68.8 years and 58.0 % were males. Patient characteristics across three distinct time periods are shown in Table 1. Initially, the majority of patients were male, but in the most recent period 2008–2018, the sex ratio became nearly equal. The mean age at diagnosis rose from 67.7 to 70.4 years. There was a significant decrease in the proportion of younger patients and an increase in those aged 70–79 years or 80 years and older ($P < 0.01$). Additionally, 651,574 matched comparison subjects were included in the analyses.

Overall, the prevalence of comorbidity (defined as CCI >0) increased steadily among both lung cancer patients and comparison subjects over the three periods 1980–1993, 1994–2007, 2008–2018 (Fig. 1). However, lung cancer patients showed a significantly higher increase in comorbidities compared to comparison subjects (25.8 percentage points versus 12.4 percentage points, for lung cancer patients and comparison subjects, respectively; $P < 0.01$). Consequently, almost half of lung cancer patients had a comorbidity in the most recent time period 2008–2018, whereas this was only true for 26 % of comparison subjects. A logistic regression analysis was conducted to determine the age groups in which comorbidities were increasing, revealing that the increase was

Table 1

Characteristics of lung cancer patients across three distinct time periods: 1980–1993, 1994–2007, 2008–2018, and the entire time period 1980–2018.

	Period I 1980–1993	Period II 1994–2007	Period III 2008–2018	Entire period 1980–2018
Lung cancer patients	53,056	56,071	53,869	162,996
Males/ females (%)	67.4/32.6	56.0/44.0	50.8/49.2	58.0/42.0
Mean age at diagnosis	67.7	68.3	70.4	68.8
Age groups < 50 years (%)	5.7	4.9	2.6	4.4
50–59 years (%)	15.4	15.7	11.4	14.2
60–69 years (%)	32.8	30.4	30.7	31.3
70–79 years (%)	33.6	34.5	36.1	34.7
80 + years (%)	12.5	14.5	19.2	15.4

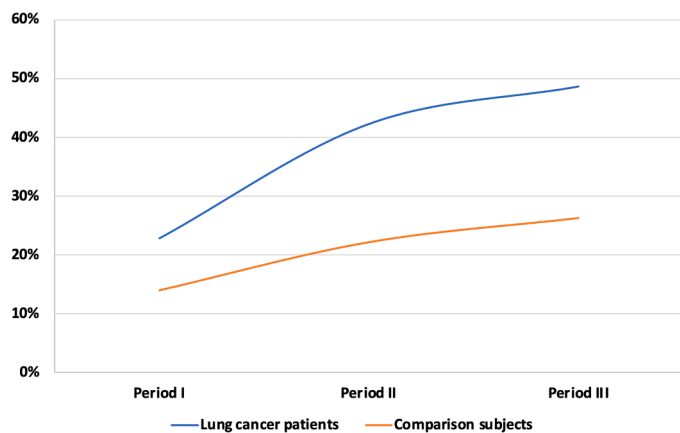


Fig. 1. Prevalence of comorbidity. Caption: Percentage of lung cancer patients and comparison subjects with Charlson comorbidity index > 0; Period I: 1980–1993; Period II: 1994–2007; Period III: 2008–2018.

observed across all age groups.

As shown in Table 2, the rise in comorbidity is not primarily due to more lung cancer patients having one comorbidity. In fact, a significant larger proportion of patients than comparators now have three or more comorbidities ($P < 0.01$).

Fig. 2 displays the top five comorbidities among both lung cancer patients and comparison subjects. In both groups, ischemic heart disease is the most common comorbidity, although it clearly affects more lung cancer patients than comparison subjects. Additionally, chronic obstructive lung disease is increasingly affecting lung cancer patients, while its impact on comparison subjects is less pronounced. Diabetes was equally prevalent in both groups during the first period 1980–1993, but lung cancer patients have shown a larger increase over the four decades compared to comparison subjects. Similarly, stroke and peripheral atherosclerosis are more prevalent in lung cancer patients, especially in the most recent period 2008–2018.

Fig. 3 shows the causes of death among lung cancer patients and comparison subjects. It is evident that the vast majority of lung cancer patients die from their lung cancer. This observation is even more pronounced in the most recent period 2008–2018, where 84 % of patients die from lung cancer. The remaining causes of death among lung cancer patients each account for only a few percent, with a notable decrease in deaths from ischemic heart disease of 3.3 percentage points (from 4.6 % to 1.3 %).

Among comparison subjects, the most common cause of death is ischemic heart disease. However, there is a significant decrease in deaths from ischemic heart disease, from 28 % in period I 1980–1993–15.6 % in period III 2008–2018. Other notable observations include an increase in deaths attributed to dementia, rising from 2.5 % to 8.2 %.

4. Discussion

The findings in this longitudinal nationwide study, spanning four decades, shed light on the changing landscape of comorbidities and causes of death among patients diagnosed with lung cancer. The study

revealed a significant increase in comorbidity burden among lung cancer patients, surpassing that of matched comparison subjects. Despite advancements in lung cancer survival rates [2], the primary cause of death among lung cancer patients remains lung cancer in the majority of cases.

The observed rise in comorbidities among lung cancer patients may have significant implications for the execution of invasive diagnostic procedures, treatment options, and prognosis. Currently, lung cancer screening is not implemented in Denmark, so screening cannot explain the rise in detected comorbidities. The increase in comorbidities was seen across all age groups and among both lung cancer patients and comparison subjects. This suggests that part of the reason is likely due to enhanced detection of comorbidities combined with an increase in the number of diagnosed lung cancer patients in the older age groups [24]. Hence, the increase in comorbidities over four decades may be linked to the rise in life expectancy [25], possibly due to reduced CVD mortality [17] and increased time for the development of lifestyle-related comorbidities [26].

Furthermore, our findings suggest a shift in the nature of comorbidities among lung cancer patients. A notable increase in the prevalence of multiple comorbidities was seen, indicating a more complex health profile among these patients. The analyses were adjusted for sex, and the lack of significant sex differences in our results may be attributed to the similar incidence of lung cancer between males and females in Denmark [27]. Chronic conditions such as ischemic heart disease, chronic obstructive lung disease, diabetes, stroke, and peripheral atherosclerosis were among the most prevalent comorbidities. This highlights the necessity for comprehensive management strategies that address both cancer and concurrent health issues [28], especially a profound focus on smoking cessation as well as promotion of an active and healthy lifestyle [29].

Unfortunately, data on tobacco exposure is unavailable for both the lung cancer and comparison cohorts, making it impossible to directly account for this factor. However, survey data indicate that smoking prevalence among males peaked in the 1950s, with 70–80 % being daily smokers, while among females, smoking prevalence peaked at 45 % before beginning to decline in the 1970s [27]. Given the widespread use of smoking in society at the time, the higher prevalence of certain comorbidities, such as chronic obstructive lung disease, among lung cancer patients compared to comparison subjects suggests a relationship between these conditions. This also implies that the comparison cohort likely had a lower smoking prevalence than the lung cancer cohort. Notably, smoking is a well-established risk factor for both emphysema and COPD, which, in turn, increase the risk of developing lung cancer [30–32]. Additionally, there may be a common genetic susceptibility to lung cancer as well as other lifestyle-related comorbidities [33], while lung cancer and its treatment may exacerbate and unmask pre-existing chronic lung conditions.

The main cause of death among lung cancer patients predominantly reflects the impact of the disease itself. Despite the significant increase in lung cancer 5-year survival rates [2], which have exceeded 25 % in Denmark [34], it is essential to note that most lung cancer patients still succumb to their illness with survival heavily dependent on the disease stage. In fact, in the most recent period 2008–2018, a higher proportion of lung cancer patients die from their disease compared to the earliest

Table 2
Charlson comorbidity index of lung cancer patients and comparison subjects.

CCI	Period I - 1980–1993		Period II - 1994–2007		Period III - 2008–2018	
	Lung cancer	Comparison subjects	Lung cancer	Comparison subjects	Lung cancer	Comparison subjects
0	77,2 %	86,1 %	57,7 %	77,8 %	51,4 %	73,7 %
1	13,2 %	7,3 %	16,3 %	10,5 %	18,5 %	11,5 %
2	5,0 %	4,2 %	11,6 %	7,0 %	13,6 %	8,6 %
3 +	4,5 %	2,4 %	14,3 %	4,7 %	16,6 %	6,2 %

CCI: Charlson comorbidity index.

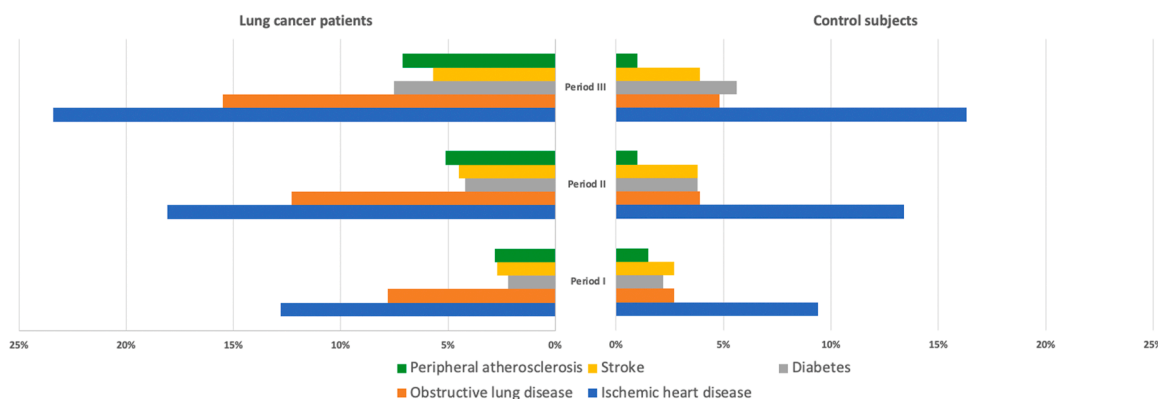


Fig. 2. Comorbidities in lung cancer patients and comparison subjects over four decades. Caption: Period I: 1980–1993; Period II: 1994–2007; Period III: 2008–2018.

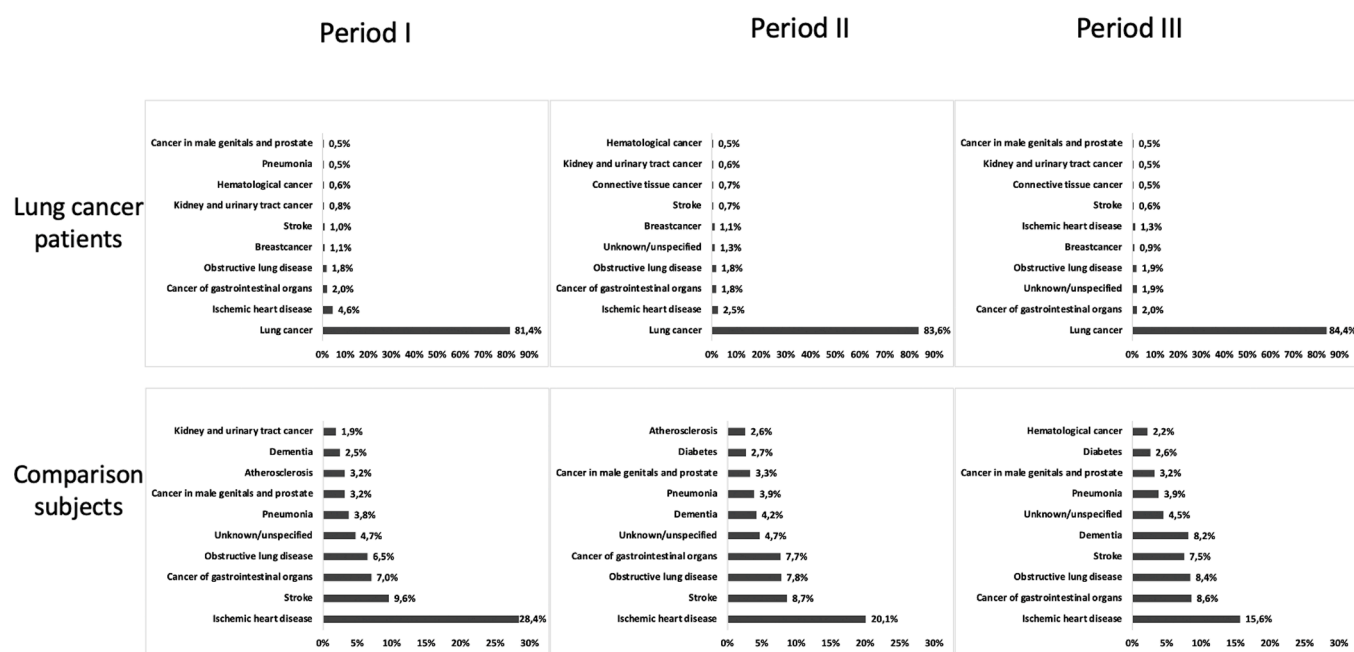


Fig. 3. Cause of death among lung cancer patients and comparison subjects across four decades. Caption: Period I: 1980–1993; Period II: 1994–2007; Period III: 2008–2018.

period 1980–1993 (84.4 % vs. 81.4 %). This emphasizes the critical importance of early detection of lung cancer, where CT screening could be a viable option—especially since it has not yet been implemented in Denmark—to facilitate curative treatment options [5], advance treatment modalities [35], and provide supportive care to extend survival and enhance the quality of life for lung cancer patients [36]. The notable decrease in deaths from ischemic heart disease among both lung cancer patients and comparison subjects over the study period underscores the significant improvements in cardiovascular care and risk factor management. Conversely, the significant increase in deaths attributed to dementia suggests a growing burden of dementia in societies with aging populations [37].

5. Strengths and limitations

Overall, the Danish registries are exceptional with national coverage, making them unique worldwide. However, some comorbidities may go undiagnosed in the secondary sector, as the registries only capture hospital-based diagnoses. Diagnoses made solely by general practitioners are not recorded in the DNPR, potentially leading to an underestimation of comorbidity prevalence, particularly for conditions such

as COPD, hypertension and diabetes. This underestimation should, however, be consistent among both lung cancer patients and comparison subjects. Additionally, pre-existing COPD may remain undiagnosed – even after a lung cancer diagnosis. Furthermore, the registries do not include details on smoking or racial characteristics.

In conclusion, our study provides valuable insights into the changing landscape of comorbidities and causes of death among lung cancer patients over four decades. These findings underscore the importance of diagnostic and treatment approaches that address both cancer and concurrent health issues including COPD and smoking cessation to optimize patient outcomes.

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CRediT authorship contribution statement

Ibsen Rikke: Writing – review & editing, Formal analysis, Conceptualization. Hilberg Ole: Writing – review & editing, Supervision,

Project administration, Conceptualization. **Borg Morten:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Løkke Anders:** Writing – review & editing, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Guarantor statement: The corresponding author takes responsibility for the content of the manuscript, including the data and analysis.

Data approval

Data from the Danish National Patient Register is analyzed without access to personally identifiable information, ensuring the privacy and confidentiality of individuals included in the registry. This study has approval from the Danish Data Protection Agency (no approval number).

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